Short Title

ClarVista CP-00002 / NCT03054649

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

1 TITLE PAGE

Protocol Number:	ClarVista CP-00002
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

TITLE PAGE

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

Protocol Number	**#CP-00002 REV.03**
Sponsor	**CLARVISTA MEDICAL, INCORPORATED** **26800 ALISO VIEJO PARKWAY, SUITE 120** **ALISO VIEJO, CA 92656** **PHONE +001 949 916-5412** **FAX +001 949 916-5412**
Original Version Date (Rev.01)	**23 March 2016**
Revised Version Date (Rev.02)	**9 May 2016**
Revised Version Date (Rev.03)	**1 Dec 2016**

This clinical investigation is being conducted in accordance with 21 CFR Parts 11, 50, 54, 56, and 812, ISO 14155 (2011) Clinical Investigation of Medical Devices for Human Subjects, ISO 11979-7:2014 Ophthalmic implants — Intraocular lenses — Part 7: Clinical investigations, ANSI Z80.7-2013 Ophthalmic Optics – Intraocular Lenses, ICH GCPs, and applicable local regulations.

CONFIDENTIAL

The information in this document is confidential and will not be disclosed to others without written authorization from ClarVista Medical, except to the extent necessary to obtain informed consent from persons involved in the clinical study or their legal guardians, or for discussions with local regulatory authorities, institutional review boards (IRB), Ethics Committees (EC) or persons participating in the conduct of the trial.

PROTOCOL CONTACTS

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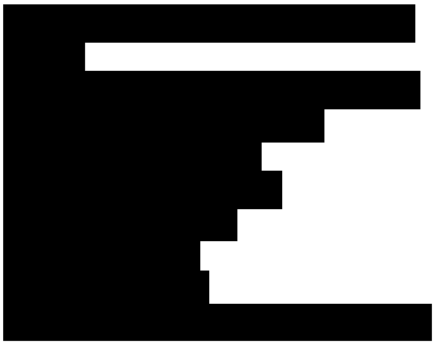


PROTOCOL APPROVAL

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

The following individuals approve Protocol #CP-00002 Rev.02 dated 9 May 2016. Any changes to this version of the protocol must have an amendment or administrative letter.

[redacted]

PROTOCOL APPROVAL

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

The following individuals approve Protocol #CP-00002 Rev.02 dated 9 May 2016. Any changes to this version of the protocol must have an amendment or administrative letter.

[redacted]

PROTOCOL APPROVAL

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

The following individuals approve Protocol #CP-00002 Rev.02 dated 9 May 2016. Any changes to this version of the protocol must have an amendment or administrative letter.

[redacted]

STUDY ACKNOWLEDGEMENT

I understand this protocol contains information that is confidential and proprietary to ClarVista Medical (ClarVista).

I have read this protocol and agree that it contains all the details necessary to conduct the study as described. I will follow this protocol in the conduct of the study and will make a reasonable effort to complete the study in the time noted.

I will provide the contents of this protocol to study staff under my direct supervision in order to conduct the study. I will discuss this information with the study staff to ensure they are fully informed about the study and the test article. I will provide the contents of the protocol to the responsible Ethics Committee. These disclosures may be made; providing the contents are not used in any other clinical study and they are not disclosed to any other person or entity without prior written consent from ClarVista. This condition does not apply to disclosure required by government regulations or laws; however, I agree to give prompt notice to ClarVista of any such disclosure.

I understand the study may be terminated or enrollment suspended at any time by ClarVista, with or without cause, or by me if it becomes necessary to protect the interests of the study subjects.

Any additional information added to this protocol is also confidential and proprietary to ClarVista and must be treated in the same manner as the contents of this protocol.

_____
Printed Name of Principal Investigator

_____ _____
Investigator Signature Date

Protocol # CP-00002 Rev.03
Date: 01 December 2016

LIST OF ABBREVIATIONS

Abbreviation/Acronym	Term
AE	Adverse Event
ACD	Anterior Chamber Depth
ADE	Adverse Device Effect
AL	Axial Length
ANSI	American National Standards Institute
BCDVA	Best-Corrected Distance Visual Acuity
CFR	Code of Federal Regulations
D	Diopter
DD	Device Deficiencies
DFE	Dilated Fundus Examination
EC	Ethics Committee
ECC	Endothelial Cell Count
ECL	Endothelial Cell Loss
eCRF	Electronic Case Report Form
ETDRS	Early Treatment Diabetic Retinopathy Study (Chart)
EtO	Ethylene oxide
FDA	United States Food and Drug Administration
GCPs	Good Clinical Practices
FE	Fellow Eye
HIPAA	Health Insurance Portability and Accountability Act
HMIOL	HARMONI™ Modular Intraocular Lens System
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	Identification
IDE	Investigational Device Exemption
IOA	Intraoperative Aberrometry
IOL	Intraocular Lens
IOP	Intraocular Pressure
IRB	Institutional Review Board
ISO	International Organization for Standardization
K	Keratometry
LASIK	Laser In-Situ Keratomileusis
MR	Manifest Refraction
MRSE	Manifest Refraction Spherical Equivalent
MST	MicroSurgical Technology
Nd:YAG	Neodymium:Yttrium-aluminum-garnet
ND	Not Done
OD	Right Eye
OS	Left Eye
OVD	Ophthalmic Viscoelastic Device
PCO	Posterior Capsule Opacification
PE	Prediction Error
PH	Pinhole
PMA	Premarket Approval

PP	Per Protocol
PRK	Photorefractive Keratectomy
RRE	Residual Refractive Error
SAE	Serious Adverse Event
SIA	Surgically Induced Astigmatism
SLE	Slit Lamp Examination
SOC	Standard of Care
SPK	Superficial Punctate Keratitis
SSI	Secondary Surgical Intervention
TRRE	Target Residual Refractive Error
UCDVA	Uncorrected Distance Visual Acuity
US	United States
VA	Visual Acuity

NOTE: The first occurrence of some abbreviations are not spelled out in the document (e.g. units of measure).

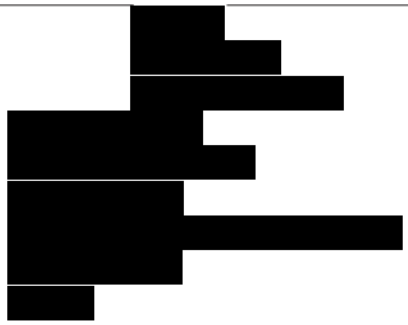
PROTOCOL SYNOPSIS

Protocol Number #CP-00002 Rev.03	
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
Regulatory Status	Phase 4 in CE countries US - Pre-IDE
Investigational Device	ClarVista HARMONI Modular Toric Intraocular Lens System (HMTIOL)
Objectives	Pilot Study to demonstrate safety and efficacy of the HMTIOL in patients with pre-existing corneal astigmatism. To evaluate endothelial cell loss after an intraoperative optic exchange. To evaluate refractive outcomes, astigmatism correction with HMTIOL used in primary surgery.
Number of Clinical Sites and Study Subjects	Up to 32 enrolled and treated subjects from up to 3 investigational sites. [redacted]

[redacted]

	[redacted]
Study Duration	All subjects will participate in the study for up to 6 months. Total study duration will be approximately 9 months.
Study Design	Prospective, multi-center clinical study. All subjects will be seen for a Preoperative Visit to capture baseline measurements. The eye with the higher corneal astigmatism will be assigned to Cohort 1 and will undergo cataract surgery receiving HMTIOL. The other eye will be assigned to Cohort 2, undergo cataract surgery, receive a HMTIOL or HMIOL (toric or non-toric), and undergo intraoperative exchange. Both Cohorts will be followed for 3 months. All patients • 1 Day, 1 Week, 1 Month, 3 Months following cataract extraction.  **FIGURE 1 - COHORT SCHEDULE**

Study Endpoints	The safety and effectiveness of HMTIOL for the treatment of pre-existing corneal astigmatism and aphakia in subjects following cataract extraction will be characterized. *Efficacy Endpoints:* 1. Post op MRCYL for eye implanted with HMTIOL 2. Post op MRCYL prediction error for eye implanted with HMTIOL 3. Post op SEQ Prediction Error 4. UCDVA by study visit 5. BCDVA by study visit 6. Rotation of IOL meridian from the day of surgery to 3 months a. Meridian rotation < 10° b. Meridian rotation < 20° c. Meridian rotation < 30° 7. Reduction in cylinder power of eye implanted with HMTIOL a. Absolute preop magnitude of K (or total corneal cylinder) minus the absolute post op magnitude of MRCYL at the corneal plane 8. Percentage reduction in cylindrical power of eye implanted with HMTIOL 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) *Safety endpoints:* 9. Percent change in ECC at the 3 Month Visit compared to Preoperative Visit 10. Preservation of BCDVA 11. SSI (other than interoperative optic exchange in Cohort 2) 12. Device deficiency 13. AEs rates as compared to ISO 11979-7:2014 Annex B SPE tables
[redacted]	[redacted]

	
Inclusion Exclusion Criteria	Inclusion criteria 1. Adult at least 22 years of age at the time of consent 2. Must be willing and able to return for scheduled treatment and follow-up examinations for up to 6 month study duration 3. Planned removal of visually significant bilateral cataract (cortical, nuclear, posterior subcapsular, or a combination) by manual phacoemulsification cataract extraction 4. Pre-existing corneal astigmatism in at least 1 eye. Magnitude of astigmatism 0.75 to 2.50D of corneal astigmatism (within the range of available toric power 1.50, 2.25 and 3.00D at the IOL plane) 5. Target dioptric lens power within the range of 16 – 26D 6. Must be willing to discontinue contact lens wear for the duration of the study and demonstrate refractive stability prior to biometry and surgery in the both eyes ***NOTE:*** Due to potential variability of VA and MR outcomes following gas permeable (GP) contact lens wear, all subjects who have worn GP contact lenses must complete the consenting process, discontinue wear for 3 weeks and exhibit a stable Manifest Refraction (as evidenced by two MR evaluations at least 1 week apart resulting in ≤0.50D MRSE difference in the two refractions) and Keratometry readings (as evidenced by two K readings at least 1 week apart resulting in ≤0.50D difference between the two readings) prior to final IOL calculations. Similarly, any subjects who currently wear soft contact lenses must also complete the consenting process, discontinue wear for a minimum of 1 week and return for repeat eligibility testing exhibit stable MR and K readings. In addition, all qualifying subjects must discontinue contact lens wear in the study eye for the duration of study participation. 7. BCVA projected to be 0.2 logMAR or lower (as determined by the medical judgment of the Investigator or measured by potential acuity meter / retinal acuity meter (PAM / RAM) if necessary) 8. Visual symptoms related to cataract

	9. Stability of the cornea has been demonstrated by keratometry 10. Dilated pupil size at least 7.0mm 11. Must be able to understand and provide informed consent themselves or through a representative with a witness present on the IRB or EC approved Informed Consent Form (ICF) Exclusion criteria 1. History of any intraocular or corneal surgery in either eye (including refractive) 2. Any type of cataract (e.g. traumatic, congenital, polar) other than those noted in inclusion criteria 3. Pregnancy and lactation 4. Participation in any other drug or device clinical trial within 30 days prior to enrolling in this study and/or during study participation 5. Previous cornea based surgery (LASIK, PRK, LRI, etc.) 6. History of any clinically significant retinal pathology or ocular diagnosis (e.g. diabetic retinopathy, ischemic diseases, macular degeneration, retinal detachment, amblyopia, optic neuropathy, etc.) in either eye that could alter or limit final postoperative visual prognosis 7. History of any ocular conditions which could affect the stability of the IOL (e.g. pseudoexfoliation, zonular dialysis, evident zonular weakness or dehiscence, etc.) in either eye 8. Any anterior segment pathology likely to increase the risk of complications from phacoemulsification cataract extraction (e.g. chronic uveitis, iritis, iridocyclitis, aniridia, rubeosis iridis, clinically significant corneal, Fuch's, or anterior membrane dystrophies, etc.) in either eye 9. Any visually significant intraocular media opacity other than cataract in either eye (as determined by the investigator) 10. Uncontrolled glaucoma in either eye (per Investigator judgement) 11. Subjects with large refractive errors (hyperopia/myopia) of axial or pathologic origin that, in the opinion of the investigator, could confound outcomes 12. Uncontrolled systemic disease (e.g. diabetes mellitus, active cancer treatment, mental illness, etc) 13. Subject who, in the clinical judgment of the investigator, is not suitable for participation in the study for another clinical reason, as documented by the investigator 14. Severe dry eye that, in the opinion of the investigator, would impair the ability to obtain reliable study measurements (e.g. specular microscopy)

	15. Taking systemic medications that, in the opinion of the investigator, may confound the outcome or increase the intraoperative and post-operative risk to the subject (e.g. Tamsulosin Hydrochloride – Flomax) or other medications including anticholinergics, alpha adrenergic blocking agents with similar side effects (e.g. small pupil/floppy iris syndrome) Exclusion Criteria During Surgery 1. Vitreous loss prior to use of the investigational device 2. Positive posterior pressure preventing safe implantation of the lens system 3. Anterior chamber hyphema preventing visualization of implantation 4. Any zonular or capsular rupture or capsular bag instability 5. Intraoperative miosis preventing visualization of fixation features 6. Need for concomitant procedures (e.g. glaucoma surgery, LRI, RK, LASIK, etc.) Subject who, in the clinical judgment of the investigator, is not suitable for participation in the study for another clinical reason, as documented by the investigator
Planned Analyses	All eyes with attempted study lens (HMTIOL or HMIOL) implantation will be included in the safety analyses. The ECL comparison will include subjects with ECL data available for both eyes. The effectiveness outcomes will be summarized based on eyes implanted with HMTIOL or HMIOL. All data summaries will be performed based on observed data and not imputation for missing clinical outcomes will be performed. The analyses may be performed based on the per-protocol population and the best-case population (Section 8). For continuous variables, mean, standard deviation, median, minimum, and maximum will be provided for Cohort 1 and Cohort 2 separately. For categorical outcomes, the counts and percentages of eyes with each categorical level of outcomes will be summarized for Cohort 1 and Cohort 2 separately. [redacted] The ISO specified cumulative and persistent adverse events will be summarized at 3 months for Cohort 1 and Cohort 2 separately [redacted]

	For BCDVA and UCDVA, the number and percentages of eyes with visual acuity 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 Cohort 1 and Cohort 2 separately. The MRSE prediction error will be calculated for each eye (Section 8) and summarized using statistics for continuous variables. The MRCYL prediction error (per cylinder power or vector analysis) will be derived for eye with HMTIOL and summarized using statistics for continuous variables. [redacted] The reduction in MRCYL (absolute power) and the percent reduction in cylinder power will be derived for each eyes implanted with HMTIOL. They will be summarized using statistics for continuous variables. [redacted] IOL rotation will be derived for each eye from Day 0 (surgery) to postoperative visit. The statistics for continuous variables will be provided. The number and percentage of eyes with rotation of < 10°, < 20°, and < 30° will be calculated [redacted]

1.0 INTRODUCTION

Cataract surgery is a minimally invasive procedure designed to restore vision with short recovery time. Advances in instrumentation and techniques over the past few decades have facilitated the enhancement in safety[1] while allowing for reproducible outcomes. While the serious adverse event rate remains low, selecting the right intraocular lens (IOL) implant for spectacle independence remains an on-going challenge. This is referred to as residual refractive error (RRE) and typically involves ~0.6 diopters (D)[2] of uncorrected focusing power. Furthermore, it is reported that current biometry measurements for selecting the correct IOL and subsequent surgical methods are associated with:

1. Up to 16% of patients undergoing additional surgical correction to achieve 20/20 unassisted vision[2].
2. Up to 55% of patients falling outside of their targeted postoperative refraction by at least 0.5D[3,4,5].
3. Between 14 and 24% of surgeries result in greater than 1 D of residual refractive error, when using manufacturer suggested constants[3].
4. Up to 6% of patients experience unintended and significant post-operative rotation of a toric IOL[4].

   Rotations between 5-40 degrees have been observed and for every 1 degree of rotation, 3% of the corrective power of the toric surface is lost.

Patients are frequently satisfied with the results of their cataract surgery and enjoy relatively quick recovery with restoration of vision. However, as expectations have evolved over time, patients are demanding the same degree of spectacle independence that other refractive surgeries such as LASIK provide. Currently available options to help achieve spectacle independence when RRE is present include: contact lenses, corneal modification (surgery or other), IOL exchange/manipulation, or sulcus placement of a "piggyback" IOL. These alternatives have significant limitations and risks.

Complications due to contact lenses are rare; however, contact lens intolerance and contact lens-related infections could be serious and sight threatening. For some patients, contact lens wear is contraindicated and they must resort to the use of spectacles. Elderly patients in particular have difficulty handling contact lenses.

If the patient is willing to accept the additional cost and risks of a secondary procedure, the physician has more options; however, each of them poses a significant risk to the patient as outlined below.

Corneal modifications have been performed on tens of millions of people across the world with some form of refractive surgery (e.g. LASIK). For example, in the U.S. (where the most extensive data exists) 11.5M Americans have had corneal refractive surgery and over the next two decades many will need cataract surgery. LASIK increases the likelihood for residual refractive error post cataract surgery due to inaccurate IOL power calculations with biometry. There is hesitation among many ophthalmologists to repeat LASIK for RRE after cataract surgery because the FDA has not specifically evaluated the safety and effectiveness of repeated LASIK in this setting. All the risks associated with the original LASIK procedure apply to retreatment, along with the increased potential for epithelial ingrowth, corneal ectasia and less robust nomograms for IOL selection for post cataract patients.

Furthermore, even for eyes that have not undergone prior corneal refractive surgery, the FDA has not specifically evaluated the safety and effectiveness of corneal refractive procedures (e.g., astigmatic keratotomy, LASIK, PRK, etc.) to address RRE following lens replacement surgery, so the use of approved lasers for this purpose in the U.S. is considered off-label and the risks are not well characterized. For example, it is unclear how optical aberrations that might be present with an IOL in place are increased by aberrations induced by corneal refractive procedures, how likely corneal refractive procedures are to induce irregular astigmatism and worsen dry eye that is induced by cataract surgery, and whether corneal refractive procedures could create potential complications related to cataract surgery wound healing or IOL stability.

Furthermore, cornea based interventions do not address the root cause of RRE after cataract extraction (imprecise IOL power selection) and expose the patient to a new and independent set of possible adverse events. Thus, it would be desirable to be able to correct or modify the optical result without the need to irreversibly and unpredictably alter corneal tissue following cataract extraction.

Sulcus placement of a "piggyback" IOL is a procedure that has not been evaluated for safety and effectiveness by the FDA so the use of approved IOLs for this purpose in the U.S. is off-label. Among the complications reported with this procedure are secondary pigment dispersion, iris/pupil irregularities, chronic iritis, hyphema, glaucoma, zonular disruption and/or posterior capsular rupture. Thus, it would be desirable to be able to correct or modify the optical result without the need to implant a "piggyback" IOL with its inherent serious risks.

IOL Exchange/Manipulation in general, is technically challenging for the surgeon and poses an iatrogenic risk to intraocular structures including the lens capsule, iris, and endothelium of the cornea. The capsular bag fibroses weeks after IOL implantation creating a strong adhesion between the capsule and the IOL. Manipulation of the capsular bag to remove an IOL is the major risk in this setting and can damage the capsular bag including posterior capsular rupture and capsular bag dislocation. The capsular bag cannot be repaired once damaged. This risk increases over time as the capsular bag adheres to the IOL and haptics. Even when IOL exchange is not required, manipulation of traditional IOL's to rotate or center the optic introduces the risk of capsular or zonular damage which can cause further lens instability and lens malposition. Thus, it would be desirable to be able to correct RRE without the need to remove the entire IOL particularly after capsular contraction or fibrosis.

The modular IOL concept will serve as a valuable addition to the armamentarium of cataract surgeons. The goal of this technology is to improve refractive (spheric and toric) outcomes and avoid the significant risks of secondary procedures currently being performed as standard practice to address RRE in an indirect manner. It is anticipated that this modular lens will provide clinical utility in two basic areas, the first being the focus of this study.

1. Post-operative correction of residual spherical refractive error – Based on existing performance of conventional cataract surgery, researchers have concluded that refractive outcomes in normal eyes should be within 0.5D for 45% and within 1D for 85% of cataract cases[5]. This theoretical performance goal still falls substantially short of the real-world outcomes seen with corneal refractive surgery and which cataract patients and surgeons increasingly demand. As a consequence, secondary procedures to optimize visual outcomes following cataract surgery can be as high as 16% in some practices, particularly for premium lens patients[2].

   Modular IOL technology is intended to directly improve refractive outcomes without the inherent risk of a full lens exchange or resorting to the use of a corneal refractive laser. With the HARMONI™ design the spherical optic component is intended to allow exchange for a different power optic or adjusted to align with the visual axis without extensive manipulation of the delicate capsular bag, thereby avoiding the potential for intraocular (e.g., capsular and endothelial) trauma that is seen with traditional IOL exchanges.

2. Post-operative correction of rotationally displaced or off-axis toric lens – For every 1 degree a toric IOL axis is off from the true postoperative axis of astigmatism, there will be a 3.3% loss of toric correction. Study data supporting a recent approval of a toric IOL (P930014/S045) showed that 6.7% of eyes underwent a secondary surgical intervention (SSI) in the form of IOL repositioning to resolve RRE. The HARMONI™ modular technology can be used to improve outcomes in patients where the toric lens has been displaced to an unintended position during the post-operative period. The HARMONI™ optic allows for adjustment to align with the astigmatic meridian or visual axis without manipulation of the base component thereby avoiding the potential for capsular trauma that is seen when toric IOLs are manipulated in the post-operative period.

2.0 OBJECTIVES

The objective of this pilot study is to demonstrate the safety and efficacy of the HARMONI™ Modular Toric IOL in patients with pre-existing astigmatism.

The specific objectives are:

- To evaluate endothelial cell loss after an intraoperative optic exchange.

- To evaluate refractive outcomes, astigmatism correction with HMTIOL used in primary surgery.

3.0 STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a prospective, multi-center, pilot study being conducted at up to 3 investigative sites. All sites will have Institutional Review Board (IRB) or Ethics Committee (EC) review and approval prior to recruiting potential subjects. Up to 32 eligible subjects with bilateral visually significant cataracts will undergo cataract extraction in each eye during participation. All subjects will be seen for a Preoperative Visit to capture baseline measurements. The eye with the higher corneal astigmatism will be assigned to Cohort 1 and will undergo cataract surgery receiving HMTIOL (toric). The other eye will be assigned to Cohort 2, undergo cataract surgery, receive a HMTIOL or HMIOL (toric or non-toric), and undergo intraoperative exchange. Both Cohorts will be followed for 3 months.

All patients

- 1 Day, 1 Week, 1 Month, 3 Months following cataract extraction.

Figure 2 - Cohort Schedule

All subjects enrolled in this study will be evaluated for 3 months following cataract extraction (see Appendix A – Schedule of Assessments).

3.2 STUDY POPULATION

After completing the informed consent process, subjects will be screened for participation in the study.

3.2.1 INCLUSION CRITERIA

1. Adult at least 22 years of age at the time of consent
2. Must be willing and able to return for scheduled treatment and follow-up examinations for up to 6 month study duration
3. Planned removal of visually significant bilateral cataract (cortical, nuclear, posterior subcapsular, or a combination) by manual phacoemulsification cataract extraction
4. Pre-existing corneal astigmatism in at least 1 eye. Magnitude of astigmatism 0.75 to 2.50D of corneal astigmatism (within the range of available toric power 1.50, 2.25 and 3.00D at the IOL plane)

5. Target dioptric lens power within the range of 16 – 26D
6. Must be willing to discontinue contact lens wear for the duration of the study and demonstrate refractive stability prior to biometry and surgery in the both eyes

   NOTE: Due to potential variability of VA and MR outcomes following gas permeable (GP) contact lens wear, all subjects who have worn GP contact lenses must complete the consenting process, discontinue wear for 3 weeks and exhibit a stable Manifest Refraction (as evidenced by two MR evaluations at least 1 week apart resulting in ≤0.50D MRSE difference in the two refractions) and Keratometry readings (as evidenced by two K readings at least 1 week apart resulting in ≤0.50D difference between the two readings) prior to final IOL calculations. Similarly, any subjects who currently wear soft contact lenses must also complete the consenting process, discontinue wear for a minimum of 1 week and return for repeat eligibility testing exhibit stable MR and K readings. In addition, all qualifying subjects must discontinue contact lens wear in the study eye for the duration of study participation.
7. BCVA projected to be 0.2 logMAR or lower (as determined by the medical judgment of the Investigator or measured by potential acuity meter / retinal acuity meter (PAM / RAM) if necessary)
8. Visual symptoms related to cataract
9. Stability of the cornea has been demonstrated by keratometry
10. Dilated pupil size at least 7.0mm
11. Must be able to understand and provide informed consent themselves or through a representative with a witness present on the IRB or EC approved Informed Consent Form (ICF)

3.2.2 EXCLUSION CRITERIA PRIOR TO SURGERY

1. History of any intraocular or corneal surgery in either eye (including refractive)
2. Any type of cataract (e.g. traumatic, congenital, polar) other than those noted in inclusion criteria
3. Pregnancy and lactation
4. Participation in any other drug or device clinical trial within 30 days prior to enrolling in this study and/or during study participation
5. Previous cornea based surgery (LASIK, PRK, LRI, etc.)
6. History of any clinically significant retinal pathology or ocular diagnosis (e.g. diabetic retinopathy, ischemic diseases, macular degeneration, retinal detachment, amblyopia, optic neuropathy, etc.) in either eye that could alter or limit final postoperative visual prognosis

7. History of any ocular conditions which could affect the stability of the IOL (e.g. pseudoexfoliation, zonular dialysis, evident zonular weakness or dehiscence, etc.) in either eye
8. Any anterior segment pathology likely to increase the risk of complications from phacoemulsification cataract extraction (e.g. chronic uveitis, iritis, iridocyclitis, aniridia, rubeosis iridis, clinically significant corneal, Fuch's, or anterior membrane dystrophies, etc.) in either eye
9. Any visually significant intraocular media opacity other than cataract in either eye (as determined by the investigator)
10. Uncontrolled glaucoma in either eye (per Investigator judgement)
11. Subjects with large refractive errors (hyperopia/myopia) of axial or pathologic origin that, in the opinion of the investigator, could confound outcomes
12. Uncontrolled systemic disease (e.g. diabetes mellitus, active cancer treatment, mental illness, etc)
13. Subject who, in the clinical judgment of the investigator, is not suitable for participation in the study for another clinical reason, as documented by the investigator
14. Severe dry eye that, in the opinion of the investigator, would impair the ability to obtain reliable study measurements (e.g. specular microscopy)
15. Taking systemic medications that, in the opinion of the investigator, may confound the outcome or increase the intraoperative and post-operative risk to the subject (e.g. Tamsulosin Hydrochloride – Flomax) or other medications including anticholinergics, alpha adrenergic blocking agents with similar side effects (e.g. small pupil/floppy iris syndrome)

3.2.3 EXCLUSION CRITERIA DURING SURGERY

1. Vitreous loss prior to use of the investigational device
2. Positive posterior pressure preventing safe implantation of the lens system
3. Anterior chamber hyphema preventing visualization of implantation
4. Any zonular or capsular rupture or capsular bag instability
5. Intraoperative miosis preventing visualization of fixation features
6. Need for concomitant procedures (e.g. glaucoma surgery, LRI, RK, LASIK, etc.)
7. Subject who, in the clinical judgment of the investigator, is not suitable for participation in the study for another clinical reason, as documented by the investigator

3.3 STUDY VISITS

The timing and frequency of each assessment to be performed at each visit, will be carried out according to "Appendix A – Schedule of Assessments."

Procedures to be followed in order to carry out each individual assessment, are under separate cover (See study specific Manual of Procedures).

In all instances, if the first study eye and secondary eye post-operative assessments cannot be seen on the same day and both remain "in-window," the subject must return for a separate visit in order to maintain "in-window" status for both eyes throughout study participation.

3.3.1 PRE-OPERATIVE VISIT – SCREENING/BASELINE (DAY -90 TO DAY 0)

After providing informed consent (see Section 4.1), prospective subjects will be screened to determine whether they meet enrollment criteria. Demographic information, relevant ocular history, and current ocular medication use will be collected. If all criteria are met, the subject will be considered enrolled, IOL calculation completed to determine appropriate HMTIOL or HMIOL power, and the subject scheduled for surgery.

3.3.2 DAY 0 VISIT (CATARACT SURGERY AND IOL IMPLANTATION)

Record any changes in concomitant medications and medical history, prepare the subject for surgery in the study eye (see Surgical Procedure Guide), and re-review inclusion/exclusion criteria to ensure subject still qualifies to participate.

All subjects with an odd subject number will have their Cohort 1 eyes done first. All subjects with and even subject number will have their Cohort 2 eyes done first.

The Investigator will carry out the surgical procedure and HMTIOL or HMIOL implantation as specified in the Surgical Procedure Manual and the following details will be captured in both Source Documents and eCRFs:

- Date of surgery
- Operative eye
- Cohort 1 or Cohort 2
- Incision location and size
- Ophthalmic Viscoelastic Device (OVD) used
- All medication used pre-, intra-, and post-operatively (ophthalmic and systemic)
- Model, serial number, and diopter of HMTIOL or HMIOL implant components
- Toric IOL power and axis orientation (for HMTIOL)
- IOL injection device

Once the subject is confirmed stable post-surgery, provide IRB / EC approved post-operative instructions and discharge.

Record any AEs, adverse device effects (ADEs), unexpected adverse device effects (UADEs), or device deficiencies (DD) (see Sections 6.1.1, 6.1.2, 6.1.3, or 6.1.4 respectively) observed pre-, intra-, or post-operatively.

In the event the subject is not implanted with the HMTIOL or HMIOL, the surgeon will provide the best care option to the patient, including implanting a commercially available IOL. In the event the optic cannot be exchanged, the surgeon will provide the best care option to the patient, including keeping the existing optic.

In the event the subject is not implanted with an HMTIOL or HMIOL device due to an intra-operative complication, the subject will be discontinued (see Section 4.5).

3.3.3 POST-OPERATIVE VISITS (DAYS 1 – 60)

All subjects implanted with a study lens will be seen for 1 Day, 1 Week, 1 and 3 Month assessments as outlined in Appendix A.

IN ADDITION, the second eye will be implanted during this time period. It is recommended (at the final discretion of the Investigator), to complete this procedure as close to the 1 Week Visit (after first eye cataract extraction) as possible. Since second eye assessments will be completed on the same schedule as the first eye assessments (see Appendix A – Table 1), this will allow the subject further convenience in attending as many post-operative bilateral assessment visits as possible.

The Investigator will carry out the second eye surgical procedure as specified in the Surgical Procedure Manual and the following details will be captured in both Source Documents and eCRFs:

- Date of surgery
- Operative eye
- Cohort 1 or Cohort 2
- Incision location and size
- Ophthalmic Viscoelastic Device (OVD) used
- All medication used pre-, intra-, and post-operatively (ophthalmic and systemic)
- Model, serial number, and diopter of HMIOL implant components
- Toric IOL power and axis orientation (for toric IOL)
- IOL injection device

Once the subject is confirmed stable post-surgery, provide post-operative instructions and discharge.

NOTE: All concomitant medication, AE, and SAE collection must be continued throughout the course of the study. Any outcomes resulting in unacceptable RRE (as determined between Investigator and Subject), can be addressed with spectacles, a contact lens, or surgical correction. Any PO surgical adjustments to outcomes (corneal refractive surgery, lens exchange, etc.) will be carried out as determined to be in the best interest of the subject. The course of treatment will follow the Investigators SOC and be collected as a concomitant procedure.

3.3.4 3 MONTH VISIT (DAY 80-100)

Bilateral assessments will be completed as indicated in Appendix A – Tables 1 and 2. In the event the second eye is out of window at this visit, the subject will return in-window to complete second eye assessments.

3.3.5 UNSCHEDULED VISITS

If at any time during the study, outside of the above scheduled visits, the subject requests or the Investigator determines the subject should be assessed, an unscheduled visit may occur. Adverse events and concomitant medications will be recorded and assessments deemed necessary by the Investigator should be performed on either or both eyes.

If a subject is seen for multiple visits during a given visit window, the data from a visit that is intended to meet the protocol requirements for the scheduled visit should be captured in the visit eCRF. Where such a determination cannot be made, the first visit within the scheduled visit window will be used for completion of the protocol required visit. If assessments are missing from that visit, however captured at subsequent visits within window, those assessments can be collected as part of the protocol visit. In such a circumstance, the visit date will remain consistent with the first visit established within the visit window, per the scenario above. Any additional and applicable data captured and associated with the Study Eye will be captured as an Unscheduled Visit.

3.3.6 MISSED VISITS

If a subject misses any scheduled visit and cannot be seen prior to the start of the next visit window, the visit will be considered "missed."

4.0 STUDY METHODS

Prior to recruitment of any subjects into the study, review and written approval of the protocol and informed consent must be obtained from the Institutional Review Board (IRB) or Ethics Committee (EC) by each participating clinical site.

4.1 INFORMED CONSENT

Informed consent must be obtained and documented in writing prior to the initiation of any study procedures. The subject (or the subject's legally authorized representative) must be allowed sufficient time to thoroughly read (or have explained), the informed consent form. The Investigator or his/her designee should answer any questions that the subject/representative might have. If the subject agrees to participate in the study, (i.e. provides informed consent) the subject/representative must sign two copies of the informed consent form. The witness and the Investigator must also sign both copies of the informed consent form. One copy of the informed consent form should be given to the subject/representative. If applicable, it will be provided in a certified translation of the local language. As part of the consenting process, the subjects will be informed of their right to treatment for any injuries related to the study. Any and all such treatment if necessary, will be paid for by the Sponsor to the extent it is not covered by a subject's healthcare coverage (subject to local ethics committee approval). Completion of the consenting process as well as the date of the subject's signature on the informed consent form should be noted in the subject's medical chart.

Subjects who complete the informed consent process will be screened for eligibility. Screened subjects will be recorded on site-specific screening logs and once they are determined as being eligible, they will be enrolled into the study and an HMIOL order placed with the Sponsor if necessary. All eligible subjects will receive a stipend to attend scheduled study visits as an allowance for food, time, and travel expenses.

4.2 ASSIGNMENT OF SUBJECT IDENTIFICATION

A unique and sequential subject identification number (ID) will be assigned at screening and never duplicated for another subject. This ID will be used on all study-related documents. To maintain confidentiality, the subject's name will not be recorded on any study document other than the informed consent form.

4.3 SCREEN FAILURE

A record of screen failures and the reasons for the screen failures will be recorded in the subject source documents and captured in the eCRF for summary.

4.4 SUBJECT COMPLETION

The subject has completed the entire study when the HMTIOL/HMIOL has been implanted and / or the Optic Exchange completed and the Sponsor receives completed electronic Case Report Form (eCRF) documentation for all visits and a Study Exit eCRF. Subjects who require further follow-up for an AE will be followed according to Section 6.3.4.

A Study Exit eCRF must be completed for all subjects who complete the clinical investigation.

4.5 SUBJECT DISCONTINUATION

A subject MUST be discontinued prior to the final study visit for any of the following reasons:

- Death
- Subject is enrolled and scheduled for surgery but is not implanted with an HMTIOL or HMIOL in at least one eye
- Surgical complication(s) unrelated to the investigational device preventing the implantation of the HMTIOL or HMIOL in both eyes (i.e. capsulorhexis tear, zonular rupture, evident zonular weakness or dehiscence, posterior capsular rupture, vitreous loss, posterior capsular plaque, significant detached Descemet's membrane, significant anterior chamber bleeding, iris incarceration or damage, corneal endothelial touch, unsuccessful/incomplete phacoemulsification, haptic and/or optic damage/haptic amputation)
- Explantation of the HMTIOL or HMIOL System in both eyes

If the study lens is explanted, one postoperative visit should be completed to record best-corrected distance visual acuity (BCDVA) before the subject is discontinued.

Subjects who withdraw from the study will be asked to complete procedures outlined in the 3 Month Visit (if withdrawn prior to that visit). Subjects who are terminated due to an AE will be followed, if possible, at least until resolution or stabilization of the AE. Subject withdrawals will be documented clearly on the source document and applicable eCRF.

Prior to discontinuing a subject, every effort should be made to contact the subject, schedule a final study visit, and obtain as much follow-up data as possible. Adverse events will be followed as described in Section 6.3.4. Discontinued subjects should be followed outside of the study protocol according to the Investigator's normal postoperative standard of care.

A Study Exit eCRF must be completed for all subjects who discontinue from the clinical investigation.

4.6 LOST TO FOLLOW-UP

Subjects who miss at least two consecutive visits, as defined by the visit windows and cannot be contacted, may be considered lost to follow-up. All follow-up attempts will be documented and kept with the subject's source documentation, and the applicable eCRFs will be completed.

Subjects that voluntarily withdraw consent after implantation with the HMIOL will be considered Lost to Follow-Up and an Exit Form will be completed.

4.7 STUDY COMPLETION

ClarVista will notify the Investigators when to contact the IRB / EC to announce study completion at the site.

4.7.1 EARLY STUDY TERMINATION

ClarVista has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or any ongoing studies involving the same technology (if applicable), indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Data recording is inaccurate or incomplete.

In the event of premature study termination, appropriate notification will be given to the Investigators, IRB / ECs, and regulatory bodies as applicable. In addition, ClarVista (or designee) will instruct all Investigators to discontinue dispensing study materials or treatments, will ensure all subjects complete appropriate follow-up, and will arrange study closeout visits at each site as appropriate.

4.8 CONCOMITANT THERAPIES

4.8.1 CONCOMITANT MEDICATION

Concomitant medications are any prescription drugs used by a subject until conclusion of study participation. Any medication the Investigator deems in the best interest of the subject, is acceptable to prescribe or administer. However, any and all are to be recorded in both the Concomitant Medication source document and eCRF as well as the reason for use (indication). An AE is to be reported and/or recorded as appropriate (see Section 6.0).

4.8.2 CONCOMITANT PROCEDURES

A concomitant procedure is any invasive or non-invasive ocular or peri-ocular procedure that takes place during study participation and will be captured in both the Concomitant Procedure Source Document and eCRF. The following are examples of two such procedures:

- Any PO surgical adjustments (i.e. corneal refractive surgery, lens exchange, etc.)
- Neodymium: Yttrium-aluminum-garnet (Nd:YAG) procedure to treat Posterior Capsule Opacification (PCO), if necessary. This will be listed as "Nd:YAG Capsulotomy."

Note: *Any Nd:YAG capsulotomy procedures prior to exit will be performed only in response to spontaneous subject complaints (i.e. not solicited by study personnel) of reduced Visual Acuity (VA) or glare that affects functional vision, which is associated with PCO or striae, and captured on the eCRF in SLE findings.*

An AE is to be reported and/or recorded as appropriate (see Section 6.0). Any procedure reported in the Concomitant Procedure eCRF must have a corresponding Indication listed in either the Ocular History or AE eCRF *(Only exception: PCO – See Section 6.1 for further details).*

4.9 PROTOCOL DEVIATIONS

All protocol deviations, the date of deviation, and reason will be documented in the Source Document and eCRF. All deviations will be categorized as either major or minor in the following manner:

Major:

- Deviations impacting subject safety (e.g. eligibility, etc)
- Deviations impacting subject rights (e.g. consent, etc)
- Deviations impacting data integrity (e.g. instrumentation, masking, etc)

Minor:

- All other deviations (e.g. out of window visits, missed data point, etc.)

All major deviations must be reported by the Investigator to the Sponsor and IRB/EC immediately. Subject assessments will continue per protocol for the duration of planned participation unless the deviations put the subject at risk or the subject's condition requires that he/she be discontinued from the study.

5.0 STUDY MATERIALS

5.1 DESCRIPTION OF TEST ARTICLE

The HARMONI™ Modular Intraocular Lens (HMIOL) System is device designed to allow safe exchange or adjustment of an IOL optic after implantation. [redacted]

[redacted]

[redacted]

5.1.1 INSTRUCTIONS FOR USE

Refer to the Surgical Guide for all use and administration details.

5.2 PACKAGING AND LABELING

All packaging and labeling will be consistent with the current study design. The labeling will include at a minimum, the following:

- Sponsor name and address
- "For Single Use Only" statement (or equivalent symbol)
- Sterility symbol
- Storage temperature range requirements or equivalent (e.g. "Store at room temperature.")
- Expiration date
- Power designation
- Unique serial number
- Model number

5.3 ACCOUNTABILITY

The Investigator is responsible for keeping accurate accountability records of the number of study lenses received, dispensed, and returned to Sponsor. The study lenses must be stored under the appropriate conditions in a secure area and are to be implanted only in subjects enrolled in the study, in accordance with the conditions specified in this protocol.

All accountability records will include the following:

- Model and serial numbers
- Receipt date
- Quantities received
- Initials (attributability) of site personnel who received, dispensed, or returned study lenses
- Date of use
- Subject and eye treated with the study lens (by Subject ID and Initials only)
- Date returned to Sponsor
- Defective or damaged study devices

Periodically throughout the study and/or upon completion, the Sponsor (or designee) will review and verify the Investigator's accountability records. Following verification, and as directed by the Sponsor, all unused and explanted products must be returned to the Sponsor.

Note: *In addition, any study lenses or components deemed defective, damaged, malfunctioning, or explanted must be retained by the site and returned to the Sponsor for evaluation. Under no circumstances are any components to be discarded or otherwise disposed of. If there is any question as to the applicability of this directive, consult the Protocol Contacts page of this protocol and discuss the situation with a Sponsor representative.*

5.4 OTHER MATERIALS

Additional materials can be provided to sites for the duration of the study on an as-needed basis and may include:

- ETDRS light box, glare source, and charts to perform the standardized VA assessments described in the Manual of Procedures
- Medicel injectors (for study lens injection only)
- IOL micro-incision cutter and forceps
- Konan Specular Microscope
- Slit lamp camera

6.0 ADVERSE EVENTS

Safety assessments include adverse events/serious adverse events, and adverse device events. The reporting time period is from the time of consent through the last study visit (3 Month Visit post cataract extraction).

6.1 DEFINITIONS

6.1.1 ADVERSE EVENT (AE)

An AE is any untoward medical event in a subject that does not necessarily have a causal relationship to the study device or protocol. AEs include Adverse Device Effects (ADEs). Conditions or diseases that are pre-existing and/or chronic but stable should not be recorded on AE pages of the eCRF. Similarly, changes in a pre-existing and/or chronic condition of disease that are consistent with natural disease progression are NOT adverse events and also should not be recorded on the AE pages of the eCRF.

Refer to Section 6.3.1 for instructions regarding events that require expedited reporting to the Sponsor and IRB/EC.

Experience with cataract surgery and the implantation of IOLs has shown that some conditions can be considered normal or expected events following these procedures. The following may be considered normal or expected events after cataract surgery and only need to be reported as AEs as specified here:

- Iritis (cell / flare) – if treated
- Persistent Corneal Stroma Edema (if present at 1 Month)
- Increased IOP only if medical/surgical intervention is required (i.e. medication, paracentesis manipulation)
- VA decrease of 10 or more letters (2 lines) from any previous visit not secondary to any underlying condition
- Any expected post-operative ocular event requiring a change in standard postoperative medication regimen

Note: *PCO is not to be reported as an AE, as per ISO 11979-7:2014.*

Particular attention should be paid to ensure timely and accurate reporting of any of the following cataract surgery related events:

- Endophthalmitis
- Capsular injury
- Vitreous loss
- Macular edema
- Retinal detachment
- Lens dislocation
- Moderate to severe corneal edema
- Pupillary block / angle closure
- Hypopyon or hyphema

6.1.2 ADVERSE DEVICE EFFECT (ADE)

An ADE is any untoward or unintended effect, event, or response surrounding and with a causal relationship with the use of a medical device. This definition may include any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device or other device malfunctions. This definition includes any event that is a result of a user error and any event that affects a user of the device (i.e. caregiver, bystander, etc).

6.1.3 UNANTICIPATED ADVERSE DEVICE EFFECT (UADE)

A UADE is any ADE, which is unanticipated and poses a risk to 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 (see Investigator Brochure [IB]). UADEs also include any unanticipated sight-threatening events and any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

6.1.4 DEVICE DEFICIENCIES (DD)

A Device Deficiency (DD) is a failure of the device to meet its performance specifications or expectations, or otherwise not perform as intended. This can include either a malfunction or damage to the device or any part thereof, regardless of the source of malfunction or damage, including user error, and regardless of the presence of injury (or lack thereof) to subject, user, or bystander.

6.2 AE EVALUATION

AEs experienced in this study may be associated with the study device (i.e. ADE) or the study protocol as demonstrated in the following non-exhaustive list of examples:

<u>Study Device (ADE)</u>

- IOL dislocation
- Explant due to haptic break/damage
- Explant due to base and/or optic damage

- Allergic reaction to dilating drops
- Lens remnants following surgery
- Capsular tear during surgery to implant study device

6.2.1 EVALUATION

All AEs will be evaluated for and by the following criteria:

- Classification (SAE, AE, ADE or combination)
- Diagnosis (or description if ADE)
- Severity
- Relationship (Causality) to study protocol or device
- Outcome
- Treatment or action taken

6.2.1.1 CLASSIFICATION

When evaluating AEs, the Investigator must determine if the event is serious using the following guidelines:

A **Serious Adverse Event (SAE)** is any AE (ocular or non-ocular) that:

- results in death
- results in serious injury, defined as:
  - life-threatening
  - permanent impairment of a body function (e.g. blindness) or structure
  - necessitates medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure, or
  - results in a potentially sight-threatening condition
- is a malfunction that might cause or contribute to a serious injury or death if it were to recur
- requires in-patient hospitalization or prolongation of existing hospitalization*, or
- leads to fetal distress, fetal health, a congenital abnormality, or birth defect

*Hospitalization is a criterion for assessment of seriousness. Hospitalization in the absence of a medical AE is not in itself an AE. For example, the following reports of hospitalization without a medical AE should not be considered either serious or an AE:

- admission for treatment of a pre-existing condition not associated with the development of a new AE or with worsening of the pre-existing condition (e.g. for work-up of persistent pretreatment lab abnormality)
- social admission (e.g. subject has no place to sleep)
- administrative admission (e.g. for yearly physical exam)
- optional admission not associated with a worsening of a pre-existing condition (e.g. elective cosmetic surgery or elective surgery for pre-existing repair of the Achilles tendon [which had not worsened while on study])

- hospitalization for admission without a medical AE

NOTE: For the purposes of this protocol, any UADE will be considered an SAE.

6.2.1.2 DIAGNOSIS OR DESCRIPTION

In all instances, it is preferable to report all AEs and SAEs by diagnosis rather than a sign or symptom if possible. This may necessitate the revision of a previously reported AE or SAE as more information is obtained.

6.2.1.3 SEVERITY

When evaluating AEs, the Investigator must determine the severity of symptoms using the following guidelines:

- Mild: Subject awareness of a sign or symptom that is easily tolerated, requires no treatment, and does not interfere with the subject's daily activities
- Moderate: Subject awareness of a sign or symptom which may be a low level of concern to the subject and may interfere with daily activities, but can be relieved by simple therapeutic care
- Severe: A sign or symptom that interrupts the subject's daily activity and requires systemic therapy or other treatment

6.2.1.4 RELATIONSHIP (CAUSALITY) TO STUDY DEVICE OR STUDY PROTOCOL

When evaluating AEs, the Investigator must evaluate the relationship of the event to the study device and study protocol, using the following guidelines:

- Not Related: AEs which are clearly and incontrovertibly due to causes other than the study device or study protocol (e.g. concomitant disease, etc)
- Related: AEs which are felt with a reasonable degree of certainty to be related to the study device or study protocol
- Unknown: Adverse events for which a connection with the study device or study protocol cannot be ruled-out with certainty, or not enough information is available to assess the relationship

6.2.1.5 OUTCOME

The clinical outcome of an AE will be categorized as follows:

- Resolved without sequellae
- Resolved with sequellae (specify)
- Ongoing (i.e. continuing at time of study discontinuation)
- Death

6.2.1.6 TREATMENT OR ACTION TAKEN

Treatment or Action Taken will be categorized as follows:

- None

- Medical Intervention (specify on Concomitant Medication Source and eCRF)
- Surgical Intervention (specify on Concomitant Procedure Source and eCRF)
- Other (specify)

6.3 REPORTING

6.3.1 ON-SITE EXPEDITED REPORTING

The Investigator is obligated to report the following to the Sponsor within 24 hours of becoming aware of the event to ensure the safety of all participants in the study and to meet regulatory reporting requirements:

- All SAEs, regardless of relationship to study device or study protocol utilizing the SAE/ADE Report Form
- All AEs determined to be related to the study device (ADEs or UADEs) utilizing the SAE/ADE Report Form
- All HMIOL explants (consult Medical Monitor listed on Protocol Contacts page prior to explant, if possible)
- All Device Deficiencies (DD) utilizing the DD Report Form

Refer to the Protocol Contacts page for appropriate Sponsor contact to report the above events.

NOTE: Any explanted HMIOL devices, exchanged HMIOL optics, or any components of the HMIOL System presenting a deficiency or malfunction are to be retained by the site until collected by the Sponsor. Under no circumstances are they to be destroyed or otherwise discarded.

When reporting these events to the Sponsor, the site should forward any supporting documents along with the appropriate reporting form and complete the corresponding eCRF, if applicable. Sites must also report applicable events to the reviewing IRB/EC per its established reporting procedures.

6.3.2 OFF-SITE SAE REPORTING

As a multicenter clinical trial, the Investigators may receive "off-site" reports (e.g. an SAE Report). These are Sponsor reports of SAEs which occurred at other sites for the same trial, or in different trials using the same test article, that met the criteria for reporting. These should be reported to the reviewing IRB per their established reporting procedures.

6.3.3 REPORTING OF COMPLAINTS FOR ANCILLARY MARKETED PRODUCTS

Any complaints, malfunctions or similar events related to ancillary marketed products used in this study should be reported by the Investigators in accordance with the reference information provided on the associated commercial packaging.

6.3.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS AT SUBJECT EXIT

Ongoing SAEs and ADEs will be followed until resolution or no further change in the condition is expected. Non-serious AEs that are ongoing at study exit visit or upon discontinuation from the study will be followed per the Investigator's standard of care. Documentation in the eCRF of this follow-up is not required although subject care should continue as appropriate.

6.4 SAFETY MONITORING AND REVIEW

All reported AEs will be reviewed on a weekly basis and assessed for trending and causality to study device or procedure. ADEs, UADEs, DDs, and SAEs will be reviewed upon receipt of expedited reporting (Section 6.3.1). Any unexpected trends or events will necessitate careful review and assessment of any change in the risks associated with participation or study continuation.

If an event occurs affecting a subject's risk of participation, Off-Site Reporting (Section 6.3.2) will be utilized to update sites and the IRB(s) / EC(s). If the safety profile of the event provides for the continuation of the study, Informed Consent Forms will be revised as necessary to ensure subjects' consent to continue participation given the known revised risks.

As outlined in Section 4.7.1, the Sponsor reserves the right to discontinue enrollment at any time.

7.0 CLINICAL ENDPOINTS

7.1 SAFETY ENDPOINTS

Safety will be evaluated by assessing the following:

- Percent change in ECC at the 3 Month Visit compared to Preoperative Visit
- Preservation of BCDVA
- SSI
- AE rates as compared to ISO 11979-7:2014 Annex B SPE tables
- Device deficiencies

7.2 EFFECTIVENESS ENDPOINTS

- 1 and 3 months MRCYL for eyes implanted with HMTIOL
- 1 and 3 months MRCYL prediction error for eyes implanted with HMTIOL
- 1 and 3 months MRCYL prediction error for eyes implanted with HMTIOL per vector analyses
- 1 and 3 months SEQ prediction error
- UCDVA by study visit
    - Percent of eyes that achieve
        - 20/20 or better
        - 20/25 or better
        - 20/32 or better
        - 20/40 or better
        - Worse than 20/40
- BCDVA by study visit
    - Percent of eyes that achieve
        - 20/20 or better
        - 20/25 or better
        - 20/32 or better
        - 20/40 or better
        - Worse than 20/40

- Rotational of IOL meridian at 1 day, 1 week, 1 and 3 months
  - Percent of eyes with rotation < 10°
  - Percent of eyes with rotation < 20°
  - Percent of eyes with rotation < 30°
- Reduction in cylinder power of the eye implanted with HMTIOL (absolute preoperative magnitude of corneal cylinder (K) minus the absolute postoperative magnitude of MRCYL at the corneal plane)
- Percentage reduction in cylindrical power of the eye implanted with HMTIOL (absolute preoperative magnitude of corneal cylinder (K) minus the absolute postoperative magnitude of MRCYL at the corneal plane, expressed as a percentage of the absolute preoperative magnitude of total corneal cylinder (K)).

8.0 STATISTICAL METHODS

This is a feasibility study to evaluate the safety and effectiveness of HTMIOL in subjects with primary cataract surgery and subjects with HTMIOL intra-operative optic exchange. In general, the analyses will be provided based on available data. The mean, standard deviation, minimum, and maximum will be prepared for the continuous clinical parameters, and counts and percentages will be presented for the categorical outcomes.

[redacted]

[redacted]

This is a feasibility study and no adjustment will be performed for the multiplicity.

8.2 ANALYSES POPULATIONS

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

8.2.1 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.

8.2.2 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, intraoperative pressure (IOP), and dilated fundus examination (DFE) will be based on the implanted-eye population. It should be noted that the ECL 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 ECL at 3 months.

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

8.2.3 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 determined reviewed by ClarVista clinical personnel prior to analysis.

8.2.4 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 purpose of the Best Case population is to evaluate BCDVA as described in ISO 11979-7:2014.

8.3 STATISTICAL METHODS

The data analyses will be based on the analysis populations described above. No imputation for missing data will be performed. The demographic data will be summarized based on study subjects, while eye-related outcomes will be prepared for Cohort 1 and Cohort 2. The eye-related data may also be separated for the [redacted]

For continuous outcomes, mean, standard deviation, median, minimum, and maximum will be provided. For categorical outcomes, the counts and percentages of eyes with each categorical level of outcomes will be summarized.

8.3.1 SAFETY OUTCOMES

8.3.1.1 ADVERSE EVENTS AND DEVICE DEFICIENCIES

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. [redacted]

[redacted]

8.3.1.2 ECC

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

[redacted]

[redacted]

[redacted]

8.3.2 EFFECTIVENESS OUTCOMES

The effectiveness outcomes will be analyzed based on the Implanted-eye Population and PP Population. The BCDVA will also be summarized based on the Best-case population as suggested by ISO. The analyses for other effectiveness outcomes are exploratory in nature.

8.3.2.1 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 for Cohort 1 and Cohort 2 separately.

[redacted]

8.3.2.2 UCDVA

[redacted] 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 pre-operative and every postoperative visits.

8.3.2.3 PREDICTION ERROR (PE)

The MRSE prediction error will be calculated for each treated eye as follows:

MRSE PE = Postoperative MRSE adjusted to 6 meters at 3 months – MRSE TRRE (target residual refractive error)

The MRCYL prediction error will be calculated for eyes implanted with HMTIOL as follows:

MRCYL PE = Postoperative MRCYL adjusted to 6 meters at 3 months – MRCYL TRRE (target residual refractive error)

[redacted]

[redacted]

8.3.2.4 ROTATION OF IOL MERIDIAN

The rotation of IOL meridian will be calculated for each eye from Day 0 to every postoperative visit. The descriptive statistics for continuous variables will be used to summarize the rotation angle at each visit for Cohort 1 and Cohort 2 separately. Additionally, the number and percentage of eyes with rotation < 10°, < 20°, and < 30° will be calculated at each visit for Cohort 1 and Cohort 2 separately. [redacted]

8.3.2.5 REDUCTION IN CYLINDER POWER

This endpoint is for eyes implanted with HMTIOL.

The reduction in cylinder power will be calculated for each eye 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.

The descriptive statistics for continuous variables will be used to summarize these outcomes at each visit for Cohort 1 and HMTIOL in Cohort 2 separately. [redacted]

9.0 DATA MANAGEMENT

9.1 DATA QUALITY ASSURANCE

All requested information must be entered on the eCRF and confirmable through source documentation. If an item is not available or not applicable, this fact should be clearly indicated.

Data will be entered into a computer database developed specifically for this trial. During the course of the trial, data queries will be generated for data points that are potentially erroneous and require appropriate clarification or correction.

9.1.1 DATA MONITORING

Periodic monitoring (either remote and/or on-site) will take place to ensure data integrity. Study monitoring involves the following elements:

ClarVista personnel, or designee, may meet with investigators prior to the initiation of the study in order to review the adequacy of the subject population, facilities, and equipment with respect to the needs of the study, and to familiarize the investigator and support staff with the study protocol.

ClarVista personnel, or designee, may meet with the investigators at the time enrollment is initiated in order to ensure that subjects are being properly selected, that the methods described in the study protocol are thoroughly understood by the investigator, and that study data are being correctly recorded.

ClarVista personnel, or designee, may visit the clinical site at any time during the course of the study to review and/or collect completed case report forms. Additionally, telephone consultation will occur as necessary during the course of the study to ensure the proper progress and documentation of the study findings.

The study data will be carefully protected, and masking utilized to the extent possible, in order to prevent bias.

9.2 RECORD RETENTION

The investigator shall maintain all subject records for whichever of the following periods is shorter:

- A period of two years after the date on which FDA approves the marketing of the device
- A period of five years after the date on which the results of the study are submitted to the FDA in support of the marketing of the device

OR

- A period equal to the minimum required by the regional authority.

The Investigator / Site must contact ClarVista as provided in the Protocol Contacts page prior to discarding or disposing of any study related supplies or documents. The Sponsor retains the right to have all study documents shipped (at Sponsor's expense) for archival purposes, as an alternative to disposal.

10.0 REFERENCES

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APPENDIX A – TABLE 1: SCHEDULE OF ASSESSMENTS – COHORTS 1 & 2

	Pre-Op Visit[1]	Op Visit		Form 3	Form 4	Form 5	Form 6
		Cohort 1	Cohort 2				
Procedure/Assessment	Day -90 to -0	Day 0 (or +3-30 Days from the first surgery)	Day 0 (or +3-30 Days from the first surgery)	1 Day Visit (Day 1-2 from Day 0 of the eye)	1 Wk Visit (Day 7-14 from Day 0 of the eye)	1 Mo Visit (Day 30-60 from Day 0 of the eye)	3 Mo Visit (Day 80-100 from Day 0 of the eye)
Informed Consent	X						
Demographics	X						
Med/Ophthalmic History	X	X	X				
Eligibility[2]	X	X	X				
UCDVA[3]	X			X	X	X	X
Manifest Refraction	X					X	X
BCDVA	X					X	X
Keratometry[4]	X					X	X
Axial Length	X						
Anterior Chamber Depth	X						
IOL/Toric Power Calculation[5]	X						
Slit Lamp Examination	X			X	X	X	X
Specular Microscopy	X						X
IOP	X			X	X	X	X
Pupil Size	X	X	X				
Surgery / IOL implantation		X	X				
Intraoperative Exchange			X				
[redacted]				X	X	X	X
IOL Rotational Stability[7]		X	X	X	X	X	X
Dilated Fundus Exam	X						X

[1] All testing to be conducted on both eyes
[2] Will include pregnancy test if applicable
[3] If UCDVA is < 20/40, perform Pinhole (PH) vision
[4] Measurements via biometry will be utilized for both calculations and data capture
[5] To be reviewed and approved by the Sponsor
[redacted]
[7] Dilated slit lamp photo submitted to IOL Stability Reading Center

[redacted]
