Short Title

ClarVista CVM-00001 Statistical Analysis Plan / NCT03681886

Long Title

EVALUATION OF VISUAL AND REFRACTIVE OUTCOMES OF THE CLARVISTA HARMONI™ MODULAR INTRAOCULAR LENS SYSTEM

1 TITLE PAGE

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

Statistical Analysis Plan for Protocol CVM-00001

EVALUATION OF VISUAL AND REFRACTIVE OUTCOMES OF THE CLARVISTA HARMONI™ MODULAR INTRAOCULAR LENS SYSTEM

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1. Purpose

This Statistical Analysis Plan documents and describes the planned analyses for the CVM-00001 study. This is a study to evaluate surgeon experience and visual and refractive outcomes of the ClarVista HARMONI™ Modular Intraocular Lens System in primary implantation and optic exchange procedure.

2. Scope

This document is based on the Investigational Plan CVM-00001, Rev.03. Changes to the Investigational Plan may require updates to this document. Analyses described here expand on and 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

The CVM-00001 study is designed as a prospective, multi-center, cohort study. Any pre-planned formal hypothesis tests for this feasibility study are not for the purposes of generating definitive conclusions to support regulatory approval.

The study was carried out at five investigational centers, in the Philippines (3 centers), Panama (1) and Mexico (1).

The study comprises patients with planned removal of cataracts (cortical, nuclear, subcapsular, or a combination) by manual phacoemulsification. The investigator will determine if the test lens is to be implanted in OD, OS, or OU based on target refraction and the best interests of the subject.

All patients will have visits scheduled for 1 Day, 1 Week, and 1 Month following primary cataract extraction. During follow up the Investigator and Subject will decide if an optic exchange in the study eye is in the best interests of the subject based on refractive outcome and target. Subjects with satisfactory outcomes, or those opting not to pursue an optic exchange, will be entered into Cohort 1.

Subjects who opt for an HMIOL optic exchange in their primary eye will be entered into Cohort 2. Optic exchange patients will have visits scheduled for 1 Day, 1 Week, and 1 Month following the optic exchange procedure. These subjects may be followed up beyond 1 month as deemed necessary by the surgeon.

Several cohorts of subjects are specified to help characterize the clinical significance of the study outcomes in eyes with and without optic exchange. These cohorts are defined as follows:

All HMIOL Eyes Cohort: Defined as all study eyes implanted with the study device.

Cohort 1: Defined as the subset of study eyes implanted with the study device without a subsequent optic exchange procedure.

Cohort 2: Defined as the subset of study eyes implanted with the study device with a subsequent optic exchange procedure. Analysis of follow-up visits for this cohort will cover two separate time periods:

- Pre-Optic Exchange, comprising visits following primary cataract extraction, prior to the optic exchange visit (through 1 month).
- Post-Optic Exchange, comprising visits following optic exchange. The baseline for the post-optic exchange visits is the last pre-optic exchange visit (1-month).

Separate analyses are planned for each cohort.

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. 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., 20/20 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.

5.2. Baseline Data

Data on enrollment, demographics (gender, race, age, implanted eye), and baseline characteristics of study eyes (IOL Power, pre-operative BCDVA, MRSE) from the pre-op visit 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 subject eyes enrolled minus total number discontinued and the total number active.

5.4. Safety Endpoints

Safety endpoints will be summarized at each visit using the Safety population (all eyes with attempted implantation):

- Device deficiencies
- Adverse Events (AE) and Serious AEs including secondary surgical Interventions.

Other safety outcomes include surgical complications, ≥ 2 lines loss of BCDVA from a prior post-op visit, persistent corneal stroma edema, IOP increase requiring intervention, and iritis requiring treatment.

5.5. Other Safety Measures

Other safety outcomes such as slit lamp examination, intraocular pressure and dilated fundus examination, will be summarized descriptively at each visit for the Safety Population. Line listings for abnormal findings for individual eyes will be provided. Summary tables of adverse events will be provided with intra-operative adverse events tabulated separately. Intra-operative adverse events are defined as those with an onset date equal to the date of the procedure. A line listing of non-ocular serious adverse events will be provided by subject.

5.6. Effectiveness Endpoints

Effectiveness endpoints will be summarized in the per-protocol population for each cohort at each study visit for which they are available. See Appendix A for a listing of scheduled assessments by visit.

[redacted]

6. Sample Size

The sample size for this study was not based on any statistical criteria. The sample size was chosen to provide sufficient experience and feedback regarding the ClarVista HARMONI™ Modular Intraocular Lens System at five investigative centers.

7. Analysis Populations

Safety Population: Eyes with attempted study lens (HMIOL) implantation, (successful or aborted after contact with the eye). The intraoperative and postoperative AEs and device deficiencies, slit lamp examination, dilated fundus examination, and IOP will be summarized based on the safety population.

Per-Protocol Population: Eyes with successful HMIOL implantation that do not have major protocol deviations (such as improperly enrolled in the study or lens power calculation errors). The effectiveness endpoints will be summarized based on the per-protocol population.

[redacted]

[redacted]

10. 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.

Interim Safety Summary: Safety outcomes will be evaluated when all eyes in Cohort 1 and Cohort 2 have completed the 1 Month Visit following primary cataract extraction and optic exchange, respectively (post-optic exchange for Cohort 2).

Final Safety and Effectiveness outcomes will be evaluated when all study subjects complete the final visit or exit the study.

11. 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.

12. References

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

Appendix A – Assessment Schedule

Table A.1. Schedule of Assessments – Cohort 1

Table 1	Cohort 1					
Procedure/Assessments	Pre-Op Visit Day -90 to -0	Op Visit 1 Day 0	Form 1 1 Day Visit (Day 1-2)	Form 2 1 Wk Visit (Day 7-14)	Form 3 1 Mo Visit (Day 30 - 60)	Optic Exchange Window (Day 1 - 30)
Informed Consent	X			X		
Demographics	X					
Med/Ophthalmic History	X	X				
Eligibility	X	X				
UCDVA			X	X	X	
Manifest Refraction	X			X	X	
BCDVA	X			X	X	
Keratometry	X				X	
IOL Power Calculation	X					
Slit Lamp Examination	X		X	X	X	
IOP	X		X	X	X	
Pupil Size	X					
Dilated Fundus Exam	X				X	
Primary Surgery (HMIOL)		X				
Surgeon Questionnaire		X				
Optic Exchange (see Table 2)						

Table A.2. Schedule of Assessments – Cohort 2

Table 2	Cohort 2 - Optic Exchange Complete			
Procedure/Assessments	Op-Visit 2 Optic Exchange Visit (+1-301 Days)	Form 1.1 OE 1 Day Visit (Day 1-2)	Form 2.1 OE 1 Wk Visit (Day 7-14)	Form 3.1 OE 1 Mo Visit (Day 30-60)
Eligibility	X			
UCDVA		X	X	X
IOL Power Calculation	X			
Keratometry				X
Manifest Refraction			X	X
BCDVA			X	X
Slit Lamp Examination		X	X	X
IOP		X	X	X
Dilated Fundus Exam				X
Optic Exchange Procedure	X			
Surgeon Questionnaire	X			

Appendix B - Surgeon Questionnaire

Primary Implantation

1. How would you rate the surgical difficulty of the base implantation?

   a. Easier than a traditional single piece IOL
   b. Slightly easier than a traditional single piece IOL
   c. The same as a traditional single piece IOL
   d. Slightly more difficult than a traditional single piece IOL
   e. More difficult than a traditional single piece IOL

2. How would you rate the surgical difficulty of the optic implantation and assembly?

   a. Very easy
   b. Easy
   c. Neutral
   d. Difficult
   e. Very difficult

Optic exchange

1. How would you rate the surgical difficulty of the optic disassembly?

   a. Very easy
   b. Easy
   c. Neutral
   d. Difficult
   e. Very difficult

2. How would you rate the surgical difficulty of the optic explantation?

   a. Very easy
   b. Easy
   c. Neutral
   d. Difficult
   e. Very difficult

3. How would you rate the surgical difficulty of the optic implantation and assembly?

   a. Very easy
   b. Easy
   c. Neutral
   d. Difficult
   e. Very difficult

[redacted]

[redacted]
