BAUSCH + LOMB

A Prospective, Multicenter, Randomized, Active-Controlled Clinical Study to Evaluate the Safety and Effectiveness of the enVista® One-Piece Hydrophobic Acrylic Trifocal Intraocular Lens in Subjects Undergoing Cataract Extraction

CLINICAL STUDY PROTOCOL

STUDY # 945

Developmental phase of study:	Pivotal IDE Trial
Study design:	Prospective, multicenter, randomized, active-controlled, partially masked binocular safety and effectiveness study
Date:	24 April 2023 (Version 8) 10 May 2022 (Version 7) 10 December 2021 (Version 6) 23 April 2021 (Version 5) 13 August 2020 (Version 4) 02 April 2019 (Version 3) 08 February 2019 (Version 2) 26 March 2018 (Version 1)
Sponsor[1]	Bausch + Lomb Incorporated 1400 North Goodman Street Rochester, NY 14609 US [redacted]

This clinical investigation is being conducted in accordance with 21CFR Parts 11, 50, 54, 56, and 812, ISO 14155 (2020 (E)) Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice, ISO 11979-7:2006/Amd 1:2012(E) Ophthalmic implants — Intraocular lenses — Part 7, ISO 11979-9: 2006/Amd 1:2014 Ophthalmic implants — Intraocular lenses — Part 9, ANSI Z80.12-2007 (R2012), 42 USC 282(j), and applicable local regulations.

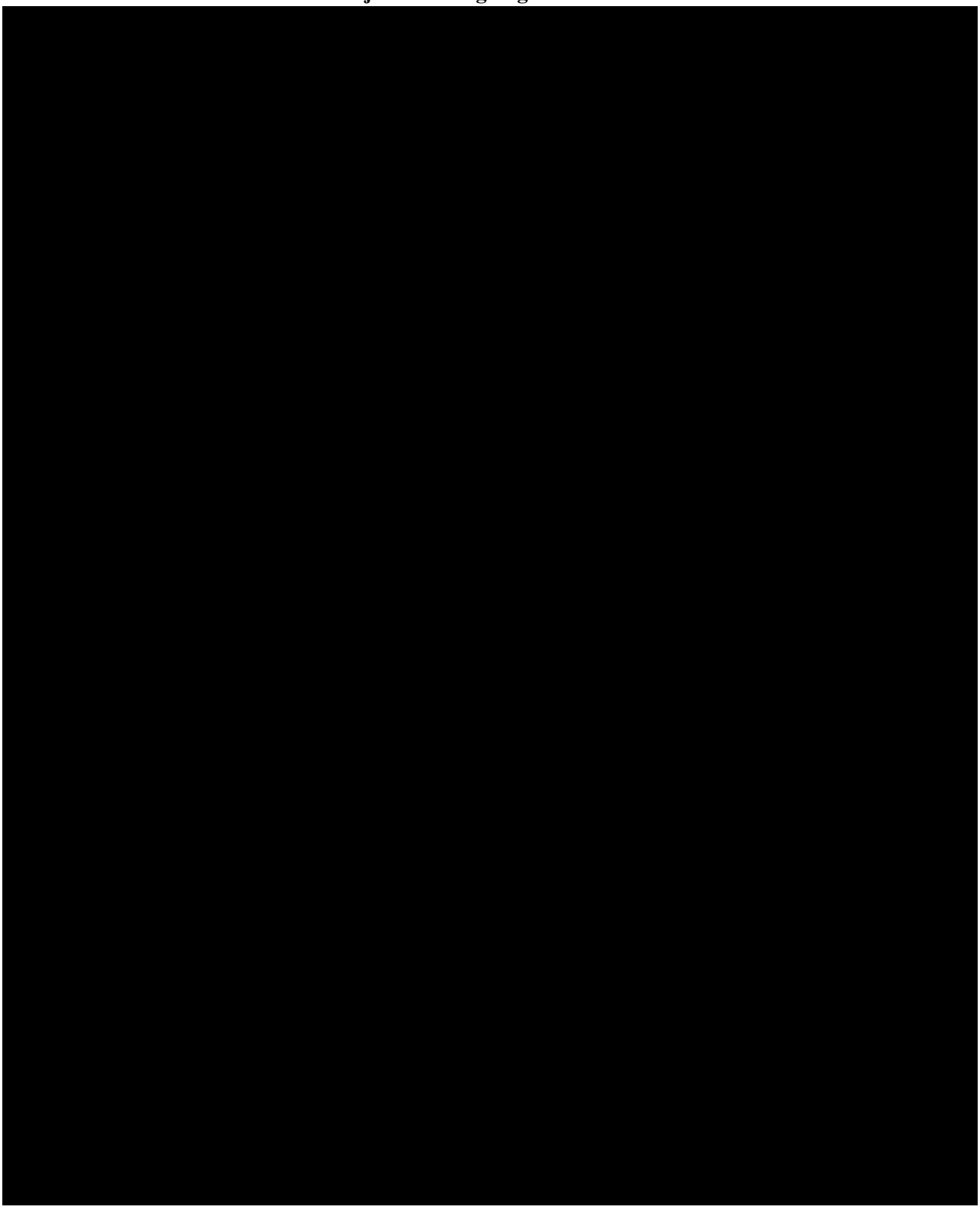
[1] The Sponsor, Bausch & Lomb, Inc., is the sole funding source for this clinical investigation.

CONFIDENTIAL

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

Protocol Review and Approvals

A Prospective, Multicenter, Randomized, Active-Controlled Clinical Study to Evaluate the Safety and Effectiveness of the enVista® One-Piece Hydrophobic Acrylic Trifocal Intraocular Lens in Subjects Undergoing Cataract Extraction



Attestation from Manufacturer Representative: The above Test and Control Article IOLs conform to the general safety and performance requirements described in accordance with ISO 11979-9:2006 (E) and associated ISO 11979-9:2006/Amd 1:2014 (E) Ophthalmic implants – Intraocular lenses – Part 9: Multifocal intraocular lenses and all normative references listed or cross-referenced therein, as well as ISO 11979-7:2018 Ophthalmic implants — Intraocular lenses — Part 7. With regard to those aspects, every precaution has been taken to protect the health and safety of subjects in this study.

[redacted]

Personnel Responsible for Conducting the Study

A Prospective, Multicenter, Randomized, Active-Controlled Clinical Study to Evaluate the Safety and Effectiveness of the enVista® One-Piece Hydrophobic Acrylic Trifocal Intraocular Lens in Subjects Undergoing Cataract Extraction

Contract Research Organization / Medical Monitor

Principal Investigator Protocol Agreement Page

COMMITMENTS OF THE INVESTIGATOR:

I agree to conduct the study 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. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study 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

Name of Investigational Device: enVista® Trifocal Intraocular Lens

Title of Study: A Prospective Multicenter, Randomized, Active-Controlled Clinical Study to Evaluate the Safety and Effectiveness of the enVista® One-Piece Hydrophobic Acrylic Trifocal Intraocular Lens in Subjects Undergoing Cataract Extraction

Number of clinical centers: Approximately twenty (20) clinical centers in North America

Objectives: To evaluate the safety and effectiveness of the enVista trifocal intraocular lens (IOL) when implanted in the capsular bag.

Methodology: The study purpose, procedures, and subject responsibilities will be explained to the potential participant. The subject's willingness and ability to meet the treatment and follow-up requirements will be determined. Written informed consent will be obtained from each study subject prior to performing any study-specific procedures that are not part of the Investigator's routine standard of care. Enrolled subjects who meet eligibility criteria will be seen at 11 or 12 visits according to the following schedule:

Visit Name	Eyes Evaluated	Visit Window
Preoperative Visit 0A/B	Both Eyes	Day -30 to -5
Operative Visit 00A	1st Eye	Day 0
Post-Operative Visit 1A	1st Eye	Day 1 to 2 post Visit 00A
Post-Operative Visit 2A	1st Eye	Day 7 to 14 post Visit 00A
Post-Operative Visit 3A	1st Eye	Day 30 to 60 post Visit 00A
Operative Visit 00B	2nd Eye	Day 7 to 30 post Visit 00A
Post-Operative Visit 1B	2nd Eye	Day 1 to 2 post Visit 00B
Post-Operative Visit 2B	2nd Eye	Day 7 to 14 post Visit 00B
Post-Operative Visit 3B	2nd Eye	Day 30 to 60 post Visit 00B
Post-Operative Visit 4	Both Eyes	Day 120 to 180 post Visit 00B
Post-Operative Visit 5	Both Eyes	Day 330 – 420 post Visit 00B
Post-Operative Visit 6 (subjects that consent at participating sites)	Both Eyes	Day 2- 30 post Visit 5

Approximately five hundred and one (501) subjects (approximately 1,002 eyes) will be enrolled in this study to obtain complete follow-up for one year on at least 300 Test subjects and 150 active Control subjects:

- Group 1 (Test): Approximately 334 subjects will be treated bilaterally with the enVista MX60EF (trifocal) multifocal IOL (MIOL);
- Group 2 (Control): Approximately 167 control subjects will be implanted bilaterally with the enVista MX60E monofocal IOL

"Treatment" is defined here as the IOL touching the eye. Subjects who meet eligibility criteria will be randomly assigned to Group 1 or 2 in a 2:1 ratio. Enrollment and randomization will occur at the first eye's Operative Visit (Day 0). Subjects and designated postoperative evaluator(s) will be

masked to the IOLs assigned. The Investigator implanting the IOL and designated site personnel will be unmasked to the Group assignment for a subject.

The first eye implanted will be designated eye A, and the second eye implanted will be designated eye B. The eye with the worse best-corrected distance visual acuity (BCDVA, CDVA) at the Preoperative Visit will be treated first (eye A) and used in the primary monocular evaluations. Glare testing of both eyes will be done if either requires it to determine eligibility. If the qualifying visual acuity is obtained with a glare source, the eye with the worse BCDVA with glare will be designated as eye A. If BCDVA is the same for both eyes, the right eye will be treated first. Postoperatively, all eyes will undergo ophthalmic examinations at regular intervals per the study visit schedule through Visit 5 (330 - 420 days after second eye IOL implantation).

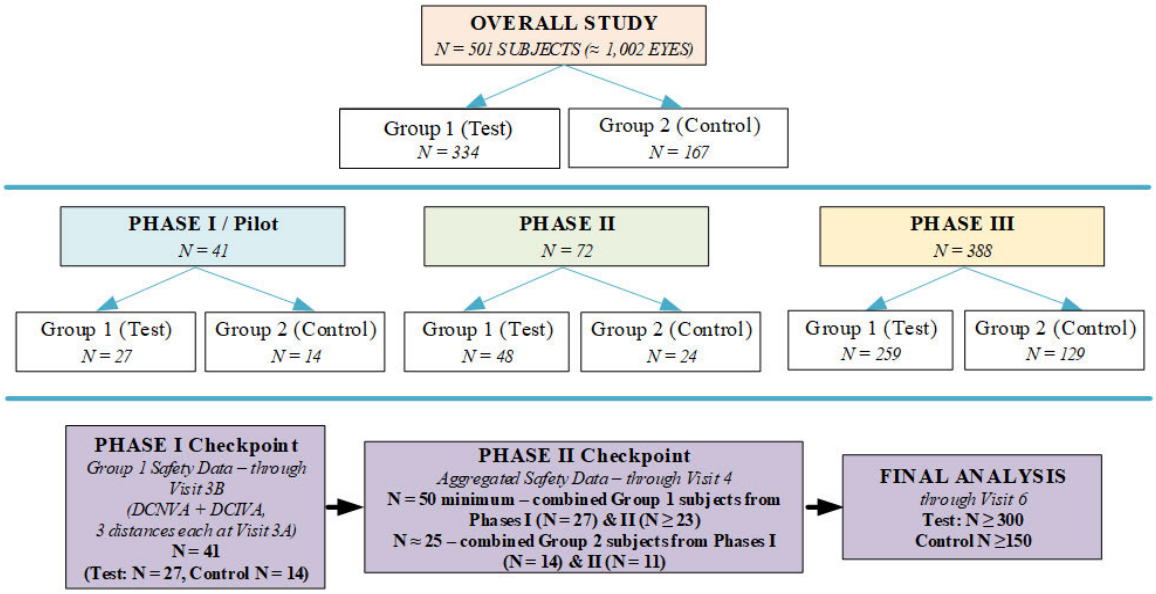
Study enrollment will occur in three Phases as follows:

Phase I/Pilot – Approximately 27 Group 1 (Test IOL) subjects will be enrolled and followed to Post-Operative Visit 3B (30 to 60 days after second eye IOL implantation) before a decision is made to initiate Phase II enrollment. Approximately 14 subjects will also be randomized to Group 2 (Control IOL) during this phase. A designated unmasked statistician(s) will summarize Phase I/Pilot distance-corrected near visual acuity (DCNVA) and distance-corrected intermediate visual acuity (DCIVA) data from Group 1 first implanted eyes for review by a clinical team not associated with the study, and the best near and intermediate distances will be selected for Phase II and Phase III evaluation. Phase I safety data will also be summarized for review by an unmasked clinical reviewer not associated with the study, and a decision to initiate Phase II will be made by the FDA based on Phase I data.

Phase II – Approximately 48 additional Group 1 subjects will be enrolled. Approximately 24 subjects will also be randomized to Group 2 during this phase. When a minimum of 50 Phase I and Phase II Group 1 subjects have been enrolled and followed through Visit 4, summaries and/or listings of all available safety data through Visit 4 will be prepared by an unmasked statistical team. Aggregated safety data for the minimum first 50 Phase I and Phase II Group 1 subjects who complete Visit 4 will be presented to the FDA to request expansion to Phase III. Safety data for approximately the corresponding minimum first 25 Phase I and Phase II Group 2 subjects who complete Visit 4 also will be submitted concurrently to the FDA. While safety data submission and FDA review for these subjects is occurring, additional subjects may be enrolled up to a maximum of approximately 72 Phase II subjects (including those whose data were submitted to FDA).

Phase III - Remainder of subjects will be enrolled and followed to Post-Operative Visit 5 or for subjects who have consented and enrolled in the Trial Frames Astigmatism sub-study, to Visit 6.

Planned enrollment in all Phases is schematized in the following diagram.



A pilot test will be conducted as Phase I/Pilot to identify the best near and intermediate distances to be tested during Phases II – III. Fixed near and intermediate distances of 40 cm and 66 cm, respectively, will be measured for all enrolled subjects. During Phase I/Pilot, DCNVA will be collected at three candidate distances: 30 cm, 35 cm, and 40 cm, and DCIVA will be collected at three candidate distances: 56, 66 and 76 cm. This phase will include approximately the first 27 subjects implanted with the enVista trifocal MIOL in Group 1 and approximately the first 14 subjects implanted with the enVista monofocal IOL in Group 2. Photopic monocular DCNVA and DCIVA will be assessed at each candidate distance at Visit 3A using ETDRS charts normalized for letter size as a function of distance tested. The near and intermediate distance VA data from Phase I/Pilot subjects will be excluded from near and intermediate VA hypothesis testing and will be summarized separately from the near and intermediate distance VA data of the other subjects. For all assessments other than near and intermediate VA measurements, Phase I/Pilot subjects' data will be pooled with the other subjects' data.

The best distances of 40 cm and 66 cm will be used for near and intermediate visual acuity testing, respectively, in Phases II and III of the study, and intermediate visual acuity will also be tested at 60 cm in Phases II and III.

Number of Subjects Planned: Approximately five hundred and one (501) subjects (approximately 1,002 eyes) will be treated in this study. Approximately 334 subjects will be implanted bilaterally with the enVista MX60EF trifocal MIOL, and approximately 167 control subjects will be implanted bilaterally with the enVista MX60E monofocal IOL.

Diagnosis and Criteria for Inclusion:

This study will include subjects who meet all of the following inclusion criteria:

1. Subjects must be 22 years of age or older on the date the Informed Consent Form (ICF) is signed.

2. Subjects must have the capability to understand and provide written informed consent on the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved Informed Consent Form (ICF) and authorization as appropriate for local privacy regulations.
3. Subjects must have a BCDVA equal to or worse than 20/40 in each eye, with or without a glare source, due to a clinically significant cataract (cortical, nuclear, subcapsular, or combination) that is considered amenable to treatment with standard phacoemulsification cataract extraction and capsular IOL implantation.
4. Subjects must have a BCDVA projected to be better than 20/32 after IOL implantation in each eye, as determined by the medical judgment of the Investigator or measured by potential acuity meter (PAM) testing, if necessary.
5. Subjects must have clear intraocular media other than the cataract in both eyes.
6. Contact lens wearers must demonstrate a stable refraction (within ±0.50 D for both sphere and cylinder) in both eyes, as determined by distance manifest refraction on two consecutive examination dates after discontinuation of contact lens wear.
7. Subjects must require an IOL power from +16.0 diopter (D) to +24.0 D in both eyes.
8. Subjects must be willing and able to comply with all treatment and follow-up study visits and procedures, and to undergo second eye surgery within 7-30 days of the first eye surgery.

Exclusion Criteria:

This study will exclude subjects (or eyes) who meet any of the following exclusion criteria:

1. Subjects who have used an investigational drug or device within 30 days prior to entry into this study and/or will participate in another investigation during the period of study participation.
2. Subjects who have any corneal pathology (e.g., significant scarring, guttata, inflammation, edema, dystrophy, etc.) in either eye.
3. Subjects who have significant anterior segment pathology that might increase intraoperative risk or compromise IOL stability (e.g., pseudoexfoliation syndrome, synechiae, iris atrophy, traumatic cataract, lens subluxation, traumatic zonulolysis, zonular dialysis, evident zonular weakness or dehiscence, hypermature or brunescent cataract, etc.) in either eye.
4. Subjects who have uncontrolled glaucoma in either eye.
5. Subjects who have previous retinal detachment or clinically significant retinal pathology involving the macula in either eye.
6. Subjects who have proliferative or non-proliferative diabetic retinopathy in either eye.
7. Subjects who have a congenital ocular anomaly (e.g., aniridia, congenital cataract) in either eye.
8. Subjects using any systemic or topical drug known to interfere with visual performance, pupil dilation, or iris structure within 30 days of enrollment or during the study (refer to the relevant attachment of the Study Reference Manual).
9. Subjects who have a history of chronic or recurrent inflammatory eye disease (e.g., iritis, scleritis, iridocyclitis, or rubeosis iridis) in either eye.
10. Subjects who have a visual disorder, other than cataracts, that could potentially cause future acuity losses to a level of 20/100 or worse in either eye.
11. Subjects who have had previous intraocular or corneal surgery in either eye, with the exception of laser trabeculoplasty.
12. Subjects with any preoperative infectious conjunctivitis, keratitis, or uveitis in either eye.
13. Subjects who have a preoperative corneal astigmatism > 1.0 D in either eye, irregular astigmatism, or skewed radial axis (note: corneal incisions intended specifically to reduce astigmatism are not allowed during the study).
14. Subjects who cannot achieve a minimum pharmacologic pupil dilation of 5.0 mm in both eyes.

15. Subjects who may be expected to require a combined or other secondary surgical procedure in either eye.
16. Subjects who during the first cataract extraction experience an anterior or posterior capsule tear or rupture, zonular dialysis, significant iris trauma, or other complication that may cause untoward effects in the judgment of the Investigator.
17. Females of childbearing potential (those who are not surgically sterilized or at least 12 months postmenopausal) are excluded from enrollment in the study if they are currently pregnant or plan to become pregnant during the study. Females of childbearing potential must be willing to practice effective contraception for the duration of the study.
18. Subjects with any other serious ocular pathology or underlying systemic medical condition (e.g., uncontrolled diabetes) or circumstance that, based on the Investigator's judgment, poses a concern for the subjects' safety or could confound the results of the study.
19. Subjects who have current or previous usage of an alpha-1-selective adrenoceptor blocking agent or an antagonist of alpha 1A adrenoceptor (e.g., Flomax® (tamsulosin HCl), Terazosin, or Cardura).

Study Materials:

Test Article: The enVista® one-piece hydrophobic acrylic trifocal MIOL (MX60EF) is an apodized, diffractive, trifocal version of the enVista® MX60E one-piece hydrophobic acrylic IOL. Test lenses will be available in powers +16.0 D to +24.0 D.

Test Article Proposed Intended Use: The enVista one-piece hydrophobic acrylic trifocal intraocular lens (IOL) is intended to replace the natural crystalline lens and is indicated for primary implantation for the visual correction of aphakia in adult patients in whom the cataractous lens has been removed. The lens is intended for placement in the capsular bag.

Active Control: The enVista® one-piece hydrophobic acrylic monofocal IOL (MX60E) is an aspheric optic one-piece lens with a square posterior edge. The biconvex lens optic has a body diameter of 6.0 mm, and the overall length (diameter) of the IOL is 12.5 mm. Control lenses will be available in powers +16.0 D to +24.0 D.

Duration of Treatment: Eligible subjects who are enrolled in the study will be followed for up to 12 months after second eye IOL implantation.

Clinical Parameters:

- Slit lamp examination
- Visual acuity
- Refractive status
- Intraocular pressure
- Pupil size
- Lens stability (decentration and tilt)
- Subject Questionnaires [Quality of Vision (QoV) Questionnaire and Near Activity Visual Questionnaire (NAVQ)[2]]
- Fundus visualization
- Incidence of posterior capsulotomy
- Adverse events

[2] Use of the exploratory NAVQ subject questionnaire will be discontinued after written FDA acceptance of protocol version 5.0, with the exception that subjects who have completed the NAVQ pre-operatively at the time of NAVQ discontinuation (protocol version 5.0) also will be asked to complete the NAVQ at Visit 4 (120 days to 180 days after second IOL implantation).

- OCT imaging
- Defocus curves
- Contrast sensitivity
- Visual acuity at near, intermediate, and distance under varying levels of simulated astigmatism using trial frames (if subject consents to sub-study)

The above evaluations will be performed as described in ISO 11979-7 [1], ISO 11979-9 [2], and ANSI Z80.12 [3] unless otherwise specified in the protocol.

Study Endpoints:

Primary Safety Endpoints

- The incidence of all serious adverse events, including secondary surgical interventions (SSIs) related to the optical properties of the IOL, in first eyes through study exit
- The rate of secondary surgical interventions due to the optical properties of the lens for first eyes through study exit
- The incidence of adverse events in first eyes compared to ISO Safety and Performance Endpoint (SPE) rates as defined in ISO 11979-7 through study exit

Secondary Safety Endpoints

- The rates of visual disturbances reported as "severe" by subjects, as well as the rates of visual disturbances reported as "very" bothersome by subjects, using the QoV questionnaire measure through Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
- Mean photopic contrast sensitivity with glare and mesopic contrast sensitivity with and without glare at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) and Post-Operative Visit 5 (Day 330 to 420 after second eye IOL implantation)
- Incidence of the types of AEs specified in the co-primary safety endpoints, but for fellow and "all" eyes
- Incidence of all other types of adverse events in primary eyes, fellow eyes, and "all" eyes

Primary Effectiveness Endpoints

- Photopic monocular best-corrected distance visual acuity (BCDVA) in first eyes at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
- Photopic monocular distance-corrected near visual acuity (DCNVA) in first eyes at 40 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
- Photopic monocular distance-corrected intermediate visual acuity (DCIVA) in first eyes at 66 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)

Secondary Effectiveness Endpoints

- Photopic binocular distance-corrected near visual acuity (DCNVA) at 40 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
- Photopic binocular uncorrected near visual acuity (UCNVA) at 40 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
- Photopic binocular distance-corrected intermediate visual acuity (DCIVA) at 66 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
- Photopic binocular uncorrected intermediate visual acuity (UCIVA) at 66 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)

- First eye BCDVA, DCNVA, and DCIVA evaluated at Visit 5

Statistical Methods:

The statistical analyses described in ISO 11979-7 [1], ISO 11979-9 [2], and ANSI Z80.12 [3] will be performed unless otherwise specified in the statistical analysis plan.

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

After IOL implantation for Phase I/Pilot subjects, enrollment will pause until the Phase I/Pilot subjects have completed Visit 3B (30 to 60 days after second eye IOL implantation) and their data have been reviewed. Data listings and/or summaries of test lens DCNVA and DCIVA data will be prepared by an unmasked statistician and presented for review by an unmasked clinical reviewer not associated with the study, and the best distances for near and intermediate VA testing will be determined. Safety data will also be prepared by an unmasked statistician and presented for review by the unmasked clinical reviewer not associated with the study. Phase I safety and VA data will be submitted to the FDA for review and acceptance to initiate Phase II. Statistical comparisons between Group 1 and Group 2 will not be made or evaluated. The decision to proceed or not to proceed to Phase II will not be based on formal statistical stopping rules.

When a minimum of 50 Phase I and Phase II Group 1 subjects have been enrolled and followed through Visit 4, summaries and/or listings of all available safety data through Visit 4 will be prepared by an unmasked statistical team. Aggregated safety data for the minimum first 50 Phase I and Phase II Group 1 subjects who complete Visit 4 for these subjects will be presented to the FDA to request expansion to Phase III. Safety data for approximately a corresponding minimum first 25 Phase I and Phase II Group 2 subjects who complete Visit 4 also will be submitted concurrently to the FDA. While safety data submission and FDA review for these subjects is occurring, additional subjects may be enrolled up to a maximum of approximately 72 Phase II subjects (including those whose data were submitted to FDA). Statistical comparisons between Group 1 and Group 2 will not be made or evaluated. The decision to proceed or not to proceed to Phase III will not be based on formal statistical stopping rules. Phase III enrollment will be initiated only after acceptance to proceed is received from FDA.

<u>Primary Safety Analyses</u>

The proportion of first modified Intent-to-Treat (mITT) eyes with at least one serious adverse event will be summarized using categorical summary statistics by treatment received. Each eye will be counted only once in the calculation of the rate.

Secondary surgical interventions related to the optical properties of the IOL will be summarized categorically by treatment received for first mITT Set eyes. Non-inferiority of the test lens compared to the control lens will be evaluated.

Adverse events in first mITT Set eyes will be compared to the ISO Safety and Performance Rates (SPE) as described in ISO 11979-7.

<u>Secondary Safety Analyses</u>

The rates of visual disturbances reported as "severe" by subjects, as well as the rates of visual disturbances reported as "very" bothersome by subjects, using the QoV questionnaire measure through Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) will be summarized categorically by treatment received for Modified Safety Set subjects. Each subject will be counted only once in the calculation of the rate.

Contrast sensitivity will be summarized using continuous summary statistics by lighting condition, spatial frequency, treatment group and visit.

The incidence of the type of AE specified in each co-primary safety endpoint will be summarized by treatment for fellow and "all" eyes.

The incidence of all other types of AEs will be summarized by treatment for primary eyes, fellow eyes, and "all" eyes for the mITT Set.

Additional supportive safety analyses are described in Section 13.5.5 and/or the study Statistical Analysis Plan (SAP).

Primary Effectiveness Analyses

The statistical success of the trial will depend on the statistical success of all three primary effectiveness endpoints.

Photopic monocular logMAR BCDVA in first implanted eyes at Post-Operative Visit 4 will be summarized using continuous summary statistics by treatment group for the mITT Set. Imputation of missing data is not conservative in non-inferiority testing. Therefore, missing data will not be imputed for a BCDVA non-inferiority test. The treatment effect (mean Test group IOL VA minus mean Control group IOL VA) in logMAR units will be estimated in addition to a two-sided 90% confidence interval. If the upper confidence limit (equivalent to a one-sided upper 95% confidence limit for the treatment effect) is less than 0.1, then the Test lens will be statistically non-inferior to the Control lens.[4]

The previous continuous summary statistics will also be provided for the Per Protocol Set. However, non-inferiority will not be evaluated with the PP Set, and statistical success will not depend upon the results of the PP analysis.

BCDVA at Visit 4 for the Test group will be summarized categorically (20/20 or better, 20/25 or better, 20/32 or better, 20/40 or better, and worse than 20/40) for the mITT and Best Case Sets. Two-sided exact binomial 90% confidence intervals around the proportions of eyes 20/40 or better will be presented.

For the analyses of the mITT and Best Case Sets, one-sided exact binomial tests comparing the proportion of multifocal IOL eyes with BCDVA 20/40 or better to the relevant control rate (92.5% for all eyes and 96.7% for best case eyes) will be performed and p-values will be presented. If the p-value is less than or equal to 0.05, then the null hypothesis will be rejected. If the null hypothesis is not rejected for the mITT and Best Case Sets in the primary analyses, then it will be concluded that the multifocal IOL is statistically successful in this outcome.

Photopic monocular distance-corrected near visual acuity (DCNVA) at 40 cm, and distance-corrected intermediate visual acuity (DCIVA) at 66 cm, in first eyes at Post-Operative Visit 4 will be summarized using continuous summary statistics in logMAR units by treatment assignment for

the mITT Set Phase II and III subjects (combined). The DCNVA and DCIVA data from the Phase I/Pilot subjects will be excluded from hypothesis testing and will be summarized separately from the data of the other subjects.

If there are missing mITT analysis set monocular DCNVA or DCIVA data at Visit 4, then missing data will be imputed using the Markov chain Monte Carlo multiple imputation method. After imputation of missing data, the statistical hypotheses will be tested using two-sided two-sample t-tests by imputation.

For each endpoint, an overall p-value resulting from the multiple imputation method will be estimated. The treatment effect (mean Test group IOL VA minus mean Control group IOL VA) in logMAR units will be summarized using continuous summary statistics and a two-sided 95% confidence interval. If the p-value from the multiple imputation analysis of treatment effect is less than or equal to 0.05 and the treatment effect is less than or equal to -0.10 logMAR units for DCIVA (i.e., the Test lens mean logMAR VA is at least 0.10 less than the mean for the control) or less than or equal to -0.20 logMAR units for DCNVA, then it will be concluded that the Test IOL is statistically and clinically successful in the corresponding outcome.

The previous continuous summary statistics will also be provided for the Per Protocol Set. However, superiority will not be evaluated with the PP Set, and statistical success will not depend upon the results of the PP analysis.

Secondary Effectiveness Analyses

Photopic binocular DCNVA, UCNVA, DCIVA, and UCIVA at 40 cm and 66 cm for near and intermediate VA, respectively, at Post-Operative Visit 4 will be compared between treatments using the methods described above for monocular DCNVA and DCIVA. The endpoints will be evaluated hierarchically in the following order: DCNVA, UCNVA, DCIVA, and UCIVA.

First eye BCDVA, DCNVA, and DCIVA (all in logMAR units) at Visit 5 will be summarized using descriptive statistics (mean, standard deviation, minimum, and maximum) for the ITT Set by treatment group (MX60EF Trifocal MIOL, MX60E Monofocal IOL). The means at Visit 5 for each of these outcomes will be compared between the treatment groups qualitatively.

Any additional supportive effectiveness analyses will be described in Section 13.5.5 and/or the SAP.

Sample size calculations:

General Justification

The sample size of 300 Test lens group subjects and 150 Control group subjects is specified in ANSI Z80.12-2007 (R2012) and ISO 11979-9:2006. Moreover, ISO 11979-7 specifies that a minimum of 300 subjects should complete a clinical evaluation of an IOL.

To allow for losses of up to 10%, approximately $\lceil 300/(1-0.1) \rceil = 334$ Test group subjects and approximately $\lceil 150/(1-0.1) \rceil = 167$ Control group subjects will be enrolled.

Phase I/Pilot Phase to Select Distances for Near and Intermediate VA Testing

A sample size of 24 DCNVA measurements at each of three distances will yield a probability of at least 98% of selecting the best distance when the difference (in logMAR units) between the best distance and the second best distance is at least 0.1 and the data are normally distributed with a standard deviation of 0.15. The first 27 Test group subjects will be enrolled in Phase I/Pilot to allow for at least 24 Test group subjects at Visit 3A.

A sample size of 24 DCIVA measurements at each of three distances will yield a probability of at least 98% of selecting the best distance when the difference (in logMAR units) between the best distance and the second best distance is at least 0.1 and the data are normally distributed with a standard deviation of 0.15. The first 27 Test group subjects will be enrolled in Phase I/Pilot to allow for at least 24 Test group subjects at Visit 3A.

Primary Safety Endpoints

Regarding the rate of all serious adverse events in first eyes, for a sample size of 300 subjects, the probability of observing at least one event will be at least 95% when the probability of an event is 1% or greater.

Regarding the rate of secondary surgical interventions due to the optical properties of the lens, the expected Control group rate is 0.1% and the expected Test group rate is 0.5%. With 150 eyes in the Control group and 300 eyes in the Test group, the upper limit of the observed one-sided 95% confidence interval will be expected to be less than 0.034 with 99% power when the Control proportion, $\boldsymbol{\pi_C}$, is 0.001 and the Test expected proportion, $\boldsymbol{\pi_T}$, is 0.005; results are based on 10000 simulations using the Newcombe-Wilson score method to construct the confidence interval.

ISO 11979-7 Annex B shows the relevant sample size calculations and assumptions for the ISO grid safety endpoints.

Secondary Safety Endpoints

Regarding the rates of visual disturbances reported as "severe" by subjects, as well as the rates of visual disturbances reported as "very" bothersome by subjects, using the QoV questionnaire measure through Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation), no statistical hypotheses will be tested. Therefore, no sample size calculation is required.

Regarding mean contrast sensitivity at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) and Post-Operative Visit 5 (Day 330 to 420 after second eye IOL implantation), no statistical hypotheses will be tested. Therefore, no sample size calculation is required.

Primary Effectiveness Endpoints

The primary effectiveness objectives are to demonstrate non-inferiority of the Test lens when compared to the Control lens and satisfactory performance of the Test lens when compared to the ISO grids (ISO 11979-7 Safety and Performance Endpoints) in photopic monocular best-corrected distance visual acuity (BCDVA) and to demonstrate superiority of the Test lens over the Control lens in distance-corrected near visual acuity (DCNVA) at 40 cm, and distance-corrected intermediate visual acuity (DCIVA) at 66 cm, in first eyes at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation). Approximately the first 24 evaluable Test group subjects and first 12 evaluable Control group subjects will be excluded from the near and intermediate visual acuity hypothesis tests, leaving an expected evaluable sample size of approximately 276 Test group

subjects implanted with the Test IOL and 138 Control group subjects to be included in the near and intermediate visual acuity effectiveness hypothesis tests.

Regarding the non-inferiority test of BCDVA, when the sample sizes in the groups are 300 (Group 1) and 150 (Group 2), a two group 0.050 one-sided t-test will have 99% power to reject the null hypothesis that the Test and Control IOLs are not equivalent (the difference in means, $\mu_T - \mu_S$, is 0.10 or farther from zero in the same direction) in favor of the alternative hypothesis that the means of the two groups are equivalent, assuming that the expected difference in means is 0.000 and the common standard deviation is 0.150.

Regarding the comparisons of BCDVA to the ISO grid, ISO 11979-7 specifies a sample size of approximately 300 completed subjects for this type of investigation.

Regarding statistical superiority tests of DCNVA and DCIVA, a two-group t-test with a 0.05 two-sided significance level will have 99% power to detect a difference in means of -0.10, assuming that the common standard deviation is 0.15, when the sample sizes in the two groups are 276 and 138 subjects, respectively (a total sample size of 414 subjects).

Regarding the assessment of clinical superiority in DCNVA and DCIVA, the probability that the Test group's mean logMAR VA will be at least 0.1 units less than the Control group's mean logMAR VA will be 89% if the true difference is -0.12 units, 97% if the true difference is -0.13 units, and 99% if the true difference is -0.14 units, assuming that the common standard deviation is 0.15 when the sample sizes in the two groups are 276 and 138 subjects, respectively (a total sample size of 414 subjects).

Secondary Effectiveness Endpoints

Secondary effectiveness endpoint hypotheses will be tested hierarchically in the order: DCNVA, UCNVA, DCIVA, and UCIVA.

All Phase I evaluable Test group subjects evaluable Control group subjects will be excluded from the near and intermediate visual acuity hypothesis tests, leaving an expected evaluable sample size of approximately 276 Test group subjects and 138 Control group subjects to be included in the near and intermediate visual acuity hypothesis tests.

Regarding photopic binocular distance-corrected near visual acuity (DCNVA) at 40 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation), a two-group t-test with a 0.050 two-sided significance level will have 99% power to detect a difference in means of -0.10 logMAR units, assuming that the common standard deviation is 0.20 units, when the sample sizes in the two groups are 276 and 138 subjects, respectively (a total sample size of 414 subjects).

Regarding photopic binocular uncorrected near visual acuity (UCNVA) at 40 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation), a two-group t-test with a 0.050 two-sided significance level will have 99% power to detect a difference in means of -0.10 logMAR units, assuming that the common standard deviation is 0.20 units, when the sample sizes in the two groups are 276 and 138 subjects, respectively (a total sample size of 414 subjects).

Regarding photopic binocular distance-corrected intermediate visual acuity (DCIVA) at 66 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation), a two group t-test with a 0.050 two-sided significance level will have 99% power to detect a difference in means of -0.10

logMAR units, assuming that the common standard deviation is 0.15 units, when the sample sizes in the two groups are 276 and 138 subjects, respectively (a total sample size of 414 subjects).

Regarding photopic binocular uncorrected intermediate visual acuity (UCIVA) at 66 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation), a two group t-test with a 0.05 two-sided significance level will have 99% power to detect a difference in means of -0.10 logMAR units, assuming that the common standard deviation is 0.20 units, when the sample sizes in the two groups are 276 and 138 subjects, respectively (a total sample size of 414 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
ANSI	American National Standards Institute
BCDVA	Best-corrected Distance Visual Acuity, synonymous with CDVA
C	Centigrade
cd/m^2	Candela per Square Meter
CDVA	Corrected Distance Visual Acuity, synonymous with BCDVA
CME	Cystoid Macular Edema
CFR	Code of Federal Regulations
cpd	Cycles Per Degree
CRF	Case Report Form
CRO	Clinical Research Organization
D	Diopter
DCIVA	Distance-corrected Intermediate Visual Acuity
DCNVA	Distance-corrected Near Visual Acuity
ETDRS	Early Treatment Diabetic Retinopathy Study
DFU	Directions for Use
F	Fahrenheit
FDA	Food and Drug Administration
FDF	Financial Disclosure Form
GCPs	Good Clinical Practices
HEMA	Hydroxyethyl Methacrylate
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Council for Harmonization
IDE	Investigational Device Exemption
IOL	Intraocular Lens
IOP	Intraocular Pressure
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISO	International Organization for Standardization
ITT	Intent to Treat
LASEK	Laser-assisted subepithelial keratectomy
LASIK	Laser-assisted in situ keratomileusis
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
MCMC	Markov chain Monte Carlo
MIOL	Multifocal Intraocular Lens
mITT	Modified Intent to Treat

Abbreviation or specialist term	Definition or Explanation
MTF	Modulation Transfer Function
NAVQ	Near Activity Visual Questionnaire
Nd:YAG	Neodymium:Yttrium Aluminium Garnet
ND	Not Done
OCT	Optical Coherence Tomography
OVD	Ophthalmic Viscoelastic Device
PAM	Potential Acuity Meter
PCO	Posterior Capsular Opacification
PMA	Pre-market Approval
polyEGPEA	Polyethylene Glycol Phenyl Ether Acrylate
PP	Per Protocol
QoV	Quality of Vision
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SPK	Superficial Punctate Keratitis
SOP	Standard Operating Procedure
SPE	Safety and Performance Endpoint
SSI	Secondary Surgical Intervention
SUN	Standardization of Uveitis Nomenclature
TASS	Toxic Anterior Segment Syndrome
UADE	Unanticipated Adverse Device Effect
UCDVA	Uncorrected Distance Visual Acuity
UCIVA	Uncorrected Intermediate Visual Acuity
UCNVA	Uncorrected Near Visual Acuity
US	United States
VA	Visual Acuity

5 Introduction

Cataracts are a common condition in adults over 40 years of age, and surgical replacement of the cataractous lens with an intraocular lens (IOL) remains an effective way to restore vision to cataract patients.[4] Monofocal IOLs provide adequate distance vision but require spectacle use for near or intermediate distance vision activities. Subsequent to monofocal IOL development and commercialization, multifocal intraocular lenses (MIOLs), including bifocal and trifocal IOLs, have been successfully developed to improve near and intermediate distance vision and increase spectacle independence following cataract surgery. [5-9]

There are currently no approved trifocal IOLs available in the United States, despite a desire by cataract surgery patients for a product that provides improved near and intermediate vision in comparison to a conventional monofocal IOL without compromising distance vision. Clinical studies have shown that intermediate add power trifocal diffractive IOLs have substantially improved intermediate vision compared to bifocal IOLs, resulting in better visual quality and excellent spectacle independence for individuals with active lifestyles. [10-14] Observational clinical studies and clinical studies comparing trifocal to bifocal IOLs also have shown high patient satisfaction in patients with trifocal MIOLs. [11, 15, 16] These studies and others indicate contrast sensitivity and levels of photic phenomena in patients with trifocal MIOL implants are similar to that of patients with bifocal MIOLs under both photopic and mesopic conditions, and spectacle independence in up to 100% of the patients has been reported. [12-19]

The enVista® MX60EF trifocal MIOL is a 1-piece hydrophobic acrylic ultraviolet-absorbing lens with aspheric biconvex optics, designed to have -0.15 µm of spherical aberration, with apodized diffractive structures on the anterior surface, a square edge on the posterior surface and modified C-loop haptics. The design and material of the lens allow it to be folded and inserted into the capsular bag through a small incision to minimize the possibility of surgically induced astigmatism. The MX60EF lens is a modification to the Bausch + Lomb enVista® 1-piece hydrophobic acrylic monofocal IOL, model MX60E, approved under PMA Supplement P920056/S024 by the FDA on 05/23/2017 as an update to PMA P910056/S010, approved on 05/30/2012 for the parent enVista MX60 monofocal IOL. PMA P910056/S010 approved a material change and design modifications to the previously approved Bausch + Lomb model C31UB IOL, including a design change from 3-piece to 1-piece design and the addition of aspheric optics with zero spherical aberration.

The enVista® Trifocal Model MX60EF will be manufactured, packaged and sterilized with the same materials and processes used for the enhanced enVista® IOL Model MX60E. The enVista Model MX60E lens material is a modification to the enVista Model MX60 material, designed to enhance the unfolding rate of the lens at the lower eye temperature encountered during surgical procedures.

The induced -0.15 µm negative spherical aberration MX60EF trifocal MIOL lens design (incorporated on the enVista EF base refractive design to give a residual spherical aberration of ~0.10µm) is expected to produce comparable decentration performance to a spherical aberration-free lens design and best contrast-related performance in the presence of other higher order aberrations. Mathematical modeling and optical bench experiments have shown that increased depth of focus due to residual spherical aberration comes at the cost of lower modulation transfer function (MTF). [20-22] Since the enVista® MX60EF lens is distance

dominant under mesopic (low light) conditions, any level of corneal spherical aberration compensation using the MX60EF trifocal MIOL should result in improving the MTF.

Thus, the rationale for the investigation described in this document is to collect and analyze data suggesting potential clinical benefit that clearly outweighs any potential risks associated with use of the MX60EF product.

6 Study Objectives and Purpose

The objective of the study is to evaluate the safety and effectiveness of the enVista trifocal intraocular lens when implanted in the capsular bag.

6.1 Study Endpoints

The following primary and secondary safety and effectiveness endpoints will be evaluated.

6.1.1 Safety

The primary safety endpoints will be:

- The incidence of all serious adverse events, including SSIs related to the optical properties of the IOL, in first eyes through study exit
- The rate of secondary surgical interventions due to the optical properties of the lens for first eyes through study exit
- The incidence of adverse events in first eyes compared to ISO Safety and Performance Endpoint (SPE) rates as defined in ISO 11979-7 through study exit

The secondary safety endpoints will be:

- The rates of visual disturbances reported as “severe” by subjects, as well as the rates of visual disturbances reported as “very” bothersome by subjects, using the QoV questionnaire measure through Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
- Mean photopic contrast sensitivity with glare and mesopic contrast sensitivity with and without glare at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) and Post-Operative Visit 5 (Day 330 to 420 after second eye IOL implantation)
- Incidence of the types of AEs specified in the co-primary endpoints, but for fellow and “all” eyes
- Incidence of all other types of adverse events in primary eyes, fellow eyes, and “all” eyes

6.1.2 Effectiveness

The primary effectiveness endpoints will be:

- Photopic monocular best-corrected distance visual acuity (BCDVA) in first eyes at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
- Photopic monocular distance-corrected near visual acuity (DCNVA) in first eyes at 40 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)

- Photopic monocular distance-corrected intermediate visual acuity (DCIVA) in first eyes at 66 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)

Secondary effectiveness endpoints will be:

- Photopic binocular distance-corrected near visual acuity (DCNVA) at 40 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
- Photopic binocular uncorrected near visual acuity (UCNVA) at 40 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
- Photopic binocular distance-corrected intermediate visual acuity (DCIVA) at 66 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
- Photopic binocular uncorrected intermediate visual acuity (UCIVA) at 66 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
- First eye BCDVA, DCNVA, and DCIVA evaluated at Visit 5

7 Investigational plan

7.1 Overall Study Design and Plan: Description

This will be a prospective, multicenter, randomized, active-controlled binocular study of the enVista one-piece hydrophobic acrylic trifocal MIOL (model MX60EF) in subjects undergoing cataract extraction compared to the enVista one-piece hydrophobic acrylic monofocal intraocular lens (model MX60E).

Subjects scheduled to undergo cataract surgery by phacoemulsification and implantation of bilateral intraocular lenses (IOLs) will be screened for eligibility. Subjects will be examined preoperatively to obtain a medical history, establish a baseline for ocular condition, and determine eligibility. Both eyes of each subject will be included in the study and must meet eligibility criteria at the Pre-Operative Visit. At the time of the first surgery, subjects will be enrolled and randomly assigned by an interactive response technology (IRT) system in a 2:1 ratio to either the enVista trifocal MIOL or the enVista monofocal IOL, respectively.

Postoperatively, subjects will undergo ophthalmic examinations at regular intervals per the study visit schedule. The Investigator will provide standardized pre-, peri-, and postoperative care for all study subjects at his/her clinical site (refer to Section 11 for additional information). A delegated examiner(s) at each site who is masked to the randomized assignment of each subject will perform postoperative measurements. Every effort will be made to ensure that postoperative assessments for a subject are completed by the same examiner.

7.2 Investigators

The clinical investigation will be conducted at approximately twenty (20) investigative sites in North America.

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 FDA Federal Regulations or local regulations and who are willing to demonstrate use of the MX60E product, if they have not already done so. Additionally, the Device Investigator Agreement (on file for each site) also verifies Investigator obligations.

Each Investigator site will attempt to enroll approximately twenty-five (25) subjects. In the event that selected sites do not meet expected enrollment, the Sponsor may decide to increase enrollment as needed at other currently active sites, replace non-enrolling sites and/or add additional site(s) for a total of up to 25 actively enrolling sites, to satisfy study enrollment requirements. No Investigator shall contribute more than 10% of the total number of treated subjects in the study.

7.3 Study Duration

Eligible subjects who are enrolled in this study will be followed for approximately one year following the second eye surgery.

8 Selection and Withdrawal of Subjects

Approximately five hundred and one (501) subjects (approximately 1,002 eyes) at approximately twenty (20) clinical sites in North America scheduled to undergo bilateral 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 eligibility, written informed consent must be obtained from each study subject prior to performing any study specific procedures that are not part of the Investigator’s routine standard of care. Enrollment will be consecutive enrollment of all eligible subjects. A complete ophthalmic examination will be done at the Preoperative Visit scheduled within 30 days before the first eye surgery.

Application of the inclusion and exclusion criteria in the following sections will result in the selection of an investigational population which is representative of the intended target population.

8.1 Subject Inclusion Criteria

This study will include subjects who meet all of the following inclusion criteria:

1. Subjects must be 22 years of age or older on the date the Informed Consent Form (ICF) is signed.
2. Subjects must have the capability to understand and provide written informed consent on the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved Informed Consent Form (ICF) and authorization as appropriate for local privacy regulations.
3. Subjects must have a BCDVA equal to or worse than 20/40 in each eye, with or without a glare source, due to a clinically significant cataract (cortical, nuclear, subcapsular, or combination) that is considered amenable to treatment with standard phacoemulsification cataract extraction and capsular IOL implantation.
4. Subjects must have a BCDVA projected to be better than 20/32 after IOL implantation in each eye, as determined by the medical judgment of the Investigator or measured by potential acuity meter (PAM) testing, if necessary.

5. Subjects must have clear intraocular media other than the cataract in both eyes.
6. Contact lens wearers must demonstrate a stable refraction (within ±0.50 D for both sphere and cylinder) in both eyes, as determined by manifest refraction on two consecutive examination dates after discontinuation of contact lens wear.
7. Subjects must require an IOL power from +16.0 diopter (D) to +24.0 D in both eyes.
8. Subjects must be willing and able to comply with all treatment and follow-up study visits and procedures, and to undergo second eye surgery within 7-30 days of the first eye surgery.

8.2 Subject Exclusion Criteria

This study will exclude subjects (or eyes) who meet any of the following exclusion criteria:

1. Subjects who have used an investigational drug or device within 30 days prior to entry into this study and/or will participate in another investigation during the period of study participation.
2. Subjects who have any corneal pathology (e.g., significant scarring, guttata, inflammation, edema, dystrophy, etc.) in either eye.
3. Subjects who have significant anterior segment pathology that might increase intraoperative risk or compromise IOL stability (e.g., pseudoexfoliation syndrome, synechiae, iris atrophy, traumatic cataract, lens subluxation, traumatic zonulolysis, zonular dialysis, evident zonular weakness or dehiscence, hypermature or brunescent cataract, etc.) in either eye.
4. Subjects who have uncontrolled glaucoma in either eye.
5. Subjects who have previous retinal detachment or clinically significant retinal pathology involving the macula in either eye.
6. Subjects who have proliferative or non-proliferative diabetic retinopathy in either eye.
7. Subjects who have a congenital ocular anomaly (e.g., aniridia, congenital cataract) in either eye.
8. Subjects using any systemic or topical drug known to interfere with visual performance, pupil dilation, or iris structure within 30 days of enrollment or during the study.
9. Subjects who have a history of chronic or recurrent inflammatory eye disease (e.g., iritis, scleritis, iridocyclitis, or rubeosis iridis) in either eye.
10. Subjects who have a visual disorder, other than cataracts, that could potentially cause future acuity losses to a level of 20/100 or worse in either eye.
11. Subjects who have had previous intraocular or corneal surgery in either eye, with the exception of laser trabeculoplasty.
12. Subjects with any preoperative infectious conjunctivitis, keratitis, or uveitis in either eye.
13. Subjects who have a preoperative corneal astigmatism > 1.0 D in either eye, irregular astigmatism, or skewed radial axis (note: corneal incisions intended specifically to reduce astigmatism are not allowed during the study).

14. Subjects who cannot achieve a minimum pharmacologic pupil dilation of 5.0 mm in both eyes.
15. Subjects who may be expected to require a combined or other secondary surgical procedure in either eye.
16. Subjects who during the first cataract extraction experience an anterior or posterior capsule tear or rupture, zonular dialysis, significant iris trauma, or other complications that may cause untoward effects in the judgment of the Investigator.
17. Females of childbearing potential (those who are not surgically sterilized or at least 12 months postmenopausal) are excluded from enrollment in the study if they are currently pregnant or plan to become pregnant during the study. Females of childbearing potential must be willing to practice effective contraception for the duration of the study.
18. Subjects with any other serious ocular pathology or underlying systemic medical condition (e.g., uncontrolled diabetes) or circumstance that, based on the Investigator's judgment, poses a concern for the subjects' safety or could confound the results of the study.
19. Subjects who have current or previous usage of an alpha-1-selective adrenoceptor blocking agent or an antagonist of alpha 1A adrenoceptor (e.g., Flomax® (tamsulosin HCl), Terazosin, or Cardura).

8.3 Subject Disposition Criteria

8.3.1 Subject Enrollment

The subject is considered enrolled in the study at the time of randomization at the first Operative Visit (Visit 00A). Randomization should follow the completion of uncomplicated cataract extraction in the first eye.

8.3.2 Subject Screen Failures

A subject who fails to meet eligibility criteria and/or discontinues from the study before randomization will be considered a screen failure.

8.3.3 Subject Completion

For those who are eligible and have consented to participate in the sub-study, a Visit 6 (Day 2- 30 post Visit 5) will be conducted as the final visit to complete the study. For those subjects who have not consented to the sub-study, Visit 5 will be the final visit to complete their participation. If the subject consented to Visit 6 but did not complete the final Visit 6, Visit 5 will be considered as the final visit for that subject, ending their participation in the study.

A subject who has missed visits or is missing study measurements will remain in the study. Subjects who require further follow-up for an AE will be followed according to Section 12.4.

8.3.4 Subject Discontinuation

A subject may be discontinued prior to the final study visit for any of the following reasons, including but not limited to:

- Investigator's request (e.g., subject non-compliance or medical decision)
- voluntary withdrawal (subject's request)

- death
- 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. Subject withdrawals will be documented clearly on the source document and applicable Case Report Form (CRF). Subjects who discontinue from the study should be seen for routinely scheduled visits according to the standard of care by the Investigator or their ophthalmologist.

Notification of subject withdrawals will be made immediately to the Sponsor.

Only subjects who are randomized but did not have the lens inserted into the eye may be replaced. Subjects for whom the lens was inserted but not implanted will not be replaced. A new subject number will be assigned, as long as the total number of treated subjects at the site does not exceed 10% of the total treated eyes in the study. 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 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. The investigator will try at least twice to reach the subject by telephone and/or electronic mail and will send a follow-up letter by certified mail before considering the subject lost to follow-up. These actions will be recorded in the source documents and a copy of the follow-up letter maintained in the investigator's file. The date of discontinuation for subjects lost to follow-up will be seven days after the date that the unanswered certified letter was sent.

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

9 Treatment Plan

9.1 Methods of Assigning Subjects to Treatment Groups

Approximately 501 subjects (1,002 eyes) will be randomized in a 2:1 ratio to receive the enVista trifocal (Test) IOL or enVista monofocal (Control) IOL in both eyes.

9.1.1 Treatment Allocation

At the time of the first surgery following uncomplicated cataract extraction, subjects will be randomly assigned to either the enVista trifocal MIOL or enVista monofocal IOL in a 2:1 ratio based upon a predetermined randomization scheme.

9.1.2 Randomization Rationale & Method

Randomization of subjects is performed to reduce potential bias. Subjects will be randomly assigned to receive either the trifocal (Test) IOL bilaterally or the monofocal (Control) IOL bilaterally according to the randomization scheme to be provided.

IRT will be utilized for randomization in this study. The randomization codes will be stratified by site such that the ratio of subjects assigned to the Test MX60EF trifocal MIOL or Control MX60E IOL at each site will be approximately 2:1.

Randomization will occur following uncomplicated cataract extraction on the date of first surgery.

9.1.3 Treatment or Subject Replacement

There is no treatment or subject replacement planned for this study.

9.2 Masking and Postoperative Masked Examiner(s)

The Investigator implanting the IOL and designated site personnel will be unmasked to the assignment of IOLs. Subjects and designated postoperative evaluator(s) will be masked to the IOLs assigned.

A qualified masked examiner at each site, who is unaware of which IOL has been implanted for each subject, shall perform post-operative measurements including manifest refraction, visual acuity, contrast sensitivity, and defocus curves. Every attempt should be made to have the same masked examiner perform the same post-operative measurements for an individual subject throughout the subject's study participation.

Pupil size measurements should be taken by an unmasked staff member.

9.3 Concomitant Medications

Documentation of all medications used by the subject within 30 days of informed consent and during the study will be made in study source documents.

Pre-, intra-, and postoperative medications may be administered per the Investigator's standard of care. A complete list of the Investigator's standard regimen of these medications will be provided to the Sponsor or its designee and approved by the Medical Monitor prior to initiation of the study. All Investigators will be required to use Amvisc® Plus viscoelastic (see Appendix C).

Medications known to interfere with visual performance, pupil dilation, or iris structure are prohibited within 30 days of enrollment and for the duration of the study. A list of prohibited medications (including alpha-1-selective adrenoceptor blocking agent or an antagonist of alpha 1A adrenoceptor (e.g., Flomax® (tamsulosin HCl), Terazosin, or Cardura) will be included as part of the Study Reference Manual provided to the site.

9.4 Protocol Deviations

A deviation from the protocol is an unintended and/or unanticipated departure from the procedures and/or processes approved by the Sponsor and the IRB/IEC and agreed to by the Investigator.

The investigator or designee must document and explain in the subjects' source documentation any deviation from the approved protocol. Protocol waivers will not be allowed under any circumstances. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study subjects without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendment(s) should be submitted to the IRB/IEC for review and approval, to the Sponsor for agreement, and to the regulatory authorities, if required.

Documentation of the deviation process and follow up (as applicable) can be found in the Study Refence Manual. Deviation impact on data analysis is described in Section 13.5.8. The date of, and reason for, deviations in all cases will be documented. Protocol deviations affecting the safety of the subject or the integrity of the study must be reported by the Investigator to the IRB/IEC promptly. Reporting of all other protocol deviations must adhere to the requirements of the governing IRB/IEC.

Protocol assessments will continue for a subject until the end of the study, unless the protocol deviation puts the subject at risk or the subject's condition requires that he/she be discontinued from the study.

Scheduled assessments missed or conducted out of window due to COVID-19 disruption will be recorded as protocol deviations.

10 Study Materials and Management

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

10.1 Description of Test Article and Intended Use

The enVista MX60EF Trifocal MIOL is manufactured by Bausch & Lomb (Clearwater, FL) and is a one-piece hydrophobic acrylic ultraviolet-absorbing lens with aspheric biconvex optics designed to have -0.15 µm of spherical aberration, with apodized diffractive structures on the anterior surface and modified C-loop haptics. The posterior aspheric optic is designed with a 360 degree square edge, to help prevent Posterior Capsular Opacification (PCO), and modified C-loop haptics. The design and material of the lens allow it to be folded and inserted into the capsular bag through a small incision to minimize the extent of surgically induced astigmatism. The enVista Trifocal MIOL (Model MX60EF) is sterile, non- pyrogenic and packaged in 0.9% saline solution, contained in a gamma grade polypropylene vial (with a heat-sealed foil lid) that is then sealed in a Tyvek peel pouch. Test lenses will be available in powers +16.0 D to +24.0 D, in 0.5 D increments.

The enVista one-piece hydrophobic acrylic trifocal intraocular lens (IOL) is intended to replace the natural crystalline lens and is indicated for primary implantation for the visual correction of aphakia in adult patients in whom the cataractous lens has been removed. The lens is intended for placement in the capsular bag. Additional details regarding this product can be found in the Investigator's Brochure for it.

10.2 Description of Active Control

The enVista One-Piece Hydrophobic Acrylic IOL (Model MX60E) is a one-piece foldable, hydrophobic acrylic, ultraviolet (UV) absorbing posterior chamber IOL with an aspheric optic and a 360-degree square edge, to help prevent PCO. The biconvex lens optic has a body diameter of 6.0 mm, and the overall length (diameter) of the IOL is 12.5 mm. Control Model MX60E lenses will be available in powers +16.0 D to +24.0 D; in 0.5 D increments. The Directions For Use for the MX60E are shown in Appendix E.

10.3 Packaging and Labeling

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

10.3.1 Packaging

EnVista trifocal MX60EF and enVista monofocal MX60E lenses will be non-pyrogenic, packaged sterile in 0.9% saline solution, and contained in a gamma grade polypropylene vial (with a heat-sealed foil lid) that is sealed in a Tyvek peel pouch. The lens is sterilized using gamma irradiation.

10.3.2 Labeling

Study lens labeling will include the following information:

- Study number
- Sponsor name and address
- Product identifier
- Quantity of contents
- Directions for use (DFU)
- Statement indicating: "Caution – Investigational Device. Limited by Federal Law to investigational use."
- Storage conditions
- Lot number
- Expiration date
- Lens number

10.4 Storage of Study Device

Store study IOLs at room temperature. Do not store study IOLs at a temperature greater than 43°C (110°F). DO NOT FREEZE. Do not autoclave the IOLs.

10.5 Surgical Directions

Refer to Appendix C for surgical directions/procedures for the MX60EF and MX60E IOLs.

10.6 Study Device Accountability

The Investigator will be responsible for keeping current and accurate records of the number of IOLs received, implanted and returned to Sponsor. The IOLs must be stored under the appropriate conditions in a secure area and are to be implanted 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 IOLs implanted, including subject identifiers.

Accountability records will include:

- the lens numbers of all IOLs received, the receipt date, and the quantity received
- the names of all site personnel who received, used, or disposed of the IOLs
- the dates of use, disposal, or return of each IOL
- a record of each subject implanted with a Test or Control IOL
- why and how many IOLs are returned to the Sponsor
- explanation for reconciliation of discrepancies

At various time points throughout the study and/or upon completion of the study, the Sponsor or 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.

10.7 Other Materials

Study materials provided by Bausch + Lomb will include:

- Bausch & Lomb single-use IOL injection system (BLIS)
- Bausch & Lomb Amvisc® Plus viscoelastic
- Visual acuity and contrast sensitivity instrumentation
- Subject questionnaires: the Quality of Vision (QoV) questionnaire [23,24] and Near Activity Visual Questionnaire [25-28] (paper forms)
- Accessory to enable capture of slit-lamp biomicroscope photos, as needed
- A digital pupillometer

11 Study Procedures and Evaluations

Subjects will be examined and evaluated according to the study schedule provided in Appendix A.

11.1 Schedule of Evaluations and Procedures

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

Visit Name	Eyes Evaluated	Visit Window
Preoperative Visit 0A/B	Both Eyes	Day -30 to -5
Operative Visit 00A	1st Eye	Day 0
Post-Operative Visit 1A	1st Eye	Day 1 to 2 post Visit 00A
Post-Operative Visit 2A	1st Eye	Day 7 to 14 post Visit 00A
Post-Operative Visit 3A	1st Eye	Day 30 to 60 post Visit 00A
Operative Visit 00B	2nd Eye	Day 7 to 30 post Visit 00A
Post-Operative Visit 1B	2nd Eye	Day 1 to 2 post Visit 00B
Post-Operative Visit 2B	2nd Eye	Day 7 to 14 post Visit 00B
Post-Operative Visit 3B	2nd Eye	Day 30 to 60 post Visit 00B

Post-Operative Visit 4	Both Eyes	Day 120 to 180 post Visit 00B
Post-Operative Visit 5	Both Eyes	Day 330 – 420 post Visit 00B
Post-Operative Visit 6 (subjects that consent at participating sites)	Both Eyes	Day 2- 30 post Visit 5

Refer to Appendix B for the schedule of visits and procedures and Appendix B for methods of clinical evaluation.

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 or his/her legal representative and the person obtaining written consent will sign and date the IRB/IEC 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 IRT, which will consist of a 3-digit site number (pre-assigned) and a 3-digit chronological order screening number, assigned by IRT and starting with 001 (e.g., 101-001, 101-002; in this example the site number is 101). 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.

11.1.1 Mitigation of COVID-19 Related Disruption to Study Visits

Study procedures performed during the COVID-19 pandemic will be conducted in accordance with medical guidance to reduce risk of COVID-19 transmission between study staff and subjects (available at www.aao.org/covid-19). It is recommended Investigators periodically revisit the **aao.org/covid-19** website to identify and implement any updated recommendations made by AAO. Local, state, and federal public health guidance also will be followed, and it is recommended these guidances also be visited once a month to see if they have changed.

Where in-person study visits are not possible due to the pandemic, remote contact with subjects may be instituted by the investigational site, as feasible, to collect any relevant safety data on health and medication changes. The decision to conduct a remote contact in lieu of an in-person visit will be made using the professional judgment of the PI - prioritizing safety, as well as adherence to local, state, and federal guidelines related to COVID-19, and in consideration of relevant guidance from national, professional ophthalmic organizations, including the American Academy of Ophthalmology and the American Society of Cataract and Refractive Surgeons.

Remote contacts will limit data collection to safety oversight and medication changes. Scheduled assessments missed or conducted out of window due to COVID-19 disruption will be recorded as protocol deviations.

11.1.2 Preoperative Visit 0: Day -30 to -5

Informed consent must be obtained prior to the Investigator performing study specific procedures that are not part of 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 30 days prior to the first surgery and will consist of a complete ophthalmic examination.

Note: Potential subjects may be identified for screening in conjunction with routine clinic cataract evaluations involving standard of care testing. To avoid having to repeat this testing within a short time period to qualify for the study, standard of care measurements, including corneal topography, targeted refraction / IOL power calculation / axial length determination / anterior chamber depth / chord length μ, keratometry, IOP, slit-lamp examination, and dilated fundus exam, may be used as qualifying pre-operative assessments, provided they meet the following criteria:

- Performed by a qualified investigator who is participating in the study;
- Performed as specified in the protocol to verify subject eligibility;
- Conducted within the pre-operative window specified in the protocol.

11.1.3 Operative Visit 00A: Day 0

Subjects will be assessed to reconfirm eligibility. In addition, any changes in concomitant medications or AEs will be recorded. If the subject is no longer eligible, he/she will be screen failed from the study. If the subject is eligible, surgery will be performed using the surgical procedure described in Appendix C. If the subject continues to meet eligibility criteria after cataract extraction, the subject will be randomized.

The eye with the worse best-corrected distance visual acuity (BCDVA) or worse BCDVA with glare at the Preoperative Visit will be treated first (eye A) and used in the primary monocular evaluations. If BCDVA is the same for both eyes, the right eye will be treated first.

11.1.4 Operative Visit 00B: Day 7 to 30

Subjects will undergo the second eye surgery (eye B) between 7 and 30 days from the first eye surgery. Postoperative Visit 2A must be completed before Visit 00B. These visits may be performed the same day at the Investigator's discretion, provided that Visit 2A is done first, and both visits are performed within window. If the subject continues to meet eligibility criteria, surgery will be performed using the surgical procedure described in Appendix C.

11.1.5 Postoperative Visits (1A through 5): Day 1 to Day 420

All treated subjects will be seen for a minimum of eight (8) postoperative visits. Postoperative Visits 3A and 3B may be performed the same day at the Investigator's discretion, provided that Visit 3A is done first, and both visits are performed within window.

11.1.6 Postoperative Visit 6: Day 2- 30 post Visit 5

This visit applies to those subjects who have consented to Visit 6 at investigative sites where the trial frame astigmatism simulation sub-study is being performed. The procedure for this visit is described in Section 8.0 of Appendix B.

11.1.7 Unscheduled Visit(s)

Additional visits may be scheduled, as necessary, to ensure the safety and well-being of subjects. All additional examinations should be fully documented in the source documents and on Unscheduled Visit CRFs, as appropriate. Visits intended to fulfill scheduled visit requirements that fall outside the designated scheduled visit window will be collected and transcribed to the appropriate 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 will be captured on the 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.

11.1.8 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 12.4.5 for follow-up of AEs following study exit.

Post-surgical follow up study visits are described in the protocol sections above. Once participation in the study is complete the subjects are encouraged to see their ophthalmologist for routinely scheduled standard of care visits.

11.3 Study Completion

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

11.3.1 Early Study Termination

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/IEC, 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 at each site as appropriate.

12 Primary and Secondary Safety and Effectiveness Variables

12.1 Evaluation of Safety

The primary safety endpoints will be:

- The incidence of all serious adverse events, including SSIs related to the optical properties of the IOL, in first eyes through study exit
- The rate of secondary surgical interventions due to the optical properties of the lens for first eyes through study exit
- The incidence of adverse events in first eyes compared to ISO Safety and Performance Endpoint (SPE) rates as defined in ISO 11979-7 through study exit

The secondary safety endpoints will be:

- The rates of visual disturbances reported as "severe" by subjects, as well as the rates of visual disturbances reported as "very" bothersome by subjects, using the QoV questionnaire measure through Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
- Mean photopic contrast sensitivity with glare and mesopic contrast sensitivity with and without glare at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) and Post-Operative Visit 5 (Day 330 to 420 after second eye IOL implantation)
- Incidence of the types of AEs specified in the co-primary safety endpoints, but for fellow and "all" eyes
- Incidence of all other types of adverse events in primary eyes, fellow eyes, and "all" eyes

12.2 Evaluation of Effectiveness

The primary effectiveness endpoints will be:

- Photopic monocular best-corrected distance visual acuity (BCDVA) in first eyes at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
- Photopic monocular distance-corrected near visual acuity (DCNVA) in first eyes at 40 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
- Photopic monocular distance-corrected intermediate visual acuity (DCIVA) in first eyes at 66 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)

Secondary effectiveness endpoints will be:

- Photopic binocular distance-corrected near visual acuity (DCNVA) at 40 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
- Photopic binocular uncorrected near visual acuity (UCNVA) at 40 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
- Photopic binocular distance-corrected intermediate visual acuity (DCIVA) at 66 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)

- Photopic binocular uncorrected intermediate visual acuity (UCIVA) at 66 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
- First eye BCDVA, DCNVA, and DCIVA evaluated at Visit 5

12.3 Risk Assessment, Risk Mitigation, and Anticipated Benefit

The model MX60EF IOL has similar properties to the FDA approved model MX60 IOL that has been shown to be safe for implantation in humans. [29, 30] Reduced contrast sensitivity and increased visual disturbances, such as glare and halo, are known to occur more frequently with multifocal IOLs and will be evaluated in this study through subject questionnaires and a contrast sensitivity sub-study.

The known risks of multifocal IOL implantation that exist in addition to the risks of monofocal IOL surgeries (cf. ISO standard 11979-7 Annex Table B.1) include the following:

- Under scotopic and mesopic conditions the patient has reduced contrast sensitivity, and
- There is an increased risk of post-operative photic effects such as halos and glare.

Studies on other adverse perception effects following multifocal IOL implantation, such as stereo acuity disturbances and aniseikonia, have generally indicated an acceptable performance range. [31]

Multifocal IOLs achieve correction of presbyopia by dividing incoming light into two or more focal points. Patient selection and counselling are particularly important with these IOLs. There may be a symptomatic reduction in the quality of distance vision, particularly if other ocular pathology is present. Therefore, the candidacy of patients with amblyopia or abnormalities of the cornea, optic disc, and macula for a multifocal IOL must be carefully considered. Although uncommon, explantation of multifocal IOLs may become necessary if optical side effects are intolerable. [32]

A Cochrane systematic review concluded that multifocal IOLs are effective at improving near vision relative to monofocal IOLs, although there is uncertainty as to the size of the effect. Whether that improvement outweighs the adverse effects of multifocal IOLs, such as glare and haloes, will vary between people. Motivation to achieve spectacle independence is likely to be a deciding factor. [33]

Mitigation of the risks related to undesirable optical phenomena of multifocal IOLs includes exclusion of potential subjects with ocular pathology which may limit the quality of postoperative vision such as abnormalities of the cornea, lens capsule-zonular apparatus and macula, as well as thorough discussion of the characteristics of dysphotopsia such as halos, glare and reduced contrast sensitivity during the informed consent process. As noted above, candidacy of patients for multifocal IOL implantation depends not only on objective findings during a complete ophthalmologic examination, but also on patients' motivation to achieve spectacle independence. The risks and benefits must be weighed on an individual basis by the investigator in consultation with each potential subject. Ensuring the subject's thorough understanding of the optical side-effects of multifocal IOLs and ascertaining the subject's degree of enthusiasm for spectacle independence form the basis of informed consent and risk mitigation.

Despite concern about risks of multifocal IOL implantation, the value of conducting a clinical study to support approval of a multifocal IOL is substantial in terms of assessing potential

continuing or new patient vision difficulties and possible improved near vision as well as providing another IOL option to increase potential patient satisfaction and improved near and intermediate vision while maintaining good distance vision. Prior studies of multifocal IOLs have shown a high degree of patient satisfaction, both in absolute terms and in comparison to monofocal IOLs, improved near vision, and a very low rate of IOL explantation due to optical side-effects. [33-36]

These results indicate that application of the principles of informed consent and patient selection to the risk of dysphotopsia and contrast sensitivity reduction will provide greater benefit than risk and justify the enrollment of subjects in this study of a multifocal IOL.

Another anticipated benefit which a subject may experience from participation in this study is an improvement of their vision as a result of the removal of cataracts. If the subject is randomized to receive the enVista MX60E monofocal IOL, it is expected they may have improvement in their distance vision and would then only require the use of corrective lenses (such as glasses or contact lenses) for near and intermediate vision. If a subject is randomized to receive the enVista MX60EF trifocal IOL, they may have improvement in their near and intermediate vision while maintaining distance visual acuity comparable to a monofocal IOL, possibly allowing them to be able to read, use a computer, and watch television without reading glasses or bifocals.

Further discussion of potential or actual risks during cataract surgery and with the use of multifocal or monofocal enVista IOLs as well as IOL injectors to be used in this study can also be found in the study Investigator's Brochure.

12.3.1 Risk Assessment of COVID-19 Specific Risks

New and unforeseen risks have arisen during the COVID-19 pandemic, including risk of infection and disruptions or delays in study conduct.

To reduce the risk of coronavirus transmission, careful precautions for interactions between subjects and study personnel, and study personnel and Sponsor and/or CRO staff must be taken when in contact, including following local, state, and national recommendations and guidance found at **www.aao.org/covid-19**. It is recommended Investigators periodically revisit the **aao.org/covid-19** website to identify and implement any updated recommendations made by AAO.

New risks to all study participants beyond those described in the preceding section include:

- Possible transmission of Coronavirus infection, and possible further complications (including but not limited to hospitalization and/or death), beyond the risk of adverse events due to the investigational test lens and/or procedure(s).
- Risk will be higher in an ophthalmic clinical study because of the close contact subjects will have with health care professionals during in-clinic procedures and assessments (since Investigators and post-surgical examiners must make measurements close to the face of subjects), in addition to the need for multiple follow-up visits/examinations

which will expose individuals to other study participants or patients and/or healthcare professionals who could be transmitting the virus even if they do not have symptoms.

- Potential disruptions to the study due to current or future pandemic-related emergency restrictions, such as possible disruption of the study as a result of COVID-19 control measures (e.g., quarantining of subjects or study staff) that may lead to delays in scheduled follow-up visits.
- If a subject experiences an adverse safety event (i.e., a safety complication) and they delay seeing their doctor because of COVID-19 restrictions and/or have concerns or fears about COVID-19 risk, a dangerous situation with serious permanent visual side effects including loss of vision could potentially occur. Adverse outcomes typically require subjects to return for additional and possibly frequent follow-up office visits and examinations, thus increasing COVID-19-related risks to subjects, Investigators, and study staff.
- If subjects are found to have contracted COVID-19 or feel ill with flu-like symptoms during participation in the study, they may not be permitted to continue routine scheduled study follow-up, thereby increasing the risk that diagnosis and treatment of potential adverse safety outcomes will be missed or delayed.

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 (AE) occurs, the first concern will be the safety and welfare of the subject; treatment should be provided as appropriate for the event.

12.4.1 Adverse Events Definitions

For the purposes of this study, adverse events include: all ocular AEs; 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.

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical sign (including abnormal laboratory finding) in a subject, user or other persons, whether or not related to the investigational medical device. This definition includes events related to the medical device or procedures involved. For users or other persons, this definition is restricted to events related to the study device.

A Serious Adverse Event (SAE) is an AE that leads to:

- death
- a serious deterioration in the health of the subject that either results in:
    - a life-threatening illness or injury, or
    - a permanent impairment of a body structure or body function (e.g., blindness), or
    - in-patient or prolonged hospitalization, or
    - a potentially vision-threatening condition, or
    - medical or surgical intervention to prevent life- or vision-threatening illness or injury or permanent impairment to a body structure or a body function
- fetal distress, fetal death, or a congenital abnormality or birth defect

An Adverse Device Effects (ADE) is any adverse event related to the use of an investigational medical device. This definition includes any events 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.

An Unanticipated Adverse Device Effect (UADE) is 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 is 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.

Anticipated AEs associated with cataract surgery and/or premium IOL implantation that might reasonably be expected to occur in this study are listed below and include, but are not limited to, the following:

Anterior capsule tear
Anterior uveitis (including iritis and iridocyclitis) *
Capsular block syndrome
Choroidal detachment/hemorrhage
Corneal edema *
Cystoid macular edema (CME) *
Difficulty with tasks in dim light resulting in secondary surgical intervention[1]
Elevated IOP *
Endophthalmitis (intraocular inflammation requiring vitreous tap and use of intraocular antibiotics)
Events resulting in unplanned secondary surgical intervention other than paracentesis to relieve pressure prior to 1 week postoperative or Nd:YAG capsulotomy
Flat anterior chamber
Hyphema
Hypopyon
Incorrect IOL power resulting in secondary surgical intervention *
Increased glare or halos
Infectious keratitis
IOL damage resulting in secondary surgical intervention *
IOL malposition resulting in secondary surgical intervention *
Iris or pupil damage

Loss of BCDVA[3]

Mechanical pupillary block (A shallowing of the peripheral and/or central anterior chamber with or without elevation of IOP by obstruction of the flow of aqueous humor from the posterior chamber through the pupil to the anterior chamber). This may be induced by the crystalline lens, vitreous face, or implanted devices.)

Multiple (or "ghost") images

Pain*

Posterior capsular rupture

Progression or onset of diabetic retinopathy

Progression or onset of macular degeneration

Reduced contrast sensitivity

Retained lens material

Retinal detachment (partial or complete RD associated with retinal tear)

Secondary IOL intervention (reposition, exchange or removal)

Synechiae formation

Thermal injury (phaco burn)

Toxic anterior segment syndrome (TASS) (An acute, noninfectious inflammation of the anterior segment of the eye that develops within 24 to 48 hours after surgery and is characterized by corneal edema and accumulation of white cells in the anterior chamber of the eye)

Undesirable optical phenomena assessed as severe by the Investigator (note; these events are to be treated as serious AEs; see Section 12.4.4 for reporting requirements)

Vitreous prolapse

Wound leak (positive Seidel)

* These events only need to be reported as AEs/SAEs if present as specified below:

- Iritis/cells/flare characterized by grade 1+ cells or greater using SUN criteria[37] if persistent for greater than 3 months after surgery, or relapses in less than 3 months after discontinuation of therapy, or the subject is maintained on therapy for more than 3 months to control inflammation
- Corneal or corneal wound edema resulting in BCDVA of ≤20/40 at Visit 3A or later in the first implanted eye or at Visit 3B or later in the second implanted eye, or any persistent corneal or corneal wound edema present at Visit 5
- Cystoid macular edema diagnosed by clinical exam and adjunct testing (eg. OCT, FA or other method), resulting in BCDVA of ≤ 20/40 at Visit 3 or later

[3] Monocular BCDVA decrease of equal to or greater than 2 lines (≥ 10 letters) from any previous visit not secondary to any underlying condition, or any monocular BCDVA decrease from any previous visit of ≥ 10 letters if persistent to the subject's last visit in the study.

- Difficulty with tasks in dim lighting resulting in secondary surgical intervention
- Elevation of IOP by ≥ 10 mmHg above baseline (pre-operative) to a minimum of 25 mmHg (*Masket S, et al. Special Report: The American Academy of Ophthalmology Task Force Consensus Statement on Adverse Events with Intraocular Lenses. Ophthalmology 2017;124(1):142-144)* after IOL implantation, or elevated IOP requiring treatment if present at Visit 5
- Postoperative refractive error different from predicted, and not due to calculation or other user error, resulting in secondary surgical intervention
- Crack, breakage or deformity of IOL haptic or optic resulting in secondary surgical intervention
- IOL decentration or tilt likely to affect visual outcome and resulting in secondary intervention
- Pain, per subjective patient reporting, graded as ≥ 4 on the standardized pain rating scale (from 0 to 10)
- Mild superficial punctate keratitis (SPK) present at Visit 3A or later in the first implanted eye or at Visit 3B or later in the second implanted eye, or moderate, severe, or very severe SPK at any post-operative visit (note: if SPK is present pre-operatively, adverse event must be reported only if there is a worsening)

Note: Posterior capsular opacification (PCO) is NOT to be reported as an AE, per ISO 11979-7.

<u>Severe or Very Bothersome Visual Disturbances on the Quality of Vision questionnaire</u>

Visual disturbances reported will be evaluated by the PI through further clinical investigation to determine if the reported symptoms are related to the optical properties of the IOL (Section 13.5.1.2). Any visual disturbance that leads to secondary surgical intervention should be considered a serious adverse event; however, the following conditions may lead to visual disturbance and secondary surgical intervention but may or may not be considered related to the optical properties of the IOL. Detailed case narratives will be created for each of these subjects for future analyses and final determination as to whether the AE is related to the optical properties of the IOL.

1) Residual refractive error which can be corrected with spectacles

2) Posterior capsular opacification evident on slit lamp examination

3) Macular edema confirmed by optical coherence tomography and/or fluorescein angiography

4) Corneal edema, punctate keratopathy due to dry eye syndrome or other corneal irregularities

5) Pre-existing or newly developed ocular pathologies, including those related to decentration, tilt or rotation of the IOL.

6) Surgical complications noted at the operative visit that may reasonably be expected to affect postoperative outcomes.

The investigator should consult with the Medical Monitor to determine if an SSI is warranted. If there is any uncertainty as to whether the SSI is related to the optical properties of the IOL or to some other unrelated factor, the Investigator should consult with the Medical Monitor.

12.4.2 Identification and Collection

Identification and collection of an AE begins after informed consent has been obtained and documented. Standard sources of 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 blurred vision since I started using this lens.")
- laboratory or test results that meet protocol requirements for classification as an AE

Specific to this protocol, ocular AEs in the study eye(s) and all SAEs (ocular and non-ocular) observed or elicited by the Investigator, reported by the subject, or resulting from a test result, etc., occurring during the clinical investigation must be reported in the CRF. 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 AEs but will be collected at the Preoperative Visit as medical history. A worsening of a pre-existing condition during the study should be documented as an AE and evaluated accordingly.

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)
- Optional admission not associated with a precipitating 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 determine the relationship of the event to the 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 or Surgical Procedure

- **Related**: There is at least a reasonable possibility the AE is related to the study device or surgical procedure. Reasonable possibility means there is evidence to suggest either a causal relationship or association between the study device or surgical procedure and the AE.
- **Unrelated**: There is little or no reasonable possibility the AE is related to the study device or surgical procedure. No reasonable possibility means there is no evidence to suggest either a causal relationship or association between the study device or surgical procedure and the AE.

12.4.4 Reporting

Actions required by Investigators for reporting non-serious ocular adverse events are summarized in **Table 1** below.

Table 1. Non-serious Adverse Events

Non-serious ocular AEs	Non-device-related	Device-related
Required Action	Recorded on Adverse Event CRF only; no expedited report to Sponsor; no report to IRB	

Actions required by Investigators for reporting all serious adverse events are summarized in **Table** 2 below.

Table 2. Serious Adverse Events

SAEs (ocular and non-ocular)	Non-device-related	Device-related	
		Anticipated	Unanticipated
Required Action	Recorded on SAE/UADE Report Form and AE CRF ⇩ Investigator submits expedited report to Sponsor and its representative within 48 hours; report to IRB, if required per IRB policy		Recorded on SAE/UADE Report Form and AE CRF ⇩ Investigator submits 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 or its representative reports to FDA, all IRBs & all Investigators within 10 working days

12.4.4.1 On-Site SAE and UADE Reporting

The Investigator must report any adverse event to the Sponsor and its representative in an expedited manner if it meets the criteria for a SAE or UADE. The Investigator must forward the SAE/UADE Report Form and any available supporting documents to the Sponsor or its designee within 48 hours of becoming aware of an event.

The contacts for reporting SAEs/UADEs are:

The Investigator must also report UADEs to the reviewing IRB/IEC within 10 working days following awareness of the UADE or according to the established reporting procedures of the IRB, whichever is shorter. The Investigator should also complete applicable CRFs within 3 working days of event identification. The Sponsor or its representative will report the UADE

to the FDA, all other IRBs, and all Investigators within 10 working days after first being informed by the Investigator.

12.4.4.2 Off-Site UADE Reporting

When participating in multicenter clinical investigations, Principal Investigators may receive off-site UADE reports. These are Sponsor reports of UADEs which occurred at other clinical 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/IEC within 10 working days or per their established reporting procedures, 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.

Investigators must evaluate, record, and report via applicable forms any complaints/deficiencies or malfunctions experienced with a Test or Control lens during this trial to the Sponsor and its representative promptly. The Sponsor shall review all device deficiencies, and, 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:

12.4.5 Adverse Events at Subject Exit

Ongoing AEs will be followed until resolution, no further change in the condition is expected (i.e., event stabilized), or as dictated by standard of care. Documentation in the CRF of this 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 the Investigator until the outcome is determined or until no further change in the condition is expected.

12.4.6 Pregnancy

During the study, all female subjects of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period). Female subjects who become pregnant during the study will be followed until completion of pregnancy. Every effort will be made to obtain the health status of the mother and infant or fetus (in cases of miscarriage or therapeutic abortion) at term. 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 to the Sponsor or designee within 48 hours of the investigator's awareness of the pregnancy.

The contacts for reporting pregnancies are:

13 Statistics

Additional details regarding statistical analyses will be provided in the statistical analysis plan (SAP), which will be prepared and approved prior to database lock.

13.1 Study Endpoints

13.1.1 Safety Endpoints

13.1.1.1 Primary Safety Endpoints

- The incidence of all serious adverse events, including SSIs related to the optical properties of the IOL, in first eyes through study exit
- The rate of secondary surgical interventions due to the optical properties of the lens for first eyes through study exit
- The incidence of adverse events in first eyes compared to ISO Safety and Performance Endpoint (SPE) rates as defined in ISO 11979-7 through study exit

13.1.1.2 Secondary Safety Endpoints

- The rates of visual disturbances reported as "severe" by subjects, as well as the rates of visual disturbances reported as "very" bothersome by subjects, using the QoV questionnaire measure through Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
- Mean photopic contrast sensitivity with glare and mesopic contrast sensitivity with and without glare at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) and Post-Operative Visit 5 (Day 330 to 420 after second eye IOL implantation)
- Incidence of the types of AEs specified in the co-primary endpoints, but for fellow and "all" eyes
- Incidence of all other types of adverse events in primary eyes, fellow eyes, and "all" eyes

13.1.2 Effectiveness Endpoints

13.1.2.1 Primary Effectiveness Endpoints

- Photopic monocular best-corrected distance visual acuity (BCDVA) in first eyes at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
- Photopic monocular distance-corrected near visual acuity (DCNVA) in first eyes at 40 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
- Photopic monocular distance-corrected intermediate visual acuity (DCIVA) in first eyes at 66 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)

13.1.2.2 Secondary Effectiveness Endpoints

- Photopic binocular distance-corrected near visual acuity (DCNVA) at 40 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
- Photopic binocular uncorrected near visual acuity (UCNVA) at 40 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
- Photopic binocular distance-corrected intermediate visual acuity (DCIVA) at 66 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
- Photopic binocular uncorrected intermediate visual acuity (UCIVA) at 66 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
- First eye BCDVA, DCNVA, and DCIVA evaluated at Visit 5

13.2 Hypotheses

The critical region for rejection of null hypotheses will be a p-value ≤ 0.05 unless otherwise specified.

13.2.1 Safety Endpoints

First Primary Safety Endpoint

There is no statistical hypothesis associated with the proportion of first mITT eyes with at least one serious adverse event.

Second Primary Safety Endpoint

The second primary safety endpoint is the rate of secondary surgical interventions due to the optical properties of the lens. The null and alternative hypotheses are as follows.

$$H_0: \pi_T - \pi_C \geq 0.034$$
$$H_1: \pi_T - \pi_C < 0.034$$

Where:

- π_T = the proportion of the Test (trifocal) group first eyes that underwent at least one secondary surgical intervention related to the optical properties of the IOL, and
- π_C = the proportion of the Control (monofocal) group first eyes that underwent at least one secondary surgical intervention related to the optical properties of the IOL

- 0.034 is the non-inferiority margin

Third Primary Safety Endpoint

For each ISO 11979-7 SPE grid AE, the null and alternative hypotheses are as follows:

$$H_0: \pi \leq \pi_0$$
$$H_1: \pi > \pi_0$$

Where:

- π = the proportion of Test (trifocal) eyes with the adverse event, and
- π_0 = the historical control proportion of eyes with the adverse event given in the ISO 11979-7 SPE grid

If none of the null hypotheses are rejected, then it will be concluded that the Test IOL is statistically successful in these outcomes.

First Secondary Safety Endpoint

There is no hypothesis associated with the incidence of subjects reporting rates of visual disturbances reported as "severe" by subjects, as well as the rates of visual disturbances reported as "very" bothersome by subjects, using the QoV questionnaire measure through Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation).

Second Secondary Safety Endpoint

There is no hypothesis associated with mean photopic or mesopic contrast sensitivity at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) and Post-Operative Visit 5 (Day 330 to 420 after second eye IOL implantation).

Third and Fourth Secondary Safety Endpoints

There are no hypotheses associated with these endpoints.

13.2.2 Effectiveness Endpoints

The statistical success of the trial will depend on the statistical success of all three primary effectiveness endpoints.

First Primary Effectiveness Endpoint

For the first primary effectiveness endpoint, photopic monocular logMAR BCDVA in first eyes at Post-Operative Visit 4, there are three hypotheses to be tested. The Test IOL must be successful in all three hypothesis tests to achieve success in this endpoint.

The first null (H_0) and alternative (H_1) hypotheses are as follows:

$$H_0: \mu_T - \mu_C \geq 0.10$$
$$H_1: \mu_T - \mu_C < 0.10$$

Where:

- μ_T = the mean logMAR BCDVA of the Test (trifocal) group, and
- μ_C = the mean logMAR BCDVA of the Control (monofocal) group

If the null hypothesis is rejected, then it will be concluded that the Test IOL is statistically successful in this evaluation.

The second null (H_0) and alternative (H_1) hypotheses are as follows:

$$H_0: \pi_T \geq 0.925$$
$$H_1: \pi_T < 0.925$$

Where π_T = the proportion of mITT Set Test (trifocal) group eyes with BCDVA 20/40 or better. The ISO standard specifies a nontraditional evaluation of these hypotheses, with failure to reject the null hypothesis indicating success. If the null hypothesis is not rejected, then it will be concluded that the Test IOL is statistically successful in this evaluation.

The third null (H_0) and alternative (H_1) hypotheses are as follows:

$$H_0: \pi_T \geq 0.967$$
$$H_1: \pi_T < 0.967$$

Where π_T = the proportion of Best Case Set Test (trifocal) group eyes with BCDVA 20/40 or better. The ISO standard specifies a nontraditional evaluation of these hypotheses, with failure to reject the null hypothesis indicating success. If the null hypothesis is not rejected, then it will be concluded that the Test IOL is statistically successful in this evaluation.

Second Primary Effectiveness Endpoint

For the second primary effectiveness endpoint, photopic monocular logMAR DCNVA in first eyes at Post-Operative Visit 4, the null and alternative hypotheses are as follows:

$$H_0: \mu_T = \mu_C$$
$$H_1: \mu_T \neq \mu_C$$

Where:

- μ_T = the mean logMAR DCNVA of the Test (trifocal) group, and
- μ_C = the mean logMAR DCNVA of the Control (monofocal) group

If the null hypothesis is rejected and the mean for the Test group is less than the mean for the Control group, then it will be concluded that the Test IOL is statistically successful in this outcome.

Third Primary Effectiveness Endpoint

For the third primary effectiveness endpoint, photopic monocular logMAR DCIVA in first eyes at Post-Operative Visit 4, the null and alternative hypotheses are as follows:

$$H_0: \mu_T = \mu_C$$
$$H_1: \mu_T \neq \mu_C$$

Where:

- μ_T = the mean logMAR DCIVA of the Test (trifocal) group, and
- μ_C = the mean logMAR DCIVA of the Control (monofocal) group

If the null hypothesis is rejected and the mean for the Test group is less than the mean for the Control group, then it will be concluded that the Test IOL is statistically successful in this outcome.

First Secondary Effectiveness Endpoint

For the first secondary effectiveness endpoint, photopic binocular DCNVA at Visit 4, the null and alternative hypotheses are as follows:

$$H_0: \mu_T = \mu_C$$
$$H_1: \mu_T \neq \mu_C$$

Where:

- μ_T = the mean logMAR DCNVA of the Test (trifocal) group, and
- μ_C = the mean logMAR DCNVA of the control (monofocal) group

If the Test IOL is statistically successful in all primary endpoints with success criteria, the null hypothesis is rejected, and the mean for the Test group is less than the mean for the Control group, then it will be concluded that the Test IOL is statistically successful in this outcome.

Second Secondary Effectiveness Endpoint

For the second secondary effectiveness endpoint, photopic binocular UCNVA at Visit 4, the null and alternative hypotheses are as follows:

$$H_0: \mu_T = \mu_C$$
$$H_1: \mu_T \neq \mu_C$$

Where:

- μ_T = the mean logMAR UCNVA of the Test (trifocal) group, and
- μ_C = the mean logMAR UCNVA of the control (monofocal) group

If the Test IOL is statistically successful in the first secondary effectiveness endpoint, the null hypothesis is rejected, and the mean for the Test group is less than the mean for the Control group, then it will be concluded that the Test IOL is statistically successful in this outcome.

Third Secondary Effectiveness Endpoint

For the third secondary effectiveness endpoint, photopic binocular DCIVA at Visit 4, the null and alternative hypotheses are as follows:

$$H_0: \mu_T = \mu_C$$
$$H_1: \mu_T \neq \mu_C$$

Where:

- μ_T = the mean logMAR DCIVA of the Test (trifocal) group, and
- μ_C = the mean logMAR DCIVA of the Control (monofocal) group

If the Test IOL is statistically successful in the second secondary effectiveness endpoint, the null hypothesis is rejected, and the mean for the Test group is less than the mean for the Control group, then it will be concluded that the Test IOL is statistically successful in this outcome.

Fourth Secondary Effectiveness Endpoint

For the fourth secondary effectiveness endpoint, photopic binocular UCIVA at Visit 4, the null and alternative hypotheses are as follows:

$$H_0: \mu_T = \mu_C$$
$$H_1: \mu_T \neq \mu_C$$

Where:

- μ_T = the mean logMAR UCIVA of the Test (trifocal) group, and
- μ_C = the mean logMAR UCIVA of the Control (monofocal) group

If the Test IOL is statistically successful in the third secondary effectiveness endpoint, the null hypothesis is rejected, and the mean for the Test group less than the mean for the Control group, then it will be concluded that the trifocal MIOL is statistically successful in this outcome.

Remaining Secondary Effectiveness Endpoints

There are no hypothesis tests associated with the remaining secondary effectiveness endpoints of first eye BCDVA, DCNVA, and DCIVA evaluated at Visit 5.

13.3 Sample Size Determination

13.3.1 Phase I / Pilot

A sample size of 24 DCNVA measurements at each of three distances will yield a probability of at least 98% of selecting the best distance when the difference (in logMAR units) between the best distance and the second-best distance is at least 0.1 and the data are normally distributed with a standard deviation of 0.15. The first 27 Test group subjects will be enrolled in Phase I/Pilot to allow for at least 24 Test group subjects at Visit 3A.

A sample size of 24 DCIVA measurements at each of three distances will yield a probability of at least 98% of selecting the best distance when the difference (in logMAR units) between the best distance and the second-best distance is at least 0.1 and the data are normally distributed with a standard deviation of 0.15. The first 27 Test group subjects will be enrolled in Phase I/Pilot to allow for at least 24 Test group subjects at Visit 3A.

13.3.2 Primary Safety Endpoints

Regarding the rate of all serious adverse events, for a sample size of 300 subjects, the probability of observing at least one event will be at least 95% when the probability of an event is 1% or greater.

Regarding the rate of secondary surgical interventions due to the optical properties of the lens, the expected Control group rate is 0.1% and the expected Test group rate is 0.5%. With 150 eyes in the Control group and 300 eyes in the Test group, the upper limit of the observed one-sided 95% confidence interval will be expected to be less than 0.034 with 99% power when the Control proportion, $\boldsymbol{\pi_C}$, is 0.001 and the Test expected proportion, $\boldsymbol{\pi_T}$, is 0.005; results are based on 10000 simulations using the Newcombe-Wilson score method to construct the confidence interval.[38]

ISO 11979-7 Annex B shows the relevant sample size calculations and assumptions for the ISO grid safety endpoints.

13.3.3 Secondary Safety Endpoints

Regarding the rates of visual disturbances reported as “severe” by subjects, as well as the rates of visual disturbances reported as “very” bothersome by subjects, using the QoV questionnaire measure through Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation), no statistical hypotheses will be tested. Therefore, no sample size calculation is required.

Regarding mean photopic (with glare) and mesopic (with and without glare) contrast sensitivity at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) and Post-Operative Visit 5 (Day 330 to 420 after second eye IOL implantation), no statistical hypotheses will be tested. Therefore, no sample size calculation is required.

Regarding the incidence of the types of AEs specified in the co-primary safety endpoints, but for fellow and "all" eyes, no statistical hypotheses will be tested. Therefore, no sample size calculation is required.

Regarding the incidence of all other types of adverse events in primary eyes, fellow eyes, and "all" eyes, no statistical hypotheses will be tested. Therefore, no sample size calculation is required.

13.3.4 Primary Effectiveness Endpoints

Approximately the first 24 evaluable Test group subjects and 12 evaluable Control group subjects will be excluded from the near and intermediate visual acuity hypothesis tests, leaving an expected evaluable sample size of approximately 276 Test group subjects and 138 Control group subjects to be included in the near and intermediate visual acuity hypothesis tests.

Regarding the non-inferiority test of BCDVA, when the sample sizes in the groups are 300 (Group 1) and 150 (Group 2), a two group 0.050 one-sided t-test will have 99% power to reject the null hypothesis that the Test and Control IOLs are not equivalent (the difference in means, $\mu_T - \mu_S$, is 0.10 or farther from zero in the same direction) in favor of the alternative hypothesis that the means of the two groups are equivalent, assuming that the expected difference in means is 0.00 and the common standard deviation is 0.15.

Regarding the comparisons of BCDVA to the ISO grid, ISO 11979-7 specifies a sample size of approximately 300 completed subjects for this type of investigation.

Regarding the superiority tests of DCNVA at 40 cm and DCIVA and 66 cm, a two-group t-test with a 0.05 two-sided significance level will have 99% power to detect a difference in means of -0.10, assuming that the common standard deviation is 0.15, when the sample sizes in the two groups are 276 and 138 subjects, respectively (a total sample size of 414 subjects).

Regarding the assessment of clinical superiority in DCNVA at 40 cm and DCIVA at 66 cm, the probability that the Test group's mean logMAR VA will be at least 0.10 units less than the Control group's mean logMAR VA will be 89% if the true difference is -0.12 units, 97% if the true difference is -0.13 units, and 99% if the true difference is -0.14 units, assuming that the common standard deviation is 0.15 when the sample sizes in the two groups are 276 and 138 subjects, respectively (a total sample size of 414 subjects).

13.3.5 Secondary Effectiveness Endpoints

Secondary effectiveness endpoint hypotheses will be tested hierarchically in the order: DCNVA, UCNVA, DCIVA, and UCIVA. Approximately the first 24 evaluable Test group (Group 1) subjects and 12 evaluable Control group (Group 2) subjects will be excluded from the near and intermediate visual acuity hypothesis tests, leaving an expected evaluable sample size of approximately 276 Test group subjects and 138 Control group subjects to be included in the near and intermediate visual acuity hypothesis tests.

Regarding photopic binocular distance-corrected near visual acuity (DCNVA) at 40 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation), a two-group t-test

with a 0.05 two-sided significance level will have 99% power to detect a difference in means of -0.10 logMAR units, assuming that the common standard deviation is 0.200 units, when the sample sizes in the two groups are 276 and 138 subjects, respectively (a total sample size of 414 subjects).

Regarding photopic binocular uncorrected near visual acuity (UCNVA) at 40 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation), a two-group t-test with a 0.05 two-sided significance level will have 99% power to detect a difference in means of -0.10 logMAR units, assuming that the common standard deviation is 0.20 units, when the sample sizes in the two groups are 276 and 138 subjects, respectively (a total sample size of 414 subjects).

Regarding photopic binocular distance-corrected intermediate visual acuity (DCIVA) at 66 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation), a two group t-test with a 0.05 two-sided significance level will have 99% power to detect a difference in means of -0.10 logMAR units, assuming that the common standard deviation is 0.15 units, when the sample sizes in the two groups are 276 and 138 subjects, respectively (a total sample size of 414 subjects).

Regarding photopic binocular uncorrected intermediate visual acuity (UCIVA) at 66 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation), a two group t-test with a 0.05 two-sided significance level will have 99% power to detect a difference in means of -0.10 logMAR units, assuming that the common standard deviation is 0.20 units, when the sample sizes in the two groups are 276 and 138 subjects, respectively (a total sample size of 414 subjects).

There are no hypothesis tests associated with first eye BCDVA, DCNVA, and DCIVA evaluated at Visit 5, so no sample size calculations are necessary for these endpoints.

13.3.6 Sub-Studies

13.3.6.1 Defocus Curves

At least ten (10) Best Case Group 1 subjects and ten (10) Best Case Group 2 subjects will be evaluated to obtain defocus curves as described in Appendix B, Section 10.0, in each of the following pupil size groups: small (≤ 3.0 mm), medium (> 3.0 mm and ≤ 4.0 mm), and large (> 4.0 mm), as determined under photopic lighting conditions. If ten subjects are not available in any pupil size category for a treatment group, then the maximum number available will be used.

13.3.6.2 Contrast Sensitivity

At least approximately 122 bilaterally implanted Group 1 subjects and 61 bilaterally implanted Group 2 subjects will participate in the contrast sensitivity sub-study. To allow for losses of up to 10%, at least approximately 136 Best Case Group 1 subjects and 68 Best Case Group 2 subjects will be enrolled in the sub-study.

13.3.6.3 Optical Coherence Tomography (OCT) Imaging

Approximately 20 Group 1 subjects and 10 Group 2 subjects will participate in OCT imaging at 2-3 clinical sites having similar or identical OCT equipment. Fundus photographs will be taken if OCT images cannot be obtained.

13.3.6.4 Trial Frame Astigmatism Simulation

Approximately 30 Group 1 subjects and 15 Group 2 subjects will participate in the trial frame astigmatism sub-study at up to 10 clinical sites. A total of 50 subjects will be enrolled in the sub-study to allow for a 10% loss. Enrollment will be sequential with consecutive subjects enrolled onto the Trial Frame astigmatism simulation sub-study at each site in order of their completion of post-operative Visit 5 and based on their eligibility. The purpose of the Trial Frame Astigmatism Simulation sub-study is to evaluate the effect of simulated residual astigmatism on distance, intermediate, and near visual acuities in eyes implanted with the enVista trifocal toric intraocular lenses (IOLs).

13.3.7 Overall Sample Size and Adjustment for Dropouts

The sample size of 300 study lens group subjects and 150 control group subjects is specified in ANSI Z80.12-2007 (R2012) and ISO 11979-9:2006. Moreover, ISO 11979-7 specifies that a minimum of 300 subjects should complete a clinical evaluation of an IOL.

To allow for losses of up to 10%, approximately $\lceil 300/(1-0.1) \rceil = 334$ Test group subjects and approximately $\lceil 150/(1-0.1) \rceil = 167$ Control group subjects will be enrolled.

13.4 Analysis Populations

13.4.1 Intent-to-Treat (ITT) Set

The Intent-to-Treat Set will include all randomized subjects. Summaries and analyses of the ITT Set will classify subjects according to the treatment to which they were randomized.

13.4.2 Modified Intent-to-Treat Set

The Modified Intent-to-Treat Set will include all randomized subjects with at least one eye in which the IOL touches the eye with a study lens. Summaries and analyses of the mITT Set will classify subjects according to the treatment to which they were randomized.

13.4.3 Modified Safety Set

The Modified Safety Set will include all subjects with at least one eye in which the IOL touches the eye with a study lens. Summaries and analyses of the Modified Safety Set will classify subjects according to the treatment received.

13.4.4 Per Protocol Set

The Per Protocol (PP) Set will include all bilaterally implanted subjects without major protocol deviations. Major protocol deviations are described in Section 13.5.8.

13.4.5 Best Case Set

The purpose of the Best Case Set is to evaluate BCDVA as a part of the primary safety analysis as described in ISO 11979-7. The Best Case Set will include subjects with all of the following characteristics:

- No clinically significant preoperative ocular pathology in the first eye, including any of the following present prior to the operative visit
  - Pseudoexfoliation
  - Glaucoma
  - Uveitis
  - Retinal detachment
  - Diabetic retinopathy
  - Macular degeneration
  - Amblyopia
  - Other preoperative pathologies that are likely to affect central acuity
- No macular degeneration detected at any time in the first eye
- No previous surgery for the correction of refractive errors in the first eye

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.

All effectiveness analyses will be presented for the ITT Set in addition to the analysis Set(s) mentioned below.

13.5.1 Primary Safety Analyses

13.5.1.1 First Eyes with at Least One Serious Adverse Event

The proportion of first mITT Set eyes with at least one serious adverse event will be summarized using categorical summary statistics by treatment received. Each eye will be counted only once in the calculation of the rate.

13.5.1.2 Secondary Surgical Interventions Related to the Optical Properties of the IOL

Secondary surgical interventions related to the optical properties of the IOL will be defined as IOL explantation, replacement, or repositioning due to subject intolerance of visual symptoms not adequately improved by spectacle correction. The investigators will apply this definition to classify each secondary surgical intervention as either related to the optical properties of the IOL or not related to the optical properties of the IOL.

Each eye will be classified as either having undergone a secondary surgical intervention related to the optical properties of the IOL or not having undergone such an intervention. Missing data will not be imputed. Secondary surgical interventions related to the optical properties of the IOL will be summarized categorically (Yes, No) by actual treatment received for mITT

subjects in a table. Secondary surgical interventions will be further subcategorized and summarized categorically as Exchange, Removal, Repositioning, or Other.

A two-sided 90% confidence interval around the difference in proportions (Test minus Control) will be constructed using the Newcombe-Wilson score method without continuity correction. If the upper confidence limit (which is equivalent to a one-sided 95% upper confidence limit) is less than 0.034 or if the proportion in both groups is zero, then the null hypothesis will be rejected and it will be concluded that the Test IOL is statistically non-inferior to the Control IOL in this outcome.

13.5.1.3 ISO Grid Adverse Events

Cumulative and persistent ISO grid AEs will be summarized categorically for first eyes of the mITT Set by treatment. Subjects will be analyzed according to treatment actually received. The primary statistical analysis will include first eyes of the mITT Set implanted with the Test IOL.

The numerator for each cumulative AE will be the number of first Test group eyes reporting the AE at least once after surgery. The denominator for cumulative AEs will be the number of first Test group eyes.

The numerator for each persistent AE will be the number of first Test group eyes with the event at Visit 5 in the first eye at exit. The denominator for persistent AEs will be the number of first Test group eyes present at Visit 5.

For each ISO grid AE, a one-sided exact binomial test comparing the proportion of Test group eyes with the AE to the relevant control rate will be completed. If the resulting p-value is less than or equal to 0.05, then the null hypothesis will be rejected.

Success with respect to comparing these endpoints to the historical controls will have been achieved if none of the null hypotheses are rejected for the Test IOL treatment group.

13.5.2 Secondary Safety Analyses

13.5.2.1 Rates of Severe or Very Bothersome Visual Disturbances

The rates of visual disturbances reported as “severe” by subjects, as well as the rates of visual disturbances reported as “very” bothersome by subjects, using the QoV questionnaire measure through Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) will be summarized categorically by treatment received for Modified Safety Set subjects. Each subject will be counted only once in the calculation of the rate.

13.5.2.2 Contrast Sensitivity

Mean photopic (with glare) and mesopic (with and without glare) contrast sensitivity at Post-Operative Visits 4 or 5 will be summarized using continuous summary statistics by lighting condition, spatial frequency, treatment group, and visit. Estimates of the differences between treatment groups, with two-sided 95% confidence intervals, will be provided by lighting condition and spatial frequency.

13.5.2.3 Incidence of the Types of AEs Specified in the Co-primary Safety Endpoints

The incidence of the type of AE specified in each co-primary safety endpoint will be summarized by treatment for fellow and "all" eyes. No hypothesis tests will be conducted.

13.5.2.4 Incidence of All Other Types of Ocular AEs

The incidence of all other types of AEs will be summarized by treatment for primary eyes, fellow eyes, and "all" eyes for the mITT Set. No hypothesis tests will be conducted.

13.5.3 Primary Effectiveness Analyses

13.5.3.1 Photopic Monocular BCDVA

Photopic monocular BCDVA in first eyes will be assessed at Post-Operative Visit 4 using the methods described in Appendix B on Methods of Clinical Evaluation. The total number of letters correct will be entered into the electronic case report form.

The number of letters correct will be converted to logMAR units using the following equation:

$$logMAR\ BCDVA = 1.7 - 0.02 \times letters\ correct$$

Photopic monocular logMAR BCDVA in first implanted eyes at Post-Operative Visit 4 will be summarized using continuous summary statistics by treatment group for the mITT Set. Imputation of missing data is not conservative in non-inferiority testing. Therefore, missing data will not be imputed for the BCDVA non-inferiority test. A statistical model will be constructed with BCDVA as the dependent variable and treatment and site as fixed factors. The treatment effect (least squares mean Test group IOL VA minus least squares mean Control group IOL VA) in logMAR units will be estimated in addition to a two-sided 90% confidence interval. If the upper confidence limit (equivalent to a one-sided upper 95% confidence limit for the treatment effect) is less than 0.1, then the Test lens will be statistically non-inferior to the control lens.

The previous continuous summary statistics will also be provided for the Per Protocol Set. However, non-inferiority will not be evaluated with the PP Set and statistical success will not depend upon the results of the PP analysis.

BCDVA at Visit 4 for the Test group will be summarized categorically (20/20 or better, 20/25 or better, 20/32 or better, 20/40 or better, and worse than 20/40) for the mITT and Best Case Sets. Two-sided exact binomial 90% confidence intervals around the proportions of eyes 20/40

or better will be presented. Categorical summaries will use whole line binning as shown in the following logMAR to Snellen conversion table (Table 3):

Table 3. logMAR to Snellen Conversion Table

logMAR Value	Snellen Value
≤ 0.00	20/20 or better
≤ 0.10	20/25 or better
≤ 0.20	20/32 or better
≤ 0.30	20/40 or better
> 0.30	Worse than 20/40

For the analyses of the mITT and Best Case Sets, one-sided exact binomial tests comparing the proportion of Multifocal IOL eyes with BCDVA 20/40 or better to the relevant control rate (92.5% for all eyes and 96.7% for best case eyes) will be performed and p-values will be presented. If the p-value is less than or equal to 0.05, then the null hypothesis will be rejected.

If the null hypothesis is not rejected for the mITT and Best Case Sets in the primary analyses, then it will be concluded that the Multifocal IOL is statistically successful in this outcome.

13.5.3.2 Photopic Monocular DCNVA

Photopic monocular distance-corrected near visual acuity (DCNVA) at 40 cm in first eyes at Post-Operative Visit 4 will be summarized using continuous summary statistics in logMAR units by treatment assignment for the mITT Set Phase II and III subjects (combined). The DCNVA best distance data from the Phase I/Pilot subjects will be excluded from hypothesis testing and will be summarized separately from the data of the other subjects.

If there are missing mITT analysis set monocular DCNVA data at Visit 4, then missing data will be imputed using the Markov chain Monte Carlo (MCMC) multiple imputation method. After imputation of missing data, the statistical hypotheses will be tested using a statistical model with treatment and site as fixed factors by imputation.

An overall p-value resulting from the multiple imputation method will be estimated. The treatment effect (mean Test group IOL VA minus mean Control group IOL VA) in logMAR units will be summarized using continuous summary statistics and a two-sided 95% confidence interval. If the p-value from the multiple imputation analysis is less than or equal to 0.05 and the treatment effect is less than or equal to -0.20 (i.e., the Test lens mean logMAR VA is at least 0.20 less than the mean for the control), then it will be concluded that the Test IOL is statistically and clinically successful (i.e., superior to the Control IOL) in this outcome.

The previous continuous summary statistics will also be provided for the Per Protocol Set. However, superiority will not be evaluated with the PP Set and statistical success will not depend upon the results of the PP analysis.

13.5.3.3 Photopic Monocular DCIVA

Photopic monocular distance-corrected intermediate visual acuity (DCIVA) at 66 cm in first eyes at Post-Operative Visit 4 will be converted from letters correct to logMAR units using the method described above for BCDVA and summarized using continuous summary statistics in logMAR units by treatment assignment for the mITT Set Phase II and III subjects (combined). The DCIVA data from the Phase I/Pilot subjects will be excluded from hypothesis testing and will be summarized separately from the data of the other subjects.

If there are missing mITT analysis set monocular DCIVA data at Visit 4, then missing data will be imputed using the MCMC multiple imputation method. After imputation of missing data, the statistical hypotheses will be tested using a statistical model with treatment and site as fixed factors by imputation.

An overall p-value resulting from the multiple imputation method will be estimated. The treatment effect (mean Test group IOL VA minus mean Control group IOL VA) in logMAR units will be summarized using continuous summary statistics and a two-sided 95% confidence interval. If the p-value from the multiple imputation analysis is less than or equal to 0.05 and the treatment effect is less than or equal to -0.10 (i.e. the Test lens mean logMAR VA is at least 0.10 less than the mean for the control), then it will be concluded that the Test IOL is statistically and clinically successful (i.e., superior to control) in this outcome.

The previous continuous summary statistics will also be provided for the Per Protocol Set. However, superiority will not be evaluated with the PP Set and statistical success will not depend upon the results of the PP analysis

13.5.4 Secondary Effectiveness Analyses

Photopic binocular DCNVA, UCNVA, DCIVA, and UCIVA at Post-Operative Visit 4 will be converted from letters correct to logMAR units and compared between treatments using the methods described above for DCNVA and DCIVA. The near and intermediate VA data from Phase I/Pilot subjects will be excluded from near and intermediate VA hypothesis testing and will be summarized separately from the near and intermediate VA data of the other subjects. The endpoints will be evaluated hierarchically in the following order: DCNVA, UCNVA, DCIVA, and UCIVA.

First eye BCDVA, DCNVA, and DCIVA (all in logMAR units) at Visit 5 will be summarized using descriptive statistics (mean, standard deviation, minimum, and maximum) for the ITT Set by treatment group (MX60EF Trifocal MIOL, MX60E IOL). The means at Visit 5 for each of these outcomes will be compared between the treatment groups qualitatively.

13.5.5 Other Analyses

13.5.5.1 Clarity of Fundus Visualization

Clarity of fundus visualization will be presented using categorical summary statistics by treatment for the mITT Set.

13.5.5.2 Adverse Events

mITT Set eyes experiencing each type of adverse event at least once will be summarized categorically by treatment group. In addition, categorical summary statistics will be provided for each AE type by relationship to the study device, by relationship to surgical procedure, and by severity.

The incidence of the following further defined AEs will be summarized categorically by treatment group.

- Endophthalmitis - intraocular inflammation requiring vitreous tap and use of intraocular antibiotics
- Toxic anterior segment syndrome (TASS) - An acute, noninfectious inflammation of the anterior segment of the eye that develops within 24 to 48 hours after surgery and is characterized by corneal edema and accumulation of white cells in the anterior chamber of the eye
- Mechanical pupillary block - Mechanical pupillary block represents a shallowing of the peripheral and/or central anterior chamber with or without elevation of intraocular pressure (IOP) by obstruction of the flow of aqueous humor from the posterior chamber through the pupil to the anterior chamber. This may be induced by the crystalline lens, vitreous face, or implanted devices
- Chronic anterior uveitis - anterior segment inflammation characterized by grade 1+ cell or greater (using the SUN criteria)[31] persistent for greater than 3 months after surgery, or relapses in less than 3 months after discontinuation of therapy, or the subject is maintained on therapy for more than 3 months to control inflammation
- Corneal edema - Corneal swelling (stromal or epithelial) resulting in BCDVA of 20/40 or worse, at ≥1 month postoperatively
- Rhegmatogenous retinal detachment (RD) – partial or complete RD associated with retinal tear
- Increased IOP - Elevation of IOP > 10 mmHg above the baseline and to a minimum of 25mmHg
- Clinically significant cystoid macular edema - Macular edema diagnosed by clinical exam and adjunct testing (e.g., OCT, fluorescein angiography or other method) and which results in reduced BCDVA to 20/40 or worse at Visit 3A for the first eye or Visit 3B for the second eye or later

13.5.5.3 Subject Questionnaires

Results of the quality of vision questionnaire and domain scores will be presented using descriptive statistics by treatment group and visit, and no comparison will be made between treatment groups. Data from the near activity vision questionnaire will be presented in a listing.

13.5.5.4 Trial Frame Astigmatism Simulation

The following will be summarized by treatment group using the sample size, mean, standard deviation, minimum, first through third quartiles, and maximum.

- logMAR VA for each assess combination of distance (40 cm, 66 cm, 4 m), cylinder power (0 D, +1.00 D, +1.50 D, +2.00 D) and axis (90 degrees, 180 degrees)
- The within-eye difference in logMAR VA between without astigmatic correction (0.00 D cylinder power) and with astigmatic correction, for each combination of distance, non-zero cylinder power, and axis

13.5.5.5 Additional Outcomes

The following additional outcomes will be presented through the use of descriptive statistics and compared between treatment arms:

- All categories of uncorrected visual acuities, by visit
- All mesopic visual acuities, by visit
- The distribution of grades of anterior chamber cells and flare, by visit
- All cases of prolonged use of anti-inflammatory medication beyond 6 weeks

The following safety analyses will also be performed:

- subject-by-subject analysis of reasons why subject failed to achieve 0.3 logMAR visual acuity
- rate of visual acuity decreases of 10 letters or more on an early treatment of diabetic retinopathy study (EDTRS) chart (or equivalent) between a form evaluation and a later form evaluation with the cause of the visual acuity decrease described in each case. Cases of such visual acuity loss will be identified programmatically from the visual acuity data rather than from the CRF question about 10 letter drops.
- Posterior capsular opacification grades and rates of posterior capsulotomies.

13.5.5.6 Additional Analyses

The accuracy of the preliminary A-constant used in the study will be assessed in a post-hoc analysis to be included in a premarket approval supplement.

Any additional supportive safety or effectiveness analyses will be described in the SAP.

13.5.6 Subject Disposition

Enrollment status will be summarized in a table by investigator and overall for the mITT analysis set. The number of randomized subjects will be summarized as well as the number and percentage of subjects that completed the entire trial, discontinued before implant, discontinued after the first implant but before the second surgery, and discontinued after the second surgery. In addition, for those subjects that did not complete the entire trial, the reason(s) for discontinuation will be summarized.

Subject and eye accountability at each visit will be summarized for the ITT, mITT, PP, and Best Case Sets in tables. The subject and eye accountability tables for the mITT Set will also be stratified by investigator and by treatment assignment.

Subjects and eyes in the ITT, mITT, PP, and Best Case analysis sets will be summarized categorically by treatment and overall.

13.5.7 Demographics and Baseline Characteristics

Race, sex, ethnicity, and age will be presented by treatment group and overall in a table using discrete summary statistics. Age will also be presented using continuous summary statistics by treatment group.

13.5.8 Protocol Deviations

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

A major protocol deviation will be defined as a deviation that is expected to impact the key safety or effectiveness outcomes, or which has an effect on subject safety.

13.5.9 Interim Analyses

After IOL implantation for Phase I/Pilot subjects, enrollment will pause until the Phase I/Pilot subjects have completed Visit 3B (30 to 60 days after second eye IOL implantation) and their data have been reviewed. A snapshot of DCNVA and DCIVA data will be obtained. Data listings and/or summaries of Test lens DCNVA and DCIVA data will be prepared by an unmasked statistician and presented for review by an unmasked clinical reviewer not associated with the study, and the best distances for near and intermediate VA testing will be determined. Safety data will also be prepared by an unmasked statistician and presented for review by an unmasked clinical reviewer not associated with the study. Phase I safety and VA data will be submitted to the FDA for review and acceptance to initiate Phase II. Statistical comparisons between Group 1 and Group 2 will not be made or evaluated. The decision to proceed or not to proceed to Phase II will not be based on formal statistical stopping rules.

When a minimum of 50 Phase I and Phase II Group 1 subjects have been enrolled and followed through Visit 4, summaries and/or listings of all available safety data through Visit 4 will be prepared by an unmasked statistical team. Aggregated safety data for the minimum first 50 Phase I and Phase II Group 1 subjects who complete Visit 4 for these subjects will be presented to the FDA to request expansion to Phase III. Safety data for approximately the corresponding minimum first 25 Phase I and Phase II Group 2 subjects who complete Visit 4 also will be submitted concurrently to the FDA. While safety data submission and FDA review for these subjects is occurring, additional subjects may be enrolled up to a maximum of approximately 72 Phase II subjects (including those whose data were submitted to FDA). Statistical comparisons between Group 1 and Group 2 will not be made or evaluated. The decision to proceed or not to proceed to Phase III will not be based on formal statistical stopping rules. Phase III enrollment will be initiated only after acceptance to proceed is received from FDA.

13.6 Additional Statistical Considerations

13.6.1 Handling of Missing Data

Imputation of missing primary endpoint data is described in Section 13.5.3 above. Unless otherwise specified in the SAP, missing data will not be imputed.

13.6.2 Multicenter Issues

Randomization will be stratified by site.

Consistency of treatment effects across sites will be evaluated using statistical methods that will be described in the SAP. A p-value less than or equal to 0.15 for treatment by site interactions will be considered statistically significant.

13.6.3 Multiplicity Issues

As all primary safety and effectiveness endpoints with success criteria described in Section 13.1 are required to demonstrate statistical success, adjustment for multiplicity is not necessary for these endpoints.

Statistical testing of the secondary endpoints with success criteria will not be evaluated for success unless all primary endpoints with success criteria are met. Primary and secondary endpoints without success criteria will not affect the evaluation of secondary endpoints with success criteria. The secondary endpoint hypotheses will be evaluated hierarchically; therefore, adjustment for multiplicity is also not necessary for these endpoints.

Any statistical tests of endpoints that are not primary or secondary endpoints will be considered exploratory and will not be adjusted for multiplicity.

13.6.4 Visit Windows

Only in-window visit data will be included in the analysis of a scheduled visit's data. All adverse events will be included in the safety analysis even if occurring or reported outside of scheduled visit windows. If a scheduled visit is completed outside of the prescribed visit window, then the visit and its window will be handled as follows:

- The out-of-window scheduled visit will be reclassified as an interim (unscheduled) visit.
- If one or more unscheduled visits occurred in the window, then the unscheduled visit that occurred closest to the center of the visit window will be reclassified as the in-window (scheduled) visit.
- If two unscheduled visits occurred in the visit window, are the closest visits to its center, and are equidistant from its center, then the later of the two visits will be reclassified as the in-window (scheduled) visit.

Each summary of unscheduled visit data will display the mean, standard deviation, median, minimum, and maximum of the absolute value of days outside of the visit windows that the summarized data were collected.

13.6.5 Management of Bias

Potential bias will be managed by randomization of subjects to treatment groups and by masking of examiners performing postoperative refractions and visual acuity testing.

Randomization will be completed using a computer system so that subjects' treatment assignments cannot be revealed prematurely. Each subject will be randomized independently, and no randomization result will be reassigned to another subject. This process should ensure there is no systematic bias in baseline characteristics, thus producing groups comparable in known and unknown potential confounding factors. The Berger-Exner test will be used to evaluate potential selection bias.

The masking of subjects and postoperative examiners described in Section 9.2 of this document will remain in effect throughout the trial. Mean logMAR DCNVA and DCIVA by site and treatment, along with the difference in means between the test and control groups by site, will be examined to determine whether any site had an unusually large or small treatment effect.

13.6.6 Management of Potential Confounding Factors

Randomization will be stratified by site. Site will be included in the statistical models for the analyses of continuous primary endpoints.

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. During the COVID-19 pandemic, when access to study site locations may be restricted, remote monitoring methods may be implemented to ensure data quality and integrity, as per the monitoring plan.

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.

Monitoring visits and telephone consultations will occur as necessary, as 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; 21 CFR Parts 11, 50, 54, 56, and 812; ISO 14155 (2020 E) Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice; ISO 11979-7:2006/Amd.1:2012(E) Ophthalmic implants — Intraocular lenses — Part 7; ISO 11979-9: 2006/Amd 1:2014 Ophthalmic implants — Intraocular lenses — Part 9; ANSI Z80.12-2007 (R2012), 42 USC 282(j); and IRB/IEC requirements
- The integrity of the data, including adequate study documentation
- The facilities remain acceptable

- The Investigator and site personnel remain qualified and able to conduct the study
- Test article accountability

During the study, if the Sponsor (or designee) determines that an Investigator is non-compliant with the study plan and/or applicable regulatory requirements, the Sponsor (or designee) will take remediation action to secure compliance. In addition, the Sponsor may terminate the Investigator's participation in the study, if appropriate, if the Investigator remains non-compliant despite the remediation 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 not to 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 Report 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 developed as part of the electronic data capture method utilized in this study.

Subject data required by this protocol are to be recorded on CRFs. The Investigator and his/her study site personnel will be responsible for completing the CRFs in a timely manner. The Investigator is required to verify that all of the requested information is accurately recorded on the CRFs. All information requested on the CRFs 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 CRFs must be traceable to source documents.

The study monitor will be responsible for reviewing and verifying the data recorded on the CRFs utilizing the original or certified copies of all source documentation and querying discrepant findings

The Investigator and study site personnel will be responsible for answering all queries in a timely manner.

14.4 Recording of Data and Retention of Documents

Subject data recorded on CRFs during the study will be documented in a coded fashion. The subject will only be identified by the unique subject number. Confidentiality of subject records must be maintained to ensure adherence to applicable local privacy regulations. Data entry information and guidelines are found in the Study Reference Manual.

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/IEC approvals for the study protocol, all amendments, ICF(s), and advertisements
- IRB/IEC annual study review
- IRB/IEC 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 CRO
- Any other documents relevant to the conduct of the study

In the event the Investigator withdraws from the study (e.g., retirement or relocation), study records will be transferred to a mutually agreed upon designee (e.g., another Investigator or the site IRB/IEC). 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 (SOPs) to evaluate compliance with the principles of GCP may take place. A regulatory authority also may wish to conduct an inspection during the study or after its completion. If an inspection is requested by a regulatory authority and/or IRB/IEC, 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 ISO 14155. 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 IRB/IEC prior to enrollment of participants in the study. Prior to initiation of the study and release of test articles to a clinical site, the Sponsor or its designee will receive documentation of the IRB/IEC approval, which specifically identifies the approved study/protocol and a list of the IRB/IEC committee members. Protocol amendments will be reviewed and approved by the IRB/IEC prior to implementation of any changes made to the study design in the amendment.

Investigators will submit progress reports to the IRB/IEC in accordance with the IRB/IEC requirements.

15.1 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol and ISO 14155, 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 his/her participation in the study, 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 his/her institution IRB/IEC, or, if not using his/her institution's IRB/IEC, by the reviewing central IRB/IEC prior to entering any subjects in the study. Documentation of IRB/IEC approval of the study protocol and informed consent must be provided to the Sponsor and any designee prior to initiation of the study. In addition, the Investigator must ensure that the reviewing IRB/IEC has provided approval for any protocol amendments prior to their 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/IEC prior to its 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/her 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 includes 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 informed consent form will be signed before the performance of any study-related activity.

15.4 Financial Disclosure, Clinical Trial Agreements, and Site Contact Information

An original financial disclosure Form (FDF) must be completed, signed and dated by the PI and any sub-investigators and study personnel listed on the Delegation of Authority Log. All FDFs will be collected by the Sponsor or its designee and filed in the study Trial Master File. A copy of all FDFs will be retained in the Investigator Site Binder. All contractual and financial agreements between clinical sites and the Sponsor will be administrated by the CRO as designated by the Sponsor and approved at a minimum by both Investigators and the

Sponsor in writing. Indemnification information is included in contractual agreements with sites.

A listing of site contact information is provided with the Study Reference Manual.

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 any publication or presentation, a copy of the final text should be forwarded by the Investigator(s) to the Sponsor or its designee, for comment. 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

Examination	Pre-Op 0A/B (Both Eyes)	Operative 00A (1st Eye)	Post-Op 1A (1st Eye)	Post-Op 2A[a] (1st Eye)	Post-Op 3A (1st Eye)	Operative 00B (2nd Eye)	Post-Op 1B (2nd Eye)	Post-Op 2B (2nd Eye)	Post-Op 3B (2nd Eye)	Post-Op 4 (Both Eyes)	Post-Op 5 (Both Eyes)	For sub-study only: Post-Op 6 (Both eyes)
	Day -30 to -5	Day 0	Day 1 to 2	Day 7 to 14	Day 30 to 60	Day 7 to 30	Day 1 to 2 Post Visit 00B	Day 7 to 14 Post Visit 00B	Day 30 to 60 Post Visit 00B	Day 120 to 180 Post Visit 00B	Day 330 to 420 Post Visit 00B	Day 2- 30 post Visit 5
Informed Consent	X										X[o]	
Demographics	X											
Ocular and Non-Ocular Medical History	X											
Inclusion/Exclusion	X	X[b]				X[b]						X[p]
Subject Questionnaires[c]	X									X		
Potential Visual Acuity	X											
Corneal Topography	X											
Targeted Refraction / IOL Power Calculation / Axial Length Determination/Anterior Chamber Depth	X											
Chord length μ	X									X	X	
Keratometry	X				X				X	X	X	

Examination	Pre-Op 0A/B (Both Eyes)	Operative 00A (1st Eye)	Post-Op 1A (1st Eye)	Post-Op 2A[a] (1st Eye)	Post-Op 3A (1st Eye)	Operative 00B (2nd Eye)	Post-Op 1B (2nd Eye)	Post-Op 2B (2nd Eye)	Post-Op 3B (2nd Eye)	Post-Op 4 (Both Eyes)	Post-Op 5 (Both Eyes)	For sub-study only: Post-Op 6 (Both eyes)
	Day -30 to -5	Day 0	Day 1 to 2	Day 7 to 14	Day 30 to 60	Day 7 to 30	Day 1 to 2 Post Visit 00B	Day 7 to 14 Post Visit 00B	Day 30 to 60 Post Visit 00B	Day 120 to 180 Post Visit 00B	Day 330 to 420 Post Visit 00B	Day 2- 30 post Visit 5
Manifest Refraction (ETDRS)	X			X	X			X[d]	X[d]	X	X	
Randomization		X										
Operative Procedures		X				X						
Photopic Pupil Size	X								X[d]	X		
Mesopic Pupil Size	X									X		
UCDVA – photopic, monocular (ETDRS)	X		X	X	X		X	X	X	X	X	
UCDVA- photopic, binocular (ETDRS)								X	X	X	X	
BCDVA – photopic, monocular (ETDRS)	X			X	X			X	X	X	X	
BCDVA – photopic, binocular (ETDRS)								X	X	X	X	
UCNVA[e,f] – photopic, monocular					X				X	X	X	
UCNVA[e,f] – photopic, binocular									X	X	X	
DCNVA[e]– photopic, monocular					X[g]				X[f]	X[f]	X[f]	

Examination	Pre-Op 0A/B (Both Eyes)	Operative 00A (1st Eye)	Post-Op 1A (1st Eye)	Post-Op 2A[a] (1st Eye)	Post-Op 3A (1st Eye)	Operative 00B (2nd Eye)	Post-Op 1B (2nd Eye)	Post-Op 2B (2nd Eye)	Post-Op 3B (2nd Eye)	Post-Op 4 (Both Eyes)	Post-Op 5 (Both Eyes)	For sub-study only: Post-Op 6 (Both eyes)
	Day -30 to -5	Day 0	Day 1 to 2	Day 7 to 14	Day 30 to 60	Day 7 to 30	Day 1 to 2 Post Visit 00B	Day 7 to 14 Post Visit 00B	Day 30 to 60 Post Visit 00B	Day 120 to 180 Post Visit 00B	Day 330 to 420 Post Visit 00B	Day 2- 30 post Visit 5
DCNVA[e,f] – photopic, binocular										X	X	
DCNVA[e,f] – mesopic, monocular					X				X	X	X	
DCNVA[e,f] – mesopic, binocular										X	X	
UCIVA[h,i] – photopic, monocular					X				X	X	X	
UCIVA[h,i] – photopic, binocular									X	X	X	
DCIVA[h] – photopic, monocular					X[j]				X[i]	X[i]	X[i]	
DCIVA[h,i] – photopic, binocular										X	X	
DCIVA[h,i] – mesopic, monocular					X				X	X	X	
DCIVA[h,i] – mesopic, binocular										X	X	
Binocular best-corrected distance contrast										X	X[l]	

Examination	Pre-Op 0A/B (Both Eyes)	Operative 00A (1st Eye)	Post-Op 1A (1st Eye)	Post-Op 2A[a] (1st Eye)	Post-Op 3A (1st Eye)	Operative 00B (2nd Eye)	Post-Op 1B (2nd Eye)	Post-Op 2B (2nd Eye)	Post-Op 3B (2nd Eye)	Post-Op 4 (Both Eyes)	Post-Op 5 (Both Eyes)	For sub-study only: Post-Op 6 (Both eyes)
	Day -30 to -5	Day 0	Day 1 to 2	Day 7 to 14	Day 30 to 60	Day 7 to 30	Day 1 to 2 Post Visit 00B	Day 7 to 14 Post Visit 00B	Day 30 to 60 Post Visit 00B	Day 120 to 180 Post Visit 00B	Day 330 to 420 Post Visit 00B	Day 2- 30 post Visit 5
sensitivity testing (photopic with glare at 3, 6, 12 and 18 cpd)[k]												
Binocular best-corrected distance contrast sensitivity (mesopic with and without glare at 1.5, 3, 6, and 12 cpd)[k]										X	X[l]	
Binocular BCDVA Defocus Curves[k]										X		
Intraocular Pressure	X		X	X	X		X	X	X	X	X	
Slit-Lamp Exam[m]	X		X	X	X		X	X	X	X	X	
Dilated Fundus Exam	X				X				X	X	X[n]	
OCT Imaging[k]										X		
Trial Frame Astigmatism Simulation sub-study (assessments below)												X
BCDVA photopic monocular (no additional sphere, cylinder or axis)												X

Examination	Pre-Op 0A/B (Both Eyes)	Operative 00A (1st Eye)	Post-Op 1A (1st Eye)	Post-Op 2A[a] (1st Eye)	Post-Op 3A (1st Eye)	Operative 00B (2nd Eye)	Post-Op 1B (2nd Eye)	Post-Op 2B (2nd Eye)	Post-Op 3B (2nd Eye)	Post-Op 4 (Both Eyes)	Post-Op 5 (Both Eyes)	For sub-study only: Post-Op 6 (Both eyes)
	Day -30 to -5	Day 0	Day 1 to 2	Day 7 to 14	Day 30 to 60	Day 7 to 30	Day 1 to 2 Post Visit 00B	Day 7 to 14 Post Visit 00B	Day 30 to 60 Post Visit 00B	Day 120 to 180 Post Visit 00B	Day 330 to 420 Post Visit 00B	Day 2- 30 post Visit 5
BCDVA photopic, monocular (simulated astigmatism 2.0 D plus cylinder, 180°)												X
BCDVA photopic, monocular (simulated astigmatism 2.0 D plus cylinder, 90°)												X
BCDVA photopic, monocular (simulated astigmatism 1.50 D plus cylinder, 180°)												X
BCDVA photopic, monocular (simulated astigmatism 1.5 D plus cylinder, 90°)												X
BCDVA photopic, monocular (simulated astigmatism 1.0 D plus cylinder, 180°)												X
BCDVA photopic, monocular (simulated astigmatism 1.0 D plus cylinder, 90°)												X

Examination	Pre-Op 0A/B (Both Eyes)	Operative 00A (1st Eye)	Post-Op 1A (1st Eye)	Post-Op 2A[a] (1st Eye)	Post-Op 3A (1st Eye)	Operative 00B (2nd Eye)	Post-Op 1B (2nd Eye)	Post-Op 2B (2nd Eye)	Post-Op 3B (2nd Eye)	Post-Op 4 (Both Eyes)	Post-Op 5 (Both Eyes)	For sub-study only: Post-Op 6 (Both eyes)
	Day -30 to -5	Day 0	Day 1 to 2	Day 7 to 14	Day 30 to 60	Day 7 to 30	Day 1 to 2 Post Visit 00B	Day 7 to 14 Post Visit 00B	Day 30 to 60 Post Visit 00B	Day 120 to 180 Post Visit 00B	Day 330 to 420 Post Visit 00B	Day 2- 30 post Visit 5
DCIVA photopic monocular (no additional sphere, cylinder or axis)												X
DCIVA photopic, monocular (simulated astigmatism 2.0 D plus cylinder, 180°)												X
DCIVA photopic, monocular (simulated astigmatism 2.0 D plus cylinder, 90°)												X
DCIVA photopic, monocular (simulated astigmatism 1.5 D plus cylinder, 180°)												X
DCIVA photopic, monocular (simulated astigmatism 1.5 D plus cylinder, 90°)												X
DCIVA photopic, monocular (simulated astigmatism 1.0 D plus cylinder, 180°)												X

Examination	Pre-Op 0A/B (Both Eyes)	Operative 00A (1st Eye)	Post-Op 1A (1st Eye)	Post-Op 2A[a] (1st Eye)	Post-Op 3A (1st Eye)	Operative 00B (2nd Eye)	Post-Op 1B (2nd Eye)	Post-Op 2B (2nd Eye)	Post-Op 3B (2nd Eye)	Post-Op 4 (Both Eyes)	Post-Op 5 (Both Eyes)	For sub-study only: Post-Op 6 (Both eyes)
	Day -30 to -5	Day 0	Day 1 to 2	Day 7 to 14	Day 30 to 60	Day 7 to 30	Day 1 to 2 Post Visit 00B	Day 7 to 14 Post Visit 00B	Day 30 to 60 Post Visit 00B	Day 120 to 180 Post Visit 00B	Day 330 to 420 Post Visit 00B	Day 2- 30 post Visit 5
DCIVA photopic, monocular (simulated astigmatism 1.0 D plus cylinder, 90°)												X
DCNVA photopic monocular (no additional sphere, cylinder or axis)												X
DCNVA photopic, monocular (simulated astigmatism 2.0 D plus cylinder, 180°)												X
DCNVA photopic, monocular (simulated astigmatism 2.0 D plus cylinder, 90°)												X
DCNVA photopic, monocular (simulated astigmatism 1.5 D plus cylinder, 180°)												X
DCNVA photopic, monocular (simulated astigmatism 1.5 D plus cylinder, 90°)												X

Examination	Pre-Op 0A/B (Both Eyes)	Operative 00A (1st Eye)	Post-Op 1A (1st Eye)	Post-Op 2A[a] (1st Eye)	Post-Op 3A (1st Eye)	Operative 00B (2nd Eye)	Post-Op 1B (2nd Eye)	Post-Op 2B (2nd Eye)	Post-Op 3B (2nd Eye)	Post-Op 4 (Both Eyes)	Post-Op 5 (Both Eyes)	For sub-study only: Post-Op 6 (Both eyes)
	Day -30 to -5	Day 0	Day 1 to 2	Day 7 to 14	Day 30 to 60	Day 7 to 30	Day 1 to 2 Post Visit 00B	Day 7 to 14 Post Visit 00B	Day 30 to 60 Post Visit 00B	Day 120 to 180 Post Visit 00B	Day 330 to 420 Post Visit 00B	Day 2- 30 post Visit 5
DCNVA photopic, monocular (simulated astigmatism 1.0 D plus cylinder, 180°)												X
DCNVA photopic, monocular (simulated astigmatism 1.0 D plus cylinder, 90°)												X
Posterior capsulotomy assessment			X	X	X		X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X

[a] Must occur before Operative Visit 00B

[b] Review of inclusion/exclusion criteria prior to surgery

[c] To additionally be completed at any post-operative Unscheduled Visit and prior to unscheduled study exit (e.g., IOL explanation).

[d] Completed for both eyes

[e] Distance for Phase II and Phase III subjects of 40 cm

[f] Phase I/Pilot: Distance of 40 cm

[g] Phase I/Pilot: Distance of 30 cm, 35cm, and 40 cm

[h] Distances for Phase II and Phase III subjects of 60 cm and 66 cm

[i] Phase I/Pilot: Distance of 66 cm

[j] Phase I/Pilot: Distance of 56 cm, 66 cm, and 76cm

[k] Conducted on a subset of subjects

[l] Done only if subject has posterior capsulotomy after Visit 4; if subject is scheduled for posterior capsulotomy during Visit 4, testing is deferred to Visit 5

[m] Includes determination of medical and lens findings/complications, including decentration, tilt and PCO (note: lens findings/complications, including decentration, tilt and PCO evaluated post-operatively only).

[n] If clinically indicated

[0] Subjects must consent to participate in the Visit 6 Trial Frame Astigmatism Simulation sub-study. New subjects who are enrolled in the study once protocol amendment 6 is instituted will consent to the Trial Frames Astigmatism Simulation sub-study at the Pre-Op Visit, if they so choose, but at a point no later than Visit 5. Existing subjects who are in the study at the time protocol amendment 6 is instituted must provide their consent to participate in the Trial Frame Astigmatism Simulation sub-study no later than Visit 5.

[p]Specific to Visit 6, overall study eligibility will be confirmed as well as criteria for participation in the Trial Frame Astigmatism Simulation sub-study.

Appendix B METHODS OF CLINICAL EVALUATIONS

Any changes to the procedures described in this appendix will be provided under separate cover. Study procedures performed during the COVID-19 pandemic will be conducted in accordance with medical guidance to reduce risk of COVID-19 transmission between study staff and subjects (available at **www.aao.org/covid-19**). It is recommended Investigators periodically revisit the **aao.org/covid-19** website to identify and implement any updated recommendations made by AAO. Local, state, and federal public health guidance also will be followed, and it is recommended these guidances also be visited once a month to see if they have changed.

1.0 MANIFEST SUBJECTIVE REFRACTION (WITHOUT CYCLOPLEGIC EYE DROPS)

It is essential that a consistent and standard procedure be used to obtain manifest refraction measurements. The measurements will be obtained by a qualified ophthalmologist, optometrist or trained ophthalmic technician using a phoropter or trial frame with loose lenses, in 0.25 D steps, in a calibrated refraction lane. The principal of maximum plus prescription while maintaining optimum visual acuity (not just darker letters) should be adhered to. At no time during the study will autorefraction be utilized as a final endpoint refraction. Autorefractor or lensometer readings may only be utilized to obtain a starting point for the refraction, if necessary.

To ensure consistency, all refractions will be performed at an optical distance of 4 meters using the M&S Clinical Trial Suite. This refraction will be considered the "unadjusted manifest refraction at 4 m". The "adjusted manifest refraction" is the "unadjusted manifest refraction " minus 0.25 D used to correct for optical infinity at 4 m. Both "adjusted" and "unadjusted" manifest refraction values will be recorded on source documentation, but only the adjusted value will entered as eCRF data. Note that the "**adjusted manifest refraction**" ("**unadjusted manifest refraction**" at 4 meters minus 0.25 D) is the value that is used for DCIVA and DCNVA measurements.

1.1 Preoperative Manifest Subjective Refraction

If the subject has a current pair of glasses for distance vision, they can be measured with a lensometer and these measurements used as the beginning approximate refraction. If the subject does not have glasses for distance vision, retinoscopy or autorefraction may be performed by an examiner proficient in this procedure as the beginning approximate refraction. If the subject is a contact lens wearer, they should be advised to arrive for the preoperative testing wearing spectacles and not their contact lenses.

AUTOREFRACTION ALONE IS NOT ALLOWED AT ANY POINT IN THIS STUDY. RESULTS MUST BE REFINED USING SUBJECTIVE TECHNIQUES.

The manifest subjective refraction at 4 meters MUST be transferred to the trial frame for BCDVA testing. If for any reason (e.g., dense cataract) manifest refraction cannot be obtained, the results should be documented as not done (ND) and not entered as zeros. In the event of

this occurrence, BCDVA will not be tested and the reason for ND will be required in the source document and eCRF.

Contact lens wearers must demonstrate a stable refraction (within ± 0.50 D for both sphere and cylinder) on two consecutive exam dates. Stability of the refraction is determined under the following conditions:

- Lenses are not worn for at least 1 week (rigid contact lenses) or 3 days (soft contact lenses) prior to the first refraction used to establish stability and through the day of surgery;
- The two refractions are performed at least 7 days apart.

1.2 Postoperative Manifest Subjective Refraction

The subject should be refracted using the same method and procedure as described in Section 1.1 of this appendix.

2.0 VISUAL ACUITY TESTING

It is essential that a standard procedure be used to obtain visual acuity (VA) measurements. The VA measurements should be obtained by a qualified ophthalmologist, optometrist or trained ophthalmic technician using the Clinical Trial Suite (M&S Technologies, Niles, IL) hardware and software that will be supplied by the Sponsor. Training on the use of Clinical Trial Suite instrumentation will be conducted and documented by a qualified representative of M&S Technologies prior to its use with enrolled subjects. VA testing will be performed by masked study personnel using a trial frame.

Visual Acuity Testing for all subjects:

- Best-corrected distance visual acuity (BCDVA) will be measured at distance of 4 meters with the manifest refraction obtained at 4 meters (**Unadjusted** Manifest Refraction)
- Uncorrected distance visual acuity (UCDVA) will be measured at distance of 4 meters with a +0.25D lens to adjust for optical infinity
- Distance corrected intermediate visual acuity (DCIVA) will be measured at distance(s) specified in Appendix A with the "adjusted manifest refraction", which is the manifest refraction obtained at 4 meters minus 0.25 D to obtain the optical infinity manifest refraction (**Adjusted** Manifest Refraction)
- Uncorrected intermediate visual acuity (UCIVA) will be measured with Phase II and Phase III subjects at distance(s) specified in Appendix A at 66 cm with no corrective lens
- Distance corrected near visual acuity (DCNVA) will be measured at distance(s) specified in Appendix A with the "adjusted manifest refraction", which is the manifest refraction obtained at 4 meters minus 0.25 D (**Adjusted** Manifest Refraction).
- Uncorrected near visual acuity (UCNVA) will be measured at distance(s) specified in Appendix A with no corrective lens

2.1 Description and Testing Methodology

The Clinical Trial Suite is a computerized vision testing system consisting of a computer tablet and frame to hold the tablet that allows it to be stationed at different distances from a seated

subject. The tablet frame also has lights attached to it that allow vision testing to be conducted with or without glare. The frame can be moved so that near, intermediate, or far VA can be determined, with the ETDRS optotype display adjusted for distance from subject to display to accommodate the effect of distance of the size of the ETDRS letters. The Clinical Trial Suite will use high contrast ETDRS letters and randomize the letter display during every use to eliminate any effect of memorization bias. The distance from subject to display for near, intermediate, and far distance VA testing will be standardized for all clinical sites and for all subjects.

The chart display on the tablet should be at a comfortable viewing angle for the subject, approximately head high. 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 subject should be told that the chart has letters only, no numbers. The subject should be asked to read slowly, about 1 letter per second, so as to achieve the best identification of each letter. Subjects should be instructed not to squint, and the tester should closely watch the subject during testing and warn him/her if squinting is observed. The subject is not to proceed to the next letter until a definite response is given.

If the subject changes a response (e.g., "that was a 'C' not an 'O') before the next letter has been read aloud, then the change must be accepted. If the subject changes a response having read the next letter, then the change is not to be accepted. The examiner should never point to the chart or to specific letters on the chart during the test. A maximum effort should be made to identify each letter on the chart. This may include encouraging the subject to guess. If the subject identified a letter as 1 of 2 letters, he or she should be asked to choose 1 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 test for that eye and those testing conditions. 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 assessments of visual acuity during the study, all visual acuity assessments at a single site must be consistently done using the same lighting conditions during the entire study.

2.2 Room Illumination

Standard lighting conditions to be used in VA testing are Photopic: 85 (± 2) cd/m^2 and Mesopic: 3 (± 0.5) cd/m^2. If an Investigator is unable to use these lighting conditions or has lighting conditions that vary slightly from these target illuminations, they should discuss their current lighting conditions with the Sponsor.

2.3 Subject Instructions

Subjects will be instructed that their vision will be tested at different distances, sometimes with the room lights on and sometimes with the room lights off. They will be asked to sit quietly during testing, with no head movements relative to the chart display allowed. If subjects need one or more brief breaks from the testing, this will be allowed.

2.4 Visual Acuity Assessments

See Appendix A for schedule of VA assessments. VA assessments should be done only once per visit for each eye (or subject, in the case of binocular VA), distance to eye chart, and lighting condition.

3.0 SLIT LAMP EXAM

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

Cataract Type

- Nuclear
- Cortical
- Posterior sub-capsular
- Combination

Cataract Density

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

Lids – Normal / Abnormal[+]

Iris/Pupil – Normal / Abnormal[+]

Conjunctiva – Normal / Abnormal[+]

[+]Abnormal is defined as beyond the normal range encountered in healthy individuals of a similar age

Hyperemia

0 None
1 Mild
2 Moderate
3 Severe
4 Very Severe

Cornea

Superficial Punctate Keratitis

0 None
1 Mild
2 Moderate
3 Severe
4 Very Severe

Corneal Wound Edema (postoperative only)

0 None
1 Mild
2 Moderate
3 Severe

Corneal Stromal Edema (preoperative and postoperative)

0	None	No evidence of corneal swelling with normal transparency
1	Mild	Mild corneal swelling
2	Moderate	Moderate corneal swelling
3	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 SUN Working Group grading system.[37] For the evaluation of cells and flare, using a 1 mm x 1 mm slit beam, the following SUN grading scheme will be used:

Anterior Chamber Cells

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

Anterior Chamber Flare

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

Posterior Capsular Haze

Assessment of the severity of any PCO will be done with pupil dilation at the slit lamp using the following grading scale:

Grade 0 – None	No growth is seen on any portion of the visible lens capsule.
Grade 1 – Trace or Mild	Lens epithelial cells can be seen in the periphery where the anterior capsule has retracted from the front of the IOL and is now interacting with the posterior capsule, but there are very few central cells.
Grade 2 – Moderate	The peripheral cells have become much denser and are starting to invade the central area.
Grade 3 – Severe	The lens epithelial cells have met one another in the middle and are forming a sheet over the posterior capsule.

4.0 INTRAOCULAR PRESSURE (IOP)

IOP measurements will be obtained using a calibrated Goldmann Type Applanation Tonometer in accordance with manufacturer's instructions.

5.0 PUPIL SIZE

Pupil size will be measured with a pupillometer at the corneal plane to the nearest 0.1 mm. Eye illumination for pupil measurement will be identical to the photopic and mesopic illumination used for visual acuity testing – 85 (± 2) cd/m^2 and 3 (± 0.5) cd/m^2, respectively. Pupil measurement will be initiated only after the eye has had time to fully adapt to the testing conditions (approximately 10 minutes).

6.0 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." If abnormal, the investigator will describe the abnormality. The investigator will also rate the clarity of fundus visualization as "adequate" or "inadequate".

7.0 OCT IMAGING

Approximately 20 Group 1 subjects and 10 Group 2 subjects will participate in OCT imaging at 2-3 clinical sites having similar or identical OCT equipment. For sites and subjects participating in OCT imaging, images of first implanted eye will be taken. OCT images will be obtained after the dilated exam, and eyes found to have any abnormality of the visual axis or retinal structures will be excluded from the imaging sub-study. For each first implanted eye, three images of the macula and three images of the optic nerve will be obtained by qualified site personnel, labeled with the Subject ID number, and submitted to the Sponsor (or designee) for assessment. The image quality will be assessed to determine adequacy for visualization of retinal structures, with the results rated on the following scale:

0 = Ungradable (including failure to visualize the macula or optic nerve)
1 = Poor quality image
2 = Fair quality image
3 = Good quality image
4 = Excellent quality image

If difficulty with visualization is encountered during the process of obtaining OCT images, conventional fundus photographs will be taken.

8.0 TRIAL FRAME ASTIGMATISM SIMULATION

Participating subjects should have the following characteristics (in both eyes) upon having consented to the Trial Frame Astigmatism Simulation sub-study:

1. Signed consent (no later than Visit 5) to participate in the sub-study
2. Completed visit 5
3. Have a best-corrected distance visual acuity of 20/25 or better as noted in each eye at Visit 5
4. Subjects should not have corneal edema, increased IOP or any AE / SAE at Visit 5, as per the reportable AEs/ SAEs clarified in section 12.4.1 of the protocol.
5. In addition, subjects must be willing to complete their participation on the Trial Frame sub-study between 2 and 30 days after completion of Visit 5.
6. Subjects with oblique post-operative residual astigmatism (axis between 30 to 60 degrees or 120 to 150 degrees) will be excluded from participation in the sub-study.

Enrollment will be sequential with consecutive subjects enrolled onto the Trial Frame astigmatism simulation sub-study at each site in order of their completion of post-operative Visit 5 and based on their eligibility. The subject will provide consent for the Trial Frame astigmatism simulation sub-study by completion of Visit 5 and return at Visit 6 to undergo the trial frame evaluation to assess distance-corrected visual acuities with various amounts of astigmatism. Eligibility for the sub-study will be confirmed by the completion of Visit 5 and

subjects will be enrolled in it when the Informed Consent document is signed. Visit 6 will include review/update of concomitant medications, adverse events, and measurement of monocular distance corrected visual acuity for far (4 m), intermediate (66 cm), and near (40 cm) distance under photopic conditions with varying degrees of simulated residual astigmatism with 2.00 D, 1.5 D, and 1.0 D CYL. Participants in the sub-study will be seen at only one visit (Visit 6) for the trial frame evaluation which will complete their participation in the study. Assessments are shown in the Study Flow Chart in Appendix A.

The below assessments will be recorded:

i. For the (4-meter) manifest-corrected distance (4 m) testing:
- Visual acuity will be assessed without astigmatic blur; and
- With astigmatic blur for each astigmatic condition (power/axis orientation);

ii. For the distance corrected intermediate (66 cm) testing :
- Visual acuity will be assessed without astigmatic blur; and
- With astigmatic blur for each astigmatic condition (power/axis orientation)

iii. For the distance corrected near (40 cm) testing:
- Visual acuity will be assessed without astigmatic blur; and
- With astigmatic blur for each astigmatic condition (power/axis orientation)

The order of testing will follow the A and B Eye pre-operative assignments relating to the order of surgical implantation of the IOL and each eye of the subject will be tested for each distance and astigmatic condition, followed by a repeat of the same testing with the other eye.

The purpose of the Trial Frame astigmatism sub-study is to evaluate the effect of simulated residual astigmatism on distance, intermediate, and near visual acuities in eyes implanted with the enVista trifocal toric intraocular lenses (IOLs).

The trial frame evaluation will assess distance-corrected visual acuities with various amounts of additional astigmatism at distance / far, intermediate, and near distances, in that order, for each eye of each subject monocularly. ETDRS charts appropriate for each distance will be used in measuring visual acuity for the various cylinder power conditions. Each eye of the participating subjects will be evaluated monocularly, beginning with the subject's A eye (Right/ Left) and repeating for the subject's B eye (Left/ Right).

The Trial Frame is placed on the subject and adjusted to sit comfortably on the subject's face. The subject's eyes are centered relative to the lens wells of the frame via adjustments to the temple length, to the nose pad for frame height , pantoscopic tilt and leveling of the frame and the interpupillary distance.

The subject's distance-corrected refraction and testing will begin at far distance (4 m) using the Clinical Trial Suite system (M&S Technologies, Niles, IL) with no additional cylinder trial lens in the trial frame for measurement of monocular distance corrected visual acuity for each eye. The distance correction used in the trial frame for testing at far distance (4 m) is the

unadjusted manifest refraction performed at 4 m; however, the distance correction used in the trial frame for testing at intermediate (66 cm) and near (40 cm) distances is the **adjusted** manifest refraction (i.e., the manifest refraction at 4 m adjusted by adding an additional -0.25 D). See Table 4 below

In order to ensure the spherical equivalent is kept at a constant, the examiner must modify the spherical power with each plus cylinder power added to the trial frame. This procedure is necessary to avoid increasing the spherical equivalence and blurring the vision with induced Hyperopia.

For example, when adding a residual plus cylinder power of 1.0D to the Trial Frame, 0.5D of spherical power must be subtracted to ensure spherical equilavence is maintained at a constant. The following examples demonstrate the proper subtraction of spherical power with the addition of each cylindrical power to maintain a constant spherical equivalent compared to the manifest refraction.

Examples

1) -0.75 sph should be placed in the trial frame with the +1.50 cylinder,
2) -0.50 sph should be placed in the trial frame with the +1.00 cylinder,
3) -1.00 sph should be placed in the trial frame with the +2.00 cylinder.

Residual astigmatism then will be optically simulated for each subject at distance / far (4 m), intermediate (66 cm), and near (40 cm) distances (in that order) using additional plus cylinder trial lenses placed at the 180º axis (i.e., simulating ATR astigmatism) and then at the 90º axis (i.e., simulating WTR astigmatism). The order of trial lenses to be used with a subject will be the 2.00 D plus cylinder lens (placed first at 180º and then at 90º) followed successively by use of the 1.50 D plus cylinder lens (placed first at 180º and then at 90º) and then the 1.00 D plus cylinder lens (placed first at 180º and then at 90º). The A eye will be measured first, using the various cylinder lenses for distance / far, intermediate, and near distances. The same order will then be repeated for the B eye.

Table 4- Trial Frame order of testing

Order of Testing Conditions	**Manifest Refraction**	**Additional Sphere Adjustment for Cylinder**	**Additional Cylinder Power**	**Additional Cylinder Axis**
Far distance (4 m) without cylinder	MR at 4 m (Unadjusted MR)	None	None	None
Far distance (4 m) with +2.00 D cylinder	MR at 4 m (Unadjusted MR)	-1.00 D	+2.00 D	180
Far distance (4 m) with +2.00 D cylinder	MR at 4 m (Unadjusted MR)	-1.00 D	+2.00 D	90
Far distance (4 m) with +1.50 D cylinder	MR at 4 m (Unadjusted MR)	-0.75 D	+1.50 D	180

Far distance (4 m) with +1.50 D cylinder	MR at 4 m (Unadjusted MR)	-0.75 D	+1.50 D	90
Far distance (4 m) with +1.00 D cylinder	MR at 4 m (Unadjusted MR)	-0.50 D	+1.00 D	180
Far distance (4 m) with +1.00 D cylinder	MR at 4 m (Unadjusted MR)	-0.50 D	+1.00 D	90
Intermediate (66 cm) without cylinder	MR at 4m with *minus* 0.25 D (Adjusted MR)	None	None	None
Intermediate (66 cm) with +2.00 D cylinder	MR at 4m with minus 0.25 D (Adjusted MR)	-1.00D	+2.00 D	180
Intermediate (66 cm) with +2.00 D cylinder	MR at 4m with minus 0.25 D (Adjusted MR)	-1.00 D	+2.00D	90
Intermediate (66 cm) with +1.50 D cylinder	MR at 4m with *minus* 0.25 D (Adjusted MR)	-0.75 D	+1.50 D	180
Intermediate (66 cm) with +1.50 D cylinder	MR at 4m with *minus* 0.25 D (Adjusted MR)	-0.75 D	+1.50 D	90
Intermediate (66 cm) with +1.00 D cylinder	MR at 4m with *minus* 0.25 D (Adjusted MR)	-0.50 D	+1.00 D	180
Intermediate (66 cm) with +1.00 D cylinder	MR at 4m with *minus* 0.25 D (Adjusted MR)	-0.50 D	+1.00 D	90
Near (40 cm) without cylinder	MR at 4m with *minus* 0.25 D (Adjusted MR)	None	None	None
Near (40 cm) with +2.00 D cylinder	MR at 4m with *minus* 0.25 D (Adjusted MR)	-1.00 D	+2.00D	180
Near (40 cm) with +2.00 D cylinder	MR at 4m with *minus* 0.25 D (Adjusted MR)	-1.00 D	+2.00 D	90
Near (40 cm) with +1.50 D cylinder	MR at 4m with *minus* 0.25 D (Adjusted MR)	-0.75 D	+1.50 D	180
Near (40 cm) with +1.50 D cylinder	MR at 4m with *minus* 0.25 D (Adjusted MR)	-0.75 D	+1.50 D	90
Near (40 cm) with +1.00 D cylinder	MR at 4m with *minus* 0.25 D (Adjusted MR)	-0.50 D	+1.00 D	180
Near (40 cm) with +1.00 D cylinder	MR at 4m with *minus* 0.25 D (Adjusted MR)	-0.50 D	+1.00 D	90

9.0 ASSESSMENT OF LENS TILT AND DECENTRATION

If upon postoperative examination, tilt and/or decentration of the IOL are not seen or deemed insignificant, rather than entering any score, a box marked “Not Detectable” will be checked. Otherwise, significant lens tilt and decentration will be assessed according to the method described by Guyton et al, [39] as refined by the American Academy of Ophthalmology Task Force Summary Statement for Measurement of Tilt, Decentration, and Chord Length. [40]

The Guyton method is a simple, rapid and accurate procedure for determining the tilt and decentration of an IOL.

Method of Determining Lens Tilt and Decentration

Using a penlight, identify the IIIrd and IVth Purkinje images. The relative lack of parallax movement of the first Purkinje image, with respect to the pupil, helps to identify it.

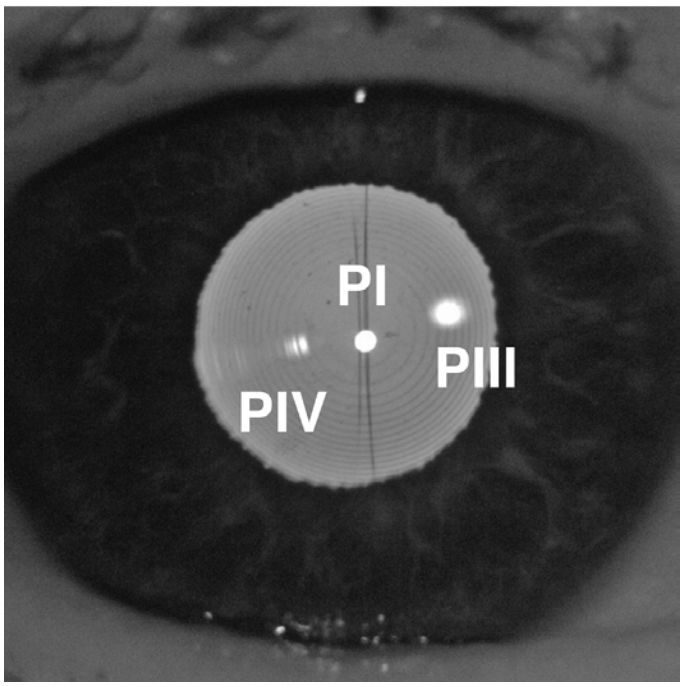


Figure 3 from Chang and Waring [41]
Purkinje images as seen through a pupilometer.

With the patient looking at the examiner's finger, the examiner moves his finger in the frontal plane until Purkinje images III and IV, as sighted by the examiner's eye, become aligned with one another. The apparent IOL tilt (**θ**') and decentration (Δ) are directly determined from this viewing situation, as described below.

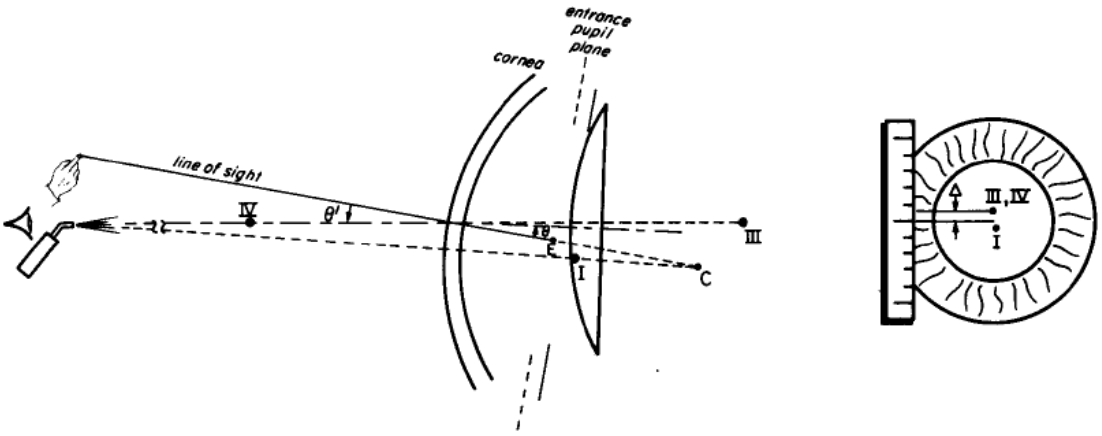


Figure 6 from Guyton et al [39]

In Figure 6, the apparent amount of tilt of the IOL (**θ**') is equal to the angle between the patient's line of sight and the aligned Purkinje images III and IV. This angle is formed by the examiner's finger, the patient's pupil, and the penlight. In the example in Figure 6, the direction of tilt is from the examiner's finger toward the penlight, directly down, in the 90° meridian.

Also, illustrated in Figure 6 is the examiner's view of the Purkinje images as projected onto the patient's pupil. Notice that images III and IV are superimposed on each other but do not coincide with image I. This is a right eye, with the first Purkinje image being displaced nasally from the center of the pupil. Also, the first Purkinje image is displaced downward, because it always falls on the line connecting the light source with the center of curvature of the cornea. With the patient's eye looking upward, therefore, the first Purkinje image (the corneal light reflex) is displaced downward with respect to the center of the pupil.

The superimposition of Purkinje images III and IV marks the optical axis of the IOL as it passes through the entrance pupil of the eye. Because the desired center point for the IOL is the center of the entrance pupil, the amount of decentration and direction of decentration of the IOL are immediately apparent from this view. The IOL is decentered directly upward, approximately 0.6 mm, in Figure 6. The decentration can be measured from this vantage point, if desired, by holding a ruler in the frontal plane of the patient's eye, perpendicular to the patient's line of sight as illustrated.

If the IOL is not decentered at all, but simply tilted about its anterior vertex, the relationship of the apparent angle of tilt to the actual angle of tilt can be calculated. For clinical purposes, it is sufficient to remember that the actual tilt of a centered IOL is 80% to 85% of the apparent tilt (**θ**'). Pure decentration of the IOL, without actual tilt, will produce a certain amount of apparent tilt, because the optical axis of the IOL will no longer be perpendicular to the cornea. By trigonometric ray tracing analysis, l mm of decentration produces 1.7° of apparent tilt, and 2 mm of decentration produces 4.14° of apparent tilt.

10.0 CHORD LENGTH μ AND KERATOMETRY

Chord length μ measurements will be recorded at the Pre-Operative Visit, Visit 4 and Visit 5 using either IOL Master or LENSTAR. Chord length μ measurements will be regarded as an adequate surrogate for angle kappa measurements. [41,42]

Keratometry values at the Pre-Operative Visit which are required for eligibility and IOL power calculations, as well as keratometry values at Post-Operative Visits 3, 4 and 5, may be obtained from automated keratometry (e.g., IOL Master or LENSTAR) or simulated keratometry (e.g., topography, Scheimpflug photography or optical coherence tomography). Note that the steep and flat axes which are reported should be orthogonal. The same method should be used for a specific subject/eye throughout the study.

11.0 DEFOCUS CURVES

Subjects will be identified based on photopic pupil size to have defocus testing performed. Approximately 10 subjects from each lens group at each of three photopic pupil sizes (small - <3.0mm; medium - ≥3.0mm and ≤4.0 mm; large - >4.0 mm) will be evaluated. If 10 subjects are not available in any one pupil size category, the maximum number available will be used. Data will be stratified by photopic pupil size (small - <3.0mm; medium - ≥3.0mm and ≤4.0 mm; and large - >4.0 mm) and axial length (short - <21.0 mm; medium - 21.0 to 26.0 mm; and long - >26.0 mm).

Binocular defocus testing will be performed under photopic lighting conditions using the Clinical Trial Suite (M&S Technologies) at Visit 4 (120-180 days after second eye IOL implantation). Each subject will be defocused with spherical minus trial lenses from their best distance-corrected (Unadjusted) manifest refraction between +1.50 D and -3.50 D in 0.5 D increments, except in the range of +0.50 D through -0.50 D, which will be in 0.25 D increments.

12.0 CONTRAST SENSITIVITY

At least approximately 136 Best Case Group 1 subjects and 68 Best Case Group 2 subjects will be enrolled to have contrast sensitivity testing performed. Binocular best-corrected distance contrast sensitivity testing will be performed using the M&S Clinical Trial Suite at all sites, using the Unadjusted Manifest Refraction. The CTS is calibrated for distance-to-subject and pixels-per-inch so that optotypes follow ANSI and ISO standards.

Sine-wave gratings will be produced on a high-resolution monitor. Outer edges of the grating will incorporate the Gabor effect, and all edges will be surrounded by a uniform field equal to the grating in space-averaged luminance. Subjects will practice the contrast sensitivity test once at all orientations, each at a different spatial frequency, under photopic conditions before beginning tests for recorded data.

Subjects undergoing contrast sensitivity testing will be dark adapted for at least 10 minutes before beginning testing to collect recorded data. Mesopic contrast sensitivity testing will be performed before photopic contrast sensitivity testing. Mesopic (2.5 to 3.2 cd/m^2) contrast sensitivity with and without glare will be tested at spatial frequencies of 1.5, 3, 6 and 12 cycles per degree (cpd) and photopic (approximately 85 cd/m^2) contrast sensitivity with glare will be

tested at spatial frequencies of 3, 6, 12, and 18 cpd. Contrast sensitivity will be assessed twice for each subject at each test condition.

13.0 SUBJECT QUESTIONNAIRES

The concepts to be explored in this study with the QoV and NAVQ subject questionnaires (each developed using patients requiring refractive correction, including cataract surgery patients) are directly related to the original concepts for which the questionnaires were developed. Results of the QoV questionnaire will find use as a secondary safety endpoint to assess subject visual disturbances (see **Section 13.5.5.3**). The NAVQ is being studied as an exploratory subject survey to assess the similarity of subject-perceived near vision functional task limitations and uncorrected near visual acuity (UCNVA) for subjects in both treatment groups, without comparison between treatment groups or seeking correlations.

The QoV Questionnaire

The QoV questionnaire [23,24] will be used to provide a standardized measure of subjective vision symptom and will allow for subjective evaluation of visual disturbances for the IOLs of each treatment group. The QoV questionnaire is specifically a non-comprehensive collection of visual dysphotopsias evaluated by frequency, intensity, and bothersomeness that may occur within a patient group. Items in the QoV questionnaire were developed through extensive literature review, discussion with subject matter experts in refractive correction, iterative focus groups with non-experts, cognitive interviews and evaluation with 900 subjects (150 subjects who were spectacle wearers, 150 contact lens wearers, 300 LASIK or LASEK or photorefractive keratectomy patients, 150 pre-operative cataract patients, and 150 cataract surgery patients who received monofocal, multifocal, or accommodative IOLs). Reliability of the QoV questionnaire was obtained through Rasch analysis of person and item separation statistics for instrument precision, questionnaire fit statistics, correlation with clinical findings (visual acuity, contrast sensitivity, and visual aberrations), and test-retest reliability. [23]

The NAVQ Questionnaire

The NAVQ[25-28] will be used as an exploratory measure of difficulties completing tasks requiring uncorrected near vision. Its use in this study is not intended to support labeling claims for the enVista MX60EF IOL and is only exploratory in nature. The NAVQ use in this study was halted upon acceptance of version 5.0 of the #945 protocol (see footnote in synopsis).

13.1 Subject Questionnaire Instructions

Questionnaires should be completed independently by subjects in a private space at the beginning of each applicable visit, prior to other study assessments being performed.

1. The QoV questionnaire [23, 24] has two main elements:

   - Ten questions, each asked for frequency, intensity, and bothersomeness of the queried symptom and each graded on a 4-point grading scale.
   - Seven photographs which relate to the first 7 questions.

   Each photograph page will be printed in color and displayed on photographic paper. The questionnaire is Rasch-scaled based on data derived from the original validation study. The questionnaire is scored across three subscales with scores ranging from 0 to 100, with higher scores indicating worse quality of vision. Subjects will not be provided with any specific instructions other than to read the written instructions that are displayed at the top of the answer page. No clinical staff are to help in answering the questions or respond to queries from subjects other than to ask subjects to answer as best they can. The QoV questionnaire instructions for subjects will state:

   - Look at the pictures on the accompanying page that relate to the first 7 symptoms and familiarize yourself with the meaning of each symptom.
   - Now answer the questions below about your eyesight in your everyday life.
   - If you have had surgery, please respond based on how you are now, not prior to surgery.
   - Please respond based on how you feel in the past week.
   - Please circle your answer.

2. The NAVQ [25, 26] has 10 questions, each scored on a 5-point grading scale, and a general vision satisfaction question. The NAVQ questions were developed through literature reviews, [27] focus groups including 10 presbyopic patients, [27] refinement of the questions, [26, 27] and test-retest reliability with 150 patients requiring vision correction, including 80 patients receiving monofocal or multifocal IOLs. [26] Rasch analysis of the responses reduced the NAVQ to a 10-question data set and confirmed a 5-point grading scale was not different from the original 6-point NAVQ grading scale; [28] the 5-point grading scale is therefore being used in the present study.

   Verbal instructions to subjects on how to complete the NAVQ will include the following:

   - The questionnaire assesses how you feel about your current vision without additional near correction such as spectacles and how it allows you to function with near and intermediate tasks.
   - Please read the questions carefully and answer them as you feel is appropriate for how you feel – there are no right or wrong answers. If you feel a particular question in not applicable to your situation, please respond with the NA option, but otherwise answer all questions.
   - Let the coordinator know when you have finished or have any questions.
   - Please answer ALL questions for the situation IF/WHEN YOU DO THE DESCRIBED ACTIVITY WITHOUT EXTRA READING SPECTACLES.
   - Circle the relevant option.

- If you do not do the described activity or you have stopped for reasons that are not related to your vision then please circle the 'N/A' option.

Written NAVQ questionnaire instructions will be displayed at the top of the first answer page and will restate:

- Please answer ALL questions for the situation IF/WHEN YOU DO THE DESCRIBED ACTIVITY WITHOUT EXTRA READING SPECTACLES.
- Circle the relevant option.
- If you do not do the described activity or you have stopped for reasons that are not related to your vision, then please circle the 'N/A' option.

Appendix C SURGICAL PROCEDURE

All cataract surgical procedures will be performed by a qualified Investigator, using a phacoemulsification system adjusted according to the surgeon's usual settings (power modulation should be used). All pre-operative, operative, and post-operative procedures performed during the COVID-19 pandemic will be conducted in accordance with medical guidance to reduce risk of COVID-19 transmission between study staff and subjects (available at **www.aao.org/covid-19**). It is recommended Investigators periodically revisit the **aao.org/covid-19** website to identify and implement any updated recommendations made by AAO. Local, state, and federal public health guidance also will be followed, and it is recommended these guidances also be visited once a month to see if they have changed.

Surgery to implant the study IOLs will be performed on Day 0 of the study for the first eye and Day 7 to 30 for the second eye, using standard microsurgical techniques. Surgery will be performed under either local or topical with or without intracameral ophthalmic anesthesia. A viscoelastic (Amvisc® Plus) should be used for the procedure. If the investigator determines that a supplemental ophthalmic viscoelastic device (OVD) is necessary, based on individual subject conditions or surgical circumstances, the use of a commercially available dispersive OVD will be permitted. In such cases, the investigator should document the reason for use of a supplemental OVD in the source document.

The study lens should not be implanted if there is zonular rupture or if the anterior or posterior capsule has been compromised, or if any complication occurs, which, in the judgment of the Investigator, may cause untoward effects.

The surgical procedure will be performed as follows:

1. The eye will be prepared for surgery and draped according to the surgeon's standard procedure.
2. Phacoemulsification and any routine adjunctive procedures will be performed according to the Investigator's usual standard of care.
3. A clear corneal or limbal incision of approximately 2.4 mm for a wound-assisted technique or 2.8 mm for direct in-the-bag placement will be made using the surgeon's standard instrumentation and technique.
4. The anterior chamber will be entered through the incision opening and Amvisc® Plus will be used to fill the anterior chamber. If the investigator determines that a supplemental OVD is necessary, based on individual subject conditions or surgical circumstances, the use of a commercially available dispersive OVD will be permitted. In such cases, the investigator should document the reason for use of a supplemental OVD in the source document.
5. The cataract will be extracted by phacoemulsification.

NOTE: The study lens should not be implanted if any of the following intraoperative complications occur:

- Capsulorhexis tear, iris damage, posterior capsular rupture, vitreous prolapse, or zonular weakness or dehiscence
- Zonular rupture
- Evident zonular weakness or dehiscence

- Posterior capsule rupture
- Vitreous loss
- Significant detachment of Descemet's membrane
- Wound burn or damage
- Anterior chamber bleeding
- Iris incarceration or damage
- Corneal endothelial touch
- Unsuccessful/incomplete phacoemulsification
- Posterior capsule plaque
- Optic and/or haptic damage/amputation

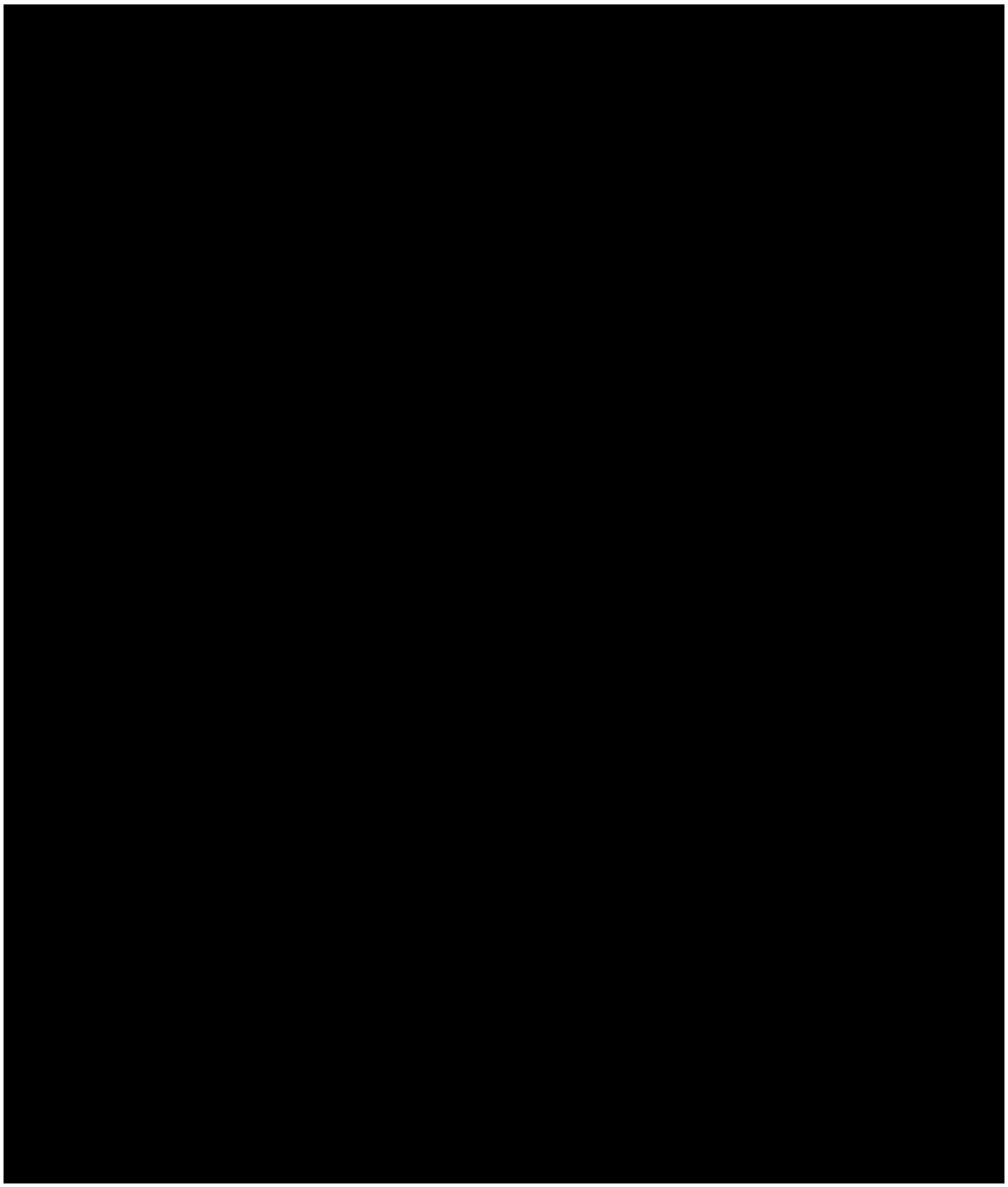
6. The study IOL will be removed from the vial and rinsed with sterile saline in accordance with the IOL instructions for use. The IOL is introduced into the eye using the BLIS IOL Injector according to inserter package insert and placed into the capsular bag. To ensure the subject remains masked to the lens type assigned, the Investigator and any unmasked surgical personnel must not verbally or visually disclose the lens type assigned.
7. Residual viscoelastic should be aspirated from the eye using the surgeon's preferred removal technique. Care should be taken during irrigation/aspiration to ensure a thorough removal of the viscoelastic material from both the anterior and posterior surfaces of the lens. It is recommended that the irrigation/aspiration handpiece be positioned behind the posterior surface of the IOL to ensure complete viscoelastic removal.
8. Incision closure will be left to the discretion of the Investigator. As a routine, no suture should be required. However, depending on the needs of the case, the cornea may be sutured at the Investigator's discretion.
9. Following completion of the surgery, topical steroid, antibiotic and anti-inflammatory medications may be applied to the eye, followed by a patch or shield, per the Investigator's standard post-operative regimen. Additional ophthalmic medications as deemed necessary may be administered at the Investigator's discretion.

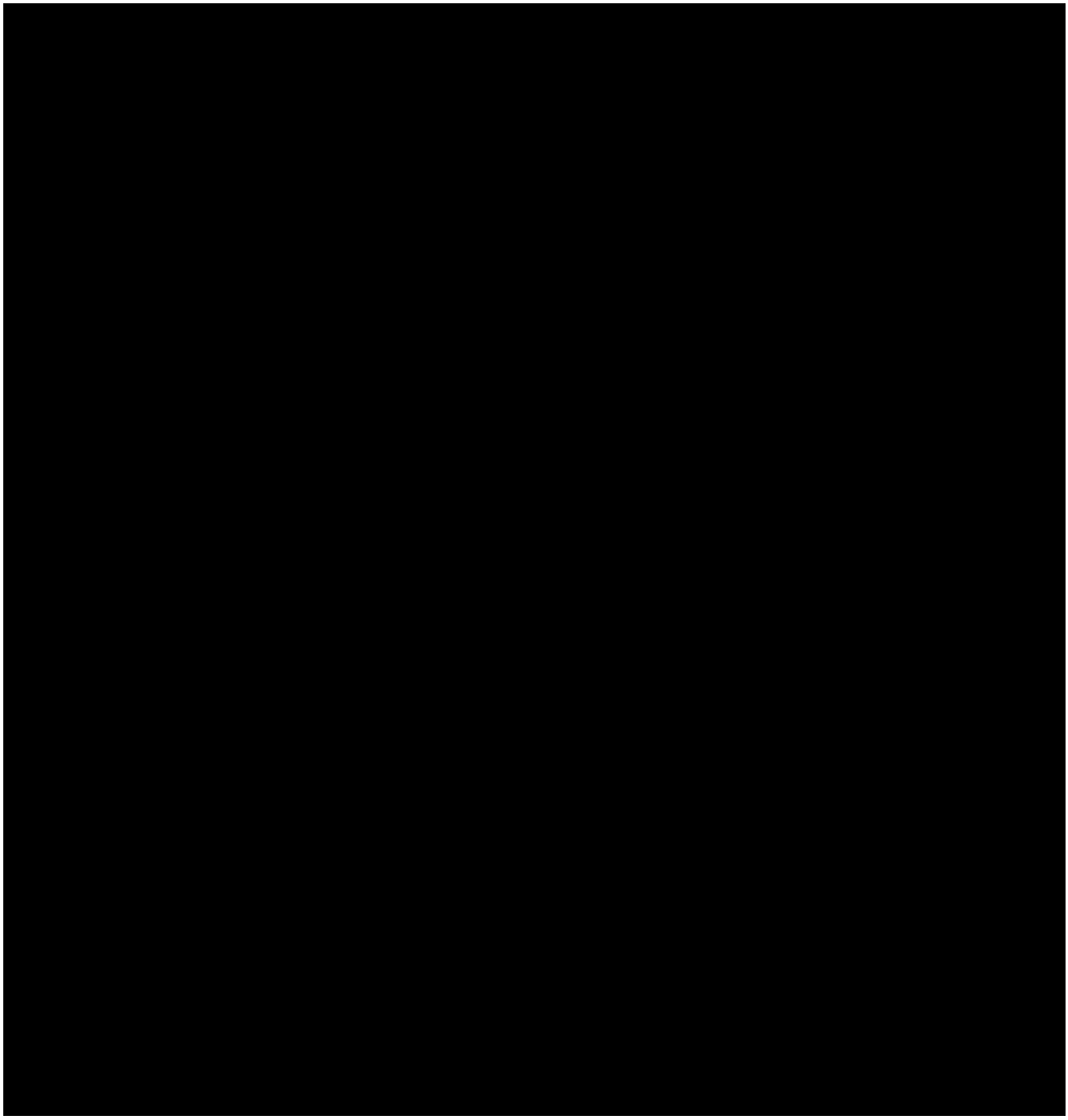
IOL Explantation

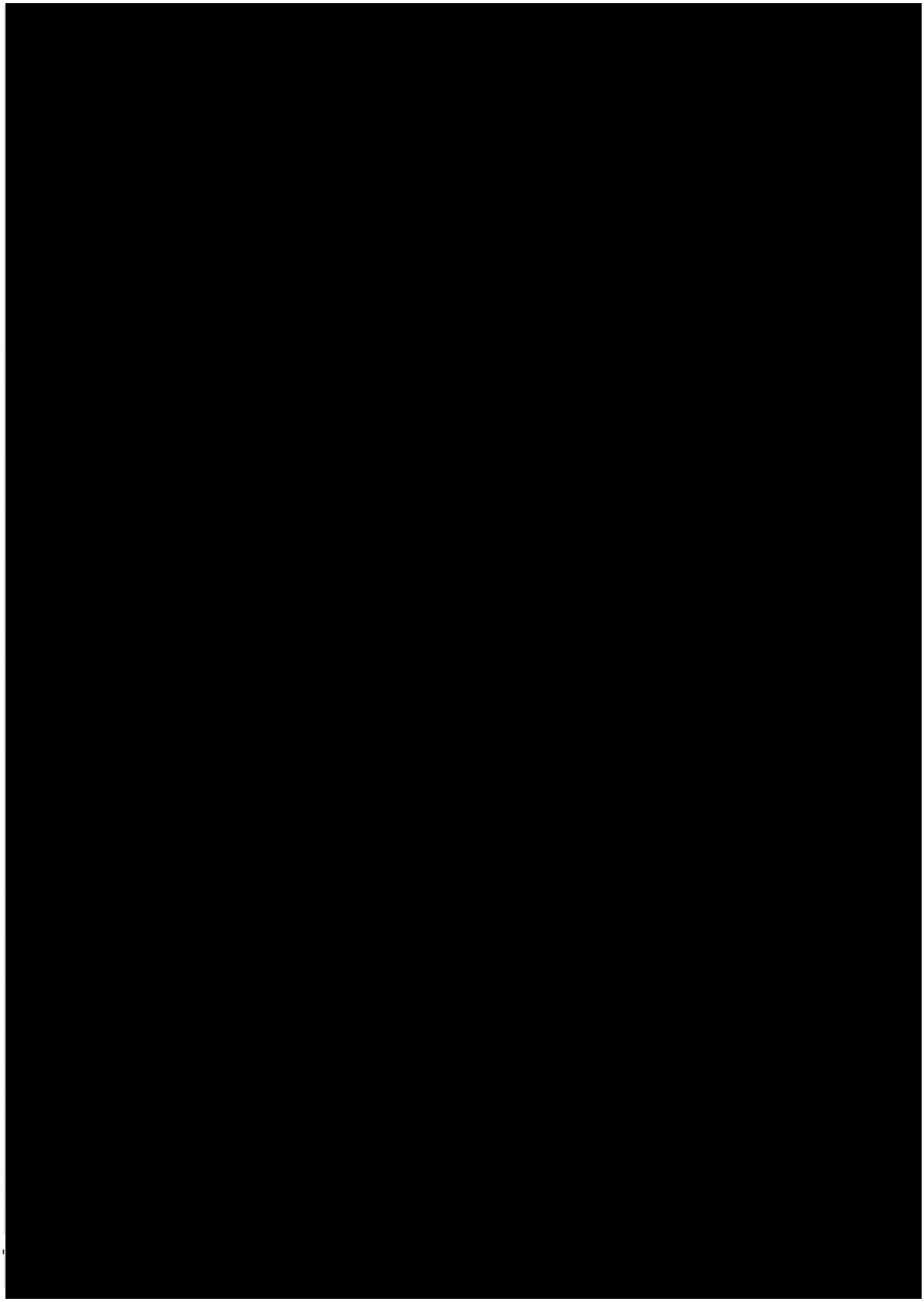
The indication of IOL explantation will be made at the discretion of the Investigator if he/she judges it appropriate and beneficial for the safety and welfare of the subject.

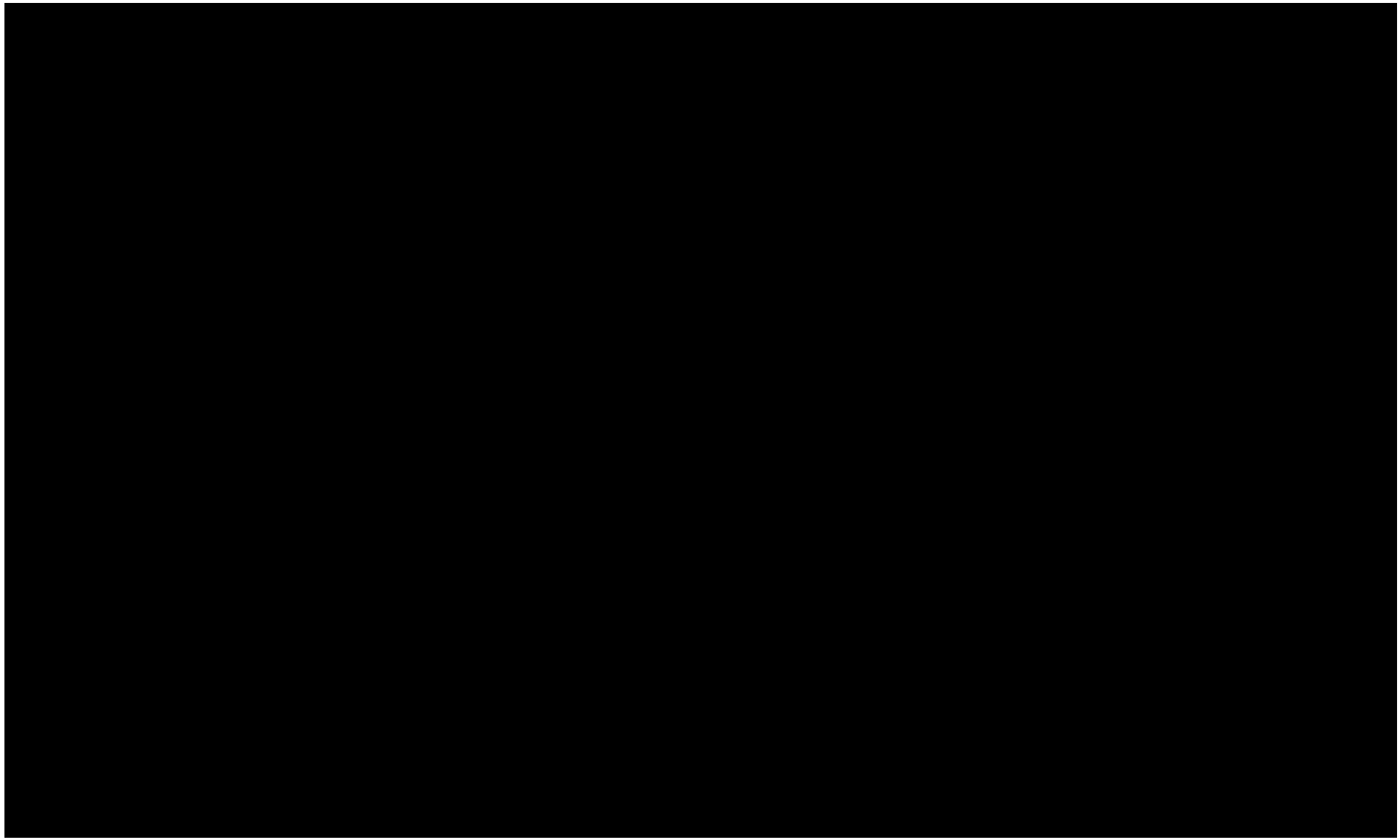
Appendix D SUBJECT QUESTIONNAIRES

1. Quality of Vision (QoV) Questionnaire – the questionnaire provided to subjects is shown below









Appendix E MX60E DIRECTIONS FOR USE

BAUSCH+LOMB

enVista

Hydrophobic Acrylic Intraocular Lens

FOLDABLE HYDROPHOBIC ACRYLIC UV ABSORBING POSTERIOR CHAMBER INTRAOCULAR LENS

DEVICE DESCRIPTION

The enVista™ intraocular lens (IOL) is a single-piece ultra-violet absorbing posterior chamber intraocular lens developed to replace the human crystalline lens in adult patients in whom the cataractous human lens has been removed. The lens is intended for placement in the capsular bag.

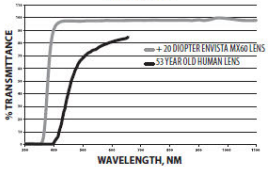
The enVista IOL has an aspheric optic and is designed to be free of spherical aberration. Clinical studies have not been conducted with the enVista IOL to assess the effect of the aspheric surface on spherical aberration, visual acuity, or contrast sensitivity.

PHYSICAL CHARACTERISTICS OF ENVISTA™ MODEL MX60

Lens/Haptic Material	Hydrophobic acrylic (hydroxyethyl methacrylate (HEMA)-polyethylene glycol phenyl ether acrylate (poly(EG)PEA)-styrene copolymer, crosslinked with ethylene glycol dimethacrylate)
Material Characteristics	Index Of Refraction: 1.54 @ 35°C ; Specific Gravity: 1.19 g/ml
Optic Type	Aspheric
Powers	0.0 to +34.0 Diopters (0.0 to +10.0 in 1.0 Diopter increments, +10.0 to +30.0 in 0.5 Diopter increments, and +30.0 to +34.0 in 1.0 Diopter increments)
Dimensions	Optic Diameter: 6.0 mm; Overall Length: 12.5 mm; Haptic Angle: 0°
Spectral Transmittance	**Ultraviolet:** 10% transmittance at 365 nm for +20.0 diopter IOL

FIGURE 1:
SPECTRAL TRANSMITTANCE CURVES
(PERCENTAGE OF ULTRAVIOLET TRANSMITTANCE)

TRANSMITTANCE CURVE FOR ENVISTA MX60 + 20 D



NOTE: Light transmittance values for an IOL material may vary slightly depending on the method of measurement.

Reference: 53 year old human lens data from Boettner, E.A. and Welter, J. R., "Transmission of the Ocular Media," Investigative Ophthalmology, 1:776-783, 1962.

INDICATIONS

Indicated for primary implantation for the visual correction of aphakia in adult patients in whom the cataractous lens has been removed. The lens is intended for placement in the capsular bag.

WARNINGS

Physicians considering lens implantation under any of the following circumstances should weigh the potential risk/benefit ratio:

1. Recurrent severe anterior or posterior segment inflammation or uveitis.
2. Patients in whom the intraocular lens may affect the ability to observe, diagnose, or treat posterior segment diseases.
3. Surgical difficulties at the time of cataract extraction, which might increase the potential for complications (e.g., persistent bleeding, significant iris damage, uncontrolled positive pressure, or significant vitreous prolapse or loss).
4. A distorted eye due to previous trauma or developmental defect in which appropriate support of the IOL is not possible.
5. Circumstances that would result in damage to the endothelium during implantation.
6. Suspected microbial infection.
7. Children under the age of 2 years are not suitable candidates for intraocular lenses.
8. Patients in whom neither the posterior capsule nor zonules are intact enough to provide support.

PRECAUTIONS

1. Do not attempt to resterilize the lens as this can produce undesirable side effects.
2. Do not use if product sterility or quality is thought to be compromised due to damaged packaging or signs of leakage (such as the loss of saline storage solution, or the presence of salt crystallization).
3. Do not soak or rinse the intraocular lens with any solution other than sterile balanced salt solution or sterile normal saline.
4. Do not store the lens at a temperature greater than 43°C (110 °F). DO NOT FREEZE. Do not autoclave the intraocular lens.
5. Do not reuse the lens. It is intended for permanent implantation. If explanted, sterility and proper function cannot be assured.
6. The safety and effectiveness of the enVista IOL have not been substantiated in patients with preexisting ocular conditions and intraoperative complications (see below). Careful preoperative evaluation and sound clinical judgment should be used by the surgeon to decide the benefit/risk ratio before implanting a lens in a patient with one or more of these conditions. Physicians considering lens implantation in such patients should explore the use of alternative methods of aphakic correction and consider lens implantation only if alternatives are deemed unsatisfactory in meeting the needs of the patient.

Before Surgery

- Retinal conditions or predisposition to retinal conditions, previous history of, or a predisposition to, retinal detachment or proliferative diabetic retinopathy, in which future treatment may be compromised by implanting this lens.
- Amblyopia
- Clinically severe corneal dystrophy (e.g., Fuchs')
- Rubella, congenital, traumatic or complicated cataracts
- Extremely shallow anterior chamber, not due to swollen cataract
- Recurrent anterior or posterior segment inflammation of unknown etiology, or any disease producing an inflammatory reaction in the eye (e.g. iritis or uveitis).
- Aniridia
- Iris neovascularization
- Glaucoma (uncontrolled or controlled with medication)
- Microphthalmos or macrophthalmos
- Optic nerve atrophy
- Previous corneal transplant
- Pre-existing ocular conditions which may negatively impact stability of the implant.

During Surgery

- Mechanical or surgical manipulation required to enlarge the pupil
- Vitreous loss (significant)
- Anterior chamber bleeding (significant)
- Uncontrollable positive intraocular pressure
- Complications in which the IOL stability could be compromised

7. Patients with preoperative problems such as corneal endothelial disease, abnormal cornea, macular degeneration, retinal degeneration, glaucoma, and chronic drug miosis may not achieve the visual acuity of patients without such problems. The physician must determine the benefits to be derived from lens implantation when such conditions exist.
8. A high level of surgical skill is required for intraocular lens implantation. The surgeon should have observed and/or assisted in numerous implantations and successfully completed one or more courses on intraocular lens implantation before attempting to implant intraocular lenses.
9. As with any surgical procedure, there is risk involved. Potential complications accompanying cataract or implant surgery may include, but are not limited to the following: corneal endothelial damage, infection (endophthalmitis), retinal detachment, vitritis, cystoid macular edema, corneal edema, pupillary block, cyclitic membrane, iris prolapse, hypopyon, transient or persistent glaucoma, and secondary surgical intervention. Secondary surgical interventions include, but are not limited to: lens repositioning, lens replacement, vitreous aspiration or iridectomy for pupillary block, wound leak repair, and retinal detachment repair.
10. Care should be taken to remove viscoelastic from the eye at the close of surgery.

PACKAGING/STERILIZATION

The enVista IOL is individually packaged in a pouch and plastic vial that should be opened under sterile conditions. The lens is stored in 0.9% sterile saline solution within the top cavity on the vial. A patient card and self adhesive labels are supplied to provide traceability of the IOL. The enVista IOL is sterilized by gamma-sterilization.

CALCULATION OF LENS POWER

The recommended A-constant listed on the lens carton is intended for use with axial length measurements obtained by optical biometry. Use of axial length measurements by other techniques (e.g. Applanation A-scan) will normally require a different lens constant. This number is a guideline only and is based on an evaluation of clinical data obtained using the IOL Master.

The physician should determine preoperatively the power of the lens to be implanted. Lens power calculation methods are described in the following references:

- Hoffer K J. The Hoffer Q formula: a comparison of theoretic and regression formulas, Journal of Cataract and Refractive Surgery Vol. 19, pp. 700-712, 1993; ERRATA, Vol. 20, pp. 677, 1994.
- Holladay JT, Musgrove KH, Prager TC, Lewis JW, Chandler TY, Ruiz RS. A three-part system for refining intraocular lens power calculations. Journal of Cataract and Refractive Surgery, Vol. 14, pp. 17-24, 1988.
- Norrby NES. Unfortunate Discrepancies, Letter to the Editor and Reply by Holladay JT. Journal of Cataract and Refractive Surgery, Vol. 24, pp. 433-434, 1998.
- Olsen T, Olesen H, Thim K, and Corydon L. Prediction of pseudophakic anterior chamber depth with the newer IOL calculation formulas. Journal of Cataract and Refractive Surgery, Vol. 18, pp. 280-285, 1992.
- Retzlaff JA, Sanders DR, Kraff MC. Development of the SRK/T intraocular lens implant power calculation formula. Journal of Cataract and Refractive Surgery, Vol. 16, pp. 333-340, 1990; ERRATA, Vol. 16, pp. 528, 1990.
- Haigis W: The Haigis Formula. In: Intraocular lens power calculations. H. John Shammas (eds), Slack Incorporated, Thorofare, NJ, USA, pp. 39-57, 2004.

DIRECTIONS FOR USE

1. Prior to implanting, examine the lens package for type, power, and proper configuration.
2. Open the peel pouch and remove the vial in a sterile environment.
3. Remove the lid from the vial.
4. With a pair of smooth forceps, remove the lens from the vial by gently grasping the lens haptic.
5. Rinse the entire lens with sterile balanced salt solution or sterile normal saline.
6. Examine the lens thoroughly to ensure particles have not become attached to it, and examine the lens optical surfaces for other defects.
7. The lens may be soaked in sterile balanced salt solution until ready for implantation.
8. Amvisc®, Amvisc® Plus, or OcuCoat® viscoelastic should be used for lubrication of the injector when inserting the IOL.
9. Bausch + Lomb recommends using a Bausch + Lomb approved delivery system.
10. There are various surgical procedures that can be utilized, and the surgeon should select a procedure that is appropriate for the patient. Surgeons should verify that appropriate instrumentation is available prior to surgery.

OVERVIEW OF CLINICAL STUDIES

Clinical studies have been conducted on the enVista single-piece IOL (model MX60) and the parent xact® X-60 three-piece IOL (model X-60). The results of these studies are described herein.

1. Summary of Clinical Study for enVista Model MX60

A clinical study of the enVista Hydrophobic Acrylic Intraocular Lens, Model MX60, began in the United States on October 19, 2010. This prospective, single arm, open label study included a total of 122 subjects (122 eyes) at 6 clinical sites. Postoperatively, subjects underwent complete ophthalmic evaluations at regularly scheduled intervals through Form 4 (Postoperative Days 120-180).

Table 1 displays demographic information of subjects enrolled in the clinical trial. Table 2 displays BCVA results for best case subjects (those without clinically significant pre-operative pathologies or macular degeneration at any time during the study) for 3 visits. At the Form 4 visit, 118 subjects (100%) achieved BCVA of 20/40 or better, which exceeds the FDA grid of 96.7%.

The key safety outcomes for this study are presented in Table 3. The rates of FDA defined potentially sight-threatening adverse events that occurred in the clinical trial at Form 4 were found to be less than the "FDA Grid" of Historical Controls. Two cumulative adverse events (2/122; 1.6%) of cystoid macular edema were reported through the Form 4 visit. One persistent adverse event (1/121; 0.8%) of cystoid macular edema was reported at the Form 4 visit. No serious ocular adverse events occurred during this study. One serious non-ocular adverse event of advanced leukemia with an outcome of death was reported during this study. The adverse event was determined by the study investigator to be unrelated to the investigational device, Model MX60 IOL.

The results of clinical investigations provide reasonable assurance that the Model MX60 IOL is safe and effective for the visual correction of aphakia following cataract extraction.

CLINICAL TABLES

TABLE 1: SUBJECT DEMOGRAPHICS

	n	%
Number of Subjects	122	100.0
Gender		
Male	53	43.44
Female	69	56.56
Race		
African-American	1	0.82
Caucasian	119	97.54
Hispanic	2	1.64
Age		
< 60	13	10.66
60 to < 70	50	40.98
70 to < 80	54	44.26
≥ 80	5	4.10
Mean ± SD	69.0 (8.0)	
Range (Min, Max)	46, 93	

TABLE 2 : BEST CORRECTED VISUAL ACUITY BY POSTOPERATIVE VISIT (BEST CASE ANALYSIS SET)

Visual Acuity	Form 2		Form 3		Form 4	
	n	%	n	%	n	%
20/20 or better	82	69.5	93	78.2	99	83.9
20/25 or better	108	91.5	113	95.0	110	93.2
20/32 or better	117	99.2	117	98.3	117	99.2
20/40 or better	118	100	118	99.2	118	100
Exact 95% CI for 20/40 or better[1]	96.9%, 100%		95.4%, 100%		96.9%, 100%	
Binomial Test p-value for comparing % of 20/40 or better, using FDA recommended p=0.967			1.0000			
20/41 to 20/63[2]	0	0.0	1	0.8	0	0.0
20/64 to 20/100	0	0.0	0	0.0	0	0.0
20/101 to 20/200	0	0.0	0	0.0	0	0.0
Worse than 20/200	0	0.0	0	0.0	0	0.0
N[3]	118		119		118	
N missing[4]	1		0		1	
Total N[5]	119		119		119	

[1]Exact 95% confidence interval for the true percent from the study.
[2]Subject No. 04-027 experienced an AE of cystoid macular edema at Form 3; however, this AE was not persistent, and the subject achieved a BCVA of 20/20 at the Form 4 visit.
[3]Number of available best case subjects, plus best case subjects who missed scheduled visit but were seen later, and with VA measurement for the corresponding group [% = (n ÷ N) x 100%].
[4]Number of subjects with missing VA measurement for the corresponding group.
[5]Total N: N + N-missing subjects for the corresponding group.

TABLE 3 : ISO DEFINED CUMULATIVE AND PERSISTENT ADVERSE EVENTS THROUGH FORM 4 (SAFETY ANALYSIS SET)

Adverse Event	n/N[1]	%	ISO Grid (%)	90% CI[2]	p-value[3]
Cumulative Safety Events[4]					
Endophthalmitis	0/122	0.0	0.1	0.00, 2.43	1.0000
Hyphema	0/122	0.0	2.2	0.00, 2.43	1.0000
Hypopyon	0/122	0.0	0.3	0.00, 2.43	1.0000
IOL Dislocation	0/122	0.0	0.1	0.00, 2.43	1.0000
Cystoid Macular Edema	2/122	1.6	3.0	0.29, 5.07	0.8059
Pupillary Block	0/122	0.0	0.1	0.00, 2.43	1.0000
Retinal Detachment	0/122	0.0	0.3	0.00, 2.43	1.0000
Secondary Surgical Intervention	0/122	0.0	0.8	0.00, 2.43	1.0000
Persistent Safety Events[5]					
Corneal Edema	0/121	0.0	0.3	0.00, 2.43	1.0000
Iritis	0/121	0.0	0.3	0.00, 2.43	1.0000
Cystoid Macular Edema	1/121	0.8	0.5	0.04, 3.86	0.4148
Raised IOP Requiring Treatment	0/121	0.0	0.4	0.00, 2.43	1.0000

[1]n: number of eyes reported with corresponding event. For cumulative event, N: number of implanted eyes. For persistent event, N: number of eyes returned for the Form 4 examination with non-missing response for the corresponding adverse event. A subject could be reported with more than one AE.
[2]Based on binomial distribution.
[3]Binomial test for the null hypothesis H_0: Percent from study ≤Percent from ISO Grid [per ISO 11979-7:2006 (E)].
[4]Occurring at any time during the study.
[5]Present at Form 4.

Other Clinical Findings

All subjects in the safety analysis set were evaluated for IOL glistenings at Form 3 and Form 4 visits. IOL glistenings were evaluated via retroillumination slit lamp examination utilizing a photographic grading scale provided in the protocol. The grading scale consisted of (in order of severity), "none, grade 0 (trace), grade 1, 2, 3, or 4." No glistenings of any grade were reported for any subject at any visit in the clinical study.

2. Summary of Clinical Study for xact® Model X-60 (Three-Piece IOL)

A clinical study of the xact Model X-60 IOL began in the United States on May 8th, 2002 and was conducted by Advanced Vision Science. A total of 383 subjects were enrolled, and 367 subjects were available for examination at one year, 312 were available at two years, and 281 were available at three years.

Table 4 displays demographic information of subjects enrolled in the clinical trial. Table 5 summarizes the best-corrected distance visual acuity (BCVA) results for best case subjects (those without clinically significant pre-operative pathologies or macular degeneration at any time during the clinical trial).

Potentially sight threatening adverse events are listed in Table 6, along with the rate of occurrence in the clinical trial of the X-60 IOL, and are compared to the FDA Grid of Historical Controls. The number of patients included in the analysis of both cumulative and persistent adverse events in some cases was less than the number of patients who returned for examination and were available for analysis as a result of missing information in certain fields on the case report forms.

The results of clinical investigations provide reasonable assurance that the X-60 IOL is safe and effective for the visual correction of aphakia following cataract extraction.

CLINICAL TABLES

TABLE 4: SUBJECT DEMOGRAPHICS

	n	%
Number of Subjects	383	100.0
Gender		
Male	152	39.7
Female	231	60.3
Race		
Black	8	2.1
Caucasian	373	97.4
Hispanic	2	0.5
Age		
< 60	43	11.2
60 to < 70	105	27.2
70 to < 80	177	46.2
≥ 80	58	15.4
Mean ± SD	71.0 (9.11)	
Range (Min, Max)	43, 93	

TABLE 5: VISUAL ACUITY IN BEST CASE POPULATION

Visual Acuity	1 Year		2 Years		3 Years	
	n	%	n	%	n	%
20/20 or better	309	65.3	163	68.8	167	72.3
20/25 or better	375	85.9	215	86.2	208	86.3
20/30 or better	387	96.9	239	89.2	225	92.7
20/40 or better	317	99.1	253	94.8	229	95.1
FDA Grid for % of 20/40 or better	96.7%		N/A		N/A	
N	320		268		242	

TABLE 6: CUMULATIVE AND PERSISTENT ADVERSE EVENTS

Adverse Events	1 Year	FDA Grid 1 Year	2 Years		3 Years	
Cumulative Safety Events:						
Number of Eyes with Postop Visits = 382	n/N	%	%	n/N	%	n/N	%
Endophthalmitis	0/382	0.0	0.1	0/382	0.0	0/382	0.0
Hyphema	0/382	0.0	2.2	0/382	0.0	0/382	0.0
Hypopyon	0/382	0.0	0.3	0/382	0.0	0/382	0.0
IOL Dislocation	0/382	0.0	0.1	0/382	0.0	0/382	0.0
Cystoid Macular Edema	3/376	0.8	3.0	3/377	0.8	3/377	0.8
Pupillary Block	0/382	0.0	0.1	0/382	0.0	0/382	0.0
Retinal Detachment	3/376	0.8	0.3	4/377	1.1	4/377	1.1
Secondary Surgical Intervention	1/382	0.3	0.8	1/382	0.3	3/382**	0.8
Persistent Safety Events	n/N	%	%	n/N	%	n/N	%
Number of Eyes Available at the Visit	367		N/A	312		281	
Corneal Edema	0/366	0.0	0.3	0/312	0.0	0/281	0.0
Iritis	1/366	0.3	0.3	0/312	0.0	0/281	0.0
Cystoid Macular Edema	0/364	0.0	0.5	0/309	0.0	0/280	0.0
Raised IOP Requiring Treatment	0/366	0.0	0.4	0/312	0.0	0/281	0.0

*IOL was exchanged due to patient complaint of blurred vision, despite good BCVA. Investigator suspected glistenings might be related, however only modest improvement of vision was achieved after IOL exchange.
**IOL with glistenings was exchanged during retinal surgery to improve fundus visualization by the surgeon. Loss of vision was the result of retinal pathology and was not associated with the IOL.
†IOL was exchanged due to patient complaint of blurred vision. Investigator suspected glistenings might be related, however vision did not improve after IOL exchange. Since vision did improve after subsequent Nd:Yag capsulotomy, the complaint of blurred vision was not associated with the IOL.

OTHER CLINICAL FINDINGS

In the IDE clinical trial, "glistenings" were observed in some cases. Glistenings, known to sometimes occur in some other hydrophobic acrylic IOLs, are microscopic vacuoles within the optic of the IOL that are visible through the slit lamp as multiple small refractile specks. Analysis of the clinical data confirmed no effect of glistenings on visual outcomes.

Testing established that glistenings were eliminated by a change in the IOL hydration solution from 10.0% saline to 0.9% saline. This was confirmed in an additional clinical trial conducted outside of the United States. In this study, 172 eyes of 142 patients were examined at least once between 1 and 6 months, and 123 eyes of 101 patients were examined at least once between 6 months and 2 years. No glistenings were observed at any time.

HOW SUPPLIED

The lens is supplied sterile in a screw-cap vial (containing a 0.9% saline solution), within a peel pouch. The package is sterilized by gamma irradiation and should be opened only under sterile conditions.

EXPIRATION DATE

Sterility is guaranteed unless the pouch is damaged or opened. The expiration date on the lens package is the sterility expiration date. This lens should not be implanted after the indicated sterility expiration date.

ADVERSE EVENT REPORTING

Adverse events and/or potentially sight threatening complications that may be regarded as lens related and that were not previously expected in nature, severity or degree of incidence should be reported within five (5) days to Bausch & Lomb Incorporated. This information is being requested from all surgeons in order to document potential long-term effects of intraocular lens implantation.

Physicians are encouraged to report these events in order to aid in identifying emerging or potential problems with intraocular lenses. These problems may be related to a specific lot of lenses or may be indicative of long-term effects associated with these lenses or with IOLs in general. If you wish to report a problem, please call Bausch + Lomb at 1-800-338-2020.

PATIENT REGISTRATION INSTRUCTIONS AND REPORTING REGISTRATION

Each patient who receives an enVista IOL must be registered with Bausch + Lomb at the time of lens implantation. Registration is accomplished by completing the Implant Registration Card that is enclosed in the lens package and mailing it to Bausch + Lomb. Patient registration is essential and will assist Bausch + Lomb in responding to adverse reaction reports and/or potentially sight-threatening complications. An implant identification card is supplied in the lens package and must be given to the patient.

RETURNED GOODS POLICY

All lenses being returned must be accompanied by a returned goods authorization number issued by Bausch + Lomb Customer Service. Call 1-800-338-2020 for return authorization and full policy information.

WARRANTY

Bausch & Lomb Incorporated warrants that the intraocular lens, when delivered, will conform to all applicable laws and the manufacturer's then current version of the published specifications for such intraocular lens in all material respects and will be free from defects in material and workmanship.

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SYMBOLS USED ON LABELING

Symbol	Description	Symbol	Description
IOL	Intraocular Lens	②	Do Not Reuse
PC	Posterior Chamber		Use By (YYYY-MM: year-month)
PCL	Posterior Chamber Lens	STERILE R	Gamma Sterilized
UV	Ultraviolet	℞ ONLY	Caution: Federal (US) law restricts this device to sale by or on the order of a physician
D	Diopter	⚠	Caution: Consult Instructions for Use
$Ø_B$	Body Diameter (Optic Diameter)		Storage Temperature Limitation
$Ø_T$	Overall Diameter (Overall Length)		Do Not Resterilize
SN	Serial Number		Member Green Dot Scheme

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EC REP

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