AcuFocus®
THE SMALL APERTURE COMPANY™

KAMRA® INLAY
PROFESSIONAL USE INFORMATION

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 diopters (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.

WARNING: The safety and effectiveness of the implantation of the device in conjunction or in sequence with LASIK or other refractive procedures is unknown.

CAUTION: Federal law restricts this device to sale by or on the order of a physician or other licensed practitioner. U.S. federal law restricts this device to practitioners who have been trained and have experience in the surgical management and treatment of refractive errors.

This document provides information concerning the intended clinical use of the KAMRA® inlay. Carefully read all instructions prior to use. Observe all contraindications, warnings, and precautions noted in these instructions. Failure to do so may result in patient and/or user complications.

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ACUFOCUS INC.
KAMRA® INLAY
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Caution: Federal law restricts this device to sale by, or on the order of, a physician.

Carefully read all instructions prior to use. Observe all contraindications, warnings, and precautions.

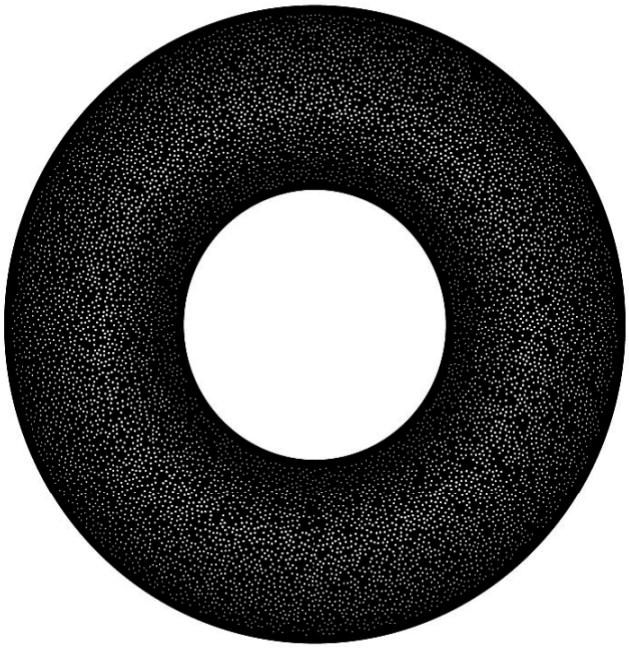
Warning: Specific training from AcuFocus, Inc. or an authorized representative of AcuFocus is required before anyone is qualified to implant the KAMRA® inlay.

SECTION 2
DEVICE DESCRIPTION

2.1 KAMRA® INLAY

The KAMRA inlay is a permanent implant shown in **Figure 1.** The device is implanted intrastromally in a femtosecond laser-created pocket. The opaque annulus of the inlay reduces the aperture of the eye, which improves near vision by providing an increased depth of focus in the implanted eye. The inlay is an opaque, porous disc made of polyvinylidine difluoride (PVDF), pigmented with carbon nano-particles.

FIGURE 1: KAMRA INLAY RENDERING SHOWING HOLE PATTERN IN ANNULUS



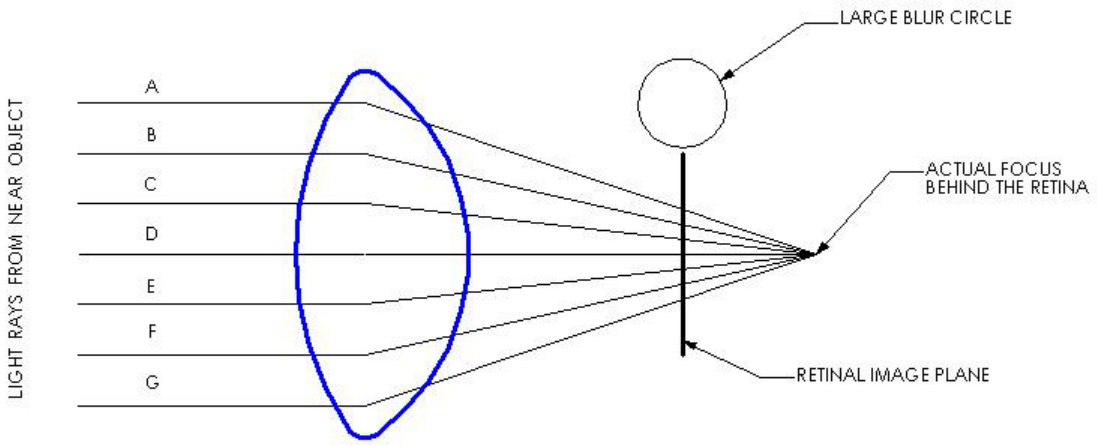
The specifications for the KAMRA inlay are provided below.

Inlay Inside Diameter:	1.6 mm
Inlay Outside Diameter:	3.8 mm
Spherical Radius:	7.5 mm
Thickness Specification	6 microns
Light Transmission Through Annulus	5% - 8,400 nutrition holes
Sterilization:	Ethylene Oxide
Packaging:	Double-Sterile Configuration
Labeling:	Single Use

The KAMRA® inlay represents technology based on the well-established concept of small-aperture optics. In cameras, depth of focus is increased by reducing the size of the aperture through which light enters: the smaller the aperture, the greater the depth of focus to a point at which the image quality becomes diffraction-limited. The KAMRA inlay aperture size has been optimized to provide the human eye with the best depth of focus and image quality.

In a presbyopic eye that does not require correction for distance vision, the crystalline lens cannot accommodate sufficiently to focus the light rays from a near object onto a single point on the retina. Thus, a point object is imaged as a blur circle on the retina. This concept is illustrated in **Figure 2.**

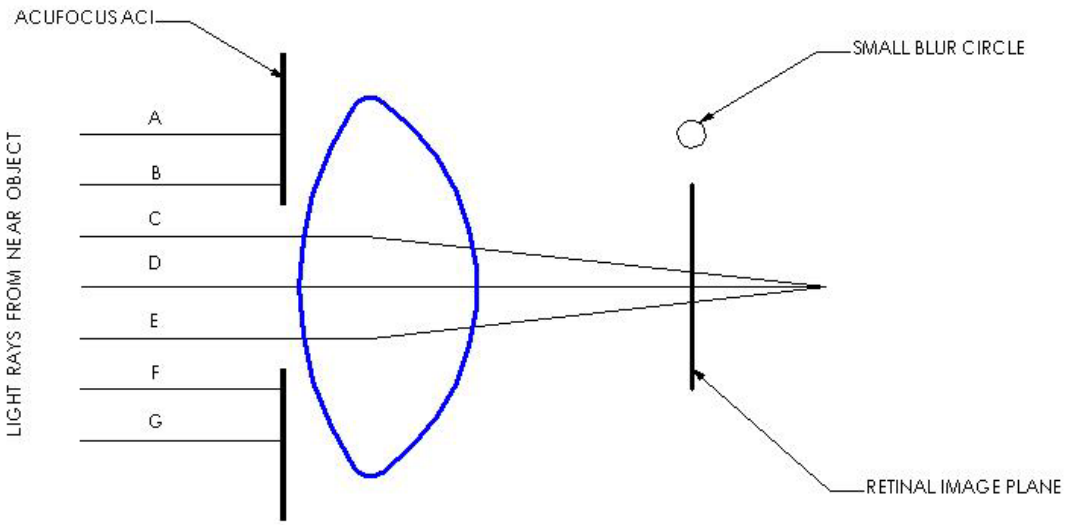
FIGURE 2. RAY TRACING FOR PRESBYOPIC EYE WITHOUT KAMRA INLAY



2.2 POTENTIAL BENEFITS OF THE KAMRA INLAY

When the KAMRA inlay is implanted in one eye of a presbyopic patient who does not require any correction for distance vision but requires correction for near vision, the increased depth of focus provides near vision while having a minimal effect on distance acuity. **Figure 3** shows that an opaque disc with a small aperture in the center placed in front of the eye obscures the peripheral rays while the central rays pass unaffected. Peripheral light rays enter the eye at a larger angle, thereby creating a larger blur circle at the retinal image plane. Therefore, eliminating these peripheral rays reduces the size of the blur circle and improves the image resolution for near.

FIGURE 3. RAY TRACING FOR PRESBYOPIC EYE WITH KAMRA INLAY (ONLY CENTRAL LIGHT RAYS C, D, AND E FORM AN IMAGE ON THE RETINA)



2.3. POTENTIAL RISKS OF THE KAMRA® INLAY

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.

Caution: 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.

- **Vision and Ocular Symptoms.** KAMRA inlay implantation may cause or worsen 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.

- **Contrast Sensitivity.** KAMRA inlay implantation may cause decreased contrast sensitivity in the implanted eye especially under dim illumination, night driving and 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, or macular degeneration or if they were to be implanted with a multifocal intraocular lens (IOL).

- **Evaluating and Managing Ocular Problems.** Diagnostic tests such as visual fields, fluorescein angiography, optical coherence tomography, binocular indirect ophthalmoscopy, and fundus photography in patients with the KAMRA inlay may

take longer and require some additional effort from the patient and the physician to perform. Furthermore, if the patient develops glaucoma or a retinal condition, some difficulty with conducting the ophthalmic examination and/or administering treatment is possible, and the inlay may need to be removed.

  - **Laser Treatments.** There are potential risks of damaging the cornea and/or inlay with the use of some medical lasers to treat certain eye conditions. In general, lasers with longer wavelengths (650 nm or more) and the lasers in the infrared spectrum are most likely to cause thermal damage to the inlay and to the surrounding corneal tissue. Thermal scarring has been reported resulting from LASIK flap creation with a femtosecond laser and photodynamic therapy. (Mita M, et al, 2013) Overlapping of the laser beam and the inlay annulus can also result in the release of pigmented carbon granules from the inlay into the corneal tissue.

- **Eye Infections.** There is a risk of infection and/or inflammation to the anterior segment of the eye, as a result of KAMRA® inlay implantation.

- **Dry Eyes.** There is a risk of developing a new dry eye condition or exacerbation of an existing dry eye condition after the implantation procedure. A patient experiencing dry eye symptoms may require treatment with artificial tears, punctal plugs, and/or other therapy depending on the severity of the dry eye condition.

- **Corneal Complications.** Other risks include, but are not limited to, complications related to the cornea, such as, scarring, haze, infection, inflammation, edema, stromal thinning, corneal melt, endothelial cell loss, and corneal decompensation. In cases of severe corneal compromise, the patient may require keratoplasty.

- **Corneal Ectasia.** Implanting the inlay in a thin cornea (less than 500 microns in thickness) or a forme fruste keratoconus condition increases the risk for corneal ectasia. If the ectasia is advanced, the patient may require keratoplasty.

- **Cataract.** There is a risk of developing a cataract in the implant eye as a result of normal aging, which could impact vision in the eye sooner and to a greater degree with the inlay present. Cataract removal with intraocular lens implantation is possible with the inlay in place. However, the safety and effectiveness of cataract extraction with intraocular lens implantation after KAMRA inlay implantation is not known.

- **Refractive Error Change.** There is a potential risk for refractive error shift in the KAMRA inlay eye.

- **Intraocular Pressure.** There is a potential risk for intraocular pressure to increase as a result of using steroid drops following the surgery.

- **Vision Loss.** Vision problems may occur that cannot be corrected, even if the device is removed. In most cases, removal of the inlay will result in a return to the preoperative vision level. However, this return may take a number of months, and it is possible that some loss of vision and/or changes in the cornea may be permanent.

- **Pulfrich Effect.** Some KAMRA® inlay patients may misperceive distances and the direction and/or location and speed of moving objects due to the difference in the amount of light hitting the retinas of the KAMRA inlay implanted eye and the non-implanted eye, also known as “Pulfrich effect”, particularly during the early postoperative period. It is anticipated that for most patients who experience symptoms related to this effect, the symptoms will diminish or disappear over time (Douthwaite WA, Morrison LC., 1975). It is possible, however, that some patients may experience permanent symptoms. The percentage of patients implanted with the KAMRA inlay that experience symptoms related to this effect and the way that these symptoms change over time were not investigated in the clinical studies.

2.4. ALTERNATIVE TREATMENTS FOR PRESBYOPIA

The KAMRA inlay procedure is an elective procedure. Other possible alternatives for treating presbyopia may be:

- Monofocal, bifocal, trifocal, and/or progressive spectacles: Spectacles can be worn, removed and replaced easily. If the power or the fitting of the spectacles is incorrect, it can lead to inadequate vision correction, headaches. and eye strain.
- Contact lenses (monofocal, bifocal, trifocal, and multifocal): In monovision, one eye is corrected for distance (or no contact lens is used in this eye, if the uncorrected distance vision is good) and the other eye is corrected for near vision. Often, patients do well with monovision, though some may have difficulty adapting to it. Contact lenses offer cosmetic benefits and can be used by patients with active lifestyles. The lenses should be cleaned and disinfected or replaced frequently to avoid redness, irritation, and eye infections.
- Conductive keratoplasty (CK): CK utilizes radio frequency energy to improve near vision by inducing myopia. CK surgically creates monovision by reshaping the cornea to improve near vision in one eye. However, this effect is temporary because the correction can diminish over time.
- Monovision LASIK (laser-assisted in situ keratomileusis): Monovision LASIK treatment may help patients see clearly both far away and close up without glasses or contact lenses. Only one eye will be treated for near distance if the patient has good uncorrected distance visual acuity. Patients may require another treatment if results are not satisfactory. There are other risks involved with the LASIK procedure, such as, dry eyes, visual symptoms, including glare, halos, starbursts, ghost images/double vision, and problems with night driving, and flap complications.

SECTION 3
INDICATIONS, CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

3.1 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 diopters (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.

3.2 CONTRAINDICATIONS

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.

3.3. WARNINGS

There is reasonable evidence of a serious hazard if the KAMRA inlay is implanted in patients with:

- dry eye syndrome, which may worsen following KAMRA inlay implantation;
- past herpes infection, which might increase the risk of corneal infections;
- controlled glaucoma, which may worsen with steroid use following KAMRA inlay implantation;
- significant change in distance manifest refraction , i.e., a change in distance manifest refraction of more than 0.50 diopter in the last 12 months, which might prevent the patient from experiencing an improvement in near vision following KAMRA inlay implantation;
- controlled autoimmune or connective tissue disease, which may affect wound healing following KAMRA inlay implantation;

- a weakened immune system or who are on chronic steroids or other immunosuppressive therapy that may affect wound healing following KAMRA inlay implantation;
- controlled diabetes, which may affect wound healing following KAMRA inlay implantation;
- taking isotretinoin, which may cause changes to patients vision following KAMRA inlay implantation;
- any corneal dystrophy or corneal degeneration that may worsen and decrease vision following KAMRA inlay implantation;
- macular degeneration, retinal detachment, cataract, or any other disease that would compromise vision and prevent patients from experiencing an improvement in near vision following implantation of the KAMRA inlay;
- an irreversible decrease in vision in either eye, e.g., resulting from amblyopia, injury, disease, or other abnormality which might prevent the patient from experiencing an improvement in near vision following implantation of the KAMRA inlay;
- chronic medications known to worsen or cause severe dry eye. These medications include anti-histamines, beta-blockers, birth control pills, diuretics, drugs for the treatment of cardiac arrhythmia, or other medications which may worsen dryness symptoms following implantation of the KAMRA inlay;
- a cornea less than 500 microns thick to allow for a minimum depth of 200 microns for the lamellar pocket and a minimum of 250 microns of residual posterior stromal bed thickness to safely perform the procedure; or
- a habit of extreme and frequent eye rubbing, which may cause the KAMRA inlay to dislodge after surgery.

The inlay should be removed prior to any laser procedure to lower intraocular pressure due to the risk of thermal damage to the inlay and the eye.

The inlay should be removed prior to any non-focal, posterior segment, laser treatment of the eye, e.g., panretinal photocoagulation, due to the risk of thermal damage to the inlay and the eye.

LASIK flap creation with a femtosecond laser (1053 nm) cannot be performed with the KAMRA inlay in place due to the risk of thermal damage to the inlay and the surrounding corneal tissue.

Remove the inlay prior to performing photodynamic therapy due to the risk of damage to the inlay and cornea.

3.4. PRECAUTIONS

- Smooth-jawed forceps should be used when handling the inlay. Toothed or textured forceps may damage or distort the inlay. If the inlay appears damaged or distorted, discard and replace the inlay.
- Do not implant the inlay under a lamellar pocket shallower than 200 microns from the epithelium.
- Do not use the inlay if primary package has been damaged or broken.
- Do not resterilize the inlay, as it may become damaged.
- Do not reuse the inlay, as it may cause infection or cross-contamination.
- Removal of the inlay may be necessary prior to any retinal or vitreal procedures.
- Removal of the inlay is recommended prior to any laser photocoagulation due to the risk of thermal damage to the inlay and the eye.
- The safety and effectiveness of KAMRA® inlay implantation in conjunction or in sequence with LASIK or other refractive procedures is not known.
- The safety and effectiveness of cataract extraction with intraocular lens implantation after KAMRA inlay implantation is not known.
- If a patient undergoes cataract extraction following KAMRA inlay implantation and requires laser capsulotomy, care should be taken to avoid direct laser contact with the inlay annulus in order to prevent damage to the inlay and cornea. The laser beam should be directed around the periphery of the inlay
- If a patient is wearing contact lenses to correct near vision, then contact lens wear should be discontinued and topographic and refractive stability confirmed prior to determining whether the patient is an appropriate candidate for KAMRA inlay implantation and prior to undergoing surgery. The time to stability of corneal changes after cessation of contact lens wear is highly variable among patients, but depends somewhat on the type of contact lens and how long the patient has been wearing contact lenses. In general, rigid gas permeable (RGP) lenses have to be discontinued for 4 weeks for every decade of wear, polymethyl methacrylate (PMMA) lenses for 6 weeks for every decade of wear, and daily wear soft contact lenses for 1-2 weeks before stability is achieved (Machat JJ, 1996). (Bergenske, PD*, et al, 2002). Contact lens wearers should exhibit a stable refraction at two examinations that are at least 7 days apart. A stable preoperative refraction is defined as when the manifest refractive spherical equivalent and topography measurements (i.e., average central keratometric measurements) obtained at*

the first visit do not differ by more than 0.50 D from the respective measurements taken at the second visit.

- Patients should be instructed not to rub their eyes, wear eye make-up, exercise, swim, garden, play contact sports, smoke, or sustain exposure to dusty environments for at least the first week following KAMRA inlay implantation.
- Some patients may experience a delayed recovery of best-corrected visual acuity during the postoperative period. This is usually mitigated through the use of aggressive dry eye treatment. In order to rule out early corneal changes that may be associated with corneal thinning, slit lamp examinations with fluorescein staining and topographic imaging should be performed at postoperative visits as necessary.

While the following are potential risks, it is not known whether the KAMRA inlay causes the following adverse events, since they were not studied:

- It is unknown whether stereoacuity is affected by implantation of the device, since this was not investigated in the clinical trial;
- Some KAMRA® inlay patients may misperceive the direction of moving objects, also known as the Pulfrich effect.

The safety and effectiveness of the KAMRA inlay has NOT been established in:

- Patients with active/history of blepharitis;
- Patients with anesthetized Schirmer's test results of less than 10 mm of wetting or tear break-up times of less than 10 seconds, and patients with slit lamp findings of corneal staining with sodium fluorescein or rose bengal;
- Patients who have worn RGP or PMMA contact lenses in the last 6 months or soft contact lenses within a week of surgery.
- Patients with corneal endothelial cell counts of <2000 cells/mm^2;
- Patients with previous eye surgeries, including refractive surgery, such as PRK, RK, LASIK, LASEK, or another type of refractive procedure, and cataract surgery;
- Patients who have a difference of 1.00 D or more between manifest and cycloplegic refraction;
- Patients with ocular hypertension and/or glaucoma suspect;
- Patients taking amiodarone hydrochloride;
- Patients taking sumatriptan;
- Patients who have a family history or signs of keratoconus, pellucid marginal degeneration, or any other condition that may cause thinning of the cornea;
- Patients with a history of eye injury;
- Patients with a history of inactive ocular infection or inflammation;

- Patients not within the age group specified in the indications for use;
- Patients with abnormal threshold visual field;
- Patients who require canthotomy to generate a lamellar dissection in the KAMRA inlay eye.

SECTION 4
SURGICAL PLANNING AND PROCEDURES

4.1 PREOPERATIVE PREPARATION

PATIENT SELECTION

Ideal KAMRA® inlay patient profile:

- Between the ages of 45 and 60 years with a cycloplegic spherical equivalent refraction between +0.50 D to -0.75 D
- Less than 0.75 D of cylinder
- Less than 1.00 D of difference between their cycloplegic and manifest spherical equivalent refraction
- Less than or equal to 0.50 D change in manifest refractive spherical equivalent in the last 12 months
- Requires near add of +1.00 to +2.50 D
- Best-corrected visual acuity of 20/20
- Is in good general health

PREOPERATIVE ASSESSMENT

A comprehensive eye examination should be performed preoperatively. During the comprehensive examination, the surgeon must evaluate the patient for conditions that could result in poor outcomes with the KAMRA inlay and for ocular dominance. Slit lamp examination must be performed to evaluate for eyelid diseases, ocular surface diseases, and cataract. Patients should be evaluated for dry eye syndrome. A dilated fundus examination should be performed to evaluate the patient for retinal and optic nerve diseases. A monovision trial, e.g., a monovision contact lens trial, should be performed in order to evaluate patient tolerance to having the distance vision slightly more blurred for distance but less blurred for near in the implanted eye compared to the fellow eye. However, the KAMRA inlay differs from monovision, since it improves near vision by increasing the depth of focus rather than changing the refraction and causes less light to enter the eye than the fellow eye. Therefore, a monovision trial is expected to be less predictive of patients who will not tolerate KAMRA inlay implantation than when such a trial is used prior to an actual monovision treatment.

4.2 SURGICAL PROCEDURE FOR IMPLANTATION OF KAMRA INLAY

- The KAMRA inlay should be implanted in the non-dominant eye.

- Instill 2% pilocarpine to create a miotic pupil 30 to 60 minutes prior to implantation. This allows the pupil diameter to become visible through or near the inner diameter of the KAMRA inlay to facilitate positioning.

- Use a pocket software approved femtosecond laser with ≤ 6 µm x 6 µm spot/line separation or equivalent to create a stromal pocket with a minimum depth of 200 microns for placement of the KAMRA® inlay.

- Remove the KAMRA inlay from the sterile package with forceps and inspect the inlay under high magnification to look for any defects or folds/creases that may have occurred during shipping or handling. The KAMRA inlay may only be placed onto a sterile surface.

- The target-depth for the intrastromal pocket should be between 200 and 250 µm

- Proper Pocket Side-Cut Incision Placement:

    - Place the incision as close as possible to the temporal limbus to avoid induced astigmatism and coma
    - Target within 0.5 mm of the limbus to avoid the limbal arcade
    - Mark this area once using the LASIK Flap Edge and Corneal Limbus Marker *or similar marker*
    - Wash away excessive ink
    - Utilize the laser centration software to adjust side cut incision to optimal location
    - After applanation, visualize the temporal limbal mark

- Mark the Cornea to Aid Inlay Centration

    - Using a coaxially sighted corneal reflex of the 1st Purkinje image for optimal inlay centration and corneal marking*, estimating the difference between the center of the pupil and the 1st Purkinje image.*
        - If the distance between the center of the pupil and the 1st Purkinje image is minimal (< 300 microns): Center the marker on the 1st Purkinje image
        - If the distance between the center of the pupil and the 1st Purkinje image is large (>300 microns): Center marker ½ way in-between the center of the pupil and the 1st Purkinje image
        - Bias inlay *centration* inferior nasal*ly* for best results
    - Mark cornea with 4 mm ring-marker
    - Wash away excessive ink
- Create the pocket with a femtosecond laser using a spot/line separation of ≤ 6 µm x 6 µm or equivalent
- Dissect Pocket:

    - Dry the fornix with a sponge to prevent fluid from entering the interface

        - This is particularly important for deep set globes
        - Fluid in the interface may cause the inlay to stick to the forceps. If fluid does enter pocket, wait a few moments for fluid to dissipate
        - Keep corneal surface moist for best visualization
    - Dissect the pocket opening with a Sinskey Hook and dissect pocket with dissector or blunt spatula
        - Extend dissection a minimum of 1 mm beyond circular centration mark
        - Use a long tip Sinskey Hook or similar instrument to hold open the pocket side cut incision
        - Use a 0.12 forceps to stabilize the globe
- What NOT to do when dissecting the pocket:
    - DO NOT proceed with inlay insertion if there is bleeding. Wait until all bleeding has stopped
    - DO NOT use *balance salt solution (*BSS*)* within the pocket
    - DO NOT leave any of the pocket undissected. Surgeons should dissect the whole pocket as they will need all available space to insert the inlay and adjust location
- Load Inlay
    - Load inlay into the forceps with the dull surface facing up
    - Outer 1/4 of the inlay edge should be exposed from the forceps
- Insert and Center Inlay
    - Have the patient fixates straight up at *the* light in *the micro*scope prior *to* and during insertion.
    - Use a long tip Sinskey hook or similar instrument to open the pocket side cut
    - Handle the inlay with care to avoid damage
    - When entering the pocket opening, align the forceps with the angle of the entry incision
    - Make small movements to keep inlay moving smoothly
    - Go past centration mark if the inlay folds and then pull it back into position

- Attempt to insert and properly align in *a* single step

- Release Inlay and Remove Forceps
  - Let inlay “set” for 3 seconds prior to removing forceps
  - Open forceps slightly and remove slowly to avoid inlay displacement
  - If the inlay sticks to forceps start again

- Confirm Centration
  - Visually inspect that the inlay is in the desired location
  - If the inlay is not properly positioned, then the inlay should be repositioned.

- Use a moist ophthalmic surgical sponge soaked in sterile balanced salt solution, gently smooth the edge of the pocket opening.

- Irrigate the surface of the eye and then use a dry ophthalmic surgical sponge to dry the corneal surface.

- At the end of the procedure, it is recommended that you administer a broad spectrum topical ophthalmic antibiotic solution and a steroid such as prednisolone acetate.

- An ocular shield may be placed over the eye. The eye should be left open and not taped shut.

4.3 POSTOPERATIVE CARE

The following postoperative procedures are recommended:

- A broad spectrum topical ophthalmic antibiotic four times a day for a minimum of 1 week;
- Steroid ophthalmic suspension four times a day for the first week, three times a day for the second week, two times a day for the third week, and once a day for the fourth postoperative week;

- Unpreserved artificial tears four times a day for up to 1 month and continued as needed;

- Punctal plugs may be inserted at any time as needed.

Regular postoperative follow-up examinations must be performed for the first year following implantation. The surgeon must monitor patient’s vision, refraction, ocular

health, and inlay position regularly. Surgeons should particularly monitor patients for any signs of dry eye syndrome, abnormal corneal wound healing, and stromal thinning, and for changes to corneal topography. If a patient has a loss in vision, the inlay may need to be repositioned.

4.4 INLAY REMOVAL

It is recommended that the surgeon consider removing the KAMRA® inlay under the following circumstances:

- Diagnosed diffuse lamellar keratitis (DLK) or any inflammatory process not resolved within one week or sooner if no improvement in condition is noted;
- Epithelial defect with no sign of healing within one week of presentation;
- Evidence of progressive lamellar resection thinning or loss of 25% of corneal thickness over the inlay or a corneal melt requiring removal of the inlay at the earliest possible opportunity, if not immediately;
- A loss of more than 3 lines in visual acuity, unless the patient is satisfied with overall visual acuity;
- Epithelial ingrowth not resolved after three scrapings; or
- If the patient has not successfully adapted to the expected changes in vision from the KAMRA inlay within a period of 12 months. (Note: Due to a period of adaptation which includes vision adaptation and improvement of visual acuity both at near and far, patients should be encouraged to continue with the implant during the first six months).

4.5 SURGICAL PROCEDURE FOR INLAY REMOVAL

The following is the recommended procedure for removal of the inlay:

- Prepare the eye as per sterile technique with anesthetic;
- Locate the pocket side cut, use an ophthalmic Sinskey Hook to open side cut with gentle superior and inferior motion. If locating the side cut is challenging, instruct the patient to look nasally to locate and cut through it;
- Enter the pocket with an ophthalmic spatula and dissect anterior and posterior to the inlay to free it of stromal adhesions;
- Remove the inlay by rotating the spatula toward the central inlay aperture;

- Perform postoperative evaluation of the cornea verifying safe removal. The surgeon should examine the corneal pocket immediately following the surgery to ensure the inlay is completely removed.

4.6 POSTOPERATIVE CARE FOLLOWING INLAY REMOVAL

The following are the recommended postoperative care instructions following the removal of the inlay:

- A broad spectrum topical ophthalmic antibiotic four times a day for a minimum of 1 week;
- Steroid ophthalmic suspension four times a day for the first week;
- Beginning the second week, switch to a weaker steroid, such as loteprednol etabonate 0.5% (or equivalent), and taper as needed;
- Monitor patient recovery with regular follow up exams. The surgeon should monitor the recovery of the patient’s best-corrected visual acuity;
- The patient may experience delayed recovery of best-corrected distance visual acuity following removal, and there is a potential for loss of uncorrected and best-corrected visual acuity. This should be described to all patients in the informed consent document.

SECTION 5
CLINICAL RESULTS

A prospective, multicenter, single-arm, open-label ("pivotal") study was conducted to evaluate the safety and effectiveness of the KAMRA® inlay implanted intrastromally in presbyopes for improvement of near vision. This study included 508 eyes of 508 study subjects, who were to be followed for 36 months after KAMRA inlay implantation. The pivotal study was extended ("continuation study") to increase the follow-up time to 60 months for eligible returning subjects who completed the pivotal study and agreed to continue to 60 months.

In the pivotal study, a total of 24 sites participated; fifteen (15) sites were in the U.S. (402 subjects enrolled and 389 subjects implanted), and nine (9) sites were outside the U.S. (119 subjects enrolled and 118 implanted). All subjects were enrolled under identical eligibility criteria and followed using the same protocol procedures. A total of 521 subjects were enrolled and 507 subjects were implanted with the KAMRA inlay in the pivotal study.

Most subjects in the study were Caucasian. No subjects were under 45 years of age or over 60 years of age. Approximately half of subjects were male and half were female. Approximately one-third of subjects were implanted with the inlay in the right eye and two-thirds were implanted in the left eye.

Results from the pivotal study that was specifically designed to support FDA approval of the KAMRA inlay, and results from the continuation study are presented below.

5.1 EFFECTIVENESS

The primary effectiveness criterion was 75% of implanted eyes should achieve uncorrected near visual acuity of 20/40 or better at 12 months. The lower bound of the 95% confidence interval (95CI) of the primary effectiveness parameter should be at or above 75% at 12 months for the studies to be considered successful.

Clinical study results demonstrated an improvement in uncorrected near vision (at 40 cm) with the KAMRA® inlay. Uncorrected intermediate vision (at 80 cm) was slightly improved, while uncorrected distance vision (at 6 m) in implanted eyes was slightly decreased. Mean changes in uncorrected near vision, intermediate vision, and distance vision at 12 months from baseline were three lines, one line, and half a line, respectively.

Uncorrected Near Visual Acuity

The effectiveness of the inlay was primarily assessed by monocular uncorrected near vision (UCNVA), and the endpoint target was 75% of the subjects with 20/40 or better uncorrected vision in the inlay eye at 12 months postoperative. Preoperatively, none (0/508) of the subjects could see 20/40 or better at near without correction in the eye planned for inlay implantation. At 12 months postoperative, 83.5% (399/478) of subjects had 20/40 or better uncorrected near vision. This increased to 87.2% (380/436) at 24 months, 87.1% (363/417) at 36 months and 87.1% (175/201) at 60 months. The study successfully met the primary effectiveness criterion of 75%, with the lower 95CI bound being 79.8% at 12 months postoperative. Results are detailed in **Table 1** and **Figure 4**.

TABLE 1

UNCORRECTED NEAR VISUAL ACUITY (UCNVA) DISTRIBUTION & MEANS IN IMPLANTED EYES

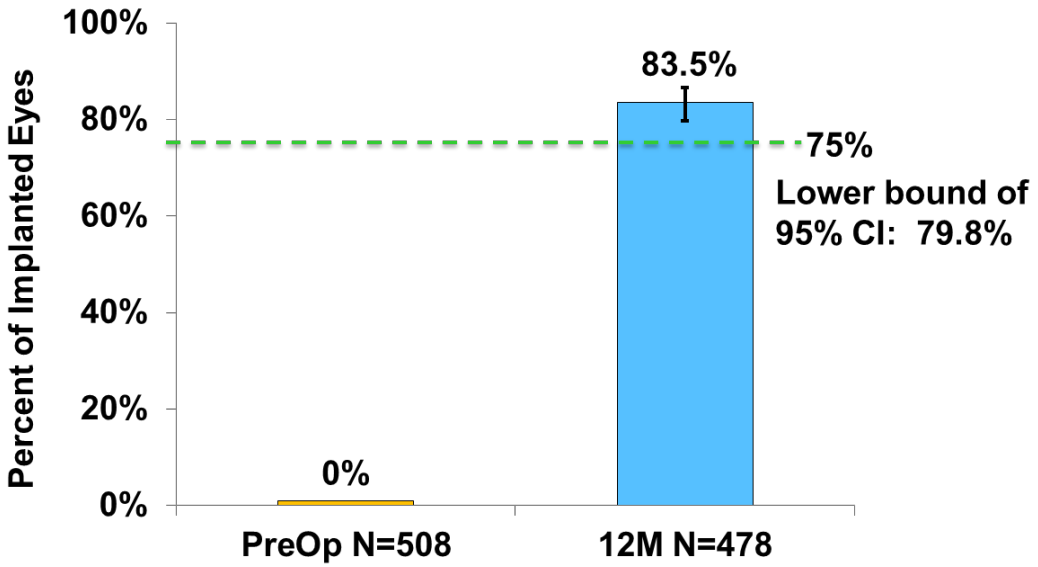
UCNVA	Preoperative n/N (%)	12 Months n/N (%)	24 Months n/N (%)	36 Months n/N (%)	60 Months n/N (%)
20/20 or better	0/508 (0.0%)	106/478 (22.2%)	122/436 (28.0%)	121/417 (29.0%)	62/201 (30.8%)
20/25 or better	0/508 (0.0%)	221/478 (46.2%)	220/436 (50.5%)	223/417 (53.5%)	97/201 (48.3%)
20/32 or better	0/508 (0.0%)	329/478 (68.8%)	305/436 (70.0%)	302/417 (72.4%)	136/201 (67.7%)
20/40 or better	0/508 (0.0%)	399/478 (83.5%)	380/436 (87.2%)	363/417 (87.1%)	175/201 (87.1%)
20/50 or better	183/508 (36.0%)	449/478 (93.9%)	418/436 (95.9%)	402/417 (96.4%)	194/201 (96.5%)
20/63 or better	413/508 (81.3%)	471/478 (98.5%)	433/436 (99.3%)	416/417 (99.8%)	199/201 (99.0%)
20/80 or better	507/508 (99.8%)	474/478 (99.2%)	435/436 (99.8%)	417/417 (100.0%)	200/201 (99.5%)
Worse than 20/80	1/508 (0.2%)	4/478 (0.8%)	1/436 (0.2%)	0/417 (0.0%)	1/201 (0.5%)
Mean (SD) letter	25.9 (3.8)	40.8 (8.2)	41.8 (8.1)	42.2 (8.1)	41.8 (8.1)
Mean Snellen Equivalent	20/60.8	20/30.6	20/29.1	20/28.7	20/29.2
Not reported*	0	0	0	0	0
Total†	508	478	436	417	201

N = Number of CRFs received with non-missing values at each visit

* Number of CRFs received with missing values at each visit

† Number of CRFs received at each visit

FIGURE 4. PRIMARY EFFECTIVENESS ENDPOINT: UCNVA IN IMPLANTED EYES



Binocular Uncorrected Near Visual Acuity

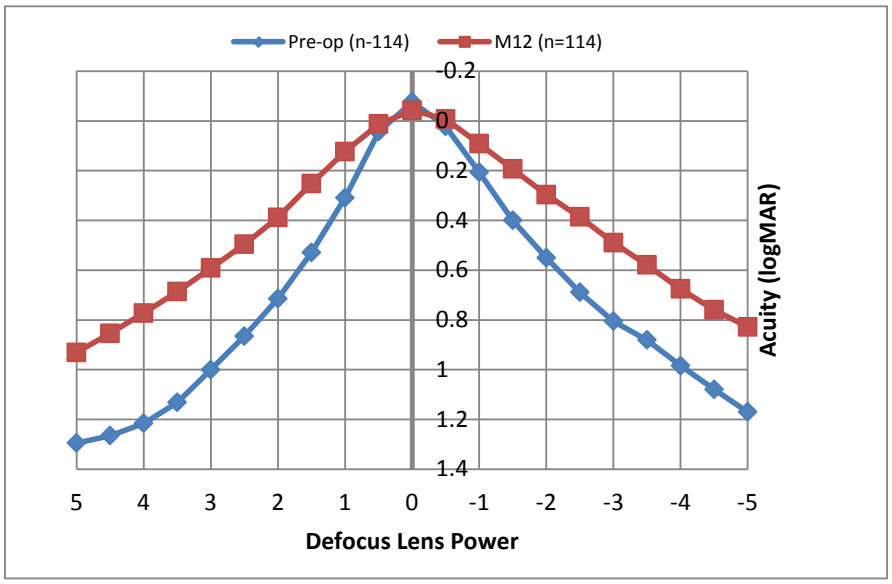
Preoperatively, 43.3% (220/508) of all study subjects had binocular uncorrected near vision of 20/40 or better. Postoperatively, 91.8% (439/478) all subjects were 20/40 or better at 12 months, 93.1% (406/436) at 24 months, 93.8% (391/417) at 36 months and 94.5% (190/201) at 60 months. This proportion of subjects with 20/40 or better binocular uncorrected near vision has remained relatively stable over the course of 60 months.

Defocus Curves

The underlying mechanism of the KAMRA® inlay, i.e., increase in depth of focus, is further substantiated in the defocus curves obtained at baseline and 12 months in a subset of 114 eyes with the KAMRA inlay.

Distance threshold acuities were determined for defocus levels ranging from +5.00 D to -5.00 D over the midpoint refraction in 0.50 D steps. Acuities were recorded in logMAR values and the mean acuities at each defocus point were used to compare preoperative and postoperative results, presented in **Figure 5**. Mean visual acuities improved for both positive and negative defocus after implantation of the KAMRA inlay. The flatter postoperative defocus curve indicates an increased depth of focus in comparison to the preoperative defocus curve.

FIGURE 5. MEAN PREOPERATIVE AND POSTOPERATIVE DEFOCUS CURVES AT 12 MONTHS (SUBGROUP)



5.2 SAFETY

The safety of the KAMRA® inlay was primarily assessed through changes in best-corrected distance visual acuity (BCDVA), the amount of induced astigmatism in inlay eyes, and adverse events in all subjects. The safety criteria for the clinical studies were as follows:

- Less than 5% of eyes should have a persistent loss of two or more lines of BCDVA at 12 months postoperative.
- Less than 1% of eyes with preoperative BCDVA of 20/20 should have BCDVA worse than 20/40 at 12 months postoperative.
- Less than 1% of eyes should have clinically significant (greater than 2-line loss of BCDVA not due to irregular astigmatism) corneal haze at 12 months postoperative.
- Less than 5% of eyes should have postoperative manifest refractive astigmatism at 12 months that is increased from preoperative baseline by greater than 2.00 D.
- Adverse events related to the inlay should occur in no more than 5% of eyes. Any single adverse event related to the inlay should occur in no more than 1% of eyes.

Additional assessments of safety covered in this section include endothelial cell density, contrast sensitivity, visual fields, and visual and ocular symptoms.

Table 2 presents the results for the key safety parameters, including the key safety endpoints as listed above (except for adverse event rates) and loss of BCDVA.

TABLE 2
SUMMARY OF KEY VISUAL SAFETY OUTCOMES

	12 Months n/N (%)	24 Months n/N (%)	36 Months n/N (%)	48 Months n/N (%)	60 Months n/N (%)
BCDVA loss ≥ 2 lines	8/479 (1.7%)	15/442 (3.4%)	9/424 (2.1%)	8/269 (3.0%)	8/202 (4.0%)
Persistent BCDVA loss ≥ 2 lines (2 consecutive visits)	3/479 (0.6%)	5/442 (1.1%)	6/424 (1.4%)	2/269 (0.7%)	2/202 (1.5 %)
BCDVA loss > 2 lines	3/479 (0.6%)	12/442 (2.7%)	5/424 (1.2%)	7/269 (2.6%)	7/202 (3.5%)
BCDVA worse than 20/40 if 20/20 or better preoperatively	0/479 (0.0%)	1/442 (0.2%)	0/424 (0.0%)	0/269 (0.0%)	0/202 (0.0%)
Haze ≥ Trace with loss of BCDVA > 2 lines	0/479 (0.0%)	1/441 (0.2%)	1/424 (0.2%)	0/269 (0.0%)	1/196 (0.5%)
Increase manifest refractive astigmatism > 2.00 D	0/477 (0.0%)	1/441 (0.2%)	2/423 (0.5%)	0/269 (0.0%)	0/201 (0.0%)

Monocular Best-Corrected Distance Visual Acuity After Surgery

All subjects had 20/20 or better BCDVA before surgery. There were no subjects (0/479) who had BCDVA worse than 20/40 at 12 months, 0.2% (1/442) at 24 months, 0% (0/424) at 36 months and 0% (0/202) at 60 months. At all times after surgery, approximately 99% of subjects had 20/25 or better BCDVA in the implanted eyes: 99.2% (475/479) at 12 months, 98.0% (433/442) at 24 months, 99.1% (420/424) at 36 months and 97.5% (197/202) at 60 months. More than 91% of the subjects had 20/20 or better BCDVA in their implanted eyes at any time after surgery, 93.9% (450/479) at 12 months, 94.1% (416/442) at 24 months, 94.8% (402/424) at 36 months and 91.6% (185/202) at 60 months.

Change in Monocular Best-Corrected Distance Visual Acuity After Surgery

At any time after surgery, less than 2% of eyes had a loss of two or more lines of BCDVA from before surgery that persisted over two consecutive visits greater than or equal to 3 months apart. There were 0.6% (3/479) of such eyes at 12 months, 1.1% (5/442) at 24 months, 1.4% (6/424) at 36 months and 1.5% (2/202) at 60 months. The average change in BCDVA for the implanted eyes after surgery was no more than half a line of visual acuity (less than or equal to a 2-letter loss) over the 36-month course of the study when compared to before surgery.

Corneal Haze and Astigmatism

There were no eyes (0/479) with significant corneal haze and decreased BCDVA of more than two lines at 12 months, 0.2% (1/442) at 24 months, 0.2% (1/424) at 36 months, and 0.5% (1/196) at 60 months.

There were no eyes (0/477) with manifest refractive astigmatism that increased by greater than 2.00 D at 12 month after surgery, 0.2% (1/441) at 24 months, 0.5% (2/423) at 36 months, and 0% (0/201) at 60 months.

Change in Uncorrected Near and Uncorrected Distance Visual Acuity After Surgery

The average gain in UCNVA after surgery was 3 lines of near acuity. At 12 months, there were 74.5% (356/478) of subjects who gained 2 or more lines of near acuity. The average change in uncorrected distance visual acuity (UCDVA) after surgery was a decrease of approximately 3 letters (equivalent to half a line) of distance acuity. At 12 months, there were 27.6% (132/478) who had a decrease of 1 or more lines of distance acuity.

When the uncorrected distance and near visual acuities are examined in combination, the proportion of subjects who did not gain 2 lines of near acuity and who lost more than 1 line of distance acuity was 10.5% (50/478) at 12 months.

The combined uncorrected near visual acuity and uncorrected distance visual acuity at 12 months showed that 78.5% (375/478) of subjects demonstrated uncorrected near visual acuity at 20/40 or better and uncorrected distance visual acuity of 20/25 or better; no subjects were in this combined visual acuity category at baseline (**Table 3**).

TABLE 3
COMBINED UCDVA AND UCNVA IN THE PIVOTAL STUDY

Combined UCDVA and UCNVA	Pre-Op (N=478)	Month 12 (N=478)
UCDVA < 20/25 & UCNVA < 20/40	12 (2.5%)	32 (6.7%)
UCDVA < 20/25 & UCNVA ≥ 20/40	0 (0.0%)	24 (5.0%)
UCDVA ≥ 20/25 & UCNVA < 20/40	466 (97.5%)	47 (9.8%)
UCDVA ≥ 20/25 & UCNVA ≥ 20/40	0 (0.0%)	375 (78.5%)

*12-month cohort = subjects who were available for both Pre-Op and 12 months effectiveness analysis

Adverse Events and Complications

Some subjects from the pivotal trial and the continuation study experienced adverse events that were possibly related to the inlay implantation procedure or to the presence of the inlay in the eye. All postoperative adverse events in the eyes possibly related or unrelated to the inlay or the surgery are reported here (**Table 4**).

TABLE 4
POSTOPERATIVE OCULAR ADVERSE EVENTS & COMPLICATIONS

		PIVOTAL STUDY FULL COHORT (N=508)						CONTINUATION STUDY FULL COHORT (N=269)	
		Through 12 Months		Through 24 Months		Through 36 Months		48-60 Months	
Category	**Adverse Events**	**# 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%)
	Conjunctival concretion	0	0 (0.0%)	1	1 (0.2%)	1	1 (0.2%)	0	0 (0.0%)
	Conjunctival cyst	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	1	1 (0.4%)
	Conjunctivitis	5	5 (1.0%)	8	7 (1.4%)	11	10 (2.0%)	0	0 (0.0%)
	Episcleritis	0	0 (0.0%)	1	1 (0.2%)	1	1 (0.2%)	0	0 (0.0%)
Cornea	Amorphous material anterior to inlay fold	1	1 (0.2%)	1	1 (0.2%)	1	1 (0.2%)	0	0 (0.0%)
	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%)
	Corneal ulcer	0	0 (0.0%)	0	0 (0.0%)	1	1 (0.2%)	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%)
	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%)
	Corneal Abrasion/Erosion	2	2 (0.4%)	2	2 (0.4%)	2	2 (0.4%)	0	0 (0.0%)
	Corneal Foreign Body	0	0 (0.0%)	0	0 (0.0%)	1	1 (0.2%)	0	0 (0.0%)
	Epithelial defect 2-5 mm	1	1 (0.2%)	1	1 (0.2%)	1	1 (0.2%)	0	0 (0.0%)
	Epithelial Ingrowth	3	3 (0.6%)	3	3 (0.6%)	3	3 (0.6%)	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%)
	Keratitis at the incision	1	1 (0.2%)	1	1 (0.2%)	1	1 (0.2%)	0	0 (0.0%)
	Limbal Foreign Body	0	0 (0.0%)	0	0 (0.0%)	1	1 (0.2%)	0	0 (0.0%)
	SPK	2	2 (0.4%)	2	2 (0.4%)	2	2 (0.4%)	1	1 (0.4%)
	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%)

TABLE 4
POSTOPERATIVE OCULAR ADVERSE EVENTS AND COMPLICATIONS (CONT'D)

		PIVOTAL STUDY FULL COHORT (N=508)						CONTINUATION STUDY FULL COHORT (N=269)	
		Through 12 Months		Through 24 Months		Through 36 Months		48-60 Months	
Category	**Adverse Events**	**# of Events**	**# of Subjects**	**# of Events**	**# of Subjects**	**# of Events**	**# of Subjects**	**# of Events**	**# of Subjects**
Flap Complication	DLK	6	6 (1.2%)	6	6 (1.2%)	6	6 (1.2%)	0	0 (0.0%)
	Flap Striae	1	1 (0.2%)	1	1 (0.2%)	1	1 (0.2%)	0	0 (0.0%)
Intraocular	Iritis	1	1 (0.2%)	2	2 (0.4%)	3	3 (0.6%)	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%)	0	0 (0.0%)
Lens	Cataract	1	1 (0.2%)	1	1 (0.2%)	1	1 (0.2%)	0	0 (0.0%)
Lids	Blepharitis	0	0 (0.0%)	1	1 (0.2%)	1	1 (0.2%)	1	1 (0.4%)
	Hordeolum	0	0 (0.0%)	0	0 (0.0%)	1	1 (0.2%)	0	0 (0.0%)
	Meibomian Gland Dysfunction	0	0 (0.0%)	1	1 (0.2%)	1	1 (0.2%)	0	0 (0.0%)
	Ptosis	0	0 (0.0%)	0	0 (0.0%)	1	1 (0.2%)	0	0 (0.0%)
Other	Herpes Zoster (face and eye)	1	1 (0.2%)	1	1 (0.2%)	1	1 (0.2%)	0	0 (0.0%)
Retina	Retinal pigment epithelium change	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	1	1 (0.4%)
	Retinoschisis	0	0 (0.0%)	0	0 (0.0%)	1	1 (0.2%)	0	0 (0.0%)
Secondary Surgical Intervention	Inlay Re-centration	1	1 (0.2%)	6	6 (1.2%)	6	6 (1.2%)	0	0 (0.0%)
	Additional Refractive Correction (AK, CK)	0	0 (0.0%)	3	2 (0.4%)	5	3 (0.6%)	2	2 (0.7%)
	Epithelial ingrowth removal	4	2 (0.4%)	4	2 (0.4%)	4	2 (0.4%)	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%)
	Inlay Removals	15	15 (3.0%)	36	36 (7.1%)	44	44 (8.7%)	1	1 (0.4%)
Symptoms	Dry eye	2	2 (0.4%)	2	2 (0.4%)	2	2 (0.4%)	0	0 (0.0%)
	Symptoms: Ghost images	0	0 (0.0%)	1	1 (0.2%)	1	1 (0.2%)	0	0 (0.0%)
	Symptoms: Glare	0	0 (0.0%)	1	1 (0.2%)	1	1 (0.2%)	0	0 (0.0%)
	Symptoms: Halos	1	1 (0.2%)	2	2 (0.4%)	2	2 (0.4%)	0	0 (0.0%)
	Symptoms: Pain in eye	1	1 (0.2%)	3	3 (0.6%)	4	4 (0.8%)	0	0 (0.0%)
Vision	Decrease in BCDVA > 2 lines Month 3 or later	18	17 (3.3%)	34	28 (5.5%)	36	30 (5.9%)	10	10 (3.7%)

The following is related to inlay removals. The KAMRA® inlay can be removed. Forty-five (8.9%; 45/508) subjects in the clinical study through 60 months elected to have their inlay removed. The reasons for removal were as follows (number of subjects = 45):

- Appearance of the inlay in the eye: 2 eyes (4.4%; 2/45)
- Medically indicated: 4 eyes (8.9%; 4/45)
    - Folds in inlay at time of implantation: 1 eye (2.2%)
    - Stromal thinning due to foreign body, trauma: 1 eye (2.2%)
    - Posterior vitreous detachment (large floater in eye): 1 eye (2.2%)
    - Sustained loss of vision due to scar in visual axis: 1 eye (2.2%)
- Visual complaints: 39 eyes (86.7%; 39/45)
    - Hyperopic shift: 25 eyes (55.6%)
    - Myopic shift: 2 eyes (4.4%)
    - Induced astigmatism: 1 eye (2.2%)
    - Inadequate benefit/inability to adapt: 7 eyes (15.6%)
    - Inlay not centered: 2 eyes (4.4%)
    - Inlay placed in non-optimal (dominant) eye: 1 eye (2.2%)

All but one patient in the study had 20/20 or better BCDVA after inlay removal; the one patient who had 20/25 BCDVA after removal had a small scar in the cornea.

Contrast Sensitivity (Monocular and Binocular)

Contrast sensitivity with best correction was analyzed in inlay eyes from a subgroup of 335 subjects in the pivotal clinical trial. On average, inlay eyes showed some decrease in photopic contrast sensitivity postoperatively and a slightly greater decrease in mesopic contrast sensitivity from preoperative levels. Binocularly, photopic and mesopic mean contrast sensitivity (CS) showed minimal decrease postoperatively through 36 months from preoperative levels. Mesopic monocular and binocular CS data are presented in **Figures 6** and **7** below.

FIGURE 6. MESOPIC CONTRAST SENSITIVITY WITHOUT GLARE (MONOCULAR)

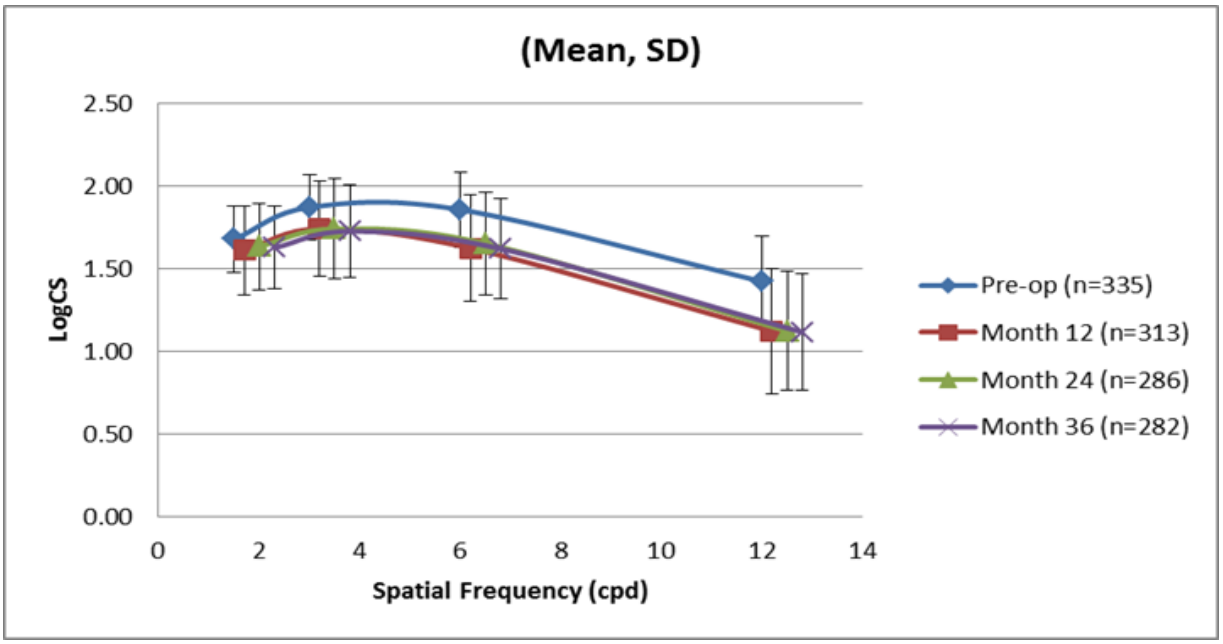
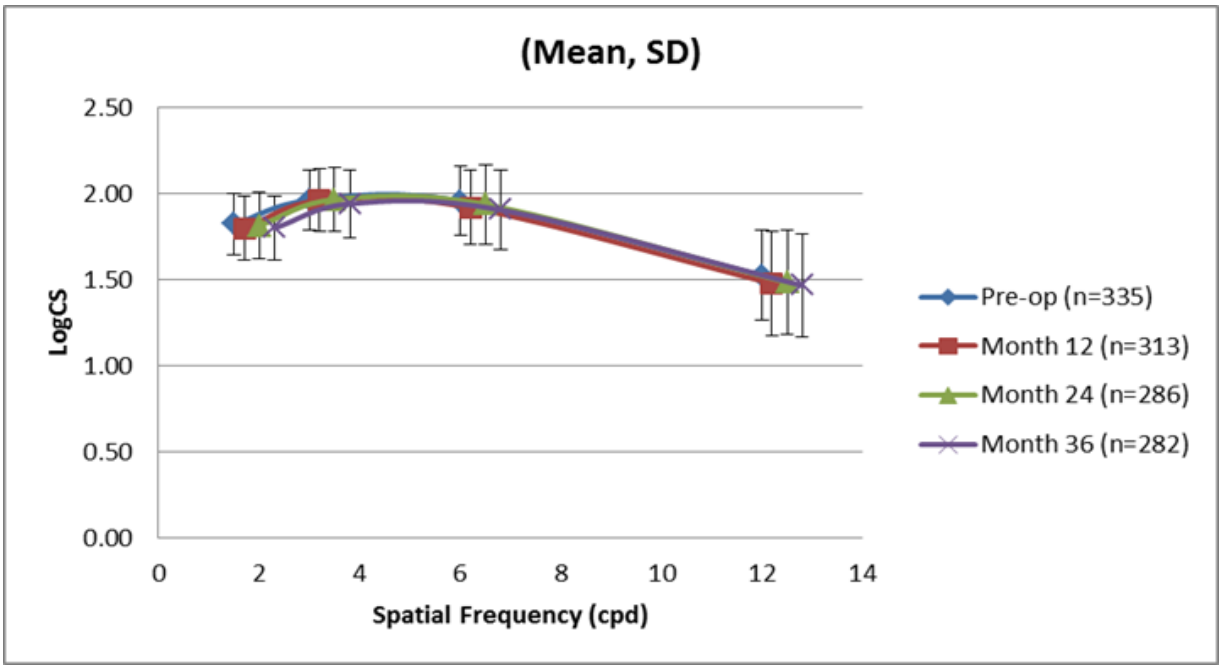


FIGURE 7. MESOPIC CONTRAST SENSITIVITY WITHOUT GLARE (BINOCULAR)

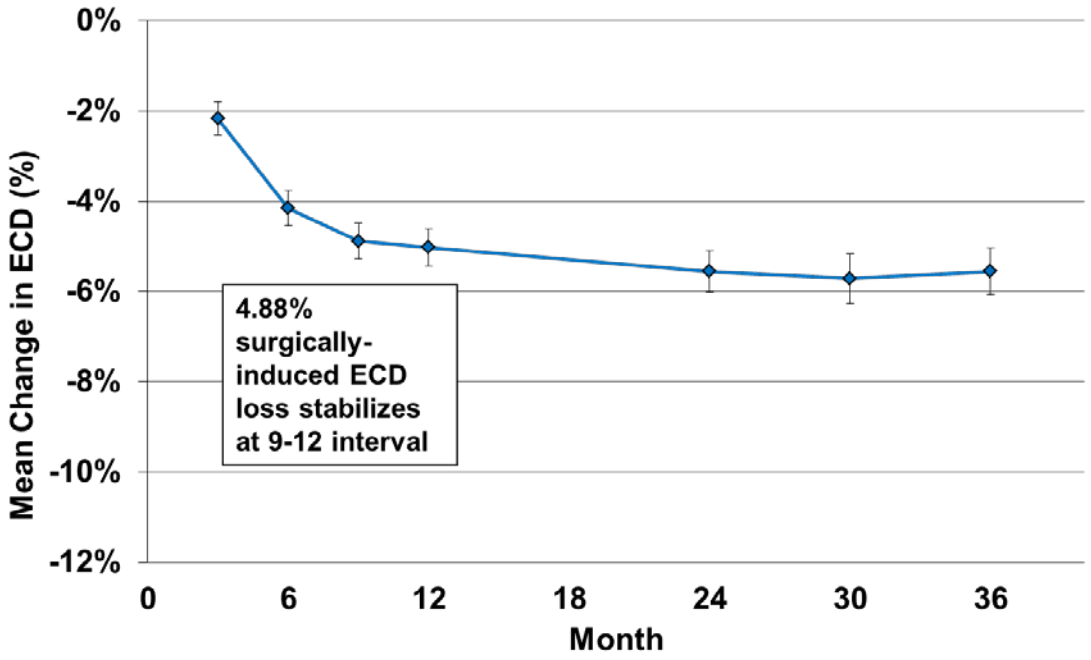


Monocular CS under mesopic with glare conditions was evaluated postoperatively in a smaller subset of 142 subjects at 36 months. A side-by-side comparison of monocular mesopic CS with glare vs. without glare showed approximately 0.2 log units lower CS with than without glare at 1.5, 3.0, and 6.0 cycles per degree (cpd).

Endothelial Cell Counts

The age-related endothelial cell density (ECD) loss rate is estimated to be approximately 0.6% [Bourne WM, Nelson LR, Hodge DO, 1997]. . In the clinical trials for the inlay, endothelial cell counts were performed before surgery and after surgery at 3, 6, 9, 12, 24, 30 and 36 months on both eyes of all subjects. The average endothelial cell count over the course of the study decreased from2564.9 cells/mm^2 before surgery to 2406.7 cells/mm^2 at 36 months after surgery. Endothelial cell loss due to the surgery was 4.88% at 9 months and 5.02% at 12 months. From 12 to 36 months after surgery, the mean annualized changes in endothelial cell count were very small, no more than 0.59% per year (**Figure 8**). The endothelium of the cornea stabilized from the surgical effects of KAMRA® inlay placement between 9 and 12 months, after which the rate of loss was similar to that due to normal aging.

FIGURE 8. MEAN AND 95% CI OF PERCENT CHANGE IN ENDOTHELIAL CELL DENSITY FROM BASELINE



Visual Fields

Visual fields were performed for both eyes of all subjects before surgery to screen for potential visual field abnormalities. Results are summarized below for 224 subjects from the pivotal trial visual field subgroup that had both mean deviation and pattern standard deviation results available at the 12-month postoperative visit as well as at baseline (the “12 Months Cohort”).

The average mean deviation (MD) for implanted eyes became slightly more negative from -0.217 preoperatively to -1.234 at 12 months and remained near this level through 24 and 36 months. The mean pattern standard deviation (PSD) was similar for inlay eyes and for fellow eyes before surgery (1.444 for implanted eyes and 1.437 for fellow eyes). Postoperatively, mean PSD increased slightly for both groups of eyes (to 1.586 for implanted eyes and 1.511 for fellow eyes at 12 months). The amount of increase in the means remained at this level through 24 and 36 months. The increase in mean PSD is minimal, indicating that this parameter is not significantly changed by the presence of the KAMRA® inlay for most subjects. Some subjects had much greater changes in the visual field than the average change, especially for PSD. The reasons for these changes in the visual field are not completely clear.

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.

Stability of Manifest Refraction

The protocol-defined criteria for the stability of manifest refraction are as follows:

a. At least 95% of eyes have a change of less than or equal to 1.00 D of manifest refractive spherical equivalent (MRSE) between two refractions performed at least
3 months apart.

b. The mean rate of change in MRSE, as determined by paired analysis, is less than or equal to 0.5 D per year (0.04 D/month) between two refractions performed at least
3 months apart.

c. The mean rate of change of MRSE decreases monotonically over time, with a projected asymptote of zero or a rate of change attributable to normal aging

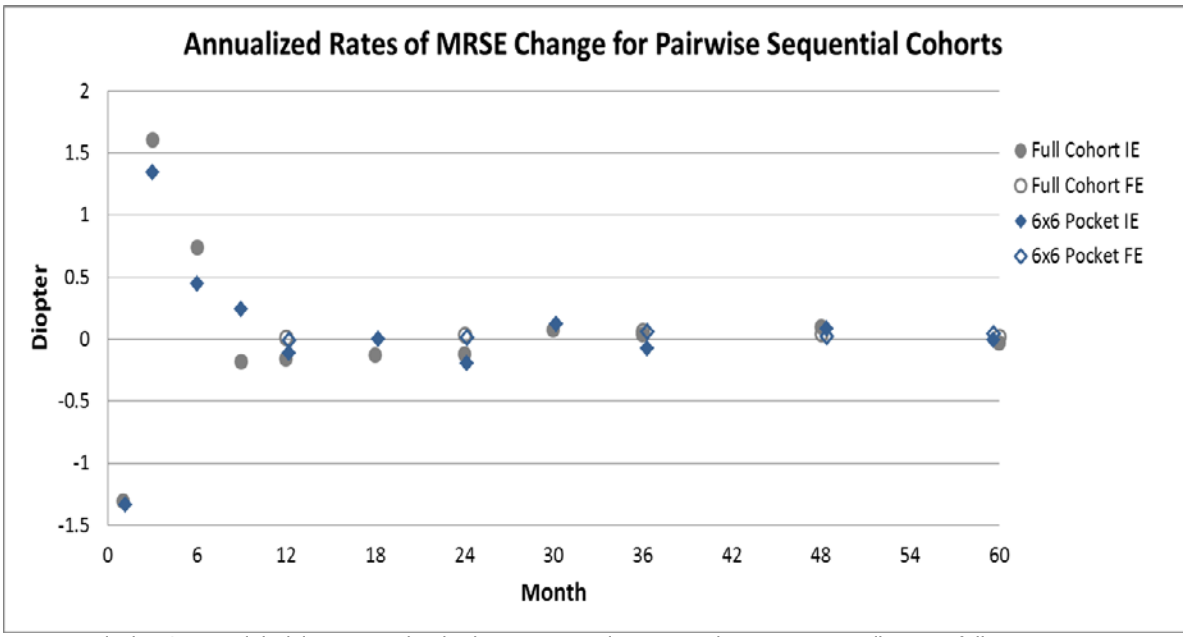
d. The 95% confidence interval for the mean rate of change includes zero or a rate of change attributable to normal aging

A summary of the stability results is presented in Table 5 below. The proportion of subjects whose manifest refraction remained within 1.00 D between consecutive visits

was more than 90% over the course of the clinical trial beginning at the 9-12 months interval, with 93.2% (441/473) between 9-12 months, 93.4% (398/426) between 18-24 months, 95.0% (378/398) between 24 and 30 months, 94.2% (373/396) between 30-36 months, and 92.1% (186/202) between 48 and 60 months. The time point of refractive stability was determined to be 24 months. The calculated average monthly change in MRSE was less than 0.01 D between visits from 24 to 60 months. There were 20/398 (5.0%) subjects in the clinical study who showed more than 1.00 D of MRSE change between 24 and 30 months; 8 of these 20 subjects showed more than 1.00 D of change in MRSE again between 30 and 36 months.

Four of these eight subjects were more hyperopic than before surgery (MRSEs of +1.00 to +1.375 D at 36 months postoperatively), and two were more myopic than before surgery (MRSEs of -1.375 D and -2.375 D); two subjects were nearly the same as before surgery (MRSEs of +0.25 D and -0.625 D). Annualized data are presented in **Figure 10**.

FIGURE 9. ANNUALIZED RATE OF MEAN CHANGE IN MRSE BETWEEN CONSECUTIVE VISITS FOR IMPLANTED AND FELLOW EYES



Pairwise Sequential Visits = Eyes that had two consecutive exams, but not necessarily every follow-up exam.

TABLE 5
STABILITY OF MANIFEST REFRACTION SPHERICAL EQUIVALENT (MRSE) IN IMPLANTED EYES

Change in MRSE	Between Preop and 1 Month	Between 1 and 3 Months	Between 3 and 6 Months	Between 6 and 9 Months	Between 9 and 12 Months	Between 12 and 18 Months	Between 18 and 24 Months	Between 24 and 30 Months	Between 30 and 36 Months	Between 36 and 48 Months	Between 48 and 60 Months
Pairwise Sequential Visits†											
Change of **MRSE** by ≤ 1.00 D											
n/N	495/503	456/496	445/494	428/484	441/473	406/442	398/426	378/398	373/396	251/267	186/202
(%)	(98.4%)	(91.9%)	(90.1%)	(88.4%)	(93.2%)	(91.9%)	(93.4%)	(95.0%)	(94.2%)	(94.0%)	(92.1%)
95% CI for %‡	(96.9%, 99.3%)	(89.2%, 94.2%)	(87.1%, 92.6%)	(85.2%, 91.1%)	(90.6%, 95.3%)	(88.9%, 94.2%)	(90.6%, 95.6%)	(92.3%, 96.9%)	(91.4%, 96.3%)	(90.5%, 96.5%)	(87.5%, 95.4%)
Change of **MRSE** (Paired-Differences) in Diopter											
Mean	-0.109	0.268	0.185	-0.046	-0.039	-0.064	-0.061	0.039	0.017	0.097	-0.033
SD	0.426	0.535	0.607	0.641	0.559	0.559	0.574	0.535	0.570	0.564	0.654
95% CI for Mean	(-0.146, -0.072)	(0.221, 0.315)	(0.131, 0.238)	(-0.104, 0.011)	(-0.090, 0.011)	(-0.117, -0.012)	(-0.116, -0.007)	(-0.014, 0.091)	(-0.040, 0.073)	(0.029, 0.165)	(-0.124, 0.057)
Monthly Change of **MRSE** in Diopter	-0.109	0.134	0.062	-0.015	-0.013	-0.011	-0.010	0.007	0.003	0.008	-0.003
Annualized Change of **MRSE** in Diopter	-1.3058	1.608	0.740	-0.184	-0.156	-0.128	-0.121	0.078	0.034	0.097	-0.033
60 Months Consistent Cohort†											
Change of **MRSE** by ≤ 1.00 D											
n/N	183/186	181/186	171/186	167/186	177/186	173/186	177/186	174/186	174/186	173/186	172/186
(%)	(98.4%)	(97.3%)	(91.9%)	(89.8%)	(95.2%)	(93.0%)	(95.2%)	(93.5%)	(93.5%)	(93.0%)	(92.5%)
95% CI for %‡	(95.4%, 99.7%)	(93.8%, 99.1%)	(87.0%, 95.4%)	(84.5%, 93.7%)	(91.0%, 97.8%)	(88.3%, 96.2%)	(91.0%, 97.8%)	(89.0%, 96.6%)	(89.0%, 96.6%)	(88.3%, 96.2%)	(87.7%, 95.8%)
Change of **MRSE** (Paired-Differences) in Diopter											
Mean	-0.108	0.202	0.217	-0.065	-0.075	-0.114	-0.083	0.034	0.042	0.115	-0.030
SD	0.421	0.482	0.533	0.593	0.519	0.518	0.496	0.542	0.573	0.577	0.655
95% CI for Mean	(-0.168, -0.047)	(0.132, 0.271)	(0.140, 0.294)	(-0.151, 0.021)	(-0.150, -0.000)	(-0.189, -0.039)	(-0.155, -0.012)	(-0.045, 0.112)	(-0.041, 0.125)	(0.031, 0.198)	(-0.124, 0.065)
Monthly Change of **MRSE** in Diopter	-0.108	0.101	0.072	-0.022	-0.025	-0.019	-0.014	0.006	0.007	0.010	-0.003
Annualized Change of **MRSE** in Diopter	-1.296	1.212	0.868	-0.260	-0.300	-0.228	-0.166	0.068	0.014	0.115	-0.030

† Pairwise Sequential Visits = Eyes that had two consecutive exams, but not necessarily every follow-up exam. Consistent Cohort = Eyes examined at Preop, 1 Month, 3 Months, 6 Months, 9 Months, 12 Months, 18 Months, 24 Months, 30 Months, 36 Months, 48 Months, 60 Months

‡ Calculated based on Clopper-Pearson exact method.

Visual and Ocular Symptoms

Some subjects from the clinical study experienced visual and ocular symptoms. The symptoms from subjects in the study were collected using the AcuFocus Corneal Inlay Presbyopic Questionnaire (ACIPQ). A summary of the frequency of symptoms pre- and postoperatively at 12, 24, and 36 months for the whole cohort are reported below. Please note that care must be taken when interpreting results from the ACIPQ, since this questionnaire was not found by the FDA to be a valid assessment of these concepts.

TABLE 6
PROPORTION OF SUBJECTS REPORTING SYMPTOMS BEFORE SURGERY AND AFTER SURGERY AT 12, 24, 36 MONTHS FOR ALL SUBJECTS

	Preop	12 Months	24 Months	36 Months
Blurry/Fluctuating Vision	101/508 (20%)	198/478 (41%)	176/440 (40%)	154/424 (36%)
Color Disturbances	13/508 (3%)	54/478 (11%)	31/440 (7%)	17/424 (4%)
Distortion	25/508 (5%)	68/478 (14%)	65/440 (15%)	48/424 (11%)
Dryness	64/508 (13%)	240/478 (50%)	229/440 (52%)	210/424 (50%)
Glare	76/508 (15%)	178/478 (37%)	135/440 (31%)	102/424 (24%)
Halos	27/508 (5%)	197/478 (41%)	151/440 (34%)	126/424 (30%)
Night Vision Problems	96/508 (19%)	200/478 (42%)	169/440 (38%)	159/424 (38%)
Pain/Burning	26/508 (5%)	64/478 (13%)	53/440 (12%)	60/424 (14%)
Double Vision	10/508 (2%)	53/478 (11%)	43/440 (10%)	40/424 (9%)
Ghost/Overlapping Images	14/508 (3%)	93/478 (19%)	74/440 (17%)	64/424 (15%)

During the peri-operative period (by the 3-month postoperative visit), 9% to 48% of subjects without visual symptoms before surgery developed visual symptoms. Of the subjects who did not have a given symptom before surgery, from 27% to 76% developed the symptom 6 months or later postoperatively as shown in the table below. The majority of the reported symptoms were mild.

TABLE 7
PROPORTION OF SUBJECTS REPORTING NO SYMPTOM BEFORE SURGERY THAT REPORTED THE SYMPTOM AT 6 MONTHS OR LATER POSTOPERATIVELY FOR ALL SUBJECTS

	At 6 months or later Postoperatively
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%)

For each symptom collected with the ACIPQ, the proportion of subjects 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. The proportion reporting symptoms seemed to decrease over time.

TABLE 8
PROPORTION OF SUBJECTS DEVELOPING NEW SYMPTOMS (MODERATE OR SEVERE) AFTER SURGERY IN SUBJECTS REPORTING NO SYMPTOMS BEFORE SURGERY FOR ALL SUBJECTS

	3-12 Months	18-24 months	30-36 months
Blurry/Fluctuating Vision	172/407 (42%)	115/407 (28%)	88/407 (22%)
Color Disturbances	51/495 (10%)	16/495 (3%)	10/495 (2%)
Distortion	73/483 (15%)	55/483 (11%)	30/483 (6%)
Dryness	185/444 (42%)	148/444 (33%)	124/444 (28%)
Glare	155/432 (36%)	76/432 (18%)	70/432 (16%)
Halos	183/481 (38%)	103/481 (21%)	79/481 (16%)
Night Vision Problems	139/412 (34%)	97/412 (24%)	78/412 (19%)
Pain/Burning	46/482 (10%)	30/482 (6%)	25/482 (5%)
Double Vision	64/498 (13%)	29/498 (6%)	28/498 (6%)
Ghost/Overlapping Images	101/494 (20%)	56/494 (11%)	51/494 (10%)

5.3 SURGICAL PARAMETERS

Results for Pivotal Study Surgical Parameters Subgroup: ≤6x6 µm spot/line separation femtosecond laser-created pocket

When the results were compared among the different ways the surgery was performed, for example, making a 'pocket' in the cornea vs. a flap, or using 6 microns by 6 microns or tighter spot/line setting of the femtosecond laser vs. using a larger spot/line setting, one way of doing the surgery seemed somewhat better than the rest. Therefore, this way of performing the surgery is the one now included in the instructions for use of the KAMRA® inlay. The results for the subjects from the pivotal clinical study who were treated using the currently recommended surgical parameters, i.e., a 'pocket' at 200 microns or deeper in the cornea by 6x6 or tighter spot/line setting of the femtosecond laser, (also known as the 6x6 pocket subgroup) are presented below.

There were 166 out of 508 subjects in the pivotal clinical study that had surgery performed in this way. More than 95% of the subjects had no more than 1.00 diopter of change in MRSE between 18-24, 24-30, and 30-36 months, and 93.3% between 48 and 60 months.

There were 135/153 (88.2%) subjects with UCNVA of 20/40 or better at 12 months, 140/149 (94.03%) at 24 months, 131/145 (90.3%) at 36 months and 63/75 (84.0%) at 60 months.

No subjects in this subgroup had postoperative BCDVA worse than 20/40, significant corneal haze, or increased manifest refractive astigmatism of more than 2.00 D at any time during the study. There were fewer than 1.5% of eyes that had a persistent loss of two lines or more of BCDVA, with none at 12 and 24 months, 1.4% (2/146) at 36 months, 1.3% (1/75) at 60 months.

The cumulative rates of adverse events that occurred after surgery through the 36-month study course are as follows (number of subjects = 166):

- Debris over inlay: 1 eye, 0.6%
- Diffuse lamellar keratitis: 1 eye, 0.6%
- Epithelial defect (2 to 5 mm): 1 eye, 0.6%
- Superficial punctate keratitis: 2 eyes, 1.2%
- Corneal abrasion: 1 eye, 0.6%
- Conjunctivitis: 6 eyes, 3.6%
- Episcleritis: 1 eye, 0.6%
- Blepharitis: 1 eye, 0.6%
- Intraocular pressure increase of > 10 mmHg above baseline or > 25 mmHg: 4 eyes, 2.4%

- Decrease of > 2 lines of BCDVA at 3 months or later: 10 eyes, 6.0%
- Symptoms of (as reported by the investigator):
    - Pain in the eye: 1 eye, 0.6%
- Second surgery:
    - Repositioning the inlay: 2 eyes, 1.2%
    - Removal: 7 eyes, 4.2%
- Other
    - Herpes Zoster: 1 eye, 0.6%
    - Retinoschisis: 1 eye, 0.6%
    - Conjunctival concretion: 1 eye, 0.6%
    - Foreign body in the cornea: 1 eye, 0.6%

This subgroup had fewer subjects who eventually had inlays removed. As of November 25, 2014, at 60 months, there were 4.8% (8/166) removals in this subgroup. The reasons for removal were as follows (number of subjects = 8):

- Appearance of the inlay in the eye: 1 eye (12.5%, 1/8)
- Medically indicated: 1 eye (12.5%, 1/8)
    - Folds in inlay at time of implantation: 1 eye (12.5%)
- Visual complaints: 6 eyes (75.0%, 6/8)
    - Hyperopic shift: 3 eyes (37.5%)
    - Myopic shift: 1 eye (12.5%)
    - Inadequate benefit/inability to adapt: 1 eye (12.5%)
    - Inlay placed in non-optimal (dominant) eye: 1 eye (12.5%)

All subjects in this subgroup had 20/20 or better BCDVA after inlay removal.

Lastly, a summary of the frequency of symptoms reporting via the ACIPQ before surgery and after surgery at 12, 24, and 36 months for this 6x6 pocket subgroup are reported below to compare to the results from the whole cohort as reported in the prior section:

TABLE 9
PROPORTION OF SUBJECTS REPORTING SYMPTOMS BEFORE SURGERY AND AFTER SURGERY AT 12, 24, AND 36 MONTHS FOR 6X6 POCKET SUBGROUP

	Preop	12 Months	24 Months	36 Months
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%)

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 the table below. The majority of these symptoms were mild.

TABLE 10
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
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%)

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. The proportion experiencing symptoms did not increase over time.

Table 11

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%)

Results from the Confirmatory Clinical Study

A smaller “confirmatory” study was conducted with 151 eyes (150 implanted) from 151 subjects to confirm initial findings from the pivotal study indicating that outcomes may be somewhat better using femtosecond laser spot/line settings of less than or equal to 6x6 microns rather than using a mechanical microkeratome or femtosecond laser spot/line settings of greater than 6x6 microns. Results in the confirmatory study were consistent with those in the IDE pivotal clinical study. In the confirmatory study, of the 130 eyes considered evaluable for effectiveness at the final 12-month follow-up visit, 90.8% of eyes achieved UCNVA of 20/40 or better (lower bound of 95% CI was 84.5%) with a mean change of approximately 3 lines improvement in UCNVA.

With regard to key safety outcomes, there was little change from the results obtained in the pivotal study to the confirmatory study. There were 139 subjects evaluable at 12 months for the safety parameters (**Figure 10**).

FIGURE 10. PRIMARY SAFETY ENDPOINTS AT 12 MONTHS

Safety Parameters	Target	Pivotal Study	Confirmatory Study
Persistent BCDVA loss of ≥ 2 lines at two consecutive visits	5%	0.6% (3/479)	0.7% (1/139)
BCDVA worse than 20/40 if 20/20 or better preoperatively	1%	0.0% (0/479)	0.0% (0/139)
Induced refractive astigmatism > 2.00 D	5%	0.0% (0/479)	0.0% (0/139)
Corneal haze in conjunction with BCDVA loss > 2 lines	1%	0.0% (0/479)	0.0% (0/139)

With regard to adverse events, the results obtained in the confirmatory trial were similar to the results from the pivotal trial (**Table 12**) (Total subjects = 151):

TABLE 12
CUMULATIVE OCULAR ADVERSE EVENTS IN IMPLANTED EYES IN CONFIRMATORY STUDY DAY 1 POSTOPERATIVE THROUGH 12 MONTHS

Category	Adverse Events	# of Events	# of Subjects
	Total N		151
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 Increase greater than 10 mmHg above baseline or IOP greater than 25 mmHg (with clinical findings)	7	7 (4.6%)
Lids	Allergic Reaction to Study Medication: Lids	1	1 (0.7%)
	Blepharitis	1	1 (0.7%)
SSI	Inlay Removals	9	9 (6.0%)
	SSI: ACI 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	6	6 (4.0%)

	later		

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