Short Title

ClarVista CP-00004 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

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

Statistical Analysis Plan for Protocol CP-00004

A Prospective, Multi-Center Study to Evaluate the Safety and Performance of the 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 Statistical Analysis Plan documents and describes the planned analyses for study CP-00004. This is a study to evaluate the safety and performance of the HARMONI Modular Toric Intraocular Lens System (HMTIOL) in patients with pre-existing corneal astigmatism. Specifically, the intent is

- To evaluate the refractive outcomes including astigmatism correction with HMTIOL in primary cataract surgery
- To evaluate axial and rotational stability of the HMTIOL

Given these goals, there are no formal hypothesis tests for safety or effectiveness. All results will be purely descriptive.

2. Scope

This document is based on the Investigational Plan CP-00004. [redacted]

As the multi-center study described in the Investigational Plan was not actually implemented, 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

CP-00004 was designed as a prospective, multi-center, cohort study. However only one center actually enrolled patients in the trial.

All patients in this study require cataract extraction and implantation with intraocular lenses. Patients have pre-existing corneal astigmatism in the study eye(s). The magnitude of astigmatism is within the range of available toric powers: 1.50, 2.25 and 3.00 D at the IOL plane, after adjusting for Surgically Induced Astigmatism.

One or both eyes of each subject will undergo cataract surgery and be implanted with the HMTIOL. Eyes with corneal astigmatism that is within the dioptric range of the toric IOL will be implanted.

All eyes will be followed for 1 Day, 1 Week, 1 Month, and 3 Months following cataract extraction.

5. Statistical Analyses

5.1. General Statistical Methods

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. [redacted] 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).

[redacted]

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. [redacted]

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 optic exchange or rotational adjustment of the HMTIOL
- Device deficiencies

5.5. Safety analyses

All endpoints listed above will be summarized by study visit and cohort as described in section 5.1. There are no formal hypothesis tests for safety.

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.

[redacted]

5.7. Effectiveness Endpoints

Performance Outcomes:

1. Post op MRCYL for eyes implanted with HMTIOL at 1 and 3 months
2. Post op MRCYL prediction error for eyes implanted with HMTIOL at 1 and 3 months
3. Post op SEQ Prediction Error at 1 and 3 months
4. UCDVA by study visit
5. BCDVA by study visit

6. IOL meridian misalignment on the day of surgery
7. Rotation of IOL meridian from the day of surgery to 3 months, and between all adjacent visits
    a. Meridian rotation ≤ 5°
    b. Meridian rotation < 10°
    c. Meridian rotation < 20°
    d. Meridian rotation < 30°
    e. Absolute value of rotation
    [redacted]
8. Reduction in cylinder power of eye implanted with HMTIOL (in Diopters) 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
9. 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)

5.8. 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. [redacted]

5.8.1. BCDVA

[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.

5.8.2. 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 at the preoperative and every postoperative visit.

5.8.3. 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. Additionally, the number and percentage of eyes with a PE within ±0.50 D of target and of ±1.00 D of target will be derived for each postoperative visit.

5.8.4. 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.

5.8.5. 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. [redacted] The number and percentage of eyes with rotation ≤ 5°, < 10°, < 20°, and < 30° will be calculated at each visit.

[redacted]

5.8.6. 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

This is a feasibility study and no hypothesis testing will be performed.

The sample size for this study was originally based on refinement of the A-constant (lens power constant). Subsequent developments led to a modification in study design from a multi-center to a single center trial. The sample size was scaled down accordingly to 17 enrolled and treated eyes.

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 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 implantation. Since it is important to evaluate HMTIOL's effect on all study eyes, slit lamp examination, intraocular pressure (IOP), and dilated fundus examination (DFE) will be based on the implanted-eye population.

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 implantations during surgeries and do not have a major protocol deviation (such as improperly enrolled in the study or lens power calculation errors) and will be considered the primary population for the analysis of performance outcomes. The performance outcomes (UCDVA, BCDVA, and prediction error) will also be evaluated based on the per protocol population.

The protocol deviations will be categorized prior to the 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 and due primarily to the study design modification from a multi-center to single center trial, without the corresponding amendment to the protocol.

10. References

1. ISO 11979-7:2014 Ophthalmic implants — Intraocular lenses — Part 7: Clinical investigations.
2. Note to File Re: Correction to Appendix A – Table 1: Schedule of Assessments_June 26, 2017

[redacted]

[redacted]
