AcuFocus™

Study Protocol

Study Title: CLINICAL EVALUATION OF A SMALL APERTURE EXTENDED DEPTH OF FOCUS INTRAOCULAR LENS

Study Number: SAIL-101-UNI

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CLINICAL EVALUATION OF A SMALL APERTURE EXTENDED DEPTH OF FOCUS INTRAOCULAR LENS

PROTOCOL NUMBER: SAIL-101-UNI

Sponsor: AcuFocus, Inc.
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I have read and agree to follow the procedures as outlined in this protocol.

This protocol contains confidential proprietary information with respect to AcuFocus products and clinical trials. I agree to hold this information in confidence and not to disclose it to any third parties for a period of five years from the date of this agreement, or until this information becomes a matter of public knowledge or until a formal agreement for that purpose has been entered into by the parties.

_____	_____	_____
Investigator Printed Name	Signature	Date
_____	_____	_____
Co-Investigator Printed Name	Signature	Date

This study will be conducted in accordance with the protocol; Good Clinical Practices (GCP); ethical principles within the Declaration of Helsinki; 21CFR812 and all other applicable Food and Drug Administration (FDA) regulations; conditions of approval imposed by the reviewing Institutional Review Board (IRB) or FDA; and all other applicable laws and regulations.

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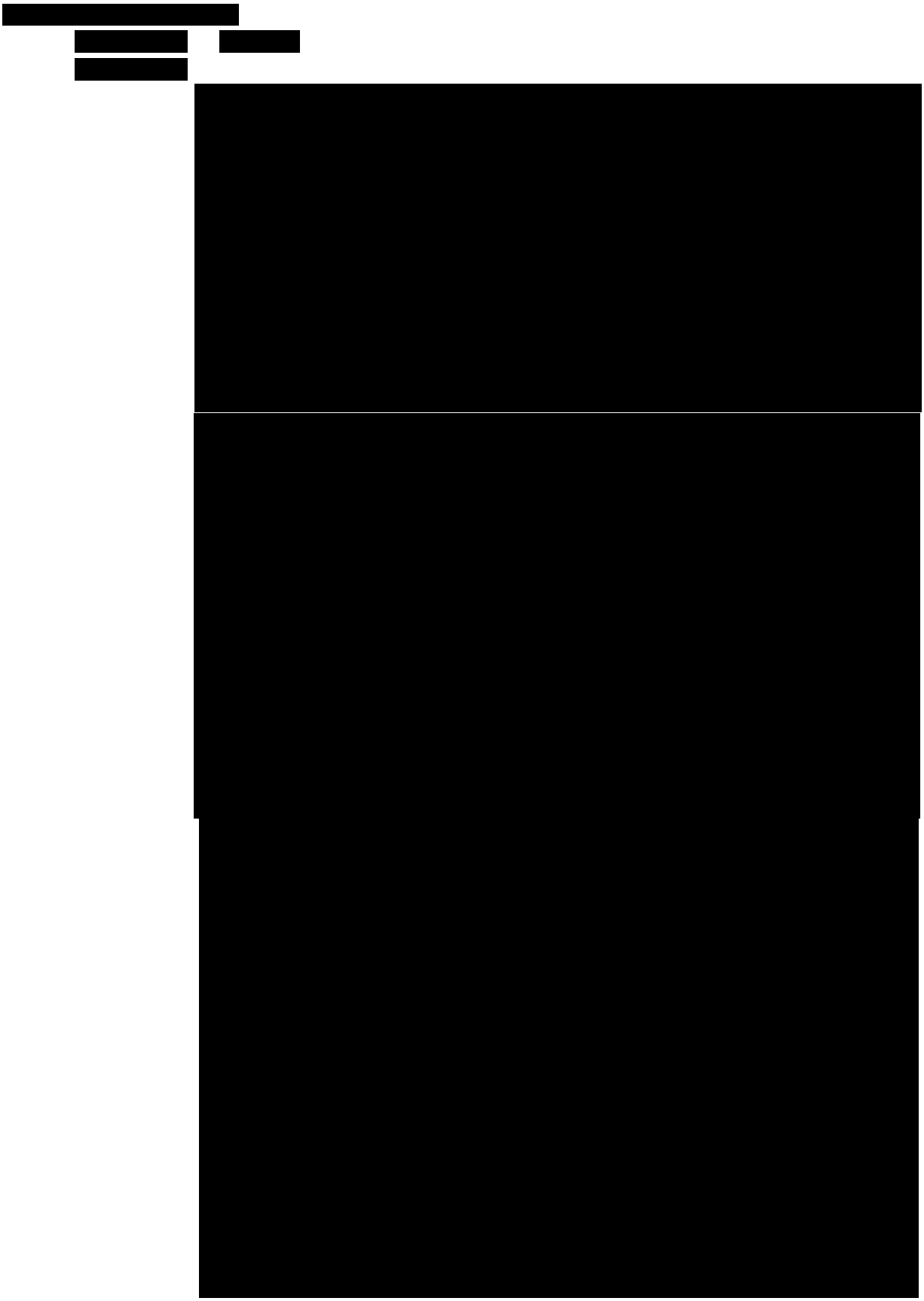

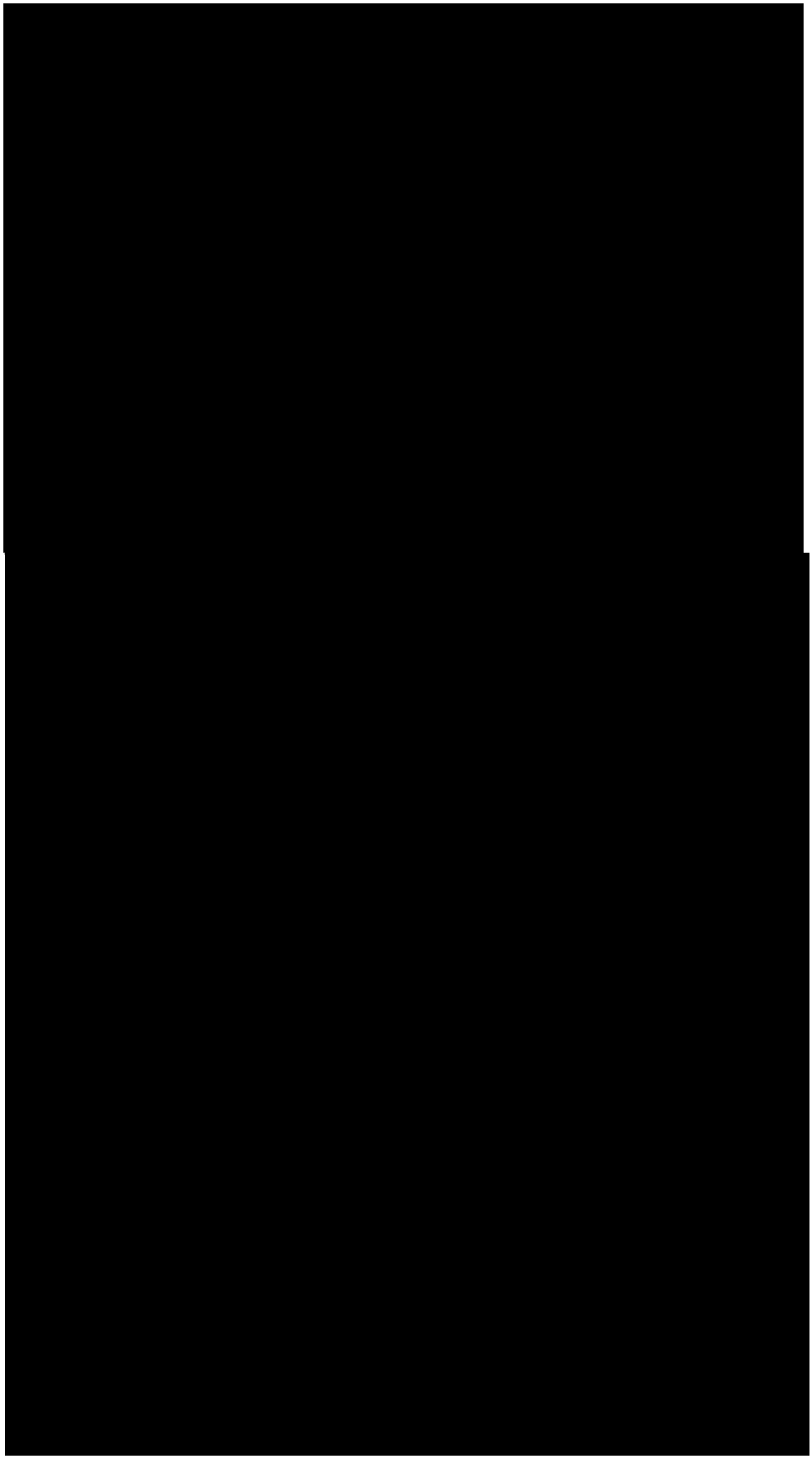

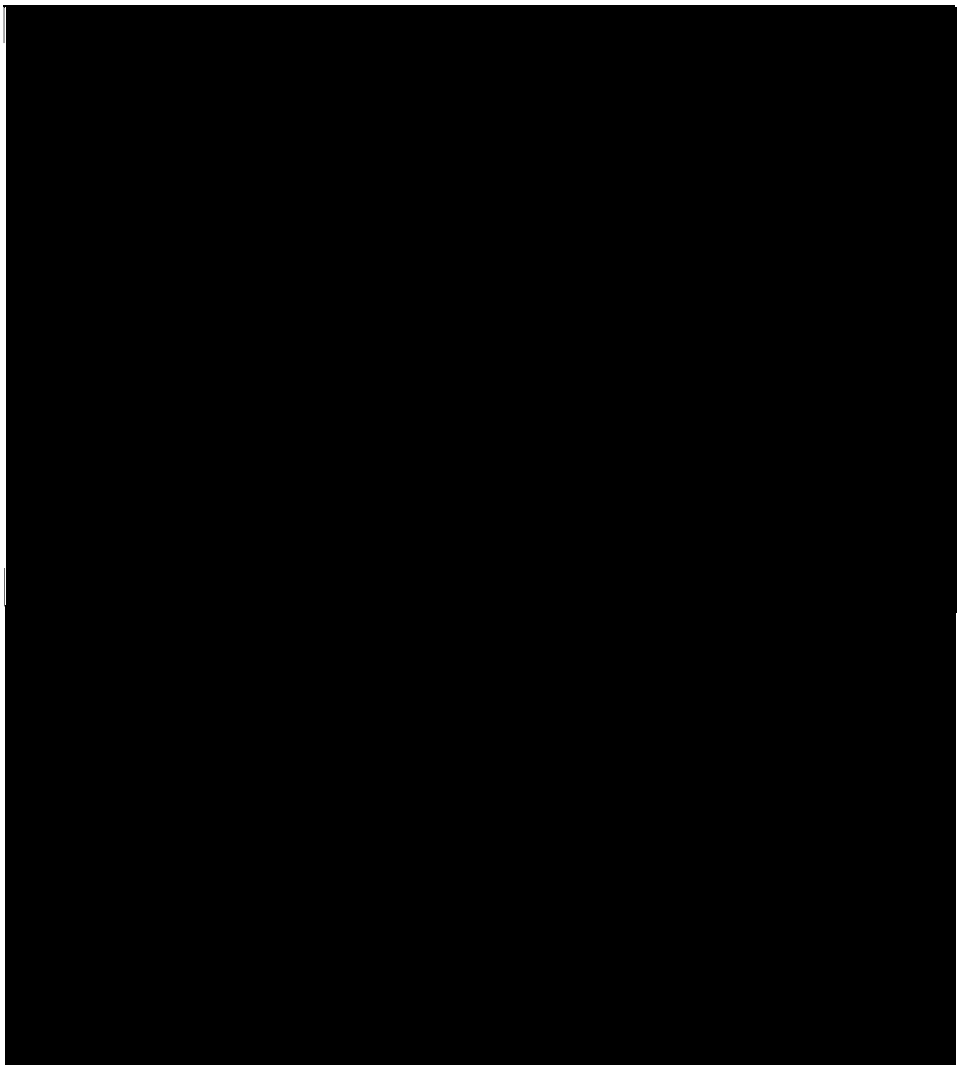

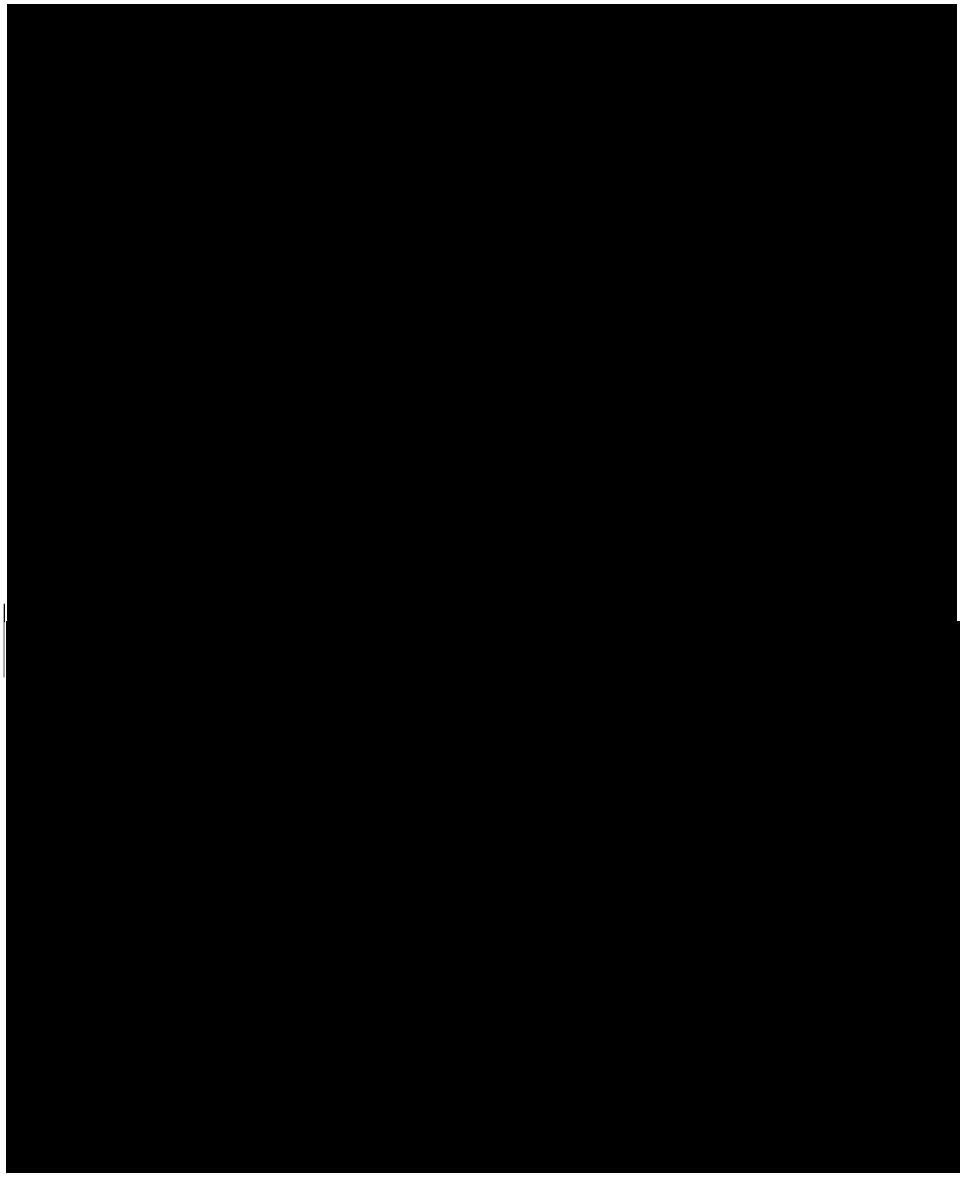

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1.0 SYNOPSIS

PROTOCOL TITLE:	Clinical Evaluation of a Small Aperture Extended Depth of Focus Intraocular Lens Protocol Number: SAIL-101-UNI
TREATMENTS:	Investigational Study Lens: Unilateral implantation of the IC-8® intraocular lens (IOL), a small aperture extended depth of focus hydrophobic acrylic intraocular lens, implanted in conjunction with an approved AcrySof® IQ or TECNIS® aspheric monofocal (SA60WF or ZCB00) or monofocal toric (SA6AT3, SA6AT4, ZCT150 or ZCT225) IOL in the fellow eye. Control Monofocal or Monofocal Toric Study Lens: Bilateral AcrySof IQ or TECNIS aspheric monofocal (SA60WF or ZCB00) or monofocal toric (SA6AT3, SA6AT4, ZCT150 or ZCT225) IOL.
CLINICAL HYPOTHESIS:	The IC-8 IOL, when implanted in conjunction with a monofocal IOL in the fellow eye, will demonstrate better binocular intermediate and near visual acuity compared to bilateral aspheric monofocal IOLs. The IC-8 IOL will demonstrate extended depth of focus compared to the monofocal IOL. Additionally, the IC-8 IOL will tolerate preoperative corneal astigmatism up to 1.50 D better than bilateral monofocal IOL implantation.
OBJECTIVE:	The objective of this study is to determine the safety and effectiveness of the IC-8 IOL implanted in one eye and a monofocal IOL implanted in the fellow eye, in accordance with the indication.
OVERALL STUDY DESIGN:	
Structure:	Prospective, multi-center, open-label, parallel-group, non-randomized, examiner-masked, one-year clinical study. The binocular performance of the subjects in the test group implanted with the IC-8 IOL will be compared to the binocular performance of the subjects in the control group implanted with monofocal IOLs. The monocular performance of the eyes implanted with the IC-8 IOL will be compared to the monocular performance of the fellow

	control eyes implanted with the monofocal IOL in subjects from the test group.
Number of sites:	Approximately 18 to 25 investigational U.S. sites
Study Duration:	One year with a possibility of two additional years for post-approval data.
Indication for Use:	The IC-8 IOL is indicated for monocular implantation within the capsular bag after cataract removal for the visual correction of aphakia in eyes with up to 1.50 D of preoperative corneal astigmatism. The fellow eye should be implanted with a monofocal IOL and achieve 20/32 or better uncorrected and 20/25 or better best-corrected distance visual acuities prior to IC-8 IOL implantation. The IC-8 IOL provides an extended depth of focus from far through intermediate and near and is intended for adult patients to mitigate the effects of presbyopia.
Administration:	The IC-8 IOL will be implanted with a supplied injector system. Aspheric monofocal IOLs will be implanted with an injector system qualified by the respective manufacturer for use with that IOL.
Visit Schedule:	Twelve scheduled visits: Preoperative; Operative for each eye, Day 1 for each eye, Week 1 for each eye, -Months 1 for each eye, 3, 6 and 12 for both eyes.

STUDY POPULATION CHARACTERISTICS:

Condition:	Patients with bilateral cataracts who desire cataract surgery and who desire to mitigate their postoperative presbyopia.
Number of Patients:	Up to 355 test subjects will be enrolled in the test group to be implanted with the investigational IC-8 IOL in one eye and a monofocal IOL in the fellow eye to ensure at least 300 subjects complete one year follow up. Up to 120 control subjects will be enrolled in the control group to be implanted with monofocal IOLs in both eyes to ensure at least 100 subjects complete one year follow up. Each site should enroll approximately 14 to 20 subjects in the test group and 5 to 7 subjects in the control group, and no site may enroll more than 25% of the intended enrollment total for each group.

Inclusion Criteria (all criteria apply to each eye):

1. Minimum 22 years of age;
2. Able to comprehend and have signed a statement of informed consent;
3. Availability, willingness, ability and sufficient cognitive awareness to comply with examination procedures and study visits;
4. Planned crystalline lens removal by phacoemulsification, with or without femtosecond laser-assisted extraction, and posterior chamber IOL implantation in both eyes;
5. Cataractous lens changes as demonstrated by best-corrected visual acuity (BCDVA) of 20/40 or worse either with or without a glare source present;
6. Potential for postoperative BCDVA of 20/25 or better in each eye after cataract removal and IOL implantation as estimated by an instrument such as a Potential Acuity Meter (PAM) or investigator estimation;
7. Clear intraocular media, other than cataract.

Exclusion Criteria (all criteria apply to each eye):

1. Requiring an IC-8 intraocular lens outside the available spherical power range of +15.5 D to +27.5 D;
2. Pharmacologically dilated pupil size less than 6 mm in either eye;
3. Inability to achieve stable keratometric readings for contact lens wearers (difference in corneal astigmatism between two visits at least 1 week apart following discontinuation of contact lens wear is within ± 0.50 diopter in magnitude and within ± 15º in axis);
4. Patients with irregular astigmatism in either eye;
5. Preoperative corneal astigmatism > 1.50 diopters in either eye (as assessed by Biometry keratometric readings);
6. Active or recurrent anterior segment pathology (chronic uveitis, iritis, iridocyclitis, rubeosis iridis, Reiter's syndrome, etc.);
7. Presence of ocular abnormalities other than cataract such as:
    a. Corneal abnormalities other than regular corneal astigmatism up to 1.50 diopters
    b. Pupil abnormalities
    c. Strabismus or amblyopia
    d. Capsular or zonular abnormalities
    e. Glaucomatous retinal nerve fiber changes
    f. Recurrent and/or persistent intraocular inflammation
    g. Known pathology that may affect visual acuity and/or is predicted to cause future acuity losses to a level worse than 20/25 BCDVA (e.g., macular degeneration)

8. Diagnosis of dry eye in which patients are unable to maintain eye comfort or adequate vision even with dry eye medication;
9. Congenital cataracts;
10. Previous corneal or intraocular surgery, except pterygium surgery, which may be allowed, based meeting all other inclusion/exclusion criteria;
11. History of ocular trauma or ocular conditions expected to require retinal laser treatment or other surgical intervention;
12. Use of systemic or ocular medications that may affect vision or likely to impact pupil dilation or iris structure, such as any prior or current use of tamsulosin or silodosin (alpha-adrenergic antagonist medications, e.g., Flomax, Flomaxtra, Rapaflo), which are likely to cause poor dilation or lack of adequate iris structure to perform standard cataract surgery;
13. Acute, chronic or uncontrolled systemic disease that would, in the opinion of the investigator, increase the operative risk or confound the outcomes of the study (e.g., immune compromised, connective tissue disease, hypertension, Type I & II diabetes etc.);
14. Use of antipsychotic and/or anti-depressant medication within the last 6 months, or plan/need to use such medications during the course of the study, which, could increase the operative risk or confound the outcome(s) of the study in the opinion of the investigator;
15. Patient is pregnant, plans to become pregnant, is lactating or has another condition associated with hormonal fluctuation that could lead to refractive changes and dry eye;
16. Concurrent participation or participation in any clinical trial up to 30 days prior to preoperative visit.

EVALUATION CRITERIA

The co-primary effectiveness endpoints are binocular uncorrected distance, intermediate, near visual acuities, monocular distance-corrected intermediate visual acuity and monocular photopic distance-corrected defocus curve. The secondary effectiveness endpoint is tolerance to astigmatism in IC-8 IOL eyes. The co-primary safety endpoints are monocular best-corrected visual acuity, adverse events and rate of removals due to visual/optical reasons in the IC-8 IOL eyes.

DATA ANALYSIS:

For mean binocular uncorrected visual acuities, mean values between IOL groups will be compared using two-sample t-tests. For mean monocular distance-corrected intermediate visual acuity, mean values between the eyes implanted with the IC-8 IOL and the fellow eyes in the test arm will be compared using two-sample t-tests. For monocular photopic distance-corrected

defocus curve, the mean depth of focus from IC-8 IOL eyes will be numerically compared to the mean from the fellow control eyes at 0.2 logMAR visual acuity threshold. For tolerance to preoperative corneal astigmatism in IC-8 IOL eyes, postoperative monocular mean UCDVA in the eyes with 1.0 D to 1.5 D of preoperative corneal astigmatism will be compared to the postoperative mean acuity in the eyes with < 1.0 D of preoperative corneal astigmatism in a non-inferiority test. Safety data on adverse events will be compared to the historical control safety and performance endpoints (SPE) rates in Table B.2 of ISO 11979-7:2014, *Ophthalmic implants - Intraocular lenses - Part 7: Clinical investigations Safety and Performance Endpoint*. Mean monocular best-corrected distance visual acuity will be compared between the IC-8 IOL eyes and the fellow eyes in the test arm using a non-inferiority test. Rate of removals due to visual/optical reasons in the IC-8 IOL eyes will be assessed to be less than 3.1%.

VISITS AND PROCEDURES:

A comprehensive eye examination will be performed preoperatively and postoperatively. The preoperative visit will include an assessment of patient qualifications for the initial inclusion of both eyes in the study according to the protocol inclusion/exclusion criteria. The Informed Consent Form (ICF) must be signed by those patients agreeing to participate prior to any study-specific procedures being performed.

Preoperative visits will include ocular and health history, patient demographic information, ocular dominance (sighting dominance), potential visual acuity, pupillary response, pupil size (mesopic, photopic, and dilated), biometry (e.g., axial length, ACD, keratometry), visual acuities (uncorrected, distance-corrected), manifest refraction, tear-break-up-time (TBUT), corneal staining, corneal topography, slit-lamp biomicroscopy examination, gonioscopy, intraocular pressure, dilated fundus exam, spectral domain ocular coherence tomography (SD-OCT), retinal diagnostic testing (subgroup only), patient-reported outcome (PRO) questionnaires and an open-ended question on visual symptoms will be administered preoperatively.

Postoperative visits will include ocular dominance (sighting dominance), pupil size (mesopic, photopic), visual acuities (uncorrected, distance-corrected, +0.75 D distance-corrected), low contrast (10%) distance, intermediate and near acuity, manifest refraction, defocus curves, photopic and mesopic contrast sensitivity (with and without glare), near stereoacuity, slit-lamp biomicroscopy examination, TBUT, corneal staining, corneal topography (keratometry), intraocular pressure, dilated fundus exam, retinal diagnostic testing (subgroup only), Patient-Reported Outcomes (PROs) and an open-ended question on visual symptoms will be administered postoperatively. Investigator's ability to evaluate the posterior segment of the eye and their ability to perform Nd:YAG capsulotomy will be captured on the source documents.

In a subgroup of test subjects specific retinal imaging tests using fundus camera, SD-OCT and visual field testing will be conducted both preoperatively and postoperatively.

2.0 BACKGROUND

Patient expectations of spectacle independence at all distances following cataract surgery have substantially increased in recent years.[1] Though most of the contemporary presbyopia-correcting premium intraocular lenses (IOLs) provide adequate functional vision and patient satisfaction, each has advantages and disadvantages. Multifocal and trifocal IOLs provide good functional vision, but they are limited by reduced contrast, visual disturbances and, with discrete non-continuous range of vision.[2-5] More recently, extended range of vision IOLs that are designed to improve vision from far to intermediate or near distances have been introduced to the market.[6,7]

The IC-8 IOL (AcuFocus, Inc.) is a small-aperture IOL that reduces defocus by decreasing the size of the blur circle to achieve extended depth of focus. The relation between reducing pinhole size and improving visual acuity in patients with refractive ametropia has been well established.[8,9] This principle is currently being used successfully via the KAMRA inlay (AcuFocus Inc.), which was FDA-approved for presbyopia correction in April 2015.[10,11] In contrast to multifocal IOLs, the small aperture IOL is thought to provide good uncorrected intermediate and near vision with fewer visual symptoms and potentially a greater tolerance to sphero-cylindrical residual refractive errors as a result of its extended depth of focus.[12,13]

For patients monocularly implanted with a monofocal IOL, the acceptability of a multifocal or trifocal IOL in the second eye may be difficult due to the differences in image quality between monofocal and multifocal or trifocal IOLs. Visual outcomes with binocular implantation of trifocal or multifocal IOLs have been shown to be more effective than monocular implantation.[14-16] The IC-8 IOL is uniquely suited for patients who have already been implanted with a monofocal IOL in one eye, and desire spectacle independence with a presbyopia-correcting IOL in the second eye. Implanting an IC-8 IOL in the second eye would provide intermediate and near vision while preserving binocular far vision for a patient with a monofocal IOL in the fellow eye. [12,13]

3.0 CLINICAL HYPOTHESIS

The IC-8 IOL, when implanted in conjunction with a monofocal IOL in the fellow eye, will demonstrate better intermediate and near visual acuity compared to bilateral aspheric monofocal IOLs. The IC-8 IOL will demonstrate extended depth of focus compared to the monofocal IOL. Additionally, the IC-8 IOL will tolerate preoperative corneal astigmatism up to 1.50 D.

4.0 STUDY OBJECTIVE

The objective of this study is to determine the safety and effectiveness of the IC-8 IOL implanted in one eye and a monofocal IOL implanted in the fellow eye, in accordance with the indication. The primary and secondary effectiveness and safety endpoints will be demonstrated in accordance with **Section 18**.

5.0 STUDY PRODUCTS

5.1. INTRAOCULAR LENSES

The IC-8 IOL is a sterile, single-use, one-piece hydrophobic acrylic aspheric monofocal IOL (asphericity of -0.28 μm) with a centrally embedded polyvinylidene difluoride (PVDF) annular mask. The annular mask has an outer diameter of 3.23 mm and a 1.36 mm inner diameter, creating a central aperture that is intended to improve intermediate and near vision by extending the depth of focus.[12,13] The IC-8 IOL material and external design are based on the one-piece hydrophobic acrylic posterior chamber monofocal IOL, [redacted] The lens has modified C-haptics, angled at 5°, with an overall diameter of 12.5 mm. The biconvex aspheric optic is designed with a 360° square posterior edge, measures 6 mm in diameter and is ultra-violet absorbent with the hydrophobic material having an index of refraction of 1.485 at 35° C and 546.1 nm. The embedded annular mask is 5 μm in thickness and contains 3,200 microperforations that are arranged in a pseudorandom fashion (sparing the periphery) and range in size from 7 to 10 μm diameters.

The IC-8 IOL is packaged in an integrated twist-cap lens holder with a bromobutyl rubber stopper that screws onto a 5 ml glass vial filled with Water for Injection (WFI). The vial is then placed in a tray and sealed with a Tyvek® lid. The sealed tray containing the IOL is then sterilized by gamma radiation in a validated sterilization cycle. Following sterilization, the IC-8 IOL and IC-8 IOL Injector System, which is ethylene oxide (EO) sterilized, are packaged together in a chipboard unit carton. The IOL and injector system are provided “STERILE” and are intended for single use only. The IOL and injector system should be opened only under sterile conditions. The device specifications for the finished IC-8 IOL are shown in **Table 1**.

Table 1: Finished Lens Specifications

CHARACTERISTICS	IC-8 IOL
Optic Body Diameter	6.0 ± 0.1 mm
Overall Diameter	12.5 ± 0.2 mm
Mask Diameter: • Inside aperture • Outside	 1.36 mm (nominal) 3.23 mm (nominal)
Mask Thickness	5 µm
Number of holes in mask annulus	3200 (7, 8, 9 and 10 micron diameters, allowing for approximately 3% of light in the visible spectrum)
Mask Material	Polyvinylidine Fluoride (PVDF)/Carbon Black
Lens Configuration	One-piece Haptic Angulation 5° Aspheric Bi-Convex optic 360° Square posterior edge
Lens Material	Hydrophobic Acrylic copolymer: 2-Phenylethylacrylate/2-Phenylethylmethacrylate
Power Range	+15.5 D to +27.5 D in 0.5 D increments
Refractive Index	1.485 at 35° C and 546.1 nm
UV Transmittance 10% Cutoff	< 10% @ 375 nm
Asphericity	-0.28 µm
Abbe Number	49
Suggested A Constant	Optical Biometry: 120.5

The monofocal IOL for implantation in first eyes will be selected by the investigator. The monofocal IOL will be a marketed single-piece acrylic, toric or non-toric, aspheric, colorless IOL. All monofocal IOLs used in the study will be either TECNIS aspheric 1-piece (ZCB00, ZCT150 or ZCT225) or AcrySof IQ (SA60WF, SA6AT3 or SA6AT4). All investigators should have established their personalized A-constant for the monofocal IOLs to be implanted. Comparison of characteristics of the TECNIS ZCB00 and AcrySof SA60WF monofocal IOLs are shown in **Table 2**.

Table 2: Comparison of TECNIS® ZCB00 and AcrySof® SA60WF

CHARACTERISTICS	TECNIS® 1-Piece IOL Model ZCB00	AcrySof® Aspheric IOL Model SA60WF
Lens Design	Single-piece acrylic monofocal with an aspheric anterior surface	Single-piece acrylic monofocal with posterior aspheric surface
Lens Material	Ultraviolet-blocking hydrophobic acrylic	Ultraviolet-absorbing Acrylate/Methacrylate Copolymer
DIMENSIONAL FEATURES		
Overall Diameter	13.0 mm	13.0 mm
Haptic Angle	No angulation, but offset from the optic body	0°
Optic Body Diameter	6.0 mm	6.0 mm
Haptic Material	Same as optic	Same as optic
Haptic Style	C-Loop	STABLEFORCE Modified-L Haptics
OPTICAL FEATURES		
Optic Shape	Biconvex	Biconvex
Anterior Optic Profile	Aspheric	Spherical
Posterior Optic Profile	Spherical	Aspheric
Asphericity	-0.27 µm	-0.20 µm
Optic Edge Design	ProTEC® frosted, continuous 360° posterior square edge	Square edge, frosted
Dioptric Power Range	+5.0 to +34.0 D in 0.50 D steps	+6.0 to +30.0 D in 0.50 D steps
Cylinder Range	1.5 to 6.0 D*	1.5 to 3.0 D*
Refractive Index	1.47	1.55
Abbe Number	55	37
Theoretical A-constant	118.8	118.7

* TECNIS Aspheric Toric Model Numbers: ZCT150 or ZCT225 and AcrySof Colorless Aspheric Toric Model Numbers: SA6AT3 or SA6AT4.

5.2. IMPLANTATION SYSTEMS

The IC-8 Injector System provides a controlled means for implanting the IC-8 IOL in the capsular bag following cataract removal. The IC-8 Injector System consists of two parts: a sterile cartridge and a sterile injector with a soft, silicone tip. The entire cartridge should be filled with Healon ophthalmic viscoelastic device (OVD). Following the OVD insertion, the IOL is placed into the cartridge with the lens anterior side up (haptics pointing counter-clockwise) while the cartridge is in the bevel down position. The loaded cartridge is placed into the injector and advanced until the locking mechanism is activated. Additional OVD is inserted into the cartridge and the plunger can then be advanced to insert the IOL into the capsular bag.

The IC-8 Injector System is manufactured from medical grade polypropylene, polycarbonate, and silicone. The injector system cartridge is treated with a LubriMATRIX™ coating. The IC-8 Injector System is the only validated injector to be used with the IC-8 IOL.

Aspheric monofocal IOLs will be implanted with an injector system qualified by the respective manufacturer for use with that IOL.

6.0 STUDY DESIGN

This will be a prospective, multi-center, open-label, parallel group, non-randomized, examiner-masked, one-year study of a small-aperture IOL that provides extended depth of focus to patients after the surgical removal of the crystalline lens. The patients will be consented for three years; the first year (with data from all fully enrolled and qualified subjects with successful or attempted IC-8 IOL implantation through 12-month follow-up) will support the Premarket Approval (PMA) with a possibility of two years of post-approval follow-up. The test group will consist of subjects who are implanted with the investigational IC-8 IOL in one eye and implanted with a monofocal or monofocal toric IOL in the fellow eye. The control group will consist of subjects who are bilaterally implanted with monofocal or monofocal toric IOLs. The monofocal control IOL will be a marketed colorless, aspheric (-0.20 to -0.28 micrometers) IOL.

The binocular performance of the subjects in the test group will be compared to the binocular performance of the subjects in the control group. The monocular performance of the eyes implanted with the IC-8 IOL will be compared to the monocular performance of the fellow control eyes implanted with the monofocal IOL in subjects from the test group.

The study enrollment period is estimated to be six to nine months; start of enrollment at each site is dependent on IRB approval. Subjects will be followed for approximately 12 months postoperatively. Study duration for all activities, including start of enrollment to completion of all postoperative visits, is estimated to be approximately 18 to 24 months.

7.0 STUDY POPULATION

Potential study subjects will be recruited from patients with bilateral cataracts who plan to undergo crystalline lens removal by phacoemulsification followed by intraocular lens implantation in the capsular bag. Eligibility for the study will be determined at the preoperative visit. If the patient meets all inclusion/exclusion criteria, he or she must give informed consent to be provisionally enrolled in the study as a subject.

To allow for approximately 10% attrition rate over the duration of the one-year study and another 5% disqualification rate for the first implanted eye, a total of 355 test subjects and 120 control subjects will be consented and provisionally enrolled to ensure 300 test and 100 control subjects are available to complete the one-year follow-up to support the PMA.

Each study site (assuming a total of 23 sites) should enroll approximately 15 subjects in the test group and 5 subjects in the control group, but no more than 25% of the total population of the study. The number of subjects intended to be enrolled in the study for each treatment arm (before

the first implanted eye's qualification to complete enrollment) is shown in **Table 3**. Furthermore, based on previous data from the IC-8 IOL European clinical study, the distribution of pre-existing corneal astigmatism between 0 and 1.5 D in the intended population consists of roughly 83-85% of patients between 0 to less than 1.0 D and roughly 15-17% of patients between 1.0 to 1.5 D. The anticipated enrollment ratio is thus approximately 5:1 for < 1.0 D of preoperative corneal astigmatism (Astigmatism Group 1) vs. 1.0 to 1.5 D of preoperative corneal astigmatism (Astigmatism Group 2). Therefore, the intended enrollment target for each astigmatism group as shown in **Table 3** should reflect the anticipated enrollment by group in the study. The overall enrollment from all sites will be monitored closely to ensure that the enrollment target should be met for each treatment arm and astigmatism group. When each and all targets are met, the sponsor will inform all sites to cease enrollment. More details on controlling the enrollment process for potential imbalance in baseline characteristics is specified in the Statistical Analysis Plan (SAP).

Table 3: Intended Enrollment Targets by Treatment Arm and Astigmatism group

	Astigmatism Group 1 (< 1.0 D of preoperative corneal astigmatism)**	**Astigmatism Group 2** (1.0 D to 1.5 D of preoperative corneal astigmatism)**
Test arm: IC-8/monofocal* IOL (n = 355 to enroll, 300 to complete)	295 to enroll (250 to complete)	60 to enroll (50 to complete)
Control arm: bilateral monofocal* IOL (n = 120 to enroll, 100 to complete)	100 to enroll (84 to complete)	20 to enroll (16 to complete)

*monofocal or monofocal toric IOL

**the astigmatic group definition only applies to one eye of the subject: IC-8 eye in the test arm, or the second eye in the control arm. The first implanted eye of the subject in both the test arm and control arm does not need to meet the same astigmatism definition of the astigmatism groups as long as the first implanted eye meets the inclusion/exclusion and entrance criteria.

This study will include patients with both eyes that meet all of the following inclusion/exclusion criteria and with the first implanted eye that meets the qualification criteria. Those patients who agree to participate will be sequentially enrolled until the enrollment goal is met or the site enrollment limit is achieved. The investigator may not waive the eligibility criteria. Any questions regarding patient eligibility are to be discussed with AcuFocus prior to patient enrollment.

7.1. INCLUSION CRITERIA (all criteria apply to each eye)

1. Minimum 22 years of age;
2. Able to comprehend and have signed a statement of informed consent;
3. Availability, willingness, ability and sufficient cognitive awareness to comply with examination procedures and study visits;
4. Planned crystalline lens removal by phacoemulsification, with or without femtosecond laser-assisted extraction, and posterior chamber IOL implantation in both eyes;
5. Cataractous lens changes as demonstrated by best-corrected visual acuity (BCDVA) of 20/40 or worse either with or without a glare source present;
6. Potential for postoperative BCDVA of 20/25 or better in each eye after cataract removal and IOL implantation as estimated by an instrument such as a Potential Acuity Meter (PAM) or surgeon investigator estimation;
7. Clear intraocular media, other than cataract.

7.2. EXCLUSION CRITERIA (all criteria apply to each eye)

1. Requiring an IC-8 intraocular lens outside the available spherical power range of +15.5 D to +27.5 D;
2. Pharmacologically dilated pupil size less than 6 mm in either eye;
3. Inability to achieve stable keratometric readings for contact lens wearers (difference in corneal astigmatism between two visits at least 1 week apart following discontinuation of contact lens wear is within ± 0.50 diopter in magnitude and within ± 15º in axis);
4. Patients with irregular astigmatism in either eye;
5. Preoperative corneal astigmatism > 1.50 diopters in either eye (as assessed by biometry keratometric readings);
6. Active or recurrent anterior segment pathology (chronic uveitis, iritis, iridocyclitis, rubeosis iridis, Reiter's syndrome, etc.);
7. Presence of ocular abnormalities other than cataract such as:
    a. Corneal abnormalities other than regular corneal astigmatism up to 1.50 diopters
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    c. Strabismus or amblyopia
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    f. Recurrent and/or persistent intraocular inflammation

g. Known pathology that may affect visual acuity and/or is predicted to cause future acuity losses to a level of worse than 20/25 BCDVA (e.g., macular degeneration)

8. Diagnosis of dry eye in which patients are unable to maintain eye comfort or adequate vision even with dry eye medication;
9. Congenital bilateral cataracts;
10. Previous corneal or intraocular surgery, except pterygium surgery, which may be allowed, based meeting all other inclusion/exclusion criteria;
11. History of ocular trauma or ocular conditions expected to require retinal laser treatment or other surgical intervention;
12. Use of systemic or ocular medications that may affect vision or likely to impact pupil dilation or iris structure, such as any prior or current use of tamsulosin or silodosin (alpha-adrenergic antagonist medications, e.g., Flomax, Flomaxtra, Rapaflo), which are likely to cause poor dilation or lack of adequate iris structure to perform standard cataract surgery;
13. Acute, chronic or uncontrolled systemic disease that would, in the opinion of the investigator, increase the operative risk or confound the outcomes of the study (e.g., immune compromised, connective tissue disease, hypertension, Type I & II diabetes etc.);
14. Use of antipsychotic and/or anti-depressant medication within the last 6 months, or plan/need to use such medications during the course of the study, which could increase the operative risk or confound the outcome(s) of the study in the opinion of the investigator;
15. Patient is pregnant, plans to become pregnant, is lactating or has another condition associated with hormonal fluctuation that could lead to refractive changes and dry eye;
16. Concurrent participation or participation in any clinical trial up to 30 days prior to preoperative visit.

7.3. QUALIFICATION CRITERIA TO COMPLETE ENROLLMENT

The 1st eye implanted with a monofocal or monofocal toric IOL must achieve the following criteria in order for the subject to qualify and proceed to implantation in the 2nd eye:

1. 20/32 or better uncorrected distance visual acuity (UCDVA) and 20/25 or better best-corrected distance visual acuity (BCDVA) (or Snellen equivalent)
2. No ongoing ocular adverse events
3. Normal corneal health as assessed by slit lamp biomicroscopy:
    a. Corneal edema (refer to Appendix C in the protocol): Grade 1+ or less
    b. Superficial punctate keratitis (SPK, refer to Oxford grading scale): Grade 1 or less

The subject must qualify within the 1-week to 1-month visit windows (7 to 45 days from the 1st eye surgery). Subjects in both the test and control groups whose first implanted eye does not achieve the qualification criteria will be disqualified and exited from the study and will not be counted toward the study cohort or analysis population.

7.4. ENROLLMENT PROCESS

Patients will not qualify for the study unless all of the inclusion/exclusion criteria are met for each eye, and the IRB-approved informed consent form is signed. The informed consent document must be signed prior to any study-specific examinations. Following the informed consent process, completion of the preoperative exam and final determination that the subject meets all of the required criteria for each eye, the subject may be scheduled for implantation per the protocol. All preoperative evaluations including whether the subject meets the inclusion/exclusion criteria should be conducted within 60 days prior to the surgical procedure for a given eye. Data from routine cataract examinations performed prior to the informed consent process may be included; provided the examination is conducted within 60 days of the surgical procedure for the given eye and the test date is documented on the source document. If the preoperative evaluation is beyond 60 days for the second eye, all evaluations including verification of the inclusion/exclusion criteria for that eye must be repeated.

8.0 INVESTIGATOR SELECTION

8.1. INVESTIGATOR QUALIFICATIONS

AcuFocus will select ophthalmic surgeons who have completed a residency in ophthalmology or its documented equivalent and are licensed to practice medicine and perform surgery in the state/province, and country where the investigator conducts the study.

Investigators for the clinical study will be selected from ophthalmic surgeons who are experienced in small incision, phacoemulsification or femtosecond-assisted IOL implantation in cataract patients. Additionally, investigators should have established their personalized A-constant for the marketed aspheric monofocal IOL to be implanted in the first eye. All study sites will be required to have adequate staff support for study conduct, reporting and patient follow-up, as well as the necessary instrumentation to perform the required assessments throughout the duration of the study.

8.2. INVESTIGATOR OBLIGATIONS

Investigators are required to fulfill the following obligations:

- Conduct the study in accordance with the relevant and current study protocol.
- Investigator will not make changes to a protocol unless after obtaining approval from AcuFocus 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 study-related duties.
- Be responsible for protecting the rights, safety and welfare of patients under the investigator's care, and be responsible for the control 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 of any subject to participate or allow any subject to participate before obtaining IRB approval and approval from the regulatory agency of the country in which the study is being conducted by the investigator (e.g., FDA).
- Document in each patient's case history that informed consent was obtained prior to participation in the study as required by 21CFR812.
- Report to AcuFocus any adverse experiences that occur during the course of the study in accordance with applicable laws and regulations.
- Maintain and make available adequate and accurate records in accordance with applicable laws and regulations for inspection by either AcuFocus, duly authorized regulatory agencies and/or the IRB.
- Submit progress reports on the investigation to AcuFocus 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, if applicable.
- Report all changes in activity and all unanticipated problems involving increased risks to patients to the IRB and AcuFocus.
- Upon completion of enrollment or termination of the study or the investigator's part of the study, or at AcuFocus' request, return to AcuFocus any remaining supply of the IC-8 IOL.
- Comply with all other obligations of clinical investigators and requirements according to all applicable 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 device being evaluated, their study-related duties and functions, and agree to fulfill their obligations in meeting the above commitments.

8.3. INVESTIGATOR APPROVAL

It is the responsibility of the investigator to obtain prospective approval or consultation on the 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. Copies of IRB approvals/recommendations should be forwarded to AcuFocus.

The investigator is required to report to AcuFocus within five working days any withdrawal of approval by the reviewing IRB for his/her participation in the study.

Study sites will obtain IRB approval and fulfill any other site-specific regulatory requirements. Prior to the start of patient enrollment, the following documents must be signed and returned to AcuFocus:

- 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

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

9.0 INVESTIGATIONAL PLAN

9.1. OVERVIEW

The study will be conducted in accordance with U.S. Code of Federal Regulations, the Declaration of Helsinki, and all other applicable laws and regulations.

This study will be conducted at approximately 18 to 25 study sites. There will be a total enrollment of 355 test and 120 control subjects to ensure 300 test and 100 control subjects complete one year of postoperative study follow-up. Patients will be consented for three years; the first year will support the PMA with a possibility of two additional years of post-approval follow-up.

Enrollment into one of the two study groups will not be randomized because an IOL with extended range of vision is currently available on the market and patients who desire an extended depth focus should have the opportunity to receive this technology. However, in order to allow for comparison, the two groups should have similar distributions on age, sex, race/ethnicity, pupil size and preoperative corneal astigmatism.

Test group: Subjects will be implanted with the IC-8 IOL in one eye, targeted at 0.75 D of myopia, which is at the near end of the emmetropic limit of the depth of focus, without sacrificing distance visual acuity and an aspheric monofocal or monofocal toric IOL, targeted for emmetropia, defined as plano manifest refractive spherical equivalent (plano MRSE) in the fellow eye.

Control group: Subjects will be bilaterally implanted with an aspheric monofocal or monofocal toric IOL, targeted for emmetropia (plano MRSE), in both eyes.

For both the test group and control groups, the first eye will be implanted with a monofocal or monofocal toric IOL. There will be no restriction on the implantation of the IC-8 IOL to the non-dominant eye only. The investigator may choose the monofocal eye based on the following factors: sighting dominance, patient's occupational and/or recreational needs, history of monovision contact lens wear, habitual spectacle prescription, worst cataract eye, or one eye outside of the IC-8 IOL available powers. The investigator must indicate the primary and secondary factor (if applicable) for choosing the monofocal eye on the source documents and when possible, preoperative and postoperative sighting dominance will be recorded and data will be stratified by eye dominance.

In order for the subject to complete the enrollment in the study, the first implanted eye in both the test and control groups must achieve the qualification criteria of 20/32 or better UCDVA and 20/25 or better BCDVA (or Snellen equivalent), have no ongoing ocular adverse events, and have normal corneal health as assessed by slit lamp biomicroscopy (Grade 1+ or less edema and Grade 1 or less SPK). The subject must qualify within the 1-week to 1-month visit windows (7 to 45 days from the 1st eye surgery). The subject will complete study enrollment and will receive the investigational device in the second eye (test group) or monofocal or monofocal toric IOL in the second eye (control group). Postoperative evaluations will be scheduled at 1 Day, 1 Week, 1, 3, 6, and 12 Months after the second eye surgery.

If the first implanted eye does not achieve the visual acuity and corneal health criteria within 7 to 45 days from the 1st eye surgery, the subject will be disqualified and exited from the study and will not be included in the study cohort or analysis population. This would ensure that the subject is not needlessly exposed to the risk of the investigational device when the safety and effectiveness of the investigational device is to be determined.

In general, the principal investigator/sub-investigator will perform the initial assessment and preoperative and postoperative procedures (with the exception of study-specific visual acuity testing, refraction, defocus testing and contrast measurements) and perform all eye surgeries in the study. To maintain consistency, a single individual examiner (e.g., study technician designated by the investigator) should conduct all study-specific visual acuity and refraction measurements. A back-up examiner should also be designated and trained. Additionally, the examiner (and back-up) will be masked to the treatment received by the subjects under examination.

9.2. VISIT SCHEDULE

The visit schedule for all patients is outlined in **Table 4**.

Table 4: Visit Schedule

Visit	Eyes evaluated	Visit Window
Preoperative	Both eyes	≤ 60 days prior to 2nd eye operative visit
1st eye Operative	1st eye	Recommended ≤ 15 days from preoperative visit
2nd eye Operative	2nd eye	≤ 45 days following 1st eye operative visit; **after** qualifying 1st eye
1 Day	1st eye or 2nd eye	1-2 days following operative visit for each eye
1 Week	1st eye or 2nd eye	7-14 days following operative visit for each eye
1 Month*	1st eye, 2nd eye, or both eyes	20 - 45 days following operative visit for each eye
3 Months**	Both eyes	60 - 110 days following 2nd eye operative visit
6 Months**	Both eyes	160 - 210 days following 2nd eye operative visit
12 Months**	Both eyes	300 - 420 days following 2nd eye operative visit

*The 1st eye 1-month visit can occur on the same day with one of the 2nd eye visits (1-day, 1-week or 1-month visit), if the visit windows align.
**Visit window is counted from the day of second eye's operative visit.

Surgery for the second eye must not be performed prior to qualifying the first eye within the 1-week to 1-month visit windows (7 to 45 days from the 1st eye surgery). Subjects should have both eyes implanted within 45 days of each other to best allow visits for each eye to be combined where intervals overlap.

A chart summary of all examinations required at each visit is provided in **Appendix A**. Detailed descriptions of examination procedures are also provided in **Sections 9.3** through **9.7**. Specific equipment necessary to perform the required procedures will be supplied for the duration of the study as applicable (**Appendix B**).

9.3. PREOPERATIVE PROCEDURES

Patients may not qualify for the study unless all of the inclusion/exclusion criteria are met for each eye, and the current IRB-approved informed consent form is signed. The informed consent must be signed prior to any study-specific examinations being performed; this must be documented on the source documents. All preoperative evaluations including whether the subject meets the inclusion/exclusion criteria should be conducted within 60 days prior to the surgical procedure for a given eye. Data from routine cataract examinations performed prior to

the informed consent process may be included; provided the examination is conducted within 60 days of the surgical procedure and the test date is documented on the source document. If the preoperative evaluation is beyond 60 days for the second eye, all evaluations including verification of the inclusion/exclusion criteria for that eye must be repeated.

Following the informed consent process, completion of the preoperative exam and final determination that the patient meets all of the required entrance criteria for each eye, the patient may be scheduled for implantation per the protocol. The preoperative measurements to be collected for each eye include the following:

Potential Visual Acuity:

The patient should be capable of achieving 20/25 or better BCDVA in each eye after cataract removal and IOL implantation. The investigator may use an instrument such as PAM or his/her clinical judgment to estimate the patient's potential acuity.

Unilateral Cover/Uncover Test:

The cover test should be performed with correction, at distance, to assess the presence or absence of strabismus. In the presence of strabismus, the eye, frequency and type of deviation should be noted in the source documents.

Uncorrected distance and near visual acuities:

Monocular uncorrected distance and near visual acuities may be measured using a standard Snellen or ETDRS chart.

Manifest refraction and best-corrected distance visual acuity:

Preoperative manifest refraction and BCDVA may be measured using a standard Snellen or ETDRS chart. BCDVA must be 20/40 or worse, with or without a glare source, for the patient to be enrolled in the study.

Pupil Size:

Photopic (full room illumination), mesopic (dim lighting), and pharmacologically dilated pupil size will be measured to the nearest one-half millimeter using a pupillometer, pupil gauge or millimeter ruler. The patient must be dark adapted for ten minutes prior to measuring mesopic pupil size. The investigator's customary dilating drops may be used for dilated pupil size measurements. Dilated pupil size should be measured when maximum dilation is achieved. For the purpose of this study, patients with a dilated pupil size < 6 mm, or with pupil abnormalities (non-reactive, fixed pupils, or abnormally shaped pupils) in either eye must be excluded from participation.

NOTE: *Pupillometry should be measured via the same method (e.g., pupillometer, pupil gauge) for all subjects, at each study visit, if at all possible. If a pupillometer is used, it is important to ensure the measured eye has a clear view of the testing environment. If the pupillometer is*

unable to measure the pupil size in the IC-8 IOL eye postoperatively, use a pupil gauge or millimeter ruler to measure the pupil size and use the same method for all remaining visits.

Swinging Flashlight Test:

The swinging flashlight test should be performed with a penlight or direct ophthalmoscope to assess the baseline pupillary response and rule out a relative afferent pupillary defect (RAPD).

Sighting Dominance:

Sighting dominance should be established by three successive consistent trials of the 'hole-in-card' test. With both eyes open the subject should hold, with both hands and comfortably at arm's length, a rectangular card with a circular hole cut at its center. Through this aperture the subject should view a small but easily visible single letter on the 4 m-distance logMAR ETDRS chart. The examiner then should alternately occlude either eye of the subject, and the dominant eye should be recorded as the one that continued to see the letter when its companion was covered. If ocular dominance cannot be established consistently, the subject is deemed to have equal dominance/unable to determine dominance.

White to White (WTW):

The horizontal distance between the two limbal areas (corneal diameter) will be measured by using biometry. The WTW value is used in the IOL calculation formula for selecting the IOL power.

Corneal Topography:

Corneal topography is to be measured with a computerized corneal topographer (e.g., Zeiss Atlas, etc.). Preoperative corneal topography should indicate no abnormalities. A printout of all topography maps should be retained.

Keratometry:

Preoperative corneal astigmatism should be determined by biometry keratometric readings. To help ensure the most accurate and consistent results, auto or manual keratometry is **not** to be used.

Contact Lens Wear:

For contact lens wearers, keratometric corneal stability following cessation of contact lens wear must be verified for study eligibility. Contact lenses are not to be worn for at least six months prior to the preoperative visit for PMMA lenses, one month for gas permeable lenses, and one week for extended-wear and daily-wear soft contact lenses. Corneal stability must be verified for any subject who has worn PMMA lenses within five years or any other type of contact lenses within six months prior to the preoperative visit. To verify stability, repeat the keratometric measurements at least one week after the initial keratometric measurement, following discontinuation of contact lens wear. Corneal curvature is considered to be stable if the difference in corneal astigmatism (steep vs. flap keratometric readings) between the two time

points is within ± 0.50 diopter in magnitude and within ± 15º in axis. If a change exceeding one of these criteria is noted, eligibility into the study will not be established until keratometric stability is demonstrated. Final biometry measurements and surgery should not take place until keratometric stability is achieved.

Axial Length:

Axial length must be taken to determine the appropriate spherical IOL power to implant using an A-constant. Biometry should be performed with the IOL Master, LenStar or Ultrasound in this study.

The IOL power should be calculated to achieve emmetropia (plano MRSE) at distance for all monofocal or monofocal toric eyes. Intentional overcorrection or undercorrection (i.e., monovision or outside plano ± 0.25 diopter) should NOT be planned for the monofocal eye in either study group. Investigators may adjust the targeted refraction as necessary to achieve emmetropia based on their surgeon factors, study subject experience and/or subject first-eye outcomes.

The IOL power should be calculated to achieve a myopic refractive target of -0.75 D for the IC-8 IOL to implant in the second eye.

IOL Power Calculation and Selection:

Barrett Universal II formula should be used with an A-constant of 120.5 for IC-8 IOL power calculation. All monofocal IOLs used in the study will be either TECNIS aspheric 1-piece (ZCB00, ZCT150, ZCT225) or AcrySof IQ (SA60WF, SA6AT3, SA6AT4). For monofocal IOLs, the surgeon's customary formula should be used for IOL power calculation.

For the aspheric monofocal IOL, the investigator's previously established personal A-constant should be used for IOL power calculations.

Blue-blocking IOLs are not allowed in this trial.

Slit-Lamp Biomicroscopy:

A biomicroscopic slit-lamp exam will be performed preoperatively to rule-out any anterior segment abnormalities other than cataract. The type and density of cataract should be graded using the grading shown in **Appendix C**.

Ocular Surface Assessments:

Ocular surfaces will be assessed by tear break-up time (TBUT) and corneal staining using the Oxford Grading Scale.

Dilated Fundus Evaluation with Binocular Indirect Ophthalmoscopy (BIO), and Slit-Lamp Fundus Exam (SLE):

Dilated fundus exam with the BIO, and slit-lamp examination with a +90 D lens will be performed preoperatively on all eyes in both groups, in keeping with the standard of care of

patients undergoing cataract surgery with intraocular lens implantation. The investigator will be required to rate the level of difficulty with retinal evaluation and their ability to achieve a stereoscopic view of the posterior pole in both eyes of the test subjects, preoperatively **(Appendix D)**. Investigator responses will be recorded on the source documents. If the site routinely performs dilated slit-lamp fundus exam with a lens other than a +90 D lens, the site will be allowed to use their preferred lens to perform standard of care to view the retina. The lens of choice, if other than a +90 D lens, will be collected on the source documents.

NOTE: *Grading of the level of difficulty with retinal evaluation must be performed by the principal investigator or the operating surgeon.*

Spectral Domain Optical Coherence Tomography (SD-OCT):

Preoperatively, dilated SD-OCT exam must be performed to rule out retinal and macular pathologies (e.g., epi-retinal membrane, age-related macular degeneration) in all eyes from the control and test groups. Assessment of normal vs. abnormal findings from dilated SD-OCT exam will be captured in the source documents.

Retinal Diagnostic Testing (subgroup):

The retinal diagnostic testing will be performed in both eyes of all test subjects that complete enrollment in the retinal diagnostic testing subgroup from approximately 3-4 sites. A minimum of 50 test subjects will be included in the retinal diagnostic testing subgroup as determined in the SAP. All available test subjects (or the first 25 test subjects if there are more than 25 test subjects enrolled at any site) from each of the sites that are participating in the subgroup will be sequentially enrolled into the subgroup. The following assessments will be performed preoperatively on the subgroup:

1. Undilated Visual Field (SITA Standard 30-2 test)
2. Dilated SD-OCT Images
3. Dilated Fundus Photography

A standard operating procedure (SOP) for retinal diagnostic testing protocols and retinal image grading procedures will be obtained from a retinal image reading center which will be used in the study. The results from the visual field testing, SD-OCT images and dilated fundus photographs should be saved and submitted to the reading center for analysis. The tests and data collected for SD-OCT, Fundus photography and Visual field for the subgroup are shown in **Table 5**.

Table 5: Retinal Diagnostic Tests for the Subgroup

Diagnostic Instrument	Tests
SD-OCT (Macula & RNFL)	Standard macula & optic nerve scans
Fundus Photography	4 Wide Field (4W-D) or Modified 7 Standard Fields (7M-D)
Visual Field	SITA Standard 30-2 test

The image quality of the SD-OCT images and fundus photos will be assessed and graded by the investigator. A sample of the grading scales for OCT and fundus photographs is shown in **Appendix D**. The investigator responses will be recorded on the source documents. Additionally, a retinal image reading center will independently assess and grade the image quality of the SD-OCT images and fundus photos per their SOP for retinal image grading procedures (**Appendix E**).

NOTE: *Image quality grading of OCT and Fundus Photos must be performed by the principal investigator or the operating surgeon.*

Questionnaires:

In an effort to better understand potential visual disturbances related to the IC-8 IOL implant, patient satisfaction, and driving task performance, the baseline questionnaires must be administered by designated study personnel at the beginning of the study visit before any study testing begins. Visual symptoms will be measured using the Quality of Vision (QoV) questionnaire and Small Aperture Patient Questionnaire (SAPQ). Driving task performance and patient satisfaction will be measured by the SAPQ. Subjects will be required to complete all questionnaires before all study testing begins. The sequence to administer the questionnaires will be QoV followed by SAPQ.

Non-directed Question:

Subjective visual symptoms will be assessed at each visit using a general open-ended question such as: “Are you having any difficulties with your vision?” Subject’s responses will be collected on the source documents.

Additional preoperative data collected on source documents:

The preoperative source documents will request the following information for both eyes:

- Informed consent documentation
- Patient demographic information
- Treatment group and eye designation for first and second surgery
- Ocular history, including presence of ocular pathology and concomitant medications

- Potential visual acuity meeting inclusion criteria
- Cataract type and density
- Uncorrected and best-corrected distance visual acuity (with glare as needed) using a standard Snellen chart
- Manifest refraction
- Power calculation formula and A-constant used
- Corneal topography
- Biomicroscopic slit lamp exam
- Gonioscopy
- Intraocular pressure
- Dilated fundus exam

9.4. QUALIFICATION OF SUBJECTS

In order for a subject to complete enrollment, the subject's first eye implanted with a monofocal or monofocal toric IOL must achieve 20/32 or better uncorrected distance visual acuity (UCDVA) and 20/25 or better BCDVA (or Snellen equivalent) have no ongoing ocular adverse events, and have normal corneal health as assessed by slit lamp biomicroscopy (Grade 1+ or less edema and Grade 1 or less SPK). The subject must qualify within the 1-week to 1-month visit windows (7 to 45 days from the 1st eye surgery). Subjects whose first implanted eye does not achieve the qualification criteria in both the test and control groups will be disqualified and exited from the study.

9.5. STUDY LENS SUPPLY

The aspheric monofocal and monofocal toric IOLs should be obtained from the site's own inventory after determining the appropriate IOL power. The IC-8 IOL will be supplied to the sites in a partial consignment method. Based on the IC-8 IOL power calculation, the investigator will select the appropriate IC-8 IOL from the consignment inventory at the site or request it from the sponsor.

9.6. OPERATIVE

9.6.1. SURGICAL TECHNIQUE OVERVIEW

Standardization of surgical techniques across all sites is key in reducing outcome variability. Therefore, the investigator will adhere to the following standardized, phacoemulsification or femtosecond-assisted cataract extraction surgical technique for all IOLs unless operative complications require otherwise.

Incision Type:	Limbal or clear corneal
Incision Location:	Temporally ± 20°
Incision Size:	Approximately 3.5 mm for IC-8 IOL
	2.2 to 2.5 mm for monofocal IOL
Phacoemulsification:	Ultrasonic technique or femtosecond-assisted technique
Closure Type:	Self-sealing preferred, sealant or sutured if necessary

Monofocal Toric IOL

For the monofocal eyes implanted with the toric IOL, the calculator used for determining the IOL power, intended axis placement, predicted residual cylinder (magnitude and axis) will be recorded on the operative source documents.

Limbal Relaxing Incisions

If the predicted residual refractive cylinder is ≥ 0.75 D and a toric IOL is not indicated, limbal relaxing incisions (LRI's) may be performed for minimization of residual astigmatism during initial surgery. This applies to all monofocal eyes in the test and the control groups. Variables such as manual vs. femtosecond LRI and the predicted residual cylinder will be recorded on the source documents.

9.6.2. LENS IMPLANTATION

The IC-8 IOL and aspheric monofocal IOL are to be implanted using the following standardized surgical technique.

Incision:

The standardized incision size for the IC-8 IOL will be approximately 3.5 mm. Investigators may use a smaller incision for phacoemulsification; however, they will need to enlarge the incision prior to IOL implantation using a 3.5 mm sized keratome (provided by AcuFocus) to ensure all incision sizes are consistent. Utilizing wound assist technique, i.e. incision less than 3.5 mm, for implantation of the IC-8 IOL is not permitted.

The lens manufacturer's recommendations will be followed to determine the incision size for the aspheric monofocal IOL.

Phacoemulsification:

The investigator may use his/her standard phacoemulsification technique. The anterior capsulotomy should be a continuous curvilinear capsulorhexis approximately 5.0 to 5.5 mm in diameter created manually or with a femtosecond laser.

Viscoelastics:

Healon® is the only ophthalmic viscoelastic device (OVD) validated for use with the IC-8 IOL Injector System.

Monofocal IOLs will be implanted with an injector system qualified by the respective manufacturer for use with that IOL, and a validated OVD for that injector system should be used.

Surgeons will be allowed to use their routine OVD for all eyes during the surgery.

All of the viscoelastic should be thoroughly removed from both the anterior and posterior sides of the IOL at the end of the case.

Lens Insertion:

All IC-8 IOLs are to be implanted and placed in the capsular bag using the supplied IC-8 IOL Injector System, qualified for use with the IC-8 IOL. All aspheric monofocal IOLs are to be implanted and placed in the capsular bag using the lens manufacturer's recommended insertion system, qualified for use with their respective lens.

Use of capsular tension rings is not permitted in this clinical study.

Lens Alignment/Orientation:

For IC-8 IOL, it is recommended to implant the IC-8 IOL so that the optic is centered in the capsular bag with haptic-optic junction orientation at 12 and 6 o'clock with a slight nasal bias when possible. For monofocal or monofocal toric IOL, the lens manufacturer's recommendations should be followed to determine the lens alignment and orientation.

Wound Closure:

Sutureless wound closure is the preferred method. However, if deemed necessary, sealant or suture(s) may be used at the surgeon's discretion.

9.6.3. ADDITIONAL PROCEDURES

For monofocal IOL, surgeons will be allowed to perform LRI during the surgery in the monofocal control eyes if the predicted residual refractive cylinder is ≥ 0.75 D and a toric IOL is not indicated.

No additional refractive procedures except for LRI at the surgery visit are to be performed in control eyes during the trial (i.e., LRI postoperatively, OCCI, PRK or LASIK).

No additional refractive procedures are to be performed on any eye implanted with the IC-8 IOL during the one-year postoperative period (i.e., LRI, OCCI, PRK or LASIK).

9.6.4. SURGICAL COMPLICATIONS

If during the implantation of the IOL, in either eye of the test or the control arm, a surgical complication such as a capsular bag tear/rupture or zonular damage/rupture should occur, the subject should be discontinued from the study. If a surgical complication occurs during the implantation of the investigational IOL, the IC-8 IOL should **not** be implanted. The investigator should treat the subject per routine standard of care and may choose to implant their choice of a back-up, non-investigational, marketed IOL based on the investigator's discretion. The subject

will be discontinued and will be followed by the investigator until the adverse event is considered resolved or stable and then exited from the study.

9.6.5. MEDICATIONS

Preoperative and intraoperative medications should be used as is customary for each investigator, as each site may have its own standardized regimen of preoperative and intraoperative medications. The standard regimen should be documented on a routine medication regimen form and sent to the medical monitor to be pre-approved as being consistent with the standard of care before initiation of enrollment for each site. Medications that are not administered as part of the standard regimen will be recorded on the concomitant medications log for each subject. Medications used to treat elevated intraocular pressure and any adverse event will also be reported on the concomitant medications log.

9.6.6. ADDITIONAL OPERATIVE INFORMATION

Additional operative information to be collected includes the following:

- Date of surgery
- Operative eye selected (OD or OS)
- IOL manufacturer, serial number, power and model
- Capsulorhexis type (manual vs. femtosecond) size and centration
- Type of viscoelastic used during the surgery
- Incision location and size
- IOL and haptic placement
- Bag polishing
- Difficulty of IOL implantation (easier than most, average, or more difficult than most; grading of difficulty will be recorded on the source documents)
- Incision closure method
- Surgical complications

9.7. POSTOPERATIVE PROCEDURES

Visual Acuity Testing:

Visual acuities will be measured using the ETDRS chart presented on a self-calibrating monitor in the M&S Clinical Trial Suite (CTS), at 4 meters for all distance vision tests, at 66 cm for all intermediate vision tests and at 40 cm for all near vision tests. CTS will automatically randomize the letter presentation to avoid memorization. **Table 6** shows the type of visual acuity measurement by eye and by visit. **Table 7** shows the infinity-adjusted refraction to be used for each visual acuity test. General instruction for all visual acuities tested using the CTS

computerized vision testing system (M&S Technologies, Inc., Niles, IL, USA) is provided in **Appendix F**. Examiners should take precautions to remind subjects not to squint at any time during vision testing.

Uncorrected and Distance-Corrected Visual Acuities:

Monocular and binocular visual acuities with and without manifest refraction will be measured at distance, intermediate and near (**Table 6** and **Appendix A**).

NOTE: *Best-corrected distance visual acuity (BCDVA) is same as Distance-corrected distance visual acuity (DCDVA).*

Monocular and Binocular +0.75 D distance-corrected visual acuity (+0.75 DCVA):

+0.75 D distance-corrected visual acuity will be achieved by correcting all eyes in both groups with their distance-corrected refraction (plus infinity adjustment to refraction for each testing distance) and then placing a +0.75 D lens in front of the second eyes in both groups. Details on the refractions to be used for +0.75 D visual acuities are specified in **Table 7**.

Monocular and Binocular uncorrected and distance-corrected low contrast visual acuities (subgroup testing):

Low contrast visual acuity will be tested at distance, intermediate and near with 10% contrast. Measurements will be performed at the 6-month postoperative visit (and repeated at the 12-month visit for those subjects that have had a posterior capsulotomy procedure after the 6-month visit) in the contrast sensitivity subgroup. The description of the contrast sensitivity subgroup is provided below under “Contrast Sensitivity Testing (subgroup testing)”.

Table 6: Visual Acuity Measurements

Visual Acuity	Illumination	Eye	Visit
Uncorrected distance visual acuity (UCDVA)	Photopic	Monocular Binocular	Day 1, Week 1, Months 1, 3, 6, 12 Months 3, 6, 12
Uncorrected visual acuity intermediate (UCIVA) and near (UCNVA)	Photopic	Monocular Binocular	Months 3, 6, 12 Months 3, 6, 12
Distance-corrected distance visual acuity (DCDVA)	Photopic	Monocular Binocular	Week 1, Month 1 Months 3, 6, 12
Distance-corrected visual acuity intermediate (DCIVA) and near (DCNVA)	Photopic	Monocular Binocular	Months 3, 6, 12 Months 3, 6, 12

+0.75 D distance-corrected visual acuity distance (+0.75 DCDVA), intermediate (+0.75 DCIVA) and near (+0.75 DCNVA)	Photopic	2nd Eye Binocular	Month 6 Month 6
Low contrast UCDVA, UCIVA, UCNVA, DCDVA, DCIVA, DCNVA (10%) (contrast sensitivity subgroup only)	Photopic	2nd Eye Binocular	Month 6 Month 6

Manifest Refraction:

Manifest refraction should be measured using the CTS at 13 feet or 4 m. Because of the extended depth of focus provided by the small-aperture optics, determination of the refractive endpoint in IC-8 IOL eyes may potentially be challenging when patients can tolerate a wider range of refractive error without necessarily exhibiting a noticeable drop in visual acuity, and the manifest refraction measurement could have a "fuzzy" endpoint. Taking this into consideration, determination of the middle point of the emmetropic range of the depth of focus should be best accomplished by using the duochrome technique. The duochrome test is less likely to be influenced by the extended depth of focus because it is based on the principle of chromatic aberration. Therefore, manifest refraction should be determined using the duochrome technique (commonly known as the red/green test) postoperatively. To maintain examiner masking and avoid bias between groups, manifest refraction should be measured using the same technique in all eyes from both groups. Manifest refraction will be measured at all postoperative visits beyond Day 1. Instructions for performing manifest refraction with the red/green test using the CTS are provided in **Appendix G**.

Infinity-Adjusted Refraction for Vision Testing:

Postoperative manifest refractions for the study are to be performed using the ETDRS charts at 4 m using the CTS. Because 4 m is not optical infinity, adjustments to the manifest refraction are necessary for visual acuity tests taking into account the vision test distances (4 m for distance vision tests, 66 cm for intermediate vision tests, and 40 cm for near vision tests) and the refraction distance (4 m). **Table 7** lists the infinity-adjusted refraction to be used for each vision test in the study when using the 4 m refraction.

Table 7: Infinity-Adjusted Refraction by Vision Test

Vision Test	Infinity-Adjusted Refraction
UCDVA	+0.25 D
UCIVA	None
UCNVA	None
DCDVA	Manifest Refraction
DCIVA	-0.25 D added to Manifest Refraction
DCNVA	-0.25 D added to Manifest Refraction
+0.75 DCDVA	+0.75 D added to Manifest Refraction
+0.75 DCIVA	+0.50 D added to Manifest Refraction
+0.75 DCNVA	+0.50 D added to Manifest Refraction
10% contrast UCDVA	+0.25 D
10% contrast UCIVA	None
10% contrast UCNVA	None
10% contrast DCDVA	Manifest Refraction
10% contrast DCIVA	-0.25 D added to Manifest Refraction
10% contrast DCNVA	-0.25 D added to Manifest Refraction

Near Stereoacuity:

Near stereoacuity testing will be performed binocularly at the 6-month visit using the Randot stereo test (circles test) once in the uncorrected near condition and once in the distance corrected near condition with add. In the distance corrected near condition, the infinity-adjusted refraction will be used for the testing, i.e., -0.25 D added to manifest refraction.

Defocus Curves:

Defocus curves will be performed monocularly and binocularly using ETDRS charts in the CTS calibrated for 4-meter test distance in standard photopic conditions, with the best-corrected distance manifest refraction. A defocus curve should be obtained by using the manifest refraction and measuring the visual acuity between +2.00 D and -5.00 D in 0.5 D defocus steps, except in the region from +0.50 D through -0.50 D, which should be done in 0.25 D steps.[17] Defocus curve

testing will be performed at the 3-month postoperative visit (refractive stability is expected to be achieved by the 3-month visit). No infinity adjustment to manifest refraction is needed for defocus curve testing. Instructions for performing defocus curve testing using the CTS are provided in **Appendix H**.

Contrast Sensitivity Testing (subgroup testing):

Contrast sensitivity under photopic and mesopic conditions will be measured at the 6-month postoperative visit (and repeated at the 12-month visit for those subjects that have had a posterior capsulotomy procedure after the 6-month visit) in a contrast sensitivity subgroup using the sine wave gratings in the CTS. Instructions for performing contrast sensitivity testing with using the CTS are provided in **Appendix I.** A minimum of 177 test subjects and 59 control subjects are needed in the contrast sensitivity subgroup as determined in the SAP. To achieve this sample size at the time of testing, approximately 12-15 sites will be included in the contrast sensitivity subgroup, and all eligible subjects from these sites will be sequentially enrolled in the subgroup.

Pupil Size:

Photopic (full room illumination) and mesopic (dim lighting) pupil size will be measured to the nearest one-half millimeter using a pupillometer, pupil gauge or millimeter ruler at the 3, 6 and 12-month postoperative visits. The patient must be dark adapted for ten minutes prior to measuring mesopic pupil size. The presence or absence of a relative afferent pupillary defect will be assessed using the "Swinging Flash Light Test" at preoperative and at the 3-month postoperative visit.

Pharmacologically dilated pupil size should be measured when maximum dilation is achieved. It is to be measured preoperatively, and at 3 months (in the retinal testing subgroup) and at 12 months.

NOTE: *Pupillometry should be measured via the same method (e.g., pupillometer, pupil gauge) for all subjects, at each study visit, if at all possible. If a pupillometer is used, it is important to ensure the measured eye has a clear view of the testing environment. If the pupillometer is unable to measure the pupil size in the IC-8 IOL eye postoperatively, use a pupil gauge or millimeter ruler to measure the pupil size and use the same method for all remaining visits.*

Corneal topography:

Corneal topography is to be measured with a computerized corneal topographer (e.g., Zeiss Atlas, etc.). Corneal topography will be measured at 6-month and 12-month visits. The same method used preoperatively must also be used at the postoperative visits. A printout of all topography maps should be retained.

Keratometry:

Postoperative keratometric readings must be obtained with a corneal topographer. Keratometry will be measured at 6-month and 12-month visits. The same corneal topographer used

preoperatively to measure corneal topography must be used to measure keratometry at the postoperative visits. A printout of all topography maps should be retained.

Slit-Lamp Biomicroscopy:

A biomicroscopic slit-lamp exam will be performed at each postoperative visit to check for any medical findings or complications. Medical findings of aqueous cells and flare, corneal edema, posterior capsule striae (wrinkles) and posterior capsule opacification are to be rated using the grading scale as shown in **Appendix C** during slit-lamp biomicroscopy.

IOL centration and tilt will be assessed at all postoperative visits. Investigators will be required to indicate the presence/absence and the amount of the decentration and/or tilt.

The Investigator may choose to measure toric IOL axis at any postoperative visit, if deemed necessary by the investigator. The assessment has to be performed with a slit lamp after the pupils are pharmacologically dilated. The slit lamp reticule should be used to measure the IOL axis.

Ocular Surface Assessments:

Ocular surfaces will be assessed by tear break-up time (TBUT) at 3, 6, and 12 months and by corneal staining at 3, 6, and 12 months for both eyes and additionally at 1 week and 1 month for the first eye (to complete at 1 month only if the first eye has not passed the SPK qualification criteria at 1 week).

Intraocular Pressure:

Intraocular pressure is to be measured using Goldmann applanation at Day 1, Week 1 and 1, 3, 6 and 12 months postoperatively. It is required that the same method be used for all patients at the site for the duration of the study.

Dilated Fundus Evaluation with Binocular Indirect Ophthalmoscopy (BIO), and Slit-Lamp Fundus Exam (SLE):

Dilated fundus exam with the BIO and slit-lamp examination with a +90 D lens will be performed postoperatively at 12 months on all eyes in both groups, in keeping with the standard of care of patients undergoing cataract surgery with IOL implantation. The surgeon will be required to rate the level of difficulty with retinal evaluation and achieving a stereoscopic view of the posterior pole in both eyes, postoperatively **(Appendix D)**. Surgeon responses will be recorded on the source documents. If the site routinely performs dilated slit-lamp fundus exam with a lens other than a +90 D lens, the site will be allowed to use their preferred lens to perform standard of care to view the retina. The lens of choice if other than a +90 D lens will be collected on the source documents.

NOTE: *Grading of the level of difficulty with retinal evaluation must be performed by the principal investigator or the operating surgeon.*

Retinal Diagnostic Testing (subgroup):

The following assessments will be performed at the 3-month postoperative visit in the subgroup.

1. Undilated Visual Field (SITA Standard 30-2)
2. Dilated Spectral-Domain Ocular Coherence Tomography (SD-OCT) images
3. Dilated fundus photography

The results and images from all retinal testing should be saved and submitted to the reading center. The same instruments must be used both preoperatively and postoperatively. The testing protocols listed in **Table 5** should be repeated at the 3-month postoperative visit.

Same as the process at preoperative visit, the image quality of the SD-OCT images and fundus photos will be assessed and graded by the investigator. A sample of the grading scales for OCT and fundus photographs is shown in **Appendix D**. The investigator responses will be recorded on the source documents. Additionally, a retinal image reading center will independently assess and grade the image quality of the SD-OCT images and fundus photos per their SOP for retinal image grading procedures (**Appendix E**).

NOTE: *Image quality grading of OCT and Fundus Photos must be performed by the principal investigator or the operating surgeon.*

Medications:

Postoperative medications should be used as is customary for each investigator, as each site may have its own standardized postoperative medications regimen. The standard postoperative regimen should be documented on a routine medication regimen form and sent to the medical monitor to be pre-approved as being consistent with the standard of care before initiation of enrollment for each site. Medications that are not administered as part of the standard regimen will be recorded on the concomitant medications log for each subject.

Questionnaires:

In an effort to better understand potential visual disturbances related to the IC-8 IOL implant, patient satisfaction, and driving task performance, the questionnaires must be administered by designated study personnel at the beginning of the study visit before any study testing begins. Visual symptoms will be measured using the Quality of Vision (QoV) questionnaire and Small Aperture Patient Questionnaire (SAPQ). Subjects will be required to complete all questionnaires before all study testing begins. Questionnaires are administered at the 3, 6 and 12 month postoperative visits. The sequence to administer the questionnaires will be QoV followed by SAPQ.

Non-directed Question:

Subjective visual symptoms will be assessed at each postoperative visit using a general open-ended question such as: “Are you having any difficulties with your vision?” Subject’s responses will be collected on the source documents.

Nd:YAG Capsulotomy:

If a Nd:YAG capsulotomy is necessary in the IC-8 eye, it is recommended that the YAG capsulotomy be performed around the mask in an omega pattern. This method creates an opening of approximately 10 clock hours around the outside of the mask with 5 to 7 o'clock leaving an inferior hinge. Nd:YAG laser energy has to be titrated to the lowest level to produce a capsular opening. Using an energy that is too high can result in damage to the periphery of the mask. The procedure has to be performed at least one week prior to a postoperative visit; and no sooner than six weeks after surgery for the second eye, unless medically indicated.

Standard manufacturer-recommended procedures should be followed for the eyes implanted with the monofocal or monofocal toric IOLs.

Nd:YAG capsulotomies should be documented on the source document for YAG procedure.

Secondary Surgical Interventions:

Secondary surgical interventions other than Nd:YAG capsulotomies are usually considered to be adverse events.

The study protocol will allow for IOL-related secondary surgical interventions in the following categories upon careful consideration of the risks and benefits:

- IOL repositioning due to IOL placement resulting in an unsatisfactory visual outcome provided placement is believed to be surgically correctable.
- IOL exchange due to incorrect IOL power resulting in an unsatisfactory uncorrected visual acuity.
- IOL exchange due to surgical or postoperative medical complications or adverse events. If the affected eye has been implanted with the IC-8 IOL, a non-investigational IOL must be used for replacement.

If the placement of a monofocal/monofocal toric or IC-8 IOL is repositioned, the patient will continue to be followed through the completion of the study. If an IC-8 IOL is exchanged for a non-investigational IOL, the subject will be discontinued, and will be followed by the investigator until the adverse event is considered resolved or stable and then exit from the study.

Secondary surgical interventions for medical complications may be considered to be in the subject's best interest. Although these procedures are at the investigator's discretion, prior agreement from the medical monitor and AcuFocus is required for any non-emergency secondary surgical procedure. In the case of an IC-8 IOL exchange for refractive error, an FDA waiver must be obtained if desired replacement is another IC-8 IOL.

No additional refractive procedures are to be performed on any study eye during the one-year postoperative period (i.e., LRI, OCCI, PRK or LASIK).

A secondary surgical intervention should be performed at least two weeks prior to a postoperative visit to prevent potential confounding influences of the additional procedure on study outcomes. The only exception is Nd:YAG capsulotomy which should be performed at least one week prior to a postoperative visit.

Secondary surgical interventions other than Nd:YAG capsulotomies should be documented on the source document for SSI procedure.

Adverse Events

Patients should be assessed at each visit for occurrence of and/or change in status of any adverse events. See **Section 10.0**, Adverse Events for further information.

NOTE: *Evaluation of Adverse Events must be completed by the principal investigator or the operating surgeon.*

9.8. UNSCHEDULED VISITS

During the postoperative period, if visit is done for the purpose of medically-indicated follow-up, data from this visit should be recorded on Unscheduled Visit source documents. 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 each investigator and are to be recorded on the appropriate section of the source documents.

Data to be collected if deemed appropriate by the investigator may include, but not limited to:

- Uncorrected, distance-corrected or best-corrected visual acuity at far, intermediate or near distance using the high contrast ETDRS chart in the CTS, monocular or binocular
- Manifest refraction
- Corneal Topography
- Intraocular pressure
- Slit-lamp examination for medical findings and other IOL-related findings
- Dilated fundus exam
- Patient-reported visual or ocular symptoms
- Adverse events
- Posterior capsulotomy performed (yes/no)

9.9. DISCONTINUATION OF SUBJECTS

Every attempt must be made to obtain complete follow-up data for all subjects enrolled. It is the responsibility of the investigator to provide complete follow-up data to AcuFocus for each subject. The investigator should notify AcuFocus prior to discontinuing a subject from the study. If a subject is discontinued from the study, the investigator will, if at all possible, have the subject return for a final visit.

Subjects may be discontinued from the study for any of the following:

- At their own request
- In case of any postoperative complication if continued participation in the study has an impact on the safety of any subject
- If irretrievably lost to follow-up for unavoidable reasons such as IC-8 IOL removal/non-IC-8 IOL replacement
- Subject moved/unable to locate
- Subject is uncooperative/refuses to return
- Subject is deceased, ill, unable to travel, or institutionalized

Subjects who plan to be traveling, relocating or otherwise unavailable for postoperative follow-up visits should not be enrolled in this study. In the event of unplanned subject relocation, efforts should be made by the investigator to collect follow-up information (i.e., general visual acuity from the patient's new physician).

When a subject is discontinued due to IC-8 IOL removal after implantation or failure to implant during the surgery, efforts must be made by the investigator to follow the subject until all ocular adverse events are resolved or stable before exiting the subject from the study.

10.0 ADVERSE EVENTS

10.1. ADVERSE EVENT DEFINITIONS

The following adverse event definitions will be used for this study:

ADVERSE EVENT (AE)

An adverse event in this study is defined per ISO 14155:2011: *Clinical investigation of medical devices for human subjects – Good clinical practice* 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 investigational medical device. For this protocol, this definition includes events related to the comparator device(s) and/or the procedures involved.

ADVERSE DEVICE EFFECTS (ADE)

An adverse event related to the use of an investigational medical device or comparator device(s).

NOTE: *This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation; any malfunction; and use error or intentional misuse of the investigational or comparator(s) medical device.*

DEVICE DEFICIENCY

Device deficiency is defined as inadequacy of the medical device with respect to its identity, quality, durability, reliability, safety or performance per 21 CFR 820.3b and International Organization for Standardization ISO 14155:2011: *Clinical investigation of medical devices for human subjects – Good clinical practice*. A device deficiency includes a product malfunction, which is the failure of the medical device to perform in accordance with its intended purpose when used in accordance with the directions for use. The investigator shall assess whether the deficiency could have led to an AE or Serious Adverse Event (SAE) if suitable action had not been taken, if intervention had not been made, or if circumstances had been less fortunate.

Use Error as defined according to ISO 14155:2011: *Clinical investigation of medical devices for human subjects – Good clinical practice* is an act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user. Use error includes slips, lapses, and mistakes. An unexpected physiological response of the subject does not in itself constitute a use error.

NOTE: *Device deficiencies must be recorded on the Device Deficiency Form source document and on the eCRF in the EDC system within 24 hours of the investigator or site's awareness. In case of a device return, please follow instructions for device returns (**Section 14.2.2**) and include a copy of the Device Deficiency Form with the product return.*

SERIOUS ADVERSE EVENT (SAE)

An adverse event is considered serious per ISO 14155:2011 if it:

a) led to death,

b) led to a serious deterioration in the health of the subject, that either resulted in

   1. a life-threatening illness or injury, or

   2. a permanent impairment of a body structure or a body function, or

   3. in-patient or prolonged hospitalization, or

   4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or body function,

c) led to fetal distress, fetal death or a congenital abnormality or birth defect.

NOTE: *Planned hospitalization for a pre-existing condition, or a procedure required by the Protocol, without serious deterioration in health, is not considered a serious adverse event. Generally, other emergency room or hospitalization > 24 hours is normally considered an SAE.* Complications during a hospitalization are considered AEs and should be reported separately. AEs during a hospitalization that satisfy the seriousness criteria are SAEs.

SERIOUS ADVERSE DEVICE EFFECT (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (USADE)

An unanticipated serious adverse device effect is defined per 21CFR 812.3(s) 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 protocol or supplementary plan such as Clinical Investigator's Brochure, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. Per this definition, USADE will be a subset of the SAEs reported in the study. USADEs are reportable per 21 CFR 812.150(a)(1):

An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

NOTE: *Vision-threatening (sight-threatening) adverse events are considered an USADE, reportable per 21 CFR 812.150(a)(1) and must be reported to AcuFocus within 48 hours of detection.*

ANTICIPATED SERIOUS ADVERSE DEVICE EFFECT

Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report. IOL-related secondary surgical interventions (i.e., IOL repositioning, IOL exchange or IOL removal) as a result of potential risks from the investigational device (**Section 10.3**) will be considered as an ASADE for this study.

10.2. REPORTING REQUIREMENTS

10.2.1. GENERAL REPORTING GUIDELINES

All adverse events, regardless of severity and whether or not attributed to the IOL, are to be reported to AcuFocus. Adverse events are also to be reported to the reviewing IRB as per their reporting requirements and to the appropriate regulatory agencies (e.g., FDA) according to all applicable laws and regulations. Detailed reporting requirements are outlined in **Section 10.2.2**.

The following is a potential list of adverse events per ISO 11979-7:2014 for posterior chamber IOL and per American Academy of Ophthalmology Task Force consensus statement on adverse events with intraocular lenses.[18] The investigator should assess each adverse event according to but not limited to this list and follow the definitions in **Section 10.1** and reporting requirements in **Section 10.2.2** for each type of adverse event upon reporting.

- Endophthalmitis – Intraocular inflammation leading to diagnostic vitreous tap and intraocular antibiotics.

- Toxic anterior segment syndrome (TASS) – Acute, non-infectious inflammation of the anterior segment that starts within 24 to 48 hours after surgery, usually resulting in hypopyon and commonly presenting with corneal edema, and that improves with steroid treatment.
- 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.
- Hyphema
- Hypopyon
- Iritis
- IOL dislocation
- Rhegmatogenous retinal detachment (RD) - Partial or complete RD associated with retinal tear
- Corneal stromal edema – Corneal swelling (stromal) resulting in BCDVA of 20/40 or worse at 1 month or later
- Corneal epithelial edema – Corneal swelling (epithelial) resulting in BCDVA of 20/40 or worse at 1 month or later
- Cystoid macular edema – Macular edema diagnosed by clinical examination and adjunct testing (e.g. OCT, FA) resulting in BCDVA of 20/40 or worse at 1 month or later
- Chronic anterior uveitis – anterior segment inflammation characterized by grade 1+ cell or greater using Standardization of Uveitis Nomenclature (SUN) criteria[19,20]that persists for greater than 3 months after surgery, or relapses in less than 3 months after discontinuation of therapy, or the subject is maintained on therapy for more than 3 months to control inflammation.
- Elevated IOP requiring treatment – Elevation of IOP greater than or equal to 10 mmHg above baseline to a minimum of 25mmHg (even during the first postoperative week, it should be considered an AE, although not an UADE)
- Any secondary surgical intervention including but not limited to IOL removal, exchange or repositioning, iridectomy/iridotomy or vitreous aspiration for pupillary block, post-surgery IOL or eye re-suturing, retinal detachment repair, or other surgical procedure, excluding Nd:YAG capsulotomies.

  NOTE: ***Posterior capsulotomy is not considered an adverse event for this study; however, posterior capsule opacification (PCO) that affects vision is considered an adverse event.***

- Any other adverse event that leads to permanent visual impairment or requires surgical or medical intervention to prevent permanent visual impairment

10.2.2. DETAILED REPORTING REQUIREMENTS

ADVERSE EVENT (AE) and ADVERSE DEVICE EFFECT (ADE) REPORTING

An adverse event is to be reported to AcuFocus within 10 working days of the investigator first becoming aware of the event. Notification by completing the AE source documents as well as the corresponding AE eCRFs is the preferred method. An adverse event is also to be reported to the reviewing IRB per their reporting requirements.

SERIOUS ADVERSE EVENT (SAE) and SERIOUS ADVERSE DEVICE EFFECT (SADE) REPORTING

In the event of a sight- or life-threatening incident or serious adverse event, which may or may not be related to use of the IC-8 IOL, AcuFocus must be notified immediately (no later than 48 hours after detection) by phone and by completing the AE form in the EDC. Any SAE and SADE should be reported to the investigator's IRB per their reporting requirements. Vision-threatening (sight-threatening) serious adverse events and serious adverse device effects are reportable per 21 CFR 812.150(a)(1). Other relevant information after the initial reporting of the event must reported to the Sponsor via the AE form in EDC as soon as the information becomes available.

In the event of unavailability of the EDC system, the SAE should be reported by telephone or email/fax at:

Fax: (949) 585-9545
Email: AcuFocus101@acufocus.com

Telephone: 714-914-5531 or 336-306-0587

UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (USADE) AND ANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (ASADE) 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 in the protocol, the investigator is to report the USADE to AcuFocus within 48 hours after detection, and report it to the investigator's IRB as soon as possible but no later than 10 working days after learning of the event as required by 21CFR812.150(a)(1). Vision-threatening (sight-threatening) ASADE are reportable per 21 CFR 812.150(a)(1) in this study.

10.3. POTENTIAL RISKS WITH INVESTIGATIONAL DEVICE

The following are potential risks associated with the investigational device or the implantation procedure:

- Night vision problems
- Dimness in vision
- Negative dysphotopsia
- Glare, halos, starbursts, loss of contrast sensitivity

- Difficulty with depth perception, Pulfrich effect
- Double vision, ghosting, blurry vision, fluctuating vision, hazy vision, difficulty focusing
- Obstructed vision
- Surgically induced astigmatism > 2D
- Difficulty with retinal diagnostic evaluation and/or performing retinal treatment
- Risk of laser treatments (possible damage can occur to the IC-8 IOL mask while performing photodynamic laser or any other ocular laser procedure)

10.4. ADVERSE EVENT FOLLOW-UP

For every adverse event, appropriate measures should be undertaken to treat and/or monitor the patient until resolution occurs. The investigator should keep AcuFocus closely informed as to the outcome, thereby allowing AcuFocus to comply with the appropriate regulatory reporting requirements. The AE status should be updated on the source documents each time the patient returns for follow-up until resolution of the event. Additionally, the investigator may supply written reports (e.g., from outside specialist evaluations) of the adverse event to AcuFocus. Any subject who is withdrawn from the study due to an adverse event will be followed by the investigator until the outcome is determined to be resolved or stable at which point the subject will be exited from the study.

10.5. RELATIONSHIP TO INVESTIGATIONAL DEVICE

The investigator should always be alert to adverse events that may be related to the IC-8 IOL. An attempt should be made in every case to determine the relationship between an adverse event and the IC-8 IOL. The relationship should be determined using the following definitions as guidelines:

Definitely Related:	There is a direct causal relationship between the device and the adverse event
Probably:	There is a reasonable possibility of a causal relationship between the device and the adverse event
Possibly:	The adverse event has not been determined to be device-related, but no other cause has been definitively identified, and the device cannot be ruled out as a possible cause
Unlikely:	The possibility of a potential causal relationship between adverse event and the device could exist, but the adverse event is most likely explained by causes other than the device
Not Related:	Some cause other than the device has been definitively identified

An attempt should also be made by the investigator to determine the relationship between an adverse event and the study procedure or protocol instructions. The relationship between an

adverse event and the study procedure or protocol instructions should be similarly determined using the following definitions as guidelines:

Definitely Related:	There is a direct causal relationship between the study procedure or protocol instructions and the adverse event
Probably:	There is a reasonable possibility of a causal relationship between the study procedure or protocol instructions and the adverse event
Possibly:	The adverse event has not been determined to be procedure-related or protocol instruction-related, but no other cause has been definitively identified, and the procedure or the protocol instructions cannot be ruled out as a possible cause
Unlikely:	The possibility of a potential causal relationship between adverse event and the study procedure or protocol instructions could exist, but the adverse event is most likely explained by causes other than the study procedure or protocol instructions
Not Related:	Some cause other than the procedure has been definitively identified

10.6. SEVERITY RATINGS

A clinical determination of the severity of an adverse event should be made by the investigator using the following definitions as guidelines:

Mild:	The event either resolved spontaneously or no treatment was required beyond administration of non-prescription medication.
Moderate:	The event required treatment with prescription medication and/or intervention, but produced no sequelae and required no hospitalization.
Severe:	The event produced sequelae that required prolonged treatment with prescription medication, intervention and/or hospitalization for longer than 24 hrs.

11.0 PROTOCOL DEVIATION AND PROCEDURES

Any deviation from the protocol done to protect the life or physical well-being of a subject in an emergency must be reported to AcuFocus and the reviewing IRB as soon as possible, but no later than five (5) working days after the deviation occurred. Unless it is an emergency, if the investigator desires to modify any procedure and/or deviate from the design of the study, he or she must contact and obtain the consent of AcuFocus regarding the proposed changes prior to implementation. If the modifications may affect the scientific soundness of the study, or the rights, safety, or welfare of study participants, approval by FDA and all appropriate regulatory agencies, as well as approval of the IRB is also required.

12.0 ETHICS REVIEW AND PATIENT WELFARE

12.1. INSTITUTIONAL REVIEW BOARD

It is the responsibility of the investigator to obtain prospective approval of or consultation on the 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's Study Files.

The investigator is responsible for notifying the IRB of reportable adverse events as well as any circumstances in which deviations from the protocol were conducted to eliminate apparent hazards to patients.

12.2. INFORMED CONSENT

The current version of the IRB approved study informed consent must be signed by each subject prior to any study-specific examinations being performed. The approved informed consent is to be signed and dated by the subject as well as the designated person (e.g., investigator, study personnel) who conducted the informed consent discussion. The signed informed consent will be maintained by the investigator as a permanent part of the subject's medical records. A signed and dated copy is to be provided to the subject. The investigator will confirm with AcuFocus by acknowledging on the Preoperative source documents that a signed informed consent has been obtained and is in the investigator's possession for each subject. As required by 21CFR812 Subpart G, the site shall document in the source documents that informed consent was obtained prior to participation in the study for each subject enrolled.

13.0 DOCUMENTATION

13.1. SOURCE DOCUMENTS

Source documents must be kept for all study subjects. The investigator is responsible for ensuring that data are properly recorded on the source documents and related documents for each subject. Source documents must be completed in a legible manner. Any correction will be made by drawing a single line through the incorrect entry, entering the correct entry, and initialing and dating the change.

Source documents may include a subject's medical records (paper or electronic), hospital charts, clinical charts, the investigator's subject study files as well as results of any diagnostic tests or procedures, photographs or instrument printouts.

M&S CTS system will be used for all vision, refraction and contrast sensitivity tests. The test results will be stored in the CTS and automatically transmitted over the internet to Medidata RaveX EDC for all visual acuities, contrast sensitivity and defocus curve data. Data saved directly in the CTS will be printed out by the non-masked study coordinator and filed in subject files as source documents. Manifest refraction will be performed using the CTS but will be manually recorded in the source documents by the masked examiner and then entered into the

electronic case report forms (eCRFs) using the RaveX EDC. More details on the data transmission are provided in **Appendix J**.

Source documents including print-outs from electronic records are to be personally signed by an investigator (who has signed the protocol signature page) to signify their agreement that the observations and findings recorded are accurate and complete. The original signed copy will be kept in the subject study file at the investigational site. AcuFocus will provide sample source documents for each subject enrolled in the study.

13.2. SUBJECT CONFIDENTIALITY

Each study subject will be assigned a unique subject identification number at the time of enrollment. Study subject confidentiality will be maintained by recording only the subject's initials and ID number as means of identification on the source documents. Subject names may possibly be disclosed to AcuFocus, the IRB or regulatory agencies during inspection of study records. However, precautions will be taken to maintain confidentiality of medical records and personal information to the extent permitted by applicable laws and regulations including Health Insurance Portability and Accountability Act (HIPAA).

13.3. ELECTRONIC CASE REPORT FORM COMPLETION

Data for each subject will be recorded on to electronic case report forms (eCRFs) using the Medidata RaveX system. Detailed instructions are outlined in **Appendix J**. The study protocol should be used as a guide for all points of data for the study. Following study visits, investigative sites should complete data entry within one week (five working days) of the study visit.

13.4. STUDY SUMMARY

A final summary is to be provided by the investigator to AcuFocus and, if required, also to the responsible IRB. The summary should be provided within the IRB specified timeframe if required by the IRB or as designated by AcuFocus (typically within three months after the completion of the study).

14.0 MONITORING PROCEDURES

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

14.1. DATA MONITORING

In order to ensure a well-controlled study and to provide ongoing safety monitoring in accordance with applicable regulations, AcuFocus will follow specific data monitoring procedures.

Medidata RaveX EDC system will be used to transmit eCRF and questionnaire data from study sites to AcuFocus. Requests for data clarification will be handled through the same system.

Detailed instructions are provided in **Appendix J**. Efforts will be taken to maintain patient confidentiality throughout data transmission and database entry.

To minimize data omissions, errors and inconsistencies, AcuFocus will monitor data both internally and during monitoring visits at the sites (see details on site monitoring in **Section 13.2.2**). AcuFocus will also monitor for patterns of missing data to safe guard against missing data due to the negligence of investigator responsibility, because missing data could have the deleterious effect on trial integrity and credibility, and could also diminish the scientific value of all subjects' altruistic contributions.

Electronic data files will be structured such that it will be able to identify data omissions, errors and inconsistencies and/or issue reports on definable subgroups of the study population.

14.2. ADMINISTRATIVE MONITORING

Administrative monitoring procedures will ensure that subjects, study product, and forms can be traced and will allow monitoring of investigator progress and compliance.

14.2.1. DEVICE ACCOUNTABILITY

Complete accountability will be maintained by both AcuFocus (or designee) and the study site for the IC-8 IOL. IC-8 IOL accountability will include documentation of all IC-8 IOLs shipped to investigators, hospitals, or groups, including the date of shipment, IOL serial number and IOL power. During monitoring visits, AcuFocus will periodically review study site records to ensure IOL accounting compliance and to ensure complete IOL traceability (receipt, use, and disposition/return). All unused and unopened IC-8 IOLs must be returned to AcuFocus upon conclusion of the study.

The aspheric monofocal and monofocal toric IOLs will be taken from the site's own inventory and accounted for by their customary methods; AcuFocus will not maintain their accountability.

14.2.2. DEVICE RETURNS

In case of an investigational device deficiency (e.g., a broken injector during loading), a Device Deficiency Form must be completed and returned with both the IC-8 IOL and the injector system, including the original product label sticker to AcuFocus:

32 Discovery, Suite 200, Irvine, CA 92618

For cases of IC-8 IOL removal or exchange, obtain approval from medical monitor and AcuFocus before procedure, and contact AcuFocus for instructions for device returns.

14.2.3. SITE MONITORING PLAN

Prior to performing any study procedures, the requirements of the study and reporting mechanisms will be explained to each investigator at study initiation, conducted either on-site at the study site, remotely (e.g., teleconference), or at a formal investigator meeting. When necessary, a site evaluation visit may be performed prior to study initiation to assess the adequacy of the site to perform the study for sites that have not worked with AcuFocus

previously, or have undergone significant changes, or have not been visited in the past year. At a minimum, a study initiation visit will be performed.

For the duration of the study, source data verification will be conducted through on-site visits or remotely to monitor compliance to this protocol for each study site. Sites will be visited at least annually during the study or more often as needed, depending on site enrollment progress, data collection and eCRF completion, exam visit compliance, occurrence of adverse events, study duration, etc. During a monitoring site visit, the data submitted to AcuFocus will be audited against subject medical charts and source documents to assure complete and accurate reporting; the only exception is when data are automatically transmitted from the CTS system to the EDC, in which case these data do not require routine monitoring. For automatically transmitted data, periodical auditing of the data transmission process should be conducted annually to ensure the software and/or hardware for this process functions properly. The subject files will also be reviewed to ensure that all adverse events have been reported in a timely manner. It is expected that a minimum of 10% of the subject data (e.g. 100% of the records for 10% of the subjects) at each site will be reviewed in this manner during each monitoring visit. If significant problems are revealed, the percentage of records reviewed in total may be increased to 100% of the subjects at the discretion of the AcuFocus personnel in attendance. Additionally, it is during these interim monitoring visits that IOL accountability will be checked. At study completion, a final close-out visit will be conducted for each site to finalize any outstanding issues.

AcuFocus personnel will monitor all clinical studies in a manner consistent with applicable health authority regulations and the clinical research standards adopted by AcuFocus. Study monitoring will involve the following elements:

- AcuFocus personnel may meet with investigator(s) prior to the initiation of the study to review the adequacy of the subject population, facilities, and equipment with respect to the needs of the study, and to familiarize the investigator with the study protocol.
- AcuFocus personnel may meet with the investigator(s) at the time study subjects begin to be enrolled to ensure that subjects are being properly selected and that study data are being correctly recorded.
- AcuFocus personnel may visit the study site at any time during the study to review investigator study files and subject files including source documents and eCRFs.
- Interim monitoring visits and telephone consultation will occur as necessary during the course of the study to ensure the proper progress and documentation of the study findings.

14.3. SAFETY MONITORING

The medical monitor(s) will review results throughout the study to ensure the continued safety of the investigational device and to ensure that no subjects are exposed to unreasonable risk. The

medical monitor(s) will be notified of SAE and UADE reports through emails as well as other significant safety findings through periodic reports. The medical monitors will be available to answer all questions from investigators. The medical monitors, as well as any other qualified personnel designated by AcuFocus, may also review all reports on the progress of the study (at enrollment and at key postoperative visits). Care will be taken to ensure analyses/reports are not disseminated to investigators/site personnel.

15.0 PUBLICATIONS

AcuFocus, the Sponsor of this evaluation, has a proprietary interest in this evaluation. AcuFocus will have the final decision regarding the publication of any manuscript until the IOL is marketed. Under no circumstances shall the investigator(s) or center personnel publish or disclose AcuFocus' confidential information concerning the evaluation, including the clinical data, without prior written approval from AcuFocus. Authorship will be determined by AcuFocus, based on contribution to the study and enrollment, and established prior to submission of a manuscript.

16.0 RECORD RETENTION

All study-related correspondence, subject records, consent forms, authorization for use/disclosure of health information form, records of the distribution and use of all investigational products, and original source documents should be maintained on file by the investigative site.

The investigator must maintain and have access to the following essential documents for a minimum of five years (or according to local laws and regulations) after completion of the study or until the sponsor informs the site as to when these documents no longer need to be retained:

- All source documents
- All adverse event information (adverse event forms, follow-up letters, etc.)
- Study product supply records/inventory
- IRB and regulatory approval documentation
- Study Correspondence (paper or electronic)
- Site visit documentation
- Protocols and the reason for any deviations from the protocol
- Subject logs
- Completed patient informed consent forms
- Subject medical chart/clinic notes

AcuFocus requires notification in writing 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.

17.0 TERMINATION OF THE INVESTIGATION

The clinical investigation will be suspended in the event of unexpectedly high levels of complications and/or the occurrence of adverse events that are unexpected in nature and/or severity. An evaluation of causality will be made to determine the relationship to the investigational IOL. If causality is not shown to be related to the investigational IOL, the study may be resumed in accordance with the IRB and regulations of the governing authorities. The study will be terminated if causality is shown to be related to the investigational IOL.

The clinical investigation will be suspended by AcuFocus if any of the following conditions occur:

- In the event of severe and alarming adverse events that have not been previously anticipated in nature and/or severity
- Government agencies or IRB, upon review of clinical investigation data and/or adverse event reports, find the level of complications and/or adverse events unacceptable for continuation of the investigation
- Unacceptable clinical performance of the investigational IOL (i.e., decreased visual acuity results, unacceptable incidence, bother or intensity of subjective visual symptoms, etc.) as deemed by AcuFocus and/or the Medical Monitors

AcuFocus may stop the study at any time for reasons it determines appropriate. However, no suspension of the study will be made to disadvantage the subjects participating in the study. Following suspension of the study for any reason, all subjects who have already received an investigational IOL will continue to be followed through completion of the 12-month postoperative course.

18.0 DATA ANALYSIS METHODS

This section (**section 18.0 through 18.4**) highlights the key statistical methods and analyses planned for this study. The SAP includes details for all statistical methods, plans, adverse events reporting methods, and sample size calculations for the study.

Some key data and analysis conventions include the following:

For the primary and secondary effectiveness endpoints, the six-month postoperative visit will be the primary analysis time point unless otherwise noted. For the primary safety endpoints, the 12-month study visit will be the primary analysis time point.

Binocular safety and effectiveness analyses will compare the test group and the control group. Monocular safety and effectiveness analyses will compare the IC-8 IOL eyes and the monofocal fellow eyes within the test group.

All co-primary effectiveness and safety endpoints have to be met to claim overall effectiveness and safety success. There is one secondary effectiveness endpoint regarding the tolerance to astigmatism in IC-8 IOL eyes, and this endpoint will only be tested when all co-primary effectiveness endpoints have been achieved. Under this plan, type I error rates will be controlled at a significance level of 0.05 per individual hypothesis without adjustment for multiplicity under any family. Other statistical comparisons in the additional analyses and supportive analyses should not be used for the purpose of claims.

18.1. ANALYSIS POPULATION

For the primary effectiveness endpoints, the primary analysis population will be an ITT (Intent-to-Treat) analysis. The ITT population includes all subjects who are fully enrolled and are binocularly implanted in the study. For the secondary effectiveness endpoint, the primary analysis population will be a mITT (modified Intent-to-Treat) analysis for all eyes implanted with IC-8 IOL and achieving BCDVA 20/25 or better. For eyes that do not have data available at the 3-, 6- or 12-month visits, data will be imputed according to the imputation methods specified in the SAP.

A Per-Protocol (PP) analysis will also be performed on the primary and secondary effectiveness endpoints to support the primary ITT analysis. The PP population will include eyes from binocularly implanted subjects, evaluated within the proper study interval and without major protocol deviations as determined prior to database lock, and evaluated at least two weeks after any SSIs. Major protocol deviations to be excluded from PP analysis are: those related to inclusion, exclusion or qualification criteria, and/or those that have the potential to either positively or negatively affect the primary and secondary study endpoints, including uncorrected or distance-corrected visual acuities, refraction, contrast sensitivity, and are unrelated to the study procedure or the study device; and they will be specified prior to database lock.

PP analyses will only include available data at the time of analysis (i.e., no data imputation). For the primary effectiveness endpoints, the PP population is usually a subset of the ITT population; for the secondary effectiveness endpoint, the PP population is usually a subset of the mITT population.

For all key safety endpoints, the primary analysis population will be the safety analysis population. The safety population will consist of all subjects who complete enrollment and have been bilaterally implanted and those subjects not successfully implanted with the IC-8 IOL but for whom the IC-8 IOL touched the eye. Safety analyses will only include available data at the time of analysis (i.e., no data imputation). Reporting of cumulative complications (occurring at any time postoperative) will include data from all subjects in the safety population. Test subjects who have undergone the IC-8 IOL surgery with attempted but failed implantation will be followed until all ocular adverse events are resolved or stable before being exited from the study, and they will be counted in the safety population.

The safety population (with no imputation) will also be used for reporting of other postoperatively measured clinical parameters that are not discussed as part of the key effectiveness or safety endpoints.

The primary reporting will be on IC-8 IOL eyes and fellow eyes in the test group or binocular outcomes from both test and control groups. However, key data such as visual acuity, refractive error, medical/lens complications and adverse events will also be reported separately for first and second eyes in the control group.

Besides the ITT (or mITT) and PP populations, key effectiveness outcomes and key safety outcome of BCDVA may also be reported for best-case subjects where appropriate. A best-case subject is defined in ISO 11979-1:2012 as a subject with no preoperative ocular pathology, no macular degeneration detected at any time, and no previous surgery for the correction of refractive errors. In this study, a best-case subject should also have no significant macular pathology at any time. Both eyes must meet the best-case criteria for inclusion in the best-case analysis.

Subjects who are disqualified prior to second-eye implantation will not be counted toward the study cohort or any analysis population. For the disqualified subjects, a listing of UCDVA and BCDVA at preoperative and before study exit will be tabulated, as well as any adverse events; no other analysis will be performed.

In addition to the above analysis populations, additional best-case analyses and exploratory subgroup analyses may also be performed as specified in the SAP.

18.2. EFFECTIVENESS ANALYSES

All co-primary effectiveness endpoints need to be achieved to claim overall effectiveness success. Therefore no multiplicity adjustment is necessary for primary effectiveness endpoints. The secondary effectiveness endpoint will be tested after the primary effectiveness endpoints have been achieved. The secondary effectiveness endpoint needs to be achieved to support the astigmatism tolerance claim. For the primary effectiveness endpoints, the primary analysis population will be the ITT analysis population. For the secondary effectiveness endpoint, the primary analysis population will be a mITT analysis population. The PP analysis population will also be used on the key effectiveness endpoints to support the primary ITT analyses.

18.2.1. CO-PRIMARY EFFECTIVENESS ENDPOINTS

1. Binocular uncorrected intermediate visual acuity (UCIVA) (at 6 months):
   a. The mean acuity from the test group is statistically superior to the mean acuity from the control group. The comparison between test and control groups for mean binocular UCIVA (logMAR) will be performed using a two-sample t-test at $\alpha = 0.05$ (two-sided). The null hypothesis is that the mean acuity for the test group is greater (i.e., worse) than or equal to that for the control group. The alternative hypothesis is

that the mean for the test group is less (i.e., better) than that for the control group. Formally put as follows:

$$H_0: \mu_T \geq \mu_C$$
$$H_A: \mu_T < \mu_C$$

Where μ_T is the mean logMAR acuity from the IC-8 test group and μ_C is the mean logMAR acuity from the control group.

The statistical success criterion is when H_0 is rejected by a p-value less than 0.05, demonstrating the mean binocular UCIVA from the test group is statistically superior to the mean binocular UCIVA from the control group.

b. At least 50% of test subjects achieve 0.1 or better logMAR and at least 25% higher than the control subjects [clinical success criteria].

2. Binocular uncorrected near visual acuity (UCNVA) (at 6 months):

a. The mean acuity from the test group is statistically superior to the mean acuity from the control group. The comparison between test and control groups for mean binocular UCNVA (logMAR) will be performed using a two-sample t-test at $\alpha = 0.05$ (two-sided). The null hypothesis is that the mean acuity for the test group is greater (i.e. worse) than or equal to that for the control group. The alternative hypothesis is that the mean for the test group is less (i.e. better) than that for the control group. Formally put as follows:

$$H_0: \mu_T \geq \mu_C$$
$$H_A: \mu_T < \mu_C$$

Where μ_T is the mean logMAR acuity from the IC-8 test group and μ_C is the mean logMAR acuity from the control group.

The statistical success criterion is when H_0 is rejected by a p-value less than 0.05, demonstrating the mean binocular UCNVA from the test group is statistically superior to the mean binocular UCNVA from the control group.

b. At least 50% of test subjects achieve 0.3 or better logMAR and at least 25% higher than the control subjects [clinical success criteria].

3. Binocular uncorrected distance visual acuity (UCDVA) (at 6 months):

a. The mean acuity from the test group is non-inferior to the mean acuity from the control group using a margin of 0.1 logMAR. The comparison between test and control groups for mean binocular UCDVA (logMAR) will be performed using a t-test for non-inferiority at $\alpha = 0.05$ (one-sided). The null hypothesis is that the mean acuity for the test group is inferior to the control group by 0.1 logMAR or more. The alternative hypothesis is that the mean acuity for the test group is inferior to the control group by less than 0.1 logMAR. Formally put as follows:

$$H_0: \mu_T - \mu_C \geq 0.1$$
$$H_A: \mu_T - \mu_C < 0.1$$

Where μ_T is the mean logMAR acuity from the IC-8 test group and μ_C is the mean logMAR acuity from the control group.

The statistical success criterion is when H_0 is rejected by a p-value less than 0.05, demonstrating the mean binocular UCDVA from the test group is statistically non-inferior to the mean binocular UCDVA from the control group using a margin of 0.1 logMAR.

b. At least 50% of test subjects achieve 0.1 or better logMAR [clinical success criteria].

4. Monocular distance-corrected intermediate visual acuity (DCIVA) of the IC-8 IOL eyes (at 6 months):

a. The mean acuity of the IC-8 IOL eyes is statistically superior to the fellow control eyes in the test group. The comparison between IC-8 IOL eyes and fellow eyes in the test group for mean monocular DCIVA (logMAR) will be performed using a two-sample t-test at $\alpha = 0.05$ (two-sided). The null hypothesis is that the mean acuity for the IC-8 IOL eyes is greater (i.e., worse) than or equal to that for the fellow eyes. The alternative hypothesis is that the mean for the IC-8 IOL eyes is less (i.e., better) than that for the fellow eyes. Formally put as follows:

$$H_0: \mu_T \geq \mu_C$$
$$H_A: \mu_T < \mu_C$$

Where μ_T is the mean logMAR acuity from the IC-8 eyes and μ_C is the mean acuity from the fellow eyes.

The statistical success criterion is when H_0 is rejected by a p-value less than 0.05, demonstrating the mean DCIVA from IC-8 eyes is statistically superior to the mean DCIVA from the control eyes.

b. At least 50% of IC-8 IOL eyes should achieve DCIVA of logMAR 0.2 or better [clinical success criteria].

5. Monocular photopic distance-corrected depth of defocus (measure only negative direction from zero) of the IC-8 IOL eyes (at 3 months):

- The mean depth of focus from IC-8 IOL eyes is at least 0.5 D greater than the mean from the fellow control eyes at 0.2 logMAR visual acuity threshold [clinical success criteria]. There is no specific statistical success criterion.

18.2.2. SECONDARY EFFECTIVENESS ENDPOINT

There is one secondary effectiveness endpoint in the study, which is assessing tolerance to astigmatism in IC-8 IOL eyes at 3 months (analysis done on IC-8 IOL eyes with

BCDVA 20/25 or better) by comparing eyes with 1.0 to 1.5 D of preoperative corneal astigmatism (Astigmatism Group 2) to eyes with < 1.0 D of preoperative corneal astigmatism (Astigmatism Group 1):

a. The mean UCDVA from Astigmatism Group 2 is non-inferior to that from Astigmatism Group 1 using a margin of 0.12 logMAR (equivalent to 6 letters on ETDRS chart). The comparison between Astigmatism Group 2 and Astigmatism Group 1 for the mean monocular UCDVA (logMAR) will be performed using a t-test for non-inferiority at $\alpha = 0.05$ (one-sided). The null hypothesis is that the mean acuity in Astigmatism Group 2 is inferior to Astigmatism Group 1 by 0.12 logMAR or more. The alternative hypothesis is that the mean acuity in Astigmatism Group 2 is inferior to Astigmatism Group 1 by less than 0.12 logMAR. Formally put as follows:

$$H_0: \mu_T - \mu_C \geq 0.12$$

$$H_A: \mu_T - \mu_C < 0.12$$

Where μ_T is the mean logMAR acuity from Astigmatism Group 2 and μ_C is the mean acuity from Astigmatism Group 1.

The statistical success criterion is when H_0 is rejected by a p-value less than 0.05, demonstrating the mean monocular UCDVA from Astigmatism Group 2 is statistically non-inferior to the mean monocular UCDVA from Astigmatism Group 1 using a margin of 0.12 logMAR.

b. Scatter plot and regression analysis will be generated to depict the mean uncorrected visual acuities (separately for UCDVA, UCIVA and UCNVA) as a function of preoperative corneal astigmatism.

c. No claim will be made with regard to comparing IC-8 IOL to the monofocal or monofocal toric IOL.

18.2.3. PROPENSITY SCORE ANALYSIS

As a supplemental analysis for all primary endpoints, propensity score methods will be used to adjust for potential imbalance in measured baseline characteristics between the IC-8 and control patients. All primary analyses described in **section 18.2.1** will be repeated as a stratified analysis, using propensity score quintiles to partition the patients into five strata. Results from these analyses will be reported by stratum and overall. Details are specified in the SAP.

18.2.4. ADDITIONAL EFFECTIVENESS ANALYSES

1. Compare mean monocular uncorrected distance (UCDVA), intermediate (UCIVA) and near (UCNVA) visual acuity of the IC-8 eyes to the fellow control eyes.

2. Binocular +0.75 D Distance Corrected Visual Acuity compared between the test group and the control group: +0.75 D distance correction will be achieved by correcting all eyes in both groups with their best distance-corrected refraction and then placing a +0.75 D lens in front of the IC-8 IOL eyes in the test group and in front of the second eyes in the monofocal control group.
    a. Binocular +0.75 D Distance Corrected Intermediate Visual Acuity (+0.75 DCIVA): Proportion of subjects achieving 20/25 or better in the test group is at least 25% more than the control group.
    b. Binocular +0.75 D Distance Corrected Near Visual Acuity (+0.75 DCNVA): Proportion of subjects achieving 20/40 or better in the test group is at least 25% more than the control group.
    c. Binocular +0.75 D Distance Corrected Distance Visual Acuity (+0.75 DCDVA): Proportion of subjects achieving 20/25 or better in the test group is not less than the control group by more than 10%.
    d. The monocular visual acuities from the IC-8 IOL eyes in the test group will be similarly compared to the second eyes in the control group.
3. Supportive analyses:
    a. The monocular co-primary endpoint analyses on DCIVA and depth of focus will be repeated by comparing IC-8 IOL eyes to the second eyes in the control group to support the primary endpoint analyses.
    b. The co-primary endpoint analyses on binocular UCDVA, UCIVA, UCNVA and monocular DCIVA will be repeated at 12 months to support the primary endpoint analyses performed at 6 months.
    c. The secondary endpoint on tolerance to astigmatism in IC-8 IOL eyes is repeated on the postoperative refractive cylinder with the same grouping and test to support the results from preoperative corneal astigmatism and to check the influence from postoperative refractive cylinder on the effectiveness of the device.

18.3. SAFETY ANALYSES

All co-primary safety endpoints need to be achieved to claim overall safety success. Therefore no multiplicity adjustment is necessary for primary safety endpoints. For all key safety endpoints, the primary analysis population will be the safety analysis population.

18.3.1. CO-PRIMARY SAFETY ENDPOINTS

1. Monocular BCDVA in the IC-8 IOL eyes (at 12 months):
    a. The mean BCDVA from the IC-8 IOL eyes is non-inferior to that from the fellow control eyes using a margin of 0.1 logMAR. The comparison between IC-8 IOL eyes and fellow eyes for mean monocular BCDVA (logMAR) will be performed using a t-test for non-inferiority at $\alpha = 0.05$ (one-sided). The null hypothesis is that the mean acuity for the IC-8 IOL eyes is inferior to the fellow eyes by 0.1 logMAR or more.

The alternative hypothesis is that the mean acuity for the IC-8 IOL eyes is inferior to the fellow eyes by less than 0.1 logMAR. Formally put as follows:

$H_0: \mu_T - \mu_C \geq 0.1$

$H_A: \mu_T - \mu_C < 0.1$

Where μ_T is the mean logMAR acuity from the IC-8 eyes and μ_C is the mean acuity from the fellow eyes.

The statistical success criterion is when H_0 is rejected by a p-value less than 0.05, demonstrating the mean BCDVA from the IC-8 eyes is statistically non-inferior to the mean BCDVA from the control eyes using a margin of 0.1 logMAR.

b. The proportion of IC-8 eyes achieving BCDVA 0.3 logMAR or better is not less than the safety and performance endpoints (SPE) rate listed in ISO 11979-7:2014 Table B.3. The comparison between the proportion for the IC-8 eyes and the SPE rate for posterior chamber IOL (92.5%) will be performed using the exact test based on binomial distribution at $\alpha = 0.05$ (one-sided). The null hypothesis is that the proportion for the IC-8 eyes is not less than 92.5%. The alternative hypothesis is that the proportion for the IC-8 eyes is less than 92.5%. Formally put as follows:

$H_0: p_T \geq 92.5\%$

$H_A: p_T < 92.5\%$

Where p_T is the proportion of IC-8 eyes achieving BCDVA 0.3 logMAR or better and 92.5% is the SPE rate for posterior chamber IOL.

The statistical success criterion is when H_0 is not rejected, i.e. the test result is a p-value greater than 0.05, demonstrating the proportion of IC-8 eyes achieving BCDVA 0.3 logMAR or better is not less than the SPE rate.

c. The proportion of best-case IC-8 eyes achieving BCDVA 0.3 logMAR or better is not less than the safety and performance endpoints (SPE) rate listed in ISO 11979-7:2014 Table B.4. The comparison between the proportion for the best-case IC-8 eyes and the SPE rate for posterior chamber IOL (96.7%) will be performed using the exact test based on binomial distribution at $\alpha = 0.05$ (one-sided). The null hypothesis is that the proportion for the best-case IC-8 eyes is not less than 96.7%. The alternative hypothesis is that the proportion for the best-case IC-8 eyes is less than 96.7%. Formally put as follows:

$H_0: p_T \geq 96.7\%$

$H_A: p_T < 96.7\%$

Where p_T is the proportion of best-case IC-8 eyes achieving BCDVA 0.3 logMAR or better and 96.7% is the SPE rate for posterior chamber IOL.

As specified in ISO 11979-7:2014, the statistical success criterion is when H_0 is not rejected, i.e. the test result is a p-value greater than 0.05, demonstrating the proportion of best-case IC-8 eyes achieving BCDVA 0.3 logMAR or better is not less than the SPE rate.

Note that a best-case subject is defined in Section 18.1 Analysis Population of this study protocol. For this analysis, only the IC-8 eye but not both eyes of a subject has to meet the best-case criteria.

2. Rates of ocular adverse events (the rate of adverse events are based on the proportion of eyes with events cumulative or persistent through database lock, as applicable):

   a. For each type of adverse event listed in the ISO 11979-7:2014 Table B.2, the rate for the IC-8 IOL eyes is not statistically greater than the SPE rate for that event. The comparison between the adverse event rate for the IC-8 eyes and the SPE rate for posterior chamber IOL for each adverse event will be performed using the exact test based on binomial distribution at $\alpha = 0.05$ (one-sided). The null hypothesis is that the adverse event rate for the IC-8 eyes is not greater than SPE rate. The alternative hypothesis is that the adverse event rate for the IC-8 eyes is greater than the SPE rate. Formally put as follows:

   $$H_0: p_T \leq \hat{p}$$

   $$H_A: p_T > \hat{p}$$

   Where p_T is the adverse event rate for the IC-8 eyes and $\hat{p}$ is the SPE rate, for each adverse event listed in ISO 11979-7:2014 Table B.2.

   As specified in ISO 11979-7:2014, the statistical success criterion is when H_0 is not rejected, i.e. the test result is a p-value greater than 0.05, demonstrating the adverse event rate for the IC-8 eyes is not greater than SPE rate. The statistical success criterion is equivalent to showing the one-sided 95% lower confidence limit of the rate is not greater than the historical control rate based on an exact binomial distribution.

   b. Descriptive statistics (mean, two-sided 90% confidence interval) for the rates of all key adverse events including but not limited to adverse events per ISO 11979-7:2014, adverse events that may be specifically related to the EDOF IOL design, e.g., related to the optical characteristics of the lens, and any other significant ocular adverse events. Summary statistics will be provided for the IC-8 eyes and fellow eyes in the test group, and for first eyes and second eyes in the control group.

3. Rate of IC-8 IOL removals due to visual/optical reasons (the rate is based on eyes with events, cumulative through 12 months):

Rate of removals due to visual/optical reasons in the IC-8 IOL eyes is < 3.1%. The one-sided 95% upper confidence limit of the rate (using exact binomial distribution) must be less than 3.1% to claim statistical success.

18.3.2. SECONDARY SAFETY ENDPOINT

There is one secondary safety endpoint in the study which is contrast sensitivity. Following Draft ANSI Z80-35 for Extended Depth of Focus Intraocular Lenses, monocular and binocular contrast sensitivity (photopic and mesopic with and without glare) in each eye and both eyes in the contrast sensitivity subgroup as measured by a computerized contrast sensitivity testing system at 6 months will be analyzed in the following manner (there is no specific hypothesis testing or success criterion):

a. Between-eye mean difference in log contrast sensitivity (logCS) between IC-8 IOL eyes and their fellow control eyes with two-sided 90% confidence interval on the mean difference at each spatial frequency.

b. Compare the mean binocular logCS between the test group and the control group with two-sided 90% confidence interval at each spatial frequency.

c. Provide descriptive statistics for the logCS for each eye and both eyes (mean, standard deviation, two-sided 90% confidence interval, median, 0^{th}, 25^{th}, 50^{th}, 75^{th}, and 100^{th} percentiles) and for each spatial frequency.

d. Using a computerized contrast sensitivity testing system should minimize the floor and ceiling effects in contrast sensitivity testing. However, in the event that a subject is unable to see a targeted spatial frequency at the highest contrast possible in the display (e.g., 100% contrast), the highest contrast or, equivalently, the lowest contrast sensitivity score will be given, preceded by the appropriate inequality symbol (< or >) to indicate that the actual sensitivity is below the given value. The number and percentage of subjects who cannot see any contrast will be recorded and tabulated for each spatial frequency to provide a qualitative extent of the bias. Descriptive tables will include a note that the corresponding mean values are biased upward and variability values are biased downward (using < and > symbols).

18.3.3. ADDITIONAL SAFETY ANALYSES

1. Monocular (measured in the IC-8 eyes in the test group the second eyes in the control group) and binocular low contrast (10%) uncorrected distance, intermediate and near visual acuities in the test group and control group at 6 months (to be performed in the contrast sensitivity subgroup with BCDVA 20/25 or better in each eye) will be analyzed in the following manner:

a. Descriptive statistics (mean, standard deviation, two-sided 95% confidence interval) and vision level distributions (20/20, 20/25, 20/32, 20/40, 20/50, 20/63, 20/80 or worse) for both test and control groups.
b. Comparison of mean UCDVA and mean BCDVA in the test group to mean BCDVA in the control group for monocular and separately for binocular visual acuities.
c. Comparison of mean UCIVA and mean DCIVA in the test group to mean DCIVA in the control group for monocular and separately for binocular visual acuities.
d. Comparison of mean UCNVA and mean DCNVA in the test group to mean DCNVA in the control group for monocular and separately for binocular visual acuities.

2. Descriptive statistics (mean, two-sided 90% confidence interval) for the rate of removals due to visual/optical reasons in the IC-8 eyes, fellow monofocal eyes, first eyes and second eyes in the monofocal control group.

18.4. DATA CONVENTIONS

Descriptive and summary statistics will typically include sample size (N), mean, standard deviation (SD), minimum (Min), and maximum (Max) as appropriate for continuous variables. For categorical data and some ordinal variables, the sample size, frequency and proportion will be computed. Each statistical comparison will be tested at two-sided $\alpha = 0.05$ unless otherwise specified. For continuous variables, statistical tests assuming normality will generally be used. However, the data will be reviewed to evaluate if the normality assumption is appropriate. If it is not, an appropriate transformation of the data (i.e., logarithmic) or the corresponding non-parametric tests may be used. Details for adverse event reporting, other data analysis not discussed in the protocol including stratification analysis and sensitivity analysis, sample size calculation and other statistical methods are specified in the SAP.

19.0 REFERENCES

1. Hawker MJ, Madge SN, Baddeley PA, Perry SR. Refractive expectations of patients having cataract surgery. J Cataract Refract Surg. 2005;31(10):1970-5.
2. Montés-Micó R, España E, Bueno I, Charman WN, Menezo JL. Visual performance with multifocal intraocular lenses: mesopic contrast sensitivity under distance and near conditions. Ophthalmology. 2004;111(1):85-96.
3. Gil MA, Varón C, Cardona G, Vega F, Buil JA. Comparison of far and near contrast sensitivity in patients symmetrically implanted with multifocal and monofocal IOLs. Eur J Ophthalmol. 2014;24(1):44-52.
4. Chiam PJ, Chan JH, Aggarwal RK, Kasaby S. ReSTOR intraocular lens implantation in cataract surgery: quality of vision. J Cataract Refract Surg. 2006;32(9):1459-63.
5. de Vries NE, Webers CA, Touwslager WR, Bauer NJ, de Brabander J, Berendschot TT,

Nuijts RM. Dissatisfaction after implantation of multifocal intraocular lenses. J Cataract Refract Surg. 2011;37(5):859-65.

6. Weeber HA, Meijer ST, Piers PA. Extending the range of vision using diffractive intraocular lens technology. Journal of Cataract & Refractive Surgery. 2015 Dec 31;41(12):2746-54.
7. Carones F. Residual Astigmatism Threshold and Patient Satisfaction with Bifocal, Trifocal and Extended Range of Vision Intraocular Lenses (IOLs). Open Journal of Ophthalmology. 2017 Jan 10;7(01):1.
8. Atchison DA, Smith G, Efron N. The effect of pupil size on visual acuity in uncorrected and corrected myopia. Am J Optom Physiol Opt. 1979;56(5):315-23.
9. Wang B, Ciuffreda KJ. Depth-of-focus of the human eye: theory and clinical implications. Surv Ophthalmol. 2006;51(1):75-85.
10. Dexl AK, Jell G, Strohmaier C, Seyeddain O, Riha W, Rückl T, Bachernegg A, Grabner G. Long-term outcomes after monocular corneal inlay implantation for the surgical compensation of presbyopia. J Cataract Refract Surg. 2015; 41(3):566-75.
11. Vilupuru S, Lin L, Pepose JS. Comparison of Contrast Sensitivity and Through Focus in Small-Aperture Inlay, Accommodating Intraocular Lens, or Multifocal Intraocular Lens Subjects. Am J Ophthalmol. 2015;160(1):150-62.
12. Grabner G, Ang RE, Vilupuru S. The Small-Aperture IC-8 Intraocular Lens: A New Concept for Added Depth of Focus in Cataract Patients. Am J Ophthalmol. 2015; 160(6):1176-1184.
13. Dick HB, Piovella M, Vukich J, Vilupuru S, Lin L, Clinical Investigators. Prospective multicenter trial of a small-aperture intraocular lens in cataract surgery. Journal of Cataract & Refractive Surgery. 2017 Jul 31;43(7):956-68.
14. Kretz FT, Müller M, Gerl M, Gerl RH, Auffarth GU. Binocular function to increase visual outcome in patients implanted with a diffractive trifocal intraocular lens. BMC Ophthalmol. 2015; 15:110.
15. Steinert RF, Aker BL, Trentacost DJ, Smith PJ, Tarantino N. A prospective comparative study of the AMO ARRAY zonal progressive multifocal silicone intraocular lens and a monofocal intraocular lens. Ophthalmology. 1999; 106(7): 1243–1255.
16. Cionni RJ, Osher RH, Snyder ME, Nordlund ML. Visual outcome comparison of unilateral versus bilateral implantation of apodized diffractive multifocal intraocular lenses after cataract extraction: prospective 6-month study. J Cataract Refract Surg. 2009; 35(6):1033-9.
17. MacRae S, et al. Special Report: American Academy of Ophthalmology Task Force Consensus Statement for Extended Depth of Focus Intraocular Lenses.Ophthalmology.2017 Jan;124(1):139-141
18. Masket S, Rorer E, Stark W, Holladay JT, MacRae S, Tarver ME, Glasser A, Calogero D, Hilmantel G, Nguyen T, Eydelman M. Special report: The American Academy of

Ophthalmology Task Force consensus statement on adverse events with intraocular lenses. Ophthalmology. 2017 Jan 1;124(1):142-4.

19. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005;140(3):509-16.
20. Hogan MJ, Kimura SJ, Thygeson P. Signs and symptoms of uveitis: I. Anterior uveitis. Am J Ophthalmol 1964;47:155–170.

APPENDIX A – CLINICAL EVALUATIONS

Clinical Evaluation	Illumination	Testing	Group	Preop	Op*	Day 1**	Wk 1**	Mon 1**	Mon 3	Mon 6	Mon 12
Ocular & Health History	N/A	N/A	Both	X		X	X	X	X	X	X
Cover Test	N/A	N/A	Both	X							
Sighting Eye Dominance	N/A	N/A	Both	X					X		
Pupil Size	Photopic Mesopic Dilated	Monocular (OD & OS) Monocular (OD & OS) Monocular (OD & OS)	Both	X X X					X X X[A]	X X	X X X
Swinging Flash Light Test	N/A	Monocular (OD & OS)	Both	X					X		
Biometry Measurements	N/A	Monocular (OD & OS)	Both	X							
Corneal Topography	N/A	Monocular (OD & OS)	Both	X						X	X
Uncorrected Distance Visual Acuity (UCDVA)	Photopic	Monocular (OD & OS) Binocular (OU)	Both	X X		M	M	M	M M	M M	M M
Uncorrected Intermediate Visual Acuity (UCIVA)	Photopic	Monocular (OD & OS) Binocular (OU)	Both						M M	M M	M M
Uncorrected Near Visual Acuity (UCNVA)	Photopic	Monocular (OD & OS) Binocular (OU)	Both	X X					M M	M M	M M
Manifest Refraction	Photopic	Monocular (OD & OS)	Both	X			M	M	M	M	M
Add (Near)	Photopic	Monocular (OD & OS)	Both							M	
Distance-Corrected Distance Visual Acuity (DCDVA)	Photopic	Monocular (OD & OS) Binocular (OU)	Both	X			M	M	M M	M M	M M
Distance-Corrected Intermediate Visual Acuity (DCIVA)	Photopic	Monocular (OD & OS) Binocular (OU)	Both						M M	M M	M M
Distance-Corrected Near Visual Acuity (DCNVA)	Photopic	Monocular (OD & OS) Binocular (OU)	Both						M M	M M	M M
Defocus Curve Test	Photopic	Monocular (OD & OS) Binocular (OU)	Both						M M		

Clinical Evaluation	Illumination	Testing	Group	Preop	Op*	Day 1**	Wk 1**	Mon 1**	Mon 3	Mon 6	Mon 12
+0.75 D Distance Corrected Distance Visual Acuity (+0.75 DCDVA)	Photopic	Monocular (2nd eye) Binocular (OU)	Both							M M	
+0.75 D Distance Corrected Intermediate Visual Acuity (+0.75 DCIVA)	Photopic	Monocular (2nd eye) Binocular (OU)	Both							M M	
+0.75 D Distance Corrected Near Visual Acuity (+0.75 DCNVA)	Photopic	Monocular (2nd eye) Binocular (OU)	Both							M M	
Near Stereoacuity (w/ UCNVA; & w/ DCNVA with Add)	Photopic	Binocular	Both							X	
Slit-Lamp Exam (SLE)	N/A	Monocular (OD & OS)	Both	X		X	X	X	X	X	X
IOL Centration & Tilt w/ SLE	N/A	Monocular (OD & OS)	Both			X	X	X	X	X	X
Toric IOL axis w/ SLE	N/A	Monocular (OD & OS)	Both			X[C]	X[C]	X[C]	X[C]	X[C]	X[C]
TBUT	N/A	Monocular (OD & OS)	Both	X					X	X	X
Corneal Staining	N/A	Monocular (1st eye) Monocular (2nd eye)	Both	X X			X	X[D]	X X	X X	X X
Intraocular Pressure	N/A	Monocular (OD & OS)	Both	X		X	X	X	X	X	X
Gonioscopy	N/A	Monocular (OD & OS)	Both	X						X	
Dilated Fundus Exam (BIO)	N/A	Monocular (OD & OS)	Both	X							X
Dilated Slit-lamp Exam	N/A	Monocular (OD & OS)	Both	X							X
Dilated Ocular Coherence Tomography (OCT)	N/A	Monocular (OD & OS)	Both	X							
Patient Reported Outcome Questionnaire(s)	N/A	N/A	Both	X					X	X	X
Non-directed Question	N/A	N/A	Both	X		X	X	X	X	X	X

Clinical Evaluation	Illumination	Testing	Group	Preop	Op*	Day 1**	Wk 1**	Mon 1**	Mon 3	Mon 6	Mon 12
CONTRAST SENSITIVITY SUBGROUP ONLY – CONTRAST SENSITIVITY AND LOW CONTRAST ACUITY TESTING											
Distance Contrast Sensitivity (w/ glare & w/o glare)	Photopic Mesopic	Monocular (OD & OS) Binocular (OU)	Both							M[A] M[A]	M[B] M[B]
10% contrast UCDVA	Photopic	Monocular (2nd eye) Binocular (OU)	Both							M[A] M[A]	M[B] M[B]
10% contrast UCIVA	Photopic	Monocular (2nd eye) Binocular (OU)	Both							M[A] M[A]	M[B] M[B]
10% contrast UCNVA	Photopic	Monocular (2nd eye) Binocular (OU)	Both							M[A] M[A]	M[B] M[B]
10% contrast DCDVA	Photopic	Monocular (2nd eye) Binocular (OU)	Both							M[A] M[A]	M[B] M[B]
10% contrast DCIVA	Photopic	Monocular (2nd eye) Binocular (OU)	Both							M[A] M[A]	M[B] M[B]
10% contrast DCNVA	Photopic	Monocular (2nd eye) Binocular (OU)	Both							M[A] M[A]	M[B] M[B]
RETINAL DIAGNOSTIC TESTING SUBGROUP ONLY – SUBGROUP-SPECIFIC RETINAL DIAGNOSTIC TESTING											
Undilated Threshold Visual Field Testing (Central 30-2)	Photopic	Monocular (OD & OS)	Test	X[A]					X[A]		
Dilated Ocular Coherence Tomography (OCT) Images	N/A	Monocular (OD & OS)	Test	X[A]					X[A]		
Dilated Fundus Photography	N/A	Monocular (OD & OS)	Test	X[A]					X[A]		

* Op (operative) visits are repeated for each eye's surgery and the associated tests are performed on that operated eye only.

** Day 1, Week 1 and Month 1 visits are repeated after each eye's surgery and the associated tests are performed on the most recently operated eye only.

[A] Subgroup testing only. Group sizes are specified in the statistical analysis plan.

[B] Repeated at the 12-month visit for those subjects that have had a posterior capsulotomy procedure after the 6-month visit.

[C] Repeated at postop visits if medically indicated as determined by investigator.

[D] Repeated at 1 month visit if needed.

X = tests to be performed by non-masked examiner; M = tests to be performed by masked examiner.

APPENDIX B - EQUIPMENT LIST

The following equipment will be supplied to a study 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. This equipment is to be returned to AcuFocus at the completion of the study.

- M&S CTS (including a laptop, a monitor, a tablet, glare source, mesopic filter, cart)
- Table for the CTS
- Glare source for CTS
- Randot Stereogram (if site does not have a Randot Stereogram)

Site should have the following to participate in the study:

- Corneal topographer
- Optical Coherence Tomographer

APPENDIX C - SLIT-LAMP EXAM RATINGS

The biomicroscopic slit-lamp exam should be performed by the same evaluator at each study visit. Adherence to the grading scales will improve consistency across study sites.

A. CATARACT GRADING*

None	0	No opacification
Mild	1+	Obscures 10% of intra-pupillary space
Moderate	2+	Obscures 10 to 50% of intra-pupillary space
Pronounced	3+	Obscures 50-90% of intra-pupillary space
Severe	4+	Obscures 90% of intra-pupillary space

***** Optometric Clinical Practice Guideline Care of The Adult Patient with Cataract (American Optometric Association- Reference Guide for Clinicians)

B. RATINGS OF AQUEOUS CELLS AND FLARE

The Standardization of Uveitis Nomenclature (SUN) grading scales are to be used to rate aqueous cells and flare.[18,19]

CELLS

The SUN Working Group Grading Scheme for Anterior Chamber Cells	
Grade	Cells in Field†
0	<1
0.5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	>50
†Field size is a 1 mm by 1 mm slit beam	

FLARE

The SUN Working Group Grading Scheme for Anterior Chamber Cells	
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

C. 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.

None	0	Normal transparency: a. No epithelial or sub-epithelial haziness b. No microcysts c. No stromal cloudiness
Trace	1+	a. Barely discernable localized epithelial or sub-epithelial haziness and/or b. 1 to 20 microcysts c. Barely discernable 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. Significant widespread epithelial or stromal cloudiness, giving dull glass appearance to corneal or numerous coalescent bullae (note number and location of bullae), and/or b. >100 microcysts or bullae, and/or c. Numerous striae (note number and location of striae or folds)

D. POSTERIOR CAPSULE STRIAE GRADING SCALE

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

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 the retina

E. POSTERIOR CAPSULE OPACIFICATION GRADING SCALE

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

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 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 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 pearls and fibrous scarring. Red reflex barely visible.

APPENDIX D – RETINAL EVALUATION SURVEY

Retinal Evaluation Survey (all subjects)

A. Please record any difficulty in performing retinal evaluation in each eye.

0 - No difficulty
1 - A little difficulty
2 - Moderate difficulty
3 - A lot of difficulty
4 - Extreme difficulty

BIO	Optic Disc		Macula		Mid-Periphery		Periphery	
	OD	OS	OD	OS	OD	OS	OD	OS
0 - No difficulty								
1 - A little difficulty								
2 - Moderate difficulty								
3 - A lot of difficulty								
4 - Extreme difficulty								

SLE	Optic Disc		Macula	
	OD	OS	OD	OS
0 - No difficulty				
1 - A little difficulty				
2 - Moderate difficulty				
3 - A lot of difficulty				
4 - Extreme difficulty				

B. Were you able to achieve stereoscopic view of the posterior pole?

Test	OD (Mark Yes/No)		OS (Mark Yes/No)	
BIO	Yes	No	Yes	No
SLE	Yes	No	Yes	No

Comments:

SD-OCT & Fundus Photography Investigator Evaluation Survey (subgroup testing only)

A. Please grade image quality of the SD-OCT images

1- Excellent - No blurring or obstruction of retinal details

2- Adequate - Some blurring or obstruction of the retinal details

3- Inadequate - Marked blurring or obstruction of the retinal details

OCT	Optic disc		Macula	
	OD	OS	OD	OS
1- Excellent				
2- Adequate				
3- Inadequate				

B. Please grade image quality of the fundus photos

Fundus Photos	☐ 4 Wide Field (4W-D) or ☐ Modified 7 Standard Fields (7M-D)	
	OD	OS
1- Excellent		
2- Adequate		
3- Inadequate		

APPENDIX E – RETINAL DIAGNOSTIC TESTING SUBGROUP INVESTIGATIONAL PLAN

The retinal diagnostic testing in the subgroup will follow the investigational plan and analysis plan specified below. Detailed methods and/or SOPs for training, analysis, reports will be provided by a reputable retinal image reading center.

SITE SELECTION

Three or four sites will be chosen based on the availability of the equipment necessary for conducting the testing.

QUALIFICATION OF THE SITES

Standardized testing methods from a retinal image reading center will be used for capturing images from dilated fundus exam and dilated OCT exam. One examiner and a potential backup examiner per site will be trained and certified by a retinal image reading center.

TRANSMISSION OF IMAGES

Images will be transmitted to the reading center's secure file sharing service. Image files (including raw image files) with all supporting documents should be exported from device to the reading center, but with all identifiable information redacted or masked. The files may be re-numbered or re-named for the purpose of masking.

GRADER(S) AT THE READING CENTER

The grader(s) at the reading center would be masked to the eye in which the investigational device has been implanted.

TIME POINT FOR DATA COLLECTION

Preoperative and 3-month postoperative visits.

DATA COLLECTION AND ANALYSIS

Image Quality

The grader would grade the quality of all images (SD-OCT and Fundus Photos) using the following grading scale or in accordance with the reading center's SOP:

- Excellent - No blurring or obstruction of retinal details
- Adequate - Some blurring or obstruction of the retinal details
- Inadequate - Marked blurring or obstruction of the retinal details

SD-OCT Images

The standard macula and optic nerve images will be analyzed for the following variables:

1. Signal Strength

2. Retinal nerve fiber layer (RNFL) thickness
3. Segmentation- Retinal thickness and thickness of individual retinal layers

NOTE: *If different OCT instruments are used to capture the images, software may be used to normalize the differences in measurements of the same variables from different instruments. This shall apply to raw image files supplied to the reading center and be conducted before image analysis is performed.*

Fundus Photos

The following images will be captured and graded for image quality and presence of any artifacts: 4 Wide Field (4W-D) or Modified 7 Standard Fields (7M-D)

Visual Field (SITA Standard 30-2 Test)

Undilated visual field testing will be performed in the subgroup preoperatively and postoperatively at 3 months in both eyes. Detailed instructions will be given to the subject prior to testing. Visual field retests will be necessary for all false positives, false negatives and fixation losses > 33%. Repeat visual fields (at the 6 month postoperative visit) are necessary for results with anomalous outcomes as determined by the investigator.

The following variables will be captured and analyzed for visual field testing.

1) Fixation loss
2) False positives & negatives
3) Visual field assessment for abnormalities
4) Mean deviation
5) Pattern standard deviation

Number 1 to number 3 above may be analyzed by a reading center by way of evaluating the visual field test print-outs; numbers 4 and 5 above may be collected in the EDC system and analyzed by AcuFocus.

Planned Analysis

The following comparisons will be made for the variables collected:

a. Between preoperative and 3-month postoperative visits
b. Between eyes within subject at the 3-month postoperative visit

APPENDIX F – VISUAL ACUITY TESTING USING CTS

Distance, intermediate and near visual acuities will be measured using the ETDRS chart presented on a self-calibrating monitor on the CTS, at 4 m for all distance tests, at 66 cm for all intermediate tests and at 40 cm for all near tests. In a folded lane, the test distance is measured as the sum of the distances from the mirror to the subject and from the subject to the chart. CTS system monitor luminance can be automatically calibrated to 85 cd/m^2 and ambient room conditions (~5 lux per M&S CTS system) are measured with the integrated luminance photometer. These conditions will be established at each site study initiation visit and verified at least biannually by the Sponsor.

General Instructions

- The examiner should take precautions to remind the subject not to squint at any time during vision testing.
- Each presentation will be randomized to eliminate the memorization effect.
- The subject responds with the smallest line where all five letters can be correctly identified and the technician enters the line number and presses "Submit"
- The chart then randomizes, setting the selected line to the top line and a pointer is shown at the next smaller line
- The subject is then asked to read this line and the number of correct letters is entered; the pointer moves to the next line
- The test continues until the subject is no longer able to correctly identify any letters within a line
- When the test is complete the results are reported in the standard ETDRS Letter Score, Visual Acuity equivalent and logMAR equivalent

General Instructions for Infinity-Adjusted Vision Testing

- For each vision test, infinity-adjusted refraction must be used according to the instructions in **Table 7** (Section **9.7** in the study protocol).

For more detailed instructions refer to the CTS manual.

APPENDIX G – MANIFEST REFRACTION

Manifest refraction will be performed using the CTS. For more detailed instructions refer to the CTS manual.

Beginning Approximate Refraction

The beginning approximate refraction will be plano for all eyes to facilitate masking.

INITIAL MANIFEST REFRACTION

1. Determine spherical lens power

The phoropter is placed and centered in front of the subject's pupils for each eye. The uncorrected visual acuity of each eye is assessed and noted. Subject should be instructed to look at the smallest line that is read well. Plus power lenses should be added until the visual acuity is reduced to 20/40 or 20/50. Then reduce the power by 0.25 D at a time until the subject can read the 20/20 or 20/16 line clearly. This assumes a spherical refractive error; if the subject has some astigmatism the best visual acuity may not be 20/20. This method leads to the best sphere refraction.

2. Refine cylindrical lens axis

The Jackson Cross Cylinder (JCC) lens is used to determine astigmatism. Start with the best spherical refraction in place and any cylindrical correction that is determined from the current prescription or keratometry.

NOTE: *If the initial approximate refraction is spherical (no cylindrical power), probe for cylinder by placing 0.25 D of cylinder power in the phoropter and checking the power at 45, 90, 135 and 180 degrees. If cylinder is accepted at any of these meridians, use this meridian as a starting point for the axis check. If cylinder power is rejected at all four principal meridians, the JCC is removed and the manifest refraction is purely spherical.*

Refine cylindrical axis then the power, then refine the axis again.

A target of an isolated rounded letter on the 20/30 line (or one line worse than the best acuity) is used. The cross cylinder is placed with the lens rotated so that the red and white markings are 45 degrees from the power meridian in the phoropter. The lens is flipped to present two views of the letter. Instruct the subject that both views may be blurred but they are to choose the better of the two or respond that the choices look the same. The lens should be flipped quickly and the subject should give their first impression rather than studying the two images.

If the phoropter is a plus cylinder phoropter, the cylinder axis is rotated toward the white dot when the cross cylinder is in the position of the clearest images (rotate toward the red dot when using a minus cylinder phoropter). This procedure is repeated until the subject reports no difference between the two choices.

3. Refine cylindrical lens power

To check the power of cylinder, the cross cylinder should then be rotated 45 degrees so that the colored dots line up with the axis in the phoropter. Repeat the same instructions; the subject reports which option is clearer or if the options look about the same. Again, flip the cross cylinder lens between two choices. For a minus-cylinder phoropter, if the clearer image is seen when the white dot is aligned with the cylinder axis, remove 0.25 D of cylinder power. If the clearer image occurs when the red dot is aligned with the cylinder axis, add 0.25 D of cylinder power. The endpoint is the least cylinder power that makes both images closest to being equal. During the power refinement process, maintain the spherical equivalent by adjusting the spherical power by +0.25 D for every 0.50 D of cylinder increase (and vice versa).

4. Refine final spherical power

Perform a final spherical power check by asking the subject to view the 20/20 line (or larger if 20/20 is not easily read). Add or remove spherical power in 0.25 diopter steps until the maximum plus sphere that provides the subject's best visual acuity achieved.

MANIFEST REFRACTION DETERMINATION WITH DUOCHROME TESTING

The manifest refraction is determined monocularly using the duochrome technique:

1. Complete the initial manifest refraction and dim the room illumination completely.
2. Select the projector's Red/Green filter with the appropriate target. The subject is asked to fixate on letters one line above their BCDVA, but no smaller than 20/25.
3. Have the subject compare the letters in the red/green sides and state which letters appear sharper, clearer or better focused **or** if both sides appear equally clear. (**DO NOT** ask if the letters are "better", "darker" or "brighter")
4. RED IS CLEARER: Place an additional 0.25 D of MINUS spherical power. Continue adding MINUS until subject reports equal clarity between sides or until the "green" side appears clearer and in better focus.
5. GREEN IS CLEARER: Place an additional 0.25 D of PLUS spherical power. Continue adding PLUS until subject reports equal clarity between sides or until the "red" side appears clearer and in better focus.
6. MANIFEST REFRACTION: The lens with which the letters on both red and green sides appear equally clear.
7. Remove the Red/Green filter and recheck BCDVA.

   Example:

   - Manifest refraction is -1.50 +0.75 x 180
   - RED is CLEARER
   - ADD MINUS lens in 0.25 D steps over the manifest refraction until subject reports "EQUALLY CLEAR" or "RED CLEAR"

- -2.25 +0.75 x 180 subject reports “RED CLEAR”
- -2.00 +0.75 x 180 subject reports “EQUALLY CLEAR”
- The manifest refraction is -2.00 +0.75 x 180.

APPENDIX H – DEFOCUS CURVE TESTING

Defocus curve testing will be done using the CTS computerized testing system. For detailed instructions refer to CTS user manual. The laptop will show the test, distance, light level and the correction needed for the testing.

Defocus curves will be performed monocularly and binocularly using ETDRS charts in the CTS calibrated for 4-meter test distance in standard photopic conditions, with the best-corrected distance manifest refraction.

A defocus curve should be obtained by using the manifest refraction and measuring the visual acuity between +2.00 D and -5.00 D in 0.5 D defocus steps, except in the region from +0.50 D through -0.50 D, which should be done in 0.25 D steps. The examiner will progressively change the defocus in 0.50 D steps from +2.00 D to +0.50 D, then in 0.25 D steps from +0.50 D to -0.50 D, then in 0.50 D steps from -0.50 D to -5.00 D, while measuring visual acuity at each successive defocus step. No infinity adjustment to refraction is needed for defocus curve testing. Letters will be randomly presented to avoid memorization by CTS automatically.

The test heading on the laptop and the tablet will indicate which lens to use. With the lens in place the tester will begin the vision testing. The tablet will display all lines from 20/200 to 20/10.

General Instructions:

- The examiner should take precautions to remind the subject not to squint at any time during vision testing.
- Each presentation is automatically randomized to eliminate the memorization effect.
- The subject responds with the smallest line where all five letters can be correctly identified and the technician enters the line number and presses “Submit”
- The chart then randomizes, setting the selected line to the top line and a pointer is shown at the next smaller line
- The subject is then asked to read this line and the number of correct letters is entered; the pointer moves to the next line
- The test continues until the subject is no longer able to correctly identify any letters within a line
- When the test is complete the results are reported in the standard ETDRS Letter Score, Visual Acuity equivalent and logMAR equivalent

For more detailed instructions refer to the CTS manual.

APPENDIX I – CONTRAST SENSITIVITY TESTING

Contrast sensitivity testing will be done using the CTS computerized testing system. For detailed instructions refer to CTS user manual. Both photopic and mesopic with and without glare conditions will be tested. The photopic spatial frequencies tested will be 3 cycles/degree to 18 cycles/degree and mesopic spatial frequencies tested will be 1.5 cycles/degree to 12 cycles/degree.

The system will present a series of targets that determine the CSF for each spatial frequency. A white dot will appear on the laptop screen when a target is presented. Four demonstration targets will be shown alternately. Instruct the subject to answer which direction the target is pointing (a laminated card is included to hand the subject to aid in their recognition). The testing will begin with the highest spatial frequency, which will be is 18 cpd for photopic and 12 cpd for mesopic testing. The test will finish with the lowest spatial frequency, which is 3 cpd for photopic and 1.5 cpd for mesopic testing. Glare will activate and CSF will be measured for same spatial frequencies.

General Instructions

- The testing distance per M&S CTS instruction is at 8 feet for contrast sensitivity.
- Subjects should wear their best spherocylindrical refractive correction for the testing. ***NOTE:*** *Proper correction of astigmatism is particularly important for the CTS linear grating test, so that all grating orientations will be equally visible.*
- Infinity adjustment to refraction is not needed for linear contrast sensitivity testing.
- The most efficient testing order timewise is: 10 min. dark adaptation, mesopic without glare, mesopic with glare, photopic without glare, photopic with glare. This testing paradigm has been pre-programmed in the CTS.
- Daily luminance calibration must be performed to verify that the preset glare levels slightly raise normal thresholds under study conditions. This testing is “fixed” and pre-programmed in the CTS as part of the daily luminance calibration detailed in the CTS user manual. If the glare levels cause either no threshold elevation or too much threshold elevation (indicated by the results of the calibration testing) contact M&S® Technologies for assistance.
- Daily luminance calibration must be performed, and environmental luminance verified by the CTS photometer to ensure there are no light sources or reflecting surfaces that have higher luminance than the test chart from the subject’s vantage point. Ambient luminance should be tested in a dim exam room with no light sources positioned between the subject and CTS or behind the CTS. If a higher luminance is recorded during calibration, as indicated by the CTS, lighting should be adjusted and testing repeated until luminance is within the accepted range.

APPENDIX J- DATA ENTRY AND CORRECTION INSTRUCTIONS

Electronic Case Report Forms will be completed using the Medidata RaveX system. Medidata RaveX is an electronic clinical data management system designed to streamline data collection, database entry, data queries and resolution of data clarifications. Medidata RaveX allows for sites to electronically input data from source documents and questionnaires. Every means will be taken to maintain patient confidentiality throughout data transmission and database entry.

For data collection, all data fields on the paper source documents and other required testing printouts should be entered into the electronic database eCRFs for the study in Medidata RaveX system. Each site will only have access to general information for the study and the data for their own site. All personnel, at investigational sites and AcuFocus, performing data entry or data review must perform the required Medidata RaveX training module(s) and obtain user credentials prior to performing these activities. Individual credentials must not be shared with other users and must be stored in a secure location. A copy of the training certificate must be filed in appropriate study files for each user.

RaveX EDC will accept automatically transmitted data via internet from the M&S CTS system for all vision and contrast sensitivity tests conducted with the CTS, including all visual acuities, contrast sensitivity and defocus curve data. Manifest refraction will be performed using the CTS but will be manually recorded in the source documents by the masked examiner and then entered into the EDC. In the unlikely event that the automatic data transmission mechanism in the CTS is non-functioning, the site should first check if the internet connection is available and functioning and should re-attempt to transmit the data once proper internet connection is restored. If the issue persists, the site should contact M&S immediately to resolve the issue. If M&S cannot resolve the issue in a timely manner, the site should notify AcuFocus and use source documents for visual acuities and defocus curve data as an alternative method of data collection.

Following study visits, investigative sites should complete data entry within one week (five working days) of the study visit. For data verification, correction or clarification, a Clinical Research Associate (CRA) will review the data to ensure all data are complete and logical. The CRA will then query any data field that requires clarification or correction through Medidata RaveX for resolution.

Open data queries should be resolved by the site within 10 business days. All necessary corrections are to be made directly on the original source documents and entered on to the eCRF in the Medidata RaveX study database. All data changes and reasons for change are logged in Medidata RaveX.