STATISTICAL ANALYSIS PLAN

Protocol Number: 945

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Terms or Abbreviations	Definitions
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BCDVA	Best-Corrected Distance Visual Acuity
CI	Confidence Interval
CSR	Clinical Study Report
D	Diopter
DCIVA	Distance-Corrected Intermediate Visual Acuity
DCNVA	Distance-Corrected Near Visual Acuity
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
IOL	Intraocular Lens
IOP	Intraocular Pressure
IRT	Interactive Response Technology
ISO	International Organization for Standardization
ITT	Intent-to-Treat
logMAR	Logarithm of the Minimum Angle of Resolution
LS	Least Squares
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
NAVQ	Near Acuity Visual Questionnaire
NCS	Not Clinically Significant
OD	Right Eye
OS	Left Eye
PP	Per Protocol
PT	Preferred Term
QoV	Quality of Vision
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SPE	Safety and Performance Endpoint
SSI	Secondary Surgical Intervention

Terms or Abbreviations	Definitions
TEAE	Treatment-Emergent Adverse Event
TE-SAE	Treatment-Emergent Serious Adverse Event
UCDVA	Uncorrected Distance Visual Acuity
UCIVA	Uncorrected Intermediate Visual Acuity
UCNVA	Uncorrected Near Visual Acuity
VA	Visual Acuity
WHO	World Health Organization

2 Introduction

This statistical analysis plan (SAP) has been written in support of protocol number 945 (Version 8.0, 24 April 2023) and finalized before any analyses of the data. The SAP contains detailed information to aid in the performance of the statistical analyses and reporting of the study data for use in the final clinical study report (CSR). This SAP was written with due consideration of the recommendations outlined in the most recent International Conference on Harmonization (ICH) E9 Guideline entitled: Statistical Principles for Clinical Trials, the most recent ICH E3 Guideline entitled: Structure and Content of Clinical Study Reports, and International Organization for Standardization (ISO) 11979-7:2018.

This SAP describes the data that will be analyzed and the subject characteristics, efficacy, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. If additional analyses are required to supplement the planned analyses described in this SAP, they may be completed and will be identified in the CSR.

3 Study Objective and Clinical Parameters

3.1 Study Objective

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

3.2 Study Endpoints

3.2.1 Primary Safety Endpoints

Primary safety endpoints are:

- The incidence of all serious adverse events (SAEs), including secondary surgical interventions (SSIs) related to the optical properties of the IOL, in first eyes through study exit
- Rate of SSIs due to the optical properties of the IOL for first eyes through study exit
- The incidence of treatment-emergent adverse events (TEAEs) in first eyes compared to International Organization for Standardization (ISO) safety and performance endpoint (SPE) rates as defined in ISO 11979-7:2018 through study exit.

3.2.2 Secondary Safety Endpoints

Secondary Safety Endpoints are:

- The rate of visual disturbances reported as “severe” by subjects as well as the rate of visual disturbances reported as “very” bothersome by subjects using the quality of vision (QoV) questionnaire 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 second and "all" eyes
- Incidence of all other types of adverse events in first eyes, second eyes, and "all" eyes

3.2.3 Primary Effectiveness Endpoints

Primary effectiveness endpoints are:

- Photopic monocular best-corrected distance visual acuity (BCDVA; logarithm of the minimum angle of resolution [logMAR]) 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; logMAR) 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; logMAR) in first eyes at 66 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)

3.2.4 Secondary Effectiveness Endpoints

Secondary effectiveness endpoints are:

- Photopic binocular DCNVA (logMAR) at 40 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
- Photopic binocular uncorrected near visual acuity (UCNVA; logMAR) at 40 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
- Photopic binocular DCIVA (logMAR) at 66 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
- Photopic binocular uncorrected intermediate visual acuity (UCIVA; logMAR) at 66 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
- Photopic monocular BCDVA (logMAR), DCNVA (logMAR) and DCIVA (logMAR) in first eyes at Post-Operative Visit 5 (Day 330 to 420 after second eye IOL implantation)

3.2.5 Other Effectiveness Assessments

Other effectiveness assessments are:

1. Photopic monocular UCDVA (logMAR) by eye and visit
2. Photopic binocular UCDVA (logMAR) by visit
3. Photopic monocular BCDVA (logMAR) by eye and visit, except for first eyes at Post-Operative Visit 4 (Day 330 to 420 after second eye IOL implantation)
4. Photopic binocular BCDVA (logMAR) by visit
5. Photopic monocular UCNVA (logMAR) at 40 cm by eye and visit
6. Photopic binocular UCNVA (logMAR) at 40 cm by visit, except for Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
7. Photopic monocular DCNVA (logMAR) at 40 cm by eye and visit, except for first eyes at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) and Visit 5 (Day 330 to 420 after second eye IOL implantation)
8. Photopic binocular DCNVA (logMAR) at 40 cm, except for Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)

9. Mesopic monocular DCNVA (logMAR) by eye and visit
10. Mesopic binocular DCNVA (logMAR) by visit
11. Photopic monocular UCIVA (logMAR) at 66 cm by eye and visit
12. Photopic binocular UCIVA (logMAR) at 66 cm by visit, except for Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
13. Photopic monocular DCIVA (logMAR) at 66 cm by eye and visit, except for first eyes at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) and Visit 5 (Day 330 to 420 after second eye IOL implantation)
14. Photopic binocular DCIVA (logMAR) at 66 cm by visit, except for Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
15. Mesopic monocular DCIVA (logMAR) at 66 cm by eye and visit
16. Mesopic binocular DCIVA (logMAR) at 66 cm by eye and visit
17. Binocular Defocus Curves at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
18. Rate of eyes with photopic monocular BCDVA 20/40 or better at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) for first eyes, second eyes, and all eyes in the Intent-to-Treat (ITT), Modified Intent-to-Treat (mITT), and Best Case sets
19. Rate of eyes with photopic binocular BCDVA 20/40 or better at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) in the ITT, mITT, and Best Case sets

3.2.6 Other Safety Assessments

Other safety assessments are:

- Rate of eyes with visual acuity (VA) decreases of 10 letters or more between a visit and a later visit evaluation
- Adverse Events (AEs)
- Intraocular pressure (IOP) by visit
- Slit-lamp exam results by visit
- Dilated fundus exam results by visit
- Posterior capsulotomy assessment results by visit

3.2.7 Other Assessments

Other assessments are:

- Pupil size by visit
- Keratometry by visit
- Manifest refraction by visit
- IOL tilt and decentration by visit
- Chord length 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)
- QoV questionnaire at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)
- Near Activity Visual Questionnaire (NAVQ) at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) (Use of the exploratory NAVQ subject questionnaire will be discontinued after written FDA acceptance of the protocol

Version 5 [Version date 23 April 2021], with the exception that subjects who have completed the NAVQ pre-operatively at the time of NAVQ discontinuation also will be asked to complete the NAVQ at Post-Operative Visit 4 [120 days to 180 days after second IOL implantation])

- Prolonged use of anti-inflammatory medication beyond 6 weeks
- Trial frame astigmatism sub study assessments (photopic monocular BCDVA, DCIVA, and DCNVA) at Post-Operative Visit 6 (Day 2 to 30 post Visit 5)

3.3 Statistical Hypotheses

3.3.1 First Primary Safety Endpoint

There is no statistical hypothesis associated with the proportion of first eyes in the modified safety set with at least one SAE.

3.3.2 Second Primary Safety Endpoint

The second primary safety endpoint is the rate of SSIs due to the optical properties of the lens. The null (H_0) and alternative (H_1) 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 in the first eyes that underwent at least one SSI related to the optical properties of the IOL;
- π_C = the proportion of the Control (monofocal) group in the first eyes that underwent at least one SSI related to the optical properties of the IOL; and
- 0.034 is the non-inferiority margin.

3.3.3 Third Primary Safety Endpoint

The third primary safety endpoint is the incidence of TEAEs in first Test (trifocal) eyes compared to ISO SPE rates as defined in ISO 11979-7:2018. For each ISO 11979-7 SPE grid AE, the null (H_0) and alternative (H_1) 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 AE; and
- π_0 = the historical control proportion of eyes with the AE 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.

3.3.4 Secondary Safety Endpoints

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.

3.3.5 Primary 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 (Day 120 to 180 after second eye IOL implantation), 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
- μ_C = the mean logMAR BCDVA of the Control (monofocal) group
- 0.10 is the non-inferiority margin

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 (Day 120 to 180 after second eye IOL implantation), the null (H_0) and alternative (H_1) 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
- 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 (Day 120 to 180 after second eye IOL implantation), the null (H_0) and alternative (H_1) 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
- 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.

3.3.6 Secondary Effectiveness Endpoints

First Secondary Effectiveness Endpoint

For the first secondary effectiveness endpoint, photopic binocular logMAR DCNVA at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation), the null (H_0) and alternative (H_1) 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
- 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 logMAR UCNVA at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation), the null (H_0) and alternative (H_1) 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
- 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 logMAR DCIVA at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation), the null (H_0) and alternative (H_1) 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
- 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 logMAR UCIVA at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation), the null (H_0) and alternative (H_1) 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
- 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 is less than the mean for the Control group, then it will be concluded that the Test IOL 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 logMAR BCDVA, DCNVA, and DCIVA evaluated at Post-Operative Visit 5 (Day 330 to 420 after second eye IOL implantation).

4 Study Design and Procedure

4.1 General Study Design

This is a prospective, multicenter, randomized, active-controlled study to evaluate the safety and effectiveness of bilateral implantation of the enVista one-piece hydrophobic acrylic trifocal intraocular lens (Model MX60EF) in subjects undergoing cataract extraction compared to bilateral implantation of the enVista one-piece hydrophobic acrylic monofocal intraocular lens (model MX60E). Enrolled subjects who meet eligibility criteria will be seen at 11 or 12 visits according to the schedule provided in Table 1.

Table 1. Visit 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 to 420 post Visit 00B
Post-Operative Visit 6 (subjects that consent at participating sites)	Both Eyes	Day 2 to 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 implanted bilaterally with the enVista MX60EF (trifocal) multifocal IOL
- Group 2 (Control): Approximately 167 control subjects will be implanted bilaterally with the enVista MX60E monofocal IOL

Subjects who meet eligibility criteria will be randomly assigned to Group 1 or Group 2 in a 2:1 ratio on the first operative day, Day 0. 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) at the Preoperative Visit will be treated first (eye A) and used in the primary monocular evaluations. If the qualifying visual acuity is obtained with a glare source, the eye with the worse BCDVA with glare will be treated first. 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 Post-Operative Visit 5 (330 – 420 days after second eye implantation).

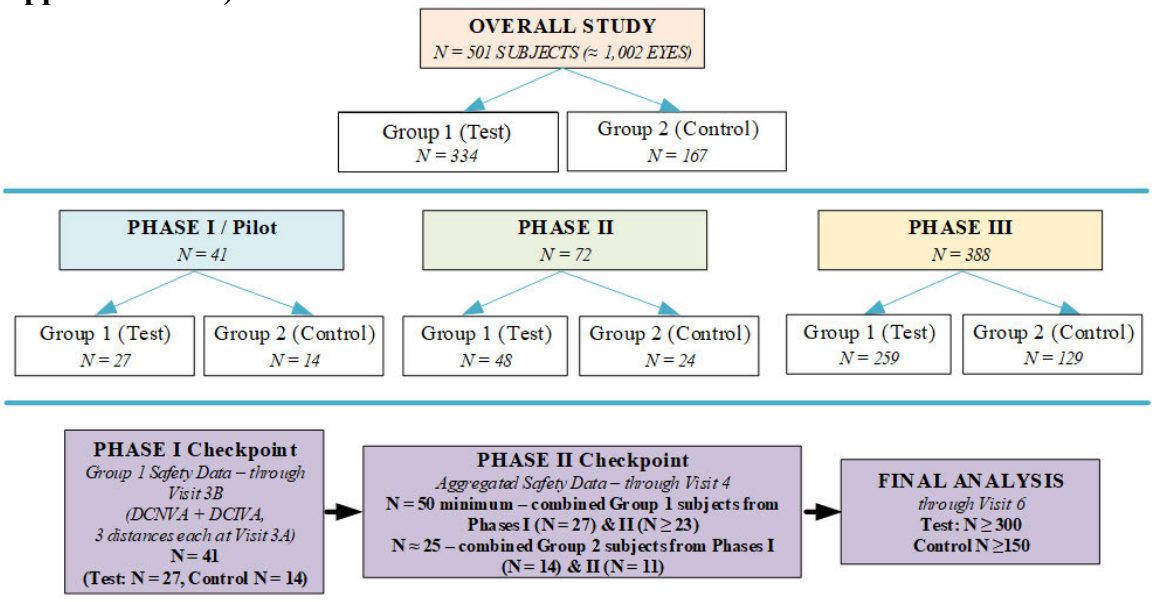
Study enrollment will occur in three Phases as follows:

- 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 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 Food and Drug Administration (FDA) based on Phase I data.

- Phase II – When a minimum of 50 Phase I and Phase II Group 1 subjects have been enrolled and followed through Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation), summaries and/or listings of all available safety data through Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) 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 Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) 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 Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) will also 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 72 Phase II subjects (including those whose data were submitted to the FDA).
- Phase III – The remainder of subjects will be enrolled and followed to Post-Operative Visit 5 (Day 330 to 420 after second eye IOL implantation) or, for subjects who have consented and enrolled in the Trial Frames Astigmatism sub-study, to Post-Operative Visit 6.

Figure 1. Study Scheme for Planned Enrollment in All Phases (Subject Numbers are Approximations)



A pilot test was 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, were measured for all enrolled subjects. During Phase I/Pilot, DCNVA was collected at three candidate distances: 30 cm, 35 cm, and 40 cm, and DCIVA was collected at three candidate distances: 56, 66 and 76 cm. This phase included approximately the first 27 subjects implanted with the enVista trifocal IOL in Group 1 and approximately the first 14

subjects implanted with the enVista monofocal IOL in Group 2. Photopic monocular DCNVA and DCIVA were assessed at each candidate distance at Visit 3A using Early Treatment Diabetic Retinopathy Study (ETDRS) charts normalized for letter size as a function of distance tested. The near and intermediate distance visual acuity (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.

Refer to Protocol Appendix A for the Study Flow Chart.

4.2 Sub-Studies

4.2.1 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 Protocol Appendix B, Section 11.0, 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.

4.2.2 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.

4.2.3 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.

4.2.4 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 (Day 330 to 420 after second eye IOL implantation) 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 IOLs.

5 Treatment Plan

5.1 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 MX60EF trifocal (Test) IOL or enVista MX60E monofocal (Control) IOL in both eyes.

5.1.1 Treatment Allocation

At the time of the first surgery following uncomplicated cataract extraction, subjects will be randomly assigned to either the enVista MX60EF trifocal IOL or enVista MX60E monofocal IOL in a 2:1 ratio based upon a predetermined randomization scheme.

5.1.2 Randomization Method

Subjects will be randomly assigned to receive either the enVista trifocal (Test) IOL bilaterally or the enVista monofocal (Control) IOL bilaterally according to the randomization scheme to be provided.

An Interactive Response Technology (IRT) system 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 IOL or Control MX60E enVista monofocal IOL at each site will be approximately 2:1.

5.1.3 Treatment or Subject Replacement

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

5.1.4 Masking and Unmasking

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, VA, 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.

6 Sample Size and Power Considerations

6.1 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 (SD) 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 Post-Operative Visit 3A (Day 30 to 60 after first eye IOL implantation).

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 SD 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 Post-Operative Visit 3A (Day 30 to 60 after first eye IOL implantation).

6.2 Primary Safety Endpoints

Regarding the rate of all SAEs, 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 SSIs 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 (CI) 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 CI.

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

6.3 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 second and “all” eyes, no statistical hypotheses will be tested. Therefore, no sample size calculation is required.

Regarding the incidence of all other types of AEs in first eyes, second eyes, and “all” eyes, no statistical hypotheses will be tested. Therefore, no sample size calculation is required.

6.4 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 VA 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, μT - μS, 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 SD 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 SD 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).

6.5 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 VA 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 SD 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 SD 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 SD 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 SD 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 Post-Operative Visit 5 (Day 330 to 420 after second eye IOL implantation), so no sample size calculations are necessary for these endpoints.

6.6 Sub-Studies

6.6.1 Defocus Curves

At least 10 test enVista trifocal IOL subjects and 10 control enVista monofocal IOL subjects will be evaluated to obtain defocus curves in each of the following photopic pupil size groups: small (≤3.0 mm), medium (>3.0 mm and ≤4.0 mm), and large (>4.0 mm), and determined under photopic lighting conditions. The defocus curve sub-study subjects will be enrolled sequentially. If ten subjects are not available in any pupil size category for a treatment group, then the maximum number available will be used.

6.6.2 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.

6.6.3 Optical Coherence Tomography 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.

6.6.4 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 (Day 330 to 420 after second eye IOL implantation) 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 IOLs.

6.7 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.

7 Output Data and Data Analysis Convention

The following reporting conventions will be used:

All data will be provided in data listings sorted by the study center, subject number, and visit will be presented in all listings, when applicable. Listings will be presented for all randomized subjects unless otherwise specified.

Descriptive statistics will include: number of non-missing values (n), mean, median, SD, minimum, maximum for continuous variables, and n (%) for categorical variables. The mean, median, and the upper and lower limits of the CI for the mean will be displayed to one more decimal place than the original data or derived analysis data. The SD values will be displayed to two more decimal places than the original data. The minimum and maximum will be displayed to the same number of decimal places as the original data.

The number and percentage of responses will be presented in the form XX (XX.X), 0, or XXX (100) unless specified otherwise, where the percentage is in parentheses. The denominator of all percentages will be number of subjects in the analysis population, unless otherwise stated. When count data are presented, the percent will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted “Missing” will be included in count tabulations where necessary to account for dropouts and missing values. Non-zero percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places.

Differences between treatment groups will be calculated as test IOL minus control IOL.
All analyses will be conducted using SAS® Version 9.4.

8 Analysis Populations

8.1 Intent-to-Treat (ITT) Set

The ITT 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.

8.2 Modified Intent-to-Treat (mITT) Set

The mITT 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. Randomized subjects who will be excluded from this set will be identified prior to database lock and unmasking.

8.3 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.

8.4 Per Protocol (PP) Set

The Per-Protocol (PP) Set will include all bilaterally implanted subjects without major protocol deviations. The PP set will summarize eyes/subjects as treated.

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. The major protocol deviations will be determined prior to treatment unmasking.

8.5 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 the following characteristics:

- No clinically significant pre-operative 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 pre-operative 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

Prior to treatment unmasking, other criteria may be added. The Best Case Set will summarize eyes/subjects as treated.

9 General Statistical Considerations

9.1 Unit of Analysis

The unit of analysis in this study will be the subject or the eyes for all efficacy and safety summaries.

9.2 Dropouts or Missing Data Handling

For primary analysis of primary and secondary effectiveness endpoints, missing data will not be imputed for the non-inferiority analyses and will be imputed using multiple imputation Markov Chain Monte Carlo (MCMC) methods for the superiority analyses (see Section 13.3.2). For analyses of safety and exploratory effectiveness endpoints, missing data will not be imputed unless specified otherwise.

Partial/missing start and end dates for AEs and concomitant medications will be imputed as follows:

Partial/missing start date:

- Dates with missing day only will be imputed as the 1st of the month unless the month and year are same as the month and year of the implant date for the corresponding eye for ocular AEs or the first implant date for the non-ocular AEs in which case missing day will be imputed as the implant day for the corresponding eye for ocular AEs or the first implant day for the non-ocular AEs.
- Dates with both day and month missing will be imputed as 1 Jan unless the year is same as the year of the implant date for the corresponding eye for ocular AEs or the first implant date for the non-ocular AEs, in which case missing day and month will be imputed as the implant day and month for the corresponding eye for ocular AEs or the first implant day and month for the non-ocular AEs.
- Completely missing dates will be imputed as the implant date for the corresponding eye for ocular AEs or the first implant date for the non-ocular AEs unless the end date is on or before the implant date for the corresponding eye for ocular AEs or the first implant date for the non-ocular AEs, in which case missing date will be imputed as 1 Jan of the same year as the end date.

Partial/missing end date for AEs reported as “Resolved:”

- Dates with missing day only will be imputed as the last day of the month.
- Dates with both day and month missing will be imputed as 31 Dec.
- Completely missing end dates will have an imputed end date of 31 Dec 2023
- If the imputed date is after the date of death, then the end date will be set equal to the date of death.

The original dates will be displayed in data listings and the imputed dates will be used in derivations only (study day, treatment-emergence status, etc.).

COVID-19-related missing data or visits will not be imputed for summaries and analyses but will be reported as protocol deviations and recorded in protocol deviation log.

9.3 Multicenter Issues

Data from all study centers will be combined for summaries/analyses, unless specified otherwise.

9.4 Multiplicity Issues

As all of the primary safety and effectiveness endpoints with success criteria described in Section 3.3 are required to demonstrate statistical success, adjustment for multiplicity is not necessary for these endpoints.

Statistical testing of the secondary effectiveness 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 effectiveness 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.

9.5 Visit Window

For analysis of data by visit, only in-window visit data will be included in the analysis of a scheduled visit's data. 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.

9.6 logMAR Calculation

The following effectiveness data will be assessed as letters read correctly (letters correct) or as count fingers (CF), hand motion (HM), light perception (LP), or no light perception (NLP):

- Photopic monocular/binocular UCDVA
- Photopic monocular/binocular BCDVA
- Photopic monocular/binocular UCNVA
- Photopic monocular/binocular DCNVA
- Mesopic monocular/binocular DCNVA
- Photopic monocular/binocular UCIVA
- Photopic monocular/binocular DCIVA
- Mesopic monocular/binocular DCIVA
- Binocular BCDVA Defocus Curves
- Photopic monocular BCDVA (simulated astigmatism)
- Photopic monocular DCNVA (simulated astigmatism)
- Photopic monocular DCIVA (simulated astigmatism)

The logMAR VA for the data listed above will be computed as follows for subjects who can read at least one letter.

$$\text{logMAR VA} = 1.70 - (0.02 \times \text{letters read correctly})$$

Subjects who cannot read any letters but who can count fingers will be assigned a logMAR VA value of 2.00. Subjects who cannot read any letters but who can perceive hand motion will be assigned a logMAR VA value of 2.30. Subjects who cannot perceive hand motion will be assigned a logMAR VA value of missing.

For UCDVA and BCDVA data, logMAR score will be captured in the Electronic Data Capture (EDC) database. The scores will not be pulled from EDC database directly.

9.7 Subject Disposition

Enrollment status for all subjects will be summarized in a table for each investigator site by randomized treatment and overall for all subjects in addition to the number of screen failures and number of randomized subjects.

Summary for subject disposition by treatment and overall for all subjects will include:

- Number of screen failures for all subjects only
- Number of randomized subjects
- Number and percentage of implanted subjects
- Number and percentage of subjects with eyes touched with study IOL
- Number and percentage of subjects for each of the study sets (ITT Set, mITT Set, Modified Safety Set, PP Set, and Best Case Set)
- Number and percentage of subjects who completed the study.
- Number and percentage of subjects discontinued from the study, with subcategories for number and percentage of subjects who discontinued before first implant, discontinued after the first implant but before the second implant, and discontinued after the second implant. In addition, for those subjects that did not complete the entire study, the reason for study discontinuation will be summarized.
- Number and percentage of subjects who completed through Visit 4 and who discontinued prior to Visit 4 and reason for discontinuation prior to Visit 4.

Percentages will be based on number of randomized subjects for subject disposition summary.

A summary for eyes disposition by treatment and overall for all subjects will include:

- Number of randomized eyes
- Number of treated eyes
- Number and percentage of implanted eyes
- Number and percentage of eyes touched with study IOL
- Number and percentage of eyes for each of the study populations (mITT, Modified Safety Set, PP Set, and Best Case Set)

Percentages will be based on number of randomized eyes for eyes disposition summary unless specified otherwise.

Subject accountability by visit up to Visit 5 will be provided for summaries of the following categories by treatment group and overall for all subjects based on the ITT Set, mITT Set, PP Set, and Best Case Set:

- Total number of all subjects
- Total number of subjects with an eye touched with study IOL
- Total number of implanted subjects
- Number of subjects available for analysis by visit
- Number of subjects discontinued by visit
- Number of subjects missing a scheduled visit but seen later by visit
- Number of subjects not seen but accounted for by visit
- Number of subjects lost to follow-up by visit
- Active (represents the number of subjects that have not reached the time associated with a visit.) by visit
- Percent accountability presented by visit. % Accountability is calculated as 100*(Available for analysis)/(Enrolled – Discontinued – Active).

Subject accountability by visit up to Visit 5 for each site will also be summarized similarly based on the ITT Set.

Eye accountability by visit up to Visit 5 will be summarized in the same way as the subject accountability by visit.

Disposition, randomization, enrollment status, inclusion/exclusion criteria, subject accountability by visit, and population listing data for randomized subjects will be presented in data listings.

10 Protocol Deviations

Protocol deviations will be evaluated for all randomized subjects. Major protocol deviations will be determined by a masked evaluation prior to the unmasking of the study treatment. Numbers of subjects with any protocol deviations, any major protocol deviations, any minor protocol deviations, and any COVID-19 related deviations will be summarized by treatment and overall for all subjects for the mITT Set. In addition, major protocol deviations leading to exclude subjects from the PP set will be determined by a masked evaluation prior to the unmasking of the study treatment. Numbers of subjects with major protocol deviations will also be summarized by treatment and overall for all subjects for the mITT Set.

All protocol deviations will be presented in a data listing.

11 Demographic, Pre-Operative, and Operative Variables

Demographics at the subject level will be summarized by treatment group for the mITT Set, Modified Safety Set, PP Set, and Best Case Set. Pre-operative variables and operative variables will be summarized by treatment group for the first eyes, the second eyes, and all eyes separately for the Modified Safety Set.

Demographic data will include gender, age in years at signing of informed consent form (ICF), age group (18 -64 years, 65 – 84 years, and ≥ 85 years), race, ethnicity, first eye (OD, OS), and study phase under which the subject enrolled. Subjects who record more than one race will be grouped into the single category denoted as multi-racial.

The pre-operative variables include:

- Potential Visual Acuity (Snellen: Better than 20/32, 20/32 or Worse, Not Done)
- Axial length (mm)
- Anterior chamber depth (mm)
- Targeted refraction (D)
- Corneal topography (Normal, Abnormal)
- Cataract type (nuclear, cortical, posterior sub-capsular, combination)
- Cataract density (slight [1+], moderate [2+], dense [3+], very dense [4+])

The operative variables will include:

- IOL Power (+16.0 to +24.0 by increments of 0.5)
- Femtosecond laser used for surgery (Yes, No) and type if laser used (corneal incision, anterior capsulotomy, cataract fragmentation)
- Was study lens successfully implanted? (Yes, No)

Data listings for demographic data, pre-operative variables, and operative variables will be presented.

12 Concomitant Medications

Medications will be coded using World Health Organization (WHO) Drug Dictionary (Global B2, March 2018). Concomitant medications will be defined as medications used during the operation or after the operation. Ocular and non-ocular concomitant medications used at the subject level will be summarized separately by the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] 4 classification), preferred name, and treatment for the Modified Safety Set. If the ATC 4 classification is not provided, the next lowest classification that is provided in the coding dictionary will be used. The preferred name will be defined as the active ingredient; if the active ingredient is not provided or includes more than two ingredients (e.g., multivitamins) then the drug name will be presented as the preferred name.

Prolonged use of anti-inflammatory medication beyond 6 weeks will also be summarized by drug class, preferred name, and treatment for the Modified Safety Set.

Reported and coded terms (drug class and preferred name) for all medications will be presented in a data listing. Prolonged use of anti-inflammatory medication beyond 6 weeks will be presented in separate listing.

13 Statistical Analyses

13.1 Primary Safety Analyses

13.1.1 First Eyes with at Least One Ocular Treatment-Emergent SAEs

The proportion of first Modified Safety Set eyes with at least one ocular treatment-emergent serious adverse event (TE-SAE) will be summarized using categorical summary statistics by treatment received. Each eye will be counted only once in the calculation of the rate. Similar supportive analyses will be presented for second eyes and all eyes for the Modified Safety Set.

13.1.2 SSIs Related to the Optical Properties of the IOL

The SSIs 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 SSI 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 an SSI related to the optical properties of the IOL or not having undergone such an intervention. Missing data will not be imputed.

First eyes with SSIs related to the optical properties of the IOL will be summarized categorically by actual treatment received for the Modified Safety Set. A two-sided 90% CI 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.

As supportive analyses, the rates of SSIs due to the optical properties of the lens in second eyes and in all eyes will be presented using descriptive statistics by treatment group.

All SSIs will be presented in a data listing.

13.1.3 ISO Grid AEs

Cumulative and persistent ISO grid AEs listed in Table 2 will be summarized categorically for the Modified Safety Set by treatment received. The primary statistical analysis will include first Modified Safety Set eyes with the Test IOL.

Table 2. SPE Rate for Posterior Chamber IOL AEs (ISO 11979-7:2018, Table E.2)

Adverse Event	SPE Rate
Cumulative	
Cystoid macular edema	3.0
Hypopyon	0.3
Endophthalmitis[a]	0.1
Lens dislocated from posterior chamber	0.1
Pupillary block	0.1
Retinal detachment	0.3
Secondary surgical intervention[b]	0.8
Persistent	
Corneal stroma oedema	0.3
Cystoid macular oedema	0.5
Iritis	0.3
Raised IOP requiring treatment	0.4

[a] Endophthalmitis is defined as intraocular inflammation (sterile or infectious) leading to diagnostic vitreous tap and use of intraocular antibiotics.
[b] Excludes posterior capsulotomies.

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 eyes in the Test group with the event at Post-Operative Visit 5. The denominator for persistent AEs will be the number of first Test group eyes present at Post-Operative 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.

Statistical 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.

As supportive analysis, the incidence of SPE AEs (as defined in ISO 11979-7) in second eyes and all eyes will be presented using descriptive statistics by AE type and by treatment group.

The summary and analysis for first eyes will also be performed by age group (<65 years and ≥65 years) and by site.

All ISO Grid AEs will be presented in a data listing.

13.2 Secondary Safety Analyses

13.2.1 Subjects Experiencing at Least One Severe Visual Disturbance

The rates of visual disturbances reported as "severe" for Questions 1B – 10B by subjects, as well as the rates of visual disturbances reported as "very" bothersome for Questions 1C-10C by subjects, using the QoV questionnaire measure through Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) will be summarized using descriptive statistics by treatment for the Modified Safety Set. Each subject will be counted only once in the calculation of the rate.

13.2.2 Contrast Sensitivity

Contrast sensitivity will be evaluated for a subset of subjects. Binocular contrast will be assessed in log units two times per subject at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) or (in the case of a capsulotomy after Visit 4) Post-Operative Visit 5 (Day 330 to 420 after second eye IOL implantation) under each of the conditions on Table 3.

Table 3. Binocular Contrast Sensitivity Conditions

Lighting Condition	**Spatial Frequencies**
Photopic lighting with glare	3, 6, 12, and 18 cycles per degree (cpd)
Mesopic lighting with glare	1.5, 3, 6, and 12 cpd
Mesopic lighting without glare	1.5, 3, 6, and 12 cpd

For each subject, the two values will be recorded under each combination of conditions. The values reported in EDC database will be converted for analyses following the rule: values of 1 will be set as missing and all remaining values will be multiplied by -1 to convert log contrast to log contrast sensitivity. The average of converted values will be used for analyses. If a subject has only one converted value for a certain condition, then the single value will be considered the average. Only the converted values will be used for tables, listings, and figures.

Contrast sensitivity (in log units) will be summarized descriptively using continuous summary statistics by lighting condition (photopic or mesopic and with glare or without glare), spatial frequency, treatment received, and visit for the Modified Safety Set. Since each subject will have been assessed once at either Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) or Post-Operative Visit 5 (Day 330 to 420 after second eye IOL implantation), summaries will also be presented by lighting condition, spatial frequency, and treatment received. If the subject was assessed at both 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), then the value from Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) will be used if no capsulotomy was performed for the subject. Otherwise, the value from Post-Operative Visit 5 (Day 330 to 420 after second eye IOL implantation) will be used.

Estimates of the differences between treatment groups, with two-sided 95% confidence intervals, will be provided by lighting condition and spatial frequency using the values

obtained at either Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) or Post-Operative Visit 5 (Day 330 to 420 after second eye IOL implantation).

Mean log contrast sensitivity will be plotted versus spatial frequency, with the treatment groups overlaid, separately by lighting condition and visit.

The contrast sensitivity data will be presented in a data listing, which will include the value used to compute statistics by lighting condition and spatial frequency.

13.2.3 Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.1. Ocular TEAEs will be defined as ocular AEs with onset dates on or after the date of study lens implantation for the eye. Non-ocular TEAEs are defined as non-ocular AEs with onset dates on or after the date of first study lens implantation. Ocular AEs will be AEs with an Eye designation of OD, OS, or OU in the electronic Case Report Form. Non-ocular AEs will be AEs with an Eye designation of N/A.

Ocular TEAEs in first eyes and second eyes will be summarized separately by treatment received for the Modified Safety Set according to the following list. Summaries of all eyes will be provided separately at the eye and subject levels.

- Overall summary of TEAEs (the number and percentage of subjects [or eyes] who experienced at least one ocular TEAE, ocular TE-SAE, ocular TEAEs by maximum severity, ocular TEAEs by strongest relationship to study device, ocular TEAEs by strongest relationship to surgical procedure, ocular TE-SAEs by strongest relationship to study device, and ocular TE-SAEs by strongest relationship to surgical procedure)
- Ocular TEAEs by system organ class (SOC) and preferred term (PT)
- Ocular TEAEs by SOC and PT and by age group (<65 years and ≥65 years)
- Ocular TEAEs by SOC and PT and by site
- Ocular TE-SAEs by SOC and PT
- Ocular TEAEs by SOC, PT, and strongest relationship to study device
- Ocular TEAEs by SOC, PT, and strongest relationship to surgical procedure
- Ocular TE-SAEs by SOC, PT, and strongest relationship to study device
- Ocular TE-SAEs by SOC, PT, and strongest relationship to surgical procedure
- Ocular TEAEs by SOC, PT, and maximum severity
- Ocular TE-SAEs by SOC, PT, and maximum severity

Non-ocular TE-SAEs at the subject level will also be summarized.

The incidence of the following further defined Ocular TEAEs of special interest 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 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 implanted eye or later

All AEs, Ocular SAEs, ocular AEs related to study device or surgical procedure, AEs of special interest, and non-ocular SAEs will be presented in separate data listings.

13.3 Primary Effectiveness Analyses

All data collected for corrected and uncorrected visual acuity assessments will be presented in data listings, separated by monocular and binocular as well as photopic and mesopic.

13.3.1 Photopic Monocular BCDVA

Photopic monocular BCDVA (logMAR) in first eyes at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) will be summarized using continuous summary statistics by treatment group. Imputation of missing data is not conservative in non-inferiority testing. Therefore, missing data will not be imputed for the BCDVA non-inferiority test. An analysis of covariance (ANCOVA) model will be constructed with BCDVA as the dependent variable and treatment and site as fixed factors. The treatment effect (least squares [LS] mean for Test group IOL minus LS mean for Control group IOL) will be estimated in addition to a two-sided 90% CI. 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 summary and analysis will be performed for both ITT and mITT Sets.

The previous continuous summary statistics will also be provided for the PP 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.

The BCDVA at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) 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 ITT, mITT, and Best Case Sets. Two-sided exact binomial 90% CIs around the proportions of eyes 20/40 or better will be presented. Categorical summaries will use whole line binning as shown in Table 4.

Table 4. logMAR to Snellen Conversion Table

logMAR Value	Cumulative Snellen Category
≤ 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 ITT, 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 in ITT and mITT Sets and 96.7% for Best Case Set 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. Similar analysis will be performed for first eyes and second eyes as supportive analysis.

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

BCDVA will also be summarized by treatment group for the mITT Set at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation), both continuously and categorically, with both mutually exclusive and cumulative categories from 20/20 or better through worse than 20/40, stratified by the following variables.

- Age group (< 65 and ≥ 65 years)
- Adverse events in the ISO Grid
- Site

13.3.2 Photopic Monocular DCNVA

Phase I/Pilot subjects will be excluded from the analysis of this endpoint.

Photopic monocular DCNVA (logMAR) at 40 cm in first eyes at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) will be summarized using continuous summary statistics in logMAR units by treatment assignment for the mITT Set.

If there are missing mITT Set monocular DCNVA data in first eyes at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation), then missing data will be imputed using the MCMC multiple imputation method. A total of 30 imputation datasets will be created. After imputation of missing data, the statistical hypotheses will be tested using an ANCOVA model with treatment and site as fixed factors by imputation.

SAS® code for the MCMC multiple imputation:

```
PROC MI DATA=indata OUT=mcmc NIMPUTE=30 SEED= 1091148178;
 BY trt
 MCMC INITIAL=EM;
 VAR V3 V4;
RUN;
```

where

- `trt` = treatment
- `v3` = actual value at Visit 3A
- `v4` = actual value at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation)

An overall p-value resulting from the multiple imputation method will be estimated. The treatment effect (LS mean for Test group IOL VA minus LS mean Control group IOL VA) in logMAR units and a two-sided 95% CI will be provided. 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 the Control IOL) in this outcome.

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

As a sensitivity analysis, observed DCNVA (logMAR) at 40 cm in first eyes at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) will be compared between treatment groups using an ANCOVA model with treatment and site as fixed factors. The treatment effect (LS mean for Test group IOL VA minus LS mean Control group IOL VA) in logMAR units and a two-sided 95% CI will be provided. The analysis will be for the ITT set.

13.3.3 Photopic Monocular DCIVA

Phase I/Pilot subjects will be excluded from the analysis of this endpoint.

Photopic monocular DCIVA (logMAR) at 66 cm in first eyes at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) will be summarized and analyzed similarly to the second primary effectiveness endpoint in Section 13.3.2 using a seed of 1340584231 for multiple imputation.

13.4 Secondary Effectiveness Analyses

13.4.1 Photopic Binocular DCNVA

Phase I/Pilot subjects will be excluded from the analysis of this endpoint.

Photopic binocular DCNVA (logMAR) at 40 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) will be analyzed using an ANCOVA with DCNVA as the dependent variable and treatment and site as fixed factors. The treatment effect (LS mean for Test group IOL minus LS mean for Control group IOL) will be estimated in addition to a two-sided 90% CI. The analysis will be based on observed data for ITT, mITT, and PP sets. Multiple imputation of missing data will not be applied.

13.4.2 Photopic Binocular UCNVA

Phase I/Pilot subjects will be excluded from the analysis of this endpoint.

Photopic binocular DCNVA (logMAR) at 40 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) will be analyzed similarly to the analyses of the second primary effectiveness endpoints described in Section 13.3.2 using a seed of 178029470 for imputation of missing data.

13.4.3 Photopic Binocular DCIVA

Phase I/Pilot subjects will be excluded from the analysis of this endpoint.

Photopic binocular DCIVA (logMAR) at 66 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) will be analyzed using an ANCOVA with DCIVA as the dependent variable and treatment and site as fixed factors. The treatment effect (LS mean for Test group IOL minus LS mean for Control group IOL) will be estimated in addition to a two-sided 90% CI. The analysis will be based on observed data for ITT, mITT, and PP sets. Multiple imputation of missing data will not be applied.

13.4.4 Photopic Binocular UCIVA

Phase I/Pilot subjects will be excluded from the analysis of this endpoint.

Photopic binocular DCIVA (logMAR) at 66 cm at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) will be analyzed similarly to the analyses of the second primary effectiveness endpoints described in Section 13.3.2 using a seed of 1303271003 for imputation of missing data.

13.4.5 BCDVA, DCNVA, and DCIVA

First eye BCDVA, DCNVA, and DCIVA evaluated at Post-Operative Visit 5 (Day 330 to 420 after second eye IOL implantation) will be summarized descriptively using continuous summary statistics by treatment.

13.5 Supportive Effectiveness Analyses

13.5.1 Visual Acuity in Phase I/Pilot Subjects

Phase I/Pilot subjects will be excluded from the primary summaries of all the outcomes related to near and intermediate VA and will be summarized separately. Missing data will not be imputed.

The VA continuous effectiveness endpoints included in Section 3.2.5 will be summarized descriptively using continuous summary statistics by treatment assignment, eye, distance, and visit.

13.5.2 Categorical Analysis of Visual Acuity

For all corrected and uncorrected visual acuity endpoints at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation), logMAR value will be converted to Snellen equivalent. Percentages of eyes that achieve VA in Snellen equivalent for each category in both mutually exclusive (20/10, 20/12.5,….. 20/200, worse than 20/100) and cumulative categories (20/200 or better, 20/160 or better, …..20/12.5 or better) for first eyes, second eyes, and all eyes will be summarized by treatment group.

Categorical summaries will use the logMAR to Snellen conversion values as shown in Table 5.

Table 5. logMAR to Snellen Equivalent Conversion

logMAR Value, Rounded to the Nearest 0.1	Snellen Equivalent
Missing	Missing
-0.3	20/10
-0.2	20/12.5
-0.1	20/16
0.0	20/20
0.1	20/25
0.2	20/32
0.3	20/40
0.4	20/50
0.5	20/63
0.6	20/80
0.7	20/100
0.8	20/125
0.9	20/160
1.0	20/200
> 1.0	Worse than 20/200

The following rates will be also provided by treatment randomized for the mITT set; and for first eyes, second eyes, and all eyes where applicable:

- Rate of loss of visual acuity of 0.2 logMAR or more from Preoperative Visit 0A/B (Day -30 to -5) to post-operative Visit 4 in UCDVA
- Rates of loss of visual acuity of 0.2 logMAR or more from Preoperative Visit 0A/B (Day -30 to -5) to post-operative Visit 4 in BDCVA

Visual acuity data will be presented in a data listing. In addition, BCDVA of $\geq$ 0.3 logMAR and visual acuity data with a loss of at least 0.2 logMAR in UCDVA and BDCVA will be presented separately in data listings.

13.5.3 Binocular Defocus Curves

Assessment

Defocus curves will be assessed binocularly at the Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) under photopic conditions and may be assessed at unscheduled visits. Defocus powers will be +1.50 D to -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. Subjects will be selected in three photopic pupil size groups as measured at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation): small (less than 3.0 mm); medium (at least 3.0 and no more than 4.0 mm); and large (greater than 4.0 mm).

The number of letters read correctly under each testing condition will be recorded in the electronic Case Report Form.

Preprocessing

Letters read correctly will be converted to logMAR units and to Snellen equivalent prior to summarization.

Tables

The results at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) will be summarized continuously (logMAR) and discretely in both the mutually exclusive Snellen categories shown in Table 4 and in cumulative Snellen categories from 20/20 or better through 20/100 or better and worse than 20/100 by defocus lens power and treatment group for subjects in sub-study in a table. In addition, these summaries will be provided by pupil size (small [< 3.0 mm], medium [3.0 – 4.0 mm], large [> 4.0 mm]) and by axial length (short [< 21.0 mm], medium [21.0 – 26.0 mm], and large [> 26.0 mm]).

Listing

Defocus curve data will be provided for all subjects in the sub-study in a listing. The listing will display the subject number, treatment group, visit (Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation), Unscheduled), visit date, OD and OS pupil sizes (mm), axial length, defocus power (D), letters correct, logMAR visual acuity, and Snellen equivalent. The listing will be sorted by subject number in ascending order and, within subjects, by visit date in ascending order and, within visit date, by defocus power in descending order.

Figures

Defocus curves will be plotted in figures for subjects in sub-study at Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) and, separately, by pupil size (small, medium, large). Mean logMAR VA versus defocus lens power (D) will be plotted with the two treatment arms overlaid in each defocus curve plot.

The vertical axis will be labeled “Mean logMAR Visual Acuity.” Vertical axis tick marks will be displayed at 0.1 logMAR intervals in descending order (e.g., 1.0 at the bottom and -0.1 at

the top). Each vertical axis tick mark will be labeled with both the logMAR and, in parentheses, Snellen values (e.g., "0.5 (20/63)").

The horizontal axis will be labeled "Defocus Lens Power (D)." Horizontal axis tick marks will be in descending order (+1.50 D on the left and -3.50 D on the right) at 0.50 D intervals. The horizontal tick mark labels will be displayed to one decimal place.

Defocus curves will be interpolated between the plotted points using SAS® software's cubic spline method invoked by the statement INTERPOL = SPLINE in the SYMBOL statement (or a similar method). Horizontal and vertical grid lines will be included at each tick mark level.

14 Additional Clinical Parameters

14.1 Slit-Lamp Biomicroscope Examination

Slit-lamp biomicroscope examination results will be summarized categorically by treatment received and visit for first eyes, second eyes, and all eyes separately for the Modified Safety Set:

- Lid (not clinically significant [NCS], mild, moderate, severe, very severe)
- Conjunctiva
  - Normal
  - Abnormal (Hyperemia: none, mild, moderate, severe, very severe)
- Conjunctiva additional abnormalities (NCS, mild, moderate, severe, very severe)
- Superficial punctate keratopathy (none, mild, moderate, severe, very severe)
- Corneal wound edema (none, mild, moderate, severe)
- Cornea stromal edema (none, mild, moderate, severe)
- Cornea additional (NCS, mild, moderate, severe, very severe)
- Anterior chamber cells (0, 0.5+, 1+, 2+, 2+, 4+)
- Anterior chamber flare (0, 1+, 2+, 3+, 4+)
- Anterior additional (NCS, mild, moderate, severe, very severe)
- Iris/Pupil (Normal, Abnormal)
- Iris/Pupil abnormalities (NCS, mild, moderate, severe, very severe)
- Cataract density (slight [1+], moderate [2+], dense [3+], very dense [4+]), collected at pre-operative visit only

Slit-lamp biomicroscopy examination data will be presented in a data listing.

14.2 Manifest Refraction

Prior to analysis, categorization, and presentation, refraction results will be converted to negative cylinder notation by application of the following steps in order.

1. If the cylinder is missing, then the negative cylinder notation sphere, cylinder, and axis will all be missing.
2. If the non-missing cylinder is less than or equal to zero, then the refraction results are already in negative cylinder notation and will not be changed.

3. If the cylinder is greater than zero, then the following steps will be completed
    a. The sphere in negative cylinder notation will equal the sum of the positive cylinder notation sphere and cylinder.
        i. However, if the positive notation sphere is missing then the negative cylinder notation sphere will also be missing.
    b. The negative cylinder notation cylinder will equal the negative of the positive cylinder notation cylinder
    c. The negative cylinder notation axis will equal the positive cylinder notation axis rotated by 90 degrees, with necessary adjustments to ensure that the resulting axis is within the interval from 1 to 180 degrees, inclusive.
        i. If the positive cylinder notation axis is missing, then the negative axis notation cylinder will also be missing.

Summaries will be by treatment received and visit for the Modified Safety Set for first eyes, second eyes, and all eyes separately.

Sphere (D), cylinder (D), and spherical equivalent (D) will be summarized using continuous summary statistics. In addition, proportion of eyes with difference between intended spherical equivalent and achieved spherical equivalent within +/- 0.50 D and within +/- 1.00 D will be summarized using categorical statistics.

Axis will be summarized using continuous and categorical (none, with-the-rule, oblique, against-the-rule) summary statistics using the following definitions.

- None: 0º
- With-the-rule: 1º to 30º or 150º to 180º
- Oblique: 31º to 59º or 121º to 149º
- Against-the-rule: 60º to 120º

14.3 Intraocular Pressure

The actual values and change from Preoperative Visit 0A/B (Day -30 to -5) in IOP will be summarized using continuous statistics by treatment received, visit and first eyes, second eyes, and all eyes for the Modified Safety Set.

IOP data will be presented in a data listing.

14.4 Pupil Size

The actual mean values at Preoperative Visit 0A/B (Day -30 to -5) and Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) and change from Preoperative Visit 0A/B (Day -30 to -5) to Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) values in photopic pupil size (mm) and mesopic pupil size (mm) will be summarized separately by pupil size using continuous statistics by treatment received and by visit for the Modified Safety Set for first eyes, second eyes, and all eyes.

Pupil size data will be presented in a data listing.

14.5 IOL Tilt and Decentration

Lens stability, IOL tilt and decentration (detectable, not detectable) will be summarized categorically by treatment received and visit for the Modified Safety Set for first eyes, second eyes, and all eyes.

Lens stability data will be presented in a data listing.

14.6 Quality of Vision Questionnaire

The QoV questionnaire includes 10 questions for each of frequency, severity, and bothersome domains. The questions and item scores are included in Table 4. The domain scores are derived from the subject reported quality of vision item scores:

- Frequency domain score = sum of the mean frequency item scores (Questions 1A to 10A).
- Severity domain score = sum of the mean severity item scores (Questions 1B to 10B).
- Bothersome domain sore = sum of the mean bothersome item scores (Questions 1C to 10C).

Actual values at Preoperative Visit 0A/B (Day -30 to -5) and Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) and change from Preoperative Visit 0A/B (Day -30 to -5) to Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) in each domain score will be summarized using continuous statistics by treatment received for the Modified Safety Set. A table of response percentages by item for each question will also be provided.

The data, including response/item score for each question and the domain scores, will be presented in data listings.

[redacted]

[redacted]

[redacted]

14.7 Near Activity Visual Questionnaire

The Near Acuity Visual Questionnaire (NAVQ) includes 10 questions regarding visual difficulty and 1 overall question, "How satisfied are you with your near vision?" Refer to the Case Report Form for the questions in details.

The NAVQ data will only be presented in a data listing.

14.8 Dilated Fundus Examination

Dilated fundus examination results will be summarized categorically by treatment received and by visit for the Modified Safety Set for first eyes, second eyes, and all eyes for the following:

- Fundus (normal, abnormal [macular degeneration, other])
- Clarity of fundus visualization (adequate, inadequate)

Dilated fundus examination data will be presented in a data listing.

14.9 Posterior Capsule Assessment

The following posterior capsule results will be summarized categorically by treatment received and visit for the Modified Safety Set for first eyes, second eyes, and all eyes:

- Is posterior capsule intact? (Yes, No)

- If posterior capsule is intact, Grade of PCO?
  - Grade 0 (none)
  - Grade 1 (trace or mild)
  - Grade 2 (moderate)
  - Grade 3 (severe)
- If posterior capsule is not intact, was posterior capsulotomy performed since last visit? (Yes, No)

Posterior capsule assessment data will be presented in a data listing.

14.10 Chord Length

Actual values at Preoperative Visit 0A/B (Day -30 to -5) and Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) and change from Preoperative Visit 0A/B (Day -30 to -5) to Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) in x-axis chord length (Pcx or Px [mm]), y-axis chord length (Pcy or Py [mm]), and chord length μ as the two-dimensional distance determined by the x- and y-axis y-values (i.e., square root of [{x-axis length}^{2} + {y-axis length}^{2}]) will be summarized using continuous statistics by treatment received for the Modified Safety Set for first eyes, second eyes, and all eyes.

14.11 Keratometry

The actual values and change from Preoperative Visit 0A/B (Day -30 to -5) values in the following keratometry parameters will be summarized using continuous statistics by treatment received and by visit for the Modified Safety Set for first eyes, second eyes, and all eyes:

- Steep power (D)
- Steep axis (°)
- Flat power (D)
- Flat axis (°)

14.12 Trial Frame Astigmatism Simulation Sub-Study Assessments

The following trial frame astigmatism simulation sub-study assessments will be conducted at Post Operative Visit 6 (Day 2 to 30 after Visit 5):

- BCDVA photopic monocular (no additional sphere, cylinder, or axis)
- BCDVA photopic monocular (simulated astigmatism +2.00 D plus cylinder, 180°)
- BCDVA photopic monocular (simulated astigmatism +2.00 D plus cylinder, 90°)
- BCDVA photopic monocular (simulated astigmatism +1.50 D plus cylinder, 180°)
- BCDVA photopic monocular (simulated astigmatism +1.50 D plus cylinder, 90°)
- BCDVA photopic monocular (simulated astigmatism +1.00 D plus cylinder, 180°)
- BCDVA photopic monocular (simulated astigmatism +1.00 D plus cylinder, 90°)
- DCIVA photopic monocular (no additional sphere, cylinder, or axis)
- DCIVA photopic monocular (simulated astigmatism +2.00 D plus cylinder, 180°)
- DCIVA photopic monocular (simulated astigmatism +2.00 D plus cylinder, 90°)
- DCIVA photopic monocular (simulated astigmatism +1.50 D plus cylinder, 180°)

- DCIVA photopic monocular (simulated astigmatism +1.50 D plus cylinder, 90°)
- DCIVA photopic monocular (simulated astigmatism +1.00 D plus cylinder, 180°)
- DCIVA photopic monocular (simulated astigmatism +1.00 D plus cylinder, 90°)
- DCNVA photopic monocular (no additional sphere, cylinder, or axis)
- DCNVA photopic monocular (simulated astigmatism +2.00 D plus cylinder, 180°)
- DCNVA photopic monocular (simulated astigmatism +2.00 D plus cylinder, 90°)
- DCNVA photopic monocular (simulated astigmatism +1.50 D plus cylinder, 180°)
- DCNVA photopic monocular (simulated astigmatism +1.50 D plus cylinder, 90°)
- DCNVA photopic monocular (simulated astigmatism +1.00 D plus cylinder, 180°)
- DCNVA photopic monocular (simulated astigmatism +1.00 D plus cylinder, 90°)

The data will be summarized using continuous statistics by treatment received for the mITT Set. The data will also be presented in a data listing.

15 Interim Analyses

15.1 Phase I/Pilot Analyses

After IOL implantation for Phase I/Pilot subjects, enrollment paused until the Phase I/Pilot subjects completed Visit 3B (30 to 60 days after second eye IOL implantation) and their data were reviewed. A snapshot of DCNVA and DCIVA data was obtained. Data listings and/or summaries of Test lens DCNVA and DCIVA data were 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 were determined. Safety data were also 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 were submitted to the FDA for review and acceptance to initiate Phase II. Statistical comparisons between the Test IOL and the Control IOL were not made or evaluated. The decision to proceed or not to proceed to Phase II was not based on formal statistical stopping rules.

Analysis methods were described in separate SAP.

15.2 Phase II Analyses

When a minimum of 50 Phase I and Phase II subjects in the Test IOL group were enrolled and followed through Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation), summaries and/or listings of all available safety data through Visit 4 were prepared by an unmasked statistical team. Aggregated safety data for the minimum first 50 Phase I and Phase II subjects in the Test IOL group who completed Post-Operative Visit 4 (Day 120 to 180 after second eye IOL implantation) for these subjects were presented to the FDA to request expansion to Phase III. Safety data for approximately the corresponding minimum first 25 Phase I and Phase II subjects in the Control IOL group who completed Visit 4 also were submitted concurrently to the FDA. While safety data submission and FDA review for these subjects was 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 the Test IOL and the Control IOL were not made or evaluated. The decision to proceed or not to proceed to Phase III was not based on formal

statistical stopping rules. Phase III enrollment was initiated only after acceptance to proceed was received from FDA.

Analysis methods were described in separate SAP.

16 Changes in Planned Analyses

The table below describes the changes from the protocol-planned analyses.

Item #	Protocol	SAP	Rational
1	Section 13.5.1.1: The proportion of first **mITT** Set eyes with at least one serious adverse event will be summarized….	Section 12.1.1: The proportion of first **Modified Safety Set** eyes with at least one ocular treatment-emergent serious adverse event (TE-SAE)	Correction of analysis population
2	Section 13.5.1.2: 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	Section 12.1.2: First eyes with SSIs related to the optical properties of the IOL (Yes, No) will be summarized categorically by actual treatment received for **the Modified Safety Set**.	Correction of analysis population
3	Section 13.5.1.3: 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.	Section 12.1.3: Cumulative and persistent ISO grid AEs listed in Table 2 will be summarized categorically for the **Modified Safety Set** by treatment received. The primary statistical analysis will include first **Modified Safety Set** eyes with the Test IOL.	Correction of analysis population

17 References

- US Federal Register. (1998) International Conference on Harmonization; Guidance for Industry: Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration. Federal Register, Vol. 63, No. 179, September 16, 1998, page 49583. (E9)
- US Federal Register. (1996) International Conference on Harmonization; Guidance for Industry: Structure and Content of Clinical Study Reports. Department of Health and Human Services: Food and Drug Administration. Federal Register Vol. 61, July 17, 1996, page 37320. (E3)
- ISO 11979-7:2018, Ophthalmic implants – Intraocular lenses – Part 7: clinical investigations