STATISTICAL ANALYSIS PLAN

Clinical Investigation of the Safety and Effectiveness of Monofocal PODEYE TORIC Intraocular Lens (IOL)

Protocol Number: PHY2302

IDE Sponsor: Beaver-Visitec International, Inc

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Statistical Analysis Plan Approval

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REVISION HISTORY

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1 ABBREVIATIONS

ADE	Adverse device effect
AE	Adverse event
ANSI	American National Standards Institute
BCDVA	Best corrected distance visual acuity
CFR	Code of Federal Regulations
CME	Cystoid macular edema
CRF	Case report form
ETDRS	Early Treatment Diabetic Retinopathy Study
FLACS	Femto Laser-Assisted Cataract Surgery
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed consent form
ICH	International Conference on Harmonisation
IOL	Intraocular lens
IOP	Intraocular pressure
OVD	Ophthalmic viscosurgical devices
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent to Treat
LOESS	Locally Estimated Scatterplot Smoothing
logMAR	Logarithm of the Minimum Angle of Resolution
MCMC	Markov chain Monte Carlo
PP	Per Protocol
SAE	Serious adverse event
SOA	Schedule of activities
SPE	Safety and Performance Endpoints
SSI	Secondary surgical intervention
TASS	Toxic anterior segment syndrome
UADE	Unanticipated Adverse Device Effect
UCDVA	Uncorrected Distance Visual Acuity
VA	Visual Acuity

2 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol PHY2302, version 1.1 dated 20 Feb 2024.

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

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

3 BACKGROUND

Cataracts are a common condition in adults over 40 years of age, and surgical replacement of the cataractous lens with an intraocular lens (IOL) remains an effective way to restore vision to cataract patients. Some of the cataract patients may have pre-existing corneal astigmatism which contributes to blurred vision at distance and/or near. Monofocal non-toric IOLs provide adequate distance vision but do not address astigmatism which can adversely affect the quality of vision. The PODEYE TORIC IOL is designed to optically correct corneal astigmatism and restore distance vision after cataract surgery.

4 STUDY OBJECTIVES

The purpose of this clinical study is to evaluate the safety and effectiveness of the PODEYE TORIC IOL. Objectives are based on ANSI Z80.30:2018)[1] and ISO 11979-7:2018)[2]. More specifically, the purpose of this clinical study is to compare the visual outcomes and safety of the PODEYE TORIC IOL to that of the AcrySof monofocal non-toric IOL Model SA60AT[3]. The study is designed to meet the requirements specified for toric IOLs in ANSI Z80.30: 2018 standard.

5 STUDY PRODUCTS

The device being evaluated in this clinical study is the PODEYE TORIC CYL 1.5D Monofocal IOL (BVI Medical). The control device is a marketed single-piece acrylic non-toric, colorless monofocal IOL. All monofocal IOLs used in the study will be the PODEYE TORIC CYL 1.5D or Alcon AcrySof® SA60AT.

6 STUDY DESIGN

6.1 OVERVIEW

This study is a prospective, multicenter, randomized, active controlled, double masked pivotal study to demonstrate the effectiveness and safety of a monofocal toric IOL, PODEYE TORIC. The control IOL will be a commercially available monofocal non-toric IOL, AcrySof SA60AT (Alcon). The study will include adult subjects with operable cataract in at least one eye along with pre-existing corneal astigmatism who are eligible for phacoemulsification cataract surgery

followed by IOL implantation. Potential subjects, after signature of the study informed consent document, will be screened for eligibility, except that assessments which are part of the Investigator's routine standard of care for cataract patients may be performed prior to obtaining informed consent. Only one eye per patient will be included in the study. In cases where a subject has significant cataracts and plans to undergo cataract surgery in both eyes, it is recommended that cataract surgery is performed in one eye prior to the subject being 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 should be 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 who meet all protocol-specified eligibility criteria will be randomized at a 1:1 ratio to receive either the PODEYE TORIC CYL 1.5 D IOL (test) or the AcrySof SA60AT IOL (control) in the study eye. Only unilateral implantation of either Test or Control IOL will be performed. Subjects will attend regular visits where they will undergo ophthalmic examinations over a period of approximately 6 months.

No interim analysis of data is planned.

Up to 300 subjects shall be screened and approximately 230 subjects will be randomized and implanted, allowing [redacted] rate. A drop-out rate of [redacted] expected after the subjects have been implanted with the test/control IOL.

Standard clinical trial methods will be used to minimize bias, including the use of masked vision assessors, masking of subjects, use of standardized test procedures, common investigator training, and common inclusion and exclusion criteria.

6.2 STUDY POPULATION

The subject population will consist of subjects with a diagnosis of cataract with pre-existing corneal astigmatism, eligible for phacoemulsification surgery followed by IOL implantation. Eligibility for the study will be determined at the preoperative visit. If the subject gives informed consent, the subject is enrolled.

Subjects will be enrolled at up to 10 investigational sites. Investigators will be encouraged to perform cataract surgery/IOL implant for at least 20 subjects per site; no Investigator may implant more than 25% of the total number of subjects planned. Site enrollment will be closely monitored to facilitate achievement of the stated enrollment goals and an even distribution across all sites.

To allow for approximately [redacted] and attrition between enrolment and randomization, a total of 300 subjects will be enrolled to ensure 230 subjects, 115 test and 115 control, will be implanted. It is anticipated that 13% of the 230 subjects will not complete the study, resulting in 200 with data at the Form 4 visit.

6.3 INCLUSION CRITERIA

Eligible subjects must meet all the following inclusion criteria to be eligible for study participation:

1. Male or female adults, age 22 years or older at the Preoperative Visit.
2. Clinically significant cataract in the study eye eligible for standard phacoemulsification cataract surgery.
3. Eligible for receipt of an IOL power within the range of the investigational IOL in the study eye. (**The Investigational IOL is available in powers from +15 D to +30 D Spherical Equivalent)**
4. Pre-operative corneal astigmatism in the range: ≥0.75 D and ≤1.50 D in the study eye
[redacted]
6. Clear intraocular media other than cataract in the study eye.
7. Best corrected visual acuity equal to or worse than 0.3 logMAR, with or without a glare source in the study eye.
8. Ability to dilate pupil sufficiently (greater than or equal to 6.0 mm) to allow visualization of Toric IOL axis markings post-implantation in the study eye.
9. Projected BCDVA of 0.2 logMAR (20/32 Snellen) or better in the study eye after cataract surgery/IOL implantation as determined by the medical judgment of the Investigator.
10. Contact lens users must be willing to discontinue wear of their lenses in the study eye in accordance with the following requirements:
    i. Rigid gas permeable and toric lenses for ≥ 7 days prior to the Preoperative Visit
    ii. Soft non-toric contact lenses for ≥ 3 days prior to the Preoperative Visit
    iii. All contact lens wearers must demonstrate a stable refraction within ± 0.50 D MRSE and 15 degrees astigmatic axis on two consecutive examinations at least 1 week apart in an eye to be treated.
11. Provide signed written consent prior to participation in any study-related procedures.
12. Ability, comprehension, and willingness to follow study instructions, and to complete all study visits.
13. Female subjects must be 1-year postmenopausal, surgically sterilized, or, if of childbearing potential, have a negative urine pregnancy test at the Preoperative 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.

6.4 EXCLUSION CRITERIA

Subjects with any of the following diseases, surgeries or conditions are ineligible for study participation.

[redacted]Subjects with irregular corneal astigmatism in the study eye ([redacted]

2. Subjects with clinically significant corneal pathology potentially affecting corneal topography in the study eye.
3. Subjects with a traumatic cataract in the study eye.
4. Subjects with uncontrolled glaucoma in the study eye.
5. Subjects with diagnosed degenerative visual disorders (e.g., macular degeneration, retinal detachment, proliferative diabetic retinopathy, or other retinal disorders) predicted to result in BCDVA worse than 0.2 LogMAR (20/32 Snellen) in the study eye during the study participation period.
6. Subjects with conditions associated with increased risk of zonular rupture during the cataract extraction procedure which may affect the postoperative centration or tilt of the lens in the study eye.
7. Significant anterior segment pathology that might increase intraoperative risk or compromise IOL stability (e.g., pseudoexfoliation syndrome) in the study eye.
8. Reasonably expected to require secondary ocular surgical intervention or laser treatment other than YAG capsulotomy in study eye during the study participation period.
9. Presence of one or more clinically significant corneal abnormalities in study eye, including corneal dystrophy, irregularity, or edema.
10. Previous intraocular, corneal, or retinal detachment surgery, including corneal transplant, LASIK, astigmatic keratotomy and limbal relaxing incisions in the study eye.
11. Clinically significant ocular inflammation or infection present ≤ 30 days in either eye prior to the Preoperative Visit.
12. Subjects with potential BCDVA of 20/200 or worse in the fellow eye.
13. Subjects with a difference of greater than 0.50 D of corneal astigmatism as measured with the IOL master/Lenstar/Argos and the topographer in the study eye using vector analysis.
14. Presence or history of one or more severe/serious ocular conditions (e.g., glaucoma, uveitis, ocular infection, severe dry eye) in study eye, or any other unstable medical condition (e.g., uncontrolled diabetes) that in the opinion of the Investigator would put the subject's health at risk, confound the results of the study and/or prevent the subject from completing all study visits.
15. Use of medications known to interfere with visual performance, pupil dilation, or iris structure ≤ 30 days prior to the Preoperative Visit.
16. Participation in any study of an investigational, interventional product within 30 days prior to the Preoperative Visit or at any time during the study period.
17. Pregnant or nursing females.

In addition to the above exclusion criteria, if, 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 (Section 5.3 of study protocol).

7 ANALYSIS POPULATIONS AND VISIT WINDOW

7.1 ANALYSIS POPULATIONS

The All-enrolled population includes all subjects who sign an informed consent form. This population will be used for disposition summaries.

The Safety population will include all subjects where the test or control IOL touched the eye.

The intent to treat (ITT) population includes all randomized subjects. Missing data will be imputed. Subjects will be analyzed as randomized. The ITT population is the primary analysis population for assessing effectiveness.

The All-implanted population includes all ITT subjects who were successfully implanted with one of the two study IOLs and who attended at least one postoperative visit. Missing data will be imputed. Subjects will be analyzed as randomized. The All-implanted population is supportive of the ITT population for assessing effectiveness.

The Per-Protocol (PP) population includes all subjects in the All-implanted population who have no major protocol deviations that could affect the interpretation of effectiveness and have attended the Form 4 visit. Exclusions from PP will be determined prior to study unmasking. Missing data will not be imputed. Subjects will be analyzed as treated. Analyses based on PP will be supportive of those based on All-implanted.

The Best Case Set will include subjects in PP with all of the following characteristics:

- No major protocol deviations potentially affecting any of the primary effectiveness endpoints (BCDVA, DCNVA). Major protocol deviations that may potentially affect the primary effectiveness endpoints include, but are not limited to:
    - Inclusion of ineligible subjects
    - Implantation of incorrect IOL
    - Missed assessments for effectiveness endpoints at Form 4
    - Receipt of medication likely to interfere with visual performance at Form 4
- One eye implanted with a study lens
- No clinically significant preoperative ocular pathology in the study eye, including any of the following present prior to the operative visit
    - Pseudoexfoliation
    - Glaucoma
    - Uveitis
    - Retinal detachment
    - Diabetic retinopathy
    - Macular degeneration
    - Amblyopia
    - Other preoperative pathologies that are likely to affect central acuity
- No macular degeneration detected at any time in the study eye
- No previous surgery for the correction of refractive errors in the study eye

7.2 VISIT WINDOW

The visit schedule and the visit window for each visit are outlined in **Table 1**. The visit schedule applies to all subjects in both test and control groups.

Table 1 VISIT SCHEDULE

Visit	Visit Window
Preoperative	1 to 90 days prior to surgery in the study eye
Form 0 (Operative)	Day 0
Form 1	1 to 2 days following surgery in the study eye
Form 2	7 to 14 days following surgery in the study eye
Form 3	30 to 60 days following surgery in the study eye
Form 4	120 to 180 days following surgery in the study eye

Unscheduled visits will occur as needed, due to an ocular intervention or a subject complaint regarding their eye. Recommended assessments at unscheduled visits are listed in Section 8.4 of the study protocol. In the event of missing data at a scheduled visit, unscheduled visit results within the visit window will used as replacements for any uncollected data. If more than one unscheduled visit falls within the window, then the unscheduled visit closest to the target date will be used. If two visits are equidistant from the target, then the latter of the two will be selected.

A summary of all examinations required at each visit is provided in the schedule of activities in Appendix A.

7.2.1 Missing Observations

If no scheduled or unscheduled visit data are available within a visit window, the visit will be considered to be missed. Imputation will be performed in the ITT and All-implanted analysis populations, as described in Section 7.4.3.

8 DATA ANALYSIS METHODS

8.1 DATA AND ANALYSIS CONVENTIONS

The following are some basic stipulations that, unless otherwise stated, apply by default throughout the plan.

- For the co-primary endpoints, the six-month postoperative visit (Form 4) will be the primary analysis time point unless otherwise noted. For the primary safety endpoints, the Form 4 visit will be the primary analysis time point.
- Monocular safety and effectiveness analyses will compare the test group and the control group.

- For all visual acuity-related endpoints in the study, best corrected distance visual acuity (BCDVA) and uncorrected distance visual acuity (UCDVA) are measured at 4 m using a ETDRS chart under photopic conditions. All postoperatively measured visual acuities are recorded and analyzed in logMAR for all endpoint analyses, summary statistics and calculations, and may be converted to Snellen equivalent values for tables, listings, and graphs.
- Safety data will not be imputed, although incomplete or missing dates may be imputed.
- Partial dates will be imputed for safety and effectiveness data, using the most conservative approach available; for safety data, dates will be imputed to result in the longest possible duration of a given adverse event; for effectiveness data, dates will be imputed to maximize the number of study days from the operative date.
- Partial dates in other contexts (e.g., medical history) will be imputed in a way to allow reasonable interpretation, such as to replace the missing date or the missing month with "1." For example, a partial date recorded as "(missing date)/(missing month)/2020" will be imputed as "1/1/2020" and will be noted as "imputed" on any line listing.
- The expression "summary statistics" indicates sample size (N), mean, standard deviation (SD), median, minimum (Min), and maximum (Max) as applied to continuous variables, and indicates sample size (N), frequency and percent of relevant total as applied to categorical and some ordinal variables.
- All co-primary effectiveness and safety endpoints have to be met to claim overall effectiveness and safety success. Additional analyses and supportive analyses should not be used for the purpose of claims. Under this plan, type 1 error rates will be controlled at a significance level of 0.05 per individual hypothesis without adjustment for multiplicity.
- Data will be pooled across sites for overall analyses unless contraindicated by the poolability analysis in Section 7.8.1.
- Keratometric cylinder categories refer to the following groupings (in diopters): 0-0.25, >0.25-0.50, >0.50-0.75, >0.75-1.00, >1.00-1.25, >1.25-1.50, and >1.50. Upper categories may be collapsed due to low counts.
- Age categories refer to the following partition of the variable Age (in years): 22-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80 or older. Considering the patient population for cataract surgery is usually elderly, the age categories from 22-29, 30-39, 40-49 and up to 50-59 may be combined for reporting if a group has less than 10% of the total enrollment.

8.2 ACCOUNTABILITY

The primary study accountability summary will be based on the All-implanted population:

- The summary will first account visit by visit for the contributing status of all enrolled subjects in the study, as of the time of a particular analysis. This accountability will follow the format of Table A.1 of ISO 11979-7:2018. Accountability will be summarized by treatment arm and overall.
- All discontinued subjects will have their refraction, BCDVA, and UCDVA history provided in a listing. A separate data listing for discontinuation due to adverse events will be generated as specified in Section 7.5.3.

8.3 DEMOGRAPHICS AND BASELINE PARAMETERS

8.3.1 Demographics and Baseline Measurements

Baseline values are those values collected preoperatively. If additional measures are taken later, but prior to surgery, then those later values will replace the prior measures.

Summary statistics based on the All-implanted population will be presented for the following demographic characteristics by treatment group: age and age categories (overall and by gender), gender, race, and ethnicity. The following baseline parameters will be summarized by treatment groups: preoperative refractive error, preoperative corneal astigmatism, preoperative vision level(s), preoperative cataract grade and biometry measurements including axial length. Comparisons between the groups will be conducted to assess comparability.

Age will be calculated as of date of enrollment.

8.3.2 Operative Parameters

Data collected on the day of surgery for the study eye Operative Visit, will be summarized based on the All-implanted population for all the parameters listed on the operative visit CRF including but not limited to the following parameters: primary incision type, estimated incision size and axis, capsulotomy shape, lens extraction method, position of the IOL, type of IOL implanted, the power and the serial number of the implanted IOL and percent of all eyes successfully implanted. Furthermore, intraoperative complications in each complication class listed on the Operative Visit CRF will be summarized.

8.4 EFFECTIVENESS ANALYSES

All co-primary effectiveness endpoints need to be achieved to claim overall effectiveness success. Therefore no multiplicity adjustment is necessary for primary effectiveness endpoints. For the primary effectiveness endpoints, the primary analysis population will be the ITT analysis population. The All-implanted, PP, and best case analysis populations will also be used for co-primary effectiveness endpoint analysis to support the primary ITT analyses.

8.4.1 Co-Primary Effectiveness Endpoints

Co-Primary Effectiveness Endpoints

[redacted]

With performance goals of:

1. Statistically significant smaller residual manifest cylinder, of 0.4D or greater, in test arm than in control arm.
2. 90% of eyes at target.
3. 95% of eyes at target.
4. 90% of eyes at target.

[redacted]

8.4.2 Secondary Effectiveness Endpoint

There are no secondary effectiveness endpoints.

8.4.3 Imputation Methods and Sensitivity Analyses for Co-Primary Effectiveness Endpoints

For ITT and All-implanted analyses, per ANSI Z80.30-2018, eyes 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 analysis. Further, 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 as the final result for analysis. Repositioning of test IOLs will result in imputation of worst observed value or assignment failure for the co-primary endpoints at Form 4 analysis, as appropriate. Imputation methods described below will retain these worst-value or failure assignments and will not overwrite them with imputed values.

For the ITT and All-implanted analysis populations missing co-primary endpoint data will be imputed where there are no available data at Form 4. The primary imputation method will be by

multiple imputation and be implemented using the MI and MI ANALYSE procedure in SAS® (Version 9.4 or later) or using the mice package (Version 3.16.0 or later) from R. A pre-specified seed of 20231026 (the date of version 1.0 of the protocol) will be used. Predictors will include attempted toric correction, age, and sex; 50 imputed datasets will be generated; the Markov Chain Monte Carlo (MCMC) method will be applied when using SAS. [redacted]

For all other co-primary endpoints, the [redacted] will be performed in which missing data are initially assumed to be failures. Then, one of the imputed failures will be imputed as a success. Then, a second failure will be assigned to a success. This process will be repeated until all missing data are imputed as successes. The point at which, if any, where the results of the hypothesis test changes its results regarding rejection of the null hypothesis will be reported.

8.4.4 Additional Effectiveness Endpoints and Associated Analyses

The following are not subject to hypothesis testing. Analyses will be performed using the All-implanted and PP analysis populations.

1) Achievement of ≤0.50D reduction in cylindrical power of the eye as a binary endpoint. Analysis will summarize the overall percentage of eyes meting endpoint 1 as well as by each 0.25D step of preoperative keratometric cylinder. Tabulation will be by both arms at Form 4.
2) Reduction in cylindrical power of the eye at Form 4. Analysis will include summary statistics of reduction in cylinder power of the eye overall and by each 0.25D step of preoperative keratometric cylinder. Summary statistics will be provided for both treatment arms, with the addition of a 95% confidence interval of the mean for each arm. Number and percentage with an absolute reduction of ≤0.5D will be provided for each arm.
3) Relationship between reduction in cylindrical power of the eye at the corneal plane and preoperative keratometric cylinder at Form 4. The association will be shown using a scatterplot with a linear regression line for each treatment arm. Intercept and slope, with associated p-values, will be provided. If the scatter of the data do not appear to be linear, a LOESS curve will be added for each arm.

4) The surgically induced change in corneal cylinder is calculated by analysis of the preoperative and postoperative keratometric readings (power and axis of meridians of highest and lowest power), converted to components in dioptric space. Change is defined as postoperative component values minus preoperative component values. Change and percentage change from baseline at Form 4 will be summarized with descriptive statistics for each treatment arm, overall, and by preoperative keratometric cylinder categories. Analyses will include:
    a. Analysis of the error in the predicted magnitude of postoperative astigmatism, including the bias, standard deviation, and mean absolute error, and a similar analysis of error in the predicted axis.
    b. Bar plot of the absolute error in predicted keratometric axis as a function of preoperative corneal astigmatism, and tabulation of the proportion of eyes with absolute error in axis by 5° wide bins (e.g., 0° to 5°, >5° to 10°).
5) Achievement of UDVA of 0.0 logMAR or better, 0.2 logMAR or better, and of 0.3 logMAR or better at Form 4. Results will be tabulated for each treatment arm by N and percentage.
6) UDVA at Form 4. UDVA will be described with summary statistics, overall and by each 0.25D step of preoperative keratometric cylinder categories. Both treatment arms will be summarized.
7) Manifest cylinder at Form 4. Analysis will include summary statistics of manifest cylinder. Summary statistics will be provided for both treatment arms. Results will be summarized overall as well as stratified by each 0.25D of preoperative keratometric cylinder.
8) Residual manifest cylinder at Form 4. Analysis will include summary statistics of residual manifest cylinder. Summary statistics will be provided for both treatment arms. Results will be summarized overall as well as stratified by each 0.25D of preoperative keratometric cylinder.
9) Achieving accuracy of cylinder to target at Form 4 within 0.25D, 0.50D, and 0.75D. Results will be tabulated for each treatment arm by N and percentage.
10) Achieving accuracy of MRSE to target at Form 4 within 0.25D, 0.50D, and 0.75D. Results will be tabulated for each treatment arm by N and percentage.
11) Axis misalignment compared to target within specified accuracy at Form 4. Results will be tabulated for the test lens only, reporting the number and percentage with axis deviation greater than 30° of target.
12) Axis misalignment at Form 4. Results for absolute and signed values will be summarized for the test lens only, with summary statistics of deviation from target. A two-sided tolerance interval around the mean of the signed value, which contains at least 90% of eyes (with 95% probability), will be provided.

8.5 SAFETY ANALYSES

All co-primary safety endpoints need to be achieved to claim overall safety success. Therefore no multiplicity adjustment is necessary for primary safety endpoints. For all key safety endpoints, the primary analysis population will be the safety analysis population.

8.5.1 Co-Primary Safety Endpoints and Testing

1. Cumulative rate of SSIs related to the optical properties of the IOL at Form 4, including IOL rotation SSIs for misalignment.
2. Rates of cumulative and persistent AEs at Form 4 via comparison to the ISO Safety and Performance Endpoint (SPE) rates as described in ISO 11979-7:2018.
3. BCVA logMAR of 0.3 or better at Form 4 for all-implanted and best-case test eyes.

[redacted]) of the observed proportion is compared with the maximum allowable SPE rate. If the lower boundary of the confidence interval does not exceed the SPE rate, then the endpoint will meet the success criterion. For safety co-primary endpoint 1, the rate of SSIs related to the optical properties of the IOL will be analyzed separately in addition to overall analysis. A 95% Clopper-Pearson confidence interval will be provided for the rate of SSIs related to the optical properties of the IOL; however, this rate will not be compared to the ISO historical SPE rate. The total SSI rate, including both rotation-related and non-rotation-related SSIs, will be compared to the corresponding ISO SPE rate.

[redacted] The number of eyes (in the safety population) with event present at any time and the number of eyes in the safety population are included for cumulative events. For persistent events, the number of eyes with the event present at Form 4 and the number of eyes present at the Form 4 visit are included without imputation. Cumulative and persistent events will be provided for the study eye and fellow eye.

[redacted] For All-Implanted, the rate used for the analysis is the number of eyes with the required level measured at Form 4 and the number of eyes present at the Form 4 visit without imputation. For Best Case, the rate used for the comparison to the ISO SPE historical rate should be defined as the number of Best Case eyes with the required acuity level at Form 4 and the number of Best Case eyes present at Form 4. The analysis will be provided for the study eye. [redacted]

[redacted]

More generally stated, for each type of adverse event listed in ISO 11979-7:2018 Table E.2, the rate for the test eyes is not statistically greater than the SPE rate for that event. The comparison between the adverse event rate for the test eyes and the SPE rate for posterior chamber IOL for each adverse event will be performed using the exact test based on binomial distribution at $\alpha = 0.10$ (one-sided).
The null hypotheses for adverse event rates is that it is greater than SPE rate. The alternative hypothesis is that the adverse event rate is not greater than the SPE rate. Formally put as follows:

$$H_0: \pi_T > \hat{p}$$

$$H_A: \pi_T \leq \hat{p}$$

Where π_T is the adverse event rate for the test eyes and $\hat{p}$ is the maximum SPE rate, for each adverse event listed in ISO 11979-7:2018 Table E.2.

As specified in ISO 11979-7:2018, the statistical success criterion is when H_0 is rejected. The statistical success criterion is equivalent to showing the one-sided 95% lower confidence limit of the rate is not greater than the historical control rate based on an exact binomial distribution.

[redacted]

The statistical success criterion is the rejection of H_0. This is equivalent to showing the one-sided 95% upper confidence limit of the rate is not lower than the historical control rate based on an exact binomial distribution.

8.5.2 Additional Safety Endpoints and Analyses

The incidence of all adverse events, other than those listed in ISO 11979-7:2018 tables E.3 and E.4, will be summarized with number and percentage by test and control eyes. 90% confidence intervals (showing both lower and upper 5% boundaries) will be provided for incidence. Data will be provided in line listings.

SPE analyses will be provided for control eyes for completeness.

The incidence of loss of 10 letters or more of BCDVA between any two postoperative visits will be summarized with number and percentage by test and control eyes. Data will be provided in line listings.

8.5.3 Adverse Event Reporting

The following definitions will characterize the nature of adverse events.

ADVERSE EVENT (AE)

An adverse event in this study is defined per ISO 14155:2020: Clinical investigation of medical devices for human subjects – Good clinical practice as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. For this protocol, this definition includes events related to the comparator device(s) and/or the procedures involved.

ADVERSE DEVICE EFFECTS (ADE)

An adverse event related to the use of an investigational medical device or comparator device(s).

NOTE: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation; any malfunction; and use error or intentional misuse of the investigational or comparator(s) medical device.

DEVICE DEFICIENCY

Device deficiencies (ISO 14155:2020) related to the identity (e.g., labeling), quality, durability, reliability, safety, effectiveness, or performance of the study device must be reported to the Sponsor, or Sponsor's designee, within 7 days of the Investigator becoming aware of the deficiency. Device deficiencies must be recorded in the subject's case report form.

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

SERIOUS ADVERSE EVENT (SAE)

A serious adverse event (SAE) is defined as any untoward medical occurrence that meets any of the following:

- 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 sight 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)

An unanticipated adverse device effect is defined per 21CFR 812.3(s) as 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 protocol or supplementary plan such as Clinical Investigator's Brochure, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. Per this definition, UADE will be a subset of the SAEs reported in the study. UADEs are reportable per 21 CFR 812.3(s).

An investigator shall submit to the sponsor and to the reviewing Institutional Review Board (IRB) a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

NOTE: Vision-threatening (sight-threatening) adverse events are considered an UADE, reportable per 21 CFR 812.3(s) and must be reported to sponsor.

GENERAL COUNTING METHODS

A subject will be said to have experienced the occurrence of a given adverse event if either a pre-existing condition has worsened and requires prescribed medical treatment after IOL implantation, or a previously non-existent condition has developed after IOL implantation and

this new condition is deemed to be a clinically untoward event. The same adverse event cannot occur more than once unless it resolves prior to occurring again. Each occurrence corresponds to a unique preferred term. Adverse event resolution is as specified on the Adverse Event Form.

A subject will be said to have experienced a persistent adverse event if a given adverse event is present at the conclusion of the clinical study (i.e., at database lock). The cumulative occurrence of an adverse event at an analytical time point refers to the total number of times a subject has experienced the occurrence of a given adverse effect between implantation and the conclusion of the clinical trial.

Incidence of adverse events (persistent or cumulative, as appropriate) listed in ISO 11979-7:2018 Table E.2 (Posterior chamber IOL adverse event rates will be compared to the historical control safety and performance endpoints (SPE) rates, as specified in **Section 7.5.1**. If none of the ISO-defined posterior chamber AE incidence rate is greater than the respective SPE rate, then investigational device will have met the co-primary safety endpoint on adverse event.

The AE tables will be listed by treatment group and will include the AE term, the event count, the incidence rate, and corresponding confidence intervals. The tables will be generated for the AEs listed in ISO 11979-7:2018, SAEs (separately for ocular and non-ocular), and all other AEs (separately for ocular and non-ocular). The table for the AEs listed in ISO 11979-7:2018 will also list *p*-values. The ocular AE tables may also be separately reported for device-related, procedure-related vs. non-related. If any UADE is reported in the study, they will be reported in a separate table.

Supplemental AE data listings will be ordered by subject and will list such information as AE term, treatment group, whether it is ocular or systemic, SAE (if applicable), date of onset, date of resolution, severity, relationship to the study device and relationship to the procedure. The onset of ocular adverse events will also be shown relative (in number of days) to the surgery date for that eye.

Per-subject data listings for death, SAEs, and premature discontinuation due to adverse events will also be produced.

Intraoperative adverse events are excluded from the above tables. An intraoperative AE is defined to be any adverse event with onset during surgery. Intraoperative adverse events will be presented in a data listing and summarized by treatment group.

8.6 SAMPLE SIZE CALCULATION

A sample size of up to 300 eyes is planned to be enrolled, where a screen failure of up to 70 eyes (23%) is anticipated. Approximately 230 eyes will be randomized and implanted with toric or control IOL.

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Given that all co-primary effectiveness endpoints must be met for study success, the worst-case study power, assuming independence among all tests, is 0.94 x 0.99 x 0.99 x 0.99 = 91%. However, given any positive correlation among the endpoints, power will exceed 91%.

8.7 OTHER STATISTICAL METHODS

8.7.1 Pooling of Data for Analyses

The clinical study will be conducted under a common protocol for each investigational site with the intention of pooling the data for analysis. Every effort will be made to promote consistency in study execution at each investigational site. The analysis of homogeneity will be conducted under the assumption that each site will have enrolled a minimum of 3 All-implanted subjects in the test group and 3 All-implanted subjects in the control group. Sites with fewer than 3 subjects will be omitted from the poolability analysis.

The consistency of treatment response will be investigated across the analysis centers subsequent to combining the data as described above. Statistical tests will be conducted to identify if there are outlier analysis centers that could affect the interpretation of common statistical and clinical conclusions. One method is to see if the treatment effect (such as mean acuity difference between eye's UCDVA, BCDVA, and residual cylinder) is significantly different across analysis centers (ANOVA test at $\alpha = 0.15$, for visual acuity (VA) and Wilcoxon rank-sum test at $\alpha = 0.15$ for residual cylinder). If it's not significantly different, then results from the analysis centers will be pooled for further analysis; if the difference is statistically significant, an investigation will be

conducted to identify which analysis center has the extreme outcomes. In the event of one or more divergent analysis center(s) being identified, further clinical investigations will be conducted to find out probable causes for the extreme results that are external and unrelated to the study device, such as clinical staff inconsistency, inconsistent measurement technique, testing equipment malfunction and so on. If such a cause has been identified as the most plausible cause for the divergent treatment effects, the analysis center(s) with extreme results will be reported separately and will be excluded from the study-level results based on pooled data from the rest of the analysis centers.

It is noted that applying this process may exclude subjects from the analysis in a non-random manner and has an unpredictable impact on the power of the statistical analyses. Due consideration of the post-hoc aspects of the process will be given when the results are interpreted. Conclusions will be presented as appropriate to the findings of the sensitivity analysis.

8.7.2 Stratification Analysis

Specific endpoint values at Form 4 will be stratified by preoperative keratometric cylinder. These include reduction of 0.5D cylindrical power as a binary endpoint, absolute reduction in cylindrical power, logMAR UDVA, and manifest refractive cylinder. Additional stratifications will be by age (per section 8.1 categorization), race, and ethnicity.

8.7.3 Interim Analysis

No interim analysis is planned.

9 SOFTWARE

The analyses described in this SAP will be performed using SAS/BASE and SAS/STAT software, Version 9.4 of the SAS System for Windows (Operating System: Windows 11 Professional 64-bit). Copyright© 2018 SAS Institute Inc. SAS and all other SAS Institute Inc. Cary, NC, USA. Other software may be used including R Version 4.3.0 (The R Foundation for Statistical Computing, 2023, platform: x86_64-apple-darwin20 (64-bit)).

10 REFERENCES

[1] ANSI Z80.30:2018; *American National Standard for Ophthalmics - Toric Intraocular Lenses*

[2] ISO 11979-7:2018 *Ophthalmic implants – intraocular lenses – part 7: clinical investigations of intraocular lenses for the correction of aphakia*

[3]ACRYSOF® Single-Piece Posterior Chamber Intraocular Lenses with Toric Optic- Summary of Safety and Effectiveness Data- Premarket Approval Application (PMA) Number: P930014/S15

[4] Chassain C, Hallak MK, Lesaffre M. Rotational stability and clinical outcomes after implantation of a new monofocal toric intraocular lens with double C-loop design. J Fr Ophtalmol. 2023 Jun;46(6):571-580. doi: 10.1016/j.jfo.2022.07.005. Epub 2023 May 11. PMID: 37179129.

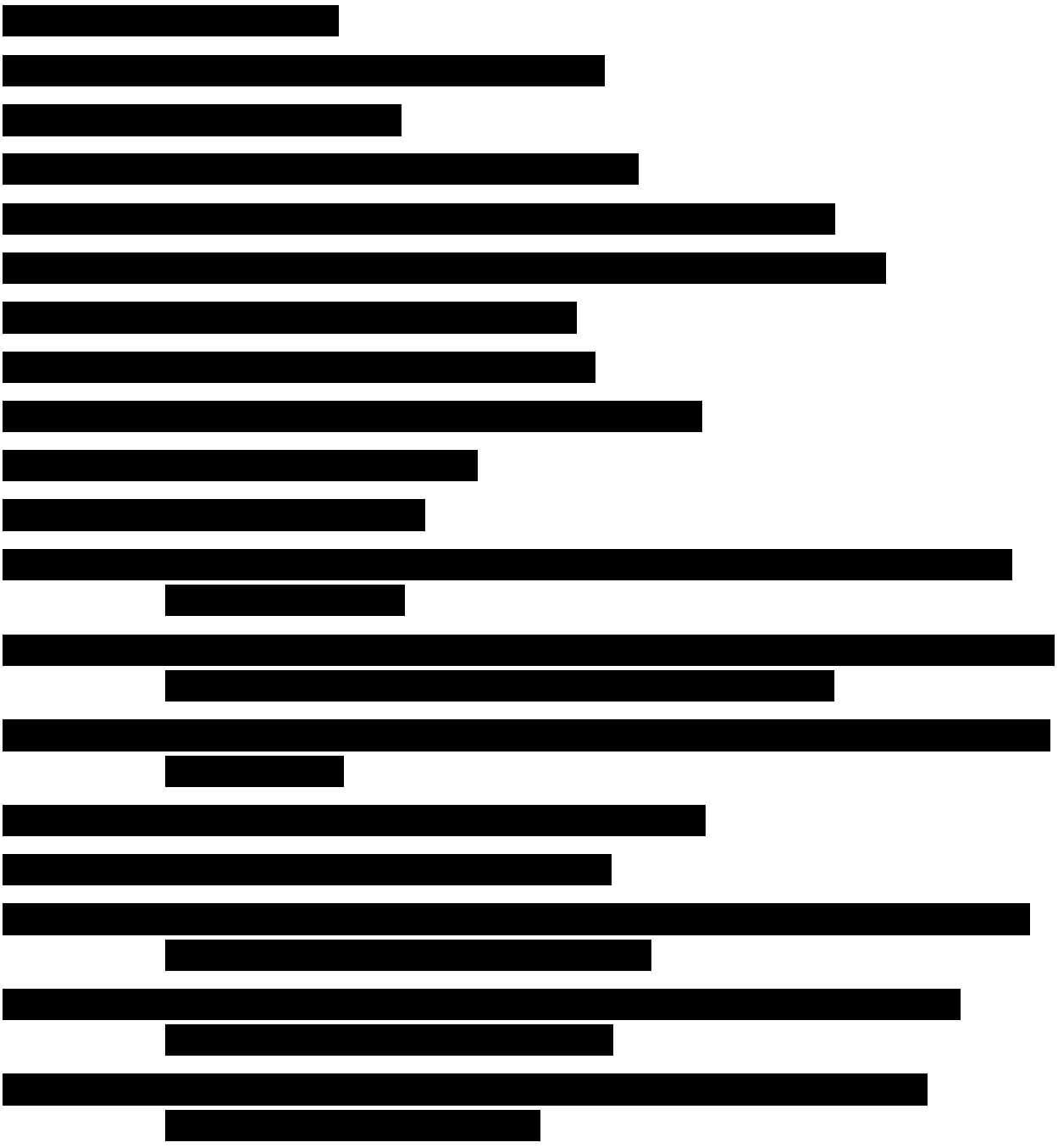
APPENDIX A – SCHEDULE OF ACTIVITIES

Examination		Pre-operative/Screening Visit	Form 0	Form 1	Form 2	Form 3	Form 4	USV[1]
Informed Consent and HIPAA		X						
Demographics		X						
Inclusion & Exclusion Criteria Evaluation		X						
Inclusion & Exclusion Criteria Review			X					
Ocular and non-ocular Medical History		X						
Urine Pregnancy Test (if applicable)		X						
Potential Visual Acuity		X						
Target Refraction		X						
IOL power calculation		X						
Axial Length and Anterior Chamber Depth		X						
Keratometry measurement		X				X	X	X
PhysIOL Toric Calculator		X						
Corneal Topography		X						
Manifest Refraction (ETDRS)-4 meters		X			X	X	X	X
Randomization		X						
Operative Procedures			X					
Intraocular Pressure		X		X	X	X	X	X
Slit Lamp Examination		X		X	X	X	X	X
IOL Tilt and Decentration Grading				X	X	X	X	X
IOL Axis Orientation[2]			X	X	X	X	X	X
Dilated pupil size		X						
Dilated Fundus Examination		X				X	X	X
IOL Observations				X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X
Device Deficiencies			X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X
Exit from Study							X	
Visual Acuity	UCDVA	X		X	X	X	X	X
	BCDVA	X			X	X	X	X

[1]USV- Unscheduled Visit; specific assessments to be completed may be determined by the investigator as appropriate based on the subject's condition. Recommended assessments for Investigator consideration are denoted in the table.
[2]Subjects must be dilated for IOL axis of orientation assessment.

APPENDIX B – PLANNED TABLES AND FIGURES

Below is a listing of the main tables and figures planned to summarize and illustrate the key outcomes and statistical analysis of the present study. Administrative tables (14.1.x) will be summarized for the Safety, ITT, All-implanted (if different from ITT), and PP analysis populations. Effectiveness tables (14.2.x) will be summarized by ITT, All-implanted, PP, and best case populations. Safety tables (14.3.x) will be summarized using the Safety population. Line listings will be provided in support of all summary tables.



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