Short Title

ClarVista CP-00001 Statistical Analysis Plan

Long Title

A PROSPECTIVE, MULTI-CENTER, FEASIBILITY TRIAL OF THE CLARVISTA HARMONI™ MODULAR INTRAOCULAR LENS SYSTEM FOR THE TREATMENT OF APHAKIA FOLLOWING CATARACT SURGERY

1 TITLE PAGE

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Medical Specialty:	Surgical
Project Name /Number:	NA
Sponsor Name & Address:	CLARVISTA MEDICAL, INCORPORATED 26800 ALISO VIEJO PARKWAY, SUITE 120 ALISO VIEJO, CA 92656 PHONE +001 949 916-5412 FAX +001 949 916-5412
Test Article(s) / Product(s):	ClarVista HARMONI® Modular Toric Intraocular Lens System

Statistical Analysis Plan for Protocol CP-00001

Sponsor

ClarVista Medical, Incorporated
26800 Aliso Viejo Parkway, Suite 120
Aliso Viejo, CA 92656
Phone +001 949 916-5412
Fax +001 949-916-5412

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1. Purpose

This Statistical Analysis Plan documents and describes the planned analyses for the CP-00001 CLEAR study. This is a feasibility study of the ClarVista HARMONI Modular Intraocular Lens System for the Treatment of Aphakia Following Cataract Surgery.

The intent of the study is to demonstrate the

- Feasibility of HARMONI IOL (HMIOL) implantation and assembly in subjects undergoing cataract surgery
- Feasibility of the HMIOL optic component exchange procedure (performed 3 months following primary cataract extraction)

Safety and effectiveness of these procedures will be characterized with the intent of supporting a future confirmatory study.

2. Scope

This document is based on the Investigational Plan CP-00001, Rev.05. 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 CP-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.

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. Analysis of follow-up visits for this cohort definition is restricted to 1 Day, 1 Week, 1 Month, and 3 Months following primary cataract extraction (PCE).

Cohort 1: Defined as the subset of study eyes implanted with the study device without a subsequent optic exchange procedure. Analysis of follow-up visits for this cohort definition is restricted to 1 Day, 1 Week and 1, 3, 6 and 12 Months following primary cataract extraction.

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 time periods:

- Pre-Optic Exchange, comprising 1 Day, 1 Week, 1 Month, and 3 Months following primary cataract extraction, prior to the optic exchange visit.
- Post-Optic Exchange, comprising 1 Day, 1 Week, 1 Month, 3 Months, 6 Months, and 12 Months following optic exchange. The baseline for the post-optic exchange visits is the 3 Month pre-optic exchange visit.

Fellow Eyes Cohort: Defined as the contralateral eyes not implanted with the study device. Analysis of follow-up visits for this cohort definition is restricted to 1 Day, 1 Week, 1 Month, 3 Months, 6 Months, and 12 Months following primary cataract extraction.

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 (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 subject eyes enrolled minus total number discontinued and the total number active.

5.4. Safety Endpoints

All HMIOL Eyes Cohort

- [redacted]
- [redacted]
- Adverse event rates as compared to ISO 11979-7:2014 Annex B Safety and Performance Endpoint (SPE) tables including SSIs
- [redacted]

Cohort 1 (No-Optic Exchange)

- [redacted]
- AE rates as compared to ISO 11979-7:2014 Annex B Safety and Performance Endpoint (SPE) tables including SSIs
- [redacted]

Cohort 2 (Optic Exchange)

- [redacted]

A hypothesis test for this endpoint will be performed to assess whether mean percent change in ECC is no worse than 14%. The null and alternative are stated as:

$$H_O: \mu \geq 14\%$$
$$H_A: \mu < 14\%$$

Where μ represents the mean percent ECC loss from pre-exchange (3 months after the primary cataract surgery) to 3-month post-exchange for the eyes with HMIOL optic exchange (6 months after the primary cataract surgery). This test will be based on a one-sided, one-sample 0.05 t-test of a mean.

- [redacted]
- [redacted]
- AE rates as compared to ISO 11979-7:2014 Annex B SPE tables (includes SSIs –optic exchange procedures due to targeted residual refractive error are excluded)
- [redacted]

Fellow Eye Cohort

- [redacted]
- AE rates as compared to ISO 11979-7:2014 Annex B SPE tables including SSIs
- Dilated fundus examination

Adverse event rates in this study will be assessed as outlined in ISO 11979-7:2014 Annex B for posterior chamber IOLs. Following this methodology, for each specified adverse event we will calculate an exact lower one-sided 95% confidence bound for the proportion of eyes with the event at the one-year time point. As described in ISO 11979-7:2014 Annex B.3-B.4, success is defined as a lower bound that is less than the safety and performance endpoint (SPE) rate for that adverse event, in other words failing to reject the hypothesis that the event rate is greater than the SPE rate. The SPE rates for posterior chamber IOLs are provided in Table 1 below.

Table 1: Rates of Specific Adverse Events as Outlined in ISO 11979-7:2014 Annex B:

Adverse Event	Incidence Threshold
Cumulative	
Cystoid macular edema	3.0%
Hypopyon	0.3%
Endophthalmitis (inflammatory reaction (sterile or infectious) involving the vitreous body	0.1%
Lens dislocated from posterior chamber	0.1%
Pupillary block	0.1%
Retinal detachment	0.3%
Secondary surgical intervention (excluding posterior capsulotomies)	0.8%
Persistent	
Corneal stroma edema	0.3%

Cystoid macular edema	0.5%
Iritis	0.3%
Raised IOP requiring treatment	0.4%

5.5. Other Safety Measures

Other safety outcomes such as slit lamp examination, intraocular pressure, posterior capsule opacification and dilated fundus examination, will be summarized descriptively at each visit for the Safety Population. Line listings for abnormal findings for individual eyes may 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

All HMIOL Eyes Cohort

- Percent of eyes with post-operative BCDVA 20/40 or better by study visit
- Percent of eyes that achieve MRSE of ±0.50 D of target by study visit
- Percent of eyes that achieve MRSE of ±1.00 D of target by study visit
- BCDVA by study visit
- UCDVA by study visit
- mBCDVA (with and without glare) by study visit

Cohort 1

- Percent of eyes with post-operative BCDVA 20/40 or better by study visit
- Percent of eyes that achieve MRSE of ±0.50 D of target by study visit
- Percent of eyes that achieve MRSE of ±1.00 D of target by study visit
- BCDVA by study visit
- UCDVA by study visit

Cohort 2 (Optic Exchange)

- Percent of eyes with post-operative BCDVA 20/40 or better by study visit
- Percent of eyes that achieve UCDVA by post-optic exchange study visit
    - 20/20 or better
    - 20/25 or better
    - 20/32 or better
    - 20/40 or better
    - Worse than 20/40
- Percent of eyes that achieve MRSE of ±0.50 D of optic exchange target by post-optic exchange study visit
- Percent of eyes that achieve MRSE of ±1.00 D of optic exchange target by post-optic exchange study visit
- BCDVA by study visit
- UCDVA by study visit

Fellow Eye Cohort

- Percent of eyes with post-operative BCDVA 20/40 or better by study visit
- BCDVA by study visit
- UCDVA by study visit
- Manifest refraction

The overall BCDVA 20/40 or better outcome will be assessed as outlined in ISO 11979-7:2014 Annex B for posterior chamber IOLs. Following this methodology, we will calculate an exact upper one-sided 95% confidence bound for the proportion of eyes with BCDVA 20/40 or better in the combined Cohort 1 and Cohort 2 eyes at 12 months following primary cataract extraction (for Cohort 1) or optic exchange (for Cohort 2). As described in ISO 11979-7:2014 Annex B.3-B.4 for posterior chamber IOLs, success is defined as an upper bound that is greater than 92.5% (that is, failing to reject the null hypothesis that the rate is less than the safety and performance endpoint (SPE) rate of 92.5%). The following Table shows the success criteria for a range of sample sizes:

Table 2: Required BCDVA 20/40 or Better Following ISO 11979-7:2014 Annex B:

Number of subjects	Minimum number of eyes with BCDVA 20/40 or better
100	88
105	92
110	97
115	102
120	106

[redacted]

6. Sample Size

The sample size for this study was calculated following methods outlined in ISO 11979-7:2014 Annex B. Using these methods, a sample of 100 eyes is sufficient for safety (for both the ISO criteria and the ECC hypothesis) and effectiveness (ISO criteria).

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 DDs, slit lamp examination, dilated fundus examination, ECC, corneal pachymetry, PCO, [redacted] and IOP will be summarized based on the safety population.

Implanted-Eye Population: Eyes with successful HMIOL implantation. The effectiveness endpoints and exploratory measures will be summarized based on the implanted-eye population.

Per Protocol Population: Defined as study eyes with successful HMIOL implantation without a major protocol deviation (such as improperly enrolled in the study or lens power calculation errors). The protocol deviations will be reviewed and categorized by ClarVista clinical personnel prior to analysis. The effectiveness endpoints and exploratory measures will be assessed for the Per Protocol population and will be considered the primary population for effectiveness outcomes.

Best-Case Population: The Best-Case population is the PP population with all of the following characteristics:

- No clinically significant preoperative ocular pathology in the study eye, including any of the following present at the preoperative visit:
  - Pseudoexfoliation
  - Glaucoma
  - Uveitis
  - Retinal detachment
  - Diabetic retinopathy
  - Macular degeneration
  - Amblyopia
  - Others as specified by unmasked sponsor clinical personnel after a review of the adverse events present at the preoperative visit
- No macular degeneration detected at any time in the study eye
- No previous surgery for the correction of refractive errors in the study eye

The percent of eyes with post-operative BCDVA 20/40 or better by study visit and BCDVA by study visit endpoints will be assessed for this population.

8. Sensitivity Analyses

As this is a feasibility study, there are no plans for sensitivity analyses. Post-hoc exploratory sensitivity analyses may be performed to help inform future studies. These may include assessments of the sensitivity results to statistical model assumptions and/or missing data.

9. Subgroup Analyses

Results will be presented separately for Cohort 1 and Cohort 2 (both pre- and post- optic exchange):

- [redacted]
- Percent of eyes with post-operative BCDVA 20/40 or better by study visit
- UCDVA by study visit

[redacted]

[redacted]

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.

REVIEWED/APPROVED BY:

[redacted]	Signature	Date
[redacted]	Signature	Date

Date/Time (mm/dd/yyyy GMT):	Signed by:	Justification:
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]