Short Title

ClarVista CP-00002 Statistical Analysis Plan

Long Title

A PROSPECTIVE, MULTI-CENTER STUDY TO EVALUATE THE SAFETY AND PERFORMANCE OF THE EXCHANGEABLE CLARVISTA HARMONI™ MODULAR TORIC INTRAOCULAR LENS SYSTEM FOR THE TREATMENT OF PRE-EXISTING CORNEAL ASTIGMATISM AND APHAKIA FOLLOWING CATARACT SURGERY

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Medical Specialty:	Surgical
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Test Article(s) / Product(s):	ClarVista HARMONI® Modular Toric Intraocular Lens System

Statistical Analysis Plan for Protocol CP-00002

A Prospective, Multi-Center Study to Evaluate the Safety and Performance of the Exchangeable ClarVista HARMONI® Modular Toric Intraocular Lens System for the Treatment of Pre-existing Corneal Astigmatism and Aphakia Following Cataract Surgery

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1. Purpose

This is a feasibility study to evaluate the safety and effectiveness of HARMONI® Modular Toric Intraocular Lens System (HMTIOL) in subjects with primary cataract surgery and subjects with HMTIOL intra-operative optic exchange. There are three objectives in this study -

- To demonstrate the safety and effectiveness of the HMTIOL in subjects with pre-existing corneal astigmatism
- To evaluate endothelial cell loss after an intraoperative optic exchange
- To evaluate refractive outcomes and astigmatism correction with the HMTIOL used in the primary surgery

2. Scope

[redacted]

Analyses described here supersede those described in the Investigational Plan.

3. Software

Statistical analyses will be performed with SAS System Software version 9.4 or above (SAS Institute, Cary, N.C.), R version 3.3 or above (R Core Team, http://www.R-project.org), or other validated statistical software package.

4. Design and Objectives

All subjects will be bilaterally implanted based on the amount of pre-existing corneal astigmatism and followed for a period of 3-months post-implantation. The eye with the higher corneal astigmatism will be assigned to Cohort 1 and will undergo cataract surgery receiving HMTIOL. The contralateral eye will be assigned to Cohort 2, undergo cataract surgery, receive a HMTIOL or HMIOL (toric or non-toric optic, respectively), and undergo intraoperative exchange.

5. Statistical Analyses

5.1. General Statistical Methods

In general, analyses will be provided based on available data.

For continuous measures, descriptive summary statistics will include the number of observations, mean, standard deviation, median, minimum, maximum, as well as the number of eyes with results not reported. For continuous measures analyzed as changes from earlier visits, the 95% confidence interval for change will also be reported. Continuous measures may also be dichotomized or otherwise split into clinically meaningful categories and additionally analyzed as categorical measures.

For categorical measures, the percentage and number of cases for each condition (e.g., 20/40 or better) will be reported. The number of eyes without results will be omitted from the numerator and denominator of such calculations (i.e. no imputation will be performed).

Any calculated p-values will be based on nominal calculations with no adjustment for multiplicity. No imputation for missing data will be performed.

5.2. Baseline Data

Data on enrollment, demographics (gender, race, age, implanted eye), and baseline characteristics (IOL Power, pre-operative MRSE, target MRSE, keratometric cylinder, axial length) will be summarized with descriptive statistics.

5.3. Accountability

Accountability will be based on eyes (not subjects). The number and percentage of eyes available for analysis at each time point will be presented. For eyes not available for analysis, a breakdown will be provided to summarize the following reasons for missing data: subject discontinued, missed study visit but seen later, missed study visit but subject accounted for (i.e., contacted), and lost to follow-up. Eyes for active subjects at a time point, defined as those enrolled but who have not yet reached the corresponding time point, will also be summarized. Accountability as a percentage will be calculated based on the total number available for analysis over the total number of eyes enrolled minus total number discontinued and the total number active.

5.4. Safety Endpoints

- Preservation of BCDVA
- Adverse Events as outlined in ISO 11979-7:2014 Annex B
- Rate of device-related Secondary Surgical Interventions (SSIs), other than initial intraoperative exchange for cohort 2.
- Percent change in Endothelial Cell Count (ECC)
- Device deficiencies

5.5. Safety analyses

Adverse events and device deficiencies will be summarized at each study visit based on the safety population for Cohort 1 and Cohort 2 separately. The number and percentage of eyes reported with the ISO specified 3-month cumulative and persistent adverse events will be calculated for Cohort 1 and Cohort 2 separately.

Events will be summarized overall for the HMTIOL Cohort 2 and HMIOL Cohort 2. The corresponding one-sided lower 95% confidence limit will be calculated based on the binomial distribution and compared to the ISO SPE rate.

The number and percentage of eyes reported with HMTIOL-related adverse events during the study will be summarized for HMTIOL Cohort 1, HMTIOL Cohort 2, and HMTIOL-eye Cohort. The two-sided 90% confidence interval of the percentage will also be provided.

The number and percentage of eyes reaching BCDVA 20/40 or better, and worse than 20/40 at each visit will be prepared.

Rates for adverse events specified in ISO 11979-7:2014 Annex B for posterior chamber IOLs will be summarized at each visit.

Rates of device-related SSIs and device deficiencies will be summarized as described in 5.1 above.

5.6. Endothelial Cell Counts

The within-eye change and percent change in ECC from preoperative to the 3-month postoperative visit will be calculated for each eye.

[redacted]

[redacted]

5.7. Other Safety Measures

[redacted]

5.8. Effectiveness Endpoints

The effectiveness parameters include the following:

- Postoperative MRCYL for eyes implanted with HMTIOL
- Postoperative MRCYL Prediction Error for eyes implanted with HMTIOL
- Postoperative MRSE Prediction Error
- UCDVA by study visit
- BCDVA by study visit
- Rotation of IOL meridian from the day of surgery to 3 months
    a. Meridian rotation < 10°
    b. Meridian rotation < 20°
    c. Meridian rotation < 30°

- Reduction in cylinder power of eye implanted with HMTIOL at 3 months
    a. Absolute preop magnitude of K (or total corneal cylinder) minus the absolute post op magnitude of MRCYL at the corneal plane
- Percentage reduction in cylindrical power of eye implanted with HMTIOL at 3 months
    a. Absolute preop magnitude of K (or total corneal cylinder) minus the absolute post op magnitude of MRCYL at the corneal plane expressed as a percentage of the absolute preop magnitude of K (or total corneal cylinder)

5.9. Effectiveness Analyses

All endpoints listed above will be summarized by study visit and cohort as described in section 5.1 based on the Implanted Eye Population. BCDVA will also be summarized based on the Best-case population as suggested by ISO.

5.9.1. BCDVA

[redacted]

[redacted] the number and percentage of eyes reaching BCDVA 20/20 or better, 20/25 or better, 20/32 or better, 20/40 or better, and worse than 20/40 at each visit will be prepared for Cohort 1 and Cohort 2 separately.

5.9.2. UCDVA

The proportion of eyes with UCDVA of 20/20 or better, 20/25 or better, 20/32 or better, 20/40 or better, and worse than 20/40 at each visit will be summarized for each Cohort at the preoperative and every postoperative visit.

5.9.3. PREDICTION ERROR (PE)

MRSE prediction error will be calculated at 3 months for each implanted eye as follows:

> MRSE PE = Postoperative MRSE adjusted to 6 meters – MRSE TRRE (target residual refractive error)

MRCYL prediction error will be calculated at 3 months for eyes implanted with HMTIOL as follows:

> MRCYL PE = Postoperative MRCYL adjusted to 6 meters – MRCYL TRRE (target residual refractive error)

Descriptive statistics for continuous outcomes will be provided for MRSE PE and MRCYL PE at each visit based on Implanted-eye Population. [redacted]

5.9.4. MISALIGNMENT OF IOL MERIDIAN

The final rotational meridian of the IOL will be compared to the planned position. The absolute value of rotation will be described by mean, median, and maximum values. The signed value of rotation will be described by mean, SD, minimum and maximum values. The number and percentage of eyes with deviation ≤ 5°, < 10°, < 20°, and < 30° from the planned meridian will be calculated.

5.9.5. ROTATION OF IOL MERIDIAN

The rotation of IOL meridian will be calculated for each eye from Day 0 to every postoperative visit. Descriptive statistics for continuous variables will be used to summarize the rotation angle at each visit. The absolute value of rotation will be described by mean, median, and maximum values. The signed value of rotation will be described by mean, SD, minimum and maximum values. The number and percentage of eyes with rotation ≤ 5°, < 10°, < 20°, and < 30° will be calculated at each visit.

Axis shift by 5° increments will also be stratified for each preoperative corneal cylinder diopter bin.

5.9.6. REDUCTION IN CYLINDER POWER

Reduction in cylinder power will be calculated for each eye implanted with the HMTIOL as follows:

> Cylinder Power Reduction = absolute value of preoperative magnitude of corneal cylinder (K) – absolute postoperative magnitude of MRCYL at the corneal plane.

The percent reduction in cylindrical power will be calculated for eyes with non-zero preoperative corneal cylinder as follows:

> Cylinder Power % Reduction = Cylinder Power Reduction/ absolute value of preoperative magnitude of corneal cylinder (K) × 100.

Descriptive statistics for continuous variables will be used to summarize these outcomes at each visit.

[redacted]

6. Sample Size

Based on a one-sided two-sample non-inferiority t-test with a significance level of 0.05, a sample size of 25 bilateral subjects (50 total eyes, 25 in each cohort) with successful implants and 3-month follow-up ECC data for each eye provides a power of 80% to reject the null hypothesis if the true difference in mean ECC percent change is 5%, the standard deviation of the ECC percent change is 12.6%.

It should be noted that some study subjects may not have successful implants in both eyes due to intraoperative eligibility, or do not have the 3-month ECC data for both eyes. These subjects will be excluded from the ECC comparisons. With an assumption of a dropout rate of approximately 20%, a sample size of 32 bilateral subjects should be enrolled.

7. Analysis Populations

Subjects that are screened but disqualified based on the preoperative and intra-operative eligibility criteria will be excluded from the safety and performance data analyses. However, their reasons for the screen failure will be summarized. The analyses populations are defined below.

7.1.1. SAFETY POPULATION

The Safety Population includes eyes with attempted study lens (HMTIOL or HMIOL) implantation, (successful or aborted after contact with the eye). The intraoperative and postoperative AEs and DDs will be summarized based on the safety population.

7.1.2. IMPLANTED-EYE POPULATION

The Implanted-Eye Population consists of eyes with successful HMTIOL or HMIOL implantations during surgeries. Since it is important to evaluate HMTIOL or HMIOL's effect on the study eyes, the assessment of ECC, slit lamp examination, intraocular pressure (IOP), and dilated fundus examination (DFE) will be based on the implanted-eye population. It should be noted that the ECC comparison between Cohort 1 and Cohort 2 of this study will be based on the subjects with successful implants in both eyes and have available ECC data at 3 months.

Additionally, the UCDVA, BCDVA, prediction error, and meridian rotation will be evaluated based on the implanted-eye population.

7.1.3. PER PROTOCOL POPULATION

The Per Protocol (PP) Population contains eyes with successful HMTIOL or HMIOL implantations during surgeries and do not have major protocol deviation (such as improperly enrolled in the study or lens power calculation errors) and will be considered the primary population for effectiveness outcomes. The effectiveness outcomes (UCDVA, BCDVA, and prediction error) will be evaluated based on the per protocol population.

The protocol deviations will be reviewed by ClarVista clinical personnel prior to analysis.

8. Interim Analyses

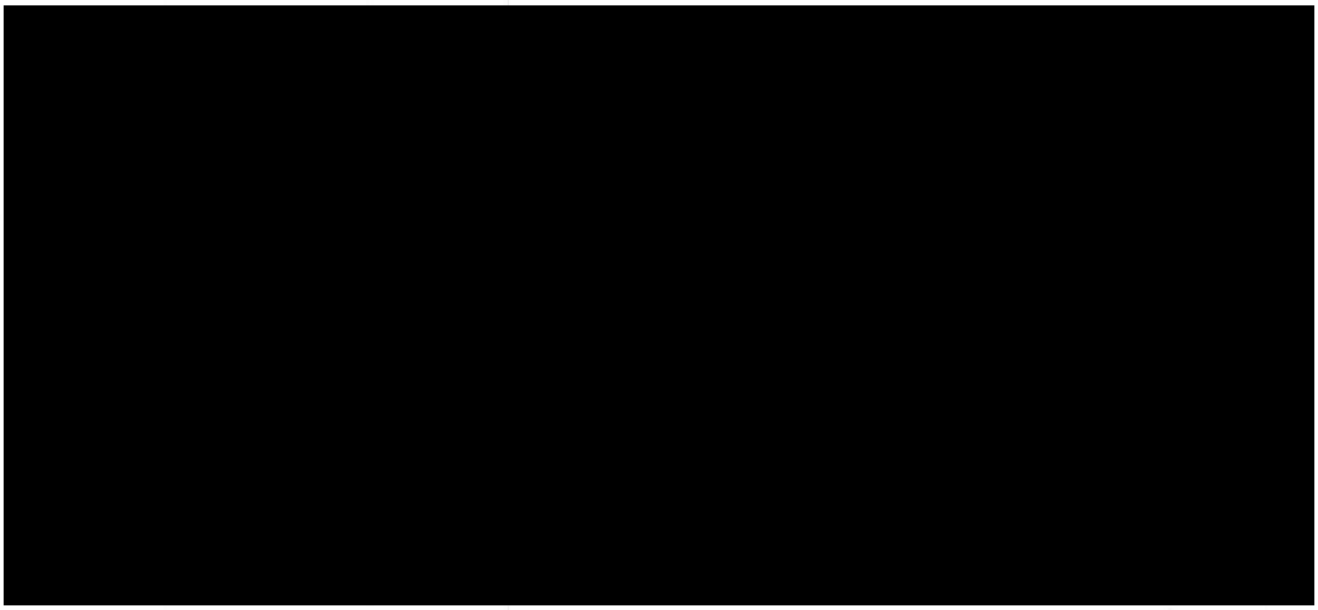
There are no plans for formal interim analyses for the purposes of study modification or possible early termination. Any interim analyses will be administrative in nature and results will not be distributed to Investigators or subjects to prevent bias from exposure to accruing study results.

9. Deviations from the Statistical Analysis Plan

Any deviations from the Statistical Analysis Plan will be noted and described with appropriate statistical and clinical rationale as needed. Discrepancies from the Investigational Plan are noted. The primary change is the use of a paired t-test instead of a two-sample t-test to test the primary hypothesis. This change more appropriately accounts for within-patient correlation in ECC. A secondary change was the use of "ECC" rather than "ECL" in Sections 6 and 7 above. ECL is defined in the protocol as follows: "a negative ECC percent change represents an ECC percent loss (ECL)." Since a comparison of 3-month to Pre-operative data may not always result in a measurable loss (e.g., due to measurement error of instrumentation combined with minimal actual ECC loss), ECC is determined to be a more appropriate term.

10. References

1. ISO 11979-7:2014 Ophthalmic implants — Intraocular lenses — Part 7: Clinical investigations.



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