Rayner

CONFIDENTIAL

The following contains confidential, proprietary information that is the property of

Rayner Intraocular Lenses Limited

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

Clinical Investigation Protocol

NCT05985304

Study Identification: WR-2023-US-03

Study Sponsor:

Rayner Intraocular Lenses Limited

10 Dominion Way

Worthing

West Sussex

BN14 8AQ

United Kingdom

Revision History

Revision	Date	Change
1.0	11Mar2023	Original Protocol
2.0	24May2023	Revised Protocol
3.0	28Aug2023	Revised Protocol (see Section 17)
4.0	19Sept2023	Revised Protocol (see Section 17)
5.0	26Jan2024	Revised Protocol (see Section 17)
6.0	16Apr2024	Revised Protocol (see Section 17)
7.0	01Aug2024	Revised Protocol (see Section 17)

SIGNATURE PAGE

To be signed and returned to Sponsor, prior to study initiation.

Study Title:	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
Investigational Device:	RayOne EMV Toric (Model RAO210T)
Sponsor Study ID:	WR-2023-US-03
Sponsor:	Rayner Intraocular Lenses Limited
Document Title:	Clinical Investigation Protocol
Document and Revision:	Rev 5.0

I,_____,

(name of principal investigator)

at_____,

(site)

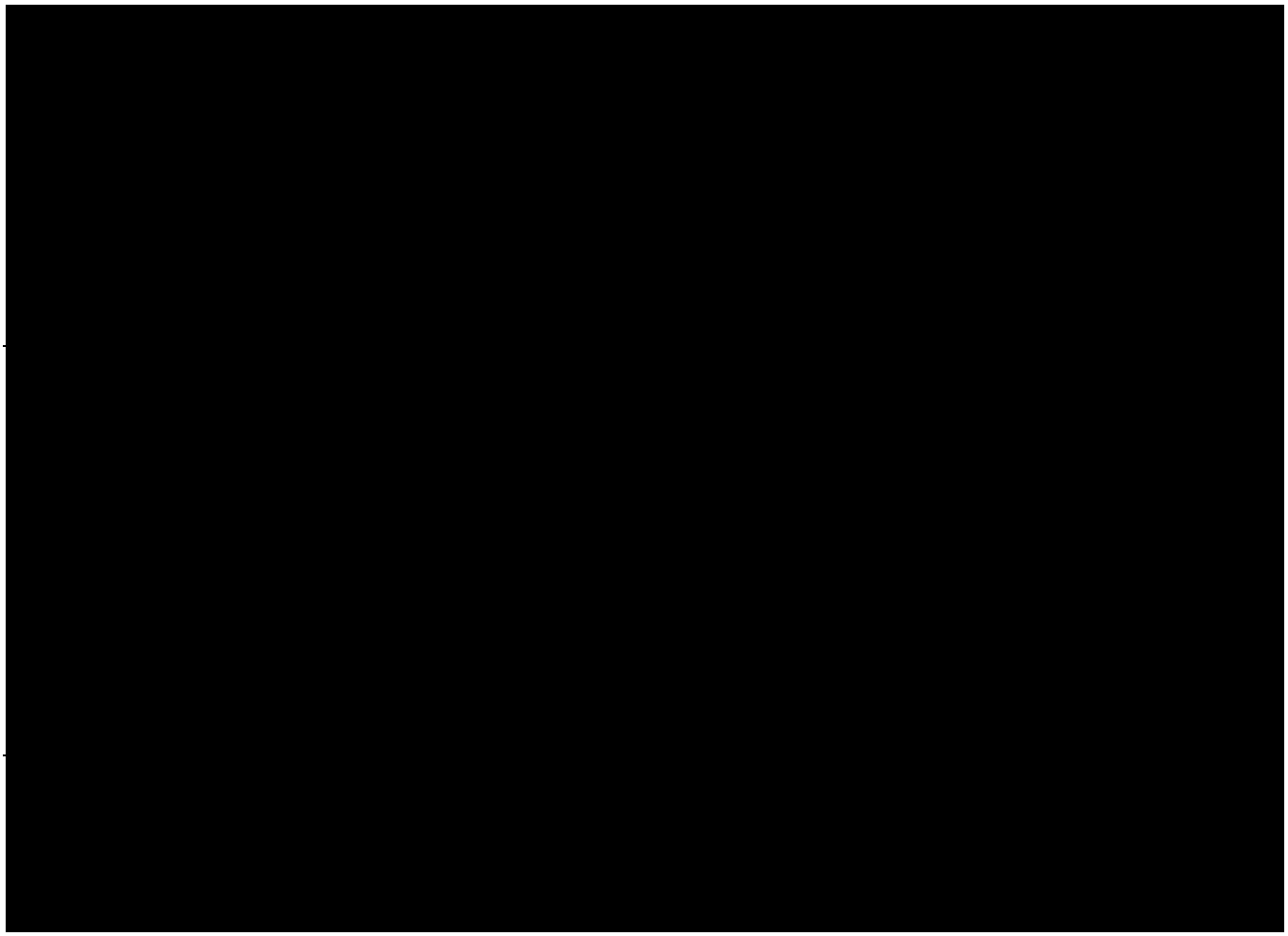
the undersigned, attest that I have read and understood this Protocol and agree and approve its content and to abide by the above-mentioned version and any subsequent amendments during my participation in the evaluation. I agree to perform and conduct the study as described in the protocol and in accordance with the relevant parts of the International Conference of Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), ISO 14155:2020, ISO 13485:2016, Regulation 2017/745 MDR, the Declaration of Helsinki, and the pertinent individual country laws/regulations.

_____ _____

Principal Investigator Signature Date

STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the design and specific provisions of this institutional review board (IRB) approved protocol, in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with International Conference of Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), ISO14155:2020, ISO 13485:2016, Regular 2017/745 ANSI Z80.30-2018 and the applicable local, state, or national regulatory/legal requirement(s). The Principal Investigators will assure that no deviation from, or changes to, the protocol will take place without prior agreement from the Sponsor and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the study subjects. The Principal Investigators will promptly report to the IRB and the Sponsor of any changes in research activity and all unanticipated problems involving risk to human subjects, or others, as required.



PROTOCOL CONFIDENTIALITY STATEMENT

Information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless National or State laws or regulations require such disclosure. Subject to the foregoing this information may be disclosed only to those persons involved in the clinical study who have a need to know. All such persons must be instructed not to disseminate this information to others.

Any individual, group, or institution obtaining confidential information of Rayner Intraocular Lenses Limited as a result of participation in this clinical study shall maintain the proprietary nature of confidential and technical information. Persons with authorized access to this document shall not photocopy, reproduce by any means, nor reveal the contents of this document to any other person without the prior written consent of Rayner Intraocular Lenses Limited

These restrictions on disclosures shall apply equally to all future information that is indicated as privileged or confidential.

LIST OF ABBREVIATIONS

AE	Adverse Event
AEHB	2-hydroxy-4-acryloxyethoxy benzophenone
ANSI	American National Standards Institute
BCS	Best Case Set
BCDVA	Best Corrected Distance Visual Acuity
CFR	Code of Federal Regulations
CME	Cystoid Macular Edema
DFU	Directions for Use
eCRF	Electronic Case Report Form
EGDMA	ethylene glycol dimethacrylate
ETDRS	Early Treatment of Diabetic Retinopathy Study
F	Fahrenheit
FA	Fluorescein Angiography
FDA	Food and Drug Administration
FLACS	Femtosecond Laser-Assisted Cataract Surgery
GCP	Good Clinical Practice
HEMA	2-hydroxy ethyl methacrylate
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IOL	Intraocular Lens
IOP	Intraocular pressure
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent-to-treat
LASIK	Laser in-situ Keratomileusis
LASEK	Laser Epithelial Keratomileusis
logMAR	Logarithm of the Minimum Angle of Resolution
MCMC	Markov Chain Monte Carlo
mm	Millimeter
mmHg	Millimeters of Mercury
MMA	methyl methacrylate
nm	Nanometer
OCT	Optical Coherence Tomography
PCO	Posterior Capsule Opacification
PP	Per Protocol
PRK	Photorefractive Keratectomy
RD	Retinal Detachment
SAE	Serious Adverse Event
SAF	Safety Set
SMILE	Small Incision Lenticule Extraction
SSI	Secondary Surgical Intervention
TASS	Toxic Anterior Segment Syndrome
UADE	Unanticipated Adverse Device Event
UCDVA	Uncorrected Distance Visual Acuity
US	United States
UV	ultraviolet
YAG	yttrium aluminum garnet

PROTOCOL SYNOPSIS

Study Title	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
Study Sites	Up to 11 U.S. sites will participate in the study
Investigational Device	RayOne EMV Toric (Model RAO210T)
Study Design	This study is a prospective, multicenter, randomized, active controlled, masked investigation for unilateral implantation of low cylinder power (1.50 D) toric IOL.
Phase	Pivotal
Masking	Partially Masked - site personnel performing post-operative manifest refraction and visual acuity assessments, will be masked to subject treatment assignment until after the final database lock. Subjects will be masked to their IOL assignment in the randomized controlled investigation evaluating 1.50 D cylinder power.
Study Arms	2 Arms: Randomized controlled 1) RayOne EMV Toric (Model RAO210T) (investigational) - low cylinder (1.50 D) 2) Rayner RAO600C aspheric monofocal IOL (control)
Study Objective	The objectives of the clinical investigation are to determine the safety and performance of the RayOne EMV Toric (Model RAO210T) following unilateral IOL implantation and approximately 6 months (120 to 180 days) of post-operative assessment, as a randomized comparison of 1.50 D cylinder IOL to aspheric monofocal control .
Estimated Enrollment	Up to 295 adult subjects will be enrolled (consented) assuming a 15% screen failure rate, then up to 250 subjects will be randomized, of which approximately 125 subjects will be randomized to receive low cylinder (1.50 D) RayOne EMV Toric (Model RAO210T) in one eye and approximately 125 subjects randomized to receive the RAO600C aspheric monofocal IOL in one eye, to complete 120-180 days follow-up for at least 100 subjects in each group. Up to 11 U.S. sites will be encouraged to enroll a minimum of 20 subjects. No site will enroll more than 25% of the subjects enrolled in the study.
Indications for Use	The RayOne EMV Toric (Model RAO210T) consists of the EMV Toric IOL (210T) preloaded within the RayOne injection system (RAO). The EMV Toric IOL is intended for primary implantation in the capsular bag of the eye for the visual correction of aphakia, in adult patients in whom a cataractous lens has been removed and providing reduction of residual refractive astigmatism in adult patients with greater than or equal to 1.00 diopter (D) of corneal astigmatism, compared to a monofocal IOL. The RayOne injection system is used to fold and assist in inserting the IOL into the eye.
Device Description	The EMV Toric IOL device is based on the family of Rayner IOLs approved for use in the US, C-Flex 570C, C-Flex 970C Aspheric and 600C Aspheric Intraocular Lenses (P060011) and carry forward the

	development of new designs using the approved Rayacryl material. Toric models are intended to provide adjustment to the astigmatism of the eye. The mechanical and optic properties of the Model 210T were assessed in compliance with ISO 11979-3 and ISO 11979-2 and found acceptable. In cases where the mechanical properties were related to the Rayacryl® material, the testing performed for the Model 600C is provided as both IOL models are manufactured from the same Rayacryl® material. The RAO210T is planned to be available in spherical equivalent power between +10.0 D to +25.0 D in 0.5 D steps and IOL cylinder power +1.50 D to +4.50 D in 0.75 D steps. The device has a closed-C-loop haptic design and 0° vaulting. The two haptics are of 0.41 mm thickness. The optic diameter is 6.0 mm and the total diameter 12.5 mm. The device has a square edge of 360° aiming at optimal lens-tissue contact. The device has a biconvex aspheric optic (+0.12 micron of positive spherical aberration). The material includes an UV blocker (< 10% transmittance at 385 nm). The devices are manufactured by lathing and milling and controlled individually for their optical and dimensional properties. The lenses are preloaded into an injector stored in a PP primary packaging tray filled with saline solution and sealed with a foil lid. The secondary packaging is a PP tray with Tyvek® lid. The finished pack is steam sterilized. The planned study injector device is the RayOne injector (Model RAO). The injector Type is a Single use, fully preloaded IOL injection system; Nozzle Size: 1.65 mm; Bevel Angle: 45°; Lens Delivery: Single handed plunger.
Duration of Study	Total study duration is expected to be approximately 12-15 months. The cohort will be enrolled in approximately 6-9 months and followed for approximately 6 months (120 to 180 days post-operatively).
Duration of Subject Participation	Subjects will complete 6 study visits. 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). <u>Summary of Visit Schedule:</u> ▪ 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)
Primary Effectiveness Endpoints	• 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 o 10 degrees o 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)
Secondary Effectiveness Endpoints	• 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)
Safety Endpoints	**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 event list 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
Additional Effectiveness Analyses	• 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 – Percentage 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
Inclusion Criteria	***Note: Inclusion and Exclusion Criteria to be applied prior to subject randomization.*** **Inclusion Criteria** Eligible subjects must meet all the following inclusion criteria. All ocular criteria must be met in the eye receiving the study lens (only one eye is to be enrolled[1]): 1) Male or female, 22 years or older at the pre-operative visit who have cataract with best corrected distance visual acuity of 0.30 logMAR (20/40) or worse in at least one eye with or without a glare source present who are eligible for phacoemulsification cataract surgery 2) Subjects who are projected to have best corrected distance visual acuity 0.20 logMAR (20/30) or better after IOL implantation by potential acuity meter (PAM) or Investigator estimation 3) Clear intraocular media other than cataract 4) Contact lens wearers must demonstrate stability of biometry 5) Have the capability to understand and sign an IRB approved informed consent form and privacy authorization in accordance with local regulations 6) Female subjects must be 1-year postmenopausal, surgically sterilized, or, if of childbearing potential, have a negative urine pregnancy test at the Pre-operative Visit. Women of childbearing potential must use an acceptable form of contraception throughout the study. *Acceptable methods include at least one of the following: intrauterine (intrauterine device), hormonal (oral, injection, patch, implant, ring), barrier with spermicide (condom, diaphragm), or abstinence.* 7) Have Investigator selected IOL spherical equivalent power between +10.0 D to +25.0 D in 0.5 D steps and IOL cylinder power of +1.50 D

[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

	8) Have pre-existing corneal astigmatism of 1.00D to 1.50 D as determined by keratometry 9) Dilated pupil size 5.5 mm or greater to allow visualization of the toric IOL axis markings post-operatively
Exclusion Criteria	**Exclusion Criteria** Eligible subjects must not meet any of the following exclusion criteria. Subjects may not participate if either eye meets any of the ocular exclusion criteria, unless otherwise noted as only the planned operative eye: 1) Previous intraocular, corneal, or retinal detachment surgery, including corneal transplant, LASIK / LASEK / PRK, SMILE, astigmatic keratotomy and limbal relaxing incisions in the planned operative eye. 2) Diagnosed degenerative visual disorders (e.g. macular degeneration, retinal detachment, proliferative diabetic retinopathy, or other retinal disorders) that are predicted to cause future acuity losses to a level of 0.20 logMAR (20/30) or worse 3) Significant anterior segment pathology that might increase intraoperative risk or compromise IOL stability (e.g. pseudoexfoliation syndrome, any iris pathology) 4) Subjects with conditions associated with increased risk of zonular rupture (that may affect post-operative centration or tilt of IOL) in the planned operative eye 5) Potentially occludable angle or ciliary body tumor, or other pathology that might increase risk to subject safety, based on gonioscopic observation 6) Subjects reasonably expected to require secondary ocular surgical intervention or laser treatment (other than YAG capsulotomy) 7) Subjects with clinically significant corneal pathology potentially affecting corneal topography 8) Subjects with traumatic cataract in the planned operative eye 9) Participating in a concurrent drug or device clinical trial or who have participated in a drug or device trial within 30 days of the pre-operative visit 10) Subjects with any other serious ocular pathology (e.g. glaucoma, severe dry eye, history of intraocular inflammation, history of retinal surgery or retinal laser procedure) or underlying systemic medical condition (e.g., uncontrolled diabetes) or circumstance that, based on the Investigator's judgment, poses a concern for the subjects' safety or could confound the results of the study (History of cataract surgery with PC-IOL in one eye is allowed.) 11) Use of medications known to interfere with visual performance, pupil dilation, or iris structure within 30 days of the pre-operative visit, at the discretion of the Investigator 12) Pregnant or nursing females 13) Irregular astigmatism in the planned operative eye

Statistical Methods	**General Considerations:** All quantitative study assessments will be summarized by visit (as applicable) using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). All qualitative study assessments will be summarized by visit (as applicable) using frequency counts and percentages. Variables and time points used for primary effectiveness and safety endpoints will be summarized descriptively for each treatment group by sex, age, racial and ethnic groups. The baseline measure will be defined as the last non-missing measure prior to initiation of investigational treatment. The following terms will be used throughout the Statistical Analysis section: **Study Populations:** • All Enrolled Set – All subjects who sign informed consent. This set will be used for disposition summaries. • Intent-to-Treat (ITT) Set – All enrolled subjects who are randomized. All ITT analyses will be done according to randomized lens assignment. • Safety Set (SAF) – All ITT subjects who undergo surgery. Summaries and analyses based on the Safety Set 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. • Per Protocol (PP) Set – All SAF subjects who are successfully implanted with a study lens and who have no major protocol deviations. Major protocol deviations will be defined in the statistical analysis plan (SAP). • Best Case Set (BCS) – All PP subjects who also meet the following criteria: o No clinically significant pre-operative ocular pathology o No macular degeneration detected at any time o No previous surgery for the correction of refractive errors, which would have resulted in exclusion of the subject from the study **Study Groups:** • Toric (test) group – all subjects randomized to be implanted with the low cylinder (1.50 D) RayOne EMV Toric IOL (Model RAO210T) (for ITT, PP and BCS analyses) or implanted with the low cylinder (1.50 D) RayOne EMV Toric IOL (Model RAO210T) (for SAF analyses) • Monofocal (control) group – all subjects randomized to be implanted with the RAO600C Monofocal IOL (for ITT, PP and BCS analyses) or implanted with the RAO600C monofocal IOL (for SAF Analyses)

Statistical Hypotheses:

Primary Effectiveness

Primary effectiveness analyses will be completed using the ITT Set. The primary effectiveness hypotheses are:

- Mean magnitude of residual manifest cylinder, (as measured by manifest refraction) at 120 to 180 days post-operatively (Visit 4)

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

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

Where μ_{te} and μ_{ce} denote the population mean residual manifest cylinder at Visit 4 for the Toric group and Monofocal group, respectively.

There is no statistical hypothesis for percentage of RayOne EMV Toric lenses with IOL axis misalignment less than 10 degrees, and percentage less than 20 degrees. This endpoint will be summarized descriptively only and 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 group.

There is no statistical hypothesis for IOL axial stability. This endpoint will be summarized descriptively only and will be considered successful if at least 90% of Toric group IOLs rotate ≤ 5 degrees postoperatively between 30 to 60 days (Visit 3) and 120 to 180 days (Visit 4).

Primary Safety

Safety analyses will be completed using the SAF for all analyses.

Regarding rates of adverse events provided in ISO 11979-7, the hypotheses are:

$H_{01s}: p_{t1s} \leq p_0$

$H_{11s}: p_{t1s} > p_0$

Where p_{t1s} denotes the true population proportion of Toric group eyes suffering from an adverse event through Visit 4, and p_0 represents the historical proportion of eyes suffering from the adverse event, as specified in ISO 11979-7.

There are no statistical hypotheses for the rates of other adverse events. They will be summarized descriptively only for the Toric group and Monofocal group IOLs.

There is no statistical hypothesis for the rate of secondary surgical intervention due to axis misalignment. This will be summarized descriptively only for the Toric group and Monofocal group IOLs.

Regarding the rate of BCDVA of 0.30 logMAR or better, the hypotheses are:

$H_{02s}: p_{t2s} \geq p_0$

$H_{12s}: p_{t2s} < p_0$

Where p_{t2s} denotes the true population proportion of Toric group eyes achieving a BCDVA of 0.30 logMAR or better at Visit 4, and p_0 represents the historical rate of eyes achieving this criterion, as specified in ISO 11979-7. This analysis will also be conducted on the BCS as described in ISO 11979-7.

Sample Size Determination:

Subjects will be enrolled with the goal of completing a total of 200 subjects through Visit 4 within the randomized groups, of whom 100 were implanted with the low cylinder RayOne EMV Toric IOL (Model RAO210T) and 100 were implanted 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 .

Effectiveness

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 H0e in favor of H1e 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.

Safety

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.

Handling of Missing Data:

Missing data will be imputed for selected endpoints using the methods specified under the analysis descriptions for the endpoints. Where possible, multiple imputation will be used. Except where mentioned in Section 7, missing data will not be imputed.

Multiplicity Considerations:

The overall type I error rate for the toric effectiveness analyses will be controlled at 0.05. The study will be considered successful if all of the primary effectiveness and safety endpoints are met. Thus, no adjustments for multiplicity are necessary.

Effectiveness Endpoints

Primary Effectiveness Analyses:

Primary effectiveness endpoint analyses will be based on the ITT set. Results will be summarized by visit for each scheduled visit and planned assessments at that visit. Selected effectiveness analyses will also be completed for the PP Set as a supportive analysis.

The co-primary effectiveness endpoints are:

- Mean magnitude of residual manifest cylinder, (as determined 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) Residual manifest cylinder will be summarized by visit for the ITT Set using continuous summary statistics. 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 adjusted mean difference between Toric and Monofocal groups will be given together with a 95% confidence interval and associated one-sided p-value. This endpoint will be considered successful if the one-sided p-value ≤ 0.025. IOL axis misalignment at 120 to 180 days post-operatively (Visit 4) for the Toric group will be summarized for the ITT Set by the frequency and percentage of eyes with IOL axis misalignment less than 10 degrees, as well as less than 20 degrees. This endpoint will be considered successful if IOL axis misalignment is less than 10 degrees for 90% of eyes from the Toric group and less than 20 degrees for 95% of eyes from the Toric group. The frequency and percentage of Toric group IOLs that rotate ≤ 5 degrees postoperatively between 30 to 60 days (Visit 3) and 120 to 180 days (Visit 4) will be reported. This endpoint will be considered successful if at least 90% of Toric group IOLs rotate ≤ 5 degrees postoperatively between 30 to 60 days (Visit 3) and 120 to 180 days (Visit 4). **Secondary Effectiveness Analyses:** Residual manifest cylinder at Visit 4 will 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. Percent reduction in absolute cylinder (as measured by magnitude of residual manifest cylinder relative to preoperative keratometric cylinder) at Visit 4 will 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. ***Safety Analyses:*** All safety analyses will be based on the Safety Set. **Primary Safety Analyses:** All primary safety analyses will be based on the study eye. The co-primary safety endpoints are: • 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 event list 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 ISO SPE rates as described in 11979-7 Frequencies and rates of cumulative and persistent adverse events from ISO 11979-7 (2018) Table E.2 will be reported by treatment group (Toric test group, Monofocal control group) and AE type. Rates of adverse events will be compared to the SPE rate from Table E.2. The one-sided p-value from the exact binomial test of each hypothesis will also be provided for each adverse event. If none of these hypothesis test results are statistically significant, this endpoint will be considered successful for the toric IOL. 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 (2018) Table E.2 through 120 to 180 days post-operatively (Visit 4) will be presented by treatment group (Toric test group, Monofocal control group). 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. 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. If neither of these hypothesis test results are statistically significant, this endpoint will be considered successful for the toric IOL. ***Adverse Events*** Analyses of adverse events will be performed separately for ocular and non-ocular events. Adverse events will also be summarized and analyzed separately for the Toric test group and the Monofocal control group. The incidence of eyes with at least one serious adverse event will be summarized using categorical summary statistics by treatment received. Cumulative and persistent adverse events from ISO 11979-7 (2018) Table E.2 will be summarized using descriptive statistics by AE type and treatment and will be compared to the maximum number of cases allowed before the ISO SPE rate is exceeded. Additionally, cumulative and persistent adverse events will be summarized separately by age group (< 65 years vs. ≥ 65 years) and by investigator. All types of adverse events will be reported and compared between arms using descriptive statistics. Separate analyses will be done for device-related events and events that are of moderate to severe severity. All adverse events reported will be summarized and listed by subject. Adverse events will also be summarized for all ocular AEs and for all SAEs. All ocular AEs will also be summarized by maximal severity, for AEs related to the study lens, and by study day of onset. In addition, the following summaries will be provided: • Ocular AEs by relationship to study device/procedure as well as unrelated Ocular and Non-ocular AEs • Ocular Serious AEs by relationship to study device/procedure as well as unrelated Ocular and Non-ocular Serious AEs

	• Ocular AEs by maximal severity • Ocular AEs by age group (< 65 years vs. ≥ 65 years) • Ocular AEs by investigator ***Other Safety Analyses*** Other safety endpoints 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 percentage 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. **Poolability Analysis:** Consistency of treatment effectiveness for primary endpoints across sites will be evaluated through summaries by site and treatment. Additionally, linear models 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 be evaluated through continuous or discrete summaries of safety variables, as appropriate. **Additional Effectiveness Analyses:** Additional effectiveness analyses 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 (2018). Additional effectiveness analyses will be based on eyes from the ITT population at 120 to 180 days post-operatively (Visit 4), unless otherwise stated. Categorical analyses include evaluation of the percentage of eyes achieving UCDVA ≤ 0.30, ≤ 0.20, and ≤ 0.00 logMAR at Visit 4; BCDVA ≤ 0.30, ≤ 0.20, and ≤ 0.00 logMAR; percentage of eyes achieving accuracy of cylinder (to target) at Visit 4 within +/- 0.25, +/- 0.50, and +/- 0.75 D; and percentage of eyes with reduction in cylinder at Visit 4 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. 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 Visit 4 will be summarized. Reduction in cylinder power, defined as pre-operative magnitude of the keratometric cylinder minus magnitude of manifest cylinder at a given 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 (Toric group minus Monofocal control group). The analysis will be repeated for subgroups of 0.25D preoperative keratometric 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. 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.

Schedule of Events

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*					
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

Table of Contents

1. Introduction

1.1. Ethical Considerations

This study will be conducted in compliance with the protocol, institutional review board (IRB) requirements, FDA Title 21 CFR 812, FDA/ICH Good Clinical Practice, and in general, consistent with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements relevant to the use of study devices in the US will be adhered to.

Each study participant must be provided with a copy of the IRB approved informed consent form (ICF) for their review. Participant's written informed consent must be provided by the participant prior to any study specific procedures being initiated. All participants will be considered enrolled in the study upon providing written informed consent.

If the ICF requires revision (e.g., due to a protocol amendment), it is the Investigator's responsibility to ensure that the amended ICF is reviewed and approved by the IRB and that it is read, signed and dated by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

2. Study Devices

2.1. General Description

Rayner intraocular lenses (IOLs) are single piece optical devices, manufactured from Rayacryl (hydroxyethyl methacrylate/methyl methacrylate copolymer with UV blocker). These devices are designed to be surgically implanted in the human eye as a replacement for the crystalline lens and are intended for placement in the capsular bag following phacoemulsification.

Rayner IOLs are intended to provide adjustment to the dioptric power of the eye. Additionally, aspheric models are aberration neutral and therefore do not add to the spherical aberration of the eye. Toric models are intended to provide adjustment to the astigmatism of the eye.

The mechanical and optic properties of the Model 210T were assessed in compliance with ISO 11979-3 and ISO 11979-2 and found acceptable. In cases where the mechanical properties were related to the Rayacryl® material, the testing performed for the Model 600C is provided as both IOL models are manufactured from the same Rayacryl® material.

The RAO210T is planned to be available in spherical equivalent power between +10.0 D to +25.0 D in 0.5 D steps and IOL cylinder power +1.50 D to +4.50 D in 0.75 D steps. The device has a closed-C-loop haptic design and 0° vaulting. The two haptics are of 0.41 mm thickness. The optic diameter is 6.0 mm and the total diameter 12.5 mm. The device has a square edge of 360° aiming at optimal lens-tissue contact. The device has a biconvex aspheric optic (+0.12 micron of positive spherical aberration). The material includes an UV blocker (< 10% transmittance at 385 nm).

The devices are manufactured by lathing and milling and controlled individually for their optical and dimensional properties. The lenses are preloaded into an injector stored in a PP primary packaging tray filled with saline solution and sealed with a foil lid. The secondary packaging is a PP tray with Tyvek lid. The finished pack is steam sterilized. The planned study injector device is the RayOne injector (Model RAO). The injector Type is a Single use, fully preloaded IOL injection system; Nozzle Size: 1.65 mm; Bevel Angle: 45°; Lens Delivery: Single handed plunger.

2.1.1. Study Device Labeling/Packaging Configuration

RayOne EMV Toric (Model RAO210T), also referred to as RAO210T Toric IOL, and RAO600C aspheric monofocal IOL lenses are supplied sterile and preloaded in the RayOne delivery system within a sterilized blister pack labeled with the serial number, lot number, expiration date. The sterilized blister pack is steam sterilized and should only be opened under sterile conditions. The RAO210T Toric IOL lenses will be delivered Investigator labeled for investigational use as follows:

> 'CAUTION Investigational device. Limited by Federal Law to investigational use'

2.1.2. Storage of Study Devices

The RAO210T Toric IOL lenses must be stored in a secure area accessible only to the Investigator and his/her designees. The study device must be stored at the following environmental conditions:

1. Stored between 41-95°F temperature
2. Keep away from sunlight
3. Keep dry

3. 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).

All primary effectiveness and primary safety endpoints as described below are required to achieve successful outcomes in order to demonstrate study success.

3.1. Primary Effectiveness Endpoints

- 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)

3.2. Secondary Effectiveness Endpoints

- 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)

3.3. 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 event list 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

3.4. Additional Effectiveness Analyses

- Percentage of eyes achieving UCDVA at 4 m 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 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) 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
  - Percentage 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

4. Study Risk/Benefit

The purpose of this study is to evaluate the visual outcomes and safety of the RAO210T toric IOL to that of the RAO600C aspheric monofocal IOL. The study is designed to meet the requirements specified for toric IOLs in the ISO 11979-7, ISO 11979-9, and ANSI Z80.30 standards.

4.1. Known Potential Risks

The device RAO210T has known risks associated with both the surgical procedure for the removal of cataract and those associated with implantation and long-term use of intraocular lenses including toric IOLs.

4.2. Known Potential Benefits

The potential benefits associated with this study are improved visual outcome for subjects undergoing cataract surgery and advancing vision care. With regards to the 210T EMV Toric IOL, the possible benefits associated with this study are visual correction of aphakia and corneal astigmatism to improve distance vision for subjects with preoperative astigmatism who are undergoing cataract surgery.

5. Subject Selection

5.1. Study Entry Procedures

5.1.1. Informed Consent

Prior to a subject's participation in the trial (i.e., study related procedures), the study will be discussed with each subject, and he or she must be provided with the informed consent form (ICF) and time to read and consider its contents, with time to ask any questions that arise thereafter. Subjects wishing to participate must give written informed consent using the most current IRB-approved version of the ICF. The original ICF will be retained in the subject's records and a copy will be provided to the subject. All participants will be considered enrolled in the study upon providing written informed consent.

5.1.2. Screen Failures

The subjects must satisfy all the inclusion and exclusion criteria prior to randomization in order to participate in the study. An enrolled subject who fails to meet eligibility criteria and/or discontinues from the study before randomization will be considered a screen failure and exited from the study.

5.1.3. Strategies for Subject Retention

Study site personnel should take the following steps to minimize the likelihood of early termination during the study:

- During the Pre-operative Visit, emphasize the importance of returning for all study follow-up visits and thoroughly evaluate the study subject for potential health or motivational issues or other life circumstances that may negatively affect compliance with the study follow-up visit schedule
- Evaluate research staff flexibility to work around personal difficulties encountered by the subject related to protocol compliance (e.g., appointment times)
- Attempt to schedule subject follow-up visits early in the visit window to facilitate rescheduling within the window, if necessary
- Attempt to follow-up on subjects who do not return for scheduled examinations

6. 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.

6.1. Inclusion Criteria

Note: Inclusion and Exclusion Criteria to be applied prior to subject randomization.

Eligible subjects must meet all the following inclusion criteria. All ocular criteria must be met in the eye receiving the study lens (only one eye is to be enrolled[2]):

1) Male or female, 22 years or older at the pre-operative visit who have cataract with best corrected distance visual acuity of 0.30 logMAR (20/40) or worse in at least one eye with or without a glare source present who are eligible for phacoemulsification cataract surgery
2) Subjects who are projected to have best corrected distance visual acuity 0.20 logMAR (20/30) or better after IOL implantation by potential acuity meter (PAM) or Investigator estimation
3) Clear intraocular media other than cataract
4) Contact lens wearers must demonstrate stability of biometry
5) Have the capability to understand and sign an IRB approved informed consent form and privacy authorization in accordance with local regulations
6) Female subjects must be 1-year postmenopausal, surgically sterilized, or, if of childbearing potential, have a negative urine pregnancy test at the Pre-operative Visit. Women of childbearing potential must use an acceptable form of contraception throughout the study.

   Acceptable methods include at least one of the following: intrauterine (intrauterine device), hormonal (oral, injection, patch, implant, ring), barrier with spermicide (condom, diaphragm), or abstinence.
7) Have Investigator selected IOL spherical equivalent power between +10.0 D to +25.0 D in 0.5 D steps and IOL cylinder power of +1.50 D
8) Have pre-existing corneal astigmatism of 1.00 D to 1.50 D as determined by keratometry

[2] 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

9) Dilated pupil size 5.5 mm or greater to allow visualization of the toric IOL axis markings post-operatively

6.2. Exclusion Criteria

Eligible subjects must not meet any of the following exclusion criteria. Subjects may not participate if either eye meets any of the ocular exclusion criteria, unless otherwise noted as only the planned operative eye:

1) Previous intraocular, corneal, or retinal detachment surgery, including corneal transplant, LASIK / LASEK / PRK, SMILE, astigmatic keratotomy and limbal relaxing incisions in the planned operative eye.
2) Diagnosed degenerative visual disorders (e.g. macular degeneration, retinal detachment, proliferative diabetic retinopathy, or other retinal disorders) that are predicted to cause future acuity losses to a level of 0.20 logMAR (20/30) or worse
3) Significant anterior segment pathology that might increase intraoperative risk or compromise IOL stability (e.g. pseudoexfoliation syndrome, any iris pathology)
4) Subjects with conditions associated with increased risk of zonular rupture (that may affect post-operative centration or tilt of IOL) in the planned operative eye
5) Potentially occludable angle or ciliary body tumor, or other pathology that might increase risk to subject safety, based on gonioscopic observation
6) Subjects reasonably expected to require secondary ocular surgical intervention or laser treatment (other than YAG capsulotomy)
7) Subjects with clinically significant corneal pathology, potentially affecting corneal topography
8) Subjects with traumatic cataract in the planned operative eye
9) Participating in a concurrent drug or device clinical trial or who have participated in a drug or device trial within 30 days of the pre-operative visit
10) Subjects with any other serious ocular pathology (e.g. glaucoma, severe dry eye, history of intraocular inflammation, history of retinal surgery or retinal laser procedure) or underlying systemic medical condition (e.g., uncontrolled diabetes) or circumstance that, based on the Investigator's judgment, poses a concern for the subjects' safety or could confound the results of the study

    (History of cataract surgery with PC-IOL in one eye is allowed.)
11) Use of medications known to interfere with visual performance, pupil dilation, or iris structure within 30 days of the pre-operative visit, at the discretion of the Investigator
12) Pregnant or nursing females
13) Irregular astigmatism in the planned operative eye

6.3. Randomization and Masking

All subjects who meet inclusion criteria will be assigned to the randomized controlled study arms 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.

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.

6.4. Study Visit Schedule

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. Methodology for study examinations is presented in the Manual of Procedures.

6.4.1. Visit 00 Pre-operative Visit Both Eyes (Day -90 to 0)

Subjects will be screened and assessed against the study inclusion/exclusion criteria to determine their eligibility after obtaining consent. Inclusion and Exclusion Criteria must be applied prior to subject randomization. All subjects screened will be documented on the Screening/Enrollment log, including the reason for non-participation for subjects who do not enroll. The following assessments should be completed:

- Informed Consent/HIPAA
- Inclusion/Exclusion Criteria Review
- Demographics
- Concomitant Medications
- Ocular and Significant Non-ocular Medical History*
- Urine Pregnancy Test (if applicable)
- Potential Visual Acuity*
- Manifest Refraction
- UCDVA – Monocular (ETDRS) – 4 m
- BCDVA – Monocular (ETDRS) – 4 m
- Corneal Topography*
- Keratometry/ Axial length/ Anterior chamber depth (biometry)/ Target refraction/ IOL power calc (Barrett Toric and any non-toric Monofocal IOL formula)*
- Intraocular Pressure*
- Gonioscopy*
- Slit lamp Biomicroscopy*
- Dilated Pupil size*
- Dilated Fundus Exam*
- Randomization
- Adverse Events

* 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.

6.4.2. Visit 0 Operative Visit Implanted Eye (Day 0)

The following assessments should be completed:

- Concomitant Medications
- Ocular and Significant Non-ocular Medical History
- Inclusion/Exclusion Criteria Review
- Operative Procedures
- IOL Axis Orientation – retroilluminated slit lamp photo (dilated) – *subjects implanted with RAO210T toric IOL only*
- Adverse Events
- Device Deficiencies

6.4.3. Visit 1 Post-operative Visit Implanted Eye (Day 1-2)

Measures will be taken to mask the site personnel performing post-operative visual acuity assessments as to the subject's treatment assignment. The following assessments should be completed:

- Concomitant Medications
- UCDVA – Monocular (ETDRS) – 4 m
- Intraocular Pressure
- Slit lamp Biomicroscopy
- Posterior Capsule Opacification (PCO) Assessment (dilated)
- IOL Observations (dilated)
- IOL Axis Orientation – retroilluminated slit lamp photo (dilated) – *subjects implanted with RAO210T toric IOL only*
- Dilated Fundus Exam
- Adverse Events
- Device Deficiencies

6.4.4. Visit 2 Post-operative Visit Implanted Eye (Day 7-14)

Measures will be taken to mask the site personnel performing post-operative manifest refraction and visual acuity assessments as to subject's treatment assignment. The following assessments should be completed:

- Concomitant Medications
- Manifest Refraction
- UCDVA – Monocular (ETDRS) – 4 m
- BCDVA – Monocular (ETDRS) – 4 m
- Intraocular Pressure
- Slit lamp Biomicroscopy
- Posterior Capsule Opacification (PCO) Assessment (dilated)
- IOL Observations (dilated)
- Lens Stability – decentration and tilt (dilated)
- IOL Axis Orientation – retroilluminated slit lamp photo (dilated) – *subjects implanted with RAO210T toric IOL only*
- Dilated Fundus Exam
- Adverse Events
- Device Deficiencies

6.4.5. Visit 3 Post-operative Visit Implanted Eye (Day 30-60)

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. The following assessments should be completed:

- Concomitant Medications
- Manifest Refraction
- UCDVA – Monocular (ETDRS) – 4 m
- BCDVA – Monocular (ETDRS) – 4 m
- Keratometry
- Intraocular Pressure
- Slit lamp Biomicroscopy
- Posterior Capsule Opacification (PCO) Assessment (dilated)
- IOL Observations (dilated)
- Lens Stability – decentration and tilt (dilated)
- IOL Axis Orientation – retroilluminated slit lamp photo (dilated) – *subjects implanted with RAO210T toric IOL only*
- Dilated Fundus Exam
- Adverse Events
- Device Deficiencies

6.4.6. Visit 4 Post-operative Visit Implanted Eye (Day 120-180)

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. The following assessments should be completed:

- Concomitant Medications
- Manifest Refraction
- UCDVA – Monocular (ETDRS) – 4 m
- BCDVA – Monocular (ETDRS) – 4 m
- Keratometry
- Intraocular Pressure
- Slit lamp Biomicroscopy
- Posterior Capsule Opacification (PCO) Assessment (dilated)
- IOL Observations (dilated)
- Lens Stability – decentration and tilt (dilated)
- IOL Axis Orientation – retroilluminated slit lamp photo (dilated) – *subjects implanted with RAO210T toric IOL only*
- Dilated Fundus Exam
- Adverse Events
- Device Deficiencies

At the end of the final visit, an implant card included in the pack to record all implant information (the supplied labels may be used) shall be given to the patient, with the instruction to keep this card. The card should be shown to any eye care professional the patient visits in future.

6.4.7. Unscheduled Visits

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. The following assessments should be completed:

- Concomitant Medications
- Manifest Refraction
- UCDVA – Monocular (ETDRS) – 4 m
- BCDVA – Monocular (ETDRS) – 4 m
- Intraocular Pressure
- Slit lamp Biomicroscopy
- Posterior Capsule Opacification (PCO) Assessment (dilated)
- IOL Observations (dilated)
- Dilated Fundus Exam – *Optional, based on Investigator's discretion*
- Adverse Events
- Device Deficiencies

6.5. Concomitant Medications

Documentation of all medications used by the subject within 30 days of the Pre-operative Visit and throughout the subject's study participation will be recorded in the subject's case report form. Pre-, intra-, and post-operative medications may be administered per the Investigator's standard of care and documented in source documents only (not required to be entered in subject's case report forms). A complete list of the Investigator's standard regimen of these medications will be provided to the Sponsor or its designee and approved by the Medical Monitor prior to initiation of the study. Medications known to interfere with visual performance, pupil dilation, or iris structure are prohibited throughout the subject's study participation.

6.6. Investigational IOL Selection, Surgically Induced Astigmatism (SIA) and Surgical Technique

IOL power calculation using Barrett Toric will be performed for all subjects prior to randomization. Subjects with estimated IOL cylinder power of 1.50 D in the study eye will be randomized to the low cylinder RAO210T toric or the aspheric monofocal RAO600C arms. The spherical equivalent for target refraction should be zero at optical infinity. The value that an Investigator will use for SIA will be a predetermined single value (for each Investigator) that is reported to the sponsor at the beginning of the study and consistently used for all subjects treated by the Investigator.

For subjects in the toric test groups, the Investigator should use the Barrett Toric IOL calculator in order to select the SE and cylinder power of the investigational IOL (RAO210T). The IOL calculation printout will form part of the subject's study CRF. The investigator will select the IOL with the closest predicted SE value to the target refraction.

For the monofocal control arm (RAO600C), a non-toric monofocal IOL formula available in biometer or available online should be used for IOL selection.

Following the selection and confirmation of IOL powers, the IOLs will be accounted for and distributed to sites by the Sponsor/CRO.

A corneal incision should be used. The incision location shall be standardized to temporal horizontal (located at 180° ± 15° for right eye and 0° ± 15° for left eye) in order to minimize variations in changes in corneal astigmatism between toric and control subjects. Incision size will be standardized to approximately 2.4 mm (range of approximately 2.2 mm to 2.6 mm). Incision size and incision location will be recorded. 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. The surgeon may then perform cataract surgery using his/her habitual technique. **However, use of capsular tension ring, iris hooks, pupil expanders etc. are NOT allowed.**

6.7. Reasons Not to Implant a Study IOL

At the time of cataract surgery, but prior to IOL implantation there are operative adverse events that may prevent implantation of the designated IOLs for this clinical study. The criteria include, but are not limited to:

1) Intraoperative complications during the phacoemulsification and IOL implant that require any other additional procedures or further intervention
2) Significant detachment of Descemet's membrane
3) Significant corneal endothelial damage
4) Wound burn
5) Capsular tear, iris incarceration or damage, posterior capsular rupture, vitreous loss or prolapse, or zonular weakness, dehiscence or rupture
6) Significant anterior chamber bleeding
7) Excessive iris mobility or need for iris manipulation
8) Mechanical or surgical manipulation required to enlarge the pupil prior to or at IOL implantation
9) Other ocular conditions or complications that could compromise IOL stability
10) Bag sulcus, sulcus-sulcus or unknown placement of haptics
11) Any method of anterior capsulotomy other than continuous curvilinear capsulorhexis, precision pulse or FLACS (e.g., eccentric anterior capsulorhexis, anterior capsular tears or any areas of 'can-opener' capsulotomy)
12) Capsular fibrosis or other opacity
13) Optic and/or haptic damage/amputation
14) Inability to fixate IOL in desired position

If an operative adverse event prevents implantation of the investigational IOL and the IOL did not touch the eye, the subject should be implanted with a non-study IOL instead and discontinued from the study, followed under the Investigator's normal standard of care.

If an operative adverse event prevents implantation of the investigational IOL and the IOL touched the eye, the Investigator should follow the subject through resolution of any adverse events (AEs) and then discontinue the subject.

6.8. Secondary Surgical Interventions (SSI)

The Investigator must make an assessment of the subject to determine if a secondary surgical intervention (SSI) is needed, including an assessment of the potential risks and benefits associated with the SSI. If an SSI is needed, subjects should be instructed to return for an unscheduled visit immediately prior to an SSI to rotate a toric IOL to assess axis alignment and manifest refraction with acuity.

Secondary IOL interventions should be categorized as IOL exchange (the investigational device is replaced with the same lens model), IOL removal (the investigational device is removed and replaced with a non-investigational lens or no lens is implanted), IOL repositioning (the existing IOL is surgically moved to another location or rotated), or other. Indications for IOL exchange,

removal, or repositioning will be recorded in the subject's case report form. Wound burps (aqueous tap or paracentesis) are regarded as secondary surgical intervention, regardless of the time point at which the procedure occurred.

NOTE: Limbal relaxing incisions during cataract surgery and refractive procedures to address residual refractive error are disallowed by the protocol.

NOTE: Nd:YAG capsulotomy for PCO will not be counted towards the analysis of secondary surgical interventions related to the comparison of adverse events to the ISO Safety and Performance Endpoint (SPE) rates as described in ISO 11979-07. However, all YAG capsulotomies will be entered in the EDC system.

- If Nd: YAG capsulotomy for PCO is necessary, it is recommended to perform the procedure at or after 3 months post-operatively. It is also recommended to perform the procedure at least one week prior to the study visit.
- If the Investigator wants to re-assess PCO or perform a post-YAG assessment between study visits, this would be recorded as an Unscheduled Visit.
- (Fellow eye surgery and/or Nd:YAG capsulotomy will be recorded separately.)

6.8.1. IOL Repositioning

If IOL repositioning is required, it should be done in the early post-operative period, preferably within the first 30 days following surgery. Repositioning should only be considered when it is necessary to improve the visual outcomes or prevent damage to the eye.

6.8.2. IOL Explantation and Replacement

If IOL explantation and replacement is required, it should be done in the early post-operative period. In the case of an incorrect IOL power or residual refractive error, if IOL replacement is expected to improve the subject's visual outcomes, the IOL should be replaced with a new lens; however, the replacement IOL cannot be an investigational IOL model.

In the case where the subject reports visual disturbances in the early post-operative period, the surgeon should remind the subject that these symptoms generally improve over time due to neural adaptation. Therefore, adequate time should be allowed for this neural adaptation to occur. If the subject is intolerant of persistent visual disturbances and the Investigator identifies the IOL properties as being the primary cause, lens replacement should be considered.

6.9. Subject Discontinuation/Withdrawal

6.9.1. Discontinued Subjects

Subjects may be discontinued prior to study completion for reasons including, but not limited to:

- Subject withdrawal of consent
- Investigator's discretion (e.g. medical decision)
- Loss to follow-up
- Death
- Sponsor termination of study

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 resolved or stabilized (considering potential late sequalae of the event). Potential sequalae include any adverse effects on ocular structure or ocular (or visual) function. Prior to discontinuing a subject, every effort

should be made to schedule a final study visit to obtain as much follow-up data as possible. Discontinued subjects (without any ongoing ocular AEs) should be followed outside of the study protocol according to the Investigator's standard of care.

The reason for subject discontinuation and whether discontinuation occurred prior to or following study IOL implantation must be recorded in the subject's case report form.

Randomized subjects who discontinue prior to receiving a study IOL may be replaced. Randomized subjects who discontinue after study IOL implantation will not be replaced.

6.9.2. Lost to Follow-up

The following actions must be taken if a subject fails to return for a study visit:

- Site personnel will attempt to contact the subject by telephone and/or electronic mail and reschedule the missed visit and counsel the subject on the importance of maintaining the assigned study visit schedule.
- Before a subject is deemed lost to follow-up, site personnel will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address). These contact attempts should be documented.
- Should the subject continue to be unreachable, he or she will be considered to have discontinued from the study with a primary reason of lost to follow-up.

These actions will be recorded in the subject's source documents and a copy of the certified letter maintained in the subject's file. The date of discontinuation for subjects lost to follow-up will be seven days after the date that the unanswered certified letter was sent.

6.10. Study Termination

The study may be stopped at any time by the Investigator, the Sponsor, study regulators, and/or Sierra Clinical with appropriate notification.

7. Statistical Analysis

7.1. Study Endpoints

Primary Effectiveness Endpoints

- 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)

Secondary Effectiveness Endpoints

- Residual manifest refractive cylinder by subgroups of 0.25 D preoperative keratometric cylinder at 120 to 180 days post-operatively (Visit 4)
- Percent change in residual manifest refractive cylinder at Visit 4 from preoperative keratometry.

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 event list 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

Additional Effectiveness Analyses

- 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

7.2. Analysis Sets

- All Enrolled Set – All subjects who sign informed consent. This set will be used for disposition summaries.
- Intent-to-Treat (ITT) Set – All enrolled subjects who are randomized. All ITT analyses will be done according to randomized lens assignment.
- Safety Set (SAF) – All ITT subjects who undergo surgery. Summaries and analyses based on the Safety Set 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.
- Per Protocol (PP) Set – All SAF subjects who are successfully implanted with a study lens and who have no major protocol deviations. Major protocol deviations will be defined in the statistical analysis plan (SAP).
- Best Case Set (BCS) – All PP subjects who also meet the following criteria:
    - No clinically significant pre-operative ocular pathology
    - 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

7.3. Study Groups

The following terms will be used throughout the Statistical Analysis section:

- Toric (test) group – all subjects randomized to be implanted with the low-cylinder (1.50 D) RayOne EMV Toric IOL (Model RAO210T) (for ITT, PP and BCS analyses) or implanted

with the low-cylinder (1.50 D) RayOne EMV Toric IOL (Model RAO210T) (for SAF analyses)

Monofocal (control) group – all subjects randomized to be implanted with the RAO600C Monofocal IOL (for ITT, PP and BCS analyses) or implanted with the RAO600C monofocal IOL (for SAF Analyses)

7.4. 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.

7.4.1. Effectiveness

All effectiveness endpoints will be analyzed using the ITT Set.

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.

7.4.2. 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. All wound burps (aqueous tap, or paracentesis) excluded from the analysis above will be summarized here.

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.

7.5. Sample Size

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.

7.5.1. Effectiveness

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.

7.5.2. Safety

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.

7.6. Statistical Analyses

7.6.1. General Considerations

Continuous measures will be summarized by the mean, standard deviation, median, minimum, and maximum, and 95% confidence interval for the mean where appropriate. Categorical and incidence measures will be summarized by both count and percentage, and 95% confidence intervals for the percentage where appropriate.

Variables and time points used for primary effectiveness and safety endpoints will be summarized descriptively for each treatment group by sex, age, racial and ethnic groups.

Effectiveness analyses will be completed using the ITT Set. For selected analyses, the PP Set will be used for supportive analyses. Results will be presented by visit for each of the scheduled visits at which the assessment was planned.

Safety analyses will be completed using the Safety Set. The BCS will also be used for selected analyses. Results will be presented by visit for each of the scheduled visits at which the assessment was planned. If a subject has multiple visits within a visit window, then safety summaries will include the worst case of the subject's observations in the window. For the purposes of these worst-case summaries, all interim visits will be considered as a single visit window.

Baseline measure will be defined as the last non-missing measure prior to initiation of investigational treatment.

7.6.2. Visit Windows

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.

7.6.3. Multiplicity

As all primary effectiveness and safety endpoints as described in section 7.1 are required to demonstrate study success, adjustment for multiplicity is not necessary for these endpoints.

The secondary effectiveness endpoints will be summarized descriptively only. Consequently, multiplicity adjustments are not needed for the secondary endpoints.

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

No interim analyses are planned.

7.6.4. Missing Data

Missing data will be imputed for primary effectiveness endpoints using the methods specified under the analysis descriptions for the endpoints. Where possible, multiple imputation will be used. Except where discussed below, missing data will not be imputed.

7.6.5. Poolability

Data poolability will be assessed by statistical comparisons and outcome variables among sites and demographic factors for all enrolled subjects. Subject age at informed consent will be compared by analysis of variance with a term for site by treatment interaction. Gender will be compared by site using a chi-squared test. The following response/outcome variables will also be summarized descriptively and tested for poolability, including, for continuous variables, the interaction between site and treatment.

- Mean residual manifest cylinder at Visit 4 (by linear model)
- Lens axis misalignment at Visit 4 (by linear model)
- IOL axial stability (rotation between consecutive visits) at Visit 4 (by linear model)
- Incidence of AEs according to the ISO 11979-7 grid (by Fisher's exact test)
- Proportion of toric eyes with BCDVA 20/40 or better at Visit 4 (by Fisher's exact test)

The critical value for rejection of the null hypothesis of equivalence across sites will be alpha = 0.15 for the sites by treatment interaction.

7.6.6. Disposition, Baseline Characteristics, and Accountability

The numbers and percentages of subjects will be summarized for each study group separately for the following subsets, overall and per site:

- Signed Informed Consent (Enrolled)
- Attended surgery
- ITT
- PP
- SAF
- BCS
- Subjects completing the study
- Subjects terminating the study early

Reasons for screen failures and early termination will additionally be tabulated.

Accountability based on ISO 11979-7 will be prepared for the ITT, PP, BCS and SAF analysis sets.

Demographics and baseline characteristics will be summarized by randomized treatment for the ITT Set and by the actual treatment group for the SAF. The outcomes will be stratified by the clinical site.

7.6.7. Effectiveness Analyses

Effectiveness endpoint analyses will be based on the ITT set. The PP set will be used for supportive analyses.

7.6.7.1. Primary Effectiveness Analyses

Primary effectiveness endpoint analyses will be based on the ITT set.

Residual Manifest Cylinder

Residual manifest cylinder will be summarized by visit for the ITT Set using continuous summary statistics.

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 adjusted mean difference between Toric and Monofocal groups will be given together with a 95% confidence interval and associated one-sided p-value.

Subjects that have a secondary surgery that is targeted to correct for postoperative toric IOL rotation shall have their residual manifest cylinder at Visit 4 set to their preoperative kerometric cylinder.

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

After imputation, the statistical hypothesis will be tested by imputation using Type II analyses from general linear models including the effects of treatment and preoperative keratometric cylinder. The results of the imputations will be combined and an overall p-value will be estimated. The treatment effect (Toric cylinder 1.50 D minus Monofocal) will be summarized using continuous summary statistics and a two-sided 95% confidence interval.

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.

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.
- The entire previous analysis will be repeated using the PP Set.

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.

- Investigator
- Absolute lens axis misalignment at Visits 2, 3, and 4

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.

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.

7.6.7.2. Secondary Effectiveness Analyses

Residual manifest cylinder will 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.

Percent reduction in absolute cylinder will be calculated as follows:

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

Percent reduction in absolute cylinder will 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.

7.6.7.3. Additional Effectiveness Analyses

Additional effectiveness analyses 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 (2018). Additional effectiveness analyses will be based on eyes from the ITT population at 120 to 180 days post-operatively (Visit 4), unless otherwise stated.

Categorical analyses include evaluation of the percentage of eyes achieving UCDVA ≤ 0.30, ≤ 0.20, and ≤ 0.00 logMAR at Visit 4; BCDVA ≤ 0.30, ≤ 0.20, and ≤ 0.00 logMAR; percentage of eyes achieving accuracy of cylinder (to target) at Visit 4 within +/- 0.25, +/- 0.50, and +/- 0.75 D; and percentage of eyes with reduction in cylinder at Visit 4 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.

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 Visit 4 will be summarized.

Reduction in cylinder power, defined as pre-operative magnitude of the keratometric cylinder minus magnitude of manifest cylinder at a given 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). The analysis will be repeated for subgroups of 0.25D preoperative keratometric 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.

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.

Any additional effectiveness analyses, along with all other analyses, will be fully described in a separate Statistical Analysis Plan (SAP).

7.6.8. Safety Analyses

All safety analyses will be based on the Safety Set unless otherwise specified.

7.6.8.1. Primary Safety Analyses

All primary safety analyses will be conducted on the toric study eyes. Additionally, as supportive analyses, descriptive summaries of each co-primary safety endpoint variable will be presented for the Monofocal control group.

Rates of IOL adverse events through 120 to 180 days post-operatively (Visit 4) compared to the ISO Safety and Performance Endpoint (SPE) rates

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.

The numerator for each persistent AE 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) 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 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. The one-sided p-value from the exact binomial test of each hypothesis will be provided for each adverse event. SSIs that involve only the removal aqueous fluid from the eye (tap, burp, paracentesis) will not be counted towards the analysis of the ISO “grid” safety endpoint. More complex ocular procedures (SSIs) will be counted in the ISO SSI “grid.”

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.

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.

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 Cohort 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. 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.

Rates of all other adverse events not included in IOL adverse event list from ISO 11979-7 through 120 to 180 days post-operatively (Visit 4)

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.

Rates of secondary surgical interventions for IOL repositioning due to IOL misalignment through 120 to 180 days post-operatively (Visit 4)

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.

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

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. If neither of these hypothesis test results are statistically significant, this endpoint will be considered successful for the Toric IOL.

7.6.8.2. Adverse Events

The incidence of eyes with at least one serious adverse event will be summarized using categorical summary statistics by treatment received.

Cumulative and persistent adverse events from ISO 11979-7 (2018) Table E.2 will be summarized using descriptive statistics by AE type and treatment and will be compared to the maximum number of cases allowed before the ISO SPE rate is exceeded. Additionally, cumulative and persistent adverse events will be summarized separately by age group (< 65 years vs. ≥ 65 years) and by investigator.

All types of adverse events will be reported and compared between arms using descriptive statistics. Separate analyses will be done for device-related events and events that are of moderate to severe severity. All adverse events reported will be summarized and listed by subject.

Adverse events will also be summarized for all ocular AEs and for all SAEs. All ocular AEs will also be summarized by maximal severity, for AEs related to the study lens, and by study day of onset.

In addition, the following summaries will be provided:

- Ocular AEs by relationship to study device/procedure as well as unrelated Ocular and Non-ocular AEs
- Ocular Serious AEs by relationship to study device/procedure as well as unrelated Ocular and Non-ocular Serious AEs
- Ocular AEs by maximal severity

- Ocular AEs by age group (< 65 years vs. ≥ 65 years)
- Ocular AEs by investigator

7.6.8.3. Other Safety Analyses

Other safety endpoints 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.

8. Protocol Deviations

A protocol deviation is any noncompliance with this clinical trial protocol or Manual of Procedures (MOP). The Investigator is responsible for adhering to IRB requirements for protocol deviation reporting.

Major protocol deviations are those that might significantly affect the completeness, accuracy, and/or reliability of study data or that might significantly affect a subject's rights, safety or well-being. Further details about the handling of protocol deviations will be included in the Statistical Analysis Plan.

9. Safety and Adverse Events (AEs)

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.

9.1. Safety and Adverse Event (AE) 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:

- 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 (21 CFR 812.3(s)).

9.2. Classification of an Adverse Event (AE)

9.2.1. Severity of Event

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.

9.2.2. 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

9.3. Adverse Events That May Prevent Implant of a Study Device

At the time of cataract surgery or during IOL implantation there are operative AEs that may prevent implantation of a study IOL. There criteria include, but are not limited to:

1) Intraoperative complications during the phacoemulsification and IOL implant that require any other additional procedures or further intervention
2) Significant detachment of Descemet's membrane
3) Significant corneal endothelial damage
4) Wound burn

5) Capsular tear, iris incarceration or damage, posterior capsular rupture, vitreous loss or prolapse, or zonular weakness, dehiscence or rupture
6) Significant anterior chamber bleeding
7) Excessive iris mobility or need for iris manipulation
8) Mechanical or surgical manipulation required to enlarge the pupil prior to or at IOL implantation
9) Other ocular conditions or complications that could compromise IOL stability
10) Bag sulcus, sulcus-sulcus or unknown placement of haptics
11) Any method of anterior capsulotomy other than continuous curvilinear capsulorhexis precision pulse or FLACS (e.g., eccentric anterior capsulorhexis, anterior capsular tears or any areas of 'can-opener' capsulotomy)
12) Capsular fibrosis or other opacity
13) Optic and/or haptic damage/amputation
14) Inability to fixate IOL in desired position

If an operative AE prevents implantation of a study IOL in the study eye *and the IOL did not touch the eye*, the subject should be implanted with a non-study IOL instead and discontinued from the study, followed under the Investigator's normal standard of care.

If an operative AE prevents implantation of a study IOL in the study eye *and the IOL touched the eye*, the Investigator should follow the subject through resolution of any AEs and then discontinue the subject.

9.4. Anticipated Adverse Events (AEs)

Anticipated AEs associated with cataract surgery and/or IOL implantation include, but are not limited to, the following:

Intraoperative Adverse Events

- Anterior capsule tear
- Hyphema
- Vitreous herniation/prolapse
- Vitreous loss
- Wound leak (positive Seidel)
- Posterior capsular rupture
- Choroidal detachment/hemorrhage
- Zonular dialysis
- Thermal injury (phaco burn)

Postoperative Adverse Events

- Anterior Uveitis (including Iritis and Iridocyclitis) – Anterior chamber (AC) cells or flare of greater than grade 2 (using the Standardization of Uveitis Nomenclature, SUN criteria at Visit 2 (Day 7-14) or later.
- Chronic Anterior uveitis - anterior segment inflammation characterized by grade 1+ cell or greater (using the Standardization of Uveitis Nomenclature criteria) that is 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.

(Note that any iritis present at the final visit is considered significant and should be counted as a "persistent" ISO SPE event.)

- Corneal Stroma edema - Edema of corneal stroma of any degree at any location regardless of effect on vision at Visit 2 (Day 7-14) or later
    - Visually Significant Corneal edema - corneal swelling (stromal or epithelial) resulting in BCDVA of 0.3 or worse at Visit 3 (Day 30-60) or later.

  (Note that any corneal stromal edema present at the final visit is considered significant and should be counted as a "persistent" ISO SPE event)
- Increased IOP - elevation of IOP greater than or equal to 10 mmHg above baseline to a minimum of 25mmHg or that requires treatment.
  (Note that elevation of IOP at any time postoperatively (including during the immediate postoperative period) for which the subject requires treatment at the final visit to control regardless of the degree of elevation is considered significant and should be counted as a "persistent" ISO SPE event of "Raised IOP requiring treatment".)
- Capsular block syndrome
- Choroidal detachment/hemorrhage
- Retrolenticular membrane
- Iris atrophy
- Cystoid macular edema – any cystic intraretinal thickening of the macula diagnosed by clinical examination and/or adjunct testing (e.g. OCT, fluorescein angiography)
    - Clinically significant cystoid macular edema: Macular edema diagnosed by clinical examination and adjunct testing (e.g., OCT, FA) resulting in BCDVA of worse than 0.30 logMAR at Visit 3 or later

  (Note that any cystoid macular edema present at the final visit is considered significant and should be counted as a "persistent" ISO SPE event)
- Endophthalmitis - defined by ISO as "inflammatory reaction (sterile or infectious) involving the vitreous body." This should include all suspected cases of endophthalmitis whether the inflammation is acute or chronic.
    - Endophthalmitis – defined by AAO Task Force report (Masket et al.) as intraocular inflammation requiring diagnostic vitreous tap and intraocular antibiotics
- Flat anterior chamber with lens/cornea touch or a shallow chamber with iridocorneal apposition without lens/cornea touch
- Hypopyon
- Keratic precipitates
- Secondary glaucoma
- Infectious keratitis
- Vitritis - Iridocyclitis and hyalitis
- Fibrin reaction
- Incorrect IOL power resulting in secondary surgical intervention
- IOL damage resulting in secondary surgical intervention
- IOL decentration/malposition resulting in secondary surgical intervention
- Iris pigment epithelium loss - New or worsening iris transillumination defects or increase in pigmented cells in the anterior chamber noted after Visit 2 (Day 7-14) when assessed before instillation of any dilating drops
- Pupil ovalization
- Best-corrected visual acuity loss of 2 lines (10 letters) or more on the ETDRS chart measured at Visit 4 or later from any prior post-operative visit

- Mechanical 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
- Chronic pain in the study eye, per subjective patient reporting, graded as ≥ 4 on the standardized pain rating scale (from 0 to 10), present greater than 3 months post-operative
- Progression or onset of diabetic retinopathy
- Progression or onset of macular degeneration
- Retained lens material
- Retinal detachment - Any type of retinal detachment regardless of degree, management, and whether rhegmatogenous, tractional, or exudative
    - Rhegmatogenous retinal detachment (RD) - partial or complete RD associated with retinal tear
- Secondary Surgical Intervention – Any ophthalmic therapeutic procedure involving the incision or destruction of tissue, including to remove fluid from the anterior chamber (aqueous 'tap' or 'burping the wound') and excluding posterior capsulotomy
    - Secondary IOL intervention - exchange (the investigational device is replaced with the same lens model), removal (the investigational device is removed and replaced with a noninvestigational lens or no lens is implanted) or reposition (the existing IOL is surgically moved to another location or rotated)
- Synechiae formation
- Toxic anterior segment syndrome (TASS) - acute, non-infectious inflammation of the anterior segment that starts within 24 to 48 hours after surgery, usually resulting in hypopyon and commonly presenting with corneal edema, and that improves with steroid treatment

The above categories of Adverse Events as well as those defined by ISO 11979-7 should be identified and recorded in the case report forms.

Note that all secondary surgical interventions (and events that cause these interventions) and all events that have sequelae should be reported as adverse events, regardless of when they occur.

Wound burps (aqueous tap or paracentesis) are regarded as secondary surgical intervention, regardless of the time point at which the procedure occurred. SSIs that involve only the removal of aqueous fluid from the eye (tap, burp, paracentesis) will not be counted towards the analysis of the ISO 11979-7 "grid" safety endpoint. More complex ocular procedures (SSIs) will be counted in the ISO 11979-7 SSI "grid."

YAG capsulotomies should be reported in the subject's case report form.

(Fellow eye surgery and/or Nd:YAG capsulotomy will be recorded separately.)

Early, low grade anterior chamber cell/flare, corneal edema, and increase in IOP can often be considered normal or expected after IOL surgery. They do not need to be reported as adverse events if they occur prior to 1 week postoperatively if they meet the following criteria:

- Anterior chamber cells or flare of grade 2 or less that requires no change in standard postoperative medication regimen (if it persists to 1 week or more it should be reported as an AE);
- Corneal edema of grade 2 or less that does not reduce acuity to 0.3 logMAR (20/40) or worse and does not require any change in standard postoperative medication regimen (if it persists to 1 week or more it should be reported as an AE);

- Increased IOP that is <10mm Hg above baseline or is < 25mmHg and requires no change in standard postoperative medications regimen or any other special treatment.

9.5. Cumulative and Persistent Adverse Events (AEs)

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.

9.6. Serious Adverse Events (SAE) and Unanticipated Adverse Device Effects (UADE) Event Notification

Any SAE or UADE, whether the event is expected or unexpected, must be reported to the Sponsor, or the Sponsor's designee, within 24 hours of the Investigator becoming aware of the event.

It is the responsibility of the Investigator to promptly notify the IRB of SAEs and per the IRBs reporting requirements. Investigators must report the occurrence of a UADE to their reviewing IRB as soon as possible, but no later than 10 working days after first learning of the event. The Sponsor must report the results of an evaluation of an UADE to FDA and all reviewing IRBs and participating investigators within 10 working days after the Sponsor first receives notice of the effect.

9.7. 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.

All device deficiencies (as defined below) must be reported to the Sponsor, or Sponsor's designee, within 24 hours of the Investigator becoming aware of the deficiency. Device deficiencies will be categories as one of the following:

- **Device failure:** A device has failed if it is used according to the labeling, including without limitation, instructions for use, and applicable standards of medical practice but does not perform according to the labeling and negatively impacts the treatment.
- **Device malfunction:** A device malfunction is a change in the function of the device that is not described in the labeling and that may or may not affect device performance.
- **Device misuse:** A misused device, i.e. one that is not used by the Investigator (in the study) in compliance with applicable standards of medical practice, including without limitation, those described in the instructions for use and labeling, will not be considered a malfunction.
- **Other:** must be described by the Investigator

10. Device Accountability

10.1. Accountability of Study Devices

The RAO210T EMV toric IOL preloaded IOL injection systems will be provided to the study site by the Sponsor or their designee. The RAO600C aspheric monofocal preloaded IOL injection systems will be provided to the study site by the Sponsor or their designee. The Investigator is responsible for the accountability of all study devices throughout the course of this study. The Investigator is responsible for proper storage of received devices and ancillary supplies at the site, and for maintaining a current study device tracking log for the duration of the study. The names of all subjects who received, used, or disposed of any device at the site will be recorded. Each study device sent to the Investigator must be accounted for and any discrepancy must have a written account, including explanation of the cause of the discrepancy.

The Investigator must ensure that the study devices are used in accordance with this protocol and the study devices' Directions for Use (DFU). The study devices are to be used only by Investigator or his/her delegated sub investigator(s). The study devices must only be used on subjects enrolled in this study.

10.2. Return or Disposal of Study Devices

The study devices will be returned to the Sponsor or their designee at the conclusion of the study according to the instructions provided by the Sponsor. The return of the study device will be specified in writing.

11. Study Monitoring

The study data will be monitored regularly by the Sponsor or designee. During the monitoring visits, information recorded in subject's case report forms will be verified against source documents to confirm accuracy and completeness. Study documents will be reviewed to confirm adherence to the protocol, IRB and Sponsor-specified reporting requirements. Study device storage and accountability will be checked.

The study monitor will review device storage conditions and the completion of the site's device tracking log. Reconciliation of device disposition will be documented.

12. Data Collection and Management

12.1. Confidentiality

The Investigator and institution involved in this study will only provide direct access to source data and documents to the Sponsor and to appropriate authorities for the purposes of monitoring, audit, or regulatory inspection. Each subject taking part in the study will have agreed explicitly to such access in writing.

All subject data will always be treated with strict adherence to professional standards of confidentiality. All reports and communications relating to subjects in the study will identify the subjects by their subject ID number only.

12.2. Source Documentation

Investigators are required to prepare and maintain adequate and accurate case histories, recording all observations and other data pertinent to the investigation on each subject. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Data recorded in the electronic case report form (eCRF) derived from source documents must be consistent with the data recorded on the source documents.

12.3. Study Document Retention

The Investigator's site will retain all records related to the study in compliance with ICH GCP Guidelines. Investigators should also be aware that they may also have local government or institutional policies for record retention. The most stringent requirement would apply.

13. Institutional Review Board (IRB) Approval

The Investigator must ensure IRB approval has been obtained for the protocol, ICF, materials used for subject recruitment and all written material provided to the subjects prior to beginning enrollment. Any amendments must receive IRB approval prior to implementation.

Ongoing study progress reports will be submitted to the IRB at least annually, and more frequently if specified by the IRB. Reports of safety events and any protocol deviations that affect the safety and welfare of a study subject will be submitted to the IRB in accordance with United States Food and Drug Administration (FDA) and IRB requirements.

14. Clinical Trial Agreement

A Clinical Trial Agreement (or equivalent) will be prepared by the Sponsor or designee, which will be executed by the participating study sites. This agreement describes the legal conditions, conditions for financial compensation, and reimbursement details for the co-operation between the Sponsor or designee and the participating site in this study.

15. COVID-19 Public Health Emergency

Ensuring the safety of trial participants is of great importance. COVID-19 public health emergency may impact the conduct of this clinical trial. Challenges may arise, for example:

- Required quarantines for study participants or study staff
- Site closures impacting a study participants ability to come into the office
- Travel limitations impacting the study participant to get to the office

    - Public transportation closures/reduction of service
    - Inability to arrange a ride due to shared space in a vehicle
- Interruptions to the supply chain for the investigational product
    - Not being able to get the necessary lens for surgery
- Site personnel or trial participants may become infected with COVID-19
    - Possibility resulting in serious illness and possible death
    - Requiring changing of appointment dates and or times
- The potential for delay in examination and treatment of eye complications
    - Possibly leading to further complications
- Some risk exists during the exam, capturing of diagnostic measurements and surgery as they may require examiner/study doctor/nurses and participant to be close together (under 6 feet for prolonged periods)

In each circumstance focus will be placed on the potential impact on the safety of the trial participant, and modification to study conduct will occur accordingly with review by the sponsor, investigators and IRB. Protocol deviations due to COVID-19 illness and or/COVID-19 control measures will be documented.

16. Publication

As the Sponsor of this study, Rayner has a proprietary interest and will have the final decision regarding the publication of any manuscript relating to the study. No study data may be presented or published until after the aggregate multi-study results are published. Thereafter, any proposed publications relating to the study must be submitted to Rayner for prior approval. Under no circumstances shall the investigator or center publish or disclose Rayner's confidential information concerning the study.