STATISTICAL ANALYSIS PLAN

Clinical trial to investigate the safety and effectiveness of a hydrophilic EMV toric lens RAO210T in the correction of aphakia and post-operative corneal astigmatism

Sponsor: Rayner Intraocular Lenses Limited

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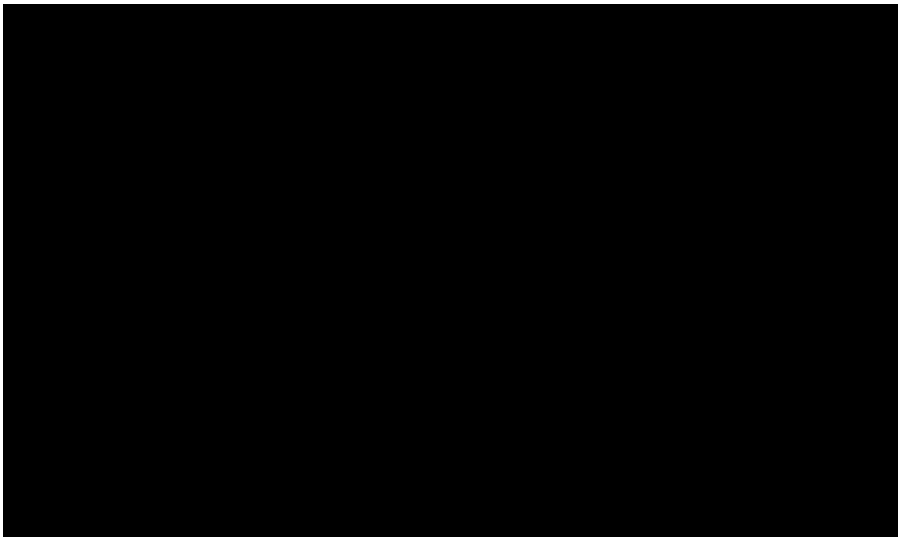
Statistical Analysis Plan Approval

Prepared by:



Approved by:

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List of Abbreviations

AE	Adverse Event
ANSI	American National Standards Institute
ATC	Anatomical Therapeutic Chemical
BCDVA	Best Corrected Distance Visual Acuity
BCIVA	Best Corrected Intermediate Visual Acuity
BCNVA	Best Corrected Near Visual Acuity
BCS	Best Case Set
CI	Confidence Interval
cm	Centimeters
DCIVA	Distance Corrected Intermediate Visual Acuity
DCNVA	Distance Corrected Near Visual Acuity
ETDRS	Early Treatment of Diabetic Retinopathy Study
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IOL	Intraocular Lens
IOP	Intraocular Pressure
ISO	International Organization for Standardization
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MCMC	Markov Chain Monte Carlo
mm	Millimeters
mmHg	Millimeters of Mercury
MNAR	Missing Not at Random
PCO	Posterior Capsule Opacification
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics & Data Corporation
SOC	System Organ Class
SSI	Secondary Safety Intervention
UCDVA	Uncorrected Distance Visual Acuity
UCIVA	Uncorrected Intermediate Visual Acuity
UCNVA	Uncorrected Near Visual Acuity
VA	Visual Acuity
WHO	World Health Organization
YAG	yttrium aluminum garnet

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol WR-2023-US-03, version 5.0 dated 26JAN2024.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP describes the data that will be analyzed and the subject characteristics, effectiveness, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in this SAP, they may be completed and will be identified in the clinical study report.

2. Study Objectives

The objectives of the clinical investigation are to determine the safety and performance of the RayOne EMV Toric (Model RAO210T) following unilateral implantation and approximately 6 months (120 to 180 days) of post-operative assessment, as a randomized comparison to aspheric monofocal control for low cylinder (1.50 D).

2.1 Study Cohort Definitions

The following terms will used throughout the Statistical Analysis Plan:

- Toric (test) group – all subjects randomized to be implanted with the low cylinder (1.50 D) RayOne EMV Toric IOL or implanted with the low cylinder (1.50 D) RayOne EMV Toric IOL

- Monofocal (control) group – all subjects randomized to be implanted with the RAO600C Monofocal IOL or implanted with the RAO600C monofocal IOL

2.2 Primary Effectiveness Variables

The primary effectiveness variables are the following:

- Mean magnitude of residual manifest cylinder, (as measured by manifest refraction) at 120 to 180 days post-operatively (Visit 4)
- Percentage of RayOne EMV Toric (Model RAO210T) IOLs with IOL axis misalignment at Visit 4 (as determined by photographic method) less than
    - 10 degrees
    - 20 degrees

- Stability of toric IOL axis orientation, expressed as percentage of RayOne EMV Toric (Model RAO210T) IOLs that rotate ≤ 5 degrees postoperatively between 30 to 60 days (Visit 3) and 120 to 180 days (Visit 4)

2.3 Secondary Effectiveness Variables

The secondary effectiveness variables are the following:

- Residual manifest refractive cylinder by subgroups of 0.25 D preoperative keratometric cylinder at 120 to 180 days post-operatively (Visit 4)
- Percent reduction in absolute cylinder (as measured by magnitude of residual manifest cylinder relative to preoperative keratometric cylinder), at 120 to 180 days post-operatively (Visit 4)

2.4 Additional Effectiveness Variables

The additional effectiveness variables include the following:

- Percentage of eyes achieving UCDVA at 4 m at 120 to 180 days post-operatively (Visit 4):
  - ≤ 0.30 logMAR
  - ≤ 0.20 logMAR
  - ≤ 0.00 logMAR
- Percentage of eyes achieving BCDVA at 4 m at 120 to 180 days post-operatively (Visit 4):
  - ≤ 0.30 logMAR
  - ≤ 0.20 logMAR
  - ≤ 0.00 logMAR
- Percentage of eyes achieving accuracy of cylinder (to target) at 120 to 180 days post-operatively (Visit 4) within:
  - +/- 0.25 D
  - +/- 0.50 D
  - +/- 0.75 D
- Lens axis misalignment (with toric IOLs) (compared to intended) at 120 to 180 days post-operatively (Visit 4)
  - Absolute value of misalignment
  - Signed value of misalignment
  - Two-sided tolerance interval around mean of the signed value of misalignment

  - Proportion of eyes with lens axis misalignment:
    - < 10 degrees
    - < 20 degrees
    - > 30 degrees

- Reduction in cylinder power at 120 to 180 days post-operatively (Visit 4), defined as the difference between pre-operative magnitude of keratometric cylinder and magnitude of manifest cylinder at Visit 4
- Reduction in cylinder power by subgroups of 0.25 D preoperative keratometric cylinder at 120 to 180 days post-operatively (Visit 4)
- Percentage of eyes with reduction of cylinder, at 120 to 180 days post-operatively (Visit 4), within 0.50 D and within 1.00 D of intended
- Descriptive statistics concerning the distribution of surgically induced astigmatism (at Visit 4)
- Scatterplots and regression analyses of the change in magnitude of corneal astigmatism (at Visit 4) from preop as a function of the incision location
- Scatterplots and regression analyses of change in corneal cylinder axis (at Visit 4) from preop, as a function of preoperative corneal cylinder magnitude
- Double-angle plots and vector analyses (intended refractive correction, surgically induced refractive correction, error vector, correction ratio, error ratio) at Visit 4, stratified by preoperative corneal cylinder magnitude

2.5 Safety Variables

The safety variables include the following primary safety endpoints:

- Rates of IOL adverse events through 120 to 180 days post-operatively (Visit 4) compared to the ISO Safety and Performance Endpoint (SPE) rates as described in ISO 11979-7
- Rates of all other adverse events not included in IOL adverse events from ISO 11979-7 through 120 to 180 days post-operatively (Visit 4)
- Rates of secondary surgical interventions for IOL repositioning due to IOL misalignment through 120 to 180 days post-operatively (Visit 4)
- Rate of BCDVA of 0.30 logMAR or better at 120 to 180 days post-operatively (Visit 4) compared to the ISO SPE rates as described in ISO 11979-7

2.6 Statistical Hypotheses

The critical region for rejection of null hypotheses will be p-value ≤ 0.025 for effectiveness and p-value ≤ 0.05 for safety unless otherwise specified.

2.6.1 Effectiveness

All effectiveness endpoints will be analyzed using the ITT Set, unless otherwise specified.

The primary effectiveness hypotheses are:

$$H_{0e}: \mu_{te} - \mu_{ce} \geq 0$$

$$H_{1e}: \mu_{te} - \mu_{ce} < 0$$

Where μ_{te} and μ_{ce} denote the population mean magnitude of residual manifest cylinder at Visit 4 for the Toric test group and Monofocal control group, respectively. If the null hypothesis is rejected at the 0.025 significance level, then it will be concluded that the 1.50 D Toric IOL is statistically successful in this outcome.

There is no hypothesis test for axis misalignment. Per ANSI Z80.30, this endpoint will be considered successful if IOL axis misalignment is less than 10 degrees for 90% of eyes and less than 20 degrees for 95% of eyes from the Toric test group.

There is no statistical hypothesis for axial stability. Per ANSI Z80.30, if at least 90% of the Toric IOL eyes rotate less than or equal to five degrees between Visits 3 and 4, then the Toric IOL will have achieved rotational stability at Visit 4 and it will be concluded that the endpoint is statistically successful in this outcome.

There is no statistical hypothesis for residual manifest refractive cylinder by subgroups of 0.25 D preoperative keratometric cylinder at 120 to 180 days post-operatively (Visit 4). This endpoint will be summarized descriptively.

Percent reduction in absolute cylinder will be calculated as follows:

$$\left(1 - \frac{|residual\ manifest\ cylinder|}{preoperative\ kerometric\ cylinder}\right) \times 100\%$$

There is no statistical hypothesis for percent reduction in absolute cylinder at 120 to 180 days post-operatively (Visit 4). This endpoint will be summarized descriptively.

There are no hypothesis tests for the additional effectiveness analyses. They will be summarized descriptively only.

2.6.2 Safety

All safety endpoints will be analyzed using the Safety Set, unless otherwise specified.

For each ISO Safety and Performance Endpoint (SPE) given in Annex E of ISO 11979-7, the null and alternative hypotheses are structured as follows :

$$H_{0s}: p_{ts} \leq p_0$$

$$H_{1s}: p_{ts} > p_0$$

Where p_{ts} denotes the true proportion of Toric test group eyes at Visit 4 suffering from the adverse event, and p_0 represents the historical proportion of eyes suffering from the adverse event as specified in ISO 11979-7. Wound burps (aqueous tap, or paracentesis) will not count toward the secondary surgical intervention portion of this analysis, provided they only involve the removal of aqueous humor. If it involves more than just removal of aqueous humor, the determination of whether it counts towards ISO 11979-7 grid event will be reviewed by the Agency.

If none of the null hypotheses are rejected for the Toric test group eyes, then it will be concluded that the Toric IOL is statistically successful in this outcome.

Rates of all other adverse events not listed in ISO 11979-7 will be summarized descriptively for the Toric test group and Monofocal control group.

Rates of secondary surgical interventions for IOL repositioning due to IOL misalignment through 120 to 180 days post-operatively (Visit 4) will be summarized descriptively for the Toric test group.

For the proportion of Toric test group eyes with 0.30 logMAR or better at Visit 4, the null and alternative hypotheses for this endpoint are as follows.

$$H_{0s}: p_{ts} \geq p_0$$

$$H_{1s}: p_{ts} < p_0$$

Where p_{ts} denotes the true proportion of Toric test group eyes achieving a BCDVA of 0.30 logMAR or better at Visit 4 and p_0 is the historical control proportion of eyes achieving a BCDVA of 20/40 or better given in ISO 11979-7 Tables E.3 and E.4. If the null hypothesis is not rejected for both the Safety and Best Case sets for Toric test group eyes at Visit 4, then it will be concluded that the Toric IOL is statistically successful in this outcome.

3. Study Design and Procedures

3.1 General Study Design

This study is a prospective, multicenter, randomized, active controlled, masked (assessor and subject) pivotal investigation for unilateral implantation of low cylinder (1.50 D) toric IOL. It compares the Rayner RAO210T toric IOL to the Rayner RAO600C aspheric monofocal IOL. Subjects who sign the ICF are

considered enrolled in the study. After signing the ICF, subjects will be screened for eligibility. Inclusion and Exclusion Criteria must be applied prior to subject randomization. Subjects who meet all protocol-specified eligibility criteria will be assigned to the randomized controlled study arms if the study eye's estimated IOL cylinder power using Barrett Toric Calculator is 1.50 D. Randomized subjects receive either the Rayner RAO210T Toric IOL (1.50 D low cylinder) or the Rayner RAO600C aspheric monofocal IOL in the study eye. The cylinder power of Rayner EMV Toric (RAO210T) and the corresponding correction range based on pre-operative keratometric astigmatism (pre-op K cyl) and predicted surgically induced astigmatism (SIA) are presented in Table 1 below.

Table 1: Rayner EMV Toric (RAO210T) Cylinder Power

	Cylinder Power (D)		*Correction Range (D)* *(based on pre-op K cyl and predicted SIA)*	
	At IOL Plane	*At Corneal Plane*		
T3	1.50	1.03	1.03	1.53

If a subject has significant cataract in both eyes, it is recommended that cataract surgery is performed in one eye before the subject is enrolled in the study. Once a subject has been enrolled, it is recommended that the fellow eye does not undergo cataract surgery (except for a YAG capsulotomy) throughout the duration of the study. At screening, if both eyes qualify for the study, the eye to undergo cataract surgery and IOL implantation is the eye with worse pre-operative BCDVA. If pre-operative BCDVA is the same for each eye, the right eye will be the study eye.

Subjects will complete 6 study visits in approximately 9 months. Subject participation is calculated as the difference between the time of the pre-operative visit to completion of Visit 4 (120 to 180 days post-operative).

Summary of Visit Schedule:

- Pre-operative Visit – Form 00 (-90 – 0 days)
- Operative Visit – Form 0 (Day 0)
- Visit 1 – Form 1 (1 to 2 days post-operative)
- Visit 2 – Form 2 (7 to 14 days post-operative)
- Visit 3 – Form 3 (30 to 60 days post-operative)
- Visit 4 – Form 4 (120 to 180 days post-operative)

Standard clinical trial methods will be used to minimize bias, such as the use of site personnel performing manifest refraction and visual acuity assessments masked to subject treatment assignment, masking of subjects in the randomized controlled investigation evaluating low cylinder power, standardized test procedures, common Investigator training and common inclusion and exclusion criteria.

Up to 11 U.S. sites will be encouraged to enroll a minimum of 20 subjects in the study. No site will enroll more than 25% of the subjects enrolled in the study.

3.2 Schedule of Visits and Assessments

The schedule of visits and assessments is provided Table 2.

Table 2. Schedule of Visits and Assessments

Procedure	Both Eyes	Study Eye[1]				
	Visit 00 Pre-Op	Visit 0 Operative	Visit 1 Post-Op	Visit 2 Post-Op	Visit 3 Post-Op	Visit 4 Post-Op
	Day -90 - 0	Day 0	Day 1-2	Day 7-14	Day 30-60	Day 120-180
Informed Consent/HIPAA	X					
Inclusion/Exclusion Criteria Review	X	X[2]				
Demographics	X					
Ocular and Significant Non-ocular Medical History	X*	X				
Urine Pregnancy Test (if applicable)	X					
Potential Visual Acuity	X*					
Corneal Topography	X*					
Axial length/ Anterior chamber depth (biometry)/ Target refraction/ IOL power calc (Barrett Toric and any non-toric Monofocal IOL formula)	X*					
Keratometry	X*				X	X
Gonioscopy	X*					

Procedure	Both Eyes	Study Eye[1]				
	Visit 00 Pre-Op	Visit 0 Operative	Visit 1 Post-Op	Visit 2 Post-Op	Visit 3 Post-Op	Visit 4 Post-Op
	Day -90 - 0	Day 0	Day 1-2	Day 7-14	Day 30-60	Day 120-180
Dilated Pupil size	X*					
Randomization (for subjects with estimated IOL cyl power of 1.50 D with Barrett Toric)	X					
Operative Procedures[3]		X				
Manifest Refraction[4]	X			X	X	X
UCDVA - Monocular (ETDRS) – 4 m[4]	X		X	X	X	X
BCDVA - Monocular (ETDRS) – 4 m[4]	X			X	X	X
Intraocular Pressure[4]	X*		X	X	X	X
Slit lamp Biomicroscopy[4]	X*		X	X	X	X
Posterior Capsule Opacification (PCO) Assessment[4] **(dilated)**			X	X	X	X
IOL Observations[4] **(dilated)**			X	X	X	X
Lens Stability - decentration and tilt **(dilated)**				X	X	X
IOL Axis Orientation - retroilluminated slit lamp photo[5] **(dilated)**		X	X	X	X	X
Dilated Fundus Exam[4]	X*		X	X	X	X
Adverse Events[4]	X	X	X	X	X	X
Device Deficiencies[4]		X	X	X	X	X
Concomitant Medications[4]	X	X	X	X	X	X
Exit from Study						X

1. If both eyes qualify, the study eye will be the eye with the worse preoperative BCDVA. If BCDVA of both eyes is the same, the study eye will be the right eye
2. Review of inclusion/exclusion criteria before surgery
3. Surgical incision will be standardized to the temporal horizontal meridian and approximately 2.4 mm incision size to minimize variations in changes in corneal astigmatism between toric and control subjects; incision location and size

information should be noted in Form 0. The intended axis will be marked preoperatively with two marks, 180 degrees apart in the peripheral cornea near the limbus, using a corneal marker such as a pre-inked RoboMarker (Surgilum, Wilmington, NC) or similar device.

4. Additionally, to be completed at any post-operative Unscheduled Visit
5. Subjects implanted with RAO210T toric IOL only. Images will be evaluated by an independent Reading center to assess IOL axis orientation from IOL axis marks correlated with intended axis and anatomic landmarks at Day 0 and all subsequent visits.

*Assessments performed as standard of care within the -90 – 0 pre-operative visit screening window may be used as qualifying assessments prior to date of informed consent.
[ ] Optional at Unscheduled Visit, based on Investigator's discretion

4. Study Treatments

4.1 Method of Assigning Subjects to Treatment Groups

During the Pre-Operative Visit, subjects who sign the informed consent form will be assigned a unique screening number. Subjects who meet inclusion criteria will be randomly assigned to receive either the RAO210T toric IOL (1.50 D low cylinder) or the RAO600C aspheric monofocal IOL in the study eye according to a 1:1 ratio. Randomization will be stratified by site. The randomization schedule will be created using computer-generated randomization methodology (e.g. the PLAN procedure in SAS® software 9.4; SAS Institute, Cary NC) by an independent statistician who is not involved in the day-to-day conduct of the study. Randomization is to occur following the completion of informed consent and screening procedures.

An independent biostatistician who is not otherwise involved in the trial will generate the randomization schedule. The subject, Sponsor, and study staff will be masked during the randomization process and throughout the study.

4.2 Masking/Blinding and Unmasking/Unblinding

In order to minimize bias, measures will be taken to mask the site personnel performing post-operative manifest refraction and visual acuity assessments, as to the subject's treatment assignment until after the final database lock. Every attempt should be made to have the same masked site personnel perform the same masked post-operative assessments for an individual subject throughout the subject's study participation.

Subjects will be masked to their IOL assignment in the randomized controlled investigation evaluating low cylinder power. All material which may indicate the subjects' assignment, e.g., packaging, documents, etc., will be removed from any areas where subjects and/or masked site personnel may see them. Unmasked personnel will further be instructed to scrupulously avoid conversation and communication with masked personnel, subjects and all other persons regarding subjects' assignments, outcomes, clinical courses, and all other information potentially relevant to the study and its conduct.

5. Sample Size and Power Considerations

Up to 295 adult subjects will be enrolled (consented) assuming a 15% screen failure rate, then up to 250 subjects will be randomized, with the goal of completing 200 subjects through Visit 4 within the randomized groups, of whom 100 were implanted in one eye with the low cylinder RayOne EMV Toric (Model RAO210T) and 100 were implanted in one eye with the RAO600C monofocal IOL and to ensure a minimum of 100 subjects with readable axis images in the toric arm, which is part of a primary endpoint.

For effectiveness, 100 subjects (eyes) randomized to the Toric (test) group (lowest cylinder power +1.50D) and 100 subjects (eyes) randomized to the Monofocal (control) group completing Visit 4 yields over 98% statistical power to reject H_{0e} in favor of H_{1e} and conclude the Toric IOL has statistically significantly lower mean residual manifest cylinder at Visit 4 compared to the monofocal IOL, using a one-sided t-test with an alpha level of 0.025 and assuming a true mean difference of 0.4 D and a standard deviation of 0.7 D in both groups.

For safety, ISO 11979-7 and ANSI Z80.30 specifies that a minimum of 100 subjects should complete a clinical evaluation of an IOL, where a parent IOL has been approved, to obtain appropriate specificity around adverse event and visual acuity rates.

6. Analysis Sets

6.1 All Enrolled

The All Enrolled set includes all subjects who sign informed consent. This set will be used for disposition summaries.

6.2 Intent-to-Treat

The intent-to-treat (ITT) set includes all randomized subjects (eyes). Summaries and analyses based on the ITT will analyze subjects as randomized.

6.3 Safety

The Safety (SAF) set will include all ITT subjects who undergo surgery. Summaries and analyses based on the SAF will be analyzed according to IOL actually implanted. If no IOL is successfully implanted, but the IOL touches the eye, the subject will be analyzed by the attempted lens. If a subject undergoes surgery yet no IOL touches the eye, the subject will be analyzed in a separate Not Treated group. If it is confirmed that a subject did not undergo surgery, then the subject will be excluded from all safety analyses.

6.4 Per Protocol

The per protocol (PP) set includes all Safety set subjects who are successfully implanted with their randomized study lens and who have no major protocol deviations. Major protocol deviations that may potentially affect the primary effectiveness endpoints include, but are not limited to:

- Inclusion of ineligible subjects
- Implantation of incorrect IOL
- Missed assessments for effectiveness endpoints at 120 to 180 days post-operatively (Visit 4)
- Receipt of medication likely to interfere with visual performance at 360 to 120 to 180 days post-operatively (Visit 4)

6.5 Best Case Set

The Best Case Set (BCS) will include PP subjects with all of the following characteristics:

- No clinically significant pre-operative ocular pathology in the first implanted eye, including any of the following present prior to the Operative Visit:
    - Pseudoexfoliation
    - Glaucoma
    - Uveitis
    - Retinal detachment
    - Diabetic retinopathy
    - Macular degeneration
    - Amblyopia
    - Other preoperative pathologies that are likely to affect central acuity
- No macular degeneration detected at any time.
- No previous surgery for the correction of refractive errors, which would have resulted in exclusion of the subject from the study.

Summaries and analyses based on the Best Case Set will analyze subjects as treated.

7. General Statistical Considerations

7.1 Unit of Analysis

The unit of analysis in this study will be the enrolled eye for all primary effectiveness and safety summaries. For those subjects whose eyes are both determined to be eligible for IOL implantations at Pre-Operative Visit 00, the eye with the worse best-corrected distance visual acuity (BCDVA) will be enrolled as the study eye. If BCDVA is the same for both eyes, the right eye will be enrolled. Additionally, non-ocular AEs and medical history will be presented at the subject level.

7.2 Missing or Inconclusive Data Handling

Missing data for primary effectiveness and primary safety analyses will be imputed under the strategies described in Section 11 and Section 12, respectively. Missing data for secondary effectiveness and additional effectiveness analyses will be excluded.

7.3 Definition of Baseline

Baseline will refer to measurements performed during the Pre-Operative Visit (Visit 00). Change from baseline will be calculated as follow-up visit minus baseline visit.

7.4 Unscheduled Visits and Visit Windows

Unscheduled Visits may be performed to ensure patient safety or to follow up on an unresolved adverse event. If the Investigator wants to re-assess PCO or perform a post-YAG assessment between study visits, this would also be recorded as an Unscheduled Visit. Measures will be taken to mask the site personnel performing post-operative visual acuity assessments to the subject's treatment assignment.

Only in-window visits will be included in the analysis of a 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 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 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 visit.

7.5 Data Analysis Conventions

Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum. Minima and maxima will be reported with the same precision as the raw values; means and medians will be presented to one additional decimal place than reported in the raw values. Standard deviations will be presented to two additional decimal places than reported in the raw values. Summaries for discrete (categorical) variables will include counts and percentages. All percentages will be rounded to one decimal place (ie, XX.X%), with the exception of 0 and 100%, which will be reported as whole numbers. Differences between test and control treatment groups will be calculated as test minus control, and change from baseline will be calculated as follow-up visit minus baseline.

All statistical tests for effectiveness will be one-sided with a significance level of 0.025 ($\alpha = 0.025$). Correspondingly, confidence intervals (CI) for differences between treatment groups will be two-sided at 95% confidence. All p values will be rounded to 4 decimal places; p-values less than 0.0001 will be presented as "<0.0001"; p-values greater than 0.9999 will be presented as ">0.9999."

Statistical tests for safety will be one-sided with a significance level of 0.05 (α = 0.05). Confidence intervals for safety endpoints will be one-sided 95% lower confidence limits based on an exact binomial distribution.

Unless otherwise specified, summaries will be presented by treatment group and, where appropriate, visit. Listings will be sorted by treatment group, subject number, visit/time point, and parameter as applicable.

7.6 Adjustments for Multiplicity

The Toric lens will be considered successful if all of the primary effectiveness and primary safety endpoints are met. Consequently, the overall type I error rate for the effectiveness analyses will be controlled at 0.05.

7.7 Adjustments for Postoperative Surgical Rotations of Toric IOLs

In accordance with ANSI Z80.30 (2018), subjects that have a secondary surgery intended to correct for postoperative toric IOL rotation will have their clinical results (axis rotation and manifest cylinder) prior to that surgical intervention carried forward as the final results for those subjects with no further imputation. In cases where axis misalignment measured at follow-up visits after a secondary surgical intervention (SSI) is greater than the axis misalignment prior to SSI, the greater misalignment error (and greater manifest cylinder) will be considered final.

For the proportion of RayOne Toric (Model RAO210T) IOLs that rotate ≤ 5 degrees postoperatively between 30 to 60 days (Visit 3) and 120 to 180 days (Visit 4), the following imputation strategy will be used for eyes which undergo an SSI to correct for postoperative toric IOL rotation:

- If the SSI occurred between Visits 3 and 4, the IOL rotation between Visits 3 and 4 will be classified as greater than 5 degrees.
- If the SSI occurred prior to Visit 3, the actual IOL rotation between Visits 3 and 4 will determine whether the IOL rotated ≤ 5 degrees between Visits 3 and 4.

8. Disposition of Subjects

Study conduct summaries including subject disposition, accountability (as in Table A.1 from ISO 11979-7), screen failures, discontinuations, and protocol deviations for the ITT, PP, Best Case Set, and Safety set will be provided. Disposition will be summarized by treatment group and for all subjects, and accountability will be summarized for each post-operative visit. A subject listing will be provided for subject discontinuations which includes the date and reason for each premature study discontinuation. Additionally, a subject listing will be provided for protocol deviations which will include the date of the deviation, the deviation category, the deviation description, and the classification of whether the deviation was judged to be major or minor in a masked review.

In addition, subject listings will be provided that include informed consent date, inclusion and exclusion criteria violations, and exclusions from the PP and Best Case Sets. Details of the study randomization, including randomization date and time, randomized treatment and actual treatment, will also be included within a subject listing.

9. Demographic and Baseline Variables

9.1 Demographic Variables

The demographic variables collected in this study include age, sex, race, and ethnicity. Subjects who record more than one race will be grouped into a single category denoted as multi-racial. Demographic variables will be summarized for the ITT population.

Age (years) will be summarized, overall and by treatment, using continuous descriptive statistics. Age will also be categorized as follows: < 65 years and ≥ 65 years. Age will be reported in years and calculated using the following formula:

Age = (Informed Consent Date – Date of Birth) / 365.25, truncated as an integer

The number and percentage of subjects will be presented, overall and by treatment, for age category, sex, race, and ethnicity.

A subject listing that includes all demographic variables will be provided.

9.2 Baseline Variables

Baseline clinical parameters will include, but not limited to, potential visual acuity, target refraction, IOL power, axial length, and anterior chamber depth. Baseline clinical parameters will be summarized for the ITT population, overall and by treatment, using continuous or categorical summary statistics as appropriate.

Pre-existing corneal astigmatism for enrolled subjects will be summarized using continuous summary statistics.

A subject listing that includes all baseline variables will be provided.

10. Medical History and Concomitant Medications

10.1 Medical History

Medical history will be coded and summarize using preferred terms.

Ocular medical history will be summarized at the subject level based on the ITT. If a subject reports the same preferred term (PT) multiple times, that PT will only be reported once within summary tables.

Ongoing non-ocular medical history will be presented in a data listing.

10.2 Concomitant Medications

Concomitant medications will be coded and summarized to the therapeutic drug class and preferred name. 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 summarized as the preferred name. Any uncoded terms will be summarized under the preferred name of "Uncoded."

Concomitant medications are defined as those medications listed as having been taken (1) prior to first eye IOL implantation and continuing for any period of time following first eye implantation or (2) at any time following the first eye IOL implantation.

Concomitant medications will be summarized using the Safety Set. Medications will be tabulated for each treatment group using counts and percentages. Subjects may have more than one medication per drug class. At each level of subject summarization, a subject will be counted once if he/she reports one or more medications. Percentages will be based on the number of subjects in each treatment group. Listings of concomitant medications will be generated separately for ocular and non-ocular data.

11. Effectiveness Analyses

Variables and time points used for primary effectiveness endpoints will be summarized descriptively for each treatment group by sex, age, racial and ethnic groups. All effectiveness variables will be presented in data listings.

11.1 Primary Effectiveness Analysis

Primary effectiveness endpoint analyses will be based on the ITT set, with the same analyses conducted on the PP set to be used as supportive. Imputation of missing data will be performed utilizing multiple imputation techniques under assumptions of missing at random (MAR) and missing not at random (MNAR) following the strategies described below. Primary effectiveness endpoint analyses will also be conducted on the PP set. If the results of the PP set analyses materially differ from the primary analyses on the ITT set, then the results of investigations into the cause of such differences will be presented.

11.1.1 Residual Manifest Cylinder at Visit 4

The hypotheses for this endpoint are

H_{0e}: $\mu_{te} - \mu_{ce} \geq 0$

H_{1e}: $\mu_{te} - \mu_{ce} < 0$

Where μ_{te} and μ_{ce} denote the population mean magnitude of residual manifest cylinder at Visit 4 for the Toric test group and monofocal control group, respectively. If the null hypothesis is rejected at the 0.025 significance level, then it will be concluded that the 1.50 D Toric IOL is statistically successful in this outcome.

The primary statistical analysis of mean residual manifest cylinder at Visit 4 will be conducted using an Analysis of Covariance (ANCOVA) model with randomized treatment as factor and preoperative keratometric cylinder as covariate. The hypotheses above will be tested using the least-squares estimate of the treatment coefficient. The adjusted mean difference between Toric and Monofocal groups will be given together with a 95% confidence interval and associated one-sided p-value.

This analysis will be repeated, without imputation, using the PP Set.

Primary Imputation Strategy

In the event of missing values, and prior to hypothesis testing, fifty imputations of missing residual manifest cylinder values at Visit 4 will be produced for the randomized sets using SAS PROC MI. The seed used to begin random number generation will be 194106140009. The Markov chain Monte Carlo method will be used to compute full imputations using the following variables.

- Randomized treatment assignment
- Preoperative keratometric cylinder
- Residual manifest cylinder at Visits 2 and 3

Nonmonotone missing data will be multiply-imputed using treatment-based Markov Chain Monte Carlo (MCMC) methods; monotone missing data will be multiply imputed using regression methods assuming data as either missing at random (MAR) or missing not at random (MNAR) as described below.

1. Withdrawal due to investigator's discretion: missing data assumed to be missing not at random. Control-based multiple imputations will be completed.
2. Missing data without withdrawal or withdrawal due to reasons other than due to investigator's request: missing data assumed to be missing at random. Treatment-based multiple imputations will be completed.

The following example SAS pseudo-code will be used to perform the multiple imputation procedure described above:

<u>Control-based Multiple Imputation</u>

```
/* Impute non-monotone missing data using MCMC */
proc mi data = adeff out = mcmc nimpute = 50 seed = 194106140009;
      mcmc impute = monotone;
      var trtn base aval_v2 aval_v3 aval_v4;
run;

/* Impute remaining monotone missing data using regression
imputation */
```

```
proc mi data = mcmc out = mi nimpute = 1 seed = 194106140010;
      by _imputation_;
      var base aval_v2 aval_v3 aval_v4;
      MONOTONE REG(aval_v2 = base);
      MONOTONE REG(aval_v3 = aval_v2 base);
      MONOTONE REG(aval_v4 = aval_v3 aval_v2 base);
      MNAR MODEL(aval_v2 aval_v3 aval_v4 / MODELOBS=(trtn=0));
run;
```

Treatment-based Multiple Imputation

```
/* Impute non-monotone missing data using MCMC */
proc mi data = out = mcmc nimpute = 50 seed = 194106140009;
      mcmc impute = monotone;
      var trtn base aval_v2 aval_v3 aval_v4;
run;

/* Impute remaining monotone missing data using regression
imputation */
proc mi data = mcmc out = mi nimpute = 1 seed = 194106140010;
      by _imputation_;
      var trtn base aval_v2 aval_v3 aval_v4;
      MONOTONE REG(aval_v2 = base trtn);
      MONOTONE REG(aval_v3 = aval_v2 base trtn);
      MONOTONE REG(aval_v4 = aval_v3 aval_v2 base trtn);
run;
```

where

- aval = actual value
- base = corresponding baseline visit value
- trtn = indicator variable for treatment; 0 = control, 1 = test.
- aval_vi = actual value at visit i.

Fifty complete datasets will be generated from the above code.

SAS code similar to the following pseudo-code will be used to perform the primary analysis for each imputed dataset and then combine inferences across the imputed datasets:

```
ODS OUTPUT diffs = diffs;
PROC MIXED DATA = mi;
      CLASS trtn;
```

```
        MODEL aval_v4 = base trtn;
        LSMEANS trtn / DIFFS=ALL ALPHA=0.05;
        BY _imputation_;
RUN;

ODS OUTPUT ParameterEstimates = test_output;
PROC MIANALYZE DATA = diffs ALPHA = alpha THETA0 = null_diff;
        MODELEFFECTS estimate;
        STDERR stderr;
RUN;
```

where

- alpha = 2-sided significance level of hypothesis test (0.05 for superiority tests)
- null_diff = difference in group means under null hypothesis (e.g. 0 for superiority tests)

The dataset `test_output` will contain the combined statistics such as p-value, estimated treatment effect coeffecient, and associated CI, which will be used to perform inference for the Residual manifest cylinder 120 to 180 days post-operatively (Visit 4) endpoint.

If the one-sided p-value for the treatment effect resulting from the multiple imputation analysis is less than or equal to 0.025, then it will be concluded that the Toric cylinder 1.50 D IOL is statistically successful in this outcome.

Secondary Imputation Strategy

If there are missing ITT data, then the following secondary analyses will be performed to assess the sensitivity of the results to missing data.

- The best case scenario will assume that:
    - Toric cylinder 1.50 D eyes with missing data had a Visit 4 residual manifest cylinder of 0 D.
    - Monofocal (control) eyes with missing data had the largest Visit 4 cylinder observed among ITT set Monofocal eyes.
- The worst case scenario will assume that:
    - Toric cylinder 1.50 D eyes with missing data had the largest Visit 4 cylinder observed among ITT set Toric cylinder 1.50 D eyes.
    - Monofocal (control) eyes with missing data had a Visit 4 residual manifest cylinder of 0 D.

- A tipping point analysis will report the difference between Toric group eyes and Monofocal (control) eyes with missing values that would result in a change of the statistical conclusion. The tipping point will be found iteratively by the following algorithm.

    1. Impute the missing values as the treatment group sample means
    2. Adjust the missing values in 0.0005 D increments in opposite directions for the two treatment groups, and recalculate mean residual manifest cylinder.
    3. Find the difference that changes the statistical conclusion.

11.1.2 IOL Axis Misalignment

IOL axis misalignment will be provided by an independent reading center using a photographic based method, relative to anatomic landmarks. This will be determined by the difference in intended axis of orientation on the day of surgery (Day 0) and the IOL axis at the Month 6 postoperative visit (Visit 4). The intended axis will be marked preoperatively with two marks, 180 degrees apart in the peripheral cornea near the limbus, using a corneal marker such as a pre-inked RoboMarker (Surgilum, Wilmington, NC) or similar device. At Day 0, the slit lamp image will be captured as soon as possible after the conclusion of IOL implantation surgery.

The absolute value of the misalignment from the intended axis at Day 0 will be summarized for the ITT Set by visit. The number and proportion of lenses with axis misalignment in the following categories will be summarized: < 5 degrees, < 10 degrees, < 20 degrees, ≤ 30 degrees, and > 30 degrees.

Subjects that have a secondary surgery that is targeted to correct for postoperative toric IOL rotation shall have their clinical results prior to that surgical intervention carried forward as the final results for that subject. In cases where axis misalignment measured at follow up visits after a secondary surgical intervention (SSI) is greater than the axis misalignment prior to SSI, the greater misalignment error shall be considered final.

If there are missing data, then fifty imputations of missing toric lens misalignment at Visit 4 will be produced for the randomized cohort using SAS PROC MI. The seed used to begin random number generation will be 767785510. The Markov chain Monte Carlo method will be used to compute full imputations using the following variables, using SAS code similar to that described above.

- Investigator
- Absolute lens axis misalignment at Visits 2 and 3

The IOL axis misalignment endpoint will be successful if IOL axis misalignment is less than 10 degrees for 90% of eyes and less than 20 degrees for 95% of eyes from the Toric test group in the fifty imputed datasets.

If there are missing ITT data, then the following secondary analyses will be performed to assess the sensitivity of the results to missing data.

- The best case scenario will assume that eyes with missing data had a misalignment equal to the smallest misalignment in the ITT set observed at Visit 4.
- The worst case scenario will assume that eyes with missing data had a misalignment equal to the largest misalignment in the ITT set observed at Visit 4.
- If the best and worst case analyses yield differing statistical conclusions, then a tipping point analysis will report the number and percentage of toric eyes with missing data that would have to experience a misalignment greater than each of 10 degrees and 20 degrees in order to change the statistical conclusion.

This analysis will be repeated using the PP set as a supportive analysis.

11.1.3 Stability of Toric IOL Axis Orientation

For the Visit 3 and 4 scheduled eye visits, the angle of IOL rotation will be provided by an independent reading center using a photographic based method.

The absolute value of Toric lens rotation between Visits 3 and 4 will be summarized using continuous statistics. The number and percentage of lenses rotating five degrees or less between the two consecutive visits will be reported along with an exact binomial 95% confidence interval for the percentage.

Visits 3 and 4 have window midpoints 105 days apart, which is greater than 3 months. Therefore, this analysis will be completed using all ITT Set Visit 3 and Visit 4 data, even if some subjects' visits actually occurred less than 3 months apart.

If there are missing data, then fifty imputations of missing absolute toric lens rotation between Forms 3 and 4 will be produced for the randomized cohort using SAS PROC MI. The seed used to begin random number generation will be 5105052291. The Markov chain Monte Carlo method will be used to compute full imputations using the following variables.

- Investigator
- Absolute toric lens rotation for the between-visit intervals ending at Visits 2, 3, and 4

Stability of the toric IOL axis will have been achieved if at least 90% of all toric lenses in the fifty imputed datasets rotate less than or equal to five degrees between Visits 3 and 4.

If there are missing ITT data, then the following secondary analyses will be performed to assess the sensitivity of the results to missing data.

- The best case scenario will assume that eyes with missing data had a rotation equal to the smallest absolute lens rotation observed in the ITT set for that visit interval.
- The worst case scenario will assume that eyes with missing data had a rotation equal to the largest absolute lens rotation observed in the ITT set for that visit interval.

- If the best and worst case analyses yield differing statistical conclusions, then a tipping point analysis will report the number and percentage of toric eyes with missing data that would have to experience rotation greater than 5 degrees in order to change the statistical conclusion.

This analysis will be repeated using the PP set as a supportive analysis.

11.2 Secondary Effectiveness Analysis

11.2.1 Residual Manifest Cylinder by Subgroup

In addition to the primary analysis above, residual manifest cylinder will also be summarized using continuous summary statistics by treatment group for each 0.25 D of preoperative keratometric cylinder, including two-sided 95% t-distribution confidence intervals for the difference in means between the two groups.

11.2.2 Percent Reduction in Absolute Cylinder

Percent reduction in absolute cylinder will be evaluated statistically using the hypotheses

$$H_{0e}: \mu_{te} - \mu_{ce} \geq 0$$

$$H_{1e}: \mu_{te} - \mu_{ce} < 0$$

Where μ_{te} and μ_{ce} denote the population mean percent reduction in absolute cylinder at Visit 4 for the Toric test group and Monofocal control group, respectively. This hypothesis will be tested using a two independent samples t-test with a one-sided alpha of 0.025.

Percent reduction in absolute cylinder will also be summarized using continuous summary statistics by treatment group, including two-sided 95% t-distribution confidence intervals for the difference in means between the two groups.

11.3 Additional Effectiveness Analyses

Additional effectiveness analyses of the toric cohort will be descriptive and no formal statistical inference will be conducted. The additional effectiveness analyses are based on recommended effectiveness analyses from ANSI Z80.30 and ISO 11979-7 (2018).

11.3.1 Uncorrected Distance Visual Acuity

The proportion of eyes achieving BCDVA ≤ 0.30, ≤ 0.20, and ≤ 0.00 logMAR will be summarized by treatment group at each visit using discrete summary statistics, including exact two-sided 95% binomial confidence intervals.

11.3.2 Best Corrected Distance Visual Acuity

The proportion of eyes achieving UCDVA ≤ 0.30, ≤ 0.20, and ≤ 0.00 logMAR will be summarized by treatment group at each visit using discrete summary statistics, including exact two-sided 95% binomial confidence intervals.

11.3.3 Accuracy of Cylinder

The proportion of eyes achieving accuracy of cylinder (to target) within +/- 0.25, +/- 0.50, and +/- 0.75 D, using manifest refraction, will be summarized by treatment group at each visit using discrete summary statistics, including exact two-sided 95% binomial confidence intervals.

11.3.4 Lens Axis Misalignment

The analysis of IOL misalignment will be based on the Toric test group. Absolute value of lens axis misalignment and signed value of lens axis misalignment will be summarized using continuous summary statistics, including two-sided 95% t-distribution confidence intervals. Two-sided tolerance intervals created to contain at least 90% of the population (with 95% probability) will also be created for the signed value of misalignment. The percentage of subjects with lens axis misalignment by < 10, < 20, and > 30 degrees at each visit will be summarized.

11.3.5 Reduction in Cylinder Power

Reduction in cylinder power, defined as pre-operative magnitude of the keratometric cylinder minus magnitude of manifest cylinder at each post-operative visit, will be summarized using continuous summary statistics by treatment group. 95% confidence intervals for the mean reduction in cylinder power will be presented by treatment group along with a 95% confidence interval for the difference in treatment group means (test group minus control group).

11.3.6 Reduction in Cylinder Power by Subgroup

In addition to the above, reduction in cylinder power will also be summarized using continuous summary statistics by treatment group for each 0.25 D of preoperative keratometric cylinder, including two-sided 95% t-distribution confidence intervals for the difference in means between the two groups.

11.3.7 Percentage of Eyes with Reduction of Cylinder

The percentage of eyes with reduction in cylinder within 0.50 D and within 1.00 D of intended, will be summarized using discrete summary statistics, including exact two-sided 95% binomial confidence intervals.

11.3.8 Surgically Induced Astigmatism

Surgically Induced Astigmatism will be summarized using continuous summary statistics by randomized treatment group. 95% confidence intervals for the mean SIA will be presented by treatment group along with a 95% confidence interval for the difference in treatment group means (test group minus control group).

11.3.9 Change in Magnitude of Corneal Astigmatism

Scatterplots of the change in magnitude of corneal astigmatism as a function of the incision location (degrees), and change in corneal cylinder axis as a function of preoperative corneal cylinder magnitude, overlaid with regression lines will be presented by treatment group. Summary statistics will also be presented.

11.3.10 Change in Corneal Cylinder

Scatterplots of the change in magnitude of corneal astigmatism as a function of the incision location, and change in corneal cylinder axis as a function of preoperative corneal cylinder magnitude, overlaid with regression lines will be presented by treatment group. Summary statistics will also be presented.

11.3.11 Vector Analyses

Double-angle plots and vector analyses (intended refractive correction, surgically induced refractive correction, error vector, correction ratio, and error ratio) at Visit 4, stratified by subgroups of 0.25D preoperative keratometric cylinder.

12. Safety Analyses

All safety analyses will be conducted using the Safety set unless otherwise specified. Variables and time points used for primary safety endpoints will be summarized descriptively for each treatment group by sex, age, racial and ethnic groups. All safety data will be included in data listings.

12.1 Adverse Events

All AEs that occur during or after the Pre-operative Visit through completion of study participation must be recorded on the subject's case report form. Subjects who experience an ocular adverse event/complication, are not to be discontinued/exited from the study until the Investigator has followed the event (within the study) for a sufficient time to ensure that AE has been resolved or stabilized (considering potential late sequalae of the event). Potential sequalae include any adverse effects on ocular structure or ocular (or visual) function.

Adverse Events will be categorically summarized according to study treatment, preferred term, severity, and relationship to study treatment, overall and by type (see Section 11.1.1).

12.1.1 Adverse Event Terms

Adverse Event (AE): any untoward medical occurrence, unintended disease or injury, or untoward clinical sign (including an abnormal laboratory finding) or symptom in subjects whether or not related to an investigational device.

Adverse Device Effect (ADE): any adverse event related to the use of a study device. This definition includes any events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation or operation, or any malfunction of the device. This definition also includes any event resulting from use error or from intentional misuse of a study device.

Serious Adverse Event (SAE): an adverse event which meets one or more of the following criteria:

- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Requires medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure;

- Is life threatening (places the subject at immediate risk of death from the event as it occurred) or vision threatening;
- Results in permanent impairment of a body function or permanent damage to a body structure;
- Results in death;
- May jeopardize the subject and require medical or surgical intervention to prevent one of the other outcomes.

Unanticipated Adverse Device Effect (UADE): any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

12.1.2 Classification of Adverse Events

Severity

The Investigator must determine the severity of an event according to the following scale:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL).
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care Activities of Daily Living (ADL).
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Relationship to Study Intervention

The relationship of each event to the study device or surgical procedure must be determined by the Investigator according to the following scale:

Definite	A clear-cut causal relationship and no other possible cause
Probable	A causal relationship is likely although alternate etiologies are also possible
Possible	A causal relationship is not definite, alternate etiologies are also possible
Not Related	The event has no causal relationship and/or there is evidence of alternative etiology such as concurrent medication or illness

12.1.3 Anticipated Adverse Events

The list of anticipated adverse events is provided in the protocol. Adverse events will be summarized by treatment group according to the frequency of each of these anticipated adverse events.

12.1.4 Cumulative and Persistent Adverse Events

The total number of the following adverse events that have occurred at any time will be reported as cumulative AEs, consistent with categories provided in ISO 11979-7:

- Cystoid macular edema
- Hypopyon
- Endophthalmitis - defined as inflammatory reaction (sterile or infectious) involving the vitreous body
- Lens dislocation from posterior chamber
- Pupillary block - shallowing of anterior chamber due to obstruction of aqueous humor flow from the posterior to anterior chamber through the pupil by the crystalline lens, vitreous face, or implanted device
- Retinal detachment
- Secondary surgical intervention (excluding posterior capsulotomies)

The total number of the following adverse events that are present at the conclusion of the clinical investigation will be reported as persistent AEs, consistent with categories provided in ISO 11979-7:

- Corneal stromal edema
- Cystoid macular edema
- Iritis
- Raised IOP requiring treatment

If an adverse event meets more than one adverse event definition from ISO 11979-7 or the adverse event definitions Protocol Section 9.4. Anticipated Adverse Events (AEs), the Investigator should record that adverse event as counting towards each adverse event.

12.1.5 Device Deficiency

A device deficiency is defined as inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequate labelling.

Device deficiencies will be summarized by type, and individually listed.

12.2 Primary Analysis

12.2.1 Rates of IOL Adverse Events Compared to ISO Grid

The numerator for each cumulative AE will be the number of toric study eyes suffering from the AE at least once after surgery. The denominator for cumulative AEs will be the total number of toric study eyes in the Safety Set.

For each ISO Safety and Performance Endpoint (SPE) given in Annex E of ISO 11979-7, the null and alternative hypotheses are structured as follows :

H_{0s}: $p_{ts} \leq p_0$

H_{1s}: $p_{ts} > p_0$

Where p_{ts} denotes the true proportion of Toric test group eyes at Visit 4 suffering from the adverse event, and p_0 represents the historical proportion of eyes suffering from the adverse event as specified in ISO 11979-7.

If none of the null hypotheses are rejected for the Toric test group eyes, then it will be concluded that the Toric IOL is statistically successful in this outcome.

The numerator for each persistent AE will be the number of toric subjects who had a follow-up visit on or after the beginning of the Visit 4 visit window (120 days after implantation) and for whom the AE was ongoing in the study eye at this visit. The denominator for persistent AEs will be the number of toric subjects who had follow-up visit on or after the beginning of the Visit 4 visit window (120 days after implantation). However, for the analysis of imputed data described below, the denominator will be the the total number of toric study eyes in the Safety Set.

Frequencies and rates of cumulative and persistent adverse events from ISO 11979-7 (2018) Annex E will be reported by treatment group and AE type. Rates of adverse events will be compared to the SPE rate from Table E.2. For each listed AE, a one-sided exact binomial test comparing the proportion of toric 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.

Prior to hypothesis testing, a single imputation of missing toric IOL AE data due to discontinuations will be produced for the randomized cohort using logistic regression. A single imputation will be used because the method of multiple imputation does not allow for exact binomial tests.

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 Toric group. If any Safety set subjects discontinue prior to the start of the Visit 4 window, then the following secondary analyses will be performed by AE to assess the sensitivity of the results to missing data.

- The best case scenario will assume that toric eyes with missing data did not have the cumulative or persistent AE
- The worst case scenario will assume that toric eyes with missing data did have the cumulative or persistent AE if at least one toric eye experienced the same AE at any visit

For each AE, if the best and worst case analyses lead to different statistical conclusions, then a tipping point analysis will iteratively find the number of eyes with missing data that would have to experience the cumulative or persistent AE in order to change the statistical conclusion. For example, if the null hypothesis was not rejected, then the minimum number of eyes with missing data that would have to experience the AE to reject the null hypothesis will be reported.

The frequency and percentage of subjects reporting each adverse event at each postoperative form visit will be summarized in tables by treatment. An AE will be reported as unscheduled only if the AE starts and ends between two consecutive visit windows (without overlapping any form visit windows). For each cumulative AE, percentages will be calculated out of the number of subjects who attended the visit or who did not attend the visit but experienced the AE during the visit window. Persistent AEs will be defined as described above. Frequencies and percentages of eyes with each of the cumulative and persistent adverse events will be presented to assess the safety of the lens.

12.2.2 Rates of All Other Adverse Events

The frequency and percentage of eyes with at least one adverse event not included in the cumulative and persistent adverse events from ISO 11979-7 Table E.2 through 120 to 180 days post-operatively (Visit 4) will be presented by treatment group (Toric test group, monofocal control group). 95% exact binomial confidence intervals for the percentage will also be presented.

12.2.3 Rates of Secondary Surgical Interventions due to IOL Misalignment

The frequency and percentage of eyes implanted with the Toric test group IOL requiring a secondary surgical intervention for IOL repositioning due to IOL misalignment through 120 to 180 days post-operatively (Visit 4), as well as a two-sided 95% exact binomial confidence interval for the percentage, will be presented.

12.2.4 Rate of BCDVA of 0.30 logMAR or Better at Visit 4

The frequency and percentage of eyes that achieve a BCDVA at 4 meters of 0.30 logMAR or better at 120 to 180 days post-operatively (Visit 4) will be presented by treatment group (Toric test group, Monofocal control group) for the Safety set and Best Case Set.

For the proportion of Toric test group eyes with 0.30 logMAR or better at Visit 4, the null and alternative hypotheses for this endpoint are as follows.

H_{0s}: $p_{ts} \geq p_0$

H_{1s}: $p_{ts} < p_0$

Where p_{ts} denotes the true proportion of Toric test group eyes achieving a BCDVA of 0.30 logMAR or better at Visit 4 and p_0 is the historical control proportion of eyes achieving a BCDVA of 20/40 or better given in ISO 11979-7 Tables E.3 and E.4. A one-sided exact binomial test comparing the proportion of toric eyes with the 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. and comp. If neither hypothesis test result from the BCS and SAF set are statistically significant, this endpoint will be considered successful for the Toric IOL.

12.3 Additional Safety Analyses

Other safety variables will be summarized descriptively by visit, including but not limited to IOP, slit lamp examination results, dilated fundus exam results, and PCO results, including rates of posterior capsulotomies. Changes or shifts from baseline will also be summarized where appropriate. In addition, BCDVA will be summarized, stratified by age (< 65 yrs, >=65 yrs), by Investigator and by AE. The proportion of eyes with any decrease in BCDVA during the study of 10 letters or more (from a post-operative visit to any later post-operative visit) will be summarized. Reasons for VA decreases of 10 letters or more will be summarized.

13. Additional Clinical Parameters

13.1 Visual Acuity (ETDRS)

The rate of visual acuity decrease of 10 letters or more in BCDVA and/or UCDVA between a form evaluation and a later form evaluation will be summarized for the Safety set. The cause of the visual acuity decrease described in each case will be provided.

13.2 Slit-Lamp Biomicroscopy Examination

A slit-lamp biomicroscopy examination will be performed for eyelid, conjunctiva, cornea, anterior chamber, lens, and iris at each visit, except for the operative visits. Observations will be graded as Normal or Abnormal.

IOL observations will be recorded at every post-operative visit.

Cells and flare, corneal edema, glistenings, posterior capsule opacification and IOL observations will be graded according to the following scales:

- Cells

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

- Flare

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

- Corneal edema

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

- IOL glistenings

Amount	Grade	Description
None	**0**	No glistenings visible
Rare	**+0.5**	<10 glistenings visible
Trace	**+1**	10-19 glistenings visible
Mild	**+2**	20-29 glistenings visible
Moderate	**+3**	30-39 glistenings visible

- Posterior capsule opacification (PCO)

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

During the posterior capsule opacification assessment, whether the subject has undergone a YAG capsulotomy (yes/no) will also be recorded.

The results will be summarized using counts and percentages for each treatment group at each visit using the Safety Set. For the analysis, the percentages are based on the number of eyes with non-missing assessment at the specific visit in the specific treatment group.

13.3 Manifest Refraction

Manifest refraction at 4 meters collected at Pre-operative Visit 00, 7 to 14 days post-operatively (Visits 2), 30 to 60 days post-operatively (Visits 3), and 120 to 180 days post-operatively (Visit 4) will be summarized using continuous summary statistics by treatment, and visit for the Safety set. Manifest refraction parameters will include sphere (D), cylinder (D), and axis (degrees).

13.4 Dilated Fundoscopy Examination

A dilated fundoscopy examination will be performed at all visits except for the operative visits. The results will be graded as normal and abnormal.

The results will be summarized using counts and percentages for each treatment group at each visit for each eye using the Safety set. For the analysis, the percentages are based on the number of eyes with

non-missing assessment at the specific visit in the specific treatment group. A shift table for dilated fundoscopy will also be provided comparing each follow-up visit to baseline.

13.5 Intraocular Pressure (IOP)

Intraocular pressure (IOP) will be assessed at all visits, except for the operative visit. Results will be recorded in mmHg. If more than one measure is obtained for a protocol specified visit, the mean IOP value will be used for the summaries.

The IOP values and changes from baseline will be summarized using continuous descriptive statistics for each treatment group and for all study eyes at each visit using the Safety set.

13.6 IOL Tilt and Decentration

Evaluation of tilt (degrees) and decentration (mm) will be performed with the pupil dilated at 7 to 14 days post-operatively (Visit 2), 30 to 60 days post-operatively (Visit 3), 120 to 180 days post-operatively (Visit 4).

IOL tilt and decentration will be summarized using continuous descriptive statistics for each treatment group and for all actively treated subjects at each visit for each eye (first eye, second eye, and all eyes separately) using the Safety set.

13.7 Keratometric Measurements

Keratometric measurements will be collected during the Pre-Operative Visit, 30 to 60 days post-operatively (Visit 3), and 120 to 180 days post-operatively (Visit 4). Listings of keratometric parameters, including flat (D), steep (D), and axis (degrees) measurements, for each eye and each visit based on the Safety set will be included.

14. Interim Analyses

There are no interim analyses planned for this study.

15. Poolability Analyses

Approximately 11 sites will be encouraged to enroll a minimum of 20 subjects. No single site will enroll more that 25% of the total subjects enrolled in the toric and non-toric cohorts.

Consistency of treatment effectiveness for primary endpoints across sites will be evaluated through summaries by site and treatment. Additionally, a linear model will be fit with explanatory variables: site, treatment and the site by treatment interaction, including sites with 6 or more subjects. Sites with fewer than 6 subjects will not be arbitrarily pooled into a single larger site to be included in this model. If the site by treatment interaction is significant at a 2-sided alpha = 0.15, the cause of the significant interaction will be evaluated and presented.

Consistency of treatment safety across sites will evaluated through continuous or discrete summaries of primary and secondary safety variables, as appropriate.

16. Changes from Protocol Stated Analyses

There are no changes from the protocol-stated analyses.

17. References

N/A