Study Protocol

Clinical Investigation of the Safety and Effectiveness of the Next-Generation TECNIS® Symfony® Intraocular Lens Model ZHR00

NCT Number: NCT03500198

Version 4.0

Document date: 01 Apr 2019

CONFIDENTIAL
The following contains confidential, proprietary information
that is the property of Johnson & Johnson Surgical Vision

Clinical Investigation of the Safety and Effectiveness of the Next-Generation TECNIS® Symfony® Intraocular Lens Model ZHR00

IDE Number: G180044

PROTOCOL NUMBER: SUR-IOL-652-2001

SPONSOR: Johnson & Johnson Surgical Vision, Inc.
1700 E. St. Andrew Place
Santa Ana, CA 92705
714-247-8200

Investigator Agreement

As an Investigator, I agree to:

- Implement and conduct this study diligently and in strict compliance with this agreement; the protocol; Good Clinical Practices; 21CFR812, ISO 14155:2011 and all other applicable FDA regulations; conditions of approval imposed by the reviewing Institutional Review Board (IRB), FDA or other regulatory authorities; and all other applicable laws and regulations.
- Supervise all testing of the device where human subjects are involved.
- Ensure that the requirements for obtaining informed consent are met.
- Obtain authorization for use/disclosure of health information (e.g., HIPAA authorization or equivalent).
- Maintain all information supplied by Johnson & Johnson Surgical Vision in confidence and, when this information is submitted to an independent IRB or any other group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety and I agree to all aspects.

Investigator Printed Name	Signature	Date
Sub-Investigator Printed Name	Signature	Date
Sub-Investigator Printed Name	Signature	Date
Sub-Investigator Printed Name	Signature	Date
Sub-Investigator Printed Name	Signature	Date

TABLE OF CONTENTS

PERSONNEL AND FACILITIES

SPONSOR:

Johnson & Johnson Surgical Vision, Inc. ("JJSV")
1700 E. Saint Andrew Place
Santa Ana, CA 92705

SPONSOR PERSONNEL:

Medical Monitor:

[redacted]

Study Manager:

[redacted]

Clinical Scientist

[redacted]

Biostatistician:

[redacted]

EMERGENCY TELEPHONE NUMBERS:

[redacted]

Protocol Change History

Version	Section(s)	Page(s)	Description of Change(s)	Rationale for Change(s)
1.0	N/A	N/A	Original	N/A
2.0	Synopsis and 8.1 Inclusion Criteria	2,13	Change Corneal Astigmatism criteria to be "Predicted postoperative corneal astigmatism of less than 1.00 D in both eyes"	To align with indications for use.
2.0	Synopsis and 8.2 Exclusion Criteria	3,14	Reference guttata for endothelial dystrophy	To clarify with an example of a sign of endothelial dystrophy.
2.0	9.1 Investigator Qualifications	15	Change requirement of established Symfony A-Constant to ZCB00 A-Constant	The control IOL in this study is ZCB00 thus surgeon needs to have an established A-Constant for the ZCB00 lens.
2.0	10.3 Keratometry	20	Add language to account for PCA in the determination of total corneal astigmatism for study qualification.	To ensure inclusion criteria are fully met.
2.0	10.3 IOL Power and Targeted Refraction	21	Add language to reflect different A-Constant for investigational vs. control lens and establish that IOL power changes will only be based on first-eye outcomes	To ensure proper calculation of IOL power for study subjects and to reduce surgeon changes intraoperatively.
2.0	10.6 Operative Procedures	23	Change astigmatism to be less than 1.00 D instead of no greater than 1.0 D.	To align with indications for use.
2.0	10.7 Postoperative Procedures (Defocus Testing) and Appendix I	27, 63	Remove two defocus increments (+0.25 D and -0.25 D) in defocus testing	The optical design is to extend depth of focus in the -2.0 to -4.0 D range so this finer defocus testing around 0.0 D is not needed.
2.0	20.1 Analysis Population	44,45	Add mean BCDVA safety endpoint to sensitivity analyses, add cumulative adverse events to safety population	Per FDA Study Considerations in Approval letter dated 30Mar2018 resulting in SAP amendment to clarify planned analyses.
2.0	Appendix A	52	Remove pupil size measurement at 1-Month visit	Correction as no testing is done at 1 Month for which pupil size stratification may be performed. All testing is photopic visual acuity only.
2.0	Appendix B	53	Add "as requested" and "as necessary" for equipment that is optional	Clarification
2.0	footer	all	Update footer to 2.0	New version
3.0	10.7 Postoperative Procedures (Questionnaires)	29, 30	Add "v2" to PRSIQ and PRVSQ, change number of symptoms to seven from eight due to removal of streaks of light	New testing of PRVSQ combined streaks of light into starbursts, resulting in v2 or PRVSQ.

3.0	10.9 Unscheduled Visits	32	Change number of symptoms to seven from eight due to removal of streaks of light	New testing of PRVSQ combined streaks of light into starbursts, resulting in v2 or PRVSQ.
3.0	Appendix M		Replace PRVSQ with PRVSQv2	Update with new PRVSQ that has undergone additional validation testing
3.0	Appendix N		Replace PRSIQ with PRSIQv2	Update with new PRSIQ that has undergone additional validation testing
3.0	footer	all	Update footer to 3.0	New version
4.0	Table of Contents	ii-iv	Renumbered pages	Updates due to changes
4.0	Synopsis, 3. Clinical Hypothesis	1, 4, 6	Changed decreased spectacle wear to increased spectacle independence	Update with PRSIQv2 validation work to use composite dichotomous score for overall spectacle independence as secondary effectiveness endpoint
4.0	Synopsis	5	Remove overall spectacle independence secondary effectiveness endpoint from mITT analysis population	Composite dichotomous scoring algorithm does not impute for missing data
4.0	6.2 Secondary Effectiveness Endpoint	8	Replace “Overall Spectacle Wear” with “Overall Spectacle Independence” Replace “do not wear spectacles…” with “are spectacle independent” and update definition of PRO instrument assessment. Replace clinical significance of “50% of subjects will report wearing glasses “None of the time”…” with “The proportion of Model ZHR00 subjects who are spectacle independent will be at least 25 percentage points higher than that for the control group”	Update with PRSIQv2 scoring algorithm to use composite dichotomous score for overall spectacle independence as secondary effectiveness endpoint instead of overall spectacle wear
4.0	20.1 Analysis Population	44, 45	Reworded to clearly define that PRSIQv2 data will be analyzed in Safety Population and Per Protocol analyses and will not be imputed for mITT analyses.	PRSIQv2 scoring algorithm requires complete data for composite dichotomous score and specifies no imputation for missing values should be used.
4.0	20.2 Secondary Effectiveness Endpoints Overall Spectacle Independence	47, 48	Replace the secondary effectiveness endpoint of Overall Spectacle Wear via Binocular Questionnaire with Overall Spectacle Independence, including all questions and conditions that are included in the composite dichotomous score. Replace clinical significance of “50% of subjects will report wearing glasses “None of the time”…” with “The proportion	Update with PRSIQv2 validation work to use composite dichotomous score for overall spectacle independence as secondary effectiveness endpoint.

			of Model ZHR00 subjects who are spectacle independent will be at least 25 percentage points higher than that for the control group" Remove logistic regression from data analysis	No imputation will be done on PRSIQv2 missing data therefore only Fisher's exact test will be used.
4.0	Appendix A	52	Added shading to Manifest refraction examination	Correction as this is an examination that is to be conducted by a masked examiner
4.0	footer	all	Update footer to 4.0	New version

1. SYNOPSIS

PROTOCOL: Clinical Investigation of the Safety and Effectiveness of the Next-Generation TECNIS® Symfony® Intraocular Lens, Model ZHR00
Protocol Number: SUR-IOL-652-2001

STUDY TREATMENTS:

Investigational Lens:

- Next-Generation TECNIS Symfony IOL, Model ZHR00

Control Lens:

- TECNIS Monofocal IOL Model ZCB00 (Johnson & Johnson Surgical Vision, Inc., Santa Ana, CA), commercially available

STUDY OBJECTIVE: The purpose of this clinical trial is to evaluate the safety and effectiveness of the Next-Generation TECNIS Symfony IOL, Model ZHR00.

CLINICAL HYPOTHESIS: The Next-Generation TECNIS Symfony IOL, Model ZHR00, will provide improved monocular, distance-corrected intermediate visual acuity (at 66 cm) and distance-corrected near visual acuity near (at 40 cm), as well as increased depth of focus at 0.2 LogMAR and increased spectacle independence compared to the control IOL, TECNIS Model ZCB00.
Complication and adverse event rates associated with the Next-Generation IOL will be within the rates for posterior chamber IOLs referenced in ISO 11979-7:2006/ Amd 1:2012(E).

OVERALL STUDY DESIGN:

Structure: Prospective, multicenter, randomized, bilateral subject/evaluator-masked clinical trial

Number of sites: Up to 10 sites in the United States

Duration: 6 months postoperative follow-up

Administration: Surgeons will perform routine, small-incision, cataract surgery and implant the study lenses using a sponsor-recommended implantation system. Refractive target outcomes will be emmetropia for both eyes.

Visit Schedule: Subjects will be bilaterally implanted with the same lens type; the second eye is to be implanted within 1 month of the first-eye surgery.

All subjects will undergo 10 scheduled visits: Preoperative for both eyes; Operative, 1-day, 1-week and 1-month visits for each eye; and a 6-month visit for both eyes.

STUDY POPULATION CHARACTERISTICS:

Condition: Bilateral cataracts with otherwise-healthy eyes

Number of Subjects: Up to 264 subjects will be enrolled to achieve approximately 110 randomized and bilaterally-implanted subjects in each lens group.

Each site should enroll at least 20 subjects, and no site may enroll more than 25% of the enrollment total.

Inclusion Criteria (all criteria apply to each study eye):

- Minimum 22 years of age
- Bilateral cataracts for which posterior chamber IOL implantation has been planned
- Preoperative best-corrected distance visual acuity (BCDVA) of 20/40 Snellen or worse with or without a glare source
- Potential for postoperative BCDVA of 20/30 Snellen or better
- Corneal astigmatism:
  - Normal corneal topography
  - Predicted postoperative corneal astigmatism of less than 1.00 D in both eyes
- Clear intraocular media other than cataract in each eye
- Availability, willingness and sufficient cognitive awareness to comply with examination procedures and study visits
- Signed informed consent and HIPAA authorization or equivalent documentation necessary to comply with applicable privacy laws pertaining to medical treatment in the governing countries
- Ability to understand and respond to a questionnaire in English

Exclusion Criteria (all criteria apply to each study eye):

- Requiring an intraocular lens power outside the available range of +14.0 D to +26.0 D

- Any clinically-significant pupil abnormalities (non-reactive, fixed pupils, or abnormally-shaped pupils)
- Irregular corneal astigmatism
- Inability to focus or fixate for prolonged periods of time (e.g., due to strabismus, nystagmus, etc.)
- Prior corneal refractive (LASIK, LASEK, RK, PRK, etc.) or intraocular surgery, Including prophylactic peripheral iridotomies and peripheral laser retinal repairs
- Corneal abnormalities such as stromal, epithelial or endothelial dystrophies (e.g., any observed guttata) that are predicted to cause visual acuity losses to a level worse than 20/30 Snellen during the study
- Inability to achieve keratometric stability for contact lens wearers
- Recent ocular trauma or ocular surgery that is not resolved/stable or may affect visual outcomes or increase risk to the subject
- Subjects with diagnosed degenerative visual disorders (e.g., macular degeneration or other retinal disorders) that are predicted to cause visual acuity losses to a level of 20/30 Snellen or worse during the study
- Subjects with conditions associated with increased risk of zonular rupture, including capsular or zonular abnormalities that may lead to IOL decentration or tilt, such as pseudoexfoliation, trauma, or posterior capsule defects
- Use of systemic or ocular medications that may affect vision
- Prior, current, or anticipated use during the course of the 6-month study of tamsulosin or silodosin (e.g., Flomax, Flomaxtra, Rapaflo) that may, in the opinion of the investigator, confound the outcome or increase the risk to the subject (e.g., poor dilation or a lack of adequate iris structure to perform standard cataract surgery)
- Poorly-controlled diabetes
- Acute, chronic, or uncontrolled systemic or ocular disease or illness that, in the opinion of the investigator, would increase the operative risk or confound the outcome(s) of the study (e.g., immunocompromised, connective tissue disease, suspected glaucoma, glaucomatous changes in the fundus or visual field, ocular inflammation, etc.). Note: controlled ocular hypertension without glaucomatous changes (optic nerve cupping and visual field loss) is acceptable.
- Known ocular disease or pathology that, in the opinion of the investigator,
  - may affect visual acuity
  - may require surgical intervention during the course of the study (macular degeneration, cystoid macular edema, diabetic retinopathy, uncontrolled glaucoma, etc.)
  - may be expected to require retinal laser treatment or other surgical intervention during the course of the study (macular degeneration, cystoid macular edema, diabetic retinopathy, etc.)
- Patient is pregnant, plans to become pregnant, is lactating or has another condition associated with the fluctuation of hormones that could lead to refractive changes
- Concurrent participation or participation within 60 days prior to preoperative visit in any other clinical trial
- Desire for monovision correction

EVALUATION CRITERIA:

The purpose of this clinical study is to evaluate the safety and effectiveness of the Next-Generation TECNIS Symfony IOL. The primary effectiveness endpoints are:

- mean monocular distance-corrected intermediate visual acuity under photopic conditions at 66 cm
- monocular distance-corrected depth of focus under photopic conditions.

The secondary effectiveness endpoints are:

- mean monocular, distance-corrected near visual acuity at 40 cm under photopic conditions
- overall spectacle independence

The safety endpoints are:

- monocular photopic, best-corrected distance visual acuity non-inferior to control
- adverse event rates versus ISO 11979-7:2006/ Amd.1:2012(E) Safety and Performance Endpoint (SPE) rates, monocular contrast sensitivity and visual symptoms via PRO questionnaire. Adverse events will include any lens-related secondary surgical intervention due to optical issues causing visual symptoms.
- contrast sensitivity
- visual symptoms as reported via PRO instrument

Other endpoints include:

- Monocular BCDVA percent 20/40 or better vs. ISO SPE rate
- Binocular best-corrected distance depth of focus
- Binocular UCDVA, UCIVA, and UCNVA
- Monocular UCDVA, UCIVA, and UCNVA
- Monocular, first-eye, low-contrast DCIVA and BCIVA (10%)
- Medical findings/complications
- Lens findings/complications
- Fundus visualization
- Residual refractive error
- Ocular/visual symptoms (non-directed responses as obtained from the open-ended question “Are you having any difficulties with your eyes or vision?”)
- Subject satisfaction and other questionnaire responses

DATA ANALYSIS:

The investigational TECNIS Model ZHR00 IOL will be compared to the TECNIS Model ZCB00 control IOL. For the primary effectiveness endpoints of monocular distance-corrected intermediate visual acuity and both secondary effectiveness endpoints at 6 months, comparisons between the Model ZHR00 group vs. the Model ZCB00 control group will be performed using one-sided, two-sample t-tests with an alpha of 0.025.

For the safety endpoints, monocular BCDVA will be compared to the control lens using non-inferiority approach and evaluated using the lower limit of the two-sided 90%

confidence interval. Adverse event rate of the Model ZHR00 IOL will be compared to the ISO grid value using one-sided exact tests with an alpha of 0.05. For contrast sensitivity, descriptive statistics (mean, standard deviation, median, minimum, maximum and 90% confidence interval) will be presented by IOL group. For ocular visual symptoms via questionnaire, frequency and proportion of each response will be presented by IOL group.

The primary analysis population for primary DCIVA and secondary DCNVA effectiveness endpoints will be the mITT. The primary analysis population for primary defocus curve effectiveness endpoint, secondary overall spectacle independence effectiveness endpoint, all safety endpoints and other endpoints will be SP. Please see a detailed description of the analysis populations in Section 20.1. The key study timeframe for all endpoints will be the 6-month postoperative visit, although data will be reviewed at other time points as well. In general, descriptive statistics will be reported for visual acuity and refractive data. The frequency and proportion will be reported for adverse events, medical findings, lens findings, and ocular visual symptoms, as well as questionnaire data.

STUDY VISITS AND PROCEDURES:

Inclusion and exclusion qualifications will be assessed at the preoperative visit according to the inclusion/exclusion criteria. The Informed Consent Form and Authorization for Use/Disclosure of Health Information form (HIPAA authorization) must be signed by any patients who agree to participate in the study prior to undergoing any study-specific procedures. Those subjects who meet the inclusion/exclusion criteria and agree to participate will be randomized to receive the same lens model in both eyes: either the test Model ZHR00 IOL or control Model ZCB00 IOL. The eye implanted first will be considered the primary study eye. All subjects are intended to have bilateral cataract surgery with the second-eye surgery occurring after the 1-week exam for the first eye but no more than 30 days after the first-eye surgery. Subjects and study personnel performing the postoperative vision testing and refractions will be masked for the duration of the study.

Key preoperative data include ocular health and history, visual acuities, manifest refraction, keratometry, biomicroscopic slit-lamp findings, ocular symptoms and biometry. The operative visit will include standard procedures for cataract surgery and IOL implantation. Key postoperative data collection includes monocular and binocular uncorrected and distance-corrected visual acuities, contrast sensitivity, defocus curve, slit-lamp findings, non-directed visual symptoms, questionnaires and adverse events.

2. BACKGROUND/INTRODUCTION

Presbyopia, defined as the age-related loss of accommodative amplitude, affects essentially all human beings beyond the age of 45 and impacts the ability of the eye to focus at near distances[1,2]. Current intraocular lens options for cataract patients who desire improved vision across a range of distances include a choice of monovision or multifocality. Patients implanted with standard monofocal lenses often need spectacles for reading or performing other near tasks, even if a monovision option is selected. Patients implanted with multifocal lenses, while being able to read and perform other near tasks without spectacles, sometimes experience dysphotopsias (e.g., halos), particularly at night, and may have limited intermediate ability (e.g., may need spectacles to work on a computer). Some accommodating lenses are also available on the market, although their effect depends upon fit within the capsular bag or capsular bag elasticity.

On July 15, 2016, another option was made available to cataract patients when the TECNIS Symfony Extended Range of Vision IOL, Model ZXR00, became commercially available in the United States. Utilizing a diffractive technology to elongate the depth of focus, the Symfony IOLs provide cataract patients with good distance vision, and improved intermediate and near vision compared to standard monofocal IOLs.

The investigational IOL device in this protocol, Model ZHR00, is an enhanced version of the commercially-available TECNIS Symfony. The diffractive technology on the posterior optic surface of the TECNIS Symfony IOL was modified for the investigational IOL model ZHR00, with the goal of providing improved intermediate vision as compared to the control IOL Model ZCB00.

3. CLINICAL HYPOTHESIS

The Next-Generation TECNIS Symfony IOL, Model ZHR00, will provide improved monocular, distance-corrected intermediate visual acuity (at 66 cm) and distance-corrected near visual acuity near (at 40 cm), as well as increased depth of focus at 0.2 LogMAR and increased spectacle independence compared to the control IOL, TECNIS Model ZCB00. Complication and adverse event rates associated with the Next-Generation ZHR00 IOL will be within the rates for posterior chamber IOLs given in ISO 11979-7:2006/ Amd 1:2012(E).

4. STUDY DESIGN

This study is a 6-month, prospective, multicenter, subject/evaluator-masked, bilateral, randomized clinical investigation of the Next-Generation TECNIS Symfony IOL Model ZHR00 versus the TECNIS Model ZCB00 IOL.

The study will be conducted at up to 10 sites in the U.S.A and will enroll up to 264 subjects to achieve approximately 220 randomized and bilaterally-implanted subjects, resulting in approximately 100 evaluable subjects in each lens group at 6 months. Subjects are to be implanted with the same IOL in both eyes: the investigational ZHR00 IOL, or the control ZCB00 IOL. The eye implanted first will be considered the primary study eye.

5. ACRONYMS

The following acronyms are used throughout this document:

- UCDVA: uncorrected distance visual acuity
- BCDVA: best-corrected distance visual acuity
- UCIVA: uncorrected intermediate visual acuity
- DCIVA: distance-corrected intermediate visual acuity
- UCNVA: uncorrected near visual acuity
- DCNVA: distance-corrected near visual acuity
- D: diopters

6. STUDY OBJECTIVES AND ENDPOINTS

The purpose of this study is to evaluate the safety and effectiveness of the Next-Generation TECNIS Model ZHR00 IOL. The key study timeframe for all endpoints will be the 6-month postoperative visit. Data for other visits will be included in the final analysis, but no interim analysis will be conducted.

6.1 PRIMARY EFFECTIVENESS ENDPOINTS

MONOCULAR, PHOTOPIC DCIVA AT 66 CM

Success criteria:

- Statistically significant improvement in mean distance-corrected intermediate visual acuity for the ZHR00 eyes vs. control eyes
- The median DCIVA of the ZHR00 lens group is at least 0.2 LogMAR

MONOCULAR, DISTANCE-CORRECTED DEFOCUS CURVE

Success criteria: The Model ZHR00 lens demonstrates at least 0.5 D greater monocular, photopic, distance-corrected depth of focus compared to the control IOL at 0.2 LogMAR visual acuity threshold, based on visual inspection of the defocus curves.

6.2 SECONDARY EFFECTIVENESS ENDPOINTS

MONOCULAR, PHOTOPIC DCNVA AT 40 CM

Success criteria:

- Statistically significant improvement in mean LogMAR distance-corrected near visual acuity for ZHR00 eyes vs. control eyes
- The median DCNVA of the ZHR00 lens group is at least 0.3 LogMAR

OVERALL SPECTACLE INDEPENDENCE

Success criteria:

- Statistically significantly greater proportion of subjects in the ZHR00 group who are spectacle independent, as determined from PRO instrument assessing need for correction, use of correction and ability to see without strain. Clinical significance will be determined as follows:
    - The proportion of Model ZHR00 subjects who are spectacle independent will be at least 25 percentage points higher than that for the control group

6.3 SAFETY ENDPOINTS

MONOCULAR BCDVA

Success criteria: The mean BCDVA for the ZHR00 eyes will be statistically non-inferior to that of the control ZCB00 IOL group using a non-inferiority margin of 0.1 LogMAR.

ADVERSE EVENT RATE

Rates of adverse events for the ZHR00 eyes vs. ISO SPE rates. Adverse events will include any lens-related secondary surgical intervention due to optical issues causing visual symptoms.

CONTRAST SENSITIVITY

Monocular best-corrected distance contrast sensitivity (mesopic with and without glare at 1.5, 3, 6, and 12 cpd photopic with glare at 3, 6, 12, and 18 cpd) will be summarized by descriptive statistics for each IOL group.

VISUAL SYMPTOMS VIA PRO INSTRUMENT

Visual symptoms, as reported and rated via the Patient Reported Visual Symptoms Questionnaire (PRVSQ), will be summarized by frequency and percentage for each IOL group.

6.4 OTHER ENDPOINTS

- Monocular BCDVA percent 20/40 or better vs. ISO SPE rate
- Binocular best-corrected distance depth of focus

- Binocular UCDVA, UCIVA, and UCNVA
- Monocular UCDVA, UCIVA, and UCNVA
- Monocular, first-eye, low-contrast DCIVA and BCIVA (10%)
- Medical findings/complications
- Lens findings/complications
- Fundus visualization
- Residual refractive error
- Ocular/visual symptoms (non-directed responses as obtained from the open-ended question “Are you having any difficulties with your eyes or vision?”)
- Subject satisfaction and other questionnaire responses

7. STUDY PRODUCTS

7.1 INTRAOCULAR LENSES

The two lens models used in this study are the investigational Next-Generation TECNIS Symfony IOL, Model ZHR00, and the control TECNIS Monofocal IOL, Model ZCB00. The investigational IOL is a modification of the TECNIS Symfony IOL, which is a single-piece, SENSAR acrylic IOL with a modified prolate (aspheric) design on the anterior optic surface to reduce spherical aberration and a diffractive posterior optic design.

Investigational TECNIS IOL Model ZHR00

The TECNIS IOL Model ZHR00 is a posterior chamber, 1-piece, aspheric, diffractive, acrylic, foldable IOL designed for placement in the capsular bag (**Figure 1**). The lens is made of the same hydrophobic SENSAR acrylic material as the material/mechanical 1-piece parent, the JJSV SENSAR 1 Piece IOL, Model AAB00, and the optical parent TECNIS Symfony IOL, Model ZXR00 (**Figure 2**). The ZHR00 lens has the same overall geometry/dimensions (13 mm overall length and 6 mm optic diameter) as the material/mechanical 1-piece parent IOL, the JJSV SENSAR IOL, Model AAB00, and the optical parent, TECNIS Symfony IOL, Model ZXR00. The investigational ZHR00 lens also has the same TECNIS modified prolate (aspheric) design on the anterior optic surface as the optical parent, the TECNIS Symfony IOL, to reduce spherical aberration.

The Model ZCB00 control IOL (**Figure 3**) shares the same lens material, general dimensions, lens geometry, and one-piece soft acrylic lens platform as the SENSAR 1-Piece IOL, Model AAB00, which is the material/mechanical parent of the ZHR00 IOL.

The posterior optic design of the ZHR00 lens has been modified from that of the optical parent IOL, model ZXR00. The modifications to the posterior diffractive optics of the investigational IOL are designed to further extend the depth of focus compared to the TECNIS Symfony IOL.

Figure 1: Drawing and Photograph of a TECNIS Model ZHR00 IOL

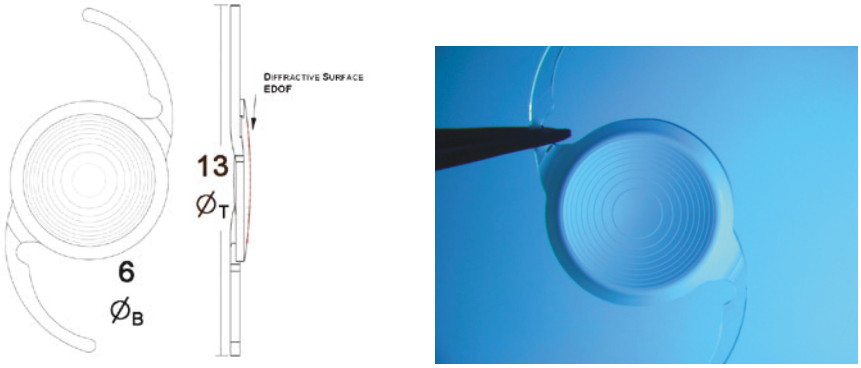


Figure 2: Drawing and Photograph of a TECNIS Symfony IOL

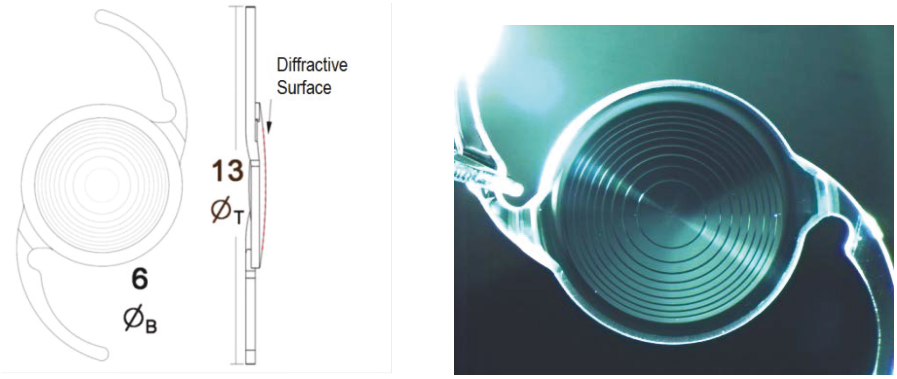
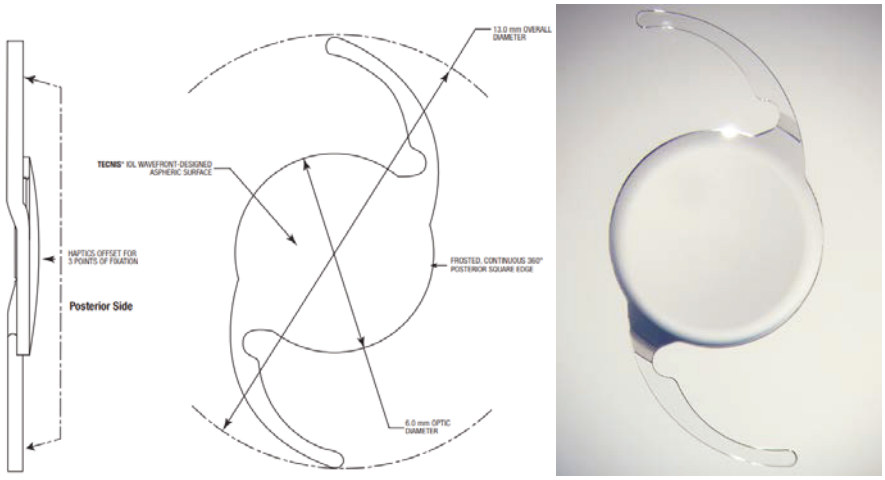


Figure 3: Drawing and Photograph of a TECNIS IOL, Model ZCB00



Like all of JJSV's 1-piece soft acrylic IOLs, investigational IOL Model ZHR00, TECNIS Symfony IOL Model ZXR00, and the TECNIS IOL Model ZCB00 have a surface treatment of Polyethylene Glycol (PEG) to reduce tackiness of the lens surface and include a ProTEC 360° barrier edge, the stability of Tri-Fix 3-point design, and a frosted-edge treatment.

INDICATIONS FOR INVESTIGATIONAL IOL

The Model ZHR00 is currently indicated for primary implantation for the visual correction of aphakia, in adult patients with less than 1 diopter of preexisting corneal astigmatism, in whom a cataractous lens has been removed. The lens mitigates the effects of presbyopia by providing an extended depth of focus. Compared to an aspheric monofocal IOL, the lens provides improved intermediate and near visual acuity, while maintaining comparable distance visual acuity. The Model ZHR00 IOL is intended for capsular bag placement only.

INDICATIONS FOR CONTROL IOL

The TECNIS monofocal IOL Model ZCB00 is indicated for the visual correction of aphakia in adult patients in whom a cataractous lens has been removed by extracapsular cataract extraction. These devices are intended to be placed in the capsular bag.

STORAGE AND DISTRIBUTION

Consignments of the investigational study lens models will be supplied to the investigative sites. All study lenses should be stored in the original packaging and kept in a dry place. Lenses should not be stored in direct sunlight or at temperatures greater than 45° C (113°F). Each lens is packaged in a lens tray and sealed in a peel-pouch. The lens is sterile as long as the package has not been opened or damaged and the shelf-life expiration date has not been exceeded. The Principal Investigator is responsible for ensuring that the investigational lenses are used only for subjects enrolled in this study.

COMPARISON CHART

Table 1 describes the dimensional and optical similarities between the study lenses and other associated JJSV lenses.

Table 1: Comparison of Design Features

	SENSAR 1-PIECE IOL MODEL AAB00 (MECHANICAL/MATERIAL PARENT)	TECNIS 1-PIECE IOL MODEL ZCB00 (MONOFOCAL ANALOG)	TECNIS SYMFONY EXTENDED RANGE OF VISION IOL MODEL ZXR00 (OPTICAL PARENT)	MODEL ZHR00 (SUBJECT DEVICE)
LENS DESIGN	1-piece acrylic monofocal with spherical anterior surface	1-piece acrylic monofocal with aspheric anterior surface	1-piece acrylic extended range of vision IOL with aspheric anterior surface	1-piece acrylic extended range of vision IOL with aspheric anterior surface
LENS MATERIAL	Surface-treated SENSAR® soft acrylic material	Same as AAB00	Same as AAB00	
DIMENSIONAL FEATURES				
OVERALL DIAMETER	13.0 mm	Same as AAB00	Same as AAB00	
OPTICAL CENTER THICKNESS	0.74 mm (20 D lens)	0.72 mm (20 D lens)	0.66 mm	Same as ZXR00
HAPTIC ANGLE	No angulation, but offset from optic body	Same as AAB00	Same as AAB00	
OPTIC BODY DIAMETER	6.0 mm	Same as AAB00	Same as AAB00	
HAPTIC MATERIAL	Same as optic	Same as AAB00	Same as AAB00	
HAPTIC WIDTH	0.39 mm	Same as AAB00	Same as AAB00	
HAPTIC THICKNESS	0.46 mm	Same as AAB00	Same as AAB00	
HAPTIC STYLE	C-Loop	Same as AAB00	Same as AAB00	
OPTICAL FEATURES				
OPTIC SHAPE	Biconvex	Same as AAB00	Same as AAB00	
ANTERIOR OPTIC PROFILE	Spherical	Aspheric	Same as ZCB00	
POSTERIOR OPTIC PROFILE	Spherical monofocal	Same as AAB00	Diffractive extended range of vision	Same as ZXR00
OPTIC EDGE DESIGN	PROTEC squared edge	Same as AAB00	Same as AAB00	
DIOPTER POWER RANGE	+6.0 to +30.0D in 0.5D increments	+5.0 to +34.0D in 0.5D increments[1]	Same as ZCB00[1]	
REFRACTIVE INDEX	1.470 (35° C)	Same as AAB00	Same as AAB00	
ADD POWER	N/A	N/A	N/A[2]	N/A[3]
RANGE OF VISION	N/A	N/A	Through 2.0 D[2]	Through 3.0 D[3]

[1] Only IOLs from +14.0 D to +26.0 D will be used in the clinical study.
[2] There is no distinct add power. Clinically, the range of the defocus with binocular visual acuity above 0.2 LogMAR is approximately 2.0 D in the near direction.
[3] There is no distinct add power.

7.2 IOL IMPLANTATION SYSTEMS

The investigational TECNIS IOL Model ZHR00 and the control TECNIS IOL Model ZCB00 lenses are to be implanted using the UNFOLDER Platinum 1 Series Implantation System (DK7796 handpiece with the UNFOLDER Platinum 1 Series cartridge, Model 1MTEC30) or the ONE SERIES Ultra Implantation System (DK7786 or DK7791 handpiece with the One Series Ultra cartridge, Model 1VIPR30).

8. STUDY POPULATION

All study subjects will be enrolled from the normal surgical cataract population at up to 10 sites in the U.S.A. Up to 264 subjects will be enrolled to achieve approximately 220 randomized and bilaterally implanted subjects, resulting in at least 200 evaluable subjects (a minimum of 100 in each test and control groups) at 6 months. This allows for a screen failure rate of approximately 15% and a drop-out rate of approximately 10% for implanted subjects. Each site should implant a minimum of 20 subjects, and no site may implant more than 25% of the enrollment total.

This study will include only subjects undergoing bilateral primary cataract extraction and IOL implantation and who meet all of the study inclusion and exclusion criteria in both eyes. All subjects who meet the eligibility criteria will be offered enrollment in the study. Eligibility criteria may not be waived by the investigator. Any questions regarding patient eligibility are to be discussed with JJSV prior to subject enrollment. Those subjects who meet the eligibility criteria and agree to participate will be randomized to receive either the Model ZHR00 or Model ZCB00 control IOLs in both eyes. Subjects will be enrolled at each site sequentially until the overall study recruitment goals are met or the site limit is reached.

8.1 INCLUSION CRITERIA

Note: All criteria apply to each eye

- Minimum 22 years of age
- Bilateral cataracts for which posterior chamber IOL implantation has been planned
- Preoperative best-corrected distance visual acuity (BCDVA) of 20/40 Snellen or worse with or without a glare source
- Potential for postoperative BCDVA of 20/30 Snellen or better
- Corneal astigmatism:
  - Normal corneal topography
  - Predicted postoperative corneal astigmatism of less than 1.00 D in both eyes
- Clear intraocular media other than cataract in each eye
- Availability, willingness and sufficient cognitive awareness to comply with examination procedures and study visits

- Signed informed consent and HIPAA authorization or equivalent documentation necessary to comply with applicable privacy laws pertaining to medical treatment in the governing countries
- Ability to understand and respond to a questionnaire in English

8.2 EXCLUSION CRITERIA

Note: All criteria apply to each eye

- Requiring an intraocular lens power outside the available range of +14.0 D to +26.0 D
- Any clinically-significant pupil abnormalities (non-reactive, fixed pupils, or abnormally-shaped pupils)
- Irregular corneal astigmatism
- Inability to focus or fixate for prolonged periods of time (e.g., due to strabismus, nystagmus, etc.)
- Prior corneal refractive (LASIK, LASEK, RK, PRK, etc.) or intraocular surgery, Including prophylactic peripheral iridotomies and peripheral laser retinal repairs
- Corneal abnormalities such as stromal, epithelial or endothelial dystrophies (e.g., any observed guttata) that are predicted to cause visual acuity losses to a level worse than 20/30 Snellen during the study
- Inability to achieve keratometric stability for contact lens wearers
- Recent ocular trauma or ocular surgery that is not resolved/stable or may affect visual outcomes or increase risk to the subject
- Subjects with diagnosed degenerative visual disorders (e.g., macular degeneration or other retinal disorders) that are predicted to cause visual acuity losses to a level of 20/30 Snellen or worse during the study
- Subjects with conditions associated with increased risk of zonular rupture, including capsular or zonular abnormalities that may lead to IOL decentration or tilt, such as pseudoexfoliation, trauma, or posterior capsule defects
- Use of systemic or ocular medications that may affect vision
- Prior, current, or anticipated use during the course of the 6-month study of tamsulosin or silodosin (e.g., Flomax, Flomaxtra, Rapaflo) that may, in the opinion of the investigator, confound the outcome or increase the risk to the subject (e.g., poor dilation or a lack of adequate iris structure to perform standard cataract surgery)
- Poorly-controlled diabetes
- Acute, chronic, or uncontrolled systemic or ocular disease or illness that, in the opinion of the investigator, would increase the operative risk or confound the outcome(s) of the study (e.g., immunocompromised, connective tissue disease, suspected glaucoma, glaucomatous changes in the fundus or visual field, ocular inflammation, etc.). Note: controlled ocular hypertension without glaucomatous changes (optic nerve cupping and visual field loss) is acceptable.
- Known ocular disease or pathology that, in the opinion of the investigator,
  - may affect visual acuity
  - may require surgical intervention during the course of the study (macular degeneration, cystoid macular edema, diabetic retinopathy, uncontrolled glaucoma, etc.)
  - may be expected to require retinal laser treatment or other surgical intervention during the course of the study (macular degeneration, cystoid macular edema, diabetic retinopathy, etc.)

- Patient is pregnant, plans to become pregnant, is lactating or has another condition associated with the fluctuation of hormones that could lead to refractive changes
- Concurrent participation or participation within 60 days prior to preoperative visit in any other clinical trial
- Desire for monovision correction

9. INVESTIGATOR SELECTION

9.1 INVESTIGATOR QUALIFICATIONS

JJSV will select ophthalmic surgeons who have completed a residency in ophthalmology (or its documented equivalent) and are licensed to practice medicine and perform surgery at his/her investigative site. Each site will have one designated principal investigator; some sites may have additional implanting sub-investigators/surgeons.

Investigators will be selected from surgeons who are experienced in small-incision, surgery and have implanted TECNIS Symfony Model ZXR00 IOLs in cataract patients. Investigators should have established their personalized A-constant for the TECNIS Monofocal Model ZCB00 IOL. All sites are required to have adequate staff support for reporting and subject follow-up, as well as the necessary instrumentation to conduct study testing.

9.2 INVESTIGATOR OBLIGATIONS

Investigators are required to fulfill the following obligations:

- Conduct the study in accordance with the relevant and current protocol. Investigator will make changes to a protocol only after notifying and obtaining approval from JJSV, the FDA and the Investigational Review Board (IRB), except when necessary to protect the safety, rights or welfare of subjects
- Personally conduct and supervise the study
- Maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties
- Be responsible for protecting the rights, safety and welfare of subjects under the investigator's care and be responsible for the control and documentation of the devices under investigation
- Inform patients that the device(s) are being used for investigational purposes and that requirements relating to obtaining informed consent and IRB approval are met according to 21CFR50, 21CFR56, 21CFR812 and all other applicable laws and regulations
- Maintain confidentiality as required by HIPAA or similar laws and regulations
- Shall not obtain written informed consent from any subject to participate or allow any subject to participate before obtaining FDA and IRB approval
- Document in each subject's case history that informed consent was obtained prior to participation in the study as required by 21CFR812

- Report to JJSV and the reviewing IRB any adverse experiences that occur during the course of the study in accordance with applicable laws and regulations
- Maintain adequate and accurate records in accordance with applicable laws and regulations and make available all study documents and subject medical records for inspection by either JJSV, duly authorized regulatory agencies (e.g., FDA, PMDA, Health Canada, MOH, etc.) and/or the IRB
- Submit progress reports on the investigation to JJSV and the reviewing IRB at regular intervals, but no less often than yearly as required by 21CFR812.150
- Ensure the IRB that is responsible for initial and continuing review of the study complies with applicable laws and regulations
- Report all changes in research activity and all unanticipated problems involving risks to patients to the IRB and JJSV
- Supervise and permit investigational device use and disposition in accordance with applicable regulations and protocol requirements. Upon completion of enrollment or termination of the study or the investigator's part of the study, or at JJSV's request, return to JJSV any remaining supply of the investigational device
- Provide sufficient accurate financial information to JJSV to allow JJSV to submit complete and accurate certification or disclosure statements as required by 21CFR54. Promptly update this information if any relevant changes occur during the course of the investigation or for up to one year following completion of the study
- Comply with all other obligations of clinical investigators and requirements according to all applicable FDA regulations (e.g., 21CFR812), all other applicable laws and regulations, and all conditions of approval imposed by the reviewing IRB and the FDA
- Ensure that all associates, colleagues and employees assisting in the conduct of the study are adequately informed about the protocol, the investigational device, their study-related duties and functions and agree to fulfill their obligations in meeting the above commitments.

Investigators shall provide adequate time and resources to conduct and report on the study. The Investigator, or delegate, shall notify JJSV of any change in the conduct of the study including changes in study personnel assigned to the study project, location of the investigational device(s), or maintenance of study records, etc.

9.3 INVESTIGATOR APPROVAL

It is the responsibility of the investigator to obtain prospective approval of the study protocol, protocol amendments or changes, informed consent forms and other relevant documents (e.g., advertisements) from the IRB. All correspondence with the IRB should be retained in the Investigator Study Files/Notebook. Copies of IRB submissions and approvals should be forwarded to JJSV. Study sites will obtain IRB approvals and fulfill any other site-specific regulatory requirements. The investigator is required to report to JJSV within five working days any withdrawal of approval by the reviewing IRB for his/her participation in the investigation.

Prior to the start of subject enrollment, the following documents must be signed and returned to JJSV:

- Confidentiality Agreement
- Clinical Trial Agreement
- Investigator Agreement/Protocol Signature page
- Clinical Investigator Brochure Signature page
- Financial Disclosure form
- Signed and dated copy of investigator's current curriculum vitae
- Copy of the investigator's current medical license
- Hospital/Ambulatory Surgery Center Clinical Study Acknowledgement, if required

By signing the study documents, the investigator agrees to conduct this study according to the obligations above and all other applicable regulatory and legal requirements.

10. EXPERIMENTAL PLAN

10.1 OVERVIEW

This study will be conducted in accordance with U.S. Code of Federal Regulations, the Declaration of Helsinki, ISO 14155:2011 and all other applicable laws and regulations. The study will not begin until regulatory and IRB approvals have been obtained.

This study will be a prospective, multicenter, bilateral, randomized, comparative subject/evaluator-masked clinical investigation conducted at up to 10 sites. Up to 264 subjects will be enrolled to achieve approximately 220 randomized and bilaterally implanted subjects, resulting in a minimum of 200 evaluable subjects (approximately 100 in each test and control groups) at 6 months. After informed consent is obtained and confirmation that all eligibility criteria are met, the eye(s) may be treated.

After signing the informed consent form, subjects meeting all eligibility criteria will be randomized to receive lenses from the same lens group in both eyes: either the investigational Model ZHR00 or the Model ZCB00 control IOL. For each subject, the investigator will choose which eye to operate on first at his/her discretion based on his/her standard clinical practice (e.g., the eye with the worse cataract, poorer best-corrected distance vision and/or more severe optical/visual complaints). All subjects are intended to have bilateral cataract surgery with the second-eye surgery occurring after the 1-week postoperative exam for the first eye, but no more than 30 days after the first-eye surgery. All subjects will be examined through 6 months postoperatively according to the visit schedule described in Section 10.2, Visit Schedule.

Although the investigators implanting the lenses cannot be masked, subjects and study evaluators responsible for conducting all vision testing will remain masked to which lenses were implanted through the 6-month study visit. Because differences between

the investigative and control lenses may be discernible upon slit-lamp examination, special care must be taken to maintain masking of study technicians. As such, it is recommended that only the investigator, sub-investigator or other designated and trained clinician perform all biomicroscopic slit-lamp exams. To maintain consistency, as well as masking, it is recommended that a single individual (study technician or coordinator designated by the investigator) conduct all postoperative study-related vision testing, although a back-up person should also be designated and trained.

Key preoperative data include ocular health and history, visual acuities, manifest refraction, keratometry, topography, biomicroscopic slit-lamp findings, ocular symptoms and biometry. The operative visit will include standard procedures for cataract surgery and IOL implantation. Key postoperative data collection includes monocular and binocular uncorrected and distance-corrected visual acuities, contrast sensitivity, defocus curve, slit-lamp findings, non-directed visual symptoms, questionnaires and adverse events. A chart summary of all examination procedures required at each study visit is provided in **Appendix A**. If needed, specific equipment necessary to perform the required procedures will be supplied for the duration of the study (**Appendix B**).

10.2 VISIT SCHEDULE

The study visit schedule for all study subjects is outlined in **Table 2**.

All subjects are intended to have bilateral cataract surgery with the second-eye surgery occurring after the 1-week exam for the first eye but no more than 30 days after the first-eye surgery. After each surgery, each eye will be postoperatively examined at 1 day (1-2 days), 1 week (7-14 days), and 1 month (30-60 days). Based on the date of the second-eye surgery, both eyes will be evaluated at 6 months (120-180 days) postoperative. Unscheduled visits may be conducted as necessary at the discretion of the investigator for medically-indicated follow-up.

TABLE 2: Visit Schedule

VISIT	EYES EVALUATED	EXAM	VISIT WINDOW
1	Both Eyes	Preoperative Exam	Within 60 days prior to 1st surgery
2	First Eye	Operative	0-60 days after preoperative exam
3	First Eye	1 day	1-2 days postoperative
4	First Eye	1 week[a]	7-14 days postoperative
5	First Eye	1 month	30-60 days postoperative
6	Second Eye	Operative[a]	No more than 30 days after 1st eye surgery
7	Second Eye	1 day	1-2 days postoperative
8	Second Eye	1 week	7-14 days postoperative
9	Second Eye	1 month	30-60 days postoperative
10	Both Eyes	6 months[b]	120-180 days postoperative from 2nd implant

[a] The 1-week exam for the first eye is to be completed prior to surgery on the second eye.

[b] If for any reason the second eye does not get implanted, the first eye should be seen for the 6-month study visit 127 - 210 days following the first-eye implant.

10.3 PREOPERATIVE PROCEDURES

All subjects treated in the study must sign the current IRB-approved informed consent form and meet the eligibility criteria. The informed consent form must be signed before any study-specific examinations are performed, and this must be documented in the source documents. An Authorization for Use/Disclosure of Health Information Form (HIPAA authorization) or similar medical treatment privacy law documentation must also be signed.

All preoperative testing for the study must be completed within 60 days prior to the first surgery. Data from routine (non-study-specific) preoperative cataract examinations performed prior to the informed consent process may be included, provided these tests are conducted no more than 60 days prior to the first-eye surgery and the test date(s) are documented on the preoperative Case Report Form (CRF). If a test/exam is required by the protocol, but is not part of the routine testing the investigator performs for the cataract evaluation, that test/exam is considered to be study-specific and is not to be done until after the informed consent form has been signed by the subject. Following the informed consent process, completion of the preoperative study exam and determination that the subject meets all of the required entrance criteria (including lens power determination), the subject may be randomized and scheduled for surgery.

As the Informed Consent Form is signed at the beginning of the preoperative study exam, some subjects may not qualify after study-specific testing is performed. Subjects will be considered screen-failures if they do not qualify, or if they qualify but decide not to

participate further in the study, or if they decide not to proceed with surgery. These subjects will be exited from the study.

Preoperative testing to be performed for each eye includes the following:

POTENTIAL DISTANCE VISUAL ACUITY

The subject must be capable of achieving Snellen 20/30 or better best-corrected distance vision in each eye after cataract extraction and IOL implantation. The surgeon may use his/her judgment, the Potential Acuity Meter (PAM), or other methods (e.g., pinhole, laser interferometer, etc.) to estimate the subject's potential postoperative acuity.

BEST-CORRECTED DISTANCE VISUAL ACUITY AND MANIFEST REFRACTION

Preoperative manifest refraction is required. Monocular, best-corrected distance visual acuity (BCDVA) is to be measured using a standard Snellen chart or equivalent and must be Snellen 20/40 or worse, with or without a glare source.

KERATOMETRY

Predicted postoperative corneal astigmatism, as measured by keratometry, should be less than 1.00 D. No irregular astigmatism should be present preoperatively. If the preoperative keratometric astigmatism is greater than 0.50 D, assess the impact of posterior corneal astigmatism (PCA) on predicted residual astigmatism by using a calculator that accounts for PCA (e.g., J&J TECNIS Toric Calculator, Barrett Toric Calculator, etc.).

CONTACT LENS WEAR AND CORNEAL STABILITY

For contact lens wearers, keratometric corneal stability following cessation of contact lens wear must be verified before surgery. PMMA contact lenses are not to be worn for at least 6 months; rigid gas-permeable contact lenses are not to be worn for at least 1 month; and extended-wear or daily-wear soft contact lenses are not to be worn for at least 1 week prior to the preoperative visit. Corneal stability must be verified for any subject who has worn PMMA lenses within 5 years or any other type of contact lenses within 6 months prior to the preoperative visit. To verify stability, repeat the keratometric measurements at least 1 week after the initial preoperative baseline keratometric measurement. Corneal curvature is considered to be stable if the difference in keratometric cylinder (vertical vs. horizontal keratometric readings) between the two time points does not exceed 0.50 D. Additionally, the difference between the two horizontal readings as well as the difference between the two vertical readings must be no more than 0.50 D. Changes in keratometric axis must be no more than ±15°. If a change exceeding these criteria is noted, surgery is to be postponed until keratometric stability is demonstrated. Final biometry measurements and surgery should not take place until

keratometric stability is achieved. Note: if this method of determining corneal stability is not a standard procedure in your practice, the subject must sign the informed consent form prior to starting the stability procedure.

IOL POWER AND TARGETED REFRACTION

Axial length and anterior chamber depth (ACD) must be measured to determine the appropriate lens power to implant using an A-Constant. IOLMaster, Lenstar or immersion biometry methods are preferred; however, surgeons should use the biometry method with which they have the most experience and that which was used in the determination of the personalized A-Constant for the TECNIS Monofocal IOL Model ZCB00. As the control and investigational lenses have different recommended A-Constants, IOL power should be determined for both the control lens, Model ZCB00 with the labeled A-Constant of 119.3, and for the investigational lens, Model ZHR00 with the labeled A-Constant of 119.1 prior to randomization. For the control lens, the investigator should use the labeled A-Constant of 119.3 or use their personalized A-Constant for the Model ZCB00 monofocal lens. For the investigational lens, the investigator should use either the labeled ZHR00 A-Constant of 119.1 or their personalized ZCB00 A-Constant **with an adjustment by -0.2 D**. The lens power should be calculated to achieve emmetropia at distance. Intentional over- or under-correction should NOT be planned for either eye; however, surgeons may adjust the targeted refraction for the second eye only as necessary to achieve emmetropia based on subject first-eye outcomes.

ADDITIONAL PREOPERATIVE INFORMATION TO BE COLLECTED:

- Informed consent documentation
- Subject demographic information
- Planned surgery dates for each eye
- Ocular history, including presence of ocular pathology for each eye
- Intraocular pressure for each eye
- Cataract type and density for each eye
- Fundus exam results for each eye
- Medical findings from a biomicroscopic slit-lamp exam for each eye
- Ocular symptoms for each eye
- Ocular and systemic medications

10.4 RANDOMIZATION AND MASKING

A randomization list will be created by the JJSV biostatistician for each investigative site and the randomization code will be uploaded into the electronic data capture system (EDC). Subjects will be randomized to the investigational Model ZHR00 IOL or the Model ZCB00 control IOL. Unmasked study personnel at the site will be trained to the randomization process through the EDC system and will randomize subjects after the

subject has signed the informed consent form, has met all eligibility criteria and the investigator has documented which eye will be the first implanted.

As part of the informed consent process, the investigator or delegate will explain to the subject the requirements of a randomized study and the differences expected between the two lens models in the study: the Model ZHR00 investigational lens and the Model ZCB00 control lens. The surgeon and the operative staff will know which lens type is implanted. There may also be site coordinators and other site study staff, such as those performing slit-lamp exams, who will be unmasked. Unmasked study site staff will be instructed not to disclose the lens type the subject received or to talk about the lens to any masked evaluators or to the study subjects.

The subjects and the study technicians performing the postoperative vision tests are to be masked through study completion. To maintain subject/technician-masking through the 6-month study exams, a masking plan will be tailored for each site to detail how lens assignment information will be concealed from masked technicians. Recommended steps to maintain masking include ensuring that all items pertaining to lens group assignment and lens implantation records are kept separately from all other study documents and subject medical records until after completion of the final study visit. For example, lens stickers (indicating the lens model implanted) may be kept in the operating room study notebook until completion of the final study visit, at which time they may be placed in the subject medical charts. In the meantime, temporary lens stickers (without lens model designations) may be used in the subject's medical chart.

To maintain subject masking, a temporary IOL implant identification card will be issued to the subject at the time of surgery. Following completion of the final study exam, each subject will be given the permanent IOL implant identification card.

10.5 STUDY LENS SUPPLY

The investigational Model ZHR00 lenses and the Model ZCB00 control lenses will be obtained from site consignments, supplied by JJSV following IRB approval. Two lenses should be available for each case, a primary lens and a back-up lens. Unused back-up lenses are to be returned to the site consignment. At the completion of study enrollment, any remaining consignment lenses will be shipped back to JJSV following reconciliation of investigational lens inventory by an JJSV CRA. Any remaining control lenses will also be returned to JJSV. At all times, the storage, access and use of all investigational lenses must be controlled and complete lens accountability maintained (See Section 15.2 Lens Accountability).

10.6 OPERATIVE PROCEDURES

The investigator should use his or her standard, small-incision, cataract extraction surgical technique. Lenses should be folded for implantation and inserted into the

capsular bag using one of the JJSV-validated insertion systems described in Section 7.2.

Investigators should manage surgical outcomes to ensure that the total postoperative refractive astigmatism is as minimal as possible. The total postoperative astigmatism, including surgically-induced astigmatism, should be targeted to be less than 1.0 D. Astigmatism may be managed by incision type and placement only. **No additional refractive procedures are to be performed during the operative procedure or throughout the postoperative study period (e.g., LRI, OCCI, CRI, AK, PRK, LASIK or LASEK).**

Operative case report forms will include the following information:

INCISION TYPE AND SIZE

Lenses should be inserted through an incision ranging in size from approximately 2.2-3.0 mm, per the investigator's standard technique when using the UNFOLDER Platinum 1 Series Implantation System or the ONE SERIES Ultra Implantation System. The incision may be clear corneal, limbal or scleral tunnel at the discretion of the investigator.

CAPSULORHEXIS SIZE AND METHOD

The anterior capsulotomy should be a continuous, curvilinear capsulorhexis approximately 5.0 to 5.5 mm in diameter to allow slight overlap of the lens optic edge. The anterior capsulotomy method may be manual (rhexis) or laser-assisted.

LENS REMOVAL

Lens removal may occur using laser fragmentation combined with phacoemulsification/aspiration or using only phacoemulsification/aspiration.

VISCOELASTIC

Viscoelastic materials should be used as is customary for each investigator and recorded on the case report form (CRF).

IMPLANT INSTRUMENTATION USED

Lenses should be folded for implantation and inserted into the capsular bag using either the UNFOLDER Platinum 1 Series Implantation System (DK7796 handpiece with the Platinum 1 Series cartridge, Model 1MTEC30) or the ONE SERIES Ultra Implantation System (DK7786 [plunger] or the DK7791 [twist] handpieces with the ONE SERIES Ultra cartridge, Model 1VIPR30).

SURGICAL COMPLICATIONS

Should a surgical complication occur, implantation of a study lens will be at the investigator's discretion. In the event of capsular bag or zonular rupture, the lens should not be implanted if the complication may result in lens instability. Additionally, the lens is not to be implanted in the sulcus. In this case, the investigator may implant his/her choice of a back-up, non-investigational IOL. The subject should be exited from the study if a non-study lens is implanted as a result of a surgical complication during the first-eye implantation; however, the eye will be followed until resolution of the complication prior to exiting the subject. Should a surgical complication occur during the second-eye surgery and result in implantation of a non-study lens, the subject will not be exited from the study; the first eye will continue to be followed per-protocol, although data may be analyzed separately, and the second eye will be followed for safety until resolution of the complication.

MEDICATIONS

Preoperative, operative and intraoperative medications should be used as is customary for each investigator and will be recorded on the CRF.

TYPE OF CLOSURE

Wound closure is left to the surgeon's discretion and will be recorded on the CRF.

ADDITIONAL OPERATIVE INFORMATION COLLECTED INCLUDES:

- Date of surgery
- Operative eye
- Lens power and serial number
- Lens placement
- Other surgical procedures
- Surgical technique according to protocol
- Product complaints
- Serious and/or device-related adverse events

10.7 POSTOPERATIVE PROCEDURES

Postoperatively, subjects will be examined according to the schedule in Section 10.2, Visit Schedule. Only the most recently operated eye will be evaluated at the respective 1-day, 1-week and 1-month visits.

NOTE: for the 1-month visits, the first and second eyes should be examined at separate visits if the visit intervals do not overlap. However, if the 1-month visit intervals for the first and second eye overlap, both eyes may be examined at a single visit.

Both eyes will be evaluated at the 6-month visit.

Study technicians responsible for conducting all vision testing will be masked. Therefore, it is recommended that only the investigator/sub-investigator or other designated and trained clinician perform the biomicroscopic slit-lamp exams. To maintain consistency and masking throughout the study, it is recommended that a single individual (study technician or coordinator designated by the investigator) conduct all postoperative study-related vision testing, although a back-up person should also be designated and trained.

Note: Subjects are not to wear contact lenses postoperatively until after completion of this study. Wearing contact lenses may potentially cause corneal edema or topography changes that may influence the visual acuity results. During the study, if correction is required, spectacles should be prescribed.

A postoperative CRF will collect the following information, although not all data are required at every visit (see **Appendix A**):

MANIFEST REFRACTION AND REFRACTION ADJUSTMENTS (MASKED PROCEDURE)

Postoperative study manifest refractions are to be performed using the M&S System at a distance of 4.0 meters. Manifest refraction (MR) is to be performed using the Maximum Plus refraction method as detailed in **Appendix C**.

Because 4.0 meters is not optical infinity, refraction adjustments are necessary to ensure proper vision testing, taking into account test distance and refraction distance. **Appendix D** lists the refraction adjustments required for the various vision tests using the BCDVA refraction.

DISTANCE VISUAL ACUITY TESTING (MASKED PROCEDURE)

Distance visual acuity will be measured postoperatively under photopic lighting conditions (85 cd/m^2, 80–110 cd/m^2 acceptable) using the M&S System at a test distance of 4.0 meters. For eyes unable to achieve a postoperative BCDVA of Snellen 20/40 (i.e., LogMAR 0.3, number of letters correct 70), a reason must be specified. Instructions for using the M&S System are detailed in **Appendix E**, and for distance visual acuity in **Appendix F**.

The following distance visual acuity measurements are to be performed per the visit schedule in **Appendix A**:

Test	Test Distance	Illumination	Type of Testing	Refraction Adjustment
UCDVA	4 m	Photopic (85 cd/m^2)	Monocular, Binocular	+0.25 D adjustment only
BCDVA	4 m	Photopic (85 cd/m^2)	Monocular only	No adjustment; ETDRS Rx only

INTERMEDIATE VISUAL ACUITY (MASKED PROCEDURE)

Intermediate visual acuity (including low contrast at 10%) will be measured under photopic conditions (85 cd/m^2, 80-110 cd/m^2 acceptable) using the M&S System at a test distance of 66 cm. Instructions for using the M&S System are detailed in **Appendix E** and for intermediate testing in **Appendix G.**

The following intermediate visual acuity measurements are to be performed per the visit schedule in **Appendix A**:

Test	Test Distance	Illumination	Type of Testing	Refraction Adjustment
UCIVA	66 cm	Photopic (85 cd/m^2)	Monocular, Binocular	No adjustment
DCIVA	66 cm	Photopic (85 cd/m^2)	Monocular only	-0.25 D added to ETDRS sphere Rx
DCIVA Low Contrast	66 cm	Photopic (85 cd/m^2)	Monocular, first eye only	-0.25 D added to ETDRS sphere Rx
BCIVA Low Contrast*	66 cm	Photopic (85 cd/m^2)	Monocular, first eye only	-0.25 D added to ETDRS sphere Rx

* With distance correction and the minimum add required to reach best intermediate visual acuity.

NEAR VISUAL ACUITY (MASKED PROCEDURE)

Near visual acuity will be measured under photopic conditions (85 cd/m^2, 80-110 cd/m^2 acceptable) using the Good-Lite self-calibrating, retro-illuminated box with 100% contrast ETDRS near charts at a test distance of 40 cm.

Instructions for using the ETDRS near chart, including setting appropriate lighting conditions, and the visual acuity conversion chart between the number of ETDRS letters read and Snellen equivalents are provided in **Appendix H**.

The following near visual acuity measurements are to be performed per the visit schedule in **Appendix A**:

Test	Test Distance	Illumination	Type of Testing	Refraction Adjustment
UCNVA	40 cm	Photopic (85 cd/m^2)	Monocular, Binocular	No adjustment
DCNVA	40 cm	Photopic (85 cd/m^2)	Monocular	-0.25 D added to ETDRS sphere Rx

DEFOCUS TESTING (MASKED PROCEDURE)

Monocular and binocular best-corrected distance defocus testing will be performed on all subjects at the 6-month visit in accordance with the methodology described in the draft standard for Extended Depth of Focus Intraocular Lenses from the American National Standards Institute (ANSI Z80.35 v7). While the testing includes plus-power defocus, the study endpoint is based upon minus-power defocus results.

Defocus testing will be performed under photopic conditions (85 cd/m^2, 80-110 cd/m^2 acceptable) using the M&S System at 4.0 meters with the ETDRS refraction in place (no adjustment necessary for test distance). The subject is to be defocused in -0.50 D increments from +2.00 D through +4.00 D. Defocusing can be done with either spherical loose trial lenses or plus- and minus-power lens racks.

At each defocus increment, a LogMAR visual acuity is to be obtained and recorded. Further instructions for defocus testing are detailed in **Appendix I**.

The following defocus curve measurements are to be performed per the visit schedule in **Appendix A**:

Test	Test Distance	Illumination	Type of Testing	Refraction Adjustment
Defocus	4 m	Photopic (85 cd/m^2)	Monocular, first eye only Binocular	No adjustment; ETDRS Rx only

PUPIL SIZE

Pupil sizes under photopic (with and without glare), and mesopic (with and without glare) lighting conditions will be measured postoperatively during the study. For consistency, the same method of measurement should be used throughout the study.

Photopic pupil size measurements are to be performed under the same lighting conditions at which photopic distance visual acuity is tested. Pupil sizes under the other

lighting conditions will be measured during the contrast sensitivity testing procedures. Instructions for measuring pupil size are detailed in **Appendix J.**

DISTANCE CONTRAST SENSITIVITY TESTING (MASKED PROCEDURE)

Best-corrected distance contrast sensitivity will be tested under mesopic with and without glare and photopic with glare conditions using the M&S System for sine-wave gratings at 1.5, 3.0, 6.0, 12.0 cycles per degree (cpd) (mesopic and mesopic with glare) and 3.0, 6.0, 12.0 and 18.0 cpd (photopic with glare). **The test distance is 8 feet (2.5 meters).** Best-corrected distance contrast sensitivity is to be performed with a +0.12 D refractive adjustment to the sphere of the manifest refraction. Detailed instructions for contrast sensitivity testing are provided in **Appendix K**.

The following contrast sensitivity measurements are to be performed per the visit schedule in **Appendix A**:

Contrast Sensitivity Test	Test Distance	Spatial Frequency	Type of Testing	Refraction Adjustment
Mesopic (3 cd/m^2) without glare	2.5 m	1.5, 3, 6 and 12 cpd	Monocular, first eye only	+0.12 D added to ETDRS sphere Rx
Mesopic (3 cd/m^2) with glare	2.5 m	1.5, 3, 6 and 12 cpd	Monocular, first eye only	+0.12 D added to ETDRS sphere Rx
Photopic (85 cd/m^2) with glare	2.5 m	3, 6, 12 and 18 cpd	Monocular, first eye only	+0.12 D added to ETDRS sphere Rx

BIOMICROSCOPIC SLIT-LAMP EXAM

A biomicroscopic slit-lamp exam must be performed at each postoperative visit to determine the presence or absence of any medical or lens findings, complications or adverse events. IOL decentration and tilt are to be determined subjectively. The center of the lens relative to the pupil can be used to determine IOL decentration, with the diffractive rings used as a guide to locate the center of the IOL. Note that the pupil center may not always be aligned with the visual axis of the eye; therefore, the investigator should consider deviations in pupil center from visual axis when reporting IOL decentration.

Findings of aqueous cells and flare, corneal edema, posterior capsule striae (wrinkles), posterior capsular opacification and IOL glistenings are to be rated using standardized grading scales of 0 to +4 (0 = none, +4 = severe) during the slit-lamp biomicroscopy. The specific grading scales are provided in **Appendix L**.

ND:YAG CAPSULOTOMY

If an Nd:YAG capsulotomy is necessary, it is recommended that the procedure be performed at least 1 week prior to a study exam; this is particularly important for the 6-month study visit, as this is the key study exam for evaluation of safety and effectiveness.

FUNDUS EXAM

A fundus exam is to be performed at the 6-month visit to evaluate retinal status and fundus visualization. Examinations may be done dilated with ophthalmoscopy or undilated with an imaging system that allows for undilated views of peripheral retina (e.g., Optomap). The same fundus examination method that was used preoperatively should be used for the 6-month study visit.

INTRAOCULAR PRESSURE

Intraocular pressure (IOP) is to be measured using the investigator's usual method. It is recommended that the same method be used for all study subjects at the site for the duration of the study.

OCULAR SYMPTOMS (NON-DIRECTED; SPONTANEOUS)

Subjective ocular symptoms are to be assessed at each postoperative visit by asking "Are you having any difficulties with your eyes/vision?" Subjects should not be prompted for specific responses; however, if a subject reports halos, night glare or starbursts, the level of severity should be determined (mild, moderate or severe).

MEDICATIONS

Postoperative ocular medications should be used as is customary for each investigator and recorded in the source document for each subject. Medications will be recorded on a medication log CRF as applicable.

ADVERSE EVENTS

Subjects should be assessed at each visit for occurrence of and/or change in status of any adverse events, particularly serious and/or device-related adverse events. See Section 11.0, Adverse Events, for further information.

QUESTIONNAIRES

Questionnaires will be administered at the 1-month and 6-month visits to collect information regarding spectacle usage, visual symptoms, visual quality and subject satisfaction. Four questionnaires will be used in this study:

1) Patient-Reported Visual Symptoms Questionnaire (PRVSQv2, **Appendix M**)
2) Patient-Reported Spectacle Independence Questionnaire (PRSIQv2, **Appendix N**)

3) Patient-Reported Spectacle Use Questionnaire (PRSUQ, **Appendix O**)
4) Patient-Reported Quality of Vision Questionnaire (Catquest-9SF, **Appendix P)**

In order to minimize any effect the doctor-patient relationship may have on a subject's responses on the questionnaire, the study questionnaires will be self-administered by the subjects. The questionnaires are to be administered at the start of the 1-month (second eye) and 6-month study visits, prior to any visual acuity testing.

In addition, if a subject is seen after the 1-month postoperative visit for an unscheduled visit due to an optical/visual symptom complaint, the PRVSQ will be administered at that visit, as well as prior to any secondary surgical intervention for an optical/visual symptom complaint. If additional unscheduled visits and/or a secondary surgical intervention due to the same optical/visual symptom complaint occur within 2 weeks of each other, it is not necessary to complete the PRO Visual Symptoms Questionnaire a second time.

The optical visual symptom complaints that trigger the PRO Visual Symptoms Questionnaire include any of the seven symptoms from the PRVSQ: halos, glare, starbursts, sensitivity to light, occlusions, double vision or poor light vision.

10.8 EXIT OF SUBJECTS

An Exit CRF will be completed for all subjects, either when they complete the study or if they exit early.

It is the responsibility of the investigator to provide complete follow-up data to JJSV for each subject, and every attempt should be made to gather that complete follow-up data for all subjects enrolled, as missing data can have a negative effect on the study results. Patients who would be traveling, relocating or otherwise unavailable for postoperative follow-up visits should not be enrolled in this clinical study.

A subject will be considered a "screen failure" if he/she does not meet the eligibility criteria or if consent is withdrawn prior to randomization.

A subject will be considered "discontinued prior to treatment" if the subject is randomized but does not undergo surgery or receive a study lens for various reasons including: the planned implant being aborted due to surgical complications, the subject withdrawing consent prior to treatment or the subject died prior to treatment.

Subjects will be "discontinued" from the study if one study lens (if implanted unilaterally) or both study lenses (if implanted bilaterally) are removed or if the subject dies.

If a subject receives at least one study lens, he/she is to be followed according to the schedule in Table 2 (Section 10.2) for visit windows.

Subjects will be considered “lost-to-follow-up” from the study only if irretrievably lost for unavoidable reasons such as: subject moved/unable to locate, subject ill/unable to travel, subject uncooperative/refuses further study participation. In the event of subject relocation, effort must be made by the investigator to secure follow-up information (i.e., slit-lamp findings and general visual acuity, etc.) from the subject’s new physician.

If a subject is exited early from the study, the investigator must indicate the reason for study exit on the CRF. In the event of a lens removal or other serious adverse event, the subject may be exited from the study; however, effort must be made by the investigator to follow the subject until resolution of the adverse event before exiting the subject from the study.

Following study completion or early exit, subjects will be informed about which lens model they received. Additionally, all study subjects are to be instructed to undergo regular eye examinations at least yearly and also to return to their doctor if any eye complications are experienced.

10.9 UNSCHEDULED VISITS

During the study period, if a non-protocol-required visit is done for the purpose of medically-indicated follow-up for a study eye, data from this visit should be reported using the Unscheduled Visit CRF. The need for unscheduled visits is at the investigator’s discretion. Specific examinations to be performed at unscheduled visits are also at the discretion of the investigator (based on the reason for the unscheduled visit) and data are to be recorded in the appropriate section of the CRF.

Data to be collected may include:

- Snellen manifest refraction
- Uncorrected and best-corrected distance visual acuity using a Snellen chart
- Intraocular pressure
- Slit-lamp examination for medical and/or lens findings
- Fundus exam
- Ocular symptoms
- Adverse events
- Medications

If, prior to the second-eye surgery, the fellow eye is re-examined (e.g., at a first-eye, 1-day visit) and there are clinically significant changes from the preoperative exam, data is to reported using the Unscheduled Visit CRF. If there are no changes or non-clinically significant changes from the original preoperative exam, an Unscheduled Visit CRF is not required.

At a second-eye 1-day or 1-week visit (or a 1-month visit, if the visit intervals for the first and second eyes do not overlap), if the first eye is examined and there are medical

and/or lens findings and/or a subject has an optical/visual symptom complaint, data are to be reported using the Unscheduled Visit CRF.

Conditions found postoperatively, but previously documented at the preoperative visit, do not trigger an unscheduled visit report. However, if the severity of the condition increases from the preoperative visit, an Unscheduled Visit CRF is needed.

In addition, if a subject is seen after the 1-month postoperative visit for an unscheduled visit due to an optical/visual symptom complaint, the PRO Visual Symptoms Questionnaire must be administered at that visit, as well as prior to any secondary surgical intervention for an optical/visual symptom complaint. If additional unscheduled visits and/or a secondary surgical intervention due to the same optical/visual symptom complaint occur within 2 weeks of each other, it is not necessary to complete the PRO Visual Symptoms Questionnaire a second time.

The optical visual symptom complaints that trigger the PRO Visual Symptoms Questionnaire include any of the seven symptoms from the PRVSQ: halos, glare, starbursts, sensitivity to light, occlusions, double vision or poor light vision.

10.10 PROTOCOL DEVIATIONS

Any departure from the protocol procedures represents a protocol deviation. Protocol deviations may be subject-based (e.g., inclusion/exclusion criteria, informed consent deviation, etc.) or procedural-based (e.g., out-of-interval visits, non-compliance with testing procedures, etc.). All protocol deviations will be documented using the protocol deviation CRF. Any deviation made to protect the life or physical well-being of a subject in an emergency as well as any use of the investigational device without obtaining informed consent must be reported to JJSV within 5 working days. Protocol deviations will be monitored by JJSV, and if the non-compliance is persistent or egregious, JJSV may take action, including but not limited to termination of the investigator's participation in the study. The investigator is also responsible for informing the reviewing IRB of instances of protocol non-compliance in accordance with the IRB requirements.

11. ADVERSE EVENTS AND PRODUCT COMPLAINTS

11.1 ADVERSE EVENT DEFINITIONS

Adverse Event (AE)

An adverse event is defined (per ISO 14155) as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the study device.

Serious Adverse Event (SAE)

An adverse event is considered serious (per ISO 14155) if it is an untoward occurrence which may or may not be related to use of the study device that

- is sight- or life-threatening,
- results in death,
- requires inpatient hospitalization or prolongation of hospitalization (a planned hospitalization for a pre-existing condition without a serious deterioration in health is not considered a serious adverse event),
- results in permanent impairment of a body structure or body function,
- necessitates medical or surgical intervention to prevent permanent impairment to a body structure or function, or
- results in fetal distress, fetal death or a congenital abnormality or birth defect

Device-Related Adverse Event/Adverse Device Effect (ADE)

A device-related adverse event is defined as any adverse event that is believed to be definitely, probably, possibly or unlikely to be related to the study device (following the guidelines in Section 11.4, Causal Relationship). A device-related event is also considered an adverse device effect (ADE; following ISO 14155) resulting from the use of the study device that may result from user error, insufficiencies or inadequacies in the instructions for use, deployment, implantation, installation, operation of any malfunction of the device.

Anticipated Study-Specific Serious Adverse Events

The following is a list including, but not limited to, ocular serious adverse events (SAE) that are anticipated and must be reported to JJSV for this study. Any events that are unlikely but anticipated (i.e., endophthalmitis) will be reported to the FDA and other appropriate regulatory agencies. Adverse event definitions in accordance with the American Academy of Ophthalmology Task Force Consensus Statement are included in **Appendix Q**.

- Endophthalmitis/Intraocular infection
- Hypopyon
- Hyphema
- IOL dislocation
- Cystoid macular edema
- Pupillary block
- Retinal detachment/tear
- Persistent corneal edema
- Persistent iritis
- Persistent uveitis
- Persistent raised IOP requiring treatment

- Toxic anterior segment syndrome
- Visual symptoms requiring secondary surgical intervention (e.g., lens removal)
- Tilt and decentration requiring secondary surgical intervention (e.g., repositioning)
- Residual refractive error resulting in a secondary surgical intervention
- Retained lens material resulting in secondary surgical intervention

NOTE 1: Wound burps during the first week postoperatively, suture removal, planned blepharoplasty and Nd:YAG capsulotomy (for PCO) are not considered adverse events for this study.

NOTE 2: IOP increase, corneal edema, and persistent uveitis/iritis will be considered serious according to the guidelines listed in **Appendix Q**. (i.e., IOP increase of 10 mm Hg from baseline to at least 25 mm Hg at any time; corneal edema resulting in BCDVA of 20/40 or worse at 1 month or later; and Grade 1+ uveitis/iritis longer than 3 months.

Unanticipated Adverse Device Effect (UADE)/Unanticipated Serious Adverse Device Effect (USADE)

Any UADE (USA 21CFR 812.3(s)) or USADE (ISO 14155) is defined as any serious adverse effect on 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 in the investigational plan (i.e., this protocol), application (including a supplementary plan or application), or risk assessment, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

11.2 PRODUCT COMPLAINT/DEVICE DEFICIENCY DEFINITION

A product complaint/device deficiency is defined (21 CFR 820.3(b) and ISO 14155) as any alleged deficiency related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device. This may include malfunctions, use error and inadequacies in labeling. Product complaints can pertain to any marketed JJSV device being used in the study as well as the investigational device. The investigator is to assess whether the deficiency could have led to a serious adverse event without suitable action or intervention or under less fortunate circumstances.

11.3 ADVERSE EVENT AND COMPLAINT REPORTING REQUIREMENTS

All adverse events and any complaint encountered using any JJSV product, regardless of severity and whether or not attributed to the study device(s), are to be reported to JJSV and recorded on the case report form corresponding to the visit during which awareness of the event occurred. Adverse events are also to be reported to the reviewing IRB as per the IRB's reporting requirements. If required, adverse events will

be reported to the appropriate regulatory agencies (e.g., FDA) according to all applicable laws and regulations.

Reporting of adverse events shall follow the USA Code of Federal Regulations (21CFR812) for sites in the USA. General guidelines are provided below:

Adverse Event Reporting

An adverse event that is not serious or device-related is to be reported to JJSV in a timely manner. Notification of non-serious and non-device related adverse events will occur by recording events on the CRF when noted. Such adverse events are also to be reported to the reviewing IRB per their reporting requirements.

Complaints/Device Deficiency Reporting

A general product complaint or device deficiency is to be reported to JJSV in a timely manner. Notification of complaints/device deficiencies will occur by recording complaints on the CRF at the visit the complaint occurs (e.g., operative visit) and/or by a phone call/email to JJSV.

Any device deficiency that could have led to a serious adverse event without suitable action or intervention, or under less fortunate circumstances, must be reported to the sponsor immediately (no later than 24 hours after detection). Device deficiencies that could have led to a serious adverse event should also be reported to the investigator's IRB per their reporting requirements.

Serious and/or Device-Related Adverse Event Reporting

SAEs and/or ADEs are to be documented using the Serious Adverse Event/Adverse Device Effect (SAE/ADE) CRF. In the event of an SAE, JJSV must be notified immediately (no later than 24 hours after detection). Any SAE/ADE is to be reported to JJSV by phone, email and/or by submitting the completed SAE/ADE CRF. Any SAE or device-related AE should also be reported to the investigator's IRB per their reporting requirements.

Unanticipated Adverse Device Effect (UADE)/Unanticipated Serious Adverse Device Effect (USADE) Reporting

If during the study, a serious adverse event occurs that may reasonably be regarded as device-related and was not previously expected in nature, severity, or degree of incidence, the investigator is to report the UADE/USADE to JJSV within 24 hours, and to the investigator's IRB as soon as possible (and no later than 10 working days after learning of the event for sites in the USA as required by 21CFR812).

11.4 CAUSAL RELATIONSHIP

The investigator should always be alert to adverse events that may be related to the study device or the use of the study device (i.e., the procedure specific to the initial application of the device). An attempt should be made in every case to determine the causality of the event. The following definitions are to be used as guidelines in determining the relationship between the event and the study device and/or use of the device.

Definitely related:	If the event is associated with the device and/or the use of the device beyond a reasonable doubt, a causal relationship exists between the adverse event and the device and/or the use of the study device.
Probably related:	There is a reasonable possibility of a causal relationship between the adverse event and the device and/or the use of the study device and/or the adverse event cannot be reasonably explained by another cause.
Possibly related:	The adverse event has not been determined to be related to the device or the use of the device, but no other cause has been identified and the device and/or the use of the study device cannot be ruled out as a possible cause.
Unlikely to be related:	The possibility of a potential causal relationship between adverse event and the device and/or the use of the device could exist, but the adverse event can be reasonably explained by another cause.
Not related:	There is no possibility of a causal relationship between the adverse event and the device and/or the use of the study device and/or the adverse event can be attributed to another cause.

If an adverse event is believed to be definitely, probably or possibly related to the study device and/or the use of the device, the event will be considered related to the study device and/or the use of the device.

11.5 ADVERSE EVENT FOLLOW-UP

For every adverse event, appropriate measures should be undertaken to treat and/or monitor the subject until resolution occurs. The subject's files are to include all pertinent medical data relating to the event including the subject’s medical records, medical reports and/or judgments from colleagues or outside specialists who assisted in the treatment and follow-up of the subject. The investigator should keep JJSV closely informed as to the outcome of serious and/or device-related adverse events, thereby allowing JJSV to comply with the appropriate regulatory reporting requirements. An SAE/ADE CRF should be completed each time the subject returns to the investigator or

other specialist(s) for follow-up of a serious and/or device-related adverse event until resolution of the event. Any subject who is to be exited from the study due to a serious and/or device-related adverse event should be followed until the outcome is determined prior to being exited from the study.

12. PROTOCOL CHANGES/AMENDMENTS

If the investigator wishes to modify any procedure and/or the design of the study, he or she must contact and obtain consent from JJSV regarding the proposed changes prior to implementation. Any modifications (including additional data collection) require approval by the FDA and all other appropriate regulatory agencies, as well as approval of the governing IRBs prior to implementation.

13. ETHICS REVIEW AND PATIENT WELFARE

13.1 INSTITUTIONAL REVIEW BOARD (IRB)

It is the responsibility of the investigator to obtain prospective approval of the study protocol, protocol amendments or changes, informed consent forms and other relevant documents (e.g., advertisements) from the IRB. All correspondence with the IRB should be retained in the Investigator Notebook. Copies of IRB submissions and approvals should be forwarded to JJSV.

The investigator is responsible for notifying the IRB of reportable adverse events as well as any other circumstance in which additional procedures outside the protocol were conducted to eliminate apparent hazards to subjects.

13.2 INFORMED CONSENT

The current version of the IRB-approved study informed consent form must be signed by each study subject prior to any study-specific examinations being performed. The IRB-approved informed consent form is to be signed and dated by the subject as well as by the person who conducted the informed consent discussion. The signed informed consent form will be maintained by the investigator as a permanent part of the subject's medical records. A copy of the signed and dated form is to be provided to the subject. The investigator will provide JJSV written acknowledgement on the preoperative case report form that a signed agreement of informed consent has been obtained and is in the investigator's possession for each subject. As required by 21CFR812 Part G, the site shall document in the source documents that informed consent was obtained prior to participation in the study for each subject enrolled.

NOTE: The informed consent process also includes obtaining the subject's signature on an Authorization for Use/Disclosure of Health Information for Research Form or

equivalent documentation necessary to comply with applicable privacy laws pertaining to medical treatment in the governing countries.

NOTE: The sponsor will secure appropriate insurance for study subjects prior to study start.

14. DOCUMENTATION

14.1 SOURCE DOCUMENTS

Source documents must be kept for all study subjects. Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's subject study files, as well as results of any diagnostic tests or procedures such as topographies or laboratory tests with photographs or instrument printouts.

Each site is expected to adhere to the clinic's own standard documentation requirements for medical charts/clinic notes. For the purposes of this clinical study, the medical charts/clinic notes must also include, at a minimum, the following data that will be considered source data and will be reviewed by JJSV:

- Subject's name and study identification number
- Subject's contact information
- Study protocol number and the Sponsor name (JJSV)
- A statement that informed consent was obtained prior to participation in the study (including the date)
- Evidence of subject eligibility
- Dates of all subject visits and surgeries throughout the duration of the study
- Implant serial number identification (NOTE: This is masked information, and may only be reviewed by unmasked study staff)
- Concurrent medications
- Corrected and uncorrected distance visual acuity (NOTE: M&S electronic data and near visual acuity score sheets are considered source documentation and are to be retained by the site. A paper copy of the M&S results will be printed and validated by the site)
- Manifest refraction
- Occurrence and status of any operative complications, postoperative medical or lens findings and adverse events
- Occurrence and status of any subject complaints, e.g., ocular/visual symptoms
- The date the subject exited the study, and a notation as to whether the subject completed the study or reason for early exit.

14.2 SUBJECT CONFIDENTIALITY

Subjects will be assigned a site/subject number to maintain subject confidentiality. Subject names may possibly be disclosed to JJSV or regulatory agencies during inspection of medical records related to the study, but reasonable precautions will be taken to maintain confidentiality of personal information to the extent permitted by applicable laws and regulations.

14.3 CASE REPORT FORM COMPLETION

This study will use an electronic data capture system. All study staff responsible for entering data into the system must complete certification prior to using the system. The investigator is responsible for ensuring that data are properly recorded on each subject's case report forms and related documents. Prior to database lock, the investigator will verify completeness and accuracy of data submitted to JJSV.

14.4 STUDY SUMMARY

A final investigator's summary (study close-out) will be provided to JJSV and the reviewing IRB after termination or the completion of the study or the investigator's part of the investigation, as directed by JJSV.

15. MONITORING

JJSV will perform three types of monitoring to ensure compliance with regulations: data monitoring, administrative monitoring, and safety monitoring.

15.1 DATA MONITORING

In order to ensure a well-controlled clinical trial, JJSV will follow specific data monitoring procedures, routinely generate reports and periodically review safety and effectiveness data. To avoid bias, any analyses generated prior to site closures will not be disseminated to any of the investigative sites.

An electronic data capture system (EDC) will be used to transmit case report forms from the investigative site to JJSV. Requests for data clarification will be handled through this same system.

To minimize data omissions and inconsistencies on clinical reports and to ensure that data are accurately transcribed to computer data files, JJSV will follow internal data processing procedures that include automated and manual quality control checks to identify any data discrepancies. Any such items will be resolved and documented as needed in EDC.

Prevention of Missing Data

Methods used to safeguard against missing data that can have deleterious effects on the study integrity and reliability of its outcomes will include training study staff with WebEx, centralized and/or on-site programs. In addition, subjects will be encouraged at the time of informed consent to avoid missing study visits, as missing data may affect the study reliability and diminish the scientific value of their contribution to the study.

15.2 ADMINISTRATIVE MONITORING

Administrative monitoring procedures will ensure that study devices, subjects, and forms can be traced and will allow monitoring of investigator progress and compliance. Accountability and traceability of study devices will be monitored by trained JJSV personnel.

Device Accountability

Complete lens accountability will be maintained at the investigative site by maintaining records of all study lenses (Models ZHR00 and ZCB00 lenses) received from and returned to JJSV. A site log will be used to track all lenses for date of receipt, eye implanted, serial number, lens power, use and disposition/return to JJSV. This site log and any other study lens information will be maintained in the operative room study binder. During periodic investigative site monitoring visits, JJSV personnel will review site lens inventory records and logs to ensure IOL accountability compliance and complete study lens traceability.

Site Monitoring Plan

Prior to performing any study implants, the requirements of the study and reporting mechanisms will be explained to each investigator either personally at the investigative site or at a formal study investigator meeting. When necessary, a pre-study site qualification visit may be performed to assess the adequacy of the site to perform the study for sites that have not previously worked with JJSV or have undergone significant changes, or have not been visited in the past year. An initial site visit will be conducted prior to the first implant for all sites.

Throughout the duration of the study, site visits to monitor compliance to this protocol will be made at each investigative site. During interim site monitoring visits, JJSV will review informed consent documents and subject eligibility, and the data on study case report forms will be verified against subject charts and other source documents to ensure complete and accurate reporting. The subject files will also be reviewed to assure that all adverse events and any issues encountered with JJSV products have been reported in a timely fashion.

JJSV will also review source documents to verify that all required items have been documented in the subject medical charts. Refer to Section 14.1, Source Documents, for a list of items that are required for source documentation. In addition to subject files, study logs will be checked and conformance to lighting levels for visual acuity tests will be verified.

Training on study-specific procedures may also be conducted during monitoring visits. For this study in particular, a training/monitoring visit is likely to occur just prior to or during the first of the 1-month and 6-month visits, wherein the most extensive vision testing occurs.

Upon study completion, a site visit will be made to each site to monitor the last of the subject data records and finalize any outstanding study issues.

A separate Study Monitoring Plan will be established prior to study start that will define the type and frequency of monitoring visits and frequency of record monitoring.

15.3 SAFETY MONITORING

The medical monitor will review results throughout the clinical trial as necessary to ensure the continued safety of the device and to ensure that no subjects are exposed to unreasonable risk. The medical monitor will be available to answer all questions from investigators. The medical monitor will review and assess any reports of serious and/or device-related adverse events as well as device deficiencies that could have led to a serious adverse event, and discuss these with the reporting investigator(s) as necessary. The medical monitor, as well as any other qualified personnel designated by JJSV, shall also review any interim progress reports, as applicable.

16. PUBLICATIONS

Refer to the Clinical Trial Agreement for information regarding JJSV publication policies.

17. RISK ANALYSIS

POTENTIAL RISKS AND RISK MANAGEMENT

RISKS OF THE NEXT-GENERATION TECNIS SYMFONY IOL, MODEL ZHR00

The TECNIS Symfony Model ZHR00 IOL is designed to provide far, intermediate and near vision; however, glasses may still be needed to improve distance vision and/or to have useful vision for intermediate or near tasks. Some visual symptoms, particularly dysphotopsias such as halos, night glare, starbursts, etc., may be expected. Dysphotopsias may become less noticeable over time; however, the IOL may be removed if necessary. There may be a reduction in contrast sensitivity under certain conditions compared to a monofocal lens although contrast sensitivity is expected to be

in between that of the TECNIS Symfony IOL and TECNIS Multifocal IOLs. Due to the diffractive optic design, the ability to perform some eye treatments (e.g., retinal photocoagulation) may be affected, and caution should be used when interpreting results of autorefractors or wavefront aberrometers that utilize infrared light, or when performing a duochrome test. These risks are not unlike other diffractive technology IOLs.

GENERAL RISKS OF CATARACT SURGERY AND IOL IMPLANTATION

There are risks and complications associated with cataract surgery and IOL implantation in general. These can include worsening of vision, hemorrhage, loss of corneal clarity, inflammation, infections, retinal detachment, pupil changes, glaucoma, etc. Complications can result in poor vision, loss of vision or loss of the eye.

RISK MANAGEMENT

Subjects will be closely monitored thought the trial duration. The occurrence of adverse events and complaints will be assessed at each study visit and reported to JJSV according to Section 11.0, Adverse Events and Product Complaints. Additionally, JJSV will monitor incoming data following the procedures outlined in Section 15.0, Monitoring. The Medical Monitor will ensure subjects are not exposed to additional risks by monitoring serious adverse events, device-related adverse events, and device-deficiencies that could have led to serious adverse events (Section 15.3, Safety Monitoring).

POTENTIAL BENEFITS

The general clinical performance of the Next-Generation TECNIS Symfony IOLs Model ZHR00 is expected to be similar to the TECNIS Model ZCB00 IOL regarding distance visual acuity and safety outcomes. Improved intermediate and near visual acuity as well as functionality may be achieved with the Next-Generation TECNIS Symfony IOL Model ZHR00 compared to the control IOL.

CONCLUSION

The hazards/risks associated with the Next-Generation TECNIS Symfony IOL Model ZHR00 are acceptable and within those of JJSV's other advanced optic IOLs. The potential clinical benefits of the Next-Generation TECNIS Symfony IOL Model ZHR00 outweigh the residual risks when the device is used as intended.

18. RECORDS RETENTION

All study-related correspondence, subject records, consent forms, Authorization for Use/Disclosure of Health Information Forms or similar medical treatment privacy law documentation, records of the distribution and use of all study products, and original case report forms should be maintained by the investigator.

The investigator must maintain and have access to the following essential documents until notified by the Sponsor. Note: This may be for a minimum of 25 years after completion of the study. JJSV requires notification if the investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably-qualified, responsible person.

- All case report forms
- All adverse event information (i.e., medical records, medical reports and/or judgments from colleagues or outside specialists who assisted in the treatment and follow-up of the subject)
- Investigational supply records/inventory
- IRB approval documentation
- Study correspondence
- Study agreements
- Site visit documentation
- Protocol(s)
- Subject log(s)
- Clinical Investigator's Brochure
- Completed subject informed consent forms and medical privacy forms (e.g., Authorization for Use/Disclosure of Health information)
- Subject medical chart/clinic notes (Not applicable for transfer of ownership to JJSV)

19. TERMINATION OF THE INVESTIGATION

The clinical investigation will be suspended in the event of high levels of complications and/or adverse events that are unexpected in nature and/or severity and evaluated as to causality relative to the study device. The clinical investigation may be suspended if the Medical Monitor or the IRB, upon review and evaluation of the clinical data, finds unacceptable clinical performance or the level of single or total complications and/or adverse events unacceptable for continuation of the investigation.

If causality is shown not to be related to the study device, the study may be resumed in accordance with the IRB and regulations of the FDA. The study will be terminated if causality is shown to be related to the study device.

Additionally, the investigator or JJSV may stop a subject's participation at any time. JJSV may also stop the study at any time for reasons it determines appropriate. However, no suspension of the study would be made to disadvantage the study subjects. Following suspension of the study for any reason, all study subjects who have already received treatment would continue to be followed through completion of the study visit schedule.

20. STATISTICAL METHODS

This section highlights the analyses to be performed for key study endpoints. The key study timeframe for all endpoints will be the 6-month postoperative visit, although data will be reviewed at other time points as well.

20.1 ANALYSIS POPULATION

The primary analysis population for the primary DCIVA and secondary DCNVA endpoints will be a modified Intent-to-Treat (mITT) analysis for all first-eyes randomized and implanted with either a test or control study IOL. Sensitivity analyses using all randomized subjects will be performed as described below. The validation work for the PRSIQv2 was based on a complete data set (i.e., with non-missing values) for each composite dichotomous score and recommended that imputations for missing values not be used. Therefore, the primary analysis population for overall spectacle independence will be the safety population (SP) with subjects who are bilaterally implanted with the same study lens in both eyes. For all subjects with missing data for the spectacle independence endpoint at the 6-month visit, information (e.g., percentage missing, reason for missing data, etc.) will be provided. There are no inferential statistics for the defocus curve primary endpoint; therefore safety population (SP) will be the primary analysis population for this endpoint. The mITT population will be used for the statistical success criterion of the primary DCIVA endpoint and secondary DCNVA effectiveness endpoint where SP will be used for the clinical success criterion of those endpoints since there is no inferential statistics comparison for the clinical success criterion.

For eyes that do not have data available at the 6-month postoperative visit, other than PRSIQv2, data will be imputed for the mITT analyses. For continuous variables (DCIVA and DCNVA), planned method to use is the MCMC full-data imputation as described in Little & Rubin[1] . Data imputation and analysis will be performed using the MI and MIANALYZE procedures[2] in SAS® (Version 9.4).

In addition to the above imputation methods, sensitivity analyses using different imputation approaches (worst-case scenario, best-case scenario and tipping point) will also be performed for primary DCIVA and secondary DCNVA and safety endpoint of mean BCDVA. These analyses will be performed using all randomized subjects with the IOL group based on the randomization. A worst-case scenario (with the worst score assigned to missing data) for the test IOL and the best score assigned to missing data for the control IOL will be performed. A best-case scenario will also be performed (assigning the best value to missing test IOL data and the worst value to missing control

[1] Little, R. and Rubin, D. Statistical Analysis with Missing Data, John Wiley & Sons, Inc. New York, Second Edition, (2002).

IOL data). A tipping point analysis will also be performed if more than 10% of mITT population is missing at the 6-month visit.

A Per-Protocol (PP) analysis will also be used for primary effectiveness and secondary endpoints. The PP population for monocular data will include eyes with a test or control lens implanted, evaluated within the proper study interval and without clinically-relevant protocol deviations (deviations that could potentially impact the primary or secondary endpoints) as determined prior to database lock. The PP population for binocular data will include subjects that do not have any of the deviations stated above in either eye. PP tables will include available data at the time of analysis.

The safety population will consist of all eyes and subjects implanted with either a test or control IOL(s) and with data available at the time of analysis (i.e., no data imputation). Reporting of cumulative complications and adverse events (occurring at any time postoperative) will include data from all study eyes implanted. For all safety endpoints, only safety population will be used. For BCDVA, a best-case population will also be used, consisting of eyes in the safety population without any clinically-relevant preoperative ocular pathologies or macular degeneration detected at any time.

For the primary DCIVA, and secondary DCNVA endpoints, the mITT, PP and safety populations will be used for data reporting. For the defocus curve primary endpoint and secondary overall spectacle independence endpoint, only safety and PP populations will be used for data reporting. For safety endpoints and other endpoints, only the safety population will be used. The primary analysis will be based on first-eye data, unless stated otherwise. However, select data such as some visual acuity variables will also be reported separately for second eyes as supportive data only. Binocular data will be reported for those who are implanted with the same (test or control) IOL in both eyes.

20.2 PRIMARY STUDY ENDPOINTS

Primary Effectiveness Endpoints

MONOCULAR DISTANCE-CORRECTED INTERMEDIATE VISUAL ACUITY (DCIVA) AT 66 CM

The first primary effectiveness endpoint for the Model ZHR00 IOL is mean (LogMAR) first-eye, monocular, distance-corrected intermediate visual acuity (66 cm) under photopic conditions at 6 months postoperative. The mean, SD, median, minimum, maximum and 95% C.I. will be reported by IOL group. Results will be reported by lens group for first eyes using one-sided, two-sample t-tests with an alpha level of 0.025. Note that a lower LogMAR value is a better acuity and a higher LogMAR value is a poorer acuity. The null hypothesis is that the mean monocular DCIVA LogMAR value for the Model ZHR00 eyes is worse than or equal to that for control eyes. The alternate

hypothesis is that the mean monocular DCIVA LogMAR value for Model ZHR00 eyes is better than that for control eyes.

H_o: $\mu_c - \mu_t \leq 0$ (Model ZHR00 lens is worse than (higher LogMAR) or equal to control)
H_1: $\mu_c - \mu_t > 0$ (Model ZHR00 lens is better (lower LogMAR) than control)

where
μ_t = mean LogMAR DCIVA for ZHR00
μ_c = mean LogMAR DCIVA for ZCB00

Reject the null hypothesis if one-sided p-value ≤ 0.025.

The success criterion is a statistically significantly lower mean LogMAR DCIVA value for the Model ZHR00 investigational lens compared to the control lens ($p \leq 0.025$). In addition, clinical significance will be determined if the median DCIVA of ZHR00 is at least 0.2 LogMAR.

MONOCULAR DISTANCE-CORRECTED DEFOCUS

The second primary effectiveness endpoint is monocular mean diopters of defocus where visual acuity is LogMAR 0.2 or better at 6 months postoperative. The diopters of defocus where the mean visual acuity of LogMAR 0.2 or better is achieved will be derived by visual inspection of the defocus curve. The defocus endpoint will only be determined from zero to the negative powers; however, the mean of each diopter will be plotted for the range the testing conducted (including positive and negative diopters).

The success criterion is that the Model ZHR00 lens will demonstrate at least 0.5 D greater monocular, photopic, distance-corrected depth of focus compared to the control IOL at 0.2 LogMAR visual acuity threshold, based upon visual inspection of the defocus curves.

Secondary Effectiveness Endpoints

Due to multiple endpoints, a closed-form hierarchical approach will be used.[2,3,4,5] Secondary endpoints will be tested in order as follows:

---

[2] Rom D and B. Holland. (1995). A new closed multiple testing procedure for hierarchical families of hypotheses. Journal of Statistical Planning and Inference 46:265-275

[3] Rom D, R. Costello, and L. Connell. (1994). On closed test procedures for dose-response analysis. Statistics in Medicine 13:1583-1596

[4] Marcus R, E. Peritz, and K. Gabriel. (1976). On closed testing procedures with special reference to ordered analysis of variance. Biometr ka 63:655-660.

[5] Huque M and A Sankoh. (1997). A reviewer's perspective on multiple endpoint issues in clinical trials. Journal of Pharmaceutical Sciences 7:545-564.

MONOCULAR DISTANCE-CORRECTED NEAR VISUAL ACUITY (DCNVA) AT 40 CM

The first secondary effectiveness endpoint is mean (LogMAR), monocular DCNVA under photopic conditions at 40 cm at 6 months. Comparisons between lens groups will be performed using a one-sided, t-test with an alpha level of 0.025. Note that a lower LogMAR value is a better acuity and a higher LogMAR value is a poorer acuity. The null hypothesis is that the mean monocular DCNVA LogMAR value for the Model ZHR00 eyes is worse than or equal to that for control eyes. The alternate hypothesis is that the mean monocular DCNVA LogMAR value for Model ZHR00 is better than that for control eyes.

H_o: $\mu_c - \mu_t \leq 0$ (ZHR00 is worse than (higher LogMAR) or equal to control)
H_1: $\mu_c - \mu_t > 0$ (ZHR00 is better (lower LogMAR) than control)

where
μ_t = the mean LogMAR DCNVA for Model ZHR00 lens

μ_c = the mean LogMAR DCNVA for control lens

Reject the null hypothesis if one-sided p-value ≤ 0.025.

The success criterion is a statistically significantly lower mean LogMAR DCNVA for ZHR00 compared to ZCB00 ($p \leq 0.025$). In addition, clinical significance will be determined by the median DCNVA of ZHR00 being at least 0.3 LogMAR.

OVERALL SPECTACLE INDEPENDENCE VIA BINOCULAR QUESTIONNAIRE

The second secondary effectiveness endpoint is overall spectacle independence via binocular questionnaire responses and is defined as the subject reporting “No” need for correction for all three conditions (distance, intermediate and near), “None of the time” for correction wear and “None of the time” for strain to see for all four conditions (distance, intermediate, near and overall). Spectacle independence results will be reported by lens group and analyzed by Fisher’s exact test with a one-sided alpha of 0.025. The null hypothesis is that the proportion of Model ZHR00 subjects who are spectacle independent is less than or equal to the proportion of control subjects. The alternative hypothesis is that the proportion of Model ZHR00 subjects who are spectacle independent is greater than that for control subjects.

H_o: $p_t - p_c \leq 0$
H_1: $p_t - p_c > 0$

where
p_t = Proportion of Model ZHR00 subjects who are spectacle independent
p_c = Proportion of Model ZCB00 subjects who are spectacle independent

Reject the null hypothesis if one-sided p-value ≤ 0.025.
The success criterion is a statistically significantly greater proportion of Model ZHR00 subjects who are spectacle independent compared to control Model ZCB00 subjects (p ≤ 0.025). In addition, clinical significance will be determined as follows:

- The proportion of Model ZHR00 subjects who are spectacle independent will be at least 25 percentage points higher than that for the control group

Safety Endpoints

MONOCULAR BEST-CORRECTED DISTANCE VISUAL ACUITY (BCDVA)

The first safety endpoint is mean (LogMAR) first-eye, monocular, best-corrected distance visual acuity (BCDVA) at 6-months postoperative. Results will be compared between lens groups for first eyes using a non-inferiority approach. The null hypothesis is that the mean difference (ZCB00 minus ZHR00) between the test and control IOLs is less than or equal to -0.1. LogMAR, with the alternative hypothesis being that the mean difference is greater than -0.1 LogMAR. A two-sided, 90% confidence interval (CI) will be used for evaluation.

H_o: $\mu_c - \mu_t \leq -0.10$
H_1: $\mu_c - \mu_t > -0.10$

where
μ_t = mean LogMAR BCDVA for ZHR00
μ_c = mean LogMAR BCDVA for ZCB00

The success criterion is that the lower 2-sided 90% confidence internal for the difference between the IOLs is greater than -0.1 LogMAR.

RATES OF ADVERSE EVENTS VS. ISO SPE RATES

Rates of adverse events as determined by ISO 11979-1 will be reported through 6 months. The frequency and proportion of first eyes and second eyes with these events will be reported over time by IOL group. Statistical comparisons to ISO SPE rates will be based on first-eye data; adverse event rates for the Model ZHR00 first eyes will be compared to the ISO SPE rates using a one-sided, exact test based on the binomial distribution. The null hypothesis is that the AE rate for the Model ZHR00 eyes is lower than or equal to the ISO rate, and the alternative hypothesis is that the AE rate for ZHR00 eyes is greater than the ISO rate. This criterion will be used for all ISO SPE rates, including secondary surgical interventions (SSI). In addition, rates for lens-related SSI due to optical issues causing visual symptoms will be presented with descriptive statistics.

H_o: $p_t \leq p_i$
H_1: $p_t > p_i$

where
p_t = proportion of Model ZHR00 investigational lens eyes with the AE
p_i = proportion of eyes reported in ISO SPE rates with the AE

Reject the null hypothesis if one-sided p-value < 0.025.

CONTRAST SENSITIVITY

For contrast sensitivity data at 6 months postoperative, descriptive analyses including mean, standard deviation, median, minimum, maximum and two-sided 90% confidence intervals will be presented by IOL group for all levels of contrast and lighting conditions.

VISUAL SYMPTOMS VIA PRO INSTRUMENT

For visual symptom data obtained from the PRVSQ instrument at 6 months postoperative, the frequency and proportion of subjects with a given response will be reported by IOL group.

20.3 OTHER ENDPOINTS

Visual Acuity

BCDVA results will also be reported over time by IOL group. The proportion of ZHR00 eyes achieving monocular BCDVA of 20/40 or better will be compared to the ISO SPE rate for posterior chamber IOLs (all first eyes) using a one-sided, exact test based on binomial distribution. The null hypothesis (based on the ISO standard) is that the proportion of investigational lens eyes achieving 20/40 or better BCDVA is greater than or equal to the ISO SPE values, and the alternative hypothesis is that the proportion of investigational lens eyes achieving 20/40 or better BCDVA is less than the ISO SPE values.

For all other intermediate and near endpoints, statistics similar to those for DCIVA analyses will be used. In addition, the frequency and proportion of first eyes achieving each line will be reported over time by IOL group.

Defocus Testing

In addition to the monocular defocus test analyses described in the effectiveness endpoints, binocular defocus testing results will also be reported using statistical methods similar to that described for monocular testing. Defocus curve will also be stratified by pupil size (≤ 2.5 mm, > 2.5 mm to < 4.0 mm and ≥ 4.0 mm). For binocular defocus curve, the average of the two pupil sizes will be used.

Other Findings

The frequency and percentage of medical findings, lens findings and non-directed ocular/visual symptoms will be reported over time by IOL group for both eyes.

Fundus Visualization

The frequency and percentage of fundus visualization will be reported at 6 months postoperative by IOL group.

Satisfaction And Other Questionnaire Data

Satisfaction and other results from the 1-month and 6-month questionnaire data will be reported for subjects who have received the same test lenses or same control lenses in both eyes. The frequency and proportion with each response will be tabulated by IOL groups.

20.4 SITE ANALYSIS

For the primary effectiveness and secondary endpoints, data will be reported by site. A mixed effects analysis will be used for primary DCIVA and both secondary endpoints. The mixed model will be used with IOL group as a fixed effect and site and site by group interaction as random effects. If the interaction term is significant at the 0.15 level then further examination of effects of site or further data stratification by site will be evaluated. Since there are no inferential statistics for the primary defocus curve endpoint, only graphs (defocus curve by site) will be presented for the site analysis. Baseline demographic data will also be reported by site.

20.5 VISUAL ACUITY CONVENTIONS AND GENERAL STATISTICS

Visual acuity data will be converted to LogMAR values prior to analysis and adjusted for the test distance used if it is not the standard distance for the chart. Descriptive statistics will typically include sample size (N), mean, standard deviation (SD), median, minimum (Min) and maximum (Max) as appropriate for continuous variables. For continuous variables, statistical tests (e.g., t-test) assuming normality will generally be used. For categorical data, the frequency and proportion will be reported and Fisher's exact test or Chi-square test will generally be applied. For ordinal categorical data, the frequency and proportion will be reported with the Wilcoxon Rank-Sum test generally used.

20.6 INTERIM REPORTS

No interim study progress reports will be conducted for this study.

20.7 SAMPLE SIZE CALCULATIONS

For the primary endpoint of distance-corrected intermediate visual acuity, there is more than 90% power to detect a 1-line or greater difference in mean visual acuity between

the investigational lens and the control groups (assume one-sided testing with an alpha of 0.025 and standard deviation of 1.6 lines) with 100 subjects in each lens group.

For the secondary endpoint of distance-corrected near visual acuity, there is more than 90% power to detect a 1-line or greater difference in mean visual acuity between the investigational lens and the control groups (assume one-sided testing with an alpha of 0.025 and standard deviation of 1.6 lines) with 100 subjects in each lens group.

Accounting for a potential 15% screen failure and 10% loss-to-follow-up rate, the study will enroll up to 264 subjects.

APPENDIX A SUMMARY OF PROCEDURES REQUIRED AT EACH VISIT

Shaded lines indicate masked testing

Examination	Preop Both eyes	Op 1st eye and 2nd eye	1 day 1st eye and 2nd eye	1 week 1st eye and 2nd eye	1 month 1st eye and 2nd eye	6 months Both eyes
Informed consent, ocular history, inclusion/exclusion criteria[a], potential visual acuity, targeted refraction, IOL power calculations, biometry and randomization if required	X					
Lens power/serial number (masked)/operative procedures		X				
Manifest refraction (Snellen preop; ETDRS postop)	X			X	X	X
UCDVA - photopic, monocular (ETDRS)			X	X	X	X
UCDVA - photopic, binocular (ETDRS)						X
BCDVA - photopic, monocular (Snellen preop; ETDRS postop)	X			X	X	X
UCIVA and DCIVA - photopic, monocular at 66 cm (ETDRS)					X	X
UCIVA - photopic, binocular at 66 cm (ETDRS)						X
UCNVA and DCNVA - photopic, monocular at 40 cm (ETDRS)					X	X
UCNVA - photopic, binocular at 40 cm (ETDRS)						X
DCIVA and BCIVA – monocular, low contrast acuity (10%)[c]						X
Defocus testing, monocular[c]						X
Defocus testing, binocular						X
Contrast Sensitivity testing, monocular[c]						X
Pupil size (mesopic with and without glare, photopic with and without glare)[d]						X
Keratometry	X					X
Intraocular pressure	X		X	X	X	X
Biomicroscopic slit-lamp exam[b]	X		X	X	X	X
Fundus exam with fundus visualization	X					X
Adverse events		X	X	X	X	X
Ocular medications	X	X	X	X	X	X
Ocular/visual symptoms (non-directed)	X		X	X	X	X
Subject questionnaires					X[e]	X

[a] With corneal stability check for contact lens wearers
[b] Includes determination of medical and lens findings/complications
[c] Monocular testing required for first-eye only
[d] Mesopic pupil size should be assessed at visits where the subject complains of severe visual symptoms beyond 1 month.
[e] Questionnaires should be administered only with 2nd eye 1-month visit.

APPENDIX B EQUIPMENT LIST

The following equipment will be supplied to an investigative site for the duration of the study provided that the site does not already have such equipment available for use. This equipment loan will be documented in the Clinical Trial Agreement, which indicates that the equipment is to be returned to JJSV at the completion of the study.

- M&S Technologies CTS-1000 Smart System© Computerized Vision Testing System, including laptop computer, tablet, and glare bracket ("M&S System")
- Good-Lite EVS-1500 retro-illuminated visual acuity light box and stand
- Four Good-Lite ETDRS near visual acuity charts (100% contrast) on two cards, for a test distance of 40 cm
- Neutral density trial frame lenses for mesopic testing
- +0.12 D trial frame lenses
- Positive and negative diopter retinoscopy lens racks (0.5 D to 4.0 D in 0.5-diopter steps), as requested
- Gossen Light Meter
- Tape measure (meters)
- Colvard or Neuroptics Pupillometer (if site does not already have either pupillometer)
- JJSV insertion systems, as necessary:
    - ONE SERIES Ultra Implantation System with 1VIPR30 cartridges, or
    - UNFOLDER Platinum 1 Series Implantation System with 1MTEC30 cartridges

APPENDIX C MAXIMUM PLUS MANIFEST REFRACTION TECHNIQUE WITH CYLINDER REFINEMENT

Manifest refraction testing will be performed using the M&S System at 4.0 meters with the room lighting set to that required for photopic distance visual acuity testing (85 cd/m^2). NOTE: Objective refraction by either retinoscopy or autorefraction can be used as a starting point for the Manifest Refraction. Always ensure that the endpoint of refraction is maximum plus (or minimum minus) power that yields maximum visual acuity.

1) Occlude the fellow eye.
2) SPHERE: Starting with the objective refraction, refine the sphere to yield best visual acuity. **Important:** Add plus power (or reduce minus) until subject demonstrates at least a 1-line loss from best visual acuity (fogging). Then step down to the most plus (or least minus) sphere power until visual acuity and clarity show no improvement.
3) CYLINDER AXIS: Refine cylinder with a cross-cylinder and the objective cylinder refraction as the starting point. Refine axis first and power second, since the correct axis can be found with an incorrect power, but the correct power cannot be found with an incorrect axis.
    a. Direct the subject's attention to 1 line above (larger letters) the best visual acuity. With the trial cylinder (axis and power) in the phoropter, introduce cross-cylinder for axis refinement. When asking the subject which cross-cylinder axis position is better, "one or two?", remind the subject to look at different letters on the line and report preference based on the overall clarity of the letters.
    b. Refine the axis based on the subject's responses, using small steps (between five and 10 degrees), until the subject reports no difference in the two choices.
    c. Cylinder axis may be further confirmed by bracketing: Slowly rotate the trial cylinder in one direction until the subject reports blurring and note the axis. Rotate the trial cylinder in the opposite direction past the presumed axis until the subject reports blurring, again noting the axis. The average of the two noted axes can be taken as the final astigmatism axis.
4) CYLINDER POWER: Set the cross cylinder to refine cylinder power and present choices to the subject, reminding the subject to look at different letters on the line and report preference based on overall clarity of the letters. Reduce or increase trial cylinder power accordingly.
    a. Maintain the spherical equivalent throughout cylinder power refinement by adjusting the sphere once for every two clicks of cylinder power change.
5) SPHERE CHECK: Introduce plus sphere in 0.25 D increments until the subject reports and demonstrates a reduction in visual acuity. Then reduce sphere power in 0.25 D steps until visual acuity and clarity show no improvement.

APPENDIX D REFRACTION ADJUSTMENTS

Postoperative study manifest refractions are to be performed using the M&S System at a distance of 4.0 meters. Because 4.0 meters is not optical infinity, refraction adjustments are necessary to ensure proper vision testing that accounts for differences between the test distance and refraction distance. The adjustment required (in diopters) is 1/test distance (in meters). To adjust a 4.0-meter refraction to optical infinity, -0.25 D is to be added to the sphere of the refraction to obtain a true distance (infinity) correction. On the other hand, to adjust optical infinity to a 4.0-meter test distance, +0.25 D is to be given. In the case where the refraction distance (4.0 meters) and the vision test distance (4.0 meters) are the same, no adjustment is necessary. The following table lists the refraction adjustments required for the various vision tests in this study:

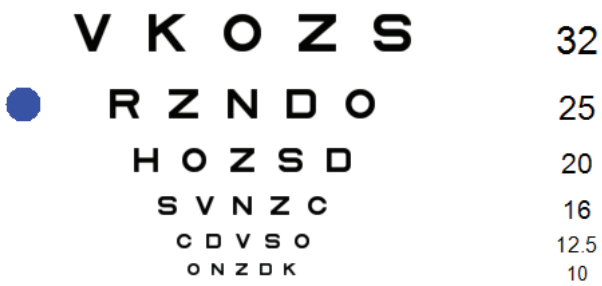
Refraction Adjustments for Vision Testing

Vision Test	Test Distance	Correction/Adjustment
Uncorrected distance visual acuity (UCDVA)	4.0 m	+0.25 D adjustment only
Best-corrected distance visual acuity (BCDVA)	4.0 m	No adjustment; ETDRS Rx only (phoropter)
Best-corrected distance defocus curve testing	4.0 m	No adjustment; ETDRS Rx only (trial frame with loose or rack lenses)
Uncorrected intermediate visual acuity (UCIVA)	66 cm	No adjustment
Distance-corrected intermediate visual acuity (DCIVA)	66 cm	-0.25 D added to ETDRS sphere Rx (trial frame)
Best-corrected intermediate visual acuity (BCIVA)	66 cm	-0.25 D added to ETDRS sphere Rx (trial frame)
Uncorrected near visual acuity (UCNVA)	40 cm	No adjustment
Distance-corrected near visual acuity (DCNVA)	40 cm	-0.25 D added to ETDRS sphere Rx (trial frame)
Best-corrected distance contrast sensitivity	2.5 m	+0.12 D added to ETDRS sphere Rx

APPENDIX E INSTRUCTIONS FOR USING THE M&S SYSTEM

Distance and intermediate visual acuity, low-contrast distance visual acuity, defocus, and contrast sensitivity testing will be performed using the M&S System. This system provides descending LogMAR charts with proportionally spaced SLOAN letters at 100% contrast for high contrast visual acuity and defocus testing, 10% contrast for low-contrast distance visual acuity and appropriate contrast levels for contrast sensitivity testing. Each presentation is randomized and is consistent and repeatable. The system is calibrated for both distance to subject and pixels/inch so that optotypes precisely follow ANSI Z80.21-2010 and ISO 8596:2000 with regard to size, spacing between optotypes and spacing between lines.

Figure 4: Example of LogMAR 4.0 meter chart screen



The M&S System background luminance is automatically set to 85 cd/m^2 (range of 80-110 cd/m^2 is acceptable) for photopic testing and, with a neutral density filter placed in front of the laptop, lighting is reduced to 3 ± 0.5 cd/m^2 for mesopic testing. Room lighting is to be set to a level lower than the illumination from the laptop screen. Ambient lighting should be dim to dark (less than 50 lux) to maximize pupil size. No surface (including reflective surfaces) within the subject's field of vision should be brighter than the chart background in luminance. The room lighting and screen luminance will be verified each time the computer is turned on using the JJSV-provided, auto-adjusting, monitor-calibration system to ensure light levels are appropriate.

The M&S System will be set up to perform required visual tests in a specific order, with prompts on the screen to allow the technician to set up the subject for monocular or binocular testing, refraction adjustments as needed and uncorrected or best-corrected testing. Letters on all charts will appear randomly, with the technician controlling movement through charts based on subject responses.

As a subject completes a visual acuity line, the technician will select the total number of letters correctly read for that line on the handheld controller, press "Enter" and then

confirm the number of letters correct at the next prompt. The M&S System will then advance to the next line of testing and the process will repeat. The system will end the test when the subject no longer has any correct responses. The number of letters correctly read will be displayed on the laptop screen, along with the LogMAR value and Snellen acuity. Record the total number of letters read. A similar process will be done for contrast sensitivity grating responses. Once a test is completed, follow the prompts on the computer screen to start the next test.

Test results are stored in the M&S computer and a hard copy will be printed and validated as a back-up.

APPENDIX F INSTRUCTIONS FOR DISTANCE VISUAL ACUITY TESTING

For distance visual acuities, the M&S System laptop should be placed at a test distance of 4.0 meters from the subject for testing distance visual acuities. A laptop setting may be used to reverse charts for rooms that require “folding” via a mirror to reach a distance of 4.0 meters. Whether standard or “folded”, measure and record the test distance accurately. If the room set-up does not allow the computer to be placed at precisely 4.0 meters, the M&S System can be adjusted to account for the actual test distance used.

The M&S System will be set up to perform the required distance visual acuity tests in a specific order, with prompts on the screen to allow the technician to set up the subject for monocular or binocular testing, refraction adjustment as needed and uncorrected or best-corrected testing. A phoropter may be used for distance acuity and refraction testing.

Subjects should be reminded prior to testing that squinting is not allowed. The technician is to observe the subject to ensure the subject is not squinting during visual acuity testing. If squinting is observed, the subject is to be reminded by the testing technician not to squint.

Distance visual acuity measurements are to be performed per the visit schedule in **Appendix A**. To test subjects monocularly, occlude the second eye in the phoropter or with an occluder if trial lenses are used.

Visual acuity measurements are based on the total number of correctly read letters. Subjects should be persuaded to read the smallest letters possible even if they must guess. Follow the testing process listed in **Appendix E**. At the end of the test, the number of letters correctly read will be displayed on the laptop screen, along with the LogMAR value and Snellen acuity. Record the total number of letters read in the EDC system.

APPENDIX G INSTRUCTIONS FOR INTERMEDIATE VISUAL ACUITY TESTING

Intermediate visual acuity will be measured using the M&S System at a test distance of 66 cm using trial frames. Subjects should be reminded prior to testing that squinting is not allowed and the testing technician should carefully observe to ensure the subject is not squinting. If squinting is observed, the subject is to be reminded by the testing technician not to squint.

The M&S System will be set up to perform the required intermediate visual acuity tests in a specific order, with prompts on the screen to allow the technician to set up the subject for monocular or binocular testing, refraction adjustment as needed, and uncorrected or distance-corrected testing.

Intermediate visual acuity measurements are to be performed per the visit schedule in **Appendix A**. To test subjects monocularly, occlude the second eye with an occluder in the trial frame.

Visual acuity measurements are based on the total number of correctly read letters. Subjects should be persuaded to read the smallest letters possible even if they have to guess. Follow the testing process listed in **Appendix E**. At the end of the test, the number of letters correctly read will be displayed on the laptop screen, along with the LogMAR value and Snellen acuity. Record the total number of letters read in the EDC system.

BEST-CORRECTED INTERMEDIATE LOW CONTRAST VISUAL ACUITY TESTING WITH ADD (BCIVA): First eye monocular best-corrected intermediate visual acuity (10% contrast) with minimum add will be performed to determine the minimum amount of add necessary to achieve an intermediate visual acuity similar to the best-corrected distance visual acuity. BCIVA is to be tested at 66 cm under photopic conditions using the M&S System at 6 months. With distance correction in place, slowly build the amount of add necessary for the subject to achieve their best monocular intermediate visual acuity in the primary eye. In order to ensure the appropriate amount of add, at least one of the criteria below must be achieved:

- BCIVA similar to the subject's BCDVA. Document the amount of add necessary to achieve a BCIVA that matches the subject's BCDVA in the first eye. For example, if the subject's BCDVA is 20/20, the minimum ADD power will be the amount of add necessary to achieve a BCIVA of 20/20 at 66 cm. When the subject reaches a BCIVA that matches the BCDVA, record the minimum add power and BCIVA (# of letters correct).

- Increasing ADD power does not lead to improvement in intermediate visual acuity. When an additional +0.50 add (in two +0.25 D increments) does not increase the subject's visual acuity by 3 or more letters, stop the test and record the minimum add power and BCIVA (# of letters correct). For example, the subject shows progressive improvement in intermediate visual acuity and achieves 20/25 with +0.75 add over the distance correction. Increasing the add further by +0.50 (in two +0.25 D increments) only allows the subject to get 20/25+2 with a total of +1.25 add power. Stop the testing and record a minimum add of +0.75 with 80 letters correct.

Add the appropriate add power over the distance correction to the subject's first eye and perform the low contrast BCIVA testing with the fellow eye occluded using the M&S system as described above.

APPENDIX H INSTRUCTIONS FOR NEAR VISUAL ACUITY TESTING

Near visual acuity will be measured using trial frames and Good-Lite 100% ETDRS near charts designed for 40 cm and the Good-Lite self-illuminated and self-calibrated illumination box. The Good-Lite illumination box is self-illuminated and self-calibrates to a light level of approximately 85 cd/m^2 (range of 80–110 cd/m^2 is acceptable). Room lighting is to be set at a level lower than the illumination from the light box, per manufacturer instructions. Ambient luminance should be from dim to dark to maximize pupil size. No surface (including reflective surfaces) within the subject's field of vision should exceed the chart background in luminance.

The light box should be placed at a test distance of 40 cm from the subject for testing near visual acuities. Subjects should be reminded prior to testing that squinting is not allowed and the testing technician should carefully observe. If squinting is observed, the subject is to be reminded by the testing technician not to squint.

To avoid chart memorization, charts will be changed between every visual acuity measurement. Monocular and binocular uncorrected testing will be completed before monocular distance-corrected testing is done.

Near visual acuity testing is to be performed per **Appendix A**. Visual acuity measurements are based on the total number of correctly read letters. Subjects should be persuaded to read the smallest letters possible even if they have to guess. Record the total number of letters read correctly for each near test on the case report form. Near score grids are to be used and must be retained as source documentation. A reference chart for the conversion of the number of correctly-read ETDRS letters to a Snellen line equivalent is provided later in this section.

PROCEDURE: At 6-month visit, begin with monocular uncorrected near visual acuity testing using trial frames with the fellow eye occluded. Instruct subjects to read each line from left to right until they cannot read any additional letters. Subjects should be persuaded to read the smallest letters possible even if they must guess. Alternate the near chart per the score sheet and perform monocular uncorrected near visual testing in the fellow eye. Change the near chart per the score sheet and ensure the refractive adjustment of -0.25 D has been added for corrected near acuities and perform monocular testing in each eye using trial frames with the fellow eye occluded. Ensure the chart is changed between eye per the score sheet. Finally, perform binocular uncorrected near visual acuity with a new chart according to the score sheet. Record the total number of letters read for each test condition on the score grid and in the EDC system.

Conversion Reference Chart for GOOD-LITE Near (40 cm) Chart (ETDRS)

Standard Snellen Line Equivalent	Number of ETDRS Letters Read at 40 cm
20/10	85
	84
	83
20/13	82
	81
	80
	79
	78
20/16	77
	76
	75
	74
	73
20/20	72
	71
	70
	69
	68
20/25	67
	66
	65
	64
	63
20/32	62
	61
	60
	59
	58
20/40	57
	56
	55
	54
	53
20/50	52
	51
	50

Standard Snellen Line Equivalent	Number of ETDRS Letters Read at 40 cm
20/50	49
	48
20/60	47
	46
	45
	44
	43
20/80	42
	41
	40
	39
	38
20/100	37
	36
	35
	34
	33
20/126	32
	31
	30
	29
	28
20/160	27
	26
	25
	24
	23
20/200	22
	21
	20
	19
	18
>20/200	17
	16
	15

APPENDIX I INSTRUCTIONS FOR DEFOCUS TESTING

All defocus testing is to be performed in accordance with the methodology described in the draft ANSI Z80.35 Extended Depth of Focus draft standard (v7), under photopic conditions using the M&S System at a test distance of 4.0 meters, a trial frame, and loose trial lenses or retinoscopy lens racks. Subjects should be reminded prior to testing that squinting is not allowed and the testing technician should carefully observe to ensure the subject is not squinting. If squinting is observed, the subject is to be reminded by the testing technician not to squint.

This test is to be done at the 6-month visit for all subjects.

Monocular Defocus Testing (First eye only): With the subject's distance correction in place for the first eye and the second eye occluded, defocus the image by +2.00 D over the manifest distance correction in the first eye, using a plus-power loose trial lens or a retinoscopy lens rack. Start the test by instructing the subject to read as many letters as possible on the M&S system, even if the subject must guess. The technician will control movement through charts based on subject responses and the system will end the testing when a threshold is reached. The number of letters correctly read and the LogMAR score will be displayed on the laptop screen; record the total number of letters correct in EDC. Continue to change the defocus in -0.50 D increments using loose trial lenses or the retinoscopy lens rack, repeating the test and recording the total number of letters correct at each level of defocus up to -4.00 D over the subject's manifest distance correction.

Binocular Defocus Testing: Begin binocular testing by defocusing the image by +2.00 D over the manifest distance correction in both eyes, using two plus-power loose trial lenses or retinoscopy lens racks. Start the test by instructing the subject to read as many letters as they can on the M&S system, even if the subject must guess. The technician will control movement through charts based on subject responses and the system will end the testing when a threshold is reached. The number of letters correctly read and the LogMAR score will be displayed on the laptop screen; record the total number of letters correct in EDC. Continue to change the defocus in -0.50 D increments for both eyes using two loose trial lenses or retinoscopy racks, repeating the test and recording the total number of letters correct at each level of defocus up to -4.00 D over the subject's manifest distance correction.

APPENDIX J INSTRUCTIONS FOR PUPIL SIZE MEASUREMENTS

Pupil size should be measured by a Colvard pupillometer (Oasis Medical) or a NeurOptics pupillometer (NeurOptics, Inc.). For consistency, the same method should be used throughout the study. Pupil size should be recorded to the nearest one-half millimeter (one-tenth millimeter for NeurOptics).

MESOPIC WITHOUT GLARE PUPIL SIZE:

Mesopic pupil size for each eye should be measured under mesopic conditions. Room lights should be off and the 1.5 ND filter placed in front of the M&S System to reduce the lighting to 3 cd/m^2. Place a 1.5 ND filter lens for each eye in the trial frames/phoropter. After 10 minutes of dark adaptation, have the subject (without glasses and/or trial frames) look at a spot on the mesopic contrast sensitivity chart and allow one eye to continuously be exposed to the lighting condition while measuring the pupil of the other eye. Repeat the measurement on the second eye, and record the mesopic pupil size for both eyes.

MESOPIC WITH GLARE PUPIL SIZE:

Mesopic with glare pupil size for each eye should be measured under mesopic with glare contrast sensitivity conditions. Room lights should be off, the 1.5 ND filter placed in front of the M&S System to reduce the lighting to 3 cd/m^2, and the glare lights from the M&S System on. Have the subject (without glasses and/or trial frames) look at a spot on the mesopic with glare contrast sensitivity chart and allow one eye to continuously be exposed to the lighting condition while measuring the pupil of the other eye. Repeat the measurement on the second eye, and record the mesopic with glare pupil size for both eyes.

PHOTOPIC WITH GLARE PUPIL SIZE:

Photopic with glare pupil size for each eye should be measured under the same lighting conditions as the photopic with glare contrast sensitivity testing conditions. To measure photopic pupil size, have the subject look at a spot on the photopic contrast sensitivity chart under ambient room lighting and with the glare lights from the M&S system turned on (without glasses). Allow one eye to be exposed to the ambient room lighting while measuring the pupil of the other eye. Repeat the measurement on the second eye, and record the photopic pupil size for both eyes.

PHOTOPIC WITHOUT GLARE PUPIL SIZE:

Photopic pupil size for each eye should be measured under the same lighting conditions as the photopic distance visual acuity testing. To measure photopic pupil size, have the subject look at a spot in the distance (without glasses) and allow one eye to be exposed to the ambient room lighting while measuring the pupil of the other eye. Repeat the measurement on the second eye, and record the photopic pupil size for both eyes.

APPENDIX K INSTRUCTIONS FOR CONTRAST SENSITIVITY TESTING

Contrast sensitivity testing will be measured using the M&S system for sine-wave gratings (1.5, 3, 6, 12 and/or 18 cycles per degree). Testing will be done under mesopic and mesopic with glare and photopic with glare lighting conditions. **The test distance for the M&S system is 8 feet (2.5 meters).** Mesopic testing without glare will be performed before contrast sensitivity with glare testing.

This test is to be done monocularly (first eye only) at the 6-month visit for all subjects. All subjects will be tested with best-corrected manifest refraction in place, and a refraction adjustment of +0.12 D over manifest refraction in place. A phoropter may be used for contrast sensitivity testing. Subjects should be shown the contrast sensitivity target samples before dark adaptation for mesopic testing is started.

Contrast sensitivity measurements are based on subject identification of the orientation of a low contrast grating (vertical, horizontal, tilted left or tilted right). For each grating presented, the subject will have to identify or guess the orientation of the grating. After an automated protocol, contrast sensitivity values will be displayed on the laptop screen for 1.5, 3, 6, 12 and/or 18 cpd.

The first test will be under the mesopic without glare lighting condition. Dim to dark room lighting will be used along with a 1.5 ND filter in front of the M&S system laptop computer screen. Dark-adapt the subject for 10 minutes and measure mesopic pupil size prior to beginning the test. Place the subject's distance correction with the +0.12 D refraction adjustment in place for the first eye implanted and occlude the second eye implanted. Place a 1.5 ND filter in front of the M&S System.

Begin the test and instruct the subject to report the orientation of the contrast grating out loud as they view the grating, documenting the subject responses on the M&S tablet. Encourage the subject to continue through all gratings, even if they must guess. The M&S System will advance to the next set of gratings based on the technician input of the subject's responses. Record the contrast sensitivity percentages displayed on the laptop computer for all the spatial frequencies in EDC.

Proceed to testing under the mesopic with glare lighting condition and then to testing under the photopic with glare lighting condition, measuring the pupil size per **Appendix J** prior to beginning each test.

APPENDIX L SLIT-LAMP EXAM RATINGS

A. Ratings of Aqueous Cells and Flare

For consistency across study sites, the SUN (Standardization of Uveitis Nomenclature) Working Group Grading Scheme is to be used for grading of anterior chamber cells and flare as reported in: Standardization of uveitis nomenclature for reporting clinical data. Results of The First International Workshop; The standardization of uveitis nomenclature (SUN) working group. *Am J Ophthalmol* 2005;140:509-516.

CELLS

Grade	Cells in Field (Field is a 1x1 mm slit beam)
0	<1
0.5+	1 - 5
1+	6 - 15
2+	16 - 25
3+	26 - 50
4+	>50

FLARE

Grade	Description
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

B. Ratings of Corneal Edema

Corneal edema should be classified according to the haziness of the epithelium, the number of microcysts observed, and the clouding of the stroma.

Amount	Grade	Description
None	**0**	Normal transparency: a. No epithelial or sub-epithelial haziness b. No microcysts c. No stromal cloudiness
Trace	**+1**	a. Barely discernible localized epithelial or sub-epithelial haziness, and/or b. 1 to 20 microcysts, and/or c. Barely discernible localized stromal cloudiness
Mild	**+2**	a. Faint but definite localized or generalized epithelial, sub-epithelial or stromal haziness/cloudiness, and/or b. 21-50 microcysts
Moderate	**+3**	a. Significant localized or generalized epithelial, sub-epithelial or stromal haziness/cloudiness and/or b. 51-100 microcysts
Severe	**+4**	a. Definite widespread epithelial or stromal cloudiness, giving dull glass appearance to cornea or numerous coalescent bullae (please note the number and location of bullae), and/or b. >100 microcysts or bullae, and/or c. Numerous striae (please note the number and location of striae or folds)

C. Posterior Capsule Striae Grading Scale

The following five-point grading scale is to be used for rating striae in the posterior capsule:

Amount	Grade	Description
None	0	None
Trace	+1	One detectable, barely noticeable striae
Mild	+2	One or two prominent striae
Moderate	+3	Three or more prominent striae, but visibility of retina is not impacted
Severe	+4	Three or more prominent striae affecting visualization of retina

D. Posterior Capsule Opacification Grading Scale

Below is the five-point grading scale to be used for PCO determination:

Amount	Grade	Description
None	0	Normal posterior capsule with no area of opacity. Red reflex bright.
Trace	+1	Some loss of transparency involving the posterior capsule. Red reflex fairly bright
Mild	+2	Mild loss of transparency with cloudiness extending through most of the posterior capsule. There may be a few Elschnig's pearls in the posterior capsule. Red reflex mildly diminished.
Moderate	+3	Moderate loss of transparency with difficulty visualizing the retina. There may be multiple Elschnig's pearls in the posterior capsule. Red reflex markedly diminished.
Severe	+4	Posterior capsule very opaque with inability to view the retina. The posterior capsule may have confluent Elschnig's pearls and fibrous scarring. Red reflex barely visible.

E. IOL Glistenings

Use the following scale to grade IOL glistenings, using a slit beam 2.0 mm wide and 10.0 mm long:

Amount	Grade	Description
None	0	No glistenings visible
Rare	+0.5	<10 glistenings visible
Trace	+1	10-19 glistenings visible
Mild	+2	20-29 glistenings visible
Moderate	+3	30-39 glistenings visible
Severe	+4	≥40 glistenings visible

APPENDIX M PATIENT REPORTED VISUAL SYMPTOMS QUESTIONNAIRE (PRVSQV2)

Patient Reported Visual Symptoms Questionnaire

(PRVSQv2)

This questionnaire asks about your visual symptoms OVER THE LAST 7 DAYS.

For each question, please mark an ☒ in the box or boxes that is your answer.

The next few questions ask about halos.

Halos are bright circles or rings that appear around a source of light. **Halos** may occur when looking at an oncoming automobile's headlights or street lights at night.

Q1a. Over the last 7 days, how often did you experience halos?

- ☐ Never **(go to question Q2a)**
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Always

If you experienced halos in the last 7 days, please answer the following questions.

Q1b. Did you experience halos… ***Check all that apply***.

- ☐ When wearing corrective glasses or contacts
- ☐ When wearing any type of sunglasses
- ☐ When **not** wearing corrective glasses, contacts or sunglasses

Q1c. Did you experience halos… ***Check all that apply***.

- ☐ During the day
- ☐ During the night
- ☐ During dawn or dusk

Q1d. Overall, how much were you bothered by halos?

- ☐ Not at all bothered
- ☐ Slightly bothered
- ☐ Moderately bothered
- ☐ Very bothered
- ☐ Extremely bothered

Q1e. Is there anything you have a lot of difficulty with, or do not do, because of halos?

- ☐ No
- ☐ Yes. If Yes, please describe: _____

The next few questions ask about starbursts.

Starbursts are one or more lines or rays that surround or appear from a source of light. **Starbursts** may occur when looking at an oncoming automobile's headlights or street lights at night.

Q2a. Over the last 7 days, how often did you experience starbursts?

- ☐ Never **(go to question Q3a)**
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Always

If you experienced starbursts in the last 7 days, please answer the following questions.

Q2b. Did you experience starbursts… ***Check all that apply.***

- ☐ When wearing corrective glasses or contacts
- ☐ When wearing any type of sunglasses
- ☐ When **not** wearing corrective glasses, contacts or sunglasses

Q2c. Did you experience starbursts… ***Check all that apply.***

- ☐ During the day
- ☐ During the night
- ☐ During dawn or dusk

Q2d. Overall, how much were you bothered by starbursts?

- ☐ Not at all bothered
- ☐ Slightly bothered
- ☐ Moderately bothered
- ☐ Very bothered
- ☐ Extremely bothered

Q2e. Is there anything you have a lot of difficulty with, or do not do, because of starbursts?

- ☐ No
- ☐ Yes. If Yes, please describe: _____

The next few questions ask about multiple or double vision.

Multiple or double vision is when objects appear as two separate or overlapping images. **Multiple or double vision** may occur when looking at words in a book or on a street sign.

Q3a. Over the last 7 days, how often did you experience multiple or double vision?

- ☐ Never **(go to question Q4a)**
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Always

If you experienced multiple or double vision in the last 7 days, please answer the following questions.

Q3b. Did you experience multiple or double vision… ***Check all that apply.***

- ☐ When wearing corrective glasses or contacts
- ☐ When wearing any type of sunglasses
- ☐ When **not** wearing corrective glasses, contacts or sunglasses

Q3c. Did you experience multiple or double vision… ***Check all that apply.***

- ☐ During the day
- ☐ During the night
- ☐ During dawn or dusk

Q3d. Overall, how much were you bothered by multiple or double vision?

- ☐ Not at all bothered
- ☐ Slightly bothered
- ☐ Moderately bothered
- ☐ Very bothered
- ☐ Extremely bothered

Q3e. Is there anything you have a lot of difficulty with, or do not do, because of multiple or double vision?

- ☐ No
- ☐ Yes. If Yes, please describe: _____

The next few questions ask about sensitivity to light.

Sensitivity to light is a decreased ability to tolerate light, such as sunlight, fluorescent light or incandescent light. **Sensitivity to light** may occur in a brightly lit grocery or department store.

Q4a. Over the last 7 days, how often did you experience sensitivity to light?

- ☐ Never **(go to question Q5a)**
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Always

If you experienced sensitivity to light in the last 7 days, please answer the following questions.

Q4b. Did you experience sensitivity to light … ***Check all that apply.***

- ☐ When wearing corrective glasses or contacts
- ☐ When wearing any type of sunglasses
- ☐ When **not** wearing corrective glasses, contacts or sunglasses

Q4c. Did you experience sensitivity to light … ***Check all that apply.***

- ☐ During the day
- ☐ During the night
- ☐ During dawn or dusk

Q4d. Overall, how much were you bothered by sensitivity to light?

- ☐ Not at all bothered
- ☐ Slightly bothered
- ☐ Moderately bothered
- ☐ Very bothered
- ☐ Extremely bothered

Q4e. Is there anything you have a lot of difficulty with, or do not do, because of sensitivity to light?

- ☐ No
- ☐ Yes. If Yes, please describe: _____

The next few questions ask about glare related to scattered light.

Glare related to scattered light decreases the ability to distinguish differences between objects and their background. **Glare related to scattered light** may occur when looking at an oncoming automobile's headlights at night.

Q5a. Over the last 7 days, how often did you experience glare related to scattered light?

- ☐ Never **(go to question Q6a)**
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Always

If you experienced glare related to scattered light in the last 7 days, please answer the following questions.

Q5b. Did you experience glare related to scattered light ***Check all that apply***.

- ☐ When wearing corrective glasses or contacts
- ☐ When wearing any type of sunglasses
- ☐ When **not** wearing corrective glasses, contacts or sunglasses

Q5c. Did you experience glare related to scattered light ***Check all that apply***.

- ☐ During the day
- ☐ During the night
- ☐ During dawn or dusk

Q5d. Overall, how much were you bothered by glare related to scattered light?

- ☐ Not at all bothered
- ☐ Slightly bothered
- ☐ Moderately bothered
- ☐ Very bothered
- ☐ Extremely bothered

Q5e. Is there anything you have a lot of difficulty with, or do not do, because of glare related to scattered light?

- ☐ No
- ☐ Yes. If Yes, please describe: _____

The next few questions ask about occlusions.

Occlusions are fixed dark or light blocked areas within your vision. **Occlusions** are constant and do not come and go.

Q6a. Over the last 7 days, how often did you experience occlusions?

- ☐ Never **(go to question Q7a)**
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Always

If you experienced occlusions in the last 7 days, please answer the following questions.

Q6b. Did you experience occlusions … ***Check all that apply***.

- ☐ When wearing corrective glasses or contacts
- ☐ When wearing any type of sunglasses
- ☐ When **not** wearing corrective glasses, contacts or sunglasses

Q6c. Did you experience occlusions … ***Check all that apply***.

- ☐ During the day
- ☐ During the night
- ☐ During dawn or dusk

Q6d. Overall, how much were you bothered by occlusions?

- ☐ Not at all bothered
- ☐ Slightly bothered
- ☐ Moderately bothered
- ☐ Very bothered
- ☐ Extremely bothered

Q6e. Is there anything you have a lot of difficulty with, or do not do, because of occlusions?

- ☐ No
- ☐ Yes. If Yes, please describe:

_____

The next few questions ask about poor low light vision.

Poor low light vision is having decreased clarity of vision in twilight or dusk conditions. **Poor low light vision** may occur when reading a restaurant menu in low light.

Q7a. Over the last 7 days, how often did you experience poor low light vision?

- ☐ Never **(go to question 8)**
- ☐ Rarely
- ☐ Sometimes
- ☐ Often
- ☐ Always

If you experienced poor low light vision in the last 7 days, please answer the following questions.

Q7b. Did you experience poor low light vision … ***Check all that apply***.

- ☐ When wearing corrective glasses or contacts
- ☐ When wearing any type of sunglasses
- ☐ When **not** wearing corrective glasses, contacts or sunglasses

Q7c. Did you experience poor low light vision … ***Check all that apply***.

- ☐ During the day
- ☐ During the night
- ☐ During dawn or dusk

Q7d. Overall, how much were you bothered by poor low light vision?

- ☐ Not at all bothered
- ☐ Slightly bothered
- ☐ Moderately bothered
- ☐ Very bothered
- ☐ Extremely bothered

Q7e. Is there anything you have a lot of difficulty with, or do not do, because of poor low light vision?

- ☐ No
- ☐ Yes. If Yes, please describe:

_____

The next question asks about any other visual symptoms.

Q8. Over the last 7 days, have you experienced any other **visual symptoms** not described above?

☐ No

☐ Yes. If Yes, please describe:

_____

_____

_____

_____

_____

APPENDIX N PATIENT REPORTED SPECTACLE INDEPENDENCE QUESTIONNAIRE (PRSIQV2)

Patient Reported Spectacle Independence Questionnaire-v2 (PRSIQv2)

The following questions ask about your vision DURING THE LAST 7 DAYS.

Please read each question carefully and answer as honestly as you can without the help of anyone.

For each question, please mark an ☒ in the one box that is your answer.

1. During the LAST 7 DAYS, did you <u>need</u> glasses (including reading glasses or a magnifier) or contacts for…

	Yes	No
a Distance vision (more than 5 feet away)	☐ 1	☐ 2
b Intermediate vision (1.5 to 5 feet away)	☐ 1	☐ 2
c Near vision (less than 1.5 feet away)	☐ 1	☐ 2

2. During the LAST 7 DAYS, how often did you <u>wear</u> glasses (including reading glasses or a magnifier) or contacts for…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Distance vision (more than 5 feet away)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Intermediate vision (1.5 to 5 feet away)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Near vision (less than 1.5 feet away)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Overall vision (all distances)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. During the LAST 7 DAYS, how often did you have to STRAIN to see when NOT wearing glasses (including reading glasses or a magnifier) or contacts for…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Distance vision (more than 5 feet away)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Intermediate vision (1.5 to 5 feet away)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Near vision (less than 1.5 feet away)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Overall vision (all distances)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. Taking all things into account, how satisfied or dissatisfied are you with your vision when NOT wearing glasses (including reading glasses or a magnifier) or contacts for …

	Completely satisfied	Mostly satisfied	Moderately satisfied	A little satisfied	Not at all satisfied
a Distance vision (more than 5 feet away)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Intermediate vision (1.5 to 5 feet away)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Near vision (less than 1.5 feet away)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Overall vision (all distances)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

APPENDIX O PATIENT REPORTED SPECTACLE USE QUESTIONNAIRE (PRSUQ)

The original version of this questionnaire was used in the EROV-106-ZXRC protocol "*Clinical Investigation of the TECNIS Symfony Extended Range of Vision IOL, Model ZXR00*".

Patient Reported Spectacle Use Questionnaire

(PRSUQ)

The following questions ask about your vision DURING THE LAST 7 DAYS.

Please read each question carefully and answer as honestly as you can without the help of anyone – there are no right or wrong answers.

For each of the following questions, please mark an ☒ in the box or boxes that best describe your answer.

Q1: Over the LAST 7 DAYS, what types of visual correction did you wear? This does NOT include sunglasses unless they are prescription sunglasses.

Check ALL that apply:

- ☐ NOT APPLICABLE, I never wear glasses or contacts
- ☐ Distance only glasses/contacts
- ☐ Intermediate only glasses/contacts (this means for computer work or other arm's length tasks)
- ☐ Reading glasses
- ☐ Monofocal contacts (distance only contacts)
- ☐ Multifocal glasses/contacts (this includes bifocal, trifocal and progressive glasses or contacts)
- ☐ Prescription sunglasses
- ☐ Other: _____

Q2: Over the LAST 7 DAYS, why did you wear glasses or contacts?

Check ALL that apply:

- ☐ NOT APPLICABLE, I never wear glasses or contacts
- ☐ I needed them for seeing clearly
- ☐ I liked the way I looked in them
- ☐ Other: _____

Q3: Over the LAST 7 DAYS, why didn't you wear glasses or contacts?

Check ALL that apply:

- ☐ NOT APPLICABLE, I always wear glasses or contacts
- ☐ They were inconvenient
- ☐ They made my vision worse
- ☐ I did not need them for seeing clearly
- ☐ I could not find my glasses or contacts
- ☐ I did not have them with me at the time
- ☐ I did not own glasses or contacts
- ☐ I did not have a current prescription
- ☐ They were scratched, broken or in bad condition
- ☐ I did not like the way I looked in them (appearance)
- ☐ Other: (provide reason)_____

Q4. During the LAST 7 DAYS, were there times you NEEDED glasses or contacts but did not USE them (besides non-prescription sunglasses)?

- ☐ Yes
- ☐ No (go to Q6)

Q5. If YES, what was the MAIN reason you did not wear your glasses or contacts?

Check ONLY one:

- ☐ They were inconvenient
- ☐ They made my vision worse
- ☐ I did not need them for seeing clearly
- ☐ I could not find my glasses or contacts
- ☐ I did not have them with me at the time
- ☐ I did not own glasses or contacts
- ☐ I did not have a current prescription
- ☐ They were scratched, broken or in bad condition
- ☐ I did not like the way I looked in them (appearance)
- ☐ Other: (provide reason)_____

Q6. During the LAST 7 DAYS, were there times you wore glasses or contacts (besides non-prescription sunglasses) but did not NEED them?

- ☐ Yes (go to Q7)
- ☐ No (please stop here)

Q7. If YES, what was the MAIN reason you wore your glasses or contacts?

Check ONLY one:

- ☐ I liked the way they made me look
- ☐ I am in the habit of always wearing them
- ☐ Other: (provide reason)_____

APPENDIX P – PATIENT REPORTED QUALITY OF VISION QUESTIONNAIRE (CATQUEST-9SF 2011)

Catquest-9SF 2011 Questionnaire 1

Name: _____

Street address: _____

Town and post code: _____

The aim of this questionnaire is to establish what difficulties you have in your daily life due to impaired sight.

So that we can develop our healthcare as well as possible we are keen for you to answer the questions in the questionnaire as honestly as you can. The questionnaire contains questions about your difficulties due to impaired sight in connection with certain everyday tasks. If you use glasses for distance and/or close-up purposes, the questions are about what it is like when you use your best glasses.

The questions in this questionnaire (Questionnaire 1) apply to your situation during the past 4 weeks.

When you answer the questions on the next page you must try to think only of the difficulties that your sight may be causing you. We appreciate that it may be difficult to decide just what your sight means to you if you also have other problems such as joint pains or dizziness for example. We would still ask you to try to answer how important you think your sight is in your ability to perform the following tasks.

When you are asked to state your difficulties, we have given three response options. We call them **very great difficulty**, **great difficulty and some difficulty**. Different people may put things differently. Try to see the three response options as three equal size parts of a scale ranging from the greatest to the least difficulty caused by your sight in performing various activities.

An example of how we envisage the scale with the three different response options:

Greatest _____ / _____ / _____least
very great difficulty great difficulty some difficulty

A. Do you find that your sight at present in some way causes you difficulty in your everyday life?

Yes, very great difficulty	Yes, great difficulty	Yes, some difficulty	No, no difficulty	Cannot decide
☐	☐	☐	☐	☐

B. Are you satisfied or dissatisfied with your sight at present?

Very dissatisfied	Fairly dissatisfied	Fairly satisfied	Very satisfied	Cannot decide
☐	☐	☐	☐	☐

C. Do you have difficulty with the following activities because of your sight?

If so, to what extent? In each row place just one tick in the box which you think best corresponds to your situation.

	Yes, very great difficulty	Yes, great difficulty	Yes, some difficulty	No, no difficulty	Cannot decide
Reading text in newspapers	☐	☐	☐	☐	☐
Recognising the faces of people you meet	☐	☐	☐	☐	☐
Seeing the prices of goods when shopping	☐	☐	☐	☐	☐
Seeing to walk on uneven surfaces, e.g. cobblestones	☐	☐	☐	☐	☐
Seeing to do handicrafts, woodwork etc.	☐	☐	☐	☐	☐
Reading subtitles on TV	☐	☐	☐	☐	☐
Seeing to engage in an activity/hobby that you are interested in	☐	☐	☐	☐	☐

Thank you very much for taking part.

APPENDIX Q – AMERICAN ACADEMY OF OPHTHALMOLOGY TASK FORCE CONSENSUS STATEMENT ON ADVERSE EVENTS FOR INTRAOCULAR LENSES

CA); Alcon Laboratories, Inc. (Fort Worth, TX); Carl Zeiss, Inc. (Oberkochen, Germany); Oculus, Inc. (Wetzlar, Germany); Consultant and Equity Owner – AcuFocus, Inc. (Irvine, CA); ArcScan (Morrison, CO); Elenza (Roanoke, VA); Visiometrics (Barcelona, Spain).

A.G.: Consultant – Abbott Medical Optics, LensAR (Orlando, FL); Medicem (Cheshire, UK); Refocus Group (Dallas, TX); Tracey Technologies (Houston, TX); Vista Ocular (North Canton, OH); Consultant and Equity Owner – Encore Vision (Fort Worth, TX); LensGen (Irvine, CA); PowerVision (Belmont, CA).

The mention of commercial products, their sources, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by the Department of Health and Human Services (DHHS). The following authors: M.E.T., G.H., T.N., E.R., D.C., and M.E. are employees of the U.S. Government and prepared this work as part of their official duties. Title 17, USC, § 105 provides that copyright protection under this title is not available for any work of the United States Government. Title 17, USC, § 101 defines a U.S. Government work as a work prepared by a military service member or employee of the U.S. Government as part of that person's official duties.

The American Academy of Ophthalmology Task Force for Developing Novel End Points for Premium Intraocular Lenses members include: Jack T. Holladay, MD, MSEE, Chair; Adrian Glasser, PhD, Co-Chair; Scott MacRae, MD, Co-Chair; Samuel Masket, MD; Walter Stark, MD; and the following U.S. Food and Drug Administration staff members: Malvina Eydelman, MD; Don Calogero, MS; Gene Hilmantel, OD; Eva Rorer, MD; Tieuvi Nguyen, PhD; and Michelle E. Tarver, MD, PhD.

Correspondence:
Flora Lum, MD, American Academy of Ophthalmology, Division of Quality and Data Science, 655 Beach Street, San Francisco, CA 94109-1336. E-mail: flum@aao.org.

References

1. Doors M, Berendschot T, Webers CA, Nuijts R. Model to predict endothelial cell loss after iris-fixated phakic intraocular lens implantation. *Invest Ophthalmol Vis Sci*. 2010;51:811-815.
2. Tahzib N, Nuijts R, Wu W, Budo C. Long-term study of Artisan phakic intraocular lens implantation for the correction of moderate to high myopia: ten-year follow-up results. *Ophthalmology*. 2007;114:1133-1142.
3. Edelhauser HF, Sanders DR, Azar R, Lamielle H, ICL in Treatment of Myopia Study Group. Corneal endothelial assessment after ICL implantation. *J Cataract Refract Surg*. 2004;30:576-583.

Special Report: The American Academy of Ophthalmology Task Force Consensus Statement on Adverse Events with Intraocular Lenses

In 1978, the US Food and Drug Administration approved the first investigational device exemption studies of intraocular lenses (IOLs). Outcomes were initially published in 1983 on pooled, publicly available data from IOL premarket approval studies that were used to support marketing approvals.[1] After publication, this "historical control" information was used as a benchmark for the assessment of the safety and effectiveness of new IOLs. These safety and effectiveness endpoints have been referred to as the "Food and Drug Administration Grid" and "Safety and Performance Endpoints" (SPEs) for IOLs. Although the SPEs were updated on the basis of additional premarket approvals in 1998, they have not been updated to reflect the development of "premium IOLs," including toric, multifocal, accommodative, and phakic IOLs.[2] Premium IOLs may present additional adverse events (AEs) to those already established for monofocal IOLs. Further, most of the AEs in the "Grid" do not have standard definitions, and the definitions used could have changed over time with advances in our understanding of ocular pathology. Considering untoward events associated with premium IOL implantation and that would be appropriate as safety endpoints in clinical studies of new premium IOLs, the American Academy of Ophthalmology's Task Force has developed consensus definitions for premium IOL SPE AEs as shown in Table 1. The AE of secondary IOL intervention has been subcategorized by the type of intervention and IOL exchange, removal, and reposition. These indications are listed and defined in Table 2 and Appendix 1.

At this time, acceptable rates for premium IOL SPE AEs have not been established. However, the definitions proposed may be used during clinical studies of new IOLs going forward to allow for the determination of appropriate SPE rates that can be applied to the assessment of new premium IOLs in the future.

SAMUEL MASKET, MD[1]
EVA RORER, MD[2]
WALTER STARK, MD[3]
JACK T. HOLLADAY, MD, MSEE[4]
SCOTT MACRAE, MD[5]
MICHELLE E. TARVER, MD, PHD[2]
ADRIAN GLASSER, PHD[6]
DON CALOGERO, MS[2]
GENE HILMANTEL, OD[2]
TIEUVI NGUYEN, PHD[2]
MALVINA EYDELMAN, MD[2]

[1]*Advanced Vision Care, Clinical Professor, David Geffen School of Medicine, Jules Stein Eye Institute, UCLA, Los Angeles, California;* [2]*Food and Drug Administration, Center for Devices and Radiological Health, Silver Spring, Maryland;* [3]*Retired Distinguished Professor of Ophthalmology, Wilmer Eye Institute, Johns Hopkins University, Baltimore, Maryland;* [4]*Clinical Professor, Department of Ophthalmology, Baylor College of Medicine, Houston, Texas;* [5]*Flaum Eye Institute, University of Rochester, Rochester, New York;* [6]*Independent Consultant, Tampa, Florida*

Financial Disclosure(s): The author(s) have made the following disclosure(s): J.T.H.: Consultant – Abbott Medical Optics (Milpitas, CA); Alcon Laboratories, Inc. (Fort Worth, TX); Carl Zeiss, Inc. (Oberkochen, Germany); Oculus, Inc. (Wetzlar, Germany); Consultant and Equity Owner – AcuFocus, Inc. (Irvine, CA); ArcScan (Morrison, CO); Elenza (Roanoke, VA); Visiometrics (Barcelona, Spain).

A.G.: Consultant – Abbott Medical Optics, LensAR (Orlando, FL); Medicem (Cheshire, UK); Refocus Group (Dallas, TX); Tracey Technologies (Houston, TX); Vista Ocular (North Canton, OH); Consultant and Equity Owner – Encore Vision (Fort Worth, TX); LensGen (Irvine, CA); PowerVision (Belmont, CA).

The mention of commercial products, their sources, or their use in connection with material reported herein is not to be construed as

Table 1. Postoperative Adverse Event Definitions for Intraocular Lenses

Adverse Event	Definition
Chronic anterior uveitis	Persistent anterior segment inflammation characterized by grade 1+ cell or greater using SUN criteria[3]
Clinically significant cystoid macular edema	Macular edema diagnosed by clinical examination and adjunct testing (e.g., OCT, FA) resulting in BCDVA of ≤20/40 at ≥1 mo
Corneal edema	Corneal swelling (stromal or epithelial) resulting in BCDVA of ≤20/40 at ≥1 mo
Endophthalmitis	Intraocular inflammation requiring diagnostic vitreous tap and intraocular antibiotics
Mechanical pupillary block	Shallowing of anterior chamber due to obstruction of aqueous humor flow from the posterior to anterior chamber through the pupil by the crystalline lens, vitreous face, or implanted device
Increased IOP	Elevation of IOP by ≥10 mmHg above baseline to a minimum of 25 mmHg
Rhegmatogenous RD	Partial or complete RD associated with retinal tear
Toxic anterior segment syndrome	Acute, noninfectious inflammation of the anterior segment that starts within 24 hrs after surgery, usually resulting in hypopyon and commonly presenting with corneal edema, that improves with steroid treatment
Secondary IOL intervention	
Exchange	The investigational device is replaced with the same lens model.
Removal	The investigational device is removed and replaced with a noninvestigational lens or no lens is implanted.
Reposition	The existing IOL is surgically moved to another location or rotated.

BCDVA = best-corrected distance visual acuity; FA = fluorescein angiography; IOL = intraocular lens; IOP = intraocular pressure; OCT = optical coherence tomography; RD = retinal detachment; SUN = Standardization of Uveitis Nomenclature.

Table 2. Definitions of Indications for Device Exchange, Removal, or Reposition

Indication	Definition
Capsular block syndrome	Hyper-distention of the lens capsular bag due to the IOL optic blocking egress of fluid through the anterior capsulotomy typically inducing a myopic refractive error
Cataract	Any opacification of the crystalline lens with or without reduced visual acuity
Chronic anterior uveitis	Persistent anterior segment inflammation characterized by grade ≥1+ cell using SUN criteria[3]
Endothelial cell loss	Chronic endothelial cell loss at a rate greater than that due to normal aging
Incorrect IOL power	Postoperative refractive error different from predicted and not due to a calculation or other user error
Iris pigment epithelium loss*	New or worsening iris transillumination defects or increase in pigmented cells in the anterior chamber noted after the 1-wk visit when assessed before instillation of any dilating drops
Lens optic abnormality	Unanticipated visual outcome (e.g., acuity, contrast sensitivity, symptoms) associated with opacification, vacuoles, microvacuoles, or subsurface nanoglistenings and not due to other causes
Malpositioned IOL	Decentration, tilt, or rotation of IOL requiring reoperation May include changes induced by Nd:YAG laser anterior or posterior capsulotomy
Early	If noted before 120 days postoperatively
Late	If noted at ≥120 days postoperatively
Damaged IOL	Crack of lens optic, breakage, or deformity of haptic, or other damage to the IOL May include changes induced by Nd:YAG laser anterior or posterior capsulotomy
Pupil ovalization	Progressive deformation of the pupil with elongation of the pupil in the meridian of the long axis of the IOL Documentation to be made under photopic conditions†
Pain	Graded as ≥4 on the standardized pain numeric rating scale of current pain intensity from 0 (no pain) to 10 (worst possible pain)
Peripheral anterior synechiae	Progressive closure of the anterior chamber angle due to propagation of anterior synechiae in the absence of obvious anterior uveitis
Patient-reported undesirable optical phenomena	Dysphotopsia (positive or negative or both), monocular diplopia, intolerable glare, halos, or other visual symptoms, not due to 1 of the indications listed

IOL = intraocular lens; Nd:YAG = neodymium-doped yttrium aluminium garnet; SUN = Standardization of Uveitis Nomenclature.
*If there is a transillumination defect preoperatively, then a photograph should be taken, and then at each subsequent visit, a photograph should be taken and compared with the preoperative photograph via a standardized photographic method.
†A consensus statement regarding a proposed methodology for standardizing assessment of pupil ovalization is available in Appendix 1.

The American Academy of Ophthalmology Task Force for Developing Novel Endpoints for Premium Intraocular Lenses Members include Jack T. Holladay, MD, MSEE, Chair; Adrian Glasser, PhD, Scott MacRae, MD, Samuel Masket, MD, Walter Stark, MD, and the following Food and Drug Administration staff members: Malvina Eydelman, MD, Don Calogero, MS, Gene Hilmantel, OD, Eva Rorer, MD, Tieuvi Nguyen, PhD, and Michelle E. Tarver, MD, PhD.

Correspondence:
Flora Lum, MD, American Academy of Ophthalmology, Division of Quality and Data Science, 655 Beach Street, San Francisco, CA 94109-1336. E-mail: flum@aao.org.

Appendix 1. Oval Pupil Measurement Background and Standard Operating Procedure

Background

The only study of the oval pupil available was by Isotani et al[3] in 1995, who studied the ratio of the major to minor diameter in healthy subjects by using infrared photography. The subjects were dark adapted, so these are scotopic pupil measurements.

Standard Operating Procedure

If the clinician observes an oval or irregularly shaped pupil (dyscoria) at any visit after surgery, photographs should be taken at that visit and each subsequent visit to determine if the ovalization is progressive. The major and minor diameters of the pupil, which may not be orthogonal, are measured on the photograph, which must be taken in photopic conditions (>200 foot-candles or 2153 lux) so the pupil is maximally constricted. The pupil constriction provides the setting for pupil ovalization. For the measurement, the diameters must pass through the center of the least-squares, best-fit ellipse or centroid of the pupil perimeter. The ratio of the major to minor diameter is then calculated and reported. The photograph may be taken with any camera, including but not limited to slit-lamp cameras, topographers, and Scheimpflug devices, but the eye image must be captured under photopic conditions as specified.

References

1. Stark WJ, Worthen DM, Holladay JT, et al. The FDA report on intraocular lenses. *Ophthalmology*. 1983;90:311-317.
2. Lum F, Tarver ME, Kahook MY, et al. Special commentary: Food and Drug Administration and American Academy of Ophthalmology sponsored: developing novel endpoints for premium intraocular lenses workshop. *Ophthalmology*. 2015;122:1522-1531.
3. Isotani H, Fukumoto Y, Kitaoka H, et al. Oval pupil in patients with diabetes mellitus: examination by measurement of the dark-adapted pupillary area and pupillary light reflex. *Diabetes Res Clin Pract*. 1995;29:43-48.

Special Report: American Academy of Ophthalmology Task Force Summary Statement for Measurement of Tilt, Decentration, and Chord Length

Currently, the measurement of tilt and decentration is not commercially available in an instrument or method that has been validated clinically. In lieu of a validated, commercially available instrument or method, the current statuses of 3 different approaches that have been used to measure tilt and decentration are described to help provide the basis for the future development of an instrument or technique.

Definitions

- Decentration of an intraocular lens (IOL) is the lateral horizontal and vertical displacement of an IOL relative to the visual axis as seen by the clinician through the cornea (subject-fixated coaxially sighted corneal light reflex, as described by Chang and Waring[1]).
- Tilt of an IOL is the horizontal and vertical angle from perpendicular of an IOL relative to the visual axis (subject-fixated coaxially sighted corneal light reflex, as described by Chang and Waring[1]).
- Chord length μ is the displacement (distance) between the subject-fixated coaxially sighted corneal light reflex and pupil center.[1] For some diffractive IOLs, the midpoint between pupil center and visual axis may be optimal.

Tilt, Decentration, and Chord Length μ

The goal is to measure tilt, apparent decentration through the cornea, and chord length μ on all subjects with a premium IOL.

Table 1. Ratio of IOL Toricity to Corneal Astigmatism

	Effective Lens Position					
A-constant—>	116.346	117.203	118.059	118.916	119.773	120.630
Surgeon Factor—>	0.287	0.772	1.257	1.742	2.227	2.713
ELP—>	4.000	4.500	5.000	5.500	6.000	6.500
IOL Power	Resulting Ratio of IOL Toricity to 2 D of Corneal Astigmatism					
10	1.359	1.424	1.494	1.571	1.654	1.745
22	1.277	1.330	1.387	1.450	1.519	1.595
34	1.198	1.239	1.284	1.334	1.390	1.452
46	1.121	1.151	1.185	1.223	1.267	1.316

D = diopter; ELP = effective lens position; IOL = intraocular lens.