Short Title

ClarVista CP-00004

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

1 TITLE PAGE

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

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-00004 REV.01**
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Th s c n ca nvest gat on s be ng conducted n accordance w th 21 CFR Parts 11, 50, 54, 56, and 812, SO 14155 (2011) C n ca nvest gat on of Med ca Dev ces for Human Sub ects, SO 11979 7:2014 Ophtha m c mp ants — ntraocu ar enses — Part 7, : C n ca nvest gat ons (where app cab e), ANS Z80 7 2013 Ophtha m c Opt cs – ntraocu ar Lenses (where app cab e), CH GCPs, and app cab e oca regu at ons

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PROTOCOL APPROVAL

A Prospect ve, Mu t -Center Study to Eva uate the Safety and Performance of the C arV sta HARMONI® Modu ar Tor c Intraocu ar Lens System for the Treatment of Pre-Ex st ng Cornea Ast gmat sm and Aphak a Fo ow ng Cataract Surgery

The fo ow ng nd v dua s approve Protoco #CP-00004 Rev.01 dated 6 June 2016. Any changes to th s vers on of the protoco must have an amendment or adm n strat ve etter.

C arV sta Approva s:

[redacted]

STUDY ACKNOWLEDGEMENT

I understand th s protoco conta ns nformat on that s conf dent a and propr etary to C arV sta Med ca (C arV sta).

I have read th s protoco and agree that t conta ns a the deta s necessary to conduct the study as descr bed. I w fo ow th s protoco n the conduct of the study and w make a reasonab e effort to comp ete the study n the t me noted.

I w prov de the contents of th s protoco to study staff under my d rect superv s on n order to conduct the study. I w d scuss th s nformat on w th the study staff to ensure they are fu y nformed about the study and the test art c e. I w prov de the contents of the protoco to the respons b e Eth cs Comm ttee. These d sc osures may be made; prov d ng the contents are not used n any other c n ca study and they are not d sc osed to any other person or ent ty w thout pr or wr tten consent from C arV sta. Th s cond t on does not app y to d sc osure requ red by government regu at ons or aws; however, I agree to g ve prompt not ce to C arV sta of any such d sc osure.

I understand the study may be term nated or enro ment suspended at any t me by C arV sta, w th or w thout cause, or by me f t becomes necessary to protect the nterests of the study subjects.

Any add t ona nformat on added to th s protoco s a so conf dent a and propr etary to C arV sta and must be treated n the same manner as the contents of th s protoco .

_____
Pr nted Name of Pr nc pa Invest gator

_____ _____
Invest gator S gnature Date

Protoco # CP-00004 Rev.01
Date: 06 June 2016

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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
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
HIPAA	Health Insurance Portability and Accountability Act
HMTIOL	HARMONI™ Modular Toric Intraocular Lens System
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	Identification
IDE	Investigational Device Exemption
OA	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
MRCYL	Manifest Refraction Cylinder
MRSE	Manifest Refraction Spherical Equivalent
Nd:YAG	Neodymium:Yttrium-aluminum-garnet
ND	Not Done
OD	Right Eye
OS	Left Eye

OVD	Ophtha m c V scoe ast c Dev ce
PCO	Poster or Capsu e Opac f cat on
PE	Pred ct on Error
PH	P nho e
PMA	Premarket Approva
PP	Per Protoco
PRK	Photorefract ve Keratectomy
RRE	Res dua Refract ve Error
SAE	Ser ous Adverse Event
SIA	Surg ca y Induced Ast gmat sm
SLE	S t Lamp Exam nat on
SOC	Standard of Care
SPK	Superf c a Punctate Kerat t s
SSI	Secondary Surg ca Intervent on
TRRE	Target Res dua Refract ve Error
UCDVA	Uncorrected D stance V sua Acu ty
US	Un ted States
VA	V sua Acu ty

NOTE: The f rst occurrence of some abbrev at ons are not spe ed out n the document (e g un ts of measure)

PROTOCOL SYNOPSIS

Protocol Number #CP-00004 Rev.01	
Title	A Prospect ve, Mu t -Center Study to Eva uate the Safety and Performance of the C arV sta HARMONI® Modu ar Tor c Intraocu ar Lens System For The Treatment Of Pre-Ex st ng Cornea Ast gmat sm and Aphak a Fo ow ng Cataract Surgery
Regulatory Status	Phase 4 n CE countr es US - Pre-IDE
Investigational Device	C arV sta HARMON Modu ar Tor c ntraocu ar Lens System (HMT OL)
Objectives	A study to eva uate the safety and performance of the HMTIOL n pat ents w th pre-ex st ng cornea ast gmat sm. Spec f ca y, • To ref ne the A-constant (ens constant) of the HMTIOL. • To eva uate the refract ve outcomes nc ud ng ast gmat sm correct on w th HMTIOL n pr mary cataract surgery. • To eva uate ax a and rotat ona stab ty of the HMTIOL
Number of Clinical Sites and Study Subjects	Up to 200 enro ed and mp anted eyes from up to 10 nvest gat ona s tes. Approx mate y 20 eyes, a max mum of 30, w be enro ed from each nvest gator/surgeon. Enro ment w be mon tored as out ned n Samp e S ze sect on and adjusted accord ng y.
Study Duration	A subjects w part c pate n the study for up to 6 months (3 months pre-op w ndow p us 3 months fo ow up per od). Tota study durat on w be approx mate y 9 months.
Study Design	Prospect ve, mu t -center c n ca study. A subjects w be seen for a Preoperat ve V s t to capture base ne measurements. One or both eyes of each subject w undergo cataract surgery and be mp anted w th the HMTIOL. Eyes w th cornea ast gmat sm wh ch s w th n the d optr c range of the tor c IOL (1.50, 2.25 and 3.00D at the IOL p ane after adjust ng for Surg ca y Induced Ast gmat sm) may be mp anted w th the study dev ce. Fo ow up:

	• 1 Day, 1 Week, 1 Month, and 3 Months fo ow ng cataract extract on.  **FIGURE 1 - COHORT SCHEDULE**
Study Outcomes	The safety and performance of HMTIOL for the treatment of pre-ex st ng cornea ast gmat sm and aphak a n subjects fo ow ng cataract extract on w be character zed. *Performance Outcomes:* 1. Post op MRCYL for eye mp anted w th HMTIOL 2. Post op MRCYL pred ct on error for eye mp anted w th HMTIOL 3. Post op SEQ Pred ct on Error 4. UCDVA by study v s t 5. BCDVA by study v s t 6. IOL mer d an m sa gnment on the day of surgery 7. Rotat on of IOL mer d an from the day of surgery to 3 months, and between a adjacent v s ts a. Mer d an rotat on ≤ 5 b. Mer d an rotat on < 10 c. Mer d an rotat on < 20 d. Mer d an rotat on < 30 e. Abso ute va ue of rotat on f. S gned va ue of the rotat on 8. Reduct on n cy nder power of eye mp anted w th HMTIOL (n D opters) a. Abso ute preop magn tude of K (or tota cornea cy nder) m nus the abso ute post op magn tude of MRCYL at the cornea p ane 9. Percentage reduct on n cy ndr ca power of eye mp anted w th HMTIOL a. Abso ute preop magn tude of K (or tota cornea cy nder) m nus the abso ute post op magn tude of MRCYL at the cornea p ane expressed as a percentage of the abso ute preop magn tude of K (or tota cornea cy nder) *Safety Outcomes:* 1. Preservat on of BCDVA

	2. Rate of device-related Secondary Surgical Intervention's (SSI's) other than optic exchange or rotation adjustment of the HMTIOL 3. Device deficiency 4. AEs rates [redacted]
[redacted]	[redacted]
Inclusion Exclusion Criteria ***both eyes do not need to be eligible**	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 months study duration 3. Planned removal of visually significant cataract (cortical, nuclear, posterior subcapsular, or a combination) by manual phacoemulsification cataract extraction 4. Pre-existing corneal astigmatism in the study eye. Magnitude of astigmatism within the range of available toric power 1.50, 2.25 and 3.00D at the IOL plane, after adjusting for Surgically Induced Astigmatism. 5. Targeted optical cylinder 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 ***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 eva uat ons at east 1 week apart resu t ng n ≤0.50D MRSE d fference n the two refract ons) and Keratometry read ngs (as ev denced by two K read ngs at east 1 week apart resu t ng n ≤0.50D d fference between the two read ngs) pr or to f na IOL ca cu at ons. S m ar y, any subjects who current y wear soft contact enses must a so comp ete the consent ng process, d scont nue wear for a m n mum of 1 week and return for repeat e g b ty test ng exh b t stab e MR and K read ngs. In add t on, a qua fy ng subjects must d scont nue contact ens wear n the study eye for the durat on of study part c pat on. 7. BCVA projected to be 0.2 LogMAR or ower (as determ ned by the med ca judgment of the Invest gator or measured by potent a acu ty meter / ret na acu ty meter (PAM / RAM) f necessary) 8. V sua symptoms re ated to cataract 9. Stab ty of the cornea has been demonstrated by keratometry 10. D ated pup s ze at east 7.0mm 11. Must be ab e to understand and prov de nformed consent themse ves or through a representat ve w th a w tness present on the IRB or EC approved Informed Consent Form (ICF) <u>Exc us on cr ter a</u> 1. H story of any ntraocu ar or cornea surgery n study eye (nc ud ng refract ve) 2. Any type of cataract (e.g. traumat c, congen ta , po ar) other than those noted n nc us on cr ter a 3. Pregnancy or actat on 4. Part c pat on n any other drug or dev ce c n ca tr a w th n 30 days pr or to enro ng n th s study and/or dur ng study part c pat on 5. Prev ous cornea based surgery (LASIK, PRK, LRI, etc.) 6. H story of any c n ca y s gn f cant ret na patho ogy or ocu ar d agnos s (e.g. d abet c ret nopathy, schem c d seases, macu ar degenerat on, ret na detachment, amb yop a, opt c neuropathy, etc.) n study eye that cou d a ter or m t f na postoperat ve v sua prognos s 7. H story of any ocu ar cond t ons wh ch cou d affect the stab ty of the IOL (e.g. pseudoexfo at on, zonu ar d a ys s, ev dent zonu ar weakness or deh scence, etc.) n study eye 8. Any anter or segment patho ogy ke y to ncrease the r sk of comp cat ons from phacoemu s f cat on cataract extract on (e.g. chron c uve t s, r t s, r docyc t s, an r d a, rubeos s r d s, c n ca y s gn f cant cornea , Fuch's, or anter or membrane dystroph es, etc.) n study eye

	9. Any visually significant intraocular media opacity other than cataract in study eye (as determined by the investigator) 10. Uncontrolled glaucoma in study eye (per Investigator judgement) 11. Subjects with large refractive errors (hyperopia/myopia) of axial or pathological origin that, in the opinion of the investigator, could confound outcomes 12. Uncontrolled systemic disease (e.g. diabetes mellitus, active cancer treatment, mentalness, 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 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 parasympathomimetic agents, alpha adrenergic blocking agents with similar side effects (e.g. small pupil/floppy iris syndrome) <u>Discontinuation Criteria during Surgery</u> 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 misoprevented 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
Planned Analyses	All eyes with attempted study lens implantation will be included in the safety analyses. The performance outcomes will be summarized based on eyes implanted with HMTIOL. All data summaries will be performed based on observed data; no imputation for missing clinical outcomes will not be performed. [redacted] For continuous variables, mean, standard deviation, median, minimum, and maximum will be provided.

	For categor ca outcomes, the counts and percentages of eyes w th each categor ca eve of outcome w be summar zed. The cumu at ve and pers stent adverse events w be summar zed at 3 months [redacted] For BCDVA and UCDVA, the number and percentages of eyes w th v sua acu ty of 20/20 or better 20/25 or better, 20/32 or better, 20/40 or better, and worse than 20/40 at each v s t w be summar zed. The MRSE pred ct on error w be ca cu ated for each eye (Sect on 8) and summar zed us ng stat st cs for cont nuous var ab es. The MRCYL pred ct on error (per cy nder power and vector ana ys s) w be der ved for eye w th HMTIOL and summar zed us ng stat st cs for cont nuous var ab es. [redacted] The reduct on n MRCYL (abso ute power) and the percent reduct on n cy nder power w be der ved for each eyes mp anted w th HMTIOL. Reduct ons w be summar zed us ng stat st cs for cont nuous var ab es. Add t ona vector ana yses on MRCYL may be prov ded. IOL rotat on w be der ved for each eye from Day 0 (surgery) to postoperat ve v s ts. The stat st cs for cont nuous var ab es w be prov ded. The number and percentage of eyes w th rotat on of ≤ 5 , < 10 , < 20 , and < 30 w be ca cu ated.

1.0 INTRODUCTION

Cataract surgery is a minimally invasive procedure designed to restore vision with short recovery time. Advances in instrumentation and technique over the past few decades have facilitated the enhancement in safety[1] while leaving room for reproducible outcomes. While the serious adverse event rate remains low, selecting the right intraocular lens (IOL) implant for spectacle independence remains an ongoing challenge. This is referred to as residual refractive error (RRE) and typically involves approximately 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 unaided vision[2].
2. Up to 55% of patients falling outside of the targeted postoperative refraction by at least 0.5D[3,4,5].
3. Between 14 and 24% of surgeries resulting 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, cornea modification (surgery or other), IOL exchange/manipulation, or supplacement 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 wearing 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 cornea 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 cornea refractive surgery, the FDA has not specifically evaluated the safety and effectiveness of cornea 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 cornea refractive procedures, how likely cornea refractive procedures are to induce irregular astigmatism and worsen dry eye that is induced by cataract surgery, and whether cornea refractive procedures could create potential complications related to cataract surgery wound healing or IOL stability.

Furthermore, cornea based intervent ons do not address the root cause of RRE after cataract extract on (mprec se IOL power se ect on) and expose the pat ent to a new and ndependent set of poss b e adverse events. Thus, t wou d be des rab e to be ab e to correct or mod fy the opt ca resu t w thout the need to rrevers b y and unpred ctab y a ter cornea t ssue fo ow ng cataract extract on.

Sulcus placement of a "piggyback" IOL s a procedure that has not been eva uated for safety and effect veness by the FDA so the use of approved IOLs for th s purpose n the U.S. s off- abe . Among the comp cat ons reported w th th s procedure are secondary p gment d spers on, r s/pup rregu ar t es, chron c r t s, hyphema, g aucoma, zonu ar d srupt on and/or poster or capsu ar rupture. Thus, t wou d be des rab e to be ab e to correct or mod fy the opt ca resu t w thout the need to mp ant a "p ggyback" IOL w th ts nherent ser ous r sks.

IOL Exchange/Manipulation n genera , s techn ca y cha eng ng for the surgeon and poses an atrogen c r sk to ntraocu ar structures nc ud ng the ens capsu e, r s, and endothe um of the cornea. The capsu ar bag f broses weeks after IOL mp antat on creat ng a strong adhes on between the capsu e and the IOL. Man pu at on of the capsu ar bag to remove an IOL s the major r sk n th s sett ng and can damage the capsu ar bag nc ud ng poster or capsu ar rupture and capsu ar bag d s ocat on. The capsu ar bag cannot be repa red once damaged. Th s r sk ncreases over t me as the capsu ar bag adheres to the IOL and hapt cs. Even when IOL exchange s not requ red, man pu at on of trad t ona IOL's to rotate or center the opt c ntroduces the r sk of capsu ar or zonu ar damage wh ch can cause further ens nstab ty and ens ma pos t on. Thus, t wou d be des rab e to be ab e to correct RRE w thout the need to remove the ent re IOL part cu ar y after capsu ar contract on or f bros s.

The C arV sta Harmon ™ Modu ar IOL System s a CE-approved dev ce des gned for safe and easy post-operat ve adjustment of res dua refract ve error (RRE). The modu ar IOL concept w serve as a va uab e add t on to the armamentar um of cataract surgeons. The goa of th s techno ogy s to mprove refract ve (spher c and tor c) outcomes and avo d the s gn f cant r sks of secondary procedures current y be ng performed as standard pract ce to address RRE n an nd rect manner. It s ant c pated that th s modu ar ens w prov de c n ca ut ty n two bas c areas, the f rst be ng the focus of th s study.

1. Post-operat ve correct on of res dua spher ca refract ve error – Based on ex st ng performance of convent ona cataract surgery, researchers have conc uded that refract ve outcomes n norma eyes shou d be w th n 0.5D for 45% and w th n 1D for 85% of cataract cases[5]. Th s theoret ca performance goa st fa s substant a y short of the rea -wor d outcomes seen w th cornea refract ve surgery and wh ch cataract pat ents and surgeons ncreas ng y demand. As a consequence, secondary procedures to opt m ze v sua outcomes fo ow ng cataract surgery can be as h gh as 16% n some pract ces, part cu ar y for prem um ens pat ents[2].

   Modu ar IOL techno ogy s ntended to d rect y mprove refract ve outcomes w thout the nherent r sk of a fu ens exchange or resort ng to the use of a cornea refract ve aser. W th the HARMONI™ des gn the spher ca opt c component s ntended to a ow exchange for a d fferent power opt c or adjusted to a gn w th the v sua ax s w thout extens ve man pu at on of the de cate capsu ar bag, thereby avo d ng the potent a for ntraocu ar (e.g., capsu ar and endothe a) trauma that s seen w th trad t ona IOL exchanges.

2. Post-operat ve correct on of rotat ona y d sp aced or off-ax s tor c ens – For every 1 degree a tor c IOL ax s s off from the true postoperat ve ax s of ast gmat sm, there w be a 3.3% oss of tor c correct on. Study data support ng a recent approva of a tor c IOL (P930014/S045) showed that 6.7% of eyes underwent a secondary surg ca ntervent on (SSI) n the form of IOL repos t on ng to reso ve RRE. The HARMONI™ modu ar techno ogy can be used to mprove outcomes n pat ents where the tor c ens has been d sp aced to an un ntended pos t on dur ng the post-operat ve per od. The HARMONI™ opt c a ows for adjustment to a gn w th the ast gmat c mer d an or v sua ax s w thout man pu at on of the base component thereby avo d ng the potent a for capsu ar trauma that s seen when tor c IOLs are man pu ated n the post-operat ve per od.

The C arV sta Harmon ™ Monofoca (non-tor c) Modu ar IOL System has been ava ab e s nce 2015. A tor c vers on, the C arV sta Harmon ™ Tor c Modu ar IOL System (HMTIOL), has been recent y CE-approved.

2.0 OBJECTIVES

The object ve of th s study s to demonstrate the safety and performance of the HARMONI™ Modu ar Tor c IOL n pat ents w th pre-ex st ng ast gmat sm.

The spec f c object ves are:

- To ref ne the A-constant (ens constant) of the HMTIOL.
- To eva uate the refract ve outcomes nc ud ng ast gmat sm correct on w th HMTIOL n pr mary cataract surgery.
- To eva uate ax a and rotat ona stab ty of the HMTIOL.

3.0 STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

Th s s a prospect ve, mu t -center study be ng conducted at up to 10 nvest gat ve s tes. A s tes w have Inst tut ona Rev ew Board (IRB) or Eth cs Comm ttee (EC) rev ew and approva pr or to recru t ng potent a subjects. Up to 200 e g b e eyes from subjects w th v sua y s gn f cant cataracts w undergo cataract extract on dur ng part c pat on. Approx mate y 20 eyes, a max mum of 30 eyes, w be enro ed by each nvest gator/surgeon. A subjects w be seen for a Preoperat ve V s t to capture base ne measurements. One or both eyes of each subject w undergo cataract surgery and be mp anted w th the HMTIOL. Eyes w th cornea ast gmat sm that s w th n the d optr c range of the tor c IOL (1.50, 2.25 and 3.00D at the IOL p ane after adjust ng for Surg ca y Induced Ast gmat sm) w be mp anted. A subjects w be fo owed for 3 months.

Fo ow up:

- 1 Day, 1 Week, 1 Month, and 3 Months fo ow ng cataract extract on.

F gure 2 - Cohort Schedu e

A subjects enro ed n th s study w be eva uated for 3 months fo ow ng cataract extract on (see Append x A – Schedu e of Assessments).

3.2 STUDY POPULATION

After comp et ng the nformed consent process, subjects w be screened for part c pat on n the study.

3.2.1 INCLUS ON CR TER A

1. Adu t at east 22 years of age at the t me of consent

2. Must be willing and able to return for scheduled treatment and follow-up examinations for up to 6 month study duration, per eye.
3. Planned removal of visually significant cataract (cortical, nuclear, posterior subcapsular, or a combination) by manual phacoemulsification cataract extraction
4. Pre-existing corneal astigmatism 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 after adjusting for Surgically Induced Astigmatism)
5. Target dioptric ensity 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

   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 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 exhibiting 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 study eye (including refractive)
2. Any type of cataract (e.g. traumatic, congenital, polar) other than those noted in inclusion criteria
3. Pregnancy or 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, schemic diseases, macular degeneration, retinal detachment, amblyopia, optic neuropathy, etc.) in study eye that could alter or limit 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 study eye
8. Any anterior or segment pathology likely to increase the risk of complications from phacoemulsification cataract extraction (e.g. chronic uveitis, retinitis, rdocyctis, and rdia, rubeosis rdis, clinically significant cornea , Fuch's, or anterior membrane dystrophies, etc.) in study eye
9. Any visually significant intraocular media opacity other than cataract in study eye (as determined by the investigator)
10. Uncontrolled glaucoma in study eye (per Investigator judgement)
11. Subjects with large refractive errors (hyperopia/myopia) of axial or pathological origin that, in the opinion of the investigator, could confound outcomes
12. Uncontrolled systemic disease (e.g. diabetes mellitus, active cancer treatment, mentalness, 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
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 small pupil/floppy iris syndrome)

3.2.3 DISCONTINUATION 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 instances for those subjects with both eyes enrolled, if the first study eye and secondary eye post-operative assessments cannot be seen on the same day and both remain in "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 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.

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

- Date of surgery
- Operative eye
- Incision location and size
- Ophthalmic Viscoscast Device (OVD) used
- All medications used pre-, intra-, and post-operatively (ophthalmic and systemic)
- Model, serial number, and diopter of HMTIOL implant components
- Toric IOL power and axis orientation
- 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, the surgeon will provide the best care option to the patient, including implanting a commercially available IOL.

In the event the subject is not implanted with an HMTIOL 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, if eligible and enrolled in the study, 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
- Incision location and size
- Ophthalmic Viscoelastic Device (OVD) used
- All medications used pre-, intra-, and post-operatively (ophthalmic and systemic)
- Model, serial number, and diopter of HMTIOL implant components
- Toric IOL power and axis orientation
- IOL injection device

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

NOTE: All concomitant medications, 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 address RRE (corneal refractive surgery, lens exchange, lens rotation, 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. If surgical correction of the RRE is performed during the investigation period, the refractive error prior to secondary surgery is reported as the final result.

3.3.4 3 MONTH VISIT (DAY 80-100)

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 center.

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 the 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 HMTIOL ordered 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 (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 fa ures and the reasons for the screen fa ures w be recorded n the subject source documents and captured n the eCRF for summary.

4.4 SUBJECT COMPLETION

The subject has comp eted the ent re study when the HMTIOL has been mp anted and the Sponsor rece ves comp eted e ectron c Case Report Form (eCRF) documentat on for a v s ts and a Study Ex t eCRF. Subjects who requ re further fo ow-up for an AE w be fo owed accord ng to Sect on 6.3.4.

A Study Ex t eCRF must be comp eted for a subjects who comp ete the c n ca nvest gat on.

4.5 SUBJECT DISCONTINUATION

A subject MUST be d scont nued pr or to the f na study v s t for any of the fo ow ng reasons:

- Death
- Subject s enro ed and schedu ed for surgery but s not mp anted w th an HMTIOL n at east one eye
- Surg ca comp cat on(s) unre ated to the nvest gat ona dev ce prevent ng the mp antat on of the HMTIOL (.e. capsu orhex s tear, zonu ar rupture, ev dent zonu ar weakness or deh scence, poster or capsu ar rupture, v treous oss, poster or capsu ar p aque, s gn f cant detached Descemet's membrane, s gn f cant anter or chamber b eed ng, r s ncarcerat on or damage, cornea endothe a touch, unsuccessfu / ncomp ete phacoemu s f cat on, hapt c and/or opt c damage/hapt c amputat on)
- Exp antat on of the HMTIOL System

If the study ens s exp anted, one postoperat ve v s t shou d be comp eted to record best-corrected d stance v sua acu ty (BCDVA) before the subject s d scont nued.

Subjects who w thdraw from the study w be asked to comp ete procedures out ned n the 3 Month V s t (f w thdrawn pr or to that v s t). Subjects who are term nated due to an AE w be fo owed, f poss b e, at east unt reso ut on or stab zat on of the AE. Subject w thdrawa s w be documented c ear y on the source document and app cab e eCRF.

Pr or to d scont nu ng a subject, every effort shou d be made to contact the subject, schedu e a f na study v s t, and obta n as much fo ow-up data as poss b e. Adverse events w be fo owed as descr bed n Sect on 6.3.4. D scont nued subjects shou d be fo owed outs de of the study protoco accord ng to the Invest gator's norma postoperat ve standard of care.

A Study Ex t eCRF must be comp eted for a subjects who d scont nue from the c n ca nvest gat on.

4.6 LOST TO FOLLOW UP

Subjects who m ss the r 3-month v s t, as def ned by the v s t w ndows and cannot be contacted, may be cons dered ost to fo ow-up. A fo ow-up attempts w be documented and kept w th the subject's source documentat on, and the app cab e eCRFs w be comp eted.

Subjects that vo untar y w thdraw consent after mp antat on w th the HMTIOL w be cons dered Lost to Fo ow-Up and an Ex t Form w be comp eted.

4.7 STUDY COMPLETION

C arV sta w not fy the Invest gators when to contact the IRB / EC to announce study comp et on at the s te.

4.7.1 EARLY STUDY TERM NAT ON

C arV sta has the r ght to term nate th s study at any t me. Reasons for term nat ng the study may nc ude, but are not m ted to, the fo ow ng:

- The nc dence or sever ty of adverse events n th s or any ongo ng stud es nvo v ng the same techno ogy (f app cab e), nd cates a potent a hea th hazard to subjects
- Subject enro ment s unsat sfactory
- Data record ng s naccurate or ncomp ete.

In the event of premature study term nat on, appropr ate not f cat on w be g ven to the Invest gators, IRB / ECs, and regu atory bod es as app cab e. In add t on, C arV sta (or des gnee) w nstruct a Invest gators to d scont nue d spens ng study mater a s or treatments, w ensure a subjects comp ete appropr ate fo ow-up, and w arrange study c oseout v s ts at each s te as appropr ate.

4.8 CONCOMITANT THERAPIES

4.8.1 CONCOM TANT MED CAT ON

Concom tant med cat ons are any prescr pt on drugs used by a subject unt conc us on of study part c pat on. Any med cat on the Invest gator deems n the best nterest of the subject, s acceptab e to prescr be or adm n ster. However, any and a are to be recorded n both the Concom tant Med cat on source document and eCRF as we as the reason for use (nd cat on). An AE s to be reported and/or recorded as appropr ate (see Sect on 6.0).

4.8.2 CONCOM TANT PROCEDURES

A concom tant procedure s any nvas ve or non- nvas ve ocu ar or per -ocu ar procedure that takes p ace dur ng study part c pat on and w be captured n both the Concom tant Procedure Source Document and eCRF. The fo ow ng are examp es of two such procedures:

- Any PO surg ca adjustments (.e. cornea refract ve surgery, ens exchange, ens rotat on, etc.)
- Neodym um: Yttr um-a um num-garnet (Nd:YAG) procedure to treat Poster or Capsu e Opac f cat on (PCO), f necessary. Th s w be sted as “Nd:YAG Capsu otomy.”

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

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 Toric Intraocular Lens (HMTIOL) System is designed to allow safe exchange or adjustment of an IOL optic after implantation. [redacted]

[redacted].

[redacted]

5.1.1 INSTRUCT ONS FOR USE

Refer to the Surg ca Gu de for a use and adm n strat on deta s.

5.2 PACKAGING AND LABELING

A packag ng and abe ng w be cons stent w th the current study des gn. The abe ng w nc ude at a m n mum, the fo ow ng:

- Sponsor name and address
- “For S ng e Use On y” statement (or equ va ent symbo)
- Ster ty symbo
- Storage temperature range requ rements or equ va ent (e.g. “Store at room temperature.”)
- Exp rat on date
- Power des gnat on
- Un que ser a number
- Mode number

5.3 ACCOUNTABILITY

The Invest gator s respons b e for keep ng accurate accountab ty records of the number of study enses rece ved, d spensed, and returned to Sponsor. The study enses must be stored under the appropr ate cond t ons n a secure area and are to be mp anted on y n subjects enro ed n the study, n accordance w th the cond t ons spec f ed n th s protoco .

Accountability records include the following:

- Model and serial numbers
- Receipt date
- Quantities received
- Initials (attributable) 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 expanted 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
- Medical injectors (for study lens injection only)
- Slit lamp camera

6.0 ADVERSE EVENTS

Safety assessments include adverse events/serious adverse events, and adverse device events. The reporting time period starts 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.

Exper ence w th cataract surgery and the mp antat on of IOLs has shown that some cond t ons can be cons dered norma or expected events fo ow ng these procedures. The fo ow ng may be cons dered norma or expected events after cataract surgery and on y need to be reported as AEs as spec f ed here:

- Ir t s (ce / f are) – f treated onger than standard post-operat ve reg men or f t recurred after comp ete reso ut on
- Pers stent Cornea Stroma Edema (f present at 1 Month)
- Increased IOP on y f med ca /surg ca ntervent on s requ red (.e. med cat on, paracentes s man pu at on)
- BCDVA decrease of 10 or more etters (2 nes) from any prev ous v s t not secondary to any under y ng cond t on present at t me of enro ment
- Any expected post-operat ve ocu ar event requ r ng a change n standard postoperat ve med cat on reg men

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

Note: *The HMTIOL is designed for safety and ease of optic exchange and rotational adjustment post-primary cataract surgery. Optic exchange and optic rotation to refine refractive outcomes are not to be reported as AE's.*

Part cu ar attent on shou d be pa d to ensure t me y and accurate report ng of any of the fo ow ng cataract surgery re ated events:

- Endophtha m t s
- Capsu ar njury
- V treous oss
- Macu ar edema
- Ret na detachment
- Lens d s ocat on
- Moderate to severe cornea edema
- Pup ary b ock / ang e c osure
- Hypopyon or hyphema

6.1.2 ADVERSE DEV CE EFFECT (ADE)

An ADE s any untoward or un ntended effect, event, or response surround ng and w th a causa re at onsh p w th the use of a med ca dev ce. Th s def n t on may nc ude any event resu t ng from nsuff c enc es or nadequac es n the nstruct ons for use or the dep oyment of the dev ce or other dev ce ma funct ons. Th s def n t on nc udes any event that s a resu t of a user error and any event that affects a user of the dev ce (.e. careg ver, bystander, etc.).

6.1.3 UNANT C PATED ADVERSE DEV CE EFFECT (UADE)

A UADE s any ADE, wh ch s unant c pated and poses a r sk to hea th or safety, or any fe-threaten ng prob em or death caused by or assoc ated w th a dev ce, f that effect, prob em, or death was not prev ous y dent f ed n nature, sever ty or degree of nc dence (see Invest gator Brochure [IB]). UADEs a so nc ude any

unanticipated serious 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

<u>Study Protocol</u>

- 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 of 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 life-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 heath, a congenital abnormality, or birth defect

* Hospitalization is a criterion for assessment of seriousness. Hospitalization in the absence of a medical AE is not 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 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 instances, it is preferable to report 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 cause for 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 sequelae
- Resolved with sequelae (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 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 HMTIOL 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 HMTIOL devices, exchanged HMTIOL optics, or any components of the HMTIOL 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 completed 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 meet 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 significant 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 changes 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 reviewed as necessary to ensure subjects' consent to continue participation given the known reviewed risks.

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

7.0 STUDY OUTCOMES

7.1 SAFETY OUTCOMES

Safety will be evaluated by assessing the following:

- Preservation of BCDVA
- Rate of device-related SSI's other than optic exchange and rotational adjustment of the HMTIOL
- AE rates
- Device deficiencies

7.2 PERFORMANCE OUTCOMES

- Calculation of Standard error of the mean (lens power A-constant for refinement)
- 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 pred ct on error
- UCDVA by study v s t
    - Percent of eyes that ach eve
        - 20/20 or better
        - 20/25 or better
        - 20/32 or better
        - 20/40 or better
        - Worse than 20/40
- BCDVA by study v s t
    - Percent of eyes that ach eve
        - 20/20 or better
        - 20/25 or better
        - 20/32 or better
        - 20/40 or better
        - Worse than 20/40
- IOL mer d an m sa gnment on the day of surgery
- Rotat ona of IOL mer d an at 1 day, 1 week, 1 and 3 months
    - Percent of eyes w th rotat on ≤ 5
    - Percent of eyes w th rotat on < 10
    - Percent of eyes w th rotat on < 20
    - Percent of eyes w th rotat on < 30
    - Abso ute va ue of rotat on
    - [redacted]
- Reduct on n cy nder power of the eye mp anted w th HMTIOL (abso ute preoperat ve magn tude of cornea cy nder (K) m nus the abso ute postoperat ve magn tude of MRCYL at the cornea p ane)
- Percentage reduct on n cy ndr ca power of the eye mp anted w th HMTIOL (abso ute preoperat ve magn tude of cornea cy nder (K) m nus the abso ute postoperat ve magn tude of MRCYL at the cornea p ane, expressed as a percentage of the abso ute preoperat ve magn tude of tota cornea cy nder (K)).

[redacted]

8.0 STATISTICAL METHODS

Th s s a study to eva uate the safety and performance of HTMIOL n subjects undergo ng cataract surgery. In genera , the ana yses w be prov ded based on ava ab e data. The mean, standard dev at on, m n mum, and max mum w be prepared for the cont nuous c n ca parameters, and counts and percentages w be presented for the categor ca outcomes.

8.1 SAMPLE SIZE CALCULATION

The sample size of this study is based on refinement of A-constant (lens power constant). To reduce bias due to surgical technique, unusual eyes and differences in equipment (A scan, keratometer, etc.) data will be obtained from a sufficient number of eyes such that the standard error of the mean in lens power constant is less than ±0.10mm (approximately ±0.2D). A minimum of 20 to 30 eyes from each surgeon should be adequate to achieve the tolerance. Each included subject should have a post-operative uncorrected visual acuity better than 20/40 to avoid inaccuracies in refraction.

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

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 performance data analyses. However, the 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 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 implantation. Since it is important to evaluate HMTIOL's effect on astigmatism eyes, stigmatism examination, intraoperative pressure (IOP), and dilated fundus examination (DFE) will be based on the implanted-eye population.

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

8.2.3 PER PROTOCOL POPULATION

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

The protocol deviations will be categorized prior to the analysis.

[redacted]

[redacted]

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.

For continuous outcomes, mean, standard deviation, median, minimum, and maximum will be provided. For categorical outcomes, the counts and percentages of eyes with each category 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. The number and percentage of eyes reported with the 3-month cumulative and persistent adverse events will be calculated. [redacted]

[redacted]

8.3.2 PERFORMANCE OUTCOMES

The performance 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.

8.3.2.1 BCDVA

[redacted]

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

[redacted]

8.3.2.2 UCDVA

[redacted]The proport on of eyes w th 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 v s t w be summar zed at the pre-operat ve and every postoperat ve v s ts.

8.3.2.3 PREDICTION ERROR (PE)

The MRSE pred ct on error w be ca cu ated at 3 months for each mp anted eye as fo ows:

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

The MRCYL pred ct on error w be ca cu ated at 3 months for eyes mp anted w th HMTIOL as fo ows:

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

The MRCYL PE w a so be ca cu ated based on the vector ana ys s approach for eyes mp anted w th the HMTIOL.

[redacted]

8.3.2.4 MISALIGNMENT OF IOL MERIDIAN

The f na rotat ona mer d an of the IOL w be compared to the p anned pos t on. The abso ute va ue of rotat on w be descr bed by mean, med an, and max mum va ues. [redacted]

8.3.2.5 ROTATION OF IOL MERIDIAN

The rotat on of IOL mer d an w be ca cu ated for each eye from Day 0 to every postoperat ve v s t. The descr pt ve stat st cs for cont nuous var ab es w be used to summar ze the rotat on ang e at each v s t. The abso ute va ue of rotat on w be descr bed by mean, med an, and max mum va ues. [redacted]The number and percentage of eyes w th rotat on ≤ 5 , < 10 , < 20 , and < 30 w be ca cu ated at each v s t.

[redacted]

8.3.2.6 REDUCTION IN CYLINDER POWER

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

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

The percent reduction in cylinder 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. [redacted]

The vector analyses (Eydeman[11]) based on the cylinder power and axis will be performed.

[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, 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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[redacted]

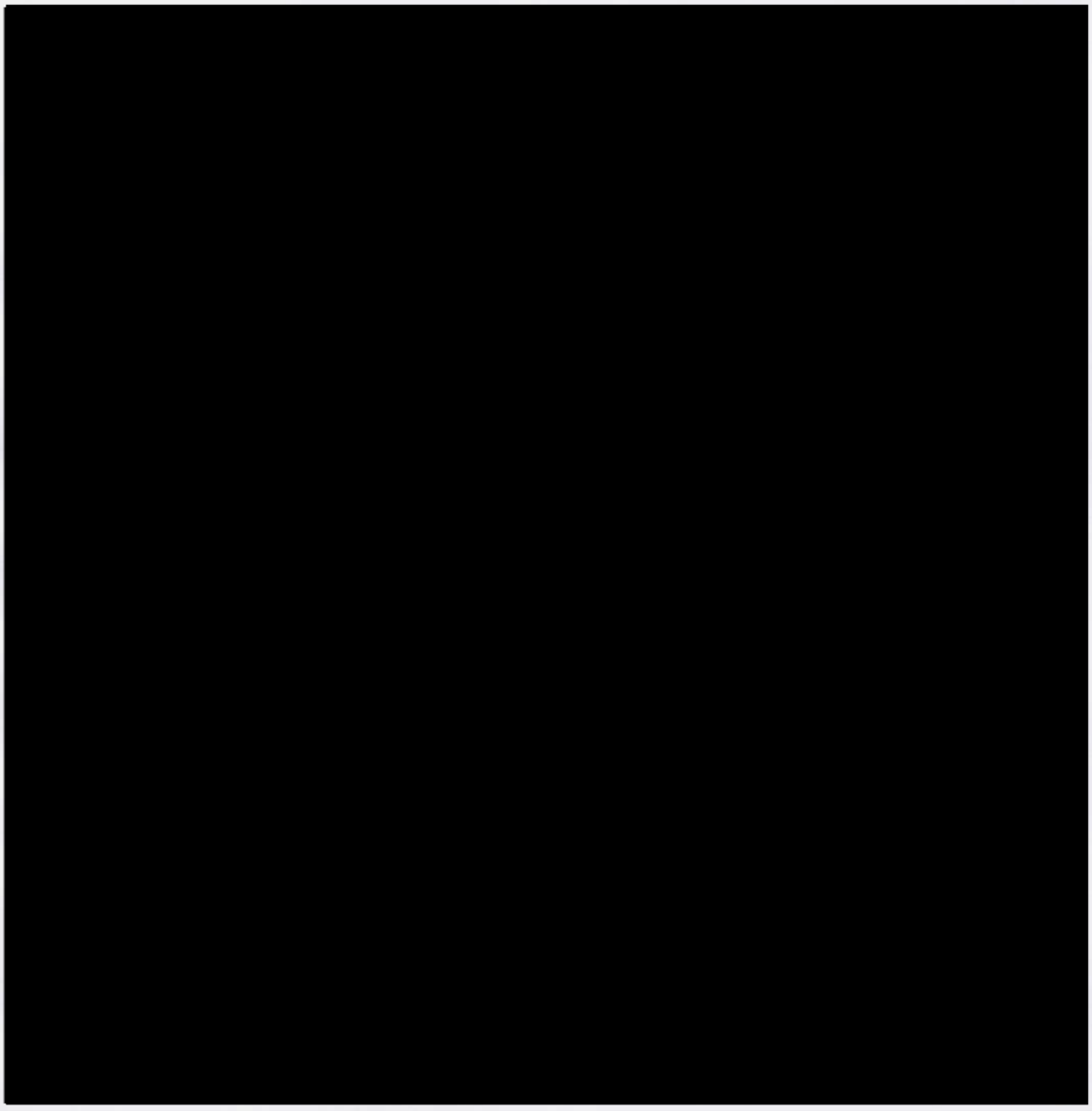
[redacted]

[redacted]

APPENDIX A – TABLE 1: SCHEDULE OF ASSESSMENTS

	Pre-Op Visit[1]	Op Visit		Form 3	Form 4	Form 5	Form 6
		First Eye	Second Eye (if enrolled)				
Procedure/Assessment	Day -90 to -0	Day 0	Day 0 (+3-30 Days from the first eye 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
Auto and Manifest Refraction	X				X	X	X
BCDVA	X				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
IOP	X			X	X	X	X
Pupil Size	X	X	X				
Surgery / IOL implantation		X	X				
IOL Rotational Stability[6]		X	X	X	X	X	X
[redacted]				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
[6] Rotational stability as assessed by Reading Center



[redacted]
