SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Corneal inlay

Device Trade Name: KAMRA® inlay

Device Procode: LQE

Applicant's Name and Address: AcuFocus™, Inc.
32 Discovery, Suite 200,
Irvine, CA 92618

Date(s) of Panel Recommendation: June 6, 2014

Premarket Approval Application (PMA) Number: P120023

Date of FDA Notice of Approval: April 17, 2015

II. INDICATIONS FOR USE

The KAMRA® inlay is indicated for intrastromal corneal implantation to improve near vision by extending the depth of focus in the non-dominant eye of phakic, presbyopic patients between the ages of 45 and 60 years old who have cycloplegic refractive spherical equivalent of +0.50 D to -0.75 D with less than or equal to 0.75 D of refractive cylinder, who do not require glasses or contact lenses for clear distance vision, and who require near correction of +1.00 D to +2.50 D of reading add.

III. CONTRAINDICATIONS

The device should not be used under the conditions listed in this section, because the risk of use clearly outweighs any possible benefit.

DO **NOT** implant the KAMRA® inlay if the patient:

- has severe dry eye syndrome;
- has an active eye infection or inflammation;
- has keratoconus or is a keratoconus suspect;
- has an abnormal corneal topographic map of the eye to be implanted;
- has a corneal thickness that does not allow for a minimum of 250 microns of stromal bed thickness below the pocket;
- has a herpes eye infection or problems resulting from a past infection;
- has uncontrolled glaucoma;
- has uncontrolled diabetes; or
- has active autoimmune or connective tissue disease.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the KAMRA® inlay labeling.

V. DEVICE DESCRIPTION

The KAMRA® inlay which is implanted intrastromally is an annulus (ring shaped device) that is 3.8mm in diameter, with a 1.6mm diameter hole in the center. It is constructed of a single piece of Polyvinylidene Fluoride (PVDF) formulated with carbon black pigment. The inlay is 6 microns thick and has a spherical radius of 7.5mm to mimic the curvature of the stromal bed of the cornea. The intention of the design is to allow the inlay to fit in a corneal pocket and allow the anterior surface of the pocket to "drape" over the inlay easily and minimize topographic changes on the anterior surface of the eye.

The KAMRA® inlay is perforated with 8,400 holes ranging in diameter size from 5.5 microns to 11.5 microns. Fifty microns of the edge of the outer and inner rims are not perforated to promote the mechanical strength of the inlay while the 8,400 perforations provide a means of transport for metabolites through the implant to maintain the health and integrity of the cornea.

The opaque annulus of the inlay reduces the aperture or opening of the eye, which improves near and intermediate vision by providing an increased depth of focus in the implanted eye. The KAMRA® inlay represents technology based on the concept of small aperture optics. In cameras, depth of focus is increased by reducing the opening through which light enters. This concept has been applied to the human eye with the KAMRA® inlay.

If an opaque disc with a small opening in the center is placed in front of the eye, the peripheral rays will be obscured while the central rays pass unaffected. Since peripheral rays enter the eye at a larger angle, they create a larger blur circle at the retinal image plane. Eliminating these peripheral rays reduces the size of the blur circle, improving image resolution.

The KAMRA® inlay is intended for monocular implantation in the non-dominant eye to assure that distance vision is not significantly compromised. The KAMRA® inlay does not work by conventional monovision. Although the implant is placed in only one eye, there is no change made in the refraction of either eye. The inlay achieves near vision through depth of focus instead of multiple powers.

The KAMRA® inlay is supplied sterile in a plastic case inside two (inner and outer) Tyvek PE/PET peel pouches. The double pouched configuration is then enclosed in a paper box with appropriate labeling.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives to improve near vision in the patient population for whom the KAMRA® inlay is intended.

Available alternatives include:

- Reading glasses - bifocal, trifocal, monofocal, and/or progressive glasses
- Monovision with Contact lenses - also bifocal, trifocal and multifocal contact lenses
- Conductive Keratoplasty (CK)
- Monovision LASIK (laser assisted in situ keratomileusis).

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The KAMRA® inlay has been marketed outside the US since 2009 and is available in 50 countries, including Australia, Austria, Canada, Chile, Hungary, Japan, Jordan, S.Korea, Lebanon, Malaysia, Netherlands, New Zealand, Oman, Saudi Arabia, Singapore, Turkey, and the United Arab Emirates. The KAMRA® inlay has not been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

It is possible that the KAMRA® inlay implantation may make the patient's best-corrected distance vision and/or uncorrected distance vision worse than it was before surgery.

In some cases, after receiving the KAMRA® inlay, patients may still require glasses or contact lenses for some activities, such as reading small print or reading in dim lighting.

The following risks are described similarly to the way they are presented in the patient labeling, for the most part, for ease of understanding:

Vision and Eye Symptoms. KAMRA® inlay implantation may cause or make worse problems with glare, halos, night vision, blurry vision, dryness, color disturbances, distortion, double vision, ghosting, and pain/burning. Some of these symptoms may be improved with additional treatment, including artificial tears, punctal plugs, repositioning of the KAMRA® inlay, or removal of the inlay. However, these symptoms may not resolve, even with treatment. The KAMRA® inlay may also cause **visual illusions** that may affect the ability to judge distances and locations of moving objects. Although it is likely that if the patient experiences this in the immediate period after surgery, it will lessen over time. However, some patients may not ever fully adapt.

Decreased Contrast Sensitivity. KAMRA® inlay implantation may cause decreased contrast sensitivity in the implanted eye in situations such as when trying to read a menu in a dimly lit restaurant, making your way through a darkened movie theater, or driving a car on a dimly lit road at night or under foggy conditions. There can be a further reduction in contrast if the inlay implanted eye and/or the fellow eye were to develop cataract, glaucoma, macular degeneration, or if they were to be implanted with a multifocal intraocular lens (IOL).

Challenges Evaluating and Managing Eye Problems. Tests to diagnose diseases (e.g, visual fields, fluorescein angiography, optical coherence tomography, etc.) in the retina (the innermost layer) of the eye with the KAMRA® inlay might take slightly longer and require some additional effort from the patient and the doctor to perform. Furthermore, if the patient were to develop glaucoma or a retinal problem, it is possible that the eye care provider may have difficulty evaluating the problem and/or administering treatment, and the inlay may need to be removed. There are potential risks of damaging the eye and/or inlay with the use of some medical lasers to treat certain eye conditions that may require special care to be taken when using a laser. Alternatively, the inlay may need to be removed prior to some laser treatments.

Eye Infections. There is a risk of infection to the cornea or other parts of the eye, as a result of the KAMRA® inlay implantation. Such infections would be treated with antibiotics.

Dry Eyes. There is a risk of developing new dry eye symptoms or having dry eye symptoms worsen after the procedures. As a result, patients may have blurry vision, a dry "scratchy" sensation, pain, burning or discomfort in the eye to inadequate tears. Dry eyes may be treated with artificial tears, prescription medications and/or punctal plugs, depending on the symptoms.

Corneal Complications. Other risks include, but are not limited to, complications related to the cornea such as scarring, clouding, infection, swelling, thinning and potential perforation of the cornea, and endothelial **cell loss** (loss of cells in the inner layer of the cornea). Loss of endothelial cells can lead to corneal swelling and eventual breakdown in the cornea, which can cause loss of vision, and potentially may require a corneal transplant (diseased cornea is replaced with healthy cornea from a donor). There is a potential risk for the cornea to **thin out and/or bulge out**, if the inlay is implanted in a thin cornea (less than 500 microns in thickness). If signs of the cornea thinning and bulging are observed, the doctor might choose to treat with rigid gas permeable contact lenses or other specialty contact lenses. In a severe case, corneal transplant might be necessary.

Cataracts. There is a risk of developing cataract in the implant eye as a result of normal aging which could decrease the vision in the eye sooner and to a greater degree than if the inlay was not there. Cataract removal with IOL implantation is possible with the inlay in place. However, the surgeon may choose to remove the inlay before cataract removal and IOL implantation.

Increased Eye Pressure. There is a potential risk for eye pressure to spike as a result of using eye drops that control the inflammation in the eye following the surgery. The clinical data showed that the average change in eye pressure was minimal with a wide variation in the degree of change before and after the inlay implantation. If pressure increases as a result of the eye drops, the doctor will treat it by prescribing another eye drop to decrease the eye pressure.

Vision Problems. Patients may experience problems seeing after the surgery. In some cases, removal of the inlay will improve the vision, but it may take many months. In other cases, removal of the inlay will not improve the vision, and the decreased vision could become permanent. Additionally, there is a potential risk for the focusing power of the eye to change, causing blurry vision and requiring glasses.

For the specific adverse events that occurred in the clinical studies, please see Sections X and XI below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

1. Biocompatibility

Due to the small size of the device, biocompatibility testing was performed on test materials consisting of the PVDF/Carbon black film that has undergone the same manufacturing and sterilization procedure as the finished device. Biocompatibility studies were conducted in conformance with FDA's blue book memorandum #G95-1, "Use of International Standard ISO 10993, Biological Evaluation of medical Devices Part 1: Evaluation and Testing", and with the relevant parts of ISO 10993. As per #G95-1, the KAMRA® inlay is categorized as a permanent (over 30 days) implant device. All biocompatibility testing was performed in compliance with Good Laboratory Practices. **Table 1** summarizes the biocompatibility tests and the results of each test.

Table 1: Biocompatibility testing

Test	Purpose	Test Method	Results
Cytotoxicity	Evaluate biocompatibility	Minimum Essential Media (MEM) Elution	Non-cytotoxic
Cytotoxicity	Evaluate biocompatibility	Agar Diffusion (Direct contact)	Non-cytotoxic
Cytotoxicity	Evaluate biocompatibility	Agar Diffusion (MEM extract)	Non-cytotoxic
Inhibition of Cell Growth	Evaluate biocompatibility	MEM extract	No cell inhibition, Non-cytotoxic
Sensitization	Evaluate biocompatibility	0.9% Sodium Chloride for Injection (SCI) and Cottonseed oil extracts	Non-sensitizer
Intracutaneous Reactivity	Evaluate biocompatibility	SCI and Cottonseed oil extracts	Non-irritant
Acute Systemic Toxicity	Evaluate biocompatibility	SCI and Cottonseed oil extracts	Non-toxic
Intramuscular Implantation	Evaluate biocompatibility	Test article strips	Mild irritant as compared to control
Genotoxicity-Bacterial Reverse Mutation	Evaluate biocompatibility	0.9% Saline and Polyethylene Glycol (PEG 400) extracts	Non-mutagenic
Genotoxicity-Chromosomal Aberration	Evaluate biocompatibility	Saline and PEG extracts	Non-clastogenic
Genotoxicity-Mouse Micronucleus	Evaluate biocompatibility	0.9% Saline and Olive oil extracts	Non-genotoxic

2. Physico-chemical testing

Physico-chemical testing was conducted to physically characterize the base material of the corneal inlay and to verify that the corneal inlay material remains stable throughout the potential implant life span. Where applicable, the physico-chemical testing was conducted in conformance with ISO 11979-5: 2006 – Ophthalmic Implants – Intraocular Lenses. **Table 2** comprises the list of physico-chemical tests conducted.

Table 2: Chemical Characterization

Test	Purpose	Test article tested	Results
Infrared scanning	Test for acceptance and identity of raw material.	PVDF base material	Pass
Exhaustive extraction	Determine the identity and amount of extractable substances from the materials used in the fabrication of the KAMRA® inlay.	Facsimile samples*	Pass
Testing for Leachables	Identify and quantify any extractable additives and other leachables from materials used in the fabrication of the KAMRA® inlay under physiologic conditions.	KAMRA® inlay and facsimile samples*	Pass
Hydrolytic stability	Demonstrate the hydrolytic stability of the materials used in the fabrication of the KAMRA® inlay for a time period equivalent to 5 years of real time hydrolytic exposure.	KAMRA® inlay and facsimile samples*	Pass
Photostability	Evaluate stability of device when exposed to UV radiation for the equivalent of 20 years under anticipated conditions of normal exposure.	KAMRA® inlay	Pass
Testing for inorganic compounds	Determine the identity and amount of inorganic contaminants from the materials used in the fabrication of the KAMRA® inlay.	Facsimile samples*	Pass

[*] Due to the small size of the device some of the testing was performed on facsimile samples. Facsimile samples were comprised of the same PVDF base material as the KAMRA inlay. In addition, facsimile samples were exposed to the same manufacturing, packaging and sterilization conditions as the subject device.

B. Animal Studies

A 1-year study was conducted in rabbits to demonstrate the long-term biocompatibility of the device. In order to create the corneal pockets for the insertion of the inlay, two techniques were used: IntrLase™ iFS Laser ("laser" eyes) and a manual technique using a diamond knife ("manual" eyes). The optical coherence tomography measurements indicated that the average depth of implantation varied between 150 ± 12 µm and 134 ± 27 µm for the laser eyes and 234 ± 24 µm and 231 ± 22 µm for the manual eyes. At 12 months, the laser eyes exhibited cornea thinning, inlay in process of extrusion, and extruded inlays, which might be attributed to the shallow implantation depth. No inlay extrusion or corneal thinning was reported for the manual eyes. Except for subtle collagen disorganization in the laser eyes, the morphology was consistent with post-surgery healing.

C. Additional Studies

1. Sterilization, Package Integrity, Shelf Life, and Transport Stability

The KAMRA® inlay is terminally sterilized using 20% ethylene oxide (EO) and 80% carbon dioxide (CO_2). The sterilization validation was performed according to ANSI/AAMI/ISO 11135 (Sterilization of health care products – Ethylene oxide) using the overkill method. Sterilization validation parameters were designed to achieve a Sterility Assurance Level (SAL) of 10^{-6}.

The KAMRA® inlay is supplied in a double-pouch package in which the inlay is confined in a small plastic case within the inner pouch. The pouches are standard Tyvek® - PE/PET peel pouches. The double-pouched inlay is enclosed in a paper box with all components appropriately labeled.

Packaging, shipping, and shelf life studies were conducted to verify that the packaging for the KAMRA® inlay maintains a sterile barrier and that device performance meets product specifications through a 2 year shelf life. Following distribution simulation and real time aging the applicant performed inner and outer dye penetration testing, inner and outer peel strength testing, visual inspection and dimensional measurement (inner and outer diameter), light transmission testing, tensile testing, cytotoxicity testing and extraction testing.

The results of the sterilization, packaging, shelf life and transport stability studies are summarized in **Table 3.**

Table 3: Sterility, Shelf Life, and Transport Stability Testing

Test	Purpose	Acceptance Criteria	Results
EO Validation	Evaluate sterility	No positive biological indicators	Pass
Ethylene Oxide Residuals	Evaluate toxicity	<1.25 µg/device	Pass
Ethylene Chlorohydrin Residuals	Evaluate toxicity	<1.25 µg/device	Pass
Bacterial endotoxin	Evaluate sterility	<0.2 EU/device	Pass
Package Evaluation – Outer Pouch Dye Penetration Testing	Evaluate Whole Package integrity	No dye observed in packaging	Pass
Package Evaluation – Inner Pouch Dye Penetration Testing	Evaluate Whole Package Integrity	Burst strength ≥ 28" in water	Pass
Package Evaluation – Seal-Peel Test	Evaluate Package Seal Integrity	Seal strength > 1.0 lbs/in.	Pass
Transport Stability	Evaluate package integrity and device stability	Manufacturing specification met after exposing samples to simulated transport conditions.	Pass

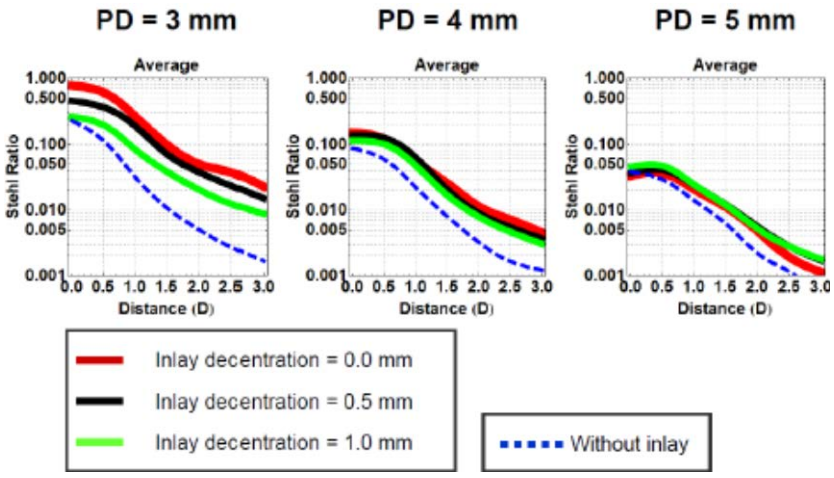
2. Preclinical Optical Studies

Preclinical optical studies were performed the KAMRA® inlay to demonstrate that the presence of the inlay in the cornea does not impede visual acuity or cause optical aberrations that would adversely affect patient vision, and to simulate the gain in depth of focus.

A mathematical model of the human eye with the KAMRA® inlay implanted in the cornea was created. Diffraction analysis and Modulation Transfer Function (MTF) calculations were conducted to evaluate the optical impact of any aberrations due to the presence of the small holes in the annulus. The MTF plots demonstrate that the glare from the diffusion holes have little effect on MTF performance. Additionally, in the model, it was demonstrated that approximately 2 D increased depth of focus was provided by the KAMRA® inlay.

The Strehl ratio (SR), was calculated to evaluate and compare retinal images as a function of inlay decentration and different natural pupil sizes. The SR reference of 0.03 was selected because of its approximate equivalence to a Jaeger (J) 2 visual acuity value. This value was determined experimentally in a previous study using an adaptive optics visual simulator.

Through-focus curves for each configuration as well as an eye without the inlay are displayed the figure below. The image quality and depth of focus (DOF) are better with the inlay, with the greatest effect for smaller natural pupils and decreasing for larger pupils to a level that is still above that of a non-implanted eye. The effect of decentration is also more evident with smaller natural pupils with the SR ratio increasing as the centration improves. Even when the inlay is decentered by 1.0 mm it still remains above the value for the non-implanted eye.



X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical trial to establish reasonable assurance of safety and effectiveness of implantation of the KAMRA® inlay in the corneal stroma to improve near vision in subjects with presbyopia in the US under IDE G080184 and outside the US (OUS). Data from this clinical trial (the "pivotal" trial) were the primary basis for the PMA approval decision. Subjects who completed the pivotal trial and were still implanted with the KAMRA® inlay were eligible to participate in the "continuation" study. After the Ophthalmic Devices Advisory Panel Meeting held on June 6, 2014, the applicant decided to limit the instructions for use to a subset of the surgical parameters used during the pivotal clinical trial. A summary of the pivotal clinical trial outcomes are presented below, including discussion of the outcomes of the subgroup that had the surgery performed using the parameters to which the instructions for use are now limited. The preliminary results of the continuation study are discussed in the Section XI, except as pertaining to refractive stability, which is included in the pertinent information below.

A. Study Design

The pivotal trial was a prospective, single-armed, non-masked, non-randomized, multicenter (24 sites), unilateral interventional, clinical trial. Each subject was implanted with the AcuFocus corneal inlay (ACI) only in the non-dominant eye. Fifteen (15) sites in the US participated under protocol ACU-P08-020, while nine (9) OUS sites participated under protocol ACU-P08-020A. The protocols for the two studies were essentially identical. For the ACU-P08-020 study, enrollment of the study population was phased, such that 75 eyes were enrolled initially. Following review of 3-month postoperative data from the first 75 eyes having undergone KAMRA® inlay implantation, an interim report was submitted to the FDA requesting expansion to the full study population of an additional 325 eyes. Enrollment was not phased for the ACU-P08-020A study, which was conducted entirely at OUS clinical sites. Post-operative evaluations were scheduled at 1-day, 1-week, 1-, 3-, 6-, 9-, 12-, 18-, 24-, 30- and 36-months. The primary time point for effectiveness and safety evaluation was at 12-months. Different subgroups from the full cohort participated in three different additional clinical evaluations from the rest of the cohort – contrast sensitivity, defocus, and visual fields. Contrast sensitivity and postoperative visual fields were additional safety assessments to determine the influence of the inlay on these aspects of vision. Defocus testing was performed in order to assess the effect of the device on vision through the full depth of focus.

The sample size was determined based on considerations of both safety and effectiveness. In order to detect an adverse event (AE) with true probability of occurrence among subjects of 1% with 95% probability, a sample of at least 299 subjects would be required. The sample was also powered to assess the primary effectiveness endpoint of at least 75% of all enrolled eyes that undergo inlay implantation achieving uncorrected near visual acuity (UCNVA) of 20/40 or better at 12 months. It was estimated that Delta = 10% (detectable difference in the success rate). Under these assumptions, a sample size of 165 subjects (eyes) has 80% power for the planned two-sided exact binomial test (α=0.05). A sample size of 400 eyes was proposed to account for a 10% drop-out rate.

Subjects that completed the pivotal trial with retention of the inlay were eligible for the continuation study with follow-up for an additional 2 years (study visits at 48 and

60 months post implantation) at 13 of the 15 US sites and 6 of the 9 OUS sites that participated in the pivotal trial.

Contrast sensitivity subgroup

To have 90% power to establish a non-inferiority margin of 15% and given a standard deviation of 0.4, with a one-sided alpha of 0.05, a sample size of at least 61 subjects was needed for the contrast sensitivity subgroup. A sample size of 75 eyes was proposed to account for a 10% drop out rate.

Defocus curve subgroup

For the defocus subgroup, a sample size of 30 subjects was proposed based on 10 subjects in each of three groups composed of small (≤2.5 mm), medium (>2.5 and <4.0 mm) and large (≥4.0 mm) pupil sizes as measured under the defocus test conditions.

Visual field subgroup

The applicant sought 90% power to establish non-inferiority margin of 0.525. Sample size calculations were then performed based on the following specifications: Given a standard deviation of 1.27, non-inferiority margin of 0.525, a power of 90% and one-sided alpha of 0.05, a sample size of 64 eyes are required. A sample size of 75 eyes was proposed to account for a 10% drop out rate.

1. Clinical Inclusion and Exclusion Criteria
   Enrollment in the pivotal trial was limited to subjects who met the following inclusion criteria:

   - Subjects must be ≥ 45 years and ≤ 60 years of age at the time of eligibility visit.
   - Subjects must be emmetropes needing a magnitude of +1.00D to +2.50D of reading add.
   - Subjects must have uncorrected near visual acuity worse than 20/40 and better than 20/100 in the eye to be implanted.
   - Subjects must have distance visual acuity correctable to at least 20/20 in both eyes.
   - Subjects must have a preoperative spherical equivalent of plano defined as +0.50D to -0.75D with no more than 0.75D of refractive cylinder as determined by cycloplegic refraction in the eye to be implanted.
   - Subjects must have a MRSE within 0.50D over prior twelve months as determined by patient history.
   - Subjects must have a minimum central corneal thickness of ≥ 500 microns in the eye to be implanted.
   - Subjects must have a corneal power of ≥ 41.00D and ≤ 47.00D in all meridians in the eye to be implanted.
   - Subjects must have an endothelial cell count ≥ 2000 cells/mm^2 in the eye to be implanted.

Subjects were not permitted to enroll in the pivotal trial if they met any of the following exclusion criteria:

- Subjects with a difference of >1.00D between the spherical equivalent manifest refraction and the spherical equivalent cycloplegic refraction
- Subjects with anterior segment pathology, including cataracts, in the eye to be implanted
- Subjects with residual, recurrent, active ocular or uncontrolled eyelid disease, or any corneal abnormality (including endothelial dystrophy, guttata, recurrent corneal erosion, etc.) in the eye to be implanted
- Subjects with ophthalmoscopic or topographic signs of keratoconus (or keratoconus suspect) or keratoectasia in the eye to be implanted
- Subjects with dry eye as determined by objective testing; anesthetized Schirmer's test result <10 mm or a tear break-up time (TBUT) less than 10 seconds are excluded
- Subjects taking chronic systemic medications known to exacerbate or induce moderate to severe dry eye in so far as measures of TBUT and Schirmer's are decreased or borderline
- Subjects with distorted or unclear corneal mires on topography maps of the eye to be implanted
- Subjects with macular degeneration, retinal detachment, or any other fundus pathology that would prevent an acceptable visual outcome in the eye to be implanted
- Subjects who have worn RGP or PMMA contact lenses within the last 6 months
- Subjects who have undergone previous intraocular or corneal surgery, including PRK, LASIK, LASEK, and cataract surgery
- Subjects with a history of herpes zoster or herpes simplex keratitis
- Subjects who have a history of steroid-responsive rise in intraocular pressure, preoperative IOP > 21 mmHg, glaucoma, ocular hypertension, or are glaucoma suspects
- Subjects with an abnormal threshold visual field
- Subjects with a history of diagnosed diabetes, diagnosed autoimmune disease, connective tissue disease, or clinically significant atopic syndrome
- Subjects on chronic systemic corticosteroids or other immunosuppressive therapy that may affect wound healing, and any immunocompromised subjects
- Subjects who are using ophthalmic medication(s) other than artificial tears for treatment of any ocular pathology including ocular allergy
- Subjects using systemic medications with significant ocular side effects.
- Subjects who are pregnant, lactating, or of child-bearing potential and not practicing a medically approved method of birth control
- Subjects with known sensitivity to planned study concomitant medications.
- Subjects who are participating in any other ophthalmic drug or device clinical trial during the time of this clinical investigation.

2. Follow-up Schedule
   All subjects were scheduled to return for follow-up examinations as listed in **Table 4**.

Table 4 –Schedule of Visits

Preoperative Evaluation	**(Day -60 to Day -1)**
Operative Evaluation	(Day 0)
Visit 1	Day 1 (24 to 36 hours post-op)
Visit 2	Week 1 (5 to 9 days post-op)
Visit 3	Month 1 (3 to 5 weeks post-op)
Visit 4	Month 3 (10 to 14 weeks post-op)
Visit 5	Month 6 (21 to 26 weeks post-op)
Visit 6	Month 9 (35-to 43 weeks post-op)
Visit 7	Month 12 (11 to 14 months post-op)
Visit 8	Month 18 (17 to 20 months post-op)
Visit 9	Month 24 (23 to 27 months post-op)
Visit 10	Month 30 (29 to 33 months post-op)
Visit 11	Month 36 (35 to 39 months post-op)

The parameters measured during the pivotal trial are summarized in **Table 5.**

Table 5: Schedules of Visits and Procedures

	Pre-Op	Intra-Op	1 Day	1 Wk	1 Mo	3 Mo	6 Mo	9 Mo	12 Mo	18 Mo	24 Mo	30 Mo	36 Mo
Ocular Dominance (motor dominance)	X												
Monovision Blur Tolerance Trial	X												
Mesopic Pupil Size	X				X								
Photopic Pupil Size	X												
Schirmer's Test and TBUT[3]	X												
Uncorrected VA - ETDRS: • Distance at 6m/20ft • Intermediate at 80cm/32in. • Near at 40cm/16in.	X		X[2]	X	X	X	X	X	X	X	X	X	X
Manifest Refraction (mid-point)	X			X	X	X	X	X	X	X	X	X	X
Distance-Corrected VA - ETDRS (No Add): • Distance at 6m/20ft • Intermediate at 80cm/32 in. • Near at 40cm/16in.	X			X	X	X	X	X	X	X	X	X	X
Distance-Corrected VA - ETDRS (With Add): • Near at 40cm/16 in.	X				X	X	X	X	X	X	X	X	X
Mesopic & Photopic Contrast Sensitivity[5]	X					X	X		X		X		X
Slit Lamp Examination w/fluorescein	X		X	X	X	X	X	X	X	X	X	X	X
Central Keratometry	X					X	X	X	X	X	X	X	X
Computerized Corneal Topography	X			X	X	X	X	X	X	X	X	X	X
Specular Microscopy	X					X	X	X	X		X		X
Pachymetry	X	X				X	X		X		X		X
Intraocular Pressure	X			X	X	X	X	X	X		X		X
Cycloplegic Refraction	X								X		X		X
Dilated Fundus Exam	X								X		X		X
Subject Satisfaction Questionnaire	X					X	X		X		X		X
Threshold Visual Fields[4]	X												
24-2 SITA Standard Visual Fields[5]	X								X		X		X
Defocus Curves[5]	X								X				

[1]Investigators were to consult the case report forms for whether just the inlay eye, each eye separately, or both eyes together were to be tested.
[2]Only uncorrected distance and near visual acuity without add will be performed on day 1 as a safety assessment.
3 Utilize either or both tests postoperatively whenever dry eye is suspected
4 Preoperatively ALL subjects will complete a threshold visual field – those subjects in the subgroup MUST complete the 24-2
5Subgroup only

Adverse events and complications were recorded at all visits.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

Primary and secondary safety endpoints were not explicitly defined in the protocol. The following were identified as key safety endpoints:

- Cumulative Ocular Adverse Events (AEs):
  - » Overall ≤5% of eyes

» Any single AE ≤1% of eyes

- Persistent loss of ≥ 2 lines best corrected distance visual acuity (BCDVA) – target < 5% of eyes
- BCDVA worse than 20/40 at 12 months, if preoperative BCDVA of 20/20– target < 1% of eyes
- Increase in manifest refractive astigmatism > 2.00 D from baseline at 12 months – target < 5% of eyes
- Haze with a decrease in BCDVA of more than two lines at 12 months (not due to irregular astigmatism) - target <1% of eyes.

The primary effectiveness endpoint and target for the study was 75% of eyes should achieve uncorrected near visual acuity (UCNVA) of 20/40 or better at 12 months. In order for the study to be considered a success, the lower limit of the confidence interval (CI) must be 75% or greater.

The secondary effectiveness endpoint was subjective improvement in near vision as measured by the AcuFocus™ Corneal inlay Presbyopic Questionnaire (ACIPQ) at the 12-month postoperative visit. The items used to measure this effectiveness endpoint were not described prior to the conduct and analysis of the clinical trial data, and hypothesis testing was not specified.

The severity of visual symptoms as measured using the ACIPQ was an additional safety measure.

B. Accountability of PMA Cohort

Accountability for the pivotal trial is shown in **Table 6**. Five hundred and eight (508) subjects underwent surgery and constitute the Safety Cohort, 507 of whom were successfully implanted with the device. Four hundred seventy-nine (479) subjects were available for analysis at 12 months, the primary time point for the analyses, with 442 available at 24 months and 424 available at 36 months. Four hundred seventy-eight (478) subjects in the Effectiveness Cohort were available for analysis at 12 months, with 436 available at 24 months and 417 available at 36 months.

Table 6: Accountability – All Operated Eyes

Total Operated Eyes (N) = 508		1 Day	1 Week	1 Month	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months	30 Months	36 Months
Available for Analysis	n/N (%)	507/508 99.8%	505/508 99.4%	505/508 99.4%	500/508 98.4%	499/508 98.2%	487/508 95.9%	479/508 94.3%	451/508 88.8%	442/508 87.0%	405/508 79.7%	424/508 83.5% 83.5%
Active (Not yet eligible for the interval)	n/N (%)	0/508 0.0%	0/508 0.0%	0/508 0.0%	0/508 0.0%	0/508 0.0%	0/508 0.0%	0/508 0.0%	0/508 0.0%	0/508 0.0%	0/508 0.0%	0/508 0.0%
Total Discontinued	n/N (%)	1/508 0.2%	1/508 0.2%	1/508 0.2%	2/508 0.4%	4/508 0.8%	9/508 1.8%	16/508 3.1%	32/508 6.3%	39/508 7.7%	48/508 9.4%	49/508 9.6%
Surgery Aborted	n/N (%)	1/508 0.2%	1/508 0.2%	1/508 0.2%	1/508 0.2%	1/508 0.2%	1/508 0.2%	1/508 0.2%	1/508 0.2%	1/508 0.2%	1/508 0.2%	1/508 0.2%
Deceased	n/N (%)	0/508 0.0%	0/508 0.0%	0/508 0.0%	0/508 0.0%	0/508 0.0%	0/508 0.0%	0/508 0.0%	0/508 0.0%	0/508 0.0%	0/508 0.0%	0/508 0.0%
Lens Change*	n/N (%)	0/508 0.0%	0/508 0.0%	0/508 0.0%	0/508 0.0%	0/508 0.0%	0/508 0.0%	0/508 0.0%	1/508 0.2%	2/508 0.4%	4/508 0.8%	4/508 0.8%
Removal**	n/N (%)	0/508 0.0%	0/508 0.0%	0/508 0.0%	1/508 0.2%	3/508 0.6%	8/508 1.6%	15/508 3.0%	30/508 5.9%	36/508 7.1%	43/508 8.5%	44/508 8.7%
Lost to Follow-up†	n/N (%)	0/508 0.0%	0/508 0.0%	0/508 0.0%	1/508 0.2%	2/508 0.4%	4/508 0.8%	5/508 1.0%	10/508 2.0%	21/508 4.1%	28/508 5.5%	35/508 6.9%
Missed Visit‡	n/N (%)	0/508 0.0%	2/508 0.4%	2/508 0.4%	5/508 1.0%	3/508 0.6%	8/508 1.6%	8/508 1.6%	15/508 3.0%	6/508 1.2%	27/508 5.3%	0/508 0.0%
% Accountability = Available for Analysis ÷ (Operated – Total Discontinued - Not yet eligible)		507/507 100.0%	505/507 99.6%	505/507 99.6%	500/506 98.8%	499/504 99.0%	487/499 97.6%	479/492 97.4%	451/476 94.7%	442/469 94.2%	405/460 88.0%	424/459 92.4%

% = (n/N)100

As of November 25, 2014, 269 subjects were seen at Month 48 in the continuation study and 202 subjects completed the 60-month visit.

The instructions for use are limited to creation of a corneal pocket using a femtosecond laser with spot/line spacings set at less than or equal to 6x6 microns at a minimum depth of 200 microns. There were 166 operated eyes treated with these surgical parameters referred to in this document as the 6x6 pocket subgroup. One-hundred and fifty-four (154) of these eyes were evaluated at Month 12, the primary time point.

C. Study Population Demographics and Baseline Parameters

As indicated in **Table 7**, out of 508 subjects that underwent surgery, 268 subjects (52.8%) were female. The average age at enrollment was 52 ± 4 years with an age range of 45 to 60 years. Among all subjects, 88.4% reported their race as Caucasian, 0.8% as African-American, 5.1% as Asian, 4.9% as Hispanic, and 0.8% as "other". The majority of surgical eyes were left eyes, 65.4%. This imbalance between right and left eyes was explained by the applicant as being due to the fact that the non-dominant eye was to be implanted with the device, and that there is literature to show the left is more frequently the non-dominant eye.

Table 7: Demographic Information

508 Eyes of 508 Enrolled Subjects		
	Number (n)	**Percentage**
Gender Female Male	 268 240	 52.8% 47.2%
Race White Black Asian Hispanic Other	 449 4 26 25 4	 88.4% 0.8% 5.1% 4.9% 0.8%
Surgical Eye Right Left	 176 332	 34.6% 65.4%
Age (In Years) N Mean Standard Deviation Minimum Maximum	 508 52 4 45 60	

% = (n/N)100

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the 508 subjects that underwent surgery. The key safety outcomes for this study are presented below, including adverse events reported in **Tables 8 to 12**. The adverse events in the tables are presented without regard to whether these were directly related to the device or not. For example, the adverse events that occurred on the operative day are most likely not directly related to the KAMRA® inlay itself, but are related to various steps involved in the implantation procedure.

Adverse events that occurred in the PMA clinical study:

Two hundred and eighty-one (281) adverse events (AEs) were reported in 170 subjects, 203 of which were ocular. There were 78 non-ocular AEs in 58 subjects.

Five ocular AEs occurred on the operative day as outlined in **Table 8**, with one flap complication (too thin flap) resulting in the device not being implanted. This latter subject "was monitored through the period of postoperative healing."

Table 8: Ocular Adverse Events in Implanted Eyes Day 0 (Operative Day)

Adverse Events	Operative N=508 n (%)	Number of Events	Number of Subjects N=508 n (%)
Allergic Drug Reaction, suspect Pilocarpine	1 (0.2%)	1	1 (0.2%)
Corneal abrasion/ Corneal erosion	2 (0.4%)	2	2 (0.4%)
Flap Complication	2 (0.4%)	2	2 (0.4%)

% = n/N(100)

Cumulative postoperative ocular AE rates are presented in **Table 9**.

Through 12 months, there were a total of 85 cases of different ocular adverse events reported during the pivotal trial, not counting multiple events of the same type in the same subject more than once, for an overall cumulative ocular postoperative AE rate of 16.7% (85 cases/ 508 operated eyes).

Table 9: Cumulative Ocular Adverse Events in inlay Implanted Eyes Day 1 Postoperative through 12 Months, 24 Months, 36 Months

		PIVOTAL STUDY FULL COHORT (N=508)						PIVOTAL STUDY 6x6 POCKET SUBSET (N=166)					
		Through 12 Months		Through 24 Months		Through 36 Months		Through 12 Months		Through 24 Months		Through 36 Months	
Category	**Adverse Events**	**# of Events**	**# of Subjects**	**# of Events**	**# of Subjects**	**# of Events**	**# of Subjects**	**# of Events**	**# of Subjects**	**# of Events**	**# of Subjects**	**# of Events**	**# of Subjects**
Conjunctiva	Conjunctival chalasis	0	0 (0.0%)	0	0 (0.0%)	1	1 (0.2%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
	Conjunctival concretion	0	0 (0.0%)	1	1 (0.2%)	1	1 (0.2%)	0	0 (0.0%)	1	1 (0.6%)	1	1 (0.6%)
	Conjunctival cyst	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
	Conjunctivitis	5	5 (1.0%)	8	7 (1.4%)	11	10 (2.0%)	3	3 (1.8%)	6	5 (3.0%)	7	6 (3.6%)
	Episcleritis	0	0 (0.0%)	1	1 (0.2%)	1	1 (0.2%)	0	0 (0.0%)	1	1 (0.6%)	1	1 (0.6%)
Cornea	Amorphous material anterior to inlay fold	1	1 (0.2%)	1	1 (0.2%)	1	1 (0.2%)	1	1 (0.6%)	1	1 (0.6%)	1	1 (0.6%)
	Corneal edema with grade of ≥ 2+ (at one month or later)	0	0 (0.0%)	0	0 (0.0%)	1	1 (0.2%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
	Corneal ulcer	0	0 (0.0%)	0	0 (0.0%)	1	1 (0.2%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
	Epithelium in the interface with loss of BCDVA of ≥ 2 lines	1	1 (0.2%)	1	1 (0.2%)	1	1 (0.2%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
	Haze - Onset beyond 6 months with loss of BCDVA of ≥ 2 lines	2	2 (0.4%)	3	3 (0.6%)	4	4 (0.8%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
	Corneal Abrasion/Erosion	2	2 (0.4%)	2	2 (0.4%)	2	2 (0.4%)	1	1 (0.6%)	1	1 (0.6%)	1	1 (0.6%)
	Corneal Foreign Body	0	0 (0.0%)	0	0 (0.0%)	1	1 (0.2%)	0	0 (0.0%)	0	0 (0.0%)	1	1 (0.6%)
	Epithelial defect 2-5 mm	1	1 (0.2%)	1	1 (0.2%)	1	1 (0.2%)	1	1 (0.6%)	1	1 (0.6%)	1	1 (0.6%)
	Epithelial Ingrowth	3	3 (0.6%)	3	3 (0.6%)	3	3 (0.6%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
	Foreign bodies over inlay with anterior corneal surface defect.	1	1 (0.2%)	1	1 (0.2%)	1	1 (0.2%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
	Keratitis at the incision	1	1 (0.2%)	1	1 (0.2%)	1	1 (0.2%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
	Limbal Foreign Body	0	0 (0.0%)	0	0 (0.0%)	1	1 (0.2%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
	SPK	2	2 (0.4%)	2	2 (0.4%)	2	2 (0.4%)	2	2 (1.2%)	2	2 (1.2%)	2	2 (1.2%)
	Stromal thinning secondary to abnormal healing response to corneal trauma **(SAE)**	1	1 (0.2%)	1	1 (0.2%)	1	1 (0.2%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)

%= # of subjects/N (100)

Table 9 (continued): Ocular Adverse Events in inlay Implanted Eyes Day 1 Postoperative through 12 Months, 24 Months, 36 Months

		PIVOTAL STUDY FULL COHORT (N=508)						PIVOTAL STUDY 6x6 POCKET SUBSET (N=166)					
		Through 12 Months		Through 24 Months		Through 36 Months		Through 12 Months		Through 24 Months		Through 36 Months	
Category	**Adverse Events**	**# of Events**	**# of Subjects n(%)**	**# of Events**	**# of Subjects n(%)**	**# of Events**	**# of Subjects n(%)**	**# of Events**	**# of Subjects n(%)**	**# of Events**	**# of Subjects n(%)**	**# of Events**	**# of Subjects n(%)**
Flap Complication	DLK	6	6 (1.2%)	6	6 (1.2%)	6	6 (1.2%)	1	1 (0.6%)	1	1 (0.6%)	1	1 (0.6%)
	Flap Striae	1	1 (0.2%)	1	1 (0.2%)	1	1 (0.2%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
Intraocular	Iritis	1	1 (0.2%)	2	2 (0.4%)	3	3 (0.6%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
IOP	IOP Increase > 10 mmHg above baseline or > 25 mmHg with clinical findings	15	15 (3.0%)	24	16 (3.1%)	27	17 (3.3%)	3	3 (1.8%)	3	3 (1.8%)	4	4 (2.4%)
Lens	Cataract	1	1 (0.2%)	1	1 (0.2%)	1	1 (0.2%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
Lids	Blepharitis	0	0 (0.0%)	1	1 (0.2%)	1	1 (0.2%)	0	0 (0.0%)	1	1 (0.6%)	1	1 (0.6%)
	Hordeolum	0	0 (0.0%)	0	0 (0.0%)	1	1 (0.2%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
	Meibomian Gland Dysfunction	0	0 (0.0%)	1	1 (0.2%)	1	1 (0.2%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
	Ptosis	0	0 (0.0%)	0	0 (0.0%)	1	1 (0.2%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
Other	Herpes Zoster (face and eye)	1	1 (0.2%)	1	1 (0.2%)	1	1 (0.2%)	1	1 (0.6%)	1	1 (0.6%)	1	1 (0.6%)
Retina	Retinal pigment epithelium change	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
	Retinoschisis	0	0 (0.0%)	0	0 (0.0%)	1	1 (0.2%)	0	0 (0.0%)	0	0 (0.0%)	1	1 (0.6%)
Secondary Surgical Intervention	inlay Re-centration	1	1 (0.2%)	6	6 (1.2%)	6	6 (1.2%)	1	1 (0.6%)	2	2 (1.2%)	2	2 (1.2%)
	Additional Refractive Correction (AK, CK)	0	0 (0.0%)	3	2 (0.4%)	5	3 (0.6%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
	Epithelial ingrowth removal	4	2 (0.4%)	4	2 (0.4%)	4	2 (0.4%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
	Lamellar interface rinse for DLK	1	1 (0.2%)	1	1 (0.2%)	1	1 (0.2%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
	Inlay Removals	15	15 (3.0%)	36	36 (7.1%)	44	44 (8.7%)	6	6 (3.6%)	7	7 (4.2%)	7	7 (4.2%)
Symptoms	Dry eye	2	2 (0.4%)	2	2 (0.4%)	2	2 (0.4%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
	Symptoms: Ghost images	0	0 (0.0%)	1	1 (0.2%)	1	1 (0.2%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
	Symptoms: Glare	0	0 (0.0%)	1	1 (0.2%)	1	1 (0.2%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
	Symptoms: Halos	1	1 (0.2%)	2	2 (0.4%)	2	2 (0.4%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
	Symptoms: Pain in eye	1	1 (0.2%)	3	3 (0.6%)	4	4 (0.8%)	0	0 (0.0%)	1	1 (0.6%)	1	1 (0.6%)
Vision	Decrease in BCDVA > 2 lines Month 3 or later	18	17 (3.3%)	34	28 (5.5%)	36	30 (5.9%)	8	7 (4.2%)	11	9 (5.4%)	12	10 (6.0%)

% = (n/N)100

Although already presented above**, Table 10** highlights the AEs by type that occurred at a rate of > 1% in the pivotal study at 12 months, including secondary surgical interventions (SSIs), diffuse lamellar keratitis (DLK), increased intraocular pressure or IOP (defined as in increase in IOP >10 mmHg above baseline or >25 mmHg with clinical findings), and decreased vision (defined as loss of BCDVA > 2 lines at 3 months or later). The cumulative rates of these adverse events increased after 12 months except for DLK. Inlay removals are a subset of secondary surgical interventions, but occurred at a rate > 1% on their own.

Table 10
Cumulative Ocular AEs occurring at rate > 1% at 12 Months: Pivotal Study

	Eyes with Events/ Operated Eyes (N=508)		
	12M n(%)	24M n(%)	36M n(%)
All SSIs	19 (3.7%)	47 (9.3%)	56 (11%)
Inlay Removals	15 (3.0%)	36 (7.1%)	44 (8.7%)
Decreased Vision[1]	17 (3.3%)	28 (5.5%)	30 (5.9%)
Increased IOP[2]	15 (3.0%)	16 (3.1%)	17 (3.3%)
Diffuse Lamellar Keratitis	6 (1.2%)	6 (1.2%)	6 (1.2%)

[1] Decrease in best corrected distance visual acuity > 2 lines at 3 months or later
[2] IOP increase >10 mmHg above baseline or IOP > 25 mmHg with clinical finding
% = (n/N)100

The reasons for removal of the corneal inlay in the pivotal trial, operated eyes cohort, and for the 6x6 pocket subgroup are shown in **Table 11**. The majority of removals (86%) were for visual reasons, and the majority of removals for visual reasons were for hyperopic shift. Out of 166 6x6 operated on pocket eyes (all at a depth of cut of 200 micrometers or deeper), there were 7 (4.2%) inlay removals through 36 months, 6 (3.6%) of these by Month 12. The medical reasons for inlay removal were for folds in the inlay, stromal thinning resulting from a postoperative foreign body, symptoms from a posterior vitreous detachment ("floater" within the optical path of the small KAMRA® aperture), and a subtle stromal opacity over the inner portion of the inlay implicated in reduction of BCDVA.

Table 11
Reason for Removals (36M): Pivotal Trial Cohort & 6x6 Pocket Subgroup

			Pivotal Study Cohort		6x6 Pocket Subgroup
Reason		Removals N=44 n(%)	Total Operated Eyes N=508 n(%)	Removals N=7 n(%)	Total Operated Eyes N=166 n(%)
Cosmesis		2 (4.6%)	2 (0.4%)	1 (14.3%)	1 (0.6%)
Medically Indicated		4 (4.6%)	4 (0.8%)	1 (14.3%)	1 (0.6%)
Visual Reasons		38 (86.4%)	38 (7.5%)	5(71.4%)	5(3.0%)
	Hyperopic Shift	25 (56.8%)	25 (4.9%)	2 (28.6%)	2 (1.2%)
	Myopic Shift	2 (4.6%)	2 (0.4%)	1 (14.3%)	1 (0.6%)
	Induced Cylinder	1 (2.3%)	1 (0.2%)	0	0
	Inadequate benefit/ Inability to adapt	7 (16.3%)	7 (1.4%)	1 (14.3%)	1 (0.6%)
	KAMRA® not Centered	2 (4.7%)	2 (0.4%)	0	0
	KAMRA® placed in the dominant eye	1 (2.3%)	1 (0.2%)	1 (14.3%)	1 (0.6%)

% = (n/N)100

Thirty-eight of the 44 subjects had at least 6 months of follow-up after inlay removal; 4 subjects were followed for 1 month and 2 for 3 months. After removal, all but one subject had BCDVA of 20/20 or better at their last visit, and that subject had BCDVA of 20/25. This was the subject that had removal due to persistent reduction in BCDVA secondary to a "subtle" stromal opacity over the inner portion of the inlay (one of the 4 medical reasons for removal). This subject had a loss in BCDVA from baseline of 7 letters at the last visit. Another of the subjects (the subject that had removal for vitreous floater in the small-aperature visual axis following inlay placement) had a loss from baseline of 6 letters in BCDVA at the last visit. This patient experienced hyperopic shift post-removal that was treated with topical steroids. All the other removal subjects did not lose more than 1 line of BCDVA post-removal.

Thirty-eight of the 44 (86.4%) subjects had a change in MRSE of $\leq$ 1.00 D at the last available post-removal visit, leaving 6 with a change in MRSE greater than this amount. According to Table A-6, the range of MRSE at baseline for these 44 subjects was -0.50 to +0.625 D, at the last available visit before removal was -1.50 to +3.25 D with a change from baseline range from -1.50 to +3.00 D, and at the last available post-removal was -0.50 to +4.25 D (in subject that had mechanical microkeratome resection) with a range of change from -1.00 to +4.00 D.

There were seven (7) AEs in the post-removal period experienced by five subjects. Two subjects had corneal edema > 2+, one subject was in the 6x6 pocket subgroup and the other had 2 separate incidences of edema. All three events were resolved without sequelae. One eye had corneal haze associated with BCDVA loss ≥ 2 lines, which resolved without sequelae after a course of topical steroid treatment. Three eyes experienced a decrease of more than 2 lines of BCDVA. The BCDVA in all three eyes was 20/20 or better at last available visit.

Although already presented above, the 16 SSIs other than inlay removals through Month 36 are again listed in **Table 12**. Two of these SSIs (both for repositioning) were in the 6x6 pocket subgroup, one of which was by Month 12. Eleven (11) of the 16 SSIs were in 9 subjects and were performed to address effectiveness issues, specifically visual complaints. Six of these 11 were for inlay repositioning (re-centering) in 6 subjects, the most common SSI after removal. The decision to re-center the inlay was generally based on subjects having insufficient gain in near without a hyperopic shift or ocular surface issues and subjective assessment of the inlay position as determined by the Principal Investigator. All of these 6 subjects, except for one, completed 36 months of follow-up. While only marginal improvements, if any, were seen in UCNVA, all subjects had BCDVA within 2 lines from baseline and all, except for one with BCDVA of 20/25 at the last available visit, maintained 20/20 or better BCDVA after the repositioning. The other 5 SSIs in 3 subjects were performed to address early postoperative findings of epithelial ingrowth (2 subjects) and diffuse lamellar keratitis (DLK).

Table 12: Adverse Events of Secondary Surgical Intervention (SSI) Other Than inlay Removals

Secondary Surgical Intervention	Number of Events	Number of Subjects
Inlay Re-positioning	6	6
Astigmatic Keratectomy, Conductive Keratoplasty	5	3
Epithelial ingrowth removal	4	2
Interface rinse for DLK	1	1
Total	16	12

*Subject 61136 had two CK procedures and had subsequent inlay removal.

Six eyes presented with DLK during the early postoperative period. Four of the 6 cases occurred at the same center. There was complete resolution in five eyes with topical steroid therapy. One of these 6 cases of DLK required irrigation of the lamellar interface in order to achieve full resolution.

There were 27 reports of intraocular pressure (IOP) increases of >10 mmHg from baseline or IOP >25 mm Hg (protocol definition of IOP AE) in 17 eyes during the entire course of the study. For 8 eyes, the IOP increases occurred during the use of the standard postoperative steroid regimen. For 9 eyes, the IOP increases were secondary to additional steroid treatment, including for the management of haze, DLK, and hyperopic shift. The applicant indicates that eventually all cases of

increased IOP resolved, with cessation of steroids and IOP-lowering medications in those who had required them for IOP control.

While there were 17 (3.3%) operated eyes at 12 months, 28 (5.5%) at 24 months and 30 (5.9%) at 36 months with a decrease in best corrected distance visual acuity of > 2 lines at 3 months or later, of the 479 implanted eyes available for analysis at 12 months, 3 (0.6%) had **loss of BCDVA of ≥ 2 lines that was persistent**. Five subjects of 442 (1.1%) available at 24 months and 6 out of 424 (1.4%) available at 36 months had loss of BCDVA of ≥ 2 lines that was considered persistent at those time points. There were a total of 16 out of the 508 operated eyes (3.1%) with BCDVA loss of ≥ 2 lines at 2 or more consecutive visits at some point during the study beginning at or after 3 months, with vision decreasing to as low as 20/63 Snellen equivalent. Eight (8/508 = 1.6%) of the 16 subjects had persistent vision loss of this degree at their final visit with the inlay still implanted, with the lowest BCDVA being 20/40 (in 2 subjects). Three subjects with persistent BCDVA loss prior to removal had BCDVA recovery to within 1 line of preoperative BCDVA. Four other subjects developed lens changes over the course of the study and three of these experienced sustained BCDVA loss (although none worse than 20/40) at study exit. One other subject had BCDVA loss attributable to corneal haze, which was unresolved at study completion. There were no subjects with **BCDVA of worse than 20/40**, **more than 2.00 D of induced manifest refractive astigmatism**, or **haze graded as ≥ trace with loss of BCDVA greater than 2 lines** at 12 months.

2. Effectiveness Results

Primary Effectiveness Endpoint – Uncorrected Near Visual Acuity:
Of the 478 evaluable eyes at 12 months postoperatively, 399 (83.5%) achieved uncorrected near visual acuity of 20/40 or better at 12 months. The lower bound of the 95% CI was 79.8%. Therefore, study success was achieved.

The applicant did not define the population for the primary effectiveness analysis *a priori* in the protocol, and excluded subjects that had removals and an SSI from the primary effectiveness analysis. Therefore, we conducted our own analysis. When counting these subjects with removals and a secondary surgical intervention as failures 80.8% of subjects in the pivotal trial achieved the primary effectiveness endpoint at 12 months. Since the lower bound of the 95% confidence interval was 77%, the primary effectiveness endpoint was met according to FDA's analysis.

While the within-subject duration of effect was not directly analyzed, the proportion of subjects with 20/40 or better UCNVA was 87.2% (380/436) at 24 months and 87.1% (363/417) at 36 months during the pivotal clinical trial.

In the 6x6 pocket subgroup, there were 135/153 (88.2%) of subjects at 12 months, 140/149 (94.03%) subjects at 24 months, 131/145 (90.3%) at 36 months with 20/40 or better UCNVA.

While the primary effectiveness endpoint information is presented above, UCNVA results were analyzed in various ways supporting effectiveness. For example, as expected due to binocular summation, binocular uncorrected near visual acuity results were somewhat better than monocular results.

Secondary Effectiveness Endpoint:
A new questionnaire (AcuFocus™ Corneal Inlay Presbyopic Questionnaire, abbreviated ACIPQ) was developed and used in this clinical study. This questionnaire was not determined to be a psychometrically valid assessment of the concept "subjective improvement in near vision." The data collected on the subjective improvement in near vision using this questionnaire was not interpretable.

3. Subgroup Analyses

The pivotal clinical trial was not powered for subgroup analysis.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study and confirmatory study included 35 investigators of which none were full-time or part-time employees of the sponsor and 19* of the investigators had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: ***none***
- Significant payment of other sorts: ***3****
- Proprietary interest in the product tested held by the investigator: ***none***
- Significant equity interest held by investigator in sponsor of covered study: ***19****

*Please note that some investigators had more than one type of disclosable financial interest/arrangement.

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

A. Additional Assessments from the Pivotal Clinical Trial

The following additional results from the pivotal clinical trial were considered:

Contrast Sensitivity:
Contrast sensitivity (CS) with best correction was analyzed in inlay eyes from a subgroup of 335 subjects in the pivotal clinical trial. Testing was performed with sine wave contrast gratings (F.A.C.T.® chart, Stereo Optical Co., Inc., Chicago, IL). Test conditions included the following:

Mesopic: Binocular without glare
Binocular with glare
Monocular without glare
Monocular with glare (36 month only)

Photopic: Binocular without glare
Monocular without glare
Monocular with glare (36 month only)

Changes from baseline were considered clinically significant if they were >0.3 $\log_{10}$ CS units at two or more spatial frequencies or if they changed between "seen" and "unseen" at any spatial frequency. The differences between clinically significant losses and gains were calculated to determine "net significant losses."

For binocular conditions, postoperative results showed little change from baseline, as expected because sensitivity is dominated by the unimplanted fellow eye.

The mean losses of monocular mesopic CS without glare are comparable to the binocular losses at 1.5 cpd, but they increase with increasing spatial frequency, exceeding -0.3 $\log_{10}$CS at 12.0 cpd. Also, more subjects have clinically significant losses than significant gains, with net losses exceeding 30% of subjects for most visits.

The original protocol omitted CS testing for the monocular mesopic with glare condition even though it is potentially the worst-case condition with regard to device-related sensitivity losses. A monocular mesopic with glare condition was added to the protocol for the last 142 subjects in the CS substudy to complete the 36-month visit. Mean $\log_{10}$CS was approximately 0.2-0.3 units lower with than without glare. Although no preoperative data for the mesopic monocular with glare condition were available for comparison, an analogous comparison of preoperative mesopic binocular conditions with and without glare shows that glare reduced $\log_{10}$CS by only about 0.1 unit.

Visual Fields:
For the subgroup of subjects undergoing postoperative visual fields, the Clinical Procedure Manual for the trial indicates that the SITA Standard or SITA Fast Central 24-2 strategies of the Humphrey Visual Field Analyzer should be used. Therefore, the subjects' visual fields peripheral to the central 24 degrees were not evaluated.

On average, the mean deviation (MD) postoperatively in comparison to preoperative levels changed for the worse in inlay eyes (in the negative direction by about -1 dB of change). However, this average change is minimal. In contrast, the average change in MD for the fellow eyes was no worse than +0.093 dB, a very slight change in the positive direction (the direction of improvement).

The inlay eyes failed the test of non-inferiority, with respect to change from baseline in MD, at every postoperative time point, while the fellow eyes were non-inferior at every postoperative time point (using pairwise comparisons at an unadjusted significance level of 0.05 and a non-inferiority margin of 0.525 dB).

For pattern standard deviation (PSD), there was a somewhat greater increase in the average PSD postoperatively from baseline in inlay eyes compared to fellow eyes (mean change of about 0.14 vs. about 0.07, respectively).

Although the mean increases for both groups were small, the ranges of change were high. In order to try to better understand the PSD visual field outcomes, the applicant was asked to identify subjects with reliable visual fields (i.e., fixation losses, false negative, and false positive indices <33%) and changes in visual field MD worse than -2.0 dB compared to baseline at any visit, and to have an expert determine those who have focal visual field defects (e.g., ring scotoma, inferior arcuate, superior arcuate, nasal step, paracentral scotoma, altitudinal defect, temporal wedge, etc.), not just generalized depression, at any time point. The applicant was also asked to identify potential causes for the focal deficits.

There were 118 (out of 654) fields of inlay eyes that met the criteria for analysis by the expert, who determined that 79 of these fields of 61 subjects did not have any focal deficits, while 39 fields of 32 subjects had focal defects. The applicant states that, for each of these inlay eyes with focal deficits, the device was noted to be well-centered and in proper position. Seventeen of the visual fields with focal deficits were at the 36-month visit, and many of the deficits noted at the earlier time points were not seen at the subsequent time points with many of these subjects being reported to have dry eye and/or artificial tear use. Stromal edema and haze was noted in one earlier case and haze at the lamellar interface was noted in another. In the former case, a subsequent visual field performed at a post-removal visit demonstrated resolution of partial superior and inferior arcuate defects.

There were 26 (out of 654) fields of fellow eyes that met the criteria for analysis by the expert, who determined that 9 of these fields of 9 subjects showed no focal depressions, while 17 fields of 15 subjects were noted to have focal defects. Five of these visual fields were at the 36-month visits, and 11 subjects that had deficits at earlier time points were noted to have dry eye and/or artificial tear use.

It should be noted that the expert was not masked with respect to whether the eye was an inlay eye or a fellow eye, which may have introduced bias into this assessment.

Intraocular Pressure

Preoperative mean intraocular pressure (IOP) was 14.5 (SD 2.7) mmHg. The mean IOP postoperatively ranged from 14.8 (SD 2.5) mmHg at 36 months to16.3 (SD 3.2) mmHg at 1 month. The mean change in IOP from baseline was greatest at Month 1 (1.8 mmHg, SD 3.2) and was no greater than 0.7 mmHg at every time point from 3 months through 36 months postoperatively.

Endothelial Cell Counts:

While the average endothelial cells counts for the cohort were submitted at each of the applicable time points, the key endothelial cell information was related to the change in endothelial cell density over time. **Table 13** shows the results of a pairwise analysis of change in endothelial cell density between consecutive postoperative visits for implanted and fellow eyes. The sample sizes vary between 297 and 468 depending on the paired postoperative visits. Statistical analysis of the data indicate that the paired postoperative intervals up to 9 months all are associated with a statistically significant difference in endothelial cell density loss between the implanted and fellow eyes. The estimated annual rate of endothelial cell loss for the implanted eyes in these intervals varies between -2.92% and -8.68%. The endothelial cell density (ECD) loss in the interval between months 12 and 24 is also statistically greater than the fellow eye change, but the annual loss in this interval of -0.59% is not clinically significant in that it is in the range of the normally expected annual loss.

The total decrease in the endothelial cell density for the implanted eyes was -4.88% at 9 months. After 9 months, the rate of endothelial cell loss is not statistically different than the loss for the fellow eye group except in the month 12-24 interval, but this change is not clinically significant. This indicates that changes in endothelial cell density due to acute endothelial cell loss are seen through 9 months postoperatively.

Table 13: Percent Change in ECD Between Consecutive Post-Operative Visits for Implanted and Fellow Eyes, Pairwise Visits

	Preop to M3	M3 to M6	M6 to M9	M9 to M12	M12 to M24	M24 to M30	M30 to M36
Implant Eyes							
N	462	457	455	446	415	308	304
Mean	-2.17%	-1.95%	-0.73%	-0.01%	-0.59%	-0.25%	0.24%
SD	4.06%	3.55%	3.31%	3.52%	3.91%	3.09%	3.24%
95% CI	-2.54%, -1.80%	-2.28%, -1.63%	-1.03%, -0.43%	-0.33%, 0.32%	-0.96%, -0.21%	-0.60%, 0.09%	-0.12%, 0.60%
Median	-2.22%	-2.03%	-0.65%	-0.10%	-0.65%	-0.26%	-0.24%
Range	-18.12%, 25.62%	-15.97%, 10.10%	-19.24%, 11.75%	-13.43%, 20.37%	-17.12%, 12.85%	-13.31%, 13.53%	-12.53%, 15.30%
Decrease >10%	10 (2.16%)	7 (1.53%)	1 (0.22%)	3 (0.67%)	6 (1.45%)	1 (0.32%)	1 (0.33%)
Increase >10%	4 (0.87%)	1 (0.22%)	1 (0.22%)	3 (0.67%)	2 (0.48%)	1 (0.32%)	2 (0.66%)
Fellow Eyes							
N	468	460	455	444	413	302	297
Mean	0.03%	0.16%	0.01%	-0.26%	0.06%	-0.37%	0.18%
SD	3.04%	2.86%	3.02%	2.92%	3.38%	2.76%	2.89%
95% CI	-0.25%, 0.30%	-0.10%, 0.43%	-0.27%, 0.29%	-0.54%, 0.01%	-0.27%, 0.38%	-0.68%, -0.06%	-0.15%, 0.50%
Median	0.00%	0.02%	-0.07%	-0.24%	-0.18%	-0.38%	0.00%
Range	-12.61%, 14.81%	-13.90%, 10.53%	-10.86%, 11.74%	-13.80%, 14.94%	-14.04%, 17.07%	-8.41%, 9.84%	-7.86%, 11.26%
Decrease >10%	2 (0.43%)	1 (0.22%)	1 (0.22%)	4 (0.90%)	2 (0.48%)	0 (0.00%)	0 (0.00%)
Increase >10%	4 (0.85%)	1 (0.22%)	1 (0.22%)	1 (0.23%)	5 (1.21%)	0 (0.00%)	2 (0.67%)
	Preop to M3	**M3 to M6**	**M6 to M9**	**M9 to M12**	**M12 to M24**	**M24 to M30**	**M30 to M36**
Difference between Implant Eyes and Fellow Eyes							
N	458	450	446	436	409	297	293
Mean	-2.26%	-2.07%	-0.72%	0.26%	-0.62%	0.13%	0.09%
SD	4.57%	4.13%	3.84%	3.96%	4.22%	3.57%	3.81%
95% CI	-2.67%, -1.84%	-2.45%, -1.68%	-1.08%, -0.36%	-0.11%, 0.63%	-1.03%, -0.21%	-0.27%, 0.54%	-0.34%, 0.53%
Median	-2.40%	-2.14%	-0.56%	0.17%	-0.62%	0.20%	0.05%
Range	-17.87%, 16.49%	-14.40%, 12.80%	-14.71%, 9.87%	-12.85%, 18.66%	-16.86%, 12.48%	-10.95%, 10.42%	-15.53%, 14.17%
Difference <-10%	20 (4.37%)	12 (2.67%)	5 (1.12%)	3 (0.69%)	6 (1.47%)	1 (0.34%)	4 (1.37%)
Difference >10%	5 (1.09%)	3 (0.67%)	0 (0.00%)	5 (1.15%)	5 (1.22%)	2 (0.67%)	3 (1.02%)
Estimated Annual Rate							
Implant Eyes	-8.68%	-7.80%	-2.92%	-0.04%	-0.59%	-0.50%	0.48%
Fellow Eyes	0.08%	0.68%	0.04%	-1.04%	0.06%	-0.74%	0.34%
T test for Comparing Mean % Change Between Visits: Implant Eyes vs. Fellow Eyes*							
P-value	<.0001*	<.0001*	0.0002*	0.8812	0.0058*	0.6877	0.6016

† Pairwise Visits = Eyes that had both pre-op and corresponding post-operative exams, but not necessarily every follow-up exam.
N = number of successfully implanted or fellow eyes returned for the visit with non-missing ECD change from prior visit.
* T Test is performed assuming unequal variances whenever the F Test for equal variances shows p-value <.05.

The chronic rate of endothelial cell density loss is provided in **Table 14**. This table contains the annualized rate of loss in the intervals between 9 and 36 months for the eyes that received the device.

Table 14: Annualized ECD Loss Rate from Period to Period After 9 Months

ECD LOSS FROM PERIOD TO PERIOD				
	9 to 12 Months	**12 to 24 Months**	**24 to 30 Months**	**30 to 36 Months**
N	446	415	308	304
Mean Change from Period to Period	-0.01%	-0.59%	-0.25%	0.24%
Annualized Mean Rate	-0.04%	-0.59%	-0.50%	0.48%
95% CI of Annualized Rate	-1.32%, 1.28%	-0.96%, -0.21%	-1.20%, 0.18%	-0.24%, 1.20%

The annualized rate of loss in the intervals after 9 months does not appear to be different from what is expected in a normal eye. There does not appear to be chronic loss of endothelial cells resulting from implantation of the device, based upon the data from this study.

The coefficient of variation and the percentage of hexagonal cells were assessed preoperatively and at each postoperative visit. There was no significant change in either of these parameters at any time in the study.

Stability of Manifest Refractive Spherical Equivalent (MRSE):
Stability of the distance refraction was evaluated. However, the manifest refraction methods normally used for clinical trials are not adequate for use with the KAMRA® inlay because of the increased depth of focus that it provides. In order to improve accuracy and precision, refractive corrections were measured by determining the far and near limits of best acuity, i.e., first noticeable blur and operationally defining the midpoint between them as the point of best correction.

The criteria for refractive stability were defined for the pivotal trial as follows (results are reported for eyes with two consecutive evaluations, "pairwise sequential cohort"):

» At least 95% of subjects should have a change in manifest refractive spherical equivalent (MRSE) $\leq$ 1.00 D between 2 consecutive visits.

This criterion was met by the full cohort at the 24-30 month interval (95%), although it dropped below this percentage at subsequent intervals - 94% between 30 and 36 months and between 36 and 48 months, and 92% between 48 and 60 months (based upon preliminary data).

This criterion was met by the 6x6 pocket subgroup at each interval starting at the 18-24 month interval, except for the 48-60 month interval – 97% between 18 and 24 months and between 24 and 30 months, 96% between 30 and 36 months, 95% between 36 and 48 months, and 93% between 48 and 60 months (based upon preliminary data).

» The mean rate of change in MRSE as determined by paired analysis should be less than or equal to 0.50 D per year (or 0.04 D/month) between 2 refractions performed at least 3 months apart.

This criterion was met by the full cohort at the 6-9 month interval with the annualized rate of change no greater than -0.184 diopters at any interval from this point onward.

This criterion was met by the 6x6 pocket subgroup at the 9-12 month interval with the annualized rate of change no greater than -0.112 diopters at any interval from this point onward.

» The 95% confidence interval for the mean rate of change should include zero or a rate of change attributable to normal aging.

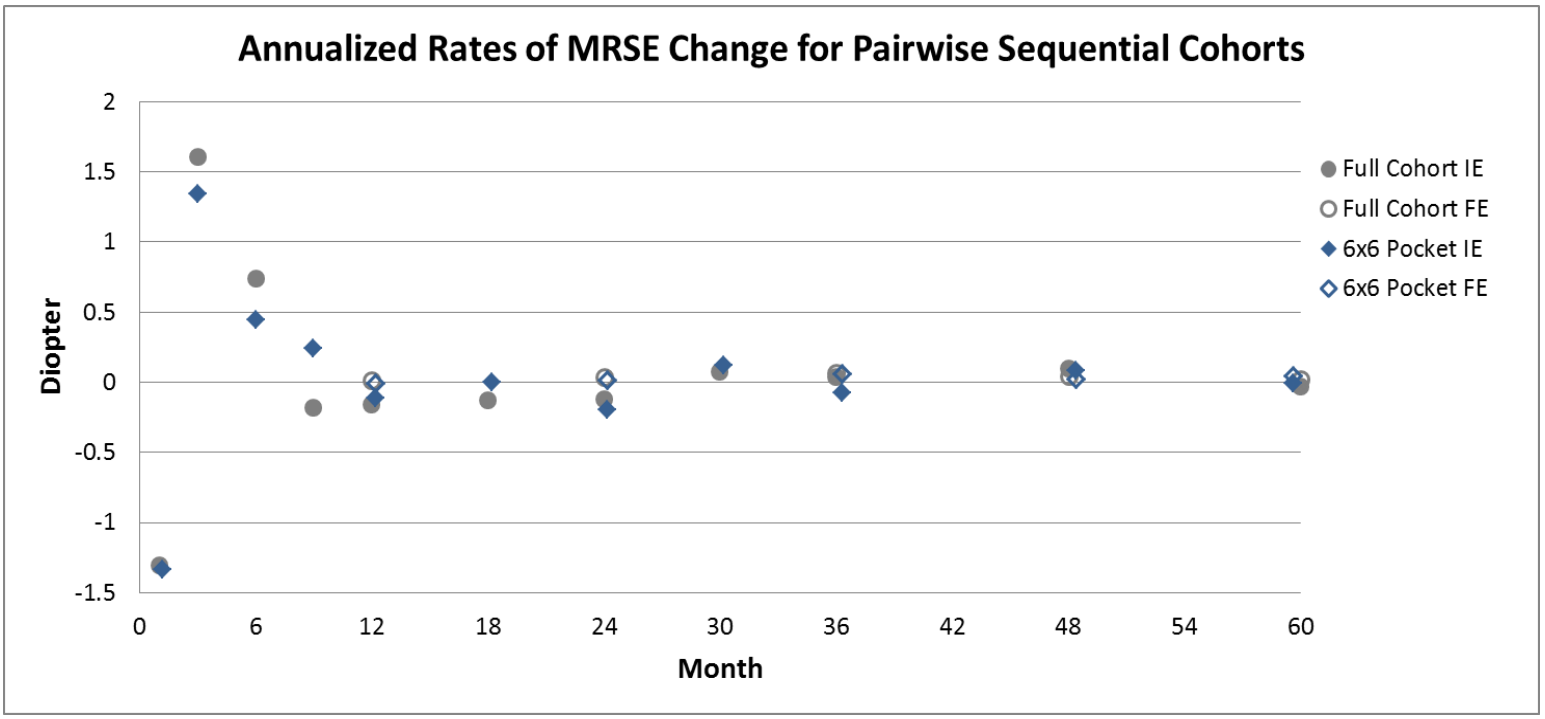
The 95% confidence interval for the mean rate of change included zero for the full cohort at the 6-9 month interval, but this criterion was not consistently met after this interval. However, the applicant showed that the rate of change could be attributed to normal aging following the 24-month time point by comparing the annualized rate of mean MRSE change between the inlay implanted eyes (IE) and the fellow eyes (FE) as shown in **Figure 1** below.

The same was true for the 6x6 pocket cohort.

» The mean rate of change of MRSE should decrease monotonically over time with a projected asymptote of zero or a rate of change attributable to normal aging.

While the rate of change was very small, especially after the 24-30 month interval, for both the full cohort (no more than 0.097 D/year) and the 6x6 pocket subgroup (no more than 0.084 D/year), it did not decrease monotonically. However, as discussed above and shown in **Figure 1** below, the rate of change could be attribute to normal aging following the 24-month time point.

Figure 1



» Stability was to be confirmed at the subsequent interval.

Visual and Ocular Symptoms (Patient-Reported Outcomes):
The AcuFocus™ Corneal inlay Presbyopic Questionnaire (ACIPQ) was a newly developed questionnaire used in this clinical study. This questionnaire was not determined to be a psychometrically valid assessment of visual symptoms. Therefore, the information from this questionnaire is not considered reliable. The percentage of subjects without visual symptoms at baseline who reported visual symptoms at or after 6 months postoperatively is shown in **Table 15**. The majority of these subjects had mild symptoms. The reported ratings of visual symptoms over time are presented in **Table 16** with over 30% of subjects reporting some degree of dryness, night vision problems, glare, halos, and blurry/fluctuating vision at the 12 month visit. This percentage remained relatively stable over the 36 months of follow up (in the pivotal study) with some improvement in the prevalence of glare and halos over time.

Table 15: Proportion of Subjects Reporting No Symptom Before Surgery That Reported the Symptom at 6 Months or Later After Surgery For All Subjects

	At 6 months or later postoperatively (n/N)
Blurry/Fluctuating Vision	296/407 (73%)
Color Disturbances	114/495 (23%)
Distortion	171/483 (35%)
Dryness	336/444 (76%)
Glare	245/432 (57%)
Halos	286/481 (59%)
Night Vision Problems	247/412 (60%)
Pain/Burning	152/482 (32%)
Double Vision	136/498 (27%)
Ghost/Overlapping Images	192/494 (39%)

% = (n/N)100

Table 16: Distribution of Subjective Symptom Ratings

	Preop	3 Months	6 Months	12 Months	18 Months	24 Months	30 Months	36 Months
Blurry/Fluctuating Vision	N = 508	N = 497	N = 497	N = 478	N = 442	N = 440	N = 391	N = 424
0, not present	407 (80%)	255 (51%)	256 (52%)	280 (59%)	244 (55%)	264 (60%)	249 (64%)	270 (64%)
1, very mild	18 (4%)	36 (7%)	29 (6%)	25 (5%)	32 (7%)	27 (6%)	24 (6%)	20 (5%)
2	31 (6%)	67 (13%)	67 (13%)	59 (12%)	60 (14%)	47 (11%)	38 (10%)	44 (10%)
3	20 (4%)	63 (13%)	53 (11%)	41 (9%)	44 (10%)	36 (8%)	25 (6%)	46 (11%)
4	13 (3%)	53 (11%)	53 (11%)	44 (9%)	40 (9%)	40 (9%)	40 (10%)	24 (6%)
5	8 (2%)	15 (3%)	31 (6%)	20 (4%)	16 (4%)	21 (5%)	12 (3%)	14 (3%)
6	10 (2%)	6 (1%)	7 (1%)	6 (1%)	5 (1%)	4 (< 1%)	3 (< 1%)	6 (1%)
7, very severe	1 (< 1%)	2 (< 1%)	1 (< 1%)	3 (< 1%)	1 (< 1%)	1 (< 1%)	0 (0%)	0 (0%)
Color Disturbances	N = 508	N = 497	N = 496	N = 478	N = 441	N = 441	N = 391	N = 424
0, not present	495 (97%)	450 (91%)	445 (90%)	424 (89%)	414 (94%)	410 (93%)	363 (93%)	407 (96%)
1, very mild	3 (< 1%)	10 (2%)	11 (2%)	14 (3%)	8 (2%)	10 (2%)	13 (3%)	5 (1%)
2	3 (< 1%)	16 (3%)	13 (3%)	20 (4%)	9 (2%)	9 (2%)	10 (3%)	6 (1%)
3	4 (< 1%)	11 (2%)	16 (3%)	6 (1%)	4 (< 1%)	5 (1%)	1 (< 1%)	5 (1%)
4	1 (< 1%)	6 (1%)	6 (1%)	5 (1%)	5 (1%)	4 (< 1%)	1 (< 1%)	0 (0%)
5	2 (< 1%)	2 (< 1%)	2 (< 1%)	7 (1%)	1 (< 1%)	2 (< 1%)	1 (< 1%)	1 (< 1%)
6	0 (0%)	1 (< 1%)	3 (< 1%)	1 (< 1%)	0 (0%)	1 (< 1%)	0 (0%)	0 (0%)
7, very severe	0 (0%)	1 (< 1%)	0 (0%)	1 (< 1%)	0 (0%)	0 (0%)	2 (< 1%)	0 (0%)
Distortion	N = 508	N = 496	N = 496	N = 477	N = 440	N = 441	N = 391	N = 424
0, not present	483 (95%)	426 (86%)	420 (85%)	409 (86%)	375 (85%)	376 (85%)	343 (88%)	376 (89%)
1, very mild	3 (< 1%)	13 (3%)	10 (2%)	10 (2%)	11 (3%)	11 (2%)	10 (3%)	11 (3%)
2	12 (2%)	18 (4%)	21 (4%)	22 (5%)	20 (5%)	22 (5%)	14 (4%)	14 (3%)
3	6 (1%)	19 (4%)	19 (4%)	15 (3%)	14 (3%)	6 (1%)	10 (3%)	9 (2%)
4	0 (0%)	15 (3%)	16 (3%)	15 (3%)	15 (3%)	15 (3%)	9 (2%)	6 (1%)
5	3 (< 1%)	4 (< 1%)	8 (2%)	6 (1%)	3 (< 1%)	11 (2%)	5 (1%)	7 (2%)
6	1 (< 1%)	0 (0%)	2 (< 1%)	0 (0%)	2 (< 1%)	0 (0%)	0 (0%)	1 (< 1%)
7, very severe	0 (0%)	1 (< 1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

	Preop	3 Months	6 Months	12 Months	18 Months	24 Months	30 Months	36 Months
Dryness	N = 507	N = 496	N = 497	N = 477	N = 441	N = 441	N = 391	N = 424
0, not present	443 (87%)	238 (48%)	253 (51%)	237 (50%)	212 (48%)	212 (48%)	199 (51%)	214 (50%)
1, very mild	28 (6%)	41 (8%)	40 (8%)	42 (9%)	40 (9%)	35 (8%)	31 (8%)	41 (10%)
2	16 (3%)	81 (16%)	78 (16%)	57 (12%)	58 (13%)	59 (13%)	49 (13%)	49 (12%)
3	12 (2%)	53 (11%)	48 (10%)	57 (12%)	51 (12%)	53 (12%)	37 (9%)	52 (12%)
4	5 (< 1%)	45 (9%)	42 (8%)	44 (9%)	48 (11%)	43 (10%)	40 (10%)	36 (8%)
5	2 (< 1%)	23 (5%)	24 (5%)	30 (6%)	19 (4%)	27 (6%)	22 (6%)	24 (6%)
6	1 (< 1%)	13 (3%)	10 (2%)	9 (2%)	10 (2%)	12 (3%)	13 (3%)	6 (1%)
7, very severe	0 (0%)	2 (< 1%)	2 (< 1%)	1 (< 1%)	3 (< 1%)	0 (0%)	0 (0%)	2 (< 1%)
Glare	N = 508	N = 497	N = 497	N = 478	N = 441	N = 440	N = 391	N = 424
0, not present	432 (85%)	304 (61%)	311 (63%)	300 (63%)	303 (69%)	305 (69%)	287 (73%)	322 (76%)
1, very mild	24 (5%)	29 (6%)	33 (7%)	27 (6%)	20 (5%)	34 (8%)	19 (5%)	21 (5%)
2	26 (5%)	56 (11%)	65 (13%)	56 (12%)	46 (10%)	33 (8%)	29 (7%)	27 (6%)
3	15 (3%)	52 (10%)	35 (7%)	37 (8%)	32 (7%)	34 (8%)	22 (6%)	25 (6%)
4	6 (1%)	38 (8%)	29 (6%)	31 (6%)	18 (4%)	20 (5%)	23 (6%)	13 (3%)
5	2 (< 1%)	15 (3%)	16 (3%)	18 (4%)	17 (4%)	10 (2%)	9 (2%)	9 (2%)
6	2 (< 1%)	3 (< 1%)	7 (1%)	5 (1%)	3 (< 1%)	3 (< 1%)	2 (< 1%)	7 (2%)
7, very severe	1 (< 1%)	0 (0%)	1 (< 1%)	4 (< 1%)	2 (< 1%)	1 (< 1%)	0 (0%)	0 (0%)
Halos	N = 508	N = 496	N = 497	N = 475	N = 440	N = 441	N = 391	N = 424
0, not present	481 (95%)	276 (56%)	294 (59%)	278 (59%)	292 (66%)	290 (66%)	268 (69%)	298 (70%)
1, very mild	12 (2%)	46 (9%)	36 (7%)	32 (7%)	30 (7%)	29 (7%)	20 (5%)	19 (4%)
2	10 (2%)	58 (12%)	66 (13%)	65 (14%)	46 (10%)	45 (10%)	44 (11%)	43 (10%)
3	4 (< 1%)	61 (12%)	35 (7%)	37 (8%)	31 (7%)	35 (8%)	24 (6%)	29 (7%)
4	1 (< 1%)	25 (5%)	35 (7%)	34 (7%)	20 (5%)	17 (4%)	15 (4%)	17 (4%)
5	0 (0%)	23 (5%)	17 (3%)	17 (4%)	17 (4%)	20 (5%)	15 (4%)	12 (3%)
6	0 (0%)	7 (1%)	13 (3%)	10 (2%)	4 (< 1%)	4 (< 1%)	5 (1%)	6 (1%)
7, very severe	0 (0%)	0 (0%)	1 (< 1%)	2 (< 1%)	0 (0%)	1 (< 1%)	0 (0%)	0 (0%)

	Preop	3 Months	6 Months	12 Months	18 Months	24 Months	30 Months	36 Months
Night Vision Problems	N = 508	N = 497	N = 496	N = 479	N = 442	N = 441	N = 390	N = 424
0, not present	412 (81%)	293 (59%)	318 (64%)	279 (58%)	275 (62%)	272 (62%)	262 (67%)	265 (63%)
1, very mild	33 (6%)	44 (9%)	33 (7%)	37 (8%)	23 (5%)	31 (7%)	17 (4%)	29 (7%)
2	37 (7%)	55 (11%)	46 (9%)	39 (8%)	49 (11%)	56 (13%)	41 (11%)	53 (13%)
3	14 (3%)	44 (9%)	39 (8%)	43 (9%)	35 (8%)	29 (7%)	35 (9%)	25 (6%)
4	8 (2%)	33 (7%)	22 (4%)	41 (9%)	32 (7%)	29 (7%)	19 (5%)	31 (7%)
5	4 (< 1%)	18 (4%)	24 (5%)	26 (5%)	21 (5%)	17 (4%)	11 (3%)	9 (2%)
6	0 (0%)	10 (2%)	10 (2%)	11 (2%)	7 (2%)	6 (1%)	5 (1%)	9 (2%)
7, very severe	0 (0%)	0 (0%)	4 (< 1%)	3 (< 1%)	0 (0%)	1 (< 1%)	0 (0%)	3 (< 1%)
Pain/Burning	N = 507	N = 498	N = 495	N = 478	N = 442	N = 440	N = 390	N = 424
0, not present	481 (95%)	423 (85%)	440 (89%)	414 (87%)	385 (87%)	387 (88%)	343 (88%)	364 (86%)
1, very mild	11 (2%)	26 (5%)	12 (2%)	22 (5%)	15 (3%)	16 (4%)	8 (2%)	11 (3%)
2	6 (1%)	18 (4%)	19 (4%)	20 (4%)	15 (3%)	15 (3%)	20 (5%)	26 (6%)
3	6 (1%)	14 (3%)	6 (1%)	10 (2%)	8 (2%)	13 (3%)	8 (2%)	8 (2%)
4	2 (< 1%)	11 (2%)	11 (2%)	9 (2%)	12 (3%)	5 (1%)	5 (1%)	8 (2%)
5	1 (< 1%)	6 (1%)	2 (< 1%)	2 (< 1%)	6 (1%)	2 (< 1%)	5 (1%)	6 (1%)
6	0 (0%)	0 (0%)	4 (< 1%)	0 (0%)	1 (< 1%)	1 (< 1%)	1 (< 1%)	0 (0%)
7, very severe	0 (0%)	0 (0%)	1 (< 1%)	1 (< 1%)	0 (0%)	1 (< 1%)	0 (0%)	1 (< 1%)
Double Vision	N = 508	N = 498	N = 496	N = 478	N = 440	N = 441	N = 390	N = 423
0, not present	498 (98%)	450 (90%)	444 (90%)	425 (89%)	402 (91%)	398 (90%)	350 (90%)	383 (91%)
1, very mild	4 (< 1%)	11 (2%)	9 (2%)	13 (3%)	14 (3%)	8 (2%)	10 (3%)	9 (2%)
2	3 (< 1%)	13 (3%)	17 (3%)	11 (2%)	9 (2%)	13 (3%)	12 (3%)	15 (4%)
3	2 (< 1%)	15 (3%)	11 (2%)	16 (3%)	5 (1%)	6 (1%)	9 (2%)	7 (2%)
4	0 (0%)	6 (1%)	11 (2%)	6 (1%)	7 (2%)	13 (3%)	3 (< 1%)	6 (1%)
5	1 (< 1%)	0 (0%)	4 (< 1%)	5 (1%)	2 (< 1%)	1 (< 1%)	5 (1%)	2 (< 1%)
6	0 (0%)	3 (< 1%)	0 (0%)	2 (< 1%)	1 (< 1%)	2 (< 1%)	1 (< 1%)	1 (< 1%)
7, very severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ghost/Overlapping Images	N = 507	N = 497	N = 496	N = 479	N = 441	N = 441	N = 391	N = 423
0, not present	493 (97%)	409 (82%)	394 (79%)	386 (81%)	365 (83%)	367 (83%)	324 (83%)	359 (85%)
1, very mild	7 (1%)	19 (4%)	17 (3%)	18 (4%)	20 (5%)	14 (3%)	17 (4%)	15 (4%)
2	3 (< 1%)	29 (6%)	24 (5%)	21 (4%)	16 (4%)	28 (6%)	13 (3%)	18 (4%)
3	1 (< 1%)	18 (4%)	23 (5%)	25 (5%)	11 (2%)	15 (3%)	17 (4%)	13 (3%)
4	1 (< 1%)	10 (2%)	17 (3%)	19 (4%)	18 (4%)	9 (2%)	8 (2%)	8 (2%)
5	2 (< 1%)	5 (1%)	15 (3%)	4 (< 1%)	8 (2%)	4 (< 1%)	9 (2%)	8 (2%)
6	0 (0%)	7 (1%)	6 (1%)	6 (1%)	1 (< 1%)	4 (< 1%)	3 (< 1%)	2 (< 1%)
7, very severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (< 1%)	0 (0%)	0 (0%)	0 (0%)

A summary of the frequency of symptoms reported on the ACIPQ before surgery and after surgery at 12, 24, and 36 months for this 6x6 pocket subgroup are reported in **Table 17** below:

TABLE 17
PROPORTION OF SUBJECTS REPORTING SYMPTOMS BEFORE SURGERY AND AFTER SURGERY AT 12, 24, AND 36 MONTHS FOR 6X6 POCKET SUBGROUP

	Preop (n/N) (%)	12 Months (n/N) (%)	24 Months (n/N) (%)	36 Months (n/N) (%)
Blurry/Fluctuating Vision	19/166 (11%)	56/154 (36%)	70/149 (47%)	56/146 (38%)
Color Disturbances	4/166 (2%)	19/154 (12%)	9/149 (6%)	4/146 (3%)
Distortion	4/166 (2%)	16/154 (10%)	21/149 (14%)	16/146 (11%)
Dryness	8/166 (5%)	73/154 (47%)	75/149 (50%)	70/146 (48%)
Glare	14/166 (8%)	47/154 (31%)	43/149 (29%)	34/146 (23%)
Halos	9/166 (5%)	56/154 (36%)	42/149 (28%)	37/146 (25%)
Night Vision Problems	20/166 (12%)	57/154 (37%)	52/149 (35%)	56/146 (38%)
Pain/Burning	7/166 (4%)	17/154 (11%)	17/149 (11%)	18/146 (12%)
Double Vision	3/166 (2%)	19/154 (12%)	15/149 (10%)	15/146 (10%)
Ghost/Overlapping Images	3/166 (2%)	27/154 (18%)	24/149 (16%)	21/146 (14%)

% = (n/N)100

During the perioperative period (by the 3-month postoperative visit), 7% to 42% of subjects without visual symptoms before surgery developed visual symptoms. Of the subjects who did not have a given symptom before surgery, between 22% and 77% reported the symptom after surgery as shown in **Table 18** below. The majority of these symptoms were mild.

TABLE 18
PROPORTION OF SUBJECTS REPORTING NO SYMPTOM BEFORE SURGERY THAT REPORTED THE SYMPTOM AT 6 MONTHS OR LATER POSTOPERATIVELY FOR 6X6 POCKET SUBGROUP

	At 6 months or later Postoperatively (n/N) (%)
Blurry/Fluctuating Vision	105/147 (71%)
Color Disturbances	35/162 (22%)
Distortion	55/162 (34%)
Dryness	122/158 (77%)
Glare	76/152 (50%)
Halos	81/157 (52%)
Night Vision Problems	87/146 (60%)
Pain/Burning	54/159 (34%)
Double Vision	44/163 (27%)
Ghost/Overlapping Images	54/163 (33%)

% = (n/N)100

For each symptom collected with the ACIPQ, the proportion of subjects in the 6x6 pocket subgroup who reported no symptoms before surgery that later reported moderate or severe symptoms during the first year, the second year, and third year following surgery are presented below in **Table 19**.

Table 19
PROPORTION OF SUBJECTS DEVELOPING NEW SYMPTOMS (MODERATE OR SEVERE) AFTER SURGERY IN SUBJECTS REPORTING NO SYMPTOMS BEFORE SURGERY FOR 6X6 POCKET SUBGROUP

	During 3-12 Months	During 18-24 months	During 30-36 months
Blurry/Fluctuating Vision	49/147 (33%)	48/147 (33%)	39/147 (27%)
Color Disturbances	10/162 (6%)	6/162 (4%)	3/162 (2%)
Distortion	20/162 (12%)	20/162 (12%)	10/162 (6%)
Dryness	57/158 (36%)	50/158 (32%)	40/158 (25%)
Glare	44/152 (29%)	18/152 (12%)	19/152 (13%)
Halos	43/157 (27%)	30/157 (19%)	26/157 (17%)
Night Vision Problems	38/146 (26%)	33/146 (23%)	29/146 (20%)
Pain/Burning	11/159 (7%)	10/159 (6%)	4/159 (3%)
Double Vision	18/163 (11%)	10/163 (6%)	10/163 (6%)
Ghost/Overlapping Images	26/163 (16%)	14/163 (9%)	15/163 (9%)

% = (n/N)100

Topography and Pachymetry:

Topography and pachymetry of the cornea were performed in order to aid in monitoring individual subject safety during the clinical trial, in the context of the other clinical information regarding a particular subject.

Of the 479 subjects evaluated at 12 months, 473 (98.7%) were deemed to have "normal" corneal topography and 6 (1.3%) were deemed "suspect." At 18 months postoperatively, 5 subjects out of 451 (1.1%) had "suspect" topographies and 3 out of 451 (0.7%) had "abnormal" topographies. Eleven of 442 (2.5%) subjects at 24 months and 16/422 (3.8%) at 36 months were deemed to have suspect topographies and none were deemed "abnormal."

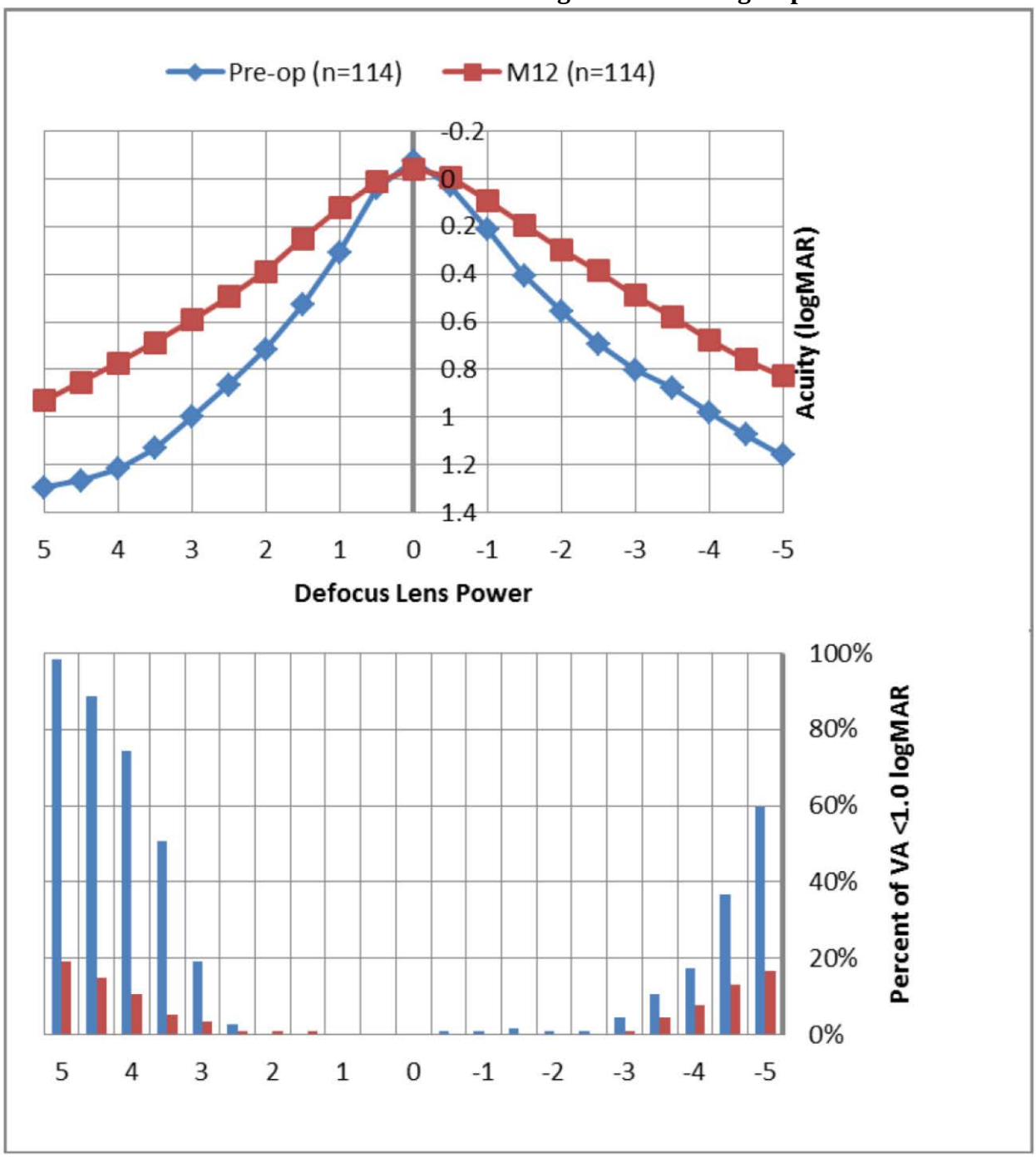
The mean change in central corneal thickness (CCT) indicated an increase from baseline at all postoperative visits at which measurements were taken ranging from 4.4 microns at 24 months to 7.4 microns at 6 months postoperatively. However, the ranges of the change in CCT were extremely large with the widest range at 24 months postoperatively of -89.0 microns to 93.0 microns.

While the results of these evaluations for the cohort did not indicate a severe safety issue, such data cannot be reliably interpreted in isolation. Therefore, the summary information is not very informative.

Within-Subject Change in UCNVA and UCDVA:
A total of 27.6% of subjects lost 1 line (5 letters of the Early Treatment Diabetic Retinopathy Study chart) or more of UCDVA from baseline at 12 months postoperatively in the inlay implanted eye. The percentage of subjects that lost more than 1 line of UCDVA while not gaining 2 or more lines of UCNVA was 10.5%. Sixty-one percent of subjects gained 2 or more lines of UCNVA while not losing 1 line or more of UCDVA.

Defocus Curve:
Figure 2 presents the defocus curve for the implanted eyes within the full subgroup. This defocus curves was constructed assuming that if no letters on the back-lit ETDRS (Early Treatment Diabetic Retinopathy Study) chart at a testing distance of 4 meters with the "best corrected distance refraction" in place were visible to the subject, the visual acuity was 1.3 logMAR. The proportion of eyes that demonstrated visual acuities worse than 1.0 logMAR at each of the measured levels of defocus are also presented in corresponding histograms below the defocus curves. It should be noted that the testing distance for determination of the "best corrected distance refraction" was at "optical infinity," while defocus curves were tested at 4 meters "using the best corrected distance refraction." The distance refraction was not adjusted for the 4-meter testing distance of the defocus curves.

Figure 2: Preoperative and Postoperative Defocus Curves and Percentage of Subjects with Visual Acuities Worse Than 1.0 LogMAR Full Subgroup



While the defocus curve shows improvement in visual acuity postoperatively compared to preoperatively, the histogram shows that the defocus curve is less of an accurate representation of actual visual acuities preoperatively compared to postoperatively. This is especially true as you move toward the extreme ends of the curves, due to the large number of subjects that could not read any lines on the chart for whom assumptions had to be made about their level of acuity.

B. Supportive Data

The applicant provided supportive data from an additional study conducted under the same IDE as the pivotal trial, referred to as the continuation study, and from a trial conducted OUS, referred to as the confirmatory trial.

The continuation study is an ongoing observational study designed to monitor the safety of subjects, who participated in the pivotal trial (ACU-P08-020/020A) and are still implanted with KAMRA® inlay, for an additional 2 years (a total of 5 years post implantation). This is a prospective, multicenter study conducted under the protocol ACU-P12-020C. Thirteen of the 15 US sites that participated in the pivotal trial under protocol ACU-P08-020 and 6 of the 9 OUS sites that participated in the pivotal trial under protocol ACU-P08-020A are participating in the continuation study. Clinical evaluations are scheduled at 48 and 60 months post implantation. Eligible subjects are considered enrolled in the study when the informed consent is signed. Based on preliminary data, out of the 424 subjects that have completed the pivotal trial, 269 subjects were seen at Month 48 and 202 subjects completed the 60-month visit as of November 25, 2014. There were additional ocular AE reported in 18 subjects as of the November database lock, the most concerning of which was a removal for refractive shift in a subject in the 6x6 pocket subgroup. The other AEs included PRK for hyperopic shift, decrease in BCDVA of greater than 2 lines (the vast majority were either associated with lens changes or had resolved by the next visit), superficial punctate keratitis, blepharitis/meibomian gland dysfunction, conjunctival cyst, and retinal pigment epithelial granularity in both eyes.

During the continuation study, 87.1% (175/201) of all subjects evaluated at 60 months postoperatively had 24/40 or better UCNVA. In the 6x6 pocket subgroup, there were 63/75 (84.0%) subjects at 60 months with 20/40 or better UCNVA.

The confirmatory study was conducted under protocol ACU-P10-020B. This was a prospective, multi-center, clinical trial conducted at 12 sites OUS. Subjects were to be followed for one year following KAMRA® inlay implantation. According to the applicant, this protocol was conducted to confirm findings observed in the IDE clinical trial related to the method employed in creating the lamellar resection required for intrastromal placement of the inlay. While in the pivotal trial, the KAMRA® inlay was implanted under a stromal flap or in a pocket created with a femtosecond laser or mechanical keratome with a target depth of at least 180 microns, in the confirmatory study, the inlay was implanted under a stromal flap or in a pocket created only with a femtosecond laser using spot/line spacings of only $\leq$ 6x6 and also with a target depth of at least 180 microns. The enrollment criteria for the confirmatory studies were the same as for the pivotal trial.

A total of 151 subjects underwent the surgical procedures (safety cohort) and 150 eyes of 150 subjects were successfully implanted with the inlay. One subject who underwent surgery was not implanted as a result of a thin lamellar resection. Of the 151 eyes that underwent surgery, 139 (92.1%) were available for analysis at the 12-month visit, and 130 were considered evaluable for effectiveness.

Cumulative post-operative ocular adverse events are listed in **Table 20.**

Table 20: Cumulative Ocular Adverse Events in inlay Implanted Eyes – Day 1 Post-Operative through 12 Months

Category	Adverse Events	# of Events	# of Subjects (N=151) n (%)
Cornea	Cornea: Corneal Edema with grade of greater than or equal to 2+ (at one month or later)	2	2 (1.3%)
	Epithelial Ingrowth	1	1 (0.7%)
IOP	IOP: IOP greater than 10mmHg above baseline or IOP greater than 25 mmHg (with clinical findings)	8	7 (4.6%)
Lids	Allergic Reaction to Study Medication: Lids	1	1 (0.7%)
	Blepharitis	1	1 (0.7%)
SSI	inlay Removal	9	9 (6.0%)
	SSI: inlay re-centration	7	5 (3.3%)
	SSI: Epithelial ingrowth removal and ACI exchange	1	1 (0.7%)
	SSI: Replacement of folded inlay	1	1 (0.7%)
Symptoms	Dry eye	1	1 (0.7%)
Vision	Vision: Decrease in BCDVA greater than 2 lines at month 3 or later	6	6 (4.0%)

% = (n/N)100

In the confirmatory study, SSIs, as well as the subgroup of inlay removal SSIs, DLK, increased IOP, and corneal edema occurred at a rate greater than 1%, as shown in **Table 21**.

Table 21:
Cumulative Ocular AEs occurring at rate > 1%: Confirmatory Study Cohort

	Eyes with Events/ Operated Eyes (N=151)
SSI	16 (10.6%)
inlay Removal	9 (6%)
Decreased Vision[1]	6 (4.0%)
Increased IOP[2]	7 (4.6%)
Corneal Edema[3]	2 (1.3%)

[1] Decrease in best corrected distance visual acuity > 2 lines at 3 months or later
[2] IOP increase >10 mmHg above baseline or IOP > 25 mmHg with clinical finding
[3]Corneal Edema with grade of 2+ at 1 month or later

A total of 18 secondary surgical interventions (SSIs) occurred in 15 subjects, 9/150 (6%) of which were inlay removals. The reasons for removal are listed in **Table 22**. As with the pivotal trial, the most common reason for removal was related to hyperopic shift.

Table 22:
Removals: Confirmatory Study Cohort

			Confirmatory
		Removals N=9	Total Operated Eye N=151
Symptoms		2 (22.2%)	2 (1.3%)
Visual Reasons n(%)		7 (77.8%)	7(4.6%)
	Hyperopic Shift	4 (44.5%)	4 (2.7%)
	Inadequate benefit/Inability to adapt	3 (33.4%)	3 (1.2%)

% = (n/N)100

There were 9 additional SSIs in 7 subjects, including 7 inlay re-centrations, 1 epithelial ingrowth removal and inlay exchange, and 1 replacement of a folded inlay.

There were 8 reports of IOP increases of >10 mmHg from baseline or IOP >25 mm Hg (protocol definition of IOP AE) in 7 subjects during the course of the study. For 4 eyes, the IOP increases occurred during the use of the standard postoperative steroid regimen. For 3 eyes, the IOP increases were secondary to additional steroid treatment used for the management of hyperopic shift and inflammation.

There were 6 subjects whose losses of BCDVA at 3 months or later met the definition for an AE. Of the six subjects, 5 (83.3%) experienced only transient loss for one visit, while 1 (16.7%) experienced loss at two consecutive examinations. Therefore, there was one subject out of 139 (1/139 = 0.7%) evaluable in the safety cohort at 12 months with **loss of BCDVA of ≥ 2 lines that was persistent**. However, there were no subjects with **BCDVA of worse than 20/40**, **more than 2.00 D of induced manifest refractive astigmatism**, or **haze graded as ≥ trace with loss of BCDVA greater than 2 lines** at 12 months.

As observed during the pivotal trial, over 30% of subjects reported some degree of dryness, night vision problems, glare, halos, and blurry/fluctuating vision at the 12-month visit on the ACIPQ.

Of the 130 evaluable eyes for effectiveness at 12 months postoperatively, 118 (90.8%) achieved uncorrected near visual acuity of 20/40 or better at 12 months. The lower bound of the 95% CI was 84.5%.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

A. Panel Meeting Recommendation

At an advisory meeting held on June 6, 2014, the Ophthalmic Devices Panel of the Medical Devices Advisory Committee to the Food and Drug Administration voted 4-5-0 (yes, no, abstain) that there is reasonable assurance the device is safe, 7-1-0 (yes, no, abstain) that there is reasonable assurance that the device is effective, and 4-3-1 (yes, no, abstain) that the benefits of the device do outweigh the risks in patients who meet the criteria specified in the proposed indication.

The 24-hour meeting summary can be found at the following: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/OphthalmicDevicesPanel/UCM400434.pdf

B. FDA's Post-Panel Action

Subsequent to the Advisory Panel, the applicant submitted a Major Amendment to the premarket application in which the following items were submitted:

- A revised indications for use
- Information that was not previously reviewed by FDA and was the basis for slides presented during the Advisory meeting, including regarding refractive stability, OUS postmarket adverse event reporting, and outcomes of surgical parameter subgroups
- Responses to review items that were previously requested by the FDA prior to the Advisory meeting, including results of the continuation study and contrast sensitivity data analyses
- Additional Information regarding the Patient-Reported Outcomes (PRO)
- A new benefit versus risk discussion

The new information that was key to FDA's decision is incorporated into the discussion in Sections X and XI where relevant.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The target for the primary effectiveness endpoint of the pivotal clinical trial was met, and the study success criterion was met.

The one Panel member's concern regarding the effectiveness of the device for the proposed indications for use was addressed by revising the indications for use to limit the indicated patient population to the key characteristics of those in the pivotal trial population.

B. Safety Conclusions

The risks of the device are based on data collected in animal studies, clinical trials conducted to support PMA approval as described above, as well as OUS postmarket data, data on prior versions of the device, and evidence from the literature.

The risks of KAMRA® inlay implantation include:

- glare, halos, night vision, blurry vision, dryness, color disturbances, distortion, double vision, ghosting, and pain/burning, and may affect the ability to judge distances and locations of moving objects
- decreased contrast sensitivity
- difficulty diagnosing and managing eye diseases, such as retinal diseases and glaucoma, as well as managing cataract
- dry eye syndrome
- corneal complications, such as, scarring, clouding, infection, inflammation, endothelial cell loss, edema, thinning (including corneal ectasia) and potential perforation of the cornea
- refractive shift
- the potential need for removal and its associated risks.

The Panel members' concerns regarding refractive stability (including refractive shift) were addressed by information provided after the Advisory Panel meeting. Although some Panel members had concerns regarding the rates of adverse events and removals, most common risks, including removals, seem to be treatable with little residual sequelae in most cases.

C. Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in a study of some of the subjects from the pivotal clinical trial for an additional two years and the confirmatory clinical trial conducted to support PMA approval as described above. This information supported the robustness of the effectiveness outcomes.

The risks may be mitigated by the revisions made to the proposed labeling, including the following:

- The applicant's proposed restrictions on the surgical parameters in the instructions for use to $\leq$ 6x6 lamellar pocket resections created by a femtosecond laser at a minimum depth of 200 microns.
- Discussion of the hazards related to the use of therapeutic lasers and photodynamic therapy and how to mitigate them in the physician labeling.

After the Advisory Panel meeting, analyses of the outcomes of the 6x6 pocket subgroup suggest that the risk/benefit ratio may be somewhat better when the procedure is performed according to parameters currently specified in the revised instructions for use.

Risks are also mitigated by the fact that the device is intended to be implanted in only one eye.

Careful patient selection according to the labeling and a thorough informed consent process will be of the utmost importance.

In conclusion, given the available information above, the data support that for intrastromal corneal implantation in the non-dominant eye of phakic subjects to improve near vision by extending the depth of focus in presbyopic subjects between the ages of 45 and 60 years old, who have cycloplegic refractive spherical equivalent of +0.50 D to -0.75 D with less than or equal to 0.75 D of refractive cylinder, who do not require glasses or contact lenses for clear distance vision, and who require near correction of +1.00 D to +2.50 D of reading add, the probable benefits outweigh the probable risks.

Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

XIV. CDRH DECISION

CDRH issued an approval order on April 17, 2015. The final conditions of approval cited in the approval order are described below.

1. Continuation Study:

The continuation study, conducted per protocol ACU-P012-020C approved under IDE G080184, is an ongoing prospective multi-center observational study designed to monitor the safety of patients who participated in the pivotal trial (ACU-P08-020/020A) and are still implanted with the KAMRA® inlay. Patients will be followed for an additional two years (a total of 5 years post implantation). Thirteen of the 15 US sites and 6 of the 9 OUS sites that participated in the pivotal trial are participating in the continuation study. Clinical evaluations are scheduled at 48 and 60 months post implantation. Eligible patients are those that completed the pivotal trial with the inlay still implanted at those sites participating in the continuation study and are considered enrolled in the study when the informed consent is signed. Both eyes of each patient are to be evaluated during the study.

The clinical parameters to be evaluated in this study are as follows:

- Specular Microscopy: all visits (implanted and fellow eyes).
- Slit lamp examination with fluorescein: all visits (implanted and fellow eyes).
- Fundus examination: all visits (implanted and fellow eye).
- Adverse Events and Complications: all visits.
- Manifest refraction (mid-point, no auto-refraction): all visits (implanted and fellow eyes)

- Uncorrected distance visual acuity (ETDRS): all visits (implanted eyes, fellow eyes, and both eyes together [OU]) at a testing distance of 6m/20 ft.
- Uncorrected near visual acuity: all visits (implanted eyes, fellow eyes, and OU) at a testing distance of 40 cm.
- Distance-corrected distance visual acuity (ETDRS): all visits (implanted eyes, fellow eyes, and OU)
- Computerized corneal topography: all visits (implanted and fellow eyes).
- Dry eye assessment (tear break-up time and anesthetisized Schirmer's test): all visits (implanted and fellow eyes)
- Mesopic & Photopic Contrast Sensitivity: all visits (implanted eye and OU)

Patients will be examined and evaluated according to the following schedule of visits:

- Visit 1 Month 48 (46 to 52 months post-op)
- Visit 2 Month 60 (58 to 64 months post-op)

Each of the clinical parameters will be evaluated at each visit.

2. New Enrollment Study:

The specific questions the study will address are: (1) What is the percentage of implanted eyes with uncorrected near visual acuity (UCNVA) of 20/40 or better through 5 years after implantation?; (2) What is the percentage of implanted eyes with a persistent loss of 2 lines or more in best-corrected distance visual acuity (BCDVA) through 5 years after implantation or 2 years after removal, whichever is longer?; and (3) What is the percentage of patient symptoms in the KAMRA® patient population?

This study will include 529 participants, which allows for a 20% dropout rate resulting in 423 participants with 60-month data. All 529 participants will take both the preoperative and postoperative version of the modified questionnaire.

This study will be conducted in two phases:

Phase 1: Questionnaire Development. Before starting enrollment for Phase 2 of the PAS, you will develop a questionnaire for the New Enrollment PAS by refining your prior Patient-Reported Outcome (PRO) questionnaire. You will conduct concept elicitation interviews to ensure measurement of relevant concepts, including Pulfrich's phenomenon, which is not addressed in the current version of the PRO questionnaire.

Cognitive debriefing interviews of the revised questionnaire should be performed with needed revisions being completed prior to starting the New Enrollment PAS. The qualitative evaluation of the PRO questionnaire, to be completed within six months of PMA approval, will consist of concept elicitation interviews and cognitive debriefing

interviews. The cognitive debriefing interviews should be conducted with a minimum of 20 patients (a minimum of 5 patients per item). The process will continue with up to 50 patients recruited from up to 5 investigative sites (or until concept saturation has been reached). The qualitative assessment will evaluate (1) the clarity of the items within the instrument; (2) how the respondents interpret the item(s); (3) ease of completion of the PROs; (4) the comprehensiveness of the PROs; and (5) the appropriateness of the format, response scales, and recall period used in the PROs.

Results of the cognitive debriefing findings will be evaluated after 50% of patients in each item group have been interviewed. After this phase, modifications (if needed) will be made to the questionnaire with the remaining 50% of the sample being debriefed on the revised questionnaire or taking the prior version of the questionnaire if no revisions are recommended. The findings including the transcripts, saturation grid, and all revisions with the data supporting those revisions should be included as part of your PAS interim reports.

Phase 2: New Enrollment. This Phase will begin after results from Phase 1 are accepted by FDA. Phase 2 will be a multicenter, prospective, single-arm study consisting of presbyopic patients with emmetropia (defined as having +0.50 D to -0.75 D refractive error) in both eyes, enrolled from 20-30 study sites in the USA for unilateral implantation of the KAMRA® inlay.

The quantitative questionnaire assessment, to be completed within nine months of initiating the Phase 2: New Enrollment study, will evaluate the psychometric properties of the revised questionnaire including evaluations of the:

1. preoperative questionnaire with a minimum of 100 patients composed of a balanced number of patients (approximately 15) in up to 12 clinical investigative sites, tested at baseline and screening (preoperative), to include and evaluation of the following: (a) Internal consistency reliability, (b)Test-retest reliability (in stable patients), (c) Clinical validity, (d) Known groups validity (differences in scores between patient reported severity and between those with and without known eye co-morbidities), (e) Item Response Theory and/or Factor Analysis to understand the factor structure and determine if scores would be more appropriate; and

2. postoperative questionnaire at the 3-month visit with a repeat administration performed between 7-14 days after the first administration with a minimum of 100 patients to examine all the aforementioned characteristics.

The primary effectiveness endpoint is the percentage of eyes with monocular photopic UCNVA of 20/40 or better (measured at 40cm/16in) at 60 months after implant must be ≥75% of best-case eyes with successful KAMRA® inlay implantation.

The primary safety endpoint tests whether fewer than 5% of eyes have a persistent loss of two lines or more of BCDVA at 60 months after inlay implantation or 24 months after removal, whichever is longer, with a one-sided alpha level of 0.05, 80% power, and a minimum detectable difference of 2.5%. Persistent loss of BCDVA is defined as a loss of two lines or more of BCDVA present at the subject's last visit. The secondary safety

endpoints will: (1) assess if less than 1% of eyes with preoperative best spectacle corrected distance visual acuity of 20/20 have BCDVA worse than 20/40 at 60 months and (2) assess whether ocular adverse events related to the device occur in no more than 10% of eyes and any single ocular adverse event related to the device should occur in no more than 2.5% of eyes.

Additional clinical outcomes include: change in distance-corrected near visual acuity (DCNVA), within participant change in UCNVA vs. uncorrected distance visual acuity (UCDVA), accommodative amplitude, stereoacuity (Randot Stereo test), refractive stability (Manifest refractive spherical equivalent – MRSE), change in topography over time, detailed ocular surface examination, assessment of dry eye syndrome, rate of corneal edema, retinal examination (dilated fundus exam; PI assessment of ease of examination), rate of adverse events, rate of device removals, information about cataract development and management, and visual symptoms (measured by PRO).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.