NCT03511638

Clinical Study Protocol

Bausch & Lomb Ophthalmic Viscosurgical Device (OVD) Dispersive (DVisc40)

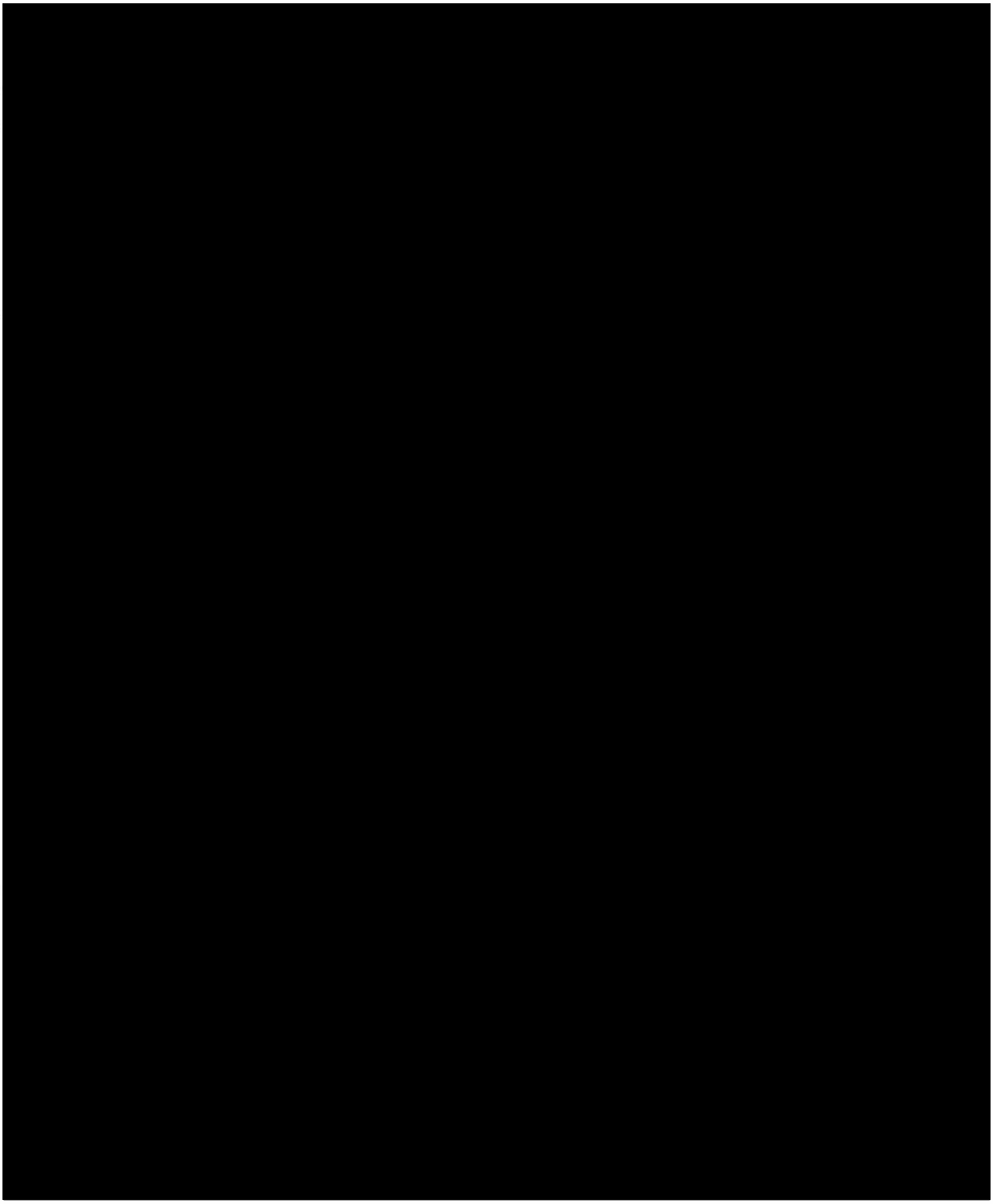
Study # S877

Developmental phase of study:	Pivotal Investigational Device Exemption (IDE) Trial
Study design:	Multicenter, controlled, randomized, monocular safety and effectiveness study
Date:	January 3, 2019 (Version 6.0)
Sponsor	Bausch & Lomb Incorporated, A subsidiary of Valeant Pharmaceuticals North America, LLC 400 Somerset Corporate Boulevard Bridgewater, NJ 08807 US Main office: (908) 927-1400

This clinical investigation is being conducted in accordance with 21 CFR Parts 50, 54, 56, and 812, ISO 15798 (2013) Ophthalmic Implants – Ophthalmic Viscosurgical Devices, ISO 14155 (2011 (E)) Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice, 42 USC 282(j), ICH GCPs and applicable local regulations.

CONFIDENTIAL

Nothing herein is to be disclosed without prior approval of the sponsor.



Personnel Responsible for Conducting the Study

A Study to Document the Safety and Effectiveness of a New Ophthalmic Viscosurgical Device (OVD) When Compared to a Control OVD

Contract Research Organization / Medical Monitor

Principal Investigator Protocol Agreement Page

COMMITMENTS OF THE INVESTIGATOR:

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after being notified by the Sponsor, except when necessary to protect the safety, rights, or welfare of subjects. I agree to comply with all requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 812.

I agree to personally conduct or supervise the described investigation(s). I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are adequately trained and qualified to fulfill their responsibilities and are informed about their obligations in conducting the study.

I agree to inform any patients, or any persons used as controls, that the device(s) are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the Sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR Part 812.150.

I agree to disclose to the Sponsor accurate financial information to allow the Sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR Part 54. I agree to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.

I agree to maintain adequate and accurate records in accordance with 21 CFR Part 812.140 and to make those records available for inspection in accordance with 21 CFR Part 812.145 and if I transfer custody of the records to any other person I will notify the Sponsor.

I will be responsible for the control of devices under investigation and will ensure that the investigational device is used only with subjects under my supervision. Upon completion or termination of the clinical investigation, I will either return all investigational devices to the Sponsor or dispose of the device as instructed by the Sponsor.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to report to the IRB all deviations in the research activity and all unanticipated problems involving risks to human subjects or others, per IRB requirements. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I have never been disqualified as an Investigator or had a research study terminated by the FDA, IRB/IEC or a Sponsor for noncompliance of an investigator agreement, investigational plan, IRB/IEC requirements or the requirements of 21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, 21 CFR Part 312, or 21 CFR Part 812. If an investigation or other research was terminated, I will provide an explanation of the circumstances that led to termination.

A current Curriculum Vitae has been provided to the Sponsor to demonstrate education, training, and experience that qualifies me to conduct clinical research as an expert in the field related to the device under investigation.

_____

Principal Investigator (print name)

_____ _____

Principal Investigator (signature) Date

2 Synopsis

Name of Sponsor/Company: Bausch & Lomb Incorporated, a subsidiary of Valeant Pharmaceuticals North America, LLC

Name of Investigational Device: Bausch & Lomb Ophthalmic Viscosurgical Device (OVD) Dispersive (DVisc40)

Title of Study: A Study to Document the Safety and Effectiveness of a New OVD When Compared to a Control OVD

Number of Clinical Centers: Up to approximately eighteen (18) clinical centers in the United States.

Objectives: To evaluate the safety and effectiveness of the Bausch & Lomb DVisc40 dispersive OVD compared to the Alcon VISCOAT® dispersive OVD when used in cataract surgery.

Methodology:

This is a multicenter, controlled, randomized, monocular trial evaluating the safety and effectiveness of the Bausch & Lomb DVisc40 dispersive OVD compared to the Alcon VISCOAT® dispersive OVD when used in cataract surgery. Subjects will be randomized to one of the two treatment groups in a 1:1 ratio (DVisc40:VISCOAT®).

The study purpose, procedures, and subject responsibilities will be explained to the potential participant. The subject's willingness and ability to meet the follow-up requirements will be determined. When it has been established that the subject is eligible and willing to participate, written informed consent will be obtained. Written informed consent must be obtained from each study subject prior to performing any study specific procedures which are NOT part of the Investigator's routine standard of care. A complete ophthalmic examination will be done at the Preoperative Visit scheduled within 60 days prior to surgery. The preoperative examination will include specular microscopy of the central corneal endothelium to obtain a baseline central endothelial cell density (ECD). Enrolled subjects who meet eligibility criteria will be seen according to the following schedule:

Preoperative Visit	Day -60 to Day -1
Operative Visit	Day 0
Postoperative Visit 1	6 Hours ± 2 hours postoperatively
Postoperative Visit 2	24 Hours ± 4 hours postoperatively
Postoperative Visit 3	7 Days ± 2 days postoperatively
Postoperative Visit 4	30 Days ± 7 days postoperatively
Postoperative Visit 5	90 Days ± 14 days postoperatively

Number of subject eyes planned: Up to three hundred sixty-eight (368) subjects eyes (one eye per subject) will be enrolled in this study.

Diagnosis and main criteria for inclusion: This study will include subjects who meet the following main inclusion criteria:

1. The subject must be at least 45 years old and have a clinically documented diagnosis of age-related non-complicated cataract that is considered amenable to treatment with standard phacoemulsification cataract extraction and intraocular lens (IOL) implantation.

2. The subject must have the capability to provide written informed consent on the Institutional Review Board (IRB)/Ethics Committee (EC) approved Informed Consent Form (ICF) and provide authorization as appropriate for local privacy regulations.
3. The subject must be willing and able to return for all scheduled follow-up examinations through 90 days following surgery.
4. The subject must have clear intraocular media other than the cataract in the operative eye.

Key exclusion criteria: This study will exclude subjects who meet the following main exclusion criteria:

1. The subject has participated in any drug or device clinical investigation within 30 days prior to entry into this study and/or during the period of study participation.
2. The subject has any corneal pathology (e.g., significant scarring, guttata, inflammation, edema, dystrophy, etc.) in the operative eye.
3. The subject has anterior segment pathology likely to increase the risk of an adverse outcome for phacoemulsification cataract surgery (e.g., pseudoexfoliation syndrome, synechiae, iris atrophy, inadequate dilation, shallow anterior chamber, traumatic cataract, lens subluxation) in the operative eye.
4. The subject has any condition which prevents reliable specular microscopy in the operative eye.
5. The subject has a congenital ocular anomaly (e.g., aniridia, congenital cataract) in the operative eye.
6. The subject has a baseline ECD < 1500 cells/mm^2 in the operative eye.
7. The subject has a grade 4+ nuclear cataract density in the planned operative eye.
8. The subject has glaucoma or ocular hypertension (IOP > 24 mmHg) in the operative eye.
9. The subject has any abnormality which prevents reliable Goldmann applanation tonometry in the operative eye.
10. The subject has a known allergy to any of the components of the test or control OVDs.
11. The subject is using any topical or systemic medications known to interfere with visual performance or complicate cataract surgery within 30 days of enrollment or during the study.
12. The subject is scheduled to undergo other combined intraocular procedures during the cataract/IOL implantation surgery in the operative eye. ***NOTE: A relaxing keratotomy is allowed.***
13. The subject has diabetic retinopathy, wet age-related macular degeneration or other retinal pathology which might limit postoperative visual acuity or predispose the subject to postoperative retinal complications in the operative eye.
14. The subject's fellow eye is already participating in this study.
15. The subject has a history of chronic or recurrent inflammatory eye disease (e.g., iritis, scleritis, uveitis, iridocyclitis, rubeosis iridis) in the operative eye.
16. The subject has a best corrected distance visual acuity (BCDVA) of LogMAR 1.0 (20/200, 6/60) or worse in the fellow eye.
17. The subject has had previous corneal surgery in the planned operative eye.
18. The subject has a previous retinal detachment in the operative eye.
19. Females of childbearing potential (those who are not surgically sterilized or not postmenopausal for at least 12 months) are excluded from participation in the study if they meet any one of the following conditions:
    - they are currently pregnant;
    - they plan to become pregnant during the study; and/or
    - they are breast-feeding.

Study Materials:

Test article: Bausch & Lomb DVisc40 OVD is a sterile nonpyrogenic solution which is supplied in a disposable glass syringe delivering 1.0 ml of highly purified, medium molecular weight Sodium Hyaluronate and Sorbitol.

Comparator: Alcon VISCOAT® OVD is a sterile, nonpyrogenic solution which is supplied in a disposable glass syringe delivering 0.75 mL of highly purified, non-inflammatory medium molecular weight fraction of Sodium Chondroitin Sulfate and Sodium Hyaluronate.

Duration of Treatment:

The duration of the treatment is anticipated to be approximately 15-20 minutes for the surgical procedure. During the surgical procedure, the OVD material should be carefully injected into the anterior chamber using standard aseptic technique. The OVD may be injected into the chamber prior to and/or following removal of the crystalline lens in the operative eye. Instillation of the OVD may protect the corneal endothelium from possible damage arising from surgical instrumentation or ultrasonic energy during the cataract extraction surgery. The OVD may also be used to coat surgical instruments prior to IOL implantation. For example, the internal surfaces of an IOL inserter are typically filled and/or coated with the OVD to provide lubricity during IOL compression and delivery into the eye. Additional OVD, of the same product, may be injected as needed throughout surgery to keep the anterior chamber fully formed and to re-inflate the capsular bag following cataract removal. At the end of the surgical procedure it is recommended that OVD be removed from the eye as completely as practical by thoroughly irrigating and aspirating with a sterile irrigating solution.

Criteria for Evaluation:

Evaluation of safety will be assessed through the monitoring of IOP, intraocular inflammation (anterior chamber cells, flare and characterization), and adverse events during all post-operative visits.

Evaluation of effectiveness will be assessed through the monitoring of ECD at postoperative follow-up visits.

The following are the primary study variables:

Safety:

- The primary safety variable will be the proportion of subjects who experience at least one IOP measurement ≥ 30 mmHg in the study eye at any follow-up visit.

Effectiveness:

- The primary effectiveness variable will be the change in ECD from baseline to Postoperative Visit 5 (90 Days ± 14 days) in the study eye.

These safety and effectiveness variables will be compared between the test and control groups.

Statistical Methods:

Summaries for continuous variables will include the sample size, mean, standard deviation, median, minimum, and maximum. Summaries for discrete variables will include the tabulation of frequencies and percentages.

Following Markov chain Monte Carlo imputation of missing IOP data, a one-sided upper 95% confidence interval for the difference between the test and control groups (i.e., test – control) in the proportion of subjects with at least one IOP measurement ≥ 30 mmHg in the study eye at any follow-up visit will be constructed using the normal approximation to test the null hypothesis for the primary safety variable that the upper confidence limit of the 95% confidence interval for the difference is ≥ 0.117. If the upper confidence limit is less than 0.117, then the null hypothesis of inferiority will be rejected in favor of the alternative hypothesis of non-inferiority.

Following Markov chain Monte Carlo imputation of missing cell density data, a one-sided upper 95% confidence limit for the mean difference in percent ECD loss between the test and comparator OVDs will be constructed. If the upper confidence limit is less than 5%, then the null hypothesis of inferiority for the primary effectiveness variable will be rejected in favor of the alternative hypothesis of non-inferiority.

Sample Size Calculations:

Regarding the proportion of subjects who experience at least one IOP measurement ≥ 30 mmHg in the study eye at any follow-up visit, when the sample size in each group is 165 subjects, a two-group large-sample normal approximation test of proportions with a one-sided 0.050 significance level will have 95.17% power to reject the null hypothesis that the test is inferior to the control (the difference in proportions, $\pi_t - \pi_c$, is 0.117 or greater) in favor of the alternative hypothesis that the test is non-inferior to the control (the difference in proportions, $\pi_t - \pi_c$, is less than 0.117), assuming that the expected difference in proportions is 0.000 and the proportion in the standard group is 0.117.

Regarding ECD loss, when the sample size in each group is 165 subjects, a two group 0.050 one-sided t-test will have 93.90% power to reject the null hypothesis that the test is inferior to the control (the difference in means, $\mu_t - \mu_c$, is 5% or greater) in favor of the alternative hypothesis that the test is non-inferior to the control (the difference in means, $\mu_t - \mu_c$, is less than 5%), assuming that the expected difference in means is 0% and the common standard deviation is 14.2%.

Assuming independence of the primary endpoints, the overall power of the study will be 95.17% x 93.90% = 89.36%. To allow for a dropout rate of up to 10%, a sample size of approximately 184 subjects per treatment arm will be targeted for enrollment. The total enrollment target consequently will be approximately 368 subjects.

3 Table of Contents

List of Tables

4 List of Abbreviations and Definitions of Terms

Abbreviation or specialist term	Definition or Explanation
ADE	Adverse device effect
AE	Adverse event
BCDVA	Best Corrected Distance Visual Acuity
cd/m^2	Candela per Meter Squared (a measure of light fluence)
CRF	Case Report Form
CRO	Clinical Research Organization
δ	Delta (statistical symbol for difference)
EC	Ethics Committee
eCRF	Electronic Case Report From
ECD	Endothelial cell density
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
FDF	Financial Disclosure Form
GCP	Good Clinical Practices
H_i	Hypothesis i (statistical term)
I/A	Irrigation and Aspiration
ICF	Informed Consent Form
ICH	International Council for Harmonization
IDE	Investigational Device Exemption
IOL	Intraocular Lens
IOP	Intraocular Pressure
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISO	International Organization for Standardization
ITT	Intent-to-Treat
IUD	Intrauterine Device
LogMAR	Logarithm of Minimum Angle Resolution
MCMC	Markov chain Monte Carlo
mL	Milliliter
mm	Millimolar
mmHg	Millimeters of Mercury
Nd-YAG	Neodynium-doped Yttrium Aluminum Garnet
NSAID	Non-steroidal Anti-inflammatory Drugs
OVD	Ophthalmic Viscosurgical Device
π_i	Proportion i (statistical term; i = c [control] or t [test])
PP	Per Protocol
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SUN	Standardization of Uveitis Nomenclature
TASS	Toxic Anterior Segment Syndrome
μ_i	Mean i (statistical term; i = c [control] or t [test])
UADE	Unanticipated adverse device effect
US	United States
VA	Visual acuity

5 Introduction

Ophthalmic viscosurgical device (OVD) materials are widely used in cataract surgery to allow the maintenance of the anterior chamber space, to re-inflate the capsular bag after cataract removal in order to create space for IOL insertion, and to form a protective coating to protect the corneal endothelium from surgical instruments and ultrasonic energy. The retention and removal properties for a number of OVD materials approved in the past 20 years has led to new OVD classifications and nomenclature based on surgical needs during cataract surgery.[1-4]

It is now recognized there are two physical qualities that generally characterize OVD in anterior eye surgery. A highly cohesive OVD will be easier to be completely removed from the eye at the end of surgery, which will reduce the likelihood of sudden increases in intraocular pressure (IOP) due to obstruction of the aqueous draining system. However, a cohesive OVD may also be removed unintentionally during the normal irrigation and aspiration process or during insertion and removal of objects through the corneal incision, potentially resulting in less anterior chamber stability and less protection for intraocular structures. Conversely, a highly dispersive OVD will maintain better levels of anterior chamber stability and endothelial coating but may prove difficult to remove completely at the end of surgery. The selection of OVD agent for each surgery can be influenced by individual patient anatomy and pre-existing medical conditions, as well as individual surgeon technique and preferences.

Bausch & Lomb OVD dispersive material (DVisc40) is intended to provide surgeons with a new option in the continuum of cohesive and dispersive properties. DVisc40 is intended for use as a surgical aid in ophthalmic anterior segment procedures, including cataract extraction and IOL implantation. DVisc40 creates and maintains space during lens extraction and IOL implantation, aids in tissue manipulation during surgery, enhances visualization during the surgical procedure, and protects the corneal endothelium and other intraocular tissues. DVisc40 may also be used to coat IOLs and instruments during ophthalmic anterior segment surgical procedures.

Two parameters have been commonly used in clinical trials to assess the performance of OVDs: 1) IOP spikes, to measure how completely the OVD can be removed from the eye at the end of surgery; and 2) ECD changes, to evaluate how effectively an OVD forms a protective coating over the corneal endothelium.

6 Study Objectives and Purpose

The objective of the study is to evaluate the safety and effectiveness of the Bausch & Lomb DVisc40 dispersive OVD compared to the Alcon VISCOAT® dispersive OVD when used in cataract surgery.

6.1 Outcome Variables

The following primary safety and effectiveness variables will be compared between the test and control groups.

6.1.1 Safety

The primary safety variable will be the proportion of subjects who experience at least one IOP measurement ≥ 30 mmHg at any post-surgical follow-up visit.

6.1.2 Effectiveness

The primary effectiveness variable will be the change in ECD from baseline to Postoperative Visit 5 (90 Days ± 14 days).

7 Investigational plan

7.1 Overall Study Design and Plan Description

This will be a multicenter, controlled, randomized, monocular trial of Bausch & Lomb DVisc40 (test) OVD compared to the currently marketed Alcon VISCOAT® (control) OVD.

Subjects scheduled to undergo cataract surgery by phacoemulsification and implantation of a posterior chamber intraocular lens (IOL) will be screened for eligibility. Subjects will be examined preoperatively to obtain a medical history, to establish a baseline for ocular condition, including ECD, and to determine eligibility. Only one eye of each subject will be included in the study. In the event that both eyes are eligible to participate in the study, the selection of the study eye will be left to the Investigator's discretion. At the time of surgery, subjects will be randomly assigned to either of the OVD groups based upon a predetermined randomization scheme. Randomization will be by a 1:1 schema (DVisc40:VISCOAT®) and will be stratified by site, age group and cataract severity. A method other than stratification may be employed to balance randomization. If so, the method will be specified in the statistical analysis plan (SAP).

Postoperatively, subjects will undergo ophthalmic examinations at regular intervals per the study visit schedule (refer to **Appendix A**). The Investigator will provide standardized pre-, intra-, and postoperative care for all study subjects at his/her site (refer to Section 11 for additional information). A delegated examiner at each site who is masked to the randomized assignment of each subject will perform all postoperative assessments.

The VISCOAT® OVD was chosen as the control because the product has been used in cataract surgery for over 20 years and has a proven record for safety. In addition, VISCOAT® OVD is classified as a dispersive OVD as is the DVisc40 OVD.

7.2 Investigators

The clinical investigation will be conducted at up to approximately eighteen (18) investigative sites located in the US.

The clinical investigation will be conducted by Investigators who are determined by the Sponsor to be suitably qualified by training and experience to conduct this study in compliance with all applicable GCPs and Food and Drug Administration (FDA) Federal Regulations or Local Regulations.

In the event that selected sites do not meet full enrollment, the Sponsor may decide to increase enrollment as needed at other currently active sites. No Investigator shall be expected to contribute less than 20 treated eyes or be allowed to contribute more than the

following percentages of the total number of treated eyes in the study, depending upon the number of sites as described in **Table 1**:

Table 1. Allowed Percent of Total Subjects Per Site

Sites	Maximum percentage of the total number of treated eyes per site
6	25%
7	21%
8	19%
9	17%
10 or more	15%

7.3 Study Duration

Eligible subjects who are enrolled in this study will be followed for approximately 90 days from the time of their surgery until their Postoperative Visit 5.

8 Selection and Withdrawal of Subjects

NOTE: Subjects for whom an analyzable specular image cannot be obtained may not receive the study treatment.

Up to approximately 368 subject eyes (one eye per enrolled subject) at up to approximately eighteen (18) clinical sites in the United States (US) scheduled to undergo phacoemulsification cataract surgery and IOL implantation will be enrolled in this clinical study.

The study purpose, procedures, and subject responsibilities will be explained to the potential participant. The subject's willingness and ability to meet the follow-up requirements will be determined. When it has been established that the subject is willing to participate, written informed consent will be obtained (**Section 15.3**). In order to determine subject's eligibility, written informed consent must be obtained from each study subject prior to performing any study specific procedures which are NOT part of the Investigator's routine standard of care during and subsequent to cataract surgery. Enrollment will be consecutive enrollment of all eligible subjects. A complete ophthalmic examination will be done at the Preoperative Visit scheduled within 60 days prior to surgery.

8.1 Subject Inclusion Criteria

1. The subject must be at least 45 years old and have a clinically documented diagnosis of age-related non-complicated cataract that is considered amenable to treatment with standard phacoemulsification cataract extraction and IOL implantation.
2. The subject must have the capability to provide written informed consent on the Institutional Review Board (IRB)/Ethics Committee (EC) approved Informed Consent Form (ICF) and provide authorization as appropriate for local privacy regulations.
3. The subject must be willing and able to return for all scheduled follow-up examinations through 90 days following surgery.

4. The subject must have clear intraocular media other than the cataract in the operative eye.

8.2 Subject Exclusion Criteria

1. The subject has participated in any drug or device clinical investigation within 30 days prior to entry into this study and/or during the period of study participation.
2. The subject has any corneal pathology (e.g., significant scarring, guttata, inflammation, edema, dystrophy, etc.) in the operative eye.
3. The subject has anterior segment pathology likely to increase the risk of an adverse outcome for phacoemulsification cataract surgery (e.g., pseudoexfoliation syndrome, synechiae, iris atrophy, inadequate dilation, shallow anterior chamber, traumatic cataract, lens subluxation) in the operative eye.
4. The subject has any condition which prevents reliable specular microscopy in the operative eye.
5. The subject has a congenital ocular anomaly (e.g., aniridia, congenital cataract) in the operative eye.
6. The subject has a baseline ECD < 1500 cells/mm^2 in the operative eye.
7. The subject has a grade 4+ nuclear cataract density in the planned operative eye.
8. The subject has glaucoma or ocular hypertension (IOP > 24 mmHg) in the operative eye.
9. The subject has any abnormality which prevents reliable Goldmann applanation tonometry in the operative eye.
10. The subject has a known allergy to any of the components of the test or control OVDs.
11. The subject is using any topical or systemic medications known to interfere with visual performance or complicate cataract surgery within 30 days of enrollment or during the study.
12. The subject is scheduled to undergo other combined intraocular procedures during the cataract/IOL implantation surgery in the operative eye. ***NOTE: A relaxing keratotomy is allowed.***
13. The subject has diabetic retinopathy, wet age-related macular degeneration or other retinal pathology which might limit postoperative visual acuity (VA) or predispose the subject to postoperative retinal complications in the operative eye.
14. The subject's fellow eye is already participating in this study.
15. The subject has a history of chronic or recurrent inflammatory eye disease (e.g., iritis, scleritis, uveitis, iridocyclitis, rubeosis iridis) in the operative eye.
16. The subject has a best corrected distance visual acuity (BCDVA) of LogMAR 1.0 (20/200, 6/60) or worse in the fellow eye.
17. The subject has had previous corneal surgery in the planned operative eye.
18. The subject has a previous retinal detachment in the operative eye.

19. Females of childbearing potential (those who are not surgically sterilized or not postmenopausal for at least 12 months) are excluded from participation in the study if they meet any one of the following conditions:
    - they are currently pregnant;
    - they plan to become pregnant during the study; and/or
    - they are breast-feeding.

8.3 Subject Withdrawal Criteria

Reasons for withdrawal may include, but are not limited to, the following:

- Either at investigator's request (e.g., non-ocular serious adverse event, subject non-compliance).
- Subject voluntarily withdraws consent.
- When the requirements of the protocol are not followed.
- When a subject is lost to follow-up. The investigator or his/her designee will try twice to reach the subject by telephone and will send a follow-up letter by certified mail before considering that the subject is lost to follow-up. These actions will be reported on the End of Study case report form (CRF) and a copy of the follow-up letter maintained in the investigator's file.

8.3.1 Subject Enrollment

The subject is considered enrolled in the study at the time the IRB/EC approved ICF is signed.

8.3.2 Subject Screen Failures

A subject who fails to meet eligibility criteria is considered a screen fail. Subjects who screen fail will not be eligible for rescreening.

8.3.3 Subject Completion

The subject has completed the study when they have completed Postoperative Visit 5. A subject who has missed visits or is missing study measurements will be continued in the study. Subjects who require further follow-up for an unresolved AE at the end of their study period will be followed according to **Section 12.4.4**.

An exit CRF must be completed for all subjects who complete, prematurely discontinue, or are lost to follow-up from the clinical investigation.

8.3.4 Subject Discontinuation

A subject MUST be discontinued **prior** to the final study visit for any of the following reasons:

- Change in eligibility prior to treatment

- Voluntary withdrawal
- Death
- Pregnancy
- Lost to follow-up
- Study terminated by Sponsor

Prior to discontinuing a subject, every effort should be made to contact the subject, schedule a final study visit, and obtain as much follow-up data as possible. Adverse events will be followed as described in **Section 12.4.4**. Subject withdrawals will be documented clearly on the source document and applicable CRF.

Notification of subject withdrawals will be made to the Sponsor or their designee through the IRT system and confirmed by the CRO.

Only subjects who are randomized but did not receive study treatment may be replaced. A new subject number will be assigned as long as the total number of treated subjects at the site does not exceed the maximum percentage of the total treated eyes in the study based on the number of active sites as outlined in **Section 7.2**. Subjects who are discontinued from the study following treatment will not be replaced.

Discontinued subjects should be followed outside of the study protocol according to the Investigator's normal standard of care.

8.3.5 Subjects Lost to Follow- up

Subjects who do not return for scheduled Postoperative Visit(s) as defined by the visit window, and cannot be contacted, may be considered lost to follow-up. All follow-up attempts will be documented and kept with the subject's source documentation, and the applicable CRFs will be completed.

Efforts shall be made to keep the number of subjects lost to follow-up to below 10% of the number of subjects treated.

9 Treatment Plan

9.1 Methods of Assigning Subjects to Treatment Groups

Up to approximately 368 subjects (368 eyes) will be randomized in a 1:1 ratio to receive DVisc40 (test) OVD or VISCOAT® (control) OVD during surgery.

9.1.1 Treatment Allocation

At the time of surgery, subjects will be randomly assigned to either the DVisc40 OVD group (test) or the VISCOAT® OVD group (control) based upon a predetermined randomization scheme. Randomization will be on a 1:1 schema.

9.1.2 Randomization Method

Subjects will be randomly assigned to one of the two OVD materials according to the randomization scheme to be provided in a computer-generated randomization code by a biostatistician otherwise not involved with the study.

Interactive Response Technology (IRT) will be utilized for randomization in this study. Randomization will be stratified by site, age group and cataract severity. A method other than stratification may be employed to balance randomization. If so, the method will be specified in the SAP. The randomization codes will be established in blocks such that approximately the same number of subjects will be assigned to the DVisc40 OVD or VISCOAT® OVD treatment groups at each site.

Subjects will be randomized to 1 of 2 treatment groups in a ratio of 1:1 (DVisc40:VISCOAT®). Each screened subject will be assigned a unique 5-digit subject number assigned by the site accessing the IRT system. The subject number assigned by the IRT system will consist of the 2-digit investigational center/site number (pre-assigned by Sponsor or its designee) and the 3-digit chronological screening order number starting with 001 (e.g. 01-001, 01-002). The study device kit will be assigned to subjects based on a randomization code and the kit will be dispensed to the subjects at Day 0 (Operative Visit) by the IRT system. The assigned kit number should be recorded in the subject's source documents and applicable case report form. A study device log will document the inventory and dispensing of study device at each investigational center.

9.1.3 Treatment Replacement

No other OVD can be used intraoperatively in conjunction with either the test or control OVD. Use of any other OVD will require immediate discontinuation of a subject from the study. If the surgeon feels more than one vial of test or control OVD is required to complete the surgery, this will be allowed and the incidence of such events will be reported.

9.2 Postoperative Masked Examiners and Masked Roles

Each site should have at least two masked examiners to perform the post-operative measurements. It is preferred that the same masked examiner perform all post-operative measurements for an individual subject.

Subjects, masked examiners, the specular microscopy reading center employees, the Sponsor (other than the assigned unmasked contact) and the CRO, with the exception of the study monitors, will be masked to the OVD treatment received.

Masking of subjects during the surgical procedure (and during the course of the study) will be discussed during a site initiation visit by the Sponsor representative with the Principal Investigator and study staff. All surgical staff present during the cataract surgery (who are unmasked) will be instructed not to discuss the OVD treatment assignment in the presence of the subject. Intraoperative surgical staff present during the cataract surgery will further confirm their commitment to not disclosing the assigned OVD treatment assignment to a subject by signing a masking commitment form prior to the initiation of the cataract surgery. Documentation will be maintained in the site files.

9.3 Concomitant Medications

9.3.1 Preoperative Medications

Preoperatively, antibiotic drops, as well as non-steroidal anti-inflammatory drugs (NSAIDs) where applicable, will be administered according to the Investigator's standard of practice. A complete list of the standard regimen of preoperative medications used at a participating clinical site will be provided to the Sponsor or its designee prior to initiation of the study. Absolutely no IOP-lowering medications may be used prophylactically.

9.3.2 Intraoperative Medications

The Investigator will use their standard surgical medications. A complete list of the standard regimen of intraoperative surgical medications used will be provided to the Sponsor or its designee prior to initiation of the study. Absolutely no IOP-lowering medications may be used prophylactically. If an IOP-lowering medication is used intraoperatively (e.g., in the case of surgical complication), the medication must be recorded in the subject's source documents and on the applicable case report form(s). Use of an IOP lowering agent under these conditions is not a reason for discontinuing a subject from the study. However, such subjects are to be excluded from the Per-Protocol (PP) and Best Case analysis populations.

9.3.3 Postoperative Medications

Investigators will use their standard regimen of postoperative medications, which may include antibiotic, steroidal, and/or NSAID drops. A complete list of the standard postoperative medications used will be provided to the Sponsor or its designee prior to initiation of the study. Absolutely no IOP-lowering medications may be used prophylactically.

Subjects requiring the postoperative use of a lubricating agent are only allowed to use unpreserved artificial tear preparations.

9.3.4 Management of Raised IOP

Treatment for IOP < 30 mmHg should be avoided if possible unless the Investigator considers it necessary for the safety and well-being of the subject. In the case of treatment of IOP < 30 mmHg, a specific justification must be documented in the subject's source records and on the case report form. Use of an IOP lowering agent under these conditions is not a reason for discontinuing a subject from the study. However, they are to be excluded from the Per Protocol (PP) and Best Case analysis populations.

For any IOP measurement ≥ 30 mmHg at a study visit (or as determined as medically necessary by the Investigator), the Investigator should institute a treatment consisting of one or a combination of the following options:

- Aqueous fluid release through corneal incision;
- Topical eye drops (e.g., *B*-blocker, prostamide, etc.);
- Oral medication (e.g., acetalozamide).

An IOP ≥ 30 mmHg at a study visit must be rechecked in approximately one (1) hour after the initial IOP measurement.

In the event of an IOP ≥ 30 mmHg or the use of an IOP lowering treatment, the Investigator should contact the Sponsor and its representative immediately.

9.4 Protocol Deviation Definition

A protocol deviation is defined as any instance(s) of failure to follow, intentionally or unintentionally, the requirements of the study protocol. In the event of a protocol deviation, the investigator or designee must document the date of the occurrence along with an explanation for the deviation in the subject's source documentation and any other applicable study form(s).

An investigator shall notify the sponsor and reviewing IRB/EC of any deviation from the protocol to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred.

All other protocol deviations must be reported by the Investigator to the IRB/EC per the IRB/EC policies. Notification of such protocol deviations should also be made to the Sponsor and/or its designee as soon as possible.

10 Study Materials and Management

In order to maintain product integrity and sterility, the investigational devices will be used as supplied in their original pouch and outer packaging. At each site, the investigational device will be dispensed by an appropriately qualified unmasked member of the study staff assigned by the investigator to this task.

10.1 Description of Test Article

Bausch & Lomb DVisc40 Dispersive OVD is a nonpyrogenic solution which is supplied sterile in a disposable glass syringe delivering 1.0 mL of highly purified, medium molecular weight fraction of Sodium Hyaluronate. DVisc40 OVD contains Sodium Hyaluronate, Sorbitol and Sodium Chloride and a dual buffering system dissolved in USP water for injection, with a solution pH of 6.8 – 7.6.

10.2 Description of Comparator Control

Alcon VISCOAT® OVD is a sterile, nonpyrogenic solution which is supplied in a disposable glass syringe delivering 0.75 ml of highly purified, non-inflammatory medium molecular weight fraction of Sodium Chondroitin Sulfate and Sodium Hyaluronate. VISCOAT® OVD contains Sodium Chondroitin Sulfate, Sodium Hyaluronate, Dibasic Sodium Phosphate Anhydrous and Sodium Chloride (with Water for Injection) with a pH of 6.8 – 7.2.

10.3 Packaging and Labeling

The study materials will be packaged and labeled in a manner consistent with the study design.

10.3.1 Labeling

The test article labeling will include the following information on the outer box:

- study number;

- product identifier
- lot number;
- kit number;
- quantity of contents;
- statement to refer to the Directions for use (DFU);
- caution statement: Caution: Investigational Device. Limited by Federal Law to investigational use;
- Sponsor name and address;
- storage conditions; and
- expiration date.

10.4 Storage of Study Device

DVisc40 OVD and VISCOAT® OVD must be stored at 2° to 8° C (35° to 46° F) and must be protected from freezing. Before use, the study material must be allowed to reach room temperature (approximately 20 to 45 minutes).

10.5 Directions for Use and Administration

The test and control OVDs will be used according to the manufacturer's directions for use document.

The test and control OVD devices (DVisc40 and VISCOAT®, respectively) will be provided in 1.0 ml and 0.75 ml syringes, respectively.

The OVD material should be carefully injected into the anterior chamber using standard aseptic technique and may be injected into the chamber prior to and/or following removal of the crystalline lens. Instillation of the solution at these points is significant, in that a coating of OVD may protect the corneal endothelium from possible damage arising from surgical instrumentation or procedures during the cataract extraction surgery. The OVD may also be used to coat the tips of surgical instruments and/or an IOL prior to implantation. For example, the internal surfaces of an IOL inserter are typically filled and/or coated with the OVD to provide lubricity during IOL compression and delivery into the eye. Additional OVD, of the same product, may be injected into the anterior chamber of the eye to fully maintain the chamber or replace any volume lost during the surgical procedure.

At the end of the surgical procedure, it is recommended that the OVD material be removed from the eye as completely as practical by thoroughly irrigating and aspirating with a sterile irrigating solution.

10.6 Study Device Accountability

The Investigator will be responsible for keeping current and accurate records of the amount of study device received and dispensed, and its disposition. The devices must be stored under the appropriate conditions in a secure area and are to be used only in subjects enrolled in the study, in accordance with the conditions specified in this protocol. During the course of the study, the Investigator must maintain an inventory of all investigational devices dispensed to a subject, including subject identifiers.

Accountability records will include:

- the lot and kit numbers of the device received, the receipt date, and the quantity received;
- the names of all persons who received, used, or disposed of the device;
- the dates of use, disposal, or return of the device;
- a record of each subject treated with device; and
- why and how many of the devices have been returned to the Sponsor.

At time points throughout the study and/or upon completion of the study, the Sponsor/Sponsor's representative will review and verify the Investigator's accountability records. Following verification, and as directed by the Sponsor, unused study devices must be returned to the Sponsor, or with the Sponsor's permission, disposed of at the site in an appropriate manner. Used devices will be disposed of after use as directed by the Sponsor and disposal will be recorded on the study Accountability Log.

10.7 Other Materials

Additional materials will include:

- ETDRS light box and charts (provided by Sponsor if needed)
- Non-contact Specular Microscope (approved by or supplied by Sponsor)
  Note: The Specular Microscope must be certified by the central reading center prior to study use and all users must be appropriately certified by the central reading center prior to subject imaging.
- Urine pregnancy test for all females of childbearing potential (to be supplied by the CRO)

11 Study Procedures and Evaluations

Subjects will be examined and evaluated according to **Appendix A**. If at any time during the course of the study the subject's IOP is ≥ 30 mmHg then the subject will be requested to come in for an unscheduled study visit(s) as necessary until the IOP is < 30 mmHg. Any treatment of IOP per investigator's discretion (paracentesis, IOP lowering drugs, etc.) at any time shall be documented and the data from those subjects shall be reported and analyzed separately.

11.1 Schedule of Evaluations and Procedures

Enrolled subjects who meet eligibility criteria will be seen according to the following schedule:

Table 2. Schedule of Evaluations and Procedures

Preoperative Visit	Days -60 to -1
Operative Examination	Day 0
Postoperative Visit 1*	6 Hours ± 2 hours postoperatively

Postoperative Visit 2	24 Hours ± 4 hours postoperatively
Postoperative Visit 3	7 Days ± 2 days postoperatively
Postoperative Visit 4	30 Days ± 7 days postoperatively
Postoperative Visit 5	90 Days ± 14 days postoperatively

* Postoperative Visit 1 must occur on the same day as the Operative Visit.

Refer to **Appendix A** for the schedule of visits and parameters and **Appendix B** for methods of clinical evaluation.

11.1.1 Preoperative Visit: Days -60 to -1

Following identification of a potential subject, the Investigator (or designee) will explain the purpose of the study, procedures, risks/benefits, and subject responsibilities to the potential subject. The subject's willingness and ability to meet the follow-up requirements of the study will be determined. If the subject chooses to participate in the investigation, written informed consent will be obtained. The subject and the person obtaining written consent, will sign and date the IRB/EC approved ICF, at which point the subject is considered part of the study population. The original signed document will be retained in the subject records, and a copy will be provided to the subject. In addition, the applicable privacy regulation requirements must be met.

The subject identification number will be assigned by the site accessing IRT, which will consist of a 2-digit site number (pre-assigned) and a 3-digit chronological order screening number, assigned by IRT and starting with 001 (e.g., 01-001, 01-002; in this example the site number is 01). That subject number will be used to identify the subject throughout the study. It will not be necessary for the surgical procedures to occur in subject number order.

Informed consent must be obtained prior to the Investigator performing study specific procedures that are NOT his/her routine standard of care. After obtaining written informed consent, prospective subjects will be screened to determine whether they meet the entry criteria for the study. Demographic information, medical history, and current medication use will be collected. The preoperative clinical evaluation will be conducted no more than 60 days prior to surgery and will consist of a complete ophthalmic examination including specular microscopy of the central corneal endothelium of the study eye to obtain a baseline central ECD.

Refer to **Appendix A** for a schedule of visits and parameters.

11.1.2 Operative Visit: Day 0

Subjects will be reassessed to reconfirm eligibility. In addition, any changes in concomitant medications, additional medical history since the preoperative study visit, or any adverse events (AEs) will be recorded. If the subject is no longer eligible, he/she will be discontinued from the study. If the subject is eligible, the subject will be randomized via IRT, surgery will be performed and the Investigator will answer questions on source documents concerning the surgery using the surgical procedure described in **Appendix C**.

Intraoperative surgical staff present during the cataract surgery will confirm their commitment to not mention the treatment assignment in the presence of a subject by signing a masking commitment form prior to the initiation of the cataract surgery. Documentation will be maintained in the site files.

11.1.3 Postoperative Visits (1 through 5): 6 Hours ± 2 hours to 90 Days ± 14 days postoperatively

All treated subjects will be seen for five (5) postoperative visits. Refer to **Appendix A** for assessments to be performed at these visits.

11.1.4 Unscheduled Visit(s)

Additional visits may be scheduled, as necessary, to ensure the safety and well-being of subjects. In cases where the subject's IOP is ≥ 30 mmHg, additional Unscheduled Visits may be scheduled as necessary to monitor the subject's IOP (see Section 11). All additional examinations should be fully documented in the site source documents and on Unscheduled Visit CRFs, as appropriate. Visits intended to fulfill scheduled visit requirements that fall outside the designated scheduled visit range, are not Unscheduled Visits. In these cases, the visit data will be collected and transcribed to the appropriate scheduled visit CRF.

If a subject is seen for multiple visits during a given visit timeframe, the data from the visit that is intended to meet the protocol requirements for the scheduled visit should be captured on the corresponding visit CRF. Where such a determination cannot be made, the first visit within the scheduled visit interval will be used for completion of the protocol required scheduled visit CRF. Data from any additional visits within a scheduled visit interval will be captured on an Unscheduled Visit CRF.

11.1.5 Missed Visit(s)

If a subject misses any scheduled follow-up visit and cannot be seen prior to the start of the visit range for the next scheduled follow-up visit, the visit is considered missed.

11.2 Post-study Follow-up

If a subject requires further follow-up upon discontinuation or completion of the study, the Investigator should schedule post-study follow-up visits, as necessary. Refer to **Section 12.4.6** for follow-up of AEs following study exit.

11.3 Study Completion

The Sponsor or its representative will notify the Investigator or the IRB/EC, as applicable, to inform them that the study is complete.

11.3.1 Early Study Termination

If any subjects in the investigation have an IOP ≥ 30 mmHg in the study eye at one (1) week or later, early termination of the study shall be considered.

If during the study it becomes evident to the Sponsor that the study should be stopped prematurely, the study will be terminated and appropriate notification will be given to the Investigator(s), IRB/EC, and FDA or Local Health Authority, as applicable. The Sponsor or

its representative will instruct the Investigators to stop enrolling and dispensing study materials/treatment and to arrange for study closeout procedures at each site.

12 Safety and Effectiveness Variables

12.1 Evaluation of Safety

The primary safety variable will be the proportion of subjects who experience at least one IOP measurement ≥ 30 mmHg at any follow-up visit.

Secondary safety variables will be:

- Mean change from baseline in IOP at the six hour post-operative visit
- Mean change from baseline in IOP at the 24 hour post-operative visit

The incidence and type of AEs reported by the subject or observed by the Investigator at each study visit will be collected from the time the subject signs the ICF until study exit.

12.2 Evaluation of Effectiveness

The primary effectiveness variable for a subject will be the change in ECD from baseline to Postoperative Visit 5 (90 Days ± 14 days). There are no secondary effectiveness endpoints.

12.3 Risk Assessment

All risks associated with the use of the DVisc40 dispersive OVD have been assessed and reduced to as low as reasonably practicable. Bausch + Lomb believe that the level of residual risk for this product is acceptable in the clinical setting where ophthalmic surgery is performed. An increase in IOP can follow anterior segment surgery in which OVDs are utilized. It is a recognized potential consequence of their use, is typically transient, and should not significantly impair ocular function or the repair of ocular tissues. A significant or prolonged increase in the IOP can cause pain or discomfort and result in permanent damage to the eye.[3] To mitigate this risk, the Sponsor scheduled the first two post-surgical follow-up visits to assess IOP at 6 Hours ± 2 hours postoperatively and at 24 Hours ± 4 hours postoperatively. Also, IOP will be assessed at all follow-up visits. Other potential adverse effects include postoperative reactions including inflammation (iritis, hypopyon, endophthalmitis), corneal edema and corneal decompensation. Subjects will be assessed at all follow-up visits.

12.4 Adverse Events

Each subject eye treated must be examined for the presence/absence of adverse events at all visits, whether scheduled or not. If an adverse event occurs, the first concern will be the safety and welfare of the subject; treatment should be provided as appropriate for the event. Depending on the severity and attribution of the event to the investigational device, FDA regulations and GCPs determine how incidences of safety events are to be recorded and/or reported during the study.

12.4.1 Adverse Events Definitions

For the purposes of this study, adverse events include: ocular adverse events (AEs) in the study eye only; all ocular and non-ocular serious adverse events (SAEs); adverse device effects (ADEs); and unanticipated adverse device effects (UADEs). AEs, SAEs, ADEs and UADEs are defined as follows:

- Adverse Event (AE): any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in a subject, user or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device, comparator or the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices.
- Adverse Device Effect (ADE): an adverse event related to the use of an investigational medical device. This definition includes AEs resulting from insufficient or inadequate instructions for use; deployment, implantation, installation, or operation; or any malfunction of the investigational medical device. This definition also includes any event resulting from use error or from intentional misuse of the investigational medical device.
- Serious Adverse Event (SAE) is an AE that:
    - led to death;
    - led to serious deterioration in the health of the subject, that resulted in:
        - a life-threatening illness or injury; or
        - a permanent impairment of a body structure or a body function (e.g., blindness); or
        - in-patient or prolonged hospitalization; or
        - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function;
    - led to fetal distress, fetal death, or a congenital abnormality or birth defect.

    NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.
- Unanticipated Adverse Device Effect (UADE): any serious adverse effect on health or safety or any-life threatening problem or death caused by, or associated with a device, if that effect, problem or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Experience with cataract surgery and the implantation of IOLs has shown that some adverse effects can be associated with either the surgical procedure or the lens implanted. The following is a non-inclusive list of anticipated ADEs which have the potential of being considered as SAEs should the circumstances meet the necessary SAE criteria:

- Corneal stromal edema
- Cystoid macular edema

- Wound leak (positive Seidel)
- Flat anterior chamber
- Iris prolapse
- Vitreous in anterior chamber
- Vitreous to wound
- Synechiae/ Fibrin in pupil
- Iritis
- Raised IOP requiring treatment
- Retained lens material
- Capsulorhexis tear
- Posterior capsular rupture
- Severe IOL optic tilt or decentration
- IOL dislocation out of the capsular bag
- Deposits on IOL
- IOL opacities
- Worsening of pre-existing macular edema or diabetic retinopathy

The following is a non-inclusive list of ADEs that are rare in incidence:

- Toxic Anterior Segment Syndrome (TASS)
- Hyphema
- Hypopyon
- Choroidal detachment/hemorrhage
- Thermal injury (i.e. phaco burn, corneal burn)
- Endophthalmitis
- Retinal detachment
- Loss of BCDVA ≥ 10 Early Treatment Diabetic Retinopathy Study (ETDRS) chart letters

12.4.2 Identification and Collection

Identification and collection of adverse events (i.e. AE, SAE, ADE or UADE) begins after informed consent has been obtained and documented. Standard sources for identifying AEs include:

- Direct observation by the Investigator;
- Asking the study participant a non-specific question (e.g., “Have you had any problems since the last visit?”);
- Unsolicited volunteering of information by the study participant (e.g., “Doctor, I have had numerous headaches since I started using this lens.”); and/or

- Laboratory or test results that meet protocol requirements for classification as an AE (e.g., IOP ≥ 30 mmHg).

Ocular AEs in the study eye only, ADEs, all ocular and non-ocular SAEs, and UADEs observed or elicited by the Investigator, reported by the subject, or resulting from a test result, etc., occurring during the clinical investigation must be documented. During the study, the Investigator should treat the study subject as appropriate to ensure his/her safety and welfare. Refer to Section 12.4.5 for additional information pertaining to ongoing AEs at subject exit.

Pre-existing conditions will not be considered as AEs/SAEs, but will be collected at the preoperative visit as medical history. A worsening of a pre-existing condition, with the exception of cataract in the fellow eye, during the study should be documented as an AE and evaluated accordingly.

Hospitalization is a criterion for assessment of seriousness. Hospitalizations for admission without a medical AE should be captured as a serious AE until the cause of hospitalization can be identified. However, the following reports of hospitalization without a medical AE should not be considered either serious or an AE:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with worsening of the pre-existing condition (e.g., for work-up of persistent pretreatment lab abnormality);
- Social admission (e.g., subject has no place to sleep);
- Administrative admission (e.g., for yearly physical exam); and/or
- Optional admission not associated with a precipitation medical AE (e.g., for elective cosmetic surgery).

12.4.3 Evaluations

When evaluating AEs, the Investigator must determine if the event is serious (refer to Section 12.4.1 for criteria), assess the severity of symptoms and the relationship of the event to the study device using the following guidelines:

a. Severity

- **Mild**: Subject awareness of a sign or symptom that is easily tolerated, requires no treatment, and does not interfere with subject's daily activities.
- **Moderate**: Subject awareness of a sign or symptom which may be a low level of concern to the subject and may interfere with daily activities, but can be relieved by simple therapeutic care.
- **Severe**: A sign or symptom that interrupts the subject's daily activity and requires systemic therapy or other treatment.

b. Relationship to Study Device

- **Related:** There is at least a reasonable possibility that the AE/SAE is related to the study device. Reasonable possibility means that there is evidence to suggest a causal

relationship or association between the study device and the AE. Also referred to as an ADE.

- **Unrelated:** There is little or no reasonable possibility that the AE/SAE is related to the study device. This assessment implies that the AE/SAE has no evidence to suggest either a causal relationship or association to the study device and more likely or certain an alternative etiology exists.

12.4.4 Reporting

Actions required by Investigators for reporting non-serious ocular adverse events in the study eye(s) are summarized in **Table 3** below:

Table 3. Non-serious Adverse Events

Adverse Events	Non-device-related	Device-related
Non-serious, ocular, in study eye(s)	AE	ADE
Required Action	Recorded on AE CRFs only. No report to IRB. No expedited report to Sponsor.	

Actions required by Investigators for reporting all serious adverse events in the study eye(s) and/or non-study eye are summarized in **Table 4** below:

Table 4. Serious Adverse Events

<table>
<tr><th rowspan="2">Serious Adverse Events</th><th rowspan="2">Non-device-related</th><th colspan="2">Device-related</th></tr>
<tr><th>Anticipated</th><th>Unanticipated</th></tr>
<tr><td>Serious, ocular, and non-ocular, in study eye(s) and/or fellow eye</td><td colspan="2">SAE</td><td>UADE</td></tr>
<tr><td>Required Action</td><td colspan="2">Recorded on AE CRF and SAE/UADE Report Form
⇩
Investigator provides expedited report to Sponsor and its representative within 48 hours

.
Report to IRB per IRB policy.
.</td><td>Recorded on AE CRF and SAE/UADE Report Form
⇩
Investigator provides expedited report to Sponsor and its representative within 48 hours.
Investigator reports to IRB within 10 working days or per IRB policy, whichever is shorter.

Sponsor Conducts Evaluation
⇩
Sponsor and its representative reports to FDA, all IRBs & all Investigators within 10 working days.</td></tr>
</table>

12.4.4.1 On-Site SAE/UADE Reporting

The site must report any adverse event to the Sponsor and its representative in an expedited manner if it meets the criteria for a SAE or a UADE. When reporting a SAE/UADE to the Sponsor and its representative, the site must forward any supporting documents along with the completed UADE Report Form to the Sponsor and its designee within 48 hours of becoming aware of such an event.

The contacts for reporting SAEs/UADEs are:

Sites must also report UADEs to the reviewing IRB per its established reporting procedures or within 10 working days following awareness of the event; whichever is shorter. The site should also complete applicable CRFs within three working days of event identification. The Sponsor or their designee will report the UADE to the FDA within 10 working days after being first informed by the Investigator.

Non-Device related SAEs should also be recorded in the applicable CRFs and submitted to the IRB per IRB policy.

12.4.4.2 Off-Site UADE Reporting

When participating in multicenter clinical investigations, Principal Investigators may receive UADE reports from other participating sites as applicable. These are Sponsor reports of UADEs which occurred at other sites for the same trial, or in different trials using the same test article, that met the criteria for reporting to a regulatory agency. These should be reported to the reviewing IRB per their established reporting procedures or within 10 working days; whichever is shorter.

12.4.4.3 Reporting Device Deficiencies

A device deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling. All device deficiencies will be reported to the Sponsor and its representatives on a Device Deficiency Report form.

Investigators must evaluate, record, and report via applicable forms any complaints/deficiencies, or malfunctions that could potentially lead to a SAE during this trial to the Sponsor and its representative without unjustified delay. As required, such reports may be provided to the reviewing IRB per their established reporting procedures and the

FDA by the Investigator. Upon the Sponsor's request, Investigators must supply any additional information related to the safety reporting of a particular event.

The contact for reporting device deficiencies is:

[redacted]

The Sponsor shall review all device deficiencies and determine and document in writing whether they could have led to a SAE. In the event of a disagreement between the Sponsor and the Investigator(s), the Sponsor shall communicate both opinions to the reviewing IRB per their established reporting procedures and the FDA as described in **Table 4**.

12.4.5 Adverse Events and Unanticipated Adverse Device Effects at Subject Exit

Ongoing AEs will be followed until resolution; no further change in the condition is expected; as dictated by standard of care; or up to 30 days post final visit, whichever is shorter. Documentation in the CRFs of such follow-up is not required although subject care should continue as appropriate.

Ongoing UADEs will be followed by the Sponsor and its representative(s) and Investigator until their medical endpoints are determined or until no further change in the condition is expected.

12.4.6 Pregnancy

All female subjects of childbearing potential must use an effective method of birth control during the course of the study, in a manner such that risk of contraceptive failure is minimized. Effective contraception is defined as stabilized on oral contraceptive for at least 3 months or use for 3 months of an intrauterine device (IUD), condom with spermicidal, diaphragm with spermicidal, implant, Nuvaring, injection, transdermal patch, and/or abstinence. Females on birth control pills must have taken the same type pill for at least three months prior to entering the study and must not change type during the study. Those who have not used birth control pills in the three months prior to being screened must not begin or resume usage during that period prior to entering the study. Abstinence is allowed as a birth control method.

Before enrolling a female subject of childbearing potential in this clinical trial, the investigator must review the following information about study participation:

- Informed consent requirements; and
- Contraceptives in current use.

Following review of this information and appropriate subject counseling, the investigator or designee and the subject must sign the informed consent before study enrollment.

During the study, all female subjects of childbearing potential are subject to urine pregnancy testing during their study visits and should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period).

If a subject or investigator suspects that the subject may be pregnant prior to study enrollment, the study product must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject must not receive study product and must not be enrolled in the study.

Subjects who become pregnant during the study will be discontinued from the study and followed until completion of pregnancy. Pregnancy itself is not considered an AE.

All confirmed pregnancies must be immediately reported to the medical monitor and CRO contact within 48 hours of the investigator's awareness of the pregnancy. All confirmed pregnancies must be reported via confirmed facsimile or email transmission and must be submitted on a Pregnancy Report Form within 48 hours of the investigator's awareness of the pregnancy.

13 Statistics

Additional details of the statistical analysis will be provided in the SAP, which will be prepared and approved prior to database lock.

13.1 Study Endpoints

The following endpoints will be compared between the test and control groups.

13.1.1 Safety Endpoints

13.1.1.1 Primary Safety Endpoint

The primary safety endpoint will be the proportion of subjects who experience at least one IOP measurement $\geqq$ 30 mmHg in the study eye at any follow-up visit. This endpoint will be evaluated cumulatively over all post-operative follow-up visits.

13.1.1.2 Secondary Safety Endpoints

- Mean change from baseline in IOP at the six hour post-operative visit
- Mean change from baseline in IOP at the 24 hour post-operative visit

13.1.2 Effectiveness Endpoint

13.1.2.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint will be corneal ECD loss (%) from baseline to Postoperative Visit 5 (90 Days ± 14 days) in the study eye.

13.1.2.2 Secondary Effectiveness Endpoints

There are no secondary effectiveness endpoints.

13.2 Hypotheses

13.2.1 Primary Hypotheses

13.2.1.1 Primary Safety Hypothesis

For the primary safety hypothesis test, the incidence of IOP observations at or above 30 mmHg refers to the number of study eyes experiencing one or more such events at any postoperative visit. Each subject will be classified as having experienced an IOP spike or not having experienced an IOP spike and will not be double counted. The safety null hypothesis (H_0) is that the test incidence (π_t) of IOP observations at or above 30 mmHg minus the control incidence (π_c) of IOP observations at or above 30 mmHg is greater than or equal to the non-inferiority margin (δ). The alternative hypothesis (H_1) is that the test incidence (π_t) of IOP observations at or above 30 mmHg minus the control incidence (π_c) of IOP observations at or above 30 mmHg is less than the non-inferiority margin (δ).

$$H_0: \pi_t - \pi_c \geq \delta$$

$$H_1: \pi_t - \pi_c < \delta$$

13.2.1.2 Primary Effectiveness Hypothesis

ECD loss will be evaluated from baseline to postoperative visit 5 (90 Days ± 14 days) in the study eye. The primary effectiveness null hypothesis (H_0) is that the mean within-eye percent ECD loss with the investigational OVD (μ_t) minus the mean within-eye percent ECD loss with the control OVD (μ_c) is greater than or equal to the non-inferiority margin (δ). The alternative hypothesis (H_1) is that the mean within-eye percent ECD loss with the investigational OVD (μ_t) minus the mean within-eye percent ECD loss with the control OVD (μ_c) is less than the non-inferiority margin (δ).

$$H_0: \mu_t - \mu_c \geq \delta$$

$$H_1: \mu_t - \mu_c < \delta$$

13.2.2 Secondary Hypotheses

The secondary null hypotheses will be eligible for rejection only if both of the primary endpoints are met. As recommended in ICH E9, the nominal alpha risk will be 0.025 for the one-sided secondary superiority hypothesis tests.

The secondary hypotheses will be tested in two sequential families, with simultaneous testing of the hypotheses in the second family.

1. Family 1: Secondary Effectiveness Hypotheses
    a. ECD loss superiority test
2. Family 2: Secondary Safety Hypotheses
    a. IOP spike rate superiority test
    b. Mean change from baseline in IOP at 6 hours post-op superiority test
    c. Mean change from baseline in IOP at 24 hours post-op superiority test

The overall type I error for the secondary endpoint hypothesis tests in Family 2 above will be controlled by application of the Holm stepwise procedure.

13.2.2.1 Secondary Safety Hypotheses

13.2.2.1.1 IOP Spike Rate Superiority Test

The secondary safety null hypothesis regarding the IOP spike rate is that the test incidence (π_t) of IOP observations at or above 30 mmHg is greater than or equal to the control incidence (π_c) of IOP observations at or above 30 mmHg. The alternative hypothesis is that the test incidence is less than the control incidence.

$$H_0: \pi_t \geq \pi_c$$

$$H_1: \pi_t < \pi_c$$

If the null hypothesis is rejected then superiority will be claimed for the test OVD in the rate of IOP spikes.

13.2.2.1.2 Mean Change from Baseline in IOP Superiority Tests

Regarding the mean change from baseline in IOP at the six-hour and 24-hour post-op visits, the null hypothesis at each visit is that the mean change from baseline IOP for the investigational OVD group is greater than or equal to the mean change from baseline IOP for the control group. The alternative hypothesis is that the mean change from baseline IOP for the investigational OVD group is less than the mean change from baseline IOP for the control group.

$$H_0: \mu_t \geq \mu_c$$

$$H_1: \mu_t < \mu_c$$

For each of the visits, if the null hypothesis is rejected then superiority will be claimed for the test OVD in mean IOP.

13.2.2.2 Secondary Effectiveness Hypothesis

The secondary effectiveness null hypothesis is that the mean within-eye percent ECD loss with the investigational OVD (μ_t) is greater than or equal to the mean within-eye percent ECD loss with the control OVD (μ_c). The alternative hypothesis is that the mean loss with the investigational OVD is less than the mean loss with the control OVD.

$$H_0: \mu_t \geq \mu_c$$

$$H_1: \mu_t < \mu_c$$

If the null hypothesis is rejected then superiority will be claimed for the test OVD in ECD loss.

13.3 Sample Size Determination

13.3.1 Incidence of IOP ≥ 30 mmHg

Due to their comparable rheological properties, DVisc40 and VISCOAT® OVDs are expected to demonstrate similar behavior during surgical procedures.

In published studies using VISCOAT®, VISCOAT® performed without anti-IOP prophylactic treatment where the frequency of IOP spikes ≥ 30 mmHg after surgery ranged from 0.0% to 47.5%.[6-23] Based on these studies the control OVD incidence of subjects who experience at least one IOP observation ≥ 30 mmHg is estimated to be 0.117 (11.7%).A doubling of the control OVD incidence would be problematic and clinically significant, thus the non-inferiority margin will be defined as equal to the expected rate of 0.117 (11.7%).

When the sample size in each group is 165 subjects, a two-group large-sample normal approximation test of proportions with a one-sided 0.050 significance level will have 95.17% power to reject the null hypothesis that the test is inferior to the control (the difference in proportions, $\pi_t - \pi_c$, is 0.117 or greater) in favor of the alternative hypothesis that the test is non-inferior to the control (the difference in proportions, $\pi_t - \pi_c$, is less than 0.117), assuming that the expected difference in proportions is 0.000 and the proportion in the standard group is 0.117.

13.3.2 ECD Loss

The standard deviation of the ECD loss percentage with VISCOAT® is estimated to be 14.2%.[24] When the sample size in each group is 165 subjects, a two group 0.050 one-sided t-test will have 93.90% power to reject the null hypothesis that the test is inferior to the control (the difference in means, $\mu_t - \mu_c$, is 5% or greater) in favor of the alternative hypothesis that the test is non-inferior to the control (the difference in means, $\mu_t - \mu_c$, is less than 5%), assuming that the expected difference in means is 0% and the common standard deviation is 14.2%.

13.3.3 Overall Power and Adjustment for Dropouts

Assuming independence of the primary endpoints, the overall power of the study will be 95.17% x 93.90% = 89.36%.

To allow for a dropout rate of up to 10%, a sample size of approximately $\lceil 165/(1-0.1) \rceil = 184$ subjects per arm will be targeted for enrollment. The total enrollment target therefore will be approximately 368 subjects.

13.3.4 Detectable Effect Sizes for the Secondary Hypothesis Tests

The secondary effectiveness hypothesis will be tested only if both primary endpoint statistical tests are successful. If the primary endpoints are met and the secondary effectiveness hypothesis is met, then the type I error rate for the three secondary safety hypothesis tests will be controlled using the Holm stepwise procedure. Under this procedure, the smallest of the three raw p-values will be compared to 0.025/3 or, equivalently, tripled

and compared to 0.025. Consequently, detectable effect sizes for one-sided tests with 80% power are presented based on an alpha risk of 0.008.

13.3.4.1 Secondary Safety Hypothesis Tests

13.3.4.1.1 Incidence of IOP ≥ 30 mmHg

A two-group χ^2 test with a 0.008 one-sided significance level will have 80% power to detect the difference between a test group proportion, π_1, of 0.117 and a control group proportion, π_2, of 0.256 when the sample size in each group is 165.

13.3.4.1.2 Mean Change from Baseline in IOP

A sample size of 165 in each group will have 80% power to detect a difference in means of 1.797 mm Hg assuming that the common standard deviation is 5.0 mm Hg using a two-group t-test with a 0.008 one-sided significance level.

13.3.4.2 Secondary Effectiveness Hypothesis Test: ECD Loss

A sample size of 165 in each group will have 80% power to detect a difference in means of 4.393 % assuming that the common standard deviation is 14.2 % using a two-group t-test with a 0.025 one-sided significance level.

13.4 Analysis Populations

13.4.1 Intent-to-Treat Population

The Intent-to-treat (ITT) Population will include all eyes that were randomized.

13.4.2 Safety Population

The Safety Population will include all eyes that were exposed to either the test OVD or the comparator OVD. Study eyes that discontinue prior to OVD exposure will be excluded from the Safety Population.

13.4.3 Per Protocol Population

The Per Protocol (PP) Population will include all randomized eyes without major protocol deviations. Protocol deviations resulting in exclusion from the PP Set are described in Section 13.5.7.

13.4.4 Best Case Population

The Best Case Population will include all Per Protocol eyes without intraoperative complications. Intraoperative complications, as documented in the Day 0 Surgeon Questionnaire (*cf.* **Appendix C**), will be reviewed in a masked fashion by the Sponsor prior to database lock to determine which PP population cases warrant exclusion from the Best Case Population.

13.5 Statistical Analysis

Summaries for continuous variables will include the sample size, mean, standard deviation, median, minimum, and maximum. Summaries for categorical variables will include the tabulation of frequencies and percentages.

13.5.1 Primary Safety Analysis

IOP will be assessed in the study eye using Goldmann tonometry at each scheduled follow-up visit and may be assessed at unscheduled visits.

Subjects with IOP ≥ 30 mmHg at any follow-up visit (IOP ≥ 30 mmHg at any follow-up visit, No IOP ≥ 30 mmHg at any follow-up visit) will be summarized using categorical summary statistics for the Safety Population by actual treatment received in a table. Missing data will not be imputed for this summary table.

Missing IOP values will be imputed using Markov chain Monte Carlo (MCMC) methods. Twenty imputed datasets will be produced using a seed of 1017144149. The variables used in the imputation model will include IOP at baseline and at each of the scheduled postoperative visits. After missing data at scheduled visits has been imputed, unscheduled visit IOP values will be added to each imputed dataset.

Within each imputed dataset, subjects will be classified as belonging to one of the following groups:

- IOP ≥ 30 mmHg at any follow-up visit
- No IOP ≥ 30 mmHg at any follow-up visit

This classification will be based on experiencing at least one IOP measurement of 30 mmHg or more at any follow up visit over the entire course of the study. Subjects experiencing one or more IOP spikes will be counted only once.

The difference between test and control in the proportion of subjects with IOP ≥ 30 mmHg at any follow-up visit and the asymptotic standard error will be estimated separately for each imputation.

An estimated difference between treatment groups and a two-sided asymptotic Wald 95% confidence interval around the difference will be constructed via combination of the proportion differences and standard errors from the imputations. If all the imputations result in the same estimated difference and confidence interval, then the results of a single imputation may be used.

If the upper confidence limit (equivalent to a one-sided upper 95% confidence limit) is less than 0.117 (11.7%), then the null hypothesis of inferiority will be rejected in favor of the alternative hypothesis of non-inferiority. A p-value will also be provided for this one-sided hypothesis test.

The primary safety analysis will be repeated using the Per Protocol Population as a sensitivity analysis with observed data only (i.e. without imputation).

In addition to the primary analysis, sensitivity analyses will include a best-case analysis, a worst-case analysis, and a complete case analysis (which will include only data from subjects who have IOP measurements at every scheduled follow-up visit).

Poolability of results across centers will be assessed by performing a Cochran-Mantel-Haenszel test comparing the endpoint between the treatment groups stratified by center. The p-value for the Breslow-Day test for homogeneity of odds ratios across centers will be compared to a critical value of 0.15.

The previous analyses will be completed for the following two groups, separately, without the sensitivity analyses and poolability test:

- Subjects who received IOP-reducing intervention; and
- Subjects who did not receive IOP-reducing intervention.

13.5.2 Primary Effectiveness Analysis

Specular microscopy of the central cornea will be completed preoperatively and at Visit 5 (90 ± 14 days postop). Images will be evaluated by a masked reading center. If multiple cell densities are obtained from the reading center for each eye visit, then the available counts will be averaged by eye and visit (Preoperative, Visit 5) to produce a single value for each eye visit.

If one or more ITT Population eyes has a missing mean ECD value either at the preoperative visit or at Visit 5 (including due to a missed visit or due to discontinuation), then the missing data will be imputed as follows. Prior to analysis, 25 imputations of missing mean densities will be produced using the Markov chain Monte Carlo method and the variables investigator, treatment, preoperative value, and postoperative value.

For each observation in the imputed datasets, the ECD loss in percent at Visit 5 will be calculated for each eye at each visit as follows:

$$\text{Loss (\%)} = \frac{\text{Preoperative Cell Density - Visit 5 Cell Density}}{\text{Preoperative Cell Density}} \times 100\%$$

The means and standard errors from the imputed datasets will be combined to produce a continuous variable summary of the ECD (cells / mm^2) at each visit (Preoperative, Visit 5) and the percent loss at Visit 5 by randomized treatment assignment for the ITT Population.

Loss (%) will be modeled as a function of the fixed class variables treatment and investigator, separately by imputation. The parameter estimates will be combined to produce a one-sided upper 95% confidence limit for the difference in percent loss between the test

and comparator OVDs and a p-value for the hypothesis test for the ITT Population. If the upper confidence limit is less than 5%, then the null hypothesis of inferiority will be rejected in favor of the alternative hypothesis of non-inferiority.

If there are no ITT Population eyes with missing ECD data, then imputation will not be performed. Instead, the available data will be analyzed and summarized as described above.

Sensitivity analyses of effectiveness will include a best-case analysis, a worst-case analysis, a tipping point analysis, and a complete case analysis (which will use only subjects who have cell density measurements at every scheduled visit), and analysis using the PP Set.

Poolability across centers will be evaluated by modeling Loss (%) as a function of the fixed class variables treatment and investigator including their interaction using the available data. Poolability will be assessed by comparing the p-value for the interaction to a critical value of 0.15.

13.5.3 Secondary Analyses

If both primary endpoints are met, then four secondary superiority tests will be evaluated. The secondary hypotheses will be tested in two sequential families, with simultaneous testing of the hypotheses in the second family.

1. Family 1: Secondary Effectiveness Hypotheses
    a. ECD loss superiority test
2. Family 2: Secondary Safety Hypotheses
    a. IOP spike rate superiority test
    b. Mean change from baseline in IOP at 6 hours post-op superiority test
    c. Mean change from baseline in IOP at 24 hours post-op superiority test

The null hypotheses in Family 2 above will be eligible for rejection only if the primary endpoints and the Family 1 secondary endpoint are met. The overall type I error for the secondary endpoint hypothesis tests in Family 2 above will be controlled by application of the Holm stepwise procedure as follows.

1. The smallest of the three raw p-values will be compared to $0.008\overline{333}$ or, equivalently, tripled and compared to 0.025. If the raw p-value is less than or equal to $0.008\overline{333}$, then the associated null hypothesis will be rejected. Equivalently, if three times the raw p-value is less than or equal to 0.025 then the associated null hypothesis will be rejected.
2. The second smallest of the three raw p-values will be compared to 0.0125 or, equivalently, doubled and compared to 0.025. If the raw p-value is less than or equal to 0.0125, then the associated null hypothesis will be rejected. Equivalently, if two times the raw p-value is less than or equal to 0.025 then the associated null hypothesis will be rejected.

3. The largest of the three raw p-values will be compared to 0.025. If the p-value is less than or equal to 0.025 then the associated null hypothesis will be rejected.

The null hypotheses will be rejected (or not rejected) based on the p-values and the Holm stepwise adjustment and not based on the confidence intervals described below.

13.5.3.1 Secondary Safety Analyses

13.5.3.1.1 Incidence of IOP ≥ 30 mmHg

The null hypothesis of no difference between treatment groups in the proportion of subjects with IOP ≥ 30 mmHg at any follow-up visit will be tested using a chi-square test for the Safety set. A two-sided 95% confidence interval will be constructed around the difference between groups using the normal approximation. If the null hypothesis is rejected then statistical superiority will be claimed for the test OVD in this endpoint.

13.5.3.1.2 Mean Change from Baseline in IOP

Change from baseline in IOP (mm Hg) will be computed as post-op IOP minus baseline IOP and will be summarized using continuous summary statistics for the Safety Population by scheduled Visit and actual treatment received in a table. A statistical model will be constructed by visit with change from baseline in IOP as the dependent variable, treatment group, investigator, as a fixed factor, baseline IOP as a continuous covariate, and subject as a random factor. For each study visit (6 hours post-op and 24 hours post-op), superiority will be claimed for the test OVD in this endpoint if the null hypothesis is rejected.

13.5.3.2 Secondary Effectiveness Analysis

The null hypothesis of no difference between treatment groups in ECD loss will be tested for the ITT set using the multiple imputation method and statistical model described above for the primary effectiveness analysis. A two-sided 95% confidence interval will be constructed around the difference between groups. If the null hypothesis is rejected then statistical superiority will be claimed for the test OVD in this endpoint.

13.5.4 Surgery Data

The surgery data described in **Appendix C** will be summarized descriptively. Any planned analyses of surgery data will be detailed in the study SAP.

13.5.5 Patient Disposition

Enrollment status will be summarized in a table by investigator and overall for the all enrolled set. The number and percentage of enrolled eyes will be summarized as well as the number and percentage of eyes that completed the entire trial, discontinued before surgery, and discontinued after surgery. In addition, for those eyes that did not complete the entire trial, the reason for discontinuation will be summarized.

Subject accountability at each form visit will be summarized for all enrolled subjects in a table. The subject accountability table will also be stratified by investigator and by treatment assignment.

Subjects in the Safety, ITT, and PP Populations will be summarized categorically by treatment and overall.

13.5.6 Demographics and Baseline Characteristics

Race, gender, ethnicity, and age and will be presented using discrete summary statistics by treatment group. Age will also be presented using continuous summary statistics by treatment group.

13.5.7 Protocol Deviations

The number of subjects within each type of protocol deviation will be presented using discrete summary statistics.

Major protocol deviations leading to exclusion from the PP Set will include the following.

- Ineligibility
- Use of an incorrect OVD including misrandomized subjects
- Disallowed concomitant treatments including IOP lowering treatments
- Missing IOP value at postoperative visit 1 or 2

Additional major protocol deviations may be identified prior to unmasking of the treatment assignments.

13.6 Interim Analyses

No interim analyses are planned.

13.7 Additional Statistical Considerations

13.7.1 Handling of Missing Data

Imputation of missing primary endpoint data is described in Section 13.3 above. Unless otherwise specified in the SAP, missing data will not be imputed.

13.7.2 Multicenter Issues

Randomization will be stratified by site. Sites will be considered in the primary effectiveness analysis as described in Section 13.3 above. Poolability will be assessed as described in Section 13.3 above.

13.7.3 Multiplicity Issues

Statistical success will require demonstration of non-inferiority in both the primary safety and effectiveness endpoints for the primary analysis populations. Therefore, no adjustments for multiplicity are required for the primary hypothesis tests. The first secondary hypothesis test will be eligible for evaluation only if the primary endpoints are met. Therefore, no adjustment for multiplicity will be necessary. The secondary hypothesis tests in the last family of hypotheses will be adjusted for multiplicity using the Holm stepwise procedure.

14 Quality Control and Quality Assurance

14.1 Study Monitoring

The Sponsor and its representatives must be allowed to visit all study site locations to assess the data, quality, and study integrity in a manner consistent with applicable health authority regulations and the procedures adopted by the Sponsor or its representative.

Prior to the start of the study, member(s) of the Sponsor (or designees) will review the protocol, CRF, regulatory obligations, and other material or equipment relevant to the conduct of the study with the Investigator/Sub-Investigator and relevant study site personnel via an Investigator Meeting and/or site initiation visits.

Monitoring visits and telephone consultations will occur as necessary, or per the monitoring plan, during the course of the investigation to verify the following:

- The rights and well-being of subjects are protected;
- The conduct of the investigation is in compliance with the currently approved protocol/amendment, 21CFR Parts 50, 54, 56, and 812, ISO 15798 (2013(E)) Ophthalmic Implants – Ophthalmic Viscosurgical Devices, and ISO 14155 (2011(E)) Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practices, 42 USC 282(j) and IRB/EC requirements;
- The integrity of the data, including adequate study documentation;
- The facilities remain acceptable;
- The Investigator and site personnel remains qualified and able to conduct the study; and
- Test article accountability.

During the course of the study, if the Sponsor determines that an Investigator is non-compliant with the study plan and/or applicable regulatory requirements, the Sponsor will take action to secure compliance. In addition, the Sponsor may terminate the Investigator's participation in the study if appropriate, or if the Investigator remains non-compliant despite the Sponsor's actions.

14.2 Source Documentation

All medical information obtained at each study visit must be recorded in the subject's record (source documentation) in real time as it is collected. Source documentation consists of original subject documents, as well as data and records with information relevant to the subject and his/her participation in the study.

Source documentation worksheets may be provided by the Sponsor or its designee to record pertinent information. The completed worksheets can then be incorporated into the subject's medical chart. If it is preferred to not use the worksheets in the subject's permanent record, then the worksheets should be used as a reference to determine the type of study data to record in the subject's permanent record.

14.3 Case Reports Forms and Data Verification

As used in this protocol, the term Case Report Form (CRF) should be understood to refer to an electronic data record or electronic CRF (eCRF) developed as part of the electronic data capture method utilized in this study.

Subject data required by this protocol are to be recorded on eCRFs. The Investigator and his/her study site personnel will be responsible for completing the eCRFs in a timely manner. The Investigator is required to verify that all of the requested information is accurately recorded on the eCRFs. All information requested on the eCRFs needs to be supplied, including subject identification and initials, date(s), assessment values, etc., and any omission or discrepancy will require explanation. All information on eCRFs must be traceable to source documents.

The study monitor will be responsible for reviewing and verifying the data recorded on the eCRFs, utilizing the original source documentation and will query discrepant findings. The Investigator and study site personnel will be responsible for answering all queries in a timely fashion. The eCRFs will be submitted to the Sponsor for quality assurance review, data entry, and statistical analysis.

Following receipt by the Sponsor, all eCRFs will be reviewed for completeness. Single-entry with verification routines and computerized editing routines will be used to reduce data entry errors and identify unusual data for verification prior to statistical analysis.

Corneal ECD data will be collected at each site and sent to a central reading center for analysis. The reading center will be masked to the OVD a subject has received and will provide the Sponsor or its designee with the results of their analysis.

14.4 Recording of Data and Retention of Documents

Subject data recorded on eCRFs during the study will be documented in a coded fashion. The subject will only be identified by the subject number. Confidentiality of subject records must be maintained to ensure adherence to applicable local privacy regulations.

The Investigator must retain essential documents indefinitely after the completion of the study, unless otherwise notified by the Sponsor. The Investigator agrees to adhere to the document retention procedures when signing the protocol Investigator Statement of Approval.

Essential documents include but are not limited to the following:

- IRB/EC approvals for the study protocol, all amendments, ICF(s), and advertisements;
- IRB/EC annual study review;
- IRB/EC correspondence and reports (e.g., SAE reports, protocol deviations, and safety updates);
- regulatory documents (e.g., financial disclosure and delegation of authority forms);
- all source documents;

- CRFs;
- subject's signed ICF;
- Device Investigator Agreement;
- accountability records for the test article(s);
- correspondence from and to the Sponsor; and
- any other documents relevant to the conduct of the study.

Should an Investigator withdraw from the study (e.g., retirement or relocation), study records will be transferred to a mutually agreed upon designee (e.g., another Investigator or a site IRB/EC). The Investigator will provide notice of such transfer in writing to the Sponsor and/or its representative.

14.5 Audits and Inspections

Audits of clinical research activities in accordance with the Sponsor's internal Standard Operating Procedures to evaluate and assure compliance with the principles of GCP may take place. A regulatory authority may also wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority and/or IRB/EC, the Investigator must inform the Sponsor and its representative immediately that this request has been made.

15 Ethics and Administrative Issues

It is the responsibility of the site's principal investigator to assure that all aspects of the ethics review are conducted in accordance with the Declaration of Helsinki as described in the International Council for Harmonisation (ICH) Guideline E6 for Good Clinical Practice (GCP). The protocol and any information supplied to the subject to obtain informed consent, including written informed consent form(s), subject recruitment procedures (e.g., advertisements), and written information to be provided to subjects (information leaflets), will be reviewed and approved by a qualified Institutional Review Board (IRB) or an Ethics Committee (EC) prior to enrollment of participants in the study. Prior to initiation of the study, the Sponsor or its designee will receive documentation of the IRB/EC approval, which specifically identifies the study/protocol, and a list of the IRB/EC committee members. Protocol amendments will be reviewed and approved by the IRB/EC prior to implementation of any changes made to the study design. Investigators submitted progress reports to the IRB/EC in accordance with the IRB/EC requirements.

15.1 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol and ICH GCP guidelines, applicable regulations and guidelines governing clinical study conduct, and the ethical principles that have their origin in the Declaration of Helsinki.

15.2 Ethics Review

The Investigator should ensure that his/her participation in the study, in addition to the protocol, subject recruitment materials (e.g., written information or materials including web pages, radio advertisements, television spots or written text developed to encourage subject

enrollment) and the ICF to be used in this study are approved by their institution IRB/EC, or if not using their institution's IRB/EC, approved by the reviewing central IRB/EC prior to entering any subjects in the study. Documentation of IRB/EC approval of the study protocol and informed consent must be provided to the Sponsor and its designee prior to initiation of the study. In addition, the Investigator must ensure that the reviewing IRB/EC has provided approval for any protocol amendments prior to implementation. If the amendment necessitates a revision to the ICF, the Investigator should ensure the revised form is also submitted to and approved by the Sponsor or its designee and the IRB/EC prior to implementation.

15.3 Written Informed Consent

Before entry into the study, the Investigator or an authorized member of the investigational staff will explain to potential subjects (or their legally acceptable representatives) the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort it may entail. The subject (or legally acceptable representative) will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent will be appropriately recorded by means of either the subject's or his legally acceptable representative's dated signature. After having obtained the consent, a copy of the signed and dated ICF will be given to the subject.

If the subject (or legally acceptable representative) is unable to read or write, an impartial witness will be present for the entire informed consent process (which included reading and explaining all written information) and will personally date and sign the ICF after the oral consent of the subject (or legally acceptable representative) is obtained.

The ICF will be signed before the performance of any study-related activity.

15.4 Financial Disclosure

Original Financial Disclosure Form (FDF) completed, signed and dated by the PI and sub-investigators and study personnel listed on the Delegation of Authority Log will be collected by the Sponsor or its designee, as applicable, and file in the Trial Master File. A copy of the FDF will be retained in the Investigator Site Binder.

15.5 Confidentiality/Publication of the Study

All study data generated as a result of this study will be regarded as confidential, until appropriate analysis and review by the Sponsor or its designee and the Investigator(s) are completed. The results of the study may be published or presented by the Investigator(s) after the review by, and in consultation and agreement with the Sponsor, and such that confidential or proprietary information is not disclosed.

Prior to publication or presentation, a copy of the final text should be forwarded by the Investigator(s) to the Sponsor or its designee, for comment within a reasonable period of time. Such comments shall aim to ensure the scientific integrity of the proposed publications and/or presentations and ensure that the data and material referring to Bausch & Lomb Incorporated products and activities receive fair, accurate, and reasonable presentation.

16 References

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17 Appendices

Appendix A: STUDY FLOW CHART

PROCEDURE/ASSESSMENTS	Preop Visit Day -60 to Day -1	Op Visit Day 0	Postop Visit 1[a] 6 Hours ± 2 hours Postop	Postop Visit 2 24 Hours ± 4 hours Postop	Postop Visit 3 7 Days ± 2 days Postop	Postop Visit 4 30 Days ± 7 days Postop	Postop Visit 5 90 Days ± 14 days Postop
Informed Consent	X						
Demographic Data	X						
Medical History	X						
Urine Pregnancy Test	X	X[b]			X	X	X
Eligibility Criteria	X	X					
Randomization		X					
Fellow Eye Status	X						
Surgical Procedure[c]		X					
Manifest Subjective Refraction	X						X
Uncorrected Distance VA	X		X	X	X	X	X
Best Corrected Distance VA	X						X
Cataract Classification	X						
Slit Lamp Exam	X		X	X	X	X	X
Intraocular Pressure (Goldmann tonometry)	X		X	X	X	X	X
Fundus Exam (Dilated)	X						X
Ultrasound Pachymetry	X			X			X
ECD via specular microscopy of the central cornea	X						X
Concomitant Medications	X	X	X	X	X	X	X
Adverse Events[d]	X	X	X	X	X	X	X

[a] Postoperative Visit 1 must occur on the day of surgery.

[b] If last urine pregnancy test was more than 21 days after the preoperative visit, test should be repeated.

[c] Required details of the surgical procedure are described in **Appendix C**.

[d] The period of collection of AEs starts from informed consent through study exit

Appendix B: METHODS OF CLINICAL EVALUATIONS

Any changes to the procedures described in this Appendix will be provided under separate cover.

1.0 Visual Acuity Testing Methods

Best-corrected visual acuity at Baseline and all scheduled follow-up visits will be measured using the Early Treatment of Diabetic Retinopathy Study (ETDRS) charts at 4 meters.

The charts were designed according to the following principles described by Bailey and Lovie[25] and the National Academy of Science-National Research Council (NAS-NRC) Committee on Vision 1980[26]:

- Letters of equal legibility;
- Combine the letters so that each line is of approximately equal difficulty as described by Ferris et al[27];
- Present five letters at each acuity level;
- Space rows by the height of the smaller letter;
- Space letters by the width of same-sized letters; and
- Use a logarithmic progression of letter size from LogMAR (Logarithm of Minimal Angle of Resolution) -0.3 (20/10) to 1.68 (20/957).

This standard describes a single method for the measurement of visual acuity (which is strongly influenced by the methods used in the ETDRS and AREDS protocols) so that measurements obtained using the procedures listed below can be compared within and between sites. [27]

The subject should attempt to read each letter, line-by-line, left to right, beginning with line 1 at the top of the chart. The subjects should be told that the chart has letters only, no numbers. If the subject reads a number, he or she should be reminded that the chart contains no numbers, and the examiner should then request a letter in lieu of the number. The subject should be asked to read slowly, about one letter per second, so as to achieve the best identification of each letter. He/she is not to proceed to the next letter until he/she has given a definite response.

A maximum effort should be made to identify each letter on the chart. When the subject says he/she cannot read a letter, the subject should be encouraged to guess. If the subject identified two (2) letters (e.g., A or B), the subject should be asked to choose one letter, and, if necessary, to guess. When it becomes evident that no further meaningful readings can be made despite encouragement to read or guess, the examiner should stop the testing for that eye. However, all letters on the last line should be attempted as letter difficulties vary and

the last letter may be the only one read correctly. The number of letters missed or read incorrectly should be noted.

In order to provide standardized and well-controlled assessment of visual acuity, all visual acuity assessments for a subject should be performed consistently (e.g., the same lighting conditions, viewing distance, etc.) at each visit.

Illumination of the ETDRS Chart and Examination Room

The internal illumination of the ETDRS chart should be turned on. This will provide the nominal contrast for each of the charts. Room illumination should be turned off to ensure that the illumination is consistent for each measurement. Ambient sources of light in the room should be kept at a minimum. The room lighting and any ambient sources should be consistent in their use and placement at each subject visit throughout the course of this study.

Manifest Refraction

Each subject must be manually refracted to his/her best correction by an ophthalmologist, optometrist, or a skilled technician using the ETDRS chart at 4 meters with a phoropter or trial frames under photopic lighting conditions. At no time during the study will autorefraction be utilized as a final end point refraction. Autorefractor or lensometer readings may only be utilized to obtain a starting point for the refraction if necessary.

All refractions will be conducted in a manner consistent with the site's standard techniques using 0.25 D steps and utilizing a Jackson cross cylinder method. Manifest refraction is adjusted for optical infinity by subtracting 0.25 D from the sphere of the manifest refraction obtained using the ETDRS chart at 4 meters. The resulting refraction will then be placed in a trial frame and utilized to obtain BCVA results.

Scoring Visual Acuity LogMAR Tests

The examiner records each letter identified correctly by circling the corresponding letter on the Visual Acuity Worksheet. Letters read incorrectly or not read at all are not marked on the form. Each letter read correctly is recorded as one. The total letters read is recorded on the source documents. The LogMAR score will be calculated by the sponsor.

During the course of the study, if the subject is unable to read any letters at 1 meter, they will be asked to count fingers at 0.5 meters (1 foot and 7 ⅝ inches). If fingers cannot be counted at 0.5 meters, the vision will be considered hand motion. Hand motion will be determined at 0.5 meters. Light perception will be determined using an indirect ophthalmoscope.

The ETDRS chart must be placed at a distance of 4.00 meters (13 feet and 1.5 inches, or 157.5 inches) from cornea to chart surface, when using a 4-meter chart. For testing at 1 meter, the distance must be 1.00 (39 and 3/8 inches). A measuring tape or meter stick should always be available to verify the chart distance, even if the examining chair is supposed to be immovable or if reference marks are placed on the floor or walls.

The 1-meter distance is measured from the eye of the participant, seated comfortably in a chair with his/her back firmly placed against the chair, to the center of the 2nd or 4th letter of the 3rd line of the chart. The measuring device can be home-made (e.g., a dowel rod accurately cut to a length of 1.00 m) or 1-meter ruler may be purchased.

If it is necessary to refract at the 1-meter distance, remember to add +0.75 sphere to the trial frame. Subtract the +0.75 sphere from the final refraction obtained at the 1-meter distance before recording the refraction.

2.0 SLIT LAMP EXAMINATION

Slit lamp examination will be performed using a slit lamp biomicroscope and observations graded per the following classifications of slit lamp observations:

Cataract Type (pre-operative)

- Nuclear
- Cortical
- Posterior sub-capsular
- Combination

Cataract Density (pre-operative)

- 1+ = Slight
- 2+ = Moderate
- 3+ = Dense
- 4+ = Very dense*

  * Very dense cataract excludes subject from study

Central Corneal Stromal Edema (pre-operative and post-operative)

- None – No evidence of central corneal stromal swelling with normal transparency
- Mild – Mild central corneal stromal swelling
- Moderate – Moderate central corneal stromal swelling
- Severe – Definite widespread cloudiness or haziness giving dull ground glass appearance to cornea, or numerous coalescent bullae

Corneal Wound Edema (post-operative only)

- None – No evidence of corneal wound swelling with normal transparency
- Mild – Mild corneal wound swelling
- Moderate – Moderate corneal wound swelling
- Severe – Definite widespread cloudiness or haziness giving dull ground glass appearance to cornea, or numerous coalescent bullae

The slit lamp examination includes the measurement of aqueous cell and flare by the Standardization of Uveitis Nomenclature (SUN) Working Group grading system.[5] For the evaluation of cells and flare, using a 1 mm x 1 mm slit beam, the following SUN grading scheme must be used:

Anterior Chamber Cells (post-operative)

Grade	Cells in Field
0	<1
0.5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	>50

Anterior Chamber Flare (post-operative)

Grade	Description	
0	None	
+1	Faint	
+2	Moderate	Iris/lens detail clear
+3	Marked	Iris/lens details hazy
+4	Intense	Fibrin/plastic aqueous

3.0 ECD

Specular microscopes that will be used in the study must first be certified by the central reading center prior to its use for study purposes. At least two study staff members that will be obtaining ECD images and using the specular microscope as delegated by the PI must be trained and certified by the central reading center to ensure proper and consistent imaging prior to capturing study subject images. Documentation of such training and qualifications will be maintained in the site files. The ECD technicians should be delegated as a primary or back-up technician with the primary ECD technician obtaining ECD images whenever possible and the back-up technician obtaining ECD images as necessary in lieu of the primary technician.

Clinical sites are to use their specular microscopes in accordance with the manufacturer's and reading center's recommendations and procedures. Calibration of specular microscopes will be documented and filed at each clinical site.

Standardized ECD count methods[28] will be used to minimize variability. The measurement of the ECD in the central cornea will be performed preoperatively and at three months postoperatively (Visit 5) at all sites using a non-contact Specular Microscope (approved by or supplied by the Sponsor). Three images from the central part of the cornea will be obtained for each applicable subject visit.

Initial eligibility determination by the sites is not dependent on receiving reading center ECD results. However, subjects with automated counts below an average of 1750 cells/mm^2 must await confirmation of >1500 cells/mm^2 from the reading center prior to enrolling the subject.

To determine ECD, sites will submit all preoperative and three month postoperative images to the reading center (which will be masked) for image analysis. The reading center will determine the mean ECD based on the three images.

4.0 INTRAOCULAR PRESSURE (IOP)

IOP measurements must be obtained using a calibrated Goldmann Type Applanation Tonometer in accordance with manufacturer's instructions. Calibration of the Goldmann Tonometer is required to be done at least monthly and the results recorded in a calibration log for the device.

5.0 DILATED FUNDUS EXAM

Using an Ophthalmoscope, light is shone into the eye and the retina and the optic nerve are examined. This exam is used to evaluate the internal structures of the eye. The Investigator will classify the fundus as “normal” or “abnormal.”

6.0 ULTRASOUND PACHYMETRY

Corneal pachymetry will be performed using an ultrasound pachymeter available at a clinical site. Measurements of corneal pachymetry are to be taken three (3) times at each study visit at which pachymetry is required, and the data for all 3 measurements will be entered in the study database. A mean for the 3 measurements will be calculated by the database system to the nearest micron. The measurements should be obtained using the standard procedure of the site, and by an ophthalmologist, optometrist, or ophthalmic technician, who has been certified for use of or appropriately trained on an ultrasound pachymeter. It is essential the site use the same procedure and device for all subjects and visits.

Appendix C: SURGICAL PROCEDURE

All cataract surgical procedures will be performed by the same surgeon at a site, using a phacoemulsification system adjusted according to the surgeon's usual settings (power modulation should be used). In the event a different surgeon (sub-investigator) will be performing the surgical procedures, the site must request in writing sponsor's approval prior to surgery.

Intraoperative surgical staff present during the cataract surgery will confirm their commitment to not mention the treatment assignment in the presence of a subject by signing a masking commitment form prior to the initiation of the cataract surgery. This documentation will be maintained in the site files.

The surgical procedure will be performed as follows:

- The IRT system will be accessed as described in Section 9.1.2 of the protocol to identify the OVD treatment to be randomly assigned to the subject. The appropriate OVD treatment will be prepared for surgery according to the relevant DFU and made available to the Investigator.
- The eye will be prepared for surgery and draped according to the surgeon's standard procedure.
- The surgery will be performed under topical anesthesia (surgeons may use their discretion to augment with additional anesthesia).
- Adequate dilation will be obtained.
- The main incision will be made using a 1.6 – 2.8 mm keratome. This incision will be used as the main incision for the IOL implantation.
- The test or control OVD will be used to fill the anterior chamber.
- The continuous curvilinear capsulorhexis will be performed using surgeon's medical judgment and standard of care. The phacoemulsification equipment will be adjusted according to the surgeon's usual settings (power modulation should be used).
- Before IOL implantation, the anterior chamber and the capsular bag will be expanded with the test or control OVD. When the lens is in the proper position, the OVD must be completely removed.
- The incision should be checked for leaks at the end of the procedure. Wound closure should be sutureless, however, when indicated, may be sutured or glued at the discretion of the surgeon.
- Following completion of the surgery, steroid, antibiotic, and/or NSAID drops, as per the surgeon's standard regimen, should be applied to the eye. A patch, or shield, dressing may be used at the discretion of the surgeon, if this represents their standard post-operative regimen. Additional medications (except IOP lowering drugs) as deemed necessary, may be used at the surgeon's discretion.
- The Investigator immediately at the end of each surgery will answer the following questions in writing on a subject-specific source document:
  - IOL manufacturer
  - IOL model
  - Start time of surgery (first incision)

- End time of surgery (wound closure)
- Absolute phaco time (APT) in sec
- Effective phaco time (EPT) in sec
- Phaco system manufacturer
- Use of venturi or peristaltic pump
- Flow rate (mL/min) for OVD removal with irrigation and aspiration (I/A)
- Vacuum level (mmHg) for OVD removal with I/A
- Total I/A time to remove OVD (post IOL implantation) in minutes:seconds:hundredth-of-seconds
- Incision location: cornea, limbus, sclera
- Incision size (mm)
- Estimated total volume of OVD used (approximate percent usage per syringe - e.g., 75%, 50%)
- Any intraoperative complications or deviations from usual surgical routine. Answers are to be Yes or No for the following:
  - Any device malfunctions, device use errors, or difficulty with device use (Note: Device deficiencies will be reported on a Device Deficiency Report form to the Sponsor and its representative; the original form will be stored with the site files)
  - Did the surgery need to be aborted for any reason
  - Achievement and maintenance of adequate pupil dilation
  - Complete removal of all lens material, including cortex
  - Removal of all viscoelastic from anterior chamber and capsular bag
  - Detection of any capsular tear, zonular tear or vitreous loss
  - If a suture was placed to seal the corneal incision
  - Use of your standard of care surgical medications without any prophylactic IOP-lowering treatments
  - If intracameral antibiotics were used
  - Any other intraoperative complication (if yes, specify)