SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Posterior Chamber IOL (IOL) UltraViolet (UV) Light Source

Device Trade Name: Light Adjustable Lens (LAL)/Light Delivery Device (LDD)

Device Procode: PZK

Applicant's Name and Address: RxSight, Inc.
100 Columbia
Aliso Viejo, CA 92656

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P160055

Date of FDA Notice of Approval: 11/22/2017

II. INDICATIONS FOR USE

The Light Adjustable Lens (LAL) and Light Delivery Device (LDD) system is indicated for the reduction of residual astigmatism to improve uncorrected visual acuity after removal of the cataractous natural lens by phacoemulsification and implantation of the intraocular lens in the capsular bag, in adult patients:

- With pre-existing corneal astigmatism of ≥ 0.75 diopters
- Without pre-existing macular disease

The system also reduces the likelihood of clinically significant residual spherical refractive errors.

III. CONTRAINDICATIONS

Use of the LAL is contraindicated in cases where:

1. The patient is taking systemic medication that may increase sensitivity to UV light such as tetracycline, doxycycline, psoralens, amiodarone, phenothiazines, chloroquine, hydrochlorothiazide, hypercin, ketoprofen, piroxicam, lomefloxacin, and methoxsalen. LDD treatment in patients taking such medications may lead to irreversible phototoxic damage to the eye. **Note:** This is only a partial list of photosensitizing medications. Evaluate all medications that the patient is taking for this effect prior to consideration for implantation.

2. The patient is taking a systemic medication that is considered toxic to the retina such as tamoxifen (e.g., Nolvadex®) as they may be at increased risk of retinal damage during LDD treatment.
3. The patient has a history of ocular herpes simplex virus due to the potential for reactivation from exposure to UV light.
4. The patient has nystagmus as they may not be able to maintain steady fixation during LDD treatment.
5. The patient is unwilling to comply with the postoperative regimen for adjustment and lock-in treatments and wearing of UV protective eyewear.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Light Adjustable Lens (LAL)/Light Delivery Device (LDD) labeling.

V. DEVICE DESCRIPTION

The Light Adjustable Lens (LAL) is a posterior chamber, UV absorbing, three-piece, foldable, photoreactive silicone intraocular lens with a squared posterior optic edge intended to be implanted in the capsular bag following phacoemulsification. Selective exposure of the implanted RxSight LAL using the Light Delivery Device (LDD) to deliver spatially profiled UV light produces modifications in the lens curvature resulting in a spherical or spherocylindrical power change post-operatively. A subsequent lock-in exposure is delivered to the implanted LAL to stabilize the lens power.

Lens Optic

- Material: Photo-reactive UV absorbing Silicone
- Light transmission: UV cut-off at 10% T 385 ± 2 nm for all lens powers
- Index of refraction: 1.43
- Diopter (D) power: +10 to +15.0 D and +25.0 to +30.0 D in 1.0 D increments; +16.0 to +24.0 D in 0.5 **D** increments
- Optic type: Biconvex
- Optic edge: Square on posterior surface and round on anterior surface
- Overall diameter: 13.0 mm
- Optic diameter: 6.0 mm

Haptics

- Configuration: Modified C
- Material: Blue core polymethylmethacrylate (PMMA) monofilament
- Haptic angle: 10°

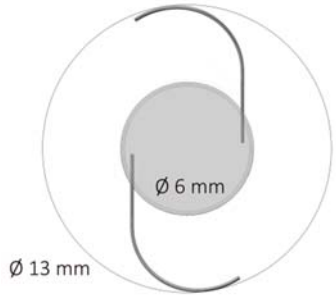


FIGURE 1: LIGHT ADJUSTABLE LENS

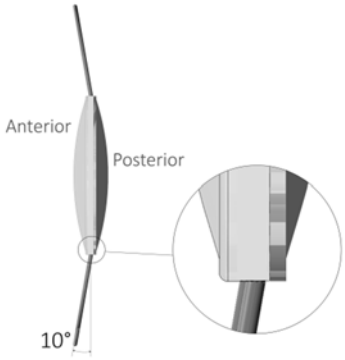
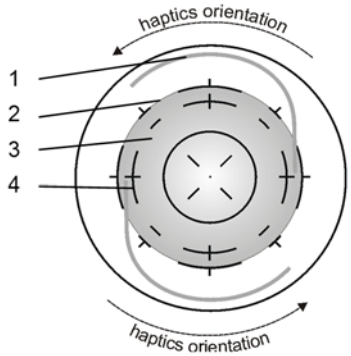


FIGURE 2: LIGHT ADJUSTABLE LENS. INSET DEPICTS BACK LAYER.

The LAL silicone material is designed to respond to a narrowband UV light of a select spatial intensity profile. The silicone material contains photoreactive additive, which is selectively photo-polymerized in targeted areas upon exposure to the near UV light to alter the lens shape thus modifying spherical and shpero-cylindrical power of the LAL.

The Light Delivery Device is a UV light projection system used to induce a predictable change in LAL power after implantation. The LDD consists of an anterior segment biomicroscope with the addition of an optical projection system, electronic control circuitry, and a UV source. The LDD device can treat postoperative manifest cylinder from -0.75 D to -2.00 D, and manifest sphere (in minus cylinder format) of -2.00 D to +2.00 D. The LDD is used to focus on the LAL with a contact lens in place on the cornea. The LDD is aligned with the irradiation reticle with the periphery of the LAL ensure to be within the target reticle, as shown in Figure 3, below.



1. LAL haptics
2. LAL edge
3. LAL
4. Target reticle

FIGURE 3: TARGET RETICLE

VI. ALTERNATIVE PRACTICES AND PROCEDURES

For the treatment of aphakia after cataract removal, there are various types of intraocular lenses (IOLs) on the market. Specifically, there are toric IOLs that are also indicated for reduction of astigmatism and improvement of uncorrected visual acuity.

There are several other alternatives for the correction of aphakia and for correcting refractive errors.Non-surgical options for correcting residual refractive astigmatism include glasses or contact lenses. These options can also reduce the visual effects of significant residual refractive errors. Surgical options at the time of cataract surgery to reduce residual astigmatism include appropriate placement of the corneal incision and the use of corneal relaxing incisions. Surgical options to treat refractive error after cataract surgery include Laser-Assisted In-Situ Keratomileusis (LASIK) or Photorefractive keratectomy (PRK), placement of a piggyback IOL or IOL exchange. 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

Commercial distribution of the LAL and LDD outside the U.S. began in 2008. Currently, the LAL and LDD are commercially available throughout the European Union and in Mexico. The device has not been withdrawn from marketing for any reason related to its safety and 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. Specific risks of the Light Adjustable Lens and Light Delivery Device include: an unpredicted change in vision resulting from ocular exposure to sunlight before the LAL is locked-in which might necessitate explantation of the LAL; transient or permanent erythropsia and color vision anomaly due to UV treatment from the LDD, corneal abrasions from the lens used for adjustment and lock-in, and other UV induced retinal damage which may potentially cause loss of vision.

Potential adverse events for all cataract or implant surgery may include but are not limited to: infection (endophthalmitis), hypopyon, corneal endothelial damage, IOL dislocation out of the posterior chamber, cystoid macular edema, corneal edema, pupillary block, iritis, retinal detachment, transient or persistent glaucoma, vitritis, iris prolapse, rupture of the capsule, and secondary surgical intervention. Increased visual symptoms related to the optical characteristics of the IOL including: halos, glare and/or double vision.

Secondary surgical interventions include, but are not limited to: lens repositioning, lens replacement, vitreous aspirations or iridectomy for pupillary block, wound leak repair, retinal detachment repair and corneal transplant.

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

Nonclinical laboratory studies performed demonstrate the safety and effectiveness of the Light Adjustable Lens. These tests were performed in accordance with the relevant parts of ISO 10993-1 and ISO 11979-5. The results of this testing are summarized below.

i. Physico-chemical testing

Test	Purpose	Acceptance Criteria	Results
Exhaustive Extraction	Analysis of quantified extractable additives under exhaustive conditions	Non-irritant release of leachables overtime	Pass
Leachables	Analysis of quantified extractable additives under physiological conditions	Non-irritant release of leachables	Pass
Hydrolytic stability	Stability of material in aqueous environment	Stability of device over time	Pass
Photostability	Photostability of material wwhen irradiated	photostability	Pass
ND-YAG exposure	Physical and chemical effects on Nd:YAG exposure	Nd:YAG stability	Pass
Insoluble Inorganics	Analsyis of quantified release of inorganics	Non-irritant release of inorganics	Pass

ii. Biocompatibility Test Summary

Biocompatibility testing was performed on the LAL and on the patient-contacting components of the LDD. The biocompatibility testing on the LAL was performed on both the non-irradiated lens (represented by the finished sterile LALs) and on the irradiated LALs (LALs that underwent the same manufacturing and sterilization procedures and irradiation in water using conditions simulating full lock-in dose). The biocompatibility testing was performed in accordance with International Standard Organization (ISO) 11979-5: Ophthalmic implants-Intraocular lenses- Part 5: Biocompatibility and relevant parts of ISO 10993-1: Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process. Testing was conducted in compliance with Good Laboratory Practices. The results of this testing are summarized below.

Test	Purpose	Acceptance Criteria	Results

Cytotoxicity	MEM Elution (LAL and LDD)	Non-cytotoxic	Pass
Cytotoxicity	Direct contact (Agar diffusion test)	Non-cytotoxic	Pass
Cell growth	LAL Extract	Non-inhibitory to cell growth	Pass
Sensitization	Guinea pig maximization study (LAL and LDD)	Non-sensitizer	Pass
Genotoxicity	Bacterial Reverse Mutation (Ames test; DMSO and saline extracts)	Non-genotoxic	Pass
Genotoxicity	Mouse Lymphoma Assay (DMSO and saline extracts)	Non-genotoxic	Pass
Genotoxicity	Mouse Peripheral Blood Micronucleaus Study (Sesame oil and Saline extracts)	Non-genotoxic	Pass
Implantation	Sub-cutaneous implantation (4 and 12 weeks) in rabbits	No significant biological local response	Pass
Irritation	Skin irritation in rabbits	Non-irritant	Pass

iii. Physical and Mechnical Testing

Test	Purpose	Acceptance Criteria	Results
Dimensional Requirements	To determine if the dimensions associated with the IOL are within maximum tolerances	Described in ISO 11979-3	Passed
Optical Requirements	To assess accuracy of optical power, meet minimum image quality specifications, and characterize the spectral transmittance of the IOL	Described in ISO 11979-2	Passed
Mechanical Requirements	To characterize the mechanical properties of the IOL	Described in ISO 11979-3	Passed
Recovery Properties	To determine if the IOL maintains its optical, dimensional properties and integrity after simulated surgical manipulation	Described in ISO 11979-3	Passed

iv. Sterilization, Packaging, and Shelf-Life Testing

Sterilization

The ethylene oxide (EtO) sterilization cycle was validated using the "overkill – half cycle method" in accordance with *ISO 11135-1: Sterilization of health care products – Ethylene Oxide.* Validation of the sterilization cycle demonstrated that the sterilization process and equipment reliably and consistently sterilized the LAL to a minimum Sterility Assurance Level (SAL) of 10^{-6}. All biological indicators (BI) were confirmed with fractional and half cycle test runs utilizing Natural Product Sterility Testing (NPRT) and Method Suitability Testing showing no growth after 14 days of incubation.

Residual ethylene oxide testing is performed after degassing to ensure acceptable levels of the sterilization residuals. In addition, biological indicator and bacterial endotoxins are tested routinely to ensure sterility prior to lot release.

LAL Endotoxin Test Validation

Endotoxin testing was conducted using the immersion method in accordance with FDA guidance *Endotoxin Testing Recommendations for Single-Use Intraocular Ophthalmic Devices / Guidance for Industry and Food and Drug Administration Staff, August 2015.* Limulus Amebocyte Lysate testing per USP on sterilized test devices demonstrated that the concentration of bacterial endotoxins were below 0.2 EU per device which are the current limits established for intraocular implants.

Shelf-life / Packaging / Transport stability

Shelf life studies have been conducted to verify that the packaging for the Light Adjustable Lens maintains a sterile barrier and adequately protects the device through the expiration date on the package label, which is 3 years from the date of sterilization. Shelf life testing has also been conducted to verify that device physical and optical properties satisfy the requirements of the engineering drawings and product specification document through the 3 year labeled expiration date.

Shelf-life Stability Testing

The testing was conducted in accordance with the relevant provisions of *ISO 11979-6:2007 - Ophthalmic implants – Intraocular lenses - Part 6: Shelf-life and transport stability* using sterile packaged, finished devices that were stored in a 25º C environmental chamber for 3 years from the date of sterilization. Samples were tested at six month intervals for dimensions, surface and bulk homogeneity, dioptric power and imaging quality, discoloration, compression force, folding and recovery, dynamic fatigue testing, haptic pull strength, extractables. The final results of this study demonstrate that the LAL is stable on the shelf for 3 years.

Package Integrity and Transport Stability

Package integrity and transport stability studies of the LAL were conducted in accordance with ISO 11979-6: Ophthalmic implants – Intraocular lenses – Part 6: Shelf-life and transport stability. Accelerated and real time package integrity testing, including dye penetration, seal strength and bubble emission, was

conducted to establish the shelf-life of the LAL in the final packaging as well as to establish the stability of the LALs in distribution and storage.

Additionally, transport stability testing was conducted with the finished device in accordance with ISO 2248:1985 and ISO 8318:2000. Tyvek pouches were evaluated for seal/closure integrity by dye penetration and seal strength.

Results of all package integrity and transport stability testing demonstrate that the product is stable and the data support 3 year expiration dating for the package components used for the LAL.

Test	Purpose	Acceptance Criteria	Results
Bacterial endotoxin	Evaluate sterility	< 0.2 EU/device	Pass
Ethylene oxide residuals via Thermal Headspace Exhaustive Extraction and Ethylene chlorohydrin residuals via water extraction	Evaluate toxicity of the device after ethylene oxide sterilization	<1.25µg/device (EO) <5.0 µg/device (ECH)	Pass
Package Evaluation – Dye Penetration Testing	Evaluate package seal integrity	No evidence of dye across seal by a defined channel	Pass
Package Evaluation – Seal Strength Testing	Evaluate package seal integrity	Compared favorably to test seals as function of storage time	Pass
Package Evaluation – Bubble Emission Test	Evaluate whole package Integrity	No bubbles visible around package or seal	Pass
Transport Stability	Evaluate package integrity and stability of device	Manufacturing specifications met after being subjected to anticipated "worse case" conditions of transportation and handling	Pass

v. Electrical Safety, Electromagnetic Compatibility, and Light Safety Testing

The Light Delivery Device (LDD) was tested by accredited third-party laboratories to ensure compliance with the applicable international standards for electromagnetic compatibility, electrical safety and light safety. Testing included all required elements of IEC 60601 – Medical electrical equipment - General requirements for basic safety and essential performance – Parts 1-2, 1-6, and 1-8 Collateral Standards for Electromagnetic disturbances, Usability and General requirements, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems. The LDD meets all pertinent design and performance standards for light-emitting products as defined in 21 CFR Part 1040. Additionally, the LDD is in conformance with ISO 15004-2:2007: Fundamental requirements and test methods – Part 2: Light hazard protection.

vi. Software Validation Testing

RxSight, Inc. procedures require the establishment and review of specifications, development of risk analysis, and adequate verifications and validation of software and hardware prior to release. Risk management procedures were applied according to current ISO 14791 and IEC 60601-1 standards.

Software testing was performed in accordance with IEC 62304 to verify and validate module and system level functions. The results of the overall validation testing demonstrate that the Light Delivery Device meets all software specifications and requirements.

B. Animal Studies

To demonstrate the in vivo biocompatibility of the LAL animal implantation studies had been conducted, as summarized below.

Ocular implantation study in New Zealand rabbits

A 6-month ocular implantation study was conducted in rabbits to demonstrate the long-term biocompatibility of the LAL. Two groups (A and B), each of nine New Zealand white rabbits, underwent phacoemulsification after general anesthesia. Both groups were implanted in one eye with a non-irradiated LAL in the capsular bag. The contralateral eye received a control silicon IOL with the same dimensions and haptic material as the LAL. The LAL was left un-irradiated in group A throughout the duration of the study. The second group of 9 rabbits (Group B) was anesthetized and the LAL was irradiated one day after implantation with an average radiant exposure of 7.92 joules (J) of UV light (365 nm) focused at the anterior surface of the LAL to mimic the maximum irradiation exposure of the LDD lock-in treatments. Slit lamp examinations were performed at week 1, 2, 4, and month 3 and 6. The rabbits were euthanized at 6 months after implantation and histopathological evaluations were conducted. LALs were explanted and examined for cells, cellular debris and fibrous deposit. There were no significant differences in any histopathology findings between the LAL and

the control group. Histopathology evaluation of both LAL groups revealed no signs of tissue damage or untoward inflammatory reactions.

Ocular implantation study in Dutch belted rabbits

A 1-week ocular implantation study was conducted in Dutch belted rabbits to evaluate the potential tissue damages from the UV light over-exposure in animals implanted with LAL. Sixteen (16) Dutch belted rabbits underwent phacoemulsification after general anesthesia. The rabbits were implanted with a non-irradiated LAL in the capsular bag. The contralateral eye received a non-UV absorbing IOL. One day after implantation the LAL was irradiated with 365 nm UV light exposure of 1, 2,3 and 5 times the maximum LDD treatment used in clinical setting at the retinal plane. The control lens was irradiated with 0.3, 0.6, 1 and 2 times the maximum LAL treatment dose at the retinal plane. Four animals were included in each group. Slit lamp examinations were performed 24 and 48 hours after irradiation. The rabbits were euthanized at 1 week after irradiation and histopathological evaluations were conducted. Histopathological evaluation of eyes implanted with LAL showed no sign of corneal or anterior segment toxicity, retinal retinal pigment epithelium or choroidal toxicity. In contrast to the LAL group, an area of focal damage to the retina consisting of retinal thinning and disruption of the retinal pigment epithelium and underlying choroids was observed in 3 eyes implanted with non-UV aborbing IOL that received 2 times the maximum LAL treatment dose at the retinal plane.

Ocular implantation study in cats

A 3-month implantation study was conducted in 12 cats to evaluate the effect of UV-treatment on the corneal endothelium. One eye of each animals was irradiated with 365 nm UV light exposure of 50.25 J/cm^2 measured at the front surface of the cornea, simulating the expected maximum irradiation treatment dose. The contralateral eye served as a non-irradiated control. Three cats each were sacrificed at one day, one week, one month, and three months post-irradiation. The corneas were then removed and evaluated for any evidence of morphological and physiological damage using light microscopy at 400X and analyzed using digital imaging system. The study did not show any differences between irradiated and non-irradiated eyes in terms of corneal endothelial cell damage, corneal endothelial cell loss, and qualitative size and shape of endothelial cells, analyzed under high magnification light microscopy examination.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the primary implantation in the capsular bag with the Light Adjustable Lens (LAL) and Light Delivery Device (LDD) system for the reduction residual astigmatism to improve uncorrected visual acuity after removal of the cataractous natural lens in the US under IDE # G100240. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

The primary objective of this study was to evaluate, for the visual correction of aphakia, the safety and effectiveness of the LAL used with the LDD for reducing astigmatism and improving uncorrected visual acuity after implantation of the intraocular lens in eyes with pre-existing astigmatism by performing a refractive adjustment of the LAL with the LDD to reduce residual refractive error. A control group was used to compare the effectiveness of the LAL to a commercially available monofocal IOL. A masked observer was used for measurement of manifest refraction, best spectacle-corrected visual acuity (BSCVA) and uncorrected visual acuity (UCVA) at key follow-up examinations. Pateints were not masked. Physicians performing evaluations of ocular health were not masked.

A. Study Design

Subjects were treated between January 31, 2012 and March 17, 2015. The database for this PMA reflected data collected through July 20, 2016 and included 600 subjects. There were 17 investigational sites.

This was a randomized, controlled prospective multi-center clinical trial designed to evaluate the safety and effectiveness of the LAL and LDD compared to a commercially available monofocal IOL of the investigator's choice. The study population consists of 600 eyes implanted monocularly with the LAL group consisting of a minimum of 390 eyes and the control group consisting of a minimum of 195 eyes implanted with a commercially available, posterior chamber, non-accommodating, monofocal IOL. Subjects were followed over a 12-month period. A maximum of 18 sites participated with all sites located in the United States.

Only subjects meeting all inclusion/exclusion criteria were to be implanted with the investigational LAL or a control IOL. Those subjects who did not meet the inclusion/exclusion requirements were considered screen failures and were withdrawn from the study prior to implantation. Subjects continued to be enrolled until a minimum of 390 eyes had undergone implantation with the LAL and a minimum of 195 eyes had undergone implantation with a commercially available monofocal IOL.

After completion of the preoperative examination and confirmation that the subject met all inclusion/exclusion criteria (with the exception of exclusion criterion related to surgical complications) and that the subject was willing to undergo study lens implantation, the subject was assigned randomly to receive either the LAL or the control IOL (a conventional monofocal IOL of the surgeon's choice) in a 2:1 ratio.

The implant lens power for the LAL was calculated based upon the ocular biometry data and a standard IOL power calculation formula. When choosing the IOL power, the two arms were treated differently. Eyes implanted with the LAL

were targeted to a postoperative MRSE of +0.50 D (to compensate for the expected 0.50 D myopic shift of the required LDD lock-in treatment). Eyes implanted with the LAL underwent spherical or spherocylindrical refractive adjustment of the LAL using the LDD.

Subjects in the LAL group were evaluated at 12 study visits and subjects in the control group were evaluated at 8 study visits as follows: preoperative, operative, 1 day, 1 week, adjustment #1 (LAL)/17-21 days (control), adjustment #2 (LAL only), lock-in #1 (LAL only), lock-in #2 (LAL only), 1-week post lock-in #2 (LAL only), and 6, 9, and 12 months postoperatively. A schedule of assessments is presented in the following section.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the G100240 study was limited to patients who met the following inclusion criteria:

   - Must sign a written Informed Consent form.
   - Undergoing cataract surgery for the implantation of an IOL and must be willing to have either the LAL or a commercially available monofocal IOL implanted based on random assignment.
   - Study eye has pre-operative regular corneal astigmatism of $\geq$ 0.75 D and $\leq$ 2.00 D by manual keratometry or >2.00 D and $\leq$ 2.5 D of regular corneal astigmatism with a steep axis between 70 degrees and 110 degrees.
   - Between the ages of 40 and 80 inclusive.
   - Study eye must have a cataract causing reduction in best spectacle-corrected visual acuity to a level of 20/40 or worse with or without a glare source.
   - Study eye has best spectacle-corrected visual acuity projected (by clinical estimate based upon past ocular history and retinal exam) to be 20/20 or better after cataract removal and IOL implantation.
   - Study eye has clear intraocular media other than cataract.
   - Potentially good vision in the fellow eye with BSCVA 20/40 or better.
   - Willing and able to comply with the requirements for study specific procedures and visits.
   - Study eye has fully dilated pupil diameter of ≥ 7.0 mm.

   Patients were not permitted to enroll in the G100240 study if they met any of the following exclusion criteria:

   - Study eye with zonular laxity or dehiscence.
   - Study eye with pseudoexfoliation.
   - Study eye with age-related macular degeneration involving the presence of geographic atrophy or soft drusen. Study eyes with hard drusen are

permitted if the density of drusen is such that impairment of acuity beyond 20/20 is not expected.

- Study eye with retinal degenerative disorder (other than macular degeneration) that is expected to cause future vision loss.
- Subjects with diabetes with any evidence of retinopathy.
- Study eye with evidence of glaucomatous optic neuropathy.
- Study eye with a history of uveitis.
- Study eye with significant anterior segment pathology, such as rubeosis iridis, aniridia, or iris coloboma.
- Study eye with corneal pathology that is either progressive or sufficient to reduce BSCVA to worse than 20/20.
- Study eye with keratoconus or suspected of having keratoconus.
- Study eye with any corneal dystrophy including basement membrane dystrophy.
- Study eye that has undergone previous corneal or intraocular surgery, except eyes with previous pterygium excision are permitted as long as the pterygium did not extend more than 2mm onto the cornea from the limbus.
- Subjects with complications in the study eye during cataract surgery before intraocular lens implantation including posterior capsule rupture, zonular rupture, radial capsulorhexis tear, vitreous loss, iris trauma, corneal complications or any intraoperative abnormality that may affect the postoperative pupillary dilation, or the centration or tilt of the intraocular lens.
- Subjects with serious co-morbid conditions that in the judgment of the investigator makes inclusion in the study not in the best interest of the subject.
- Subjects taking systemic medication that may increase sensitivity to UV light such as tetracycline, doxycycline, psoralens, amiodarone, phenothiazines, chloroquine, hydrochlorothiazide, hypericin, ketoprofen, piroxicam, lomefloxacin, and methoxsalen. This is a partial list of photosensitizing medications and is not a comprehensive list. Therefore, please evaluate all medications that the patient is taking for this effect prior to consideration for device treatment. LDD treatment in patients taking such medications may lead to irreversible phototoxic damage to the eye.
- Study eye with irregular astigmatism.
- Study eye with history of herpes simplex.
- Patients not meeting the above inclusion criteria were excluded from the study.

2. Follow-up Schedule
   All subjects were scheduled to return for follow-up examinations at 1 day, 1 week, during each light adjustment or lock-in procedure as well as at 6, 9, and 12 months postoperatively.

3. Clinical Endpoints
   With regards to safety, the key primary variables for the study were:

   - Best spectacle-corrected visual acuity: The percentage of LAL treatment group and monofocal control group eyes achieving overall and best case BSCVA of 20/40 or better at 6 months postoperatively compared to the historical grid.
   - Incidence of sight-threatening complications and adverse events for the LAL treatment group and the monofocal control group compared to the historical grid.

   With regards to effectiveness, the key primary variables for the study were:

   - Percent reduction in manifest cylinder at 6 months postoperatively from pre-adjustment (LAL) /17-21 days (control group) examination compared between the LAL treatment group and the monofocal control group.
   - Percent mean absolute reduction in MRSE by subject at 6 months postoperatively from the pre-adjustment (LAL) /17-21 days (control group) examination compared between the LAL treatment group and the monofocal control group.
   - Rotation of the meridian of the LAL at 6 months postoperatively.

The following secondary effectiveness endpoints were evaluated:

- Percent of eyes with UCVA of 20/20 or better at 6 months postoperatively compared between the LAL treatment group and the monofocal control group.
- Percent reduction in manifest cylinder at 6 months postoperatively from pre-adjustment (LAL)/17-21 days (control group) examination compared between the LAL treatment group and the monofocal control group by cylinder treatment group (0.75 to 1.25 D and 1.50-2.00 D).
- For eyes with <0.75 D of cylinder at pre-adjustment (LAL)/17-21 days (control group), percent mean absolute reduction in MRSE by subject at 6 months postoperatively from the pre-adjustment (LAL)/17-21 days (control group) examination compared between the LAL treatment group and the monofocal control group.
- Mean BSCVA for the “best case” cohort (no macular problems) at 6 months postoperatively compared between the LAL treatment group and the monofocal control group.

B. Accountability of PMA Cohort

At the time of database lock, of the 793 subjects enrolled in the PMA study, 97% of subjects were available for analysis at the completion of the study, the 12 month post-operative visit.

Seven hundred ninety three subjects signed the informed consent form and were enrolled in the clinical study. 23.2% (184/793) of subjects withdrew from the study prior to randomization. Of the enrolled subjects, 51.7% (410/793) of eyes were randomized for implantation with the LAL and 25.1% (199/793) eyes were randomized for implantation with a monofocal control IOL. Of the eyes randomized to receive the LAL, 1.7% (7/410) were withdrawn prior to implantation.

Subject accountability in both the LAL and Control groups across all follow-up visits are summarized in Table 1. Percent accountability at all scheduled visits over the course of the study was never below 97%.

TABLE 1
SUBJECT ACCOUNTABILITY
(ITT POPULATION)

	Day 1 n/N (%)*		1 Week (wk) n/N (%)*		Adjustment #1 (or 17-21 days Post-Op) n/N (%)*		LI #1 (LAL only) n/N (%)*	LI #2 (LAL only) n/N (%)*	1 Wk Post LI #2 (LAL only) n/N (%)*	6 Months n/N (%)*		9 Months n/N (%)*		12 Months n/N (%)*	
Treatment Group	**LAL**	**Control**	**LAL**	**Control**	**LAL**	**Control**	**LAL**	**LAL**	**LAL**	**LAL**	**Control**	**LAL**	**Control**	**LAL**	**Control**
Available For Analysis	402/403 (99.8%)	197/197 (100 %)	401/403 (99.5%)	195/197 (99.0%)	400/403 (99.3%)	197/197 (100 %)	399/403 (99.0%)	398/403 (98.8%)	396/403 (98.3%)	391/403 (97.0%)	193/197 (98.0%)	388/403 (96.3%)	193/197 (98.0%)	391/403 (97.0%)	188/197 (95.4%)
Visit within window	402/403 (99.8%)	197/197 (100 %)	400/403 (99.3%)	194/197 (98.5%)	379/403 (94.0%)	188/197 (95.4%)	385/403 (95.5%)	373/403 (92.6%)	381/403 (94.5%)	386/403 (95.8%)	188/197 (95.4%)	385/403 (95.5%)	190/197 (96.4%)	389/403 (96.5%)	188/197 (95.4%)
Discontinued	1/403 (0.2%)	0/197 (0.0%)	1/403 (0.2%)	0/197 (0.0%)	3/403 (0.7%)	0/197 0.0%)	3/403 (0.7%)	3/403 (0.7%)	3/403 (0.7%)	3/403 (0.7%)	2/197 (1.0%)	4/403 (1.0%)	2/197 (1.0%)	4/403 (1.0%)	4/197 (2.0%)
Explanted[1]	1/403 (0.2%)	0/197 (0.0%)	1/403 (0.2%)	0/197 (0.0%)	3/403 (0.7%)	0/197 (0.0%)	3/403 (0.7%)	3/403 (0.7%)	3/403 (0.7%)	3/403 (0.7%)	0/197 (0.0%)	3/403 (0.7%)	0/197 (0.0%)	3/403 (0.7%)	0/197 (0.0%)
Deceased	0/403 (0.0%)	0/197 (0.0%)	0/403 (0.0%)	0/197 (0.0%)	0/403 (0.0%)	0/197 (0.0%)	0/403 (0.0%)	0/403 (0.0%)	0/403 (0.0%)	0/403 (0.0%)	2/197 (1.0%)	1/403 (0.2%)	2/197 (1.0%)	1/403 (0.2%)	4/197 (2.0%)
Other	0/403 (0.0%)	0/197 (0.0%)	0/403 (0.0%)	0/197 (0.0%)	0/403 (0.0%)	0/197 (0.0%)	0/403 (0.0%)	0/403 (0.0%)	0/403 (0.0%)	0/403 (0.0%)	0/197 (0.0%)	0/403 (0.0%)	0/197 (0.0%)	0/403 (0.0%)	0/197 (0.0%)
Missed Visit	0/403 (0.0%)	0/197 (0.0%)	1/403 (0.2%)	2/197 (1.0%)	0/403 (0.0%)	0/197 (0.0%)	1/403 (0.2%)	2/403 (0.5%)	4/403 (1.0%)	7/403 (1.7%)	2/197 (1.0%)	3/403 (0.7%)	1/197 (0.5%)	0/403 (0.0%)	0/197 (0.0%)
Lost to follow-up	0/403 (0.0%)	0/197 (0.0%)	0/403 (0.0%)	0/197 (0.0%)	0/403 (0.0%)	0/197 (0.0%)	0/403 (0.0%)	0/403 (0.0%)	0/403 (0.0%)	2/403 (0.5%)	0/197 (0.0%)	8/403 (2.0%)	1/197 (0.5%)	8/403 (2.0%)	5/197 (2.5%)
Missing[3]	1/403 (0.2%)	0/197 (0.0%)	2/403 (0.5%)	2/197 (1.0%)	3/403 (0.7%)	0/197 (0.0%)	4/403 (1.0%)	5/403 (1.2%)	7/403 (1.7%)	12/403 (3.0%)	4/197 (2.0%)	15/403 (3.7%)	4/197 (2.0%)	12/403 (3.0%)	9/197 (4.6%)
Not Yet Eligible	0/403 (0.0%)	0/197 (0.0%)	0/403 (0.0%)	0/197 (0.0%)	0/403 (0.0%)	0/197 (0.0%)	0/403 (0.0%)	0/403 (0.0%)	0/403 (0.0%)	0/403 (0.0%)	0/197 (0.0%)	0/403 (0.0%)	0/197 (0.0%)	0/403 (0.0%)	0/197 (0.0%)
Accountability[2]	402/402 (100 %)	197/197 (100 %)	401/402 (99.8%)	195/197 (99.0%)	400/400[4] (100 %)	197/197 (100 %)	399/400 (99.8%)	398/400 (99.5%)	396/400 (99.0%)	391/400 (97.8%)	193/195 (99.0%)	388/399 (97.2%)	193/195 (99.0%)	391/399 (98.0%)	188/193 (97.4%)

***** Total number of all eyes treated (N) for each group is used as a denominator to calculate percentages, except for accountability; n = number in treatment group; % = n/N(100)

[1] One additional subject had the LAL lens explanted prior to the 9-Month visit, but completed the study

[2] Accountability = [Available for Analysis/(Implanted-Discontinued-Not Yet Eligible)]

[3] Sum of Discontinued, Missed Visit and Lost to Follow-up

[4] One subject did not undergo an adjustment because an LAL was not successfully implanted.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population for this randomized, prospective, multicenter clinical study are presented in Table 2 for the LAL group vs. the control group.

TABLE 2
DEMOGRAPHICS
(ITT POPULATION)

		LAL (N = 403) n(%)	Control (N = 197) N(/%)	Difference (LAL-control) [95% CI] [1]
Gender	Male	161 (40.0%)	95 (48.2%)	-8.3 [-16.7,0.2]
	Female	242 (60.0%)	102 (51.8%)	
Age (years)	Mean ± SD (n)	65.6 ± 7.9 (403)	66.6 ± 7.2 (197)	-1.0 [-2.3,0.3]
	Median	67.0	67.0	
	(Min, Max)	(41, 80)	(42, 80)	
Race	Caucasian	383 (95.0%)	188 (95.4%)	-0.4 [-4.0,3.2]
	Black/African American	15 (3.7%)	6 (3.0%)	
	Asian	4 (1.0%)	0 (0.0%)	
	American Indian/Alaska Native	1 (0.2%)	0 (0.0%)	
	Native Hawaiian/Pacific Islander	0 (0.0%)	2 (1.0%)	
	Mixed[2]	0 (0.0%)	1 (0.5%)	
Ethnicity	Hispanic or Latino	18 (4.5%)	7 (3.6%)	0.9 [-2.4,4.2]
	Not Hispanic or Latino	385 (95.5%)	190 (96.4%)	
Study Eye	Right	226 (56.1%)	96 (48.7%)	7.4 [-1.1,15.8]
	Left	177 (43.9%)	101 (51.3%)	

[1] Difference between means or proportions

		LAL (N = 403) n(%)	Control (N = 197) N(/%)	Difference (LAL-control) [95% CI] [1]

[2] One subject was of mixed race: American Indian or Alaska Native, Caucasian
% = n/N (100)

i. Study Treatments

IOL Implantation
The implant was performed on study Day 0, in accordance with the detailed procedures described in the study protocol. Standard small incision, phacoemulsification surgery and implantation of the LAL or the control lens was performed. Subjects implanted with the LAL were instructed to wear the specified UV protective eyewear at all times post-implantation until the adjustment and lock-in procedures were completed.

Note: While LAL insertion with either a Naviject Injector or the Nichamin inserter and forceps was allowed, use of the Naviject was discontinued during the course of the Phase 3 clinical study due to delivery failures, and after this change only the Nichamin inserter and forceps were allowed.

LDD Treatments
The refractive adjustment performed with the LDD in the LAL group was based on the manifest refraction with a goal of emmetropia. The protocol allowed spherical corrections from -2.0 to +2.0 D and cylindrical corrections from 0.75 to 2.0 D. Eyes with <0.75 D of cylinder had a treatment performed based on their MRSE. Eyes with a spherical or cylindrical component >2.0 D had a 2.0 D correction performed.

Three to 5 days after adjustment #1, LAL subjects returned and had a manifest refraction performed by two unmasked independent examiners. Depending on the measured refraction, either an adjustment #2 was performed or a Lock-in #1 was performed.

All LAL subjects required two treatments using the LDD to “lock-in” the LAL. The first of the two “lock-in” doses of UV light was performed at 3 to 5 days after the final adjustment treatment. The second and final “lock-in” treatment was performed 3 to 5 days after the first “lock-in” treatment.

Note: During the clinical study a modification to the LDD hardware and software was introduced, to enhance the safety of the lock-in treatment only. Termed Reduced Exposure Lock-in(REL), the revised lock-in reduced peak radiant exposure to the retina compared to the original (Pre-REL) lock-in treatment. This modified device was used in approximately half of the LAL subjects.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on a (modified) Intent to Treat (ITT) population cohort of 579 patients available for the 12 month evaluation. The key safety outcomes for this study are presented below in Tables 3 to 8. Adverse effects are reported in Tables 5 to 8.

Safety analysis using the (modified) Intent to Treat (ITT) population includes any subject who had signed the informed consent and had the procedure attempted. The ITT population consists of 600 eyes with 403 eyes randomized to the LAL and 197 eyes randomized to the control IOL.

The co-primary safety endpoints were: (a) The percentage of LAL eyes achieving BSCVA of 20/40 or better at 6 months postoperatively (compared to the historical control for intraocular lenses in ISO 11979-7), and (b) Incidence of sight-threatening adverse events for the LAL treatment group (compared to the historical control rates (ISO 11979-7) where applicable).

BSCVA Safety Endpoint

The primary BSCVA safety endpoint was a comparison of the rates of BSCVA of 20/40 or better at 6 months postoperatively compared between the LAL group and the historic control for intraocular lenses (as per ISO 11979-7). At 6 and 12 months postoperatively, 100% of eyes in both the LAL and Control groups had BSCVA of 20/40 or better, exceeding the historic control rate of 92.5% (ISO 11979-7).

Table 3 summarizes the BSCVA data at key timepoints in the study. Refer to the Adverse Event section for a complete description of cases with significant losses of BSCVA.

TABLE 3: BSCVA BY VISIT (SUBJECTS WITH DATA AT RELEVANT TIMEPOINTS)

	Pre-Operative		1-week Post-Op		Pre-Adjustment (LAL) or 17-21 days post-op (control)		Pre-Adjustment #2
BSCVA	**LAL (N=403)**	**Control (N=197)**	**LAL (N=401)**	**Control (N=195)**	**LAL (N=400)**	**Control (N=197)**	**LAL (N=262)**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
20/12.5 or better	0 (0.0%)	0 (0.0%)	13 (3.3%)	5 (2.6%)	42 (10.5%)	14 (7.1%)	37 (14.1%)
20/16 or better	3 (0.7%)	0 (0.0%)	138 (34.5%)	64 (32.8%)	229 (57.3%)	95 (48.2%)	162 (61.8%)
20/20 or better	35 (8.7%)	14 (7.1%)	320 (80.0%)	161 (82.6%)	367 (91.8%)	176 (89.3%)	250 (95.4%)
20/25 or better	140 (34.7%)	59 (29.9%)	375 (93.8%)	189 (96.9%)	394 (98.5%)	193 (98.0%)	261 (99.6%)
20/32 or better	221 (54.8%)	105 (53.3%)	392 (98.0%)	192 (98.5%)	399 (99.8%)	196 (99.5%)	262 (100.0%)
20/40 or better	300 (74.4%)	141 (71.6%)	398 (99.5%)	195 (100.0%)	399 (99.8%)	196 (99.5%)	262 (100.0%)
d20/80 or better	386 (95.8%)	189 (95.9%)	399 (99.8%)	195 (100.0%)	399 (99.8%)	197 (100.0%)	262 (100.0%)
20/200 or better	394 (97.8%)	197 (100.0%)	399 (99.8%)	195 (100.0%)	399 (99.8%)	197 (100.0%)	262 (100.0%)
Not Reported	0	0	1	0	0	0	0
Mean ± standard deviation (SD)[1] (n)	0.274 (20/37.6) 0.240 (403)	0.268 (20/37.1) 0.172 (197)	-0.002 (20/19.9) 0.124 (400)	-0.009 (20/19.6) 0.082 (195)	-0.051 (20/17.8) 0.113 (400)	-0.038 (20/18.3) 0.082 (197)	-0.068 (20/17.1) 0.072 (262)

TABLE 3 (CONTINUED): BSCVA BY VISIT (SUBJECTS WITH DATA AT RELEVANT TIMEPOINTS)

	Pre-Lock-in #1	Pre-Lock-in #2	1 week post Lock-in #2	6 months		9 months		12 months	
BSCVA	**LAL (N=399)**	**LAL (N=398)**	**LAL (N=396)**	**LAL (N=391)**	**Control (N=193)**	**LAL (N=388)**	**Control (N=193)**	**LAL (N=391)**	**Control (N=188)**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
20/12.5 or better	63 (15.8%)	61 (15.3%)	51 (12.9%)	77 (19.7%)	15 (7.8%)	67 (17.3%)	21 (10.9%)	57 (14.6%)	20 (10.6%)
20/16 or better	252 (63.2%)	260 (65.3%)	252 (63.6%)	223 (57.0%)	84 (43.5%)	236 (60.8%)	94 (48.7%)	227 (58.1%)	89 (47.3%)
20/20 or better	385 (96.5%)	381 (95.7%)	374 (94.4%)	369 (94.4%)	160 (82.9%)	364 (93.8%)	170 (88.1%)	365 (93.4%)	155 (82.4%)
20/25 or better	398 (99.7%)	395 (99.2%)	392 (99.0%)	386 (98.7%)	188 (97.4%)	385 (99.2%)	188 (97.4%)	390 (99.7%)	184 (97.9%)
20/32 or better	399 (100.0%)	398 (100.0%)	396 (100.0%)	389 (99.5%)	192 (99.5%)	388 (100.0%)	192 (99.5%)	390 (99.7%)	188 (100.0%)
20/40 or better	399 (100.0%)	398 (100.0%)	396 (100.0%)	391 (100.0%)	193 (100.0%)	388 (100.0%)	193 (100.0%)	391 (100.0%)	188 (100.0%)
20/80 or better	399 (100.0%)	398 (100.0%)	396 (100.0%)	391 (100.0%)	193 (100.0%)	388 (100.0%)	193 (100.0%)	391 (100.0%)	188 (100.0%)

20/200 or better	399 (100.0%)	398 (100.0%)	396 (100.0%)	391 (100.0%)	193 (100.0%)	388 (100.0%)	193 (100.0%)	391 (100.0%)	188 (100.0%)
Not Reported	0	0	0	0	0	0	0	0	0
Mean ± SD[1] (n)	-0.071 (20/17.0) 0.075 (399)	-0.072 (20/16.9) 0.078 (398)	-0.068 (20/17.1) 0.077 (396)	-0.066 (20/17.2) 0.084 (391)	-0.028 (20/18.8) 0.091 (193)	-0.069 (20/17.1) 0.083 (388)	-0.041 (20/18.2) 0.090 (193)	-0.063 (20/17.3) 0.079 (391)	-0.039 (20/18.3) 0.090 (188)

%=n/N(100)
[1]LogMAR (Snellen)

Adverse Events

Table 4 presents cumulative and persistent (to 12 months) adverse events as defined in ISO 11979-7. The rates of observed cumulative and persistent safety events did not exceed the rates in the ISO historical control except for the category of Secondary Surgical Interventions (SSI), which was significantly higher than the historical rate ($p<0.05$).

Because of the unique nature of the LAL/LDD device system (which includes a UV light emitting device), some additional categories of types of adverse events were evaluated, including phototoxic retinal damage causing reduction in best spectacle corrected visual acuity, induction of tritan color vision anomalies, induction of erythropsia, and distortion of the LAL optic due to premature polymerization. Rates for these and other categories of adverse events that are not in the historical control are also shown in Table 4. Additionally, information concerning device-related adverse events concerning erythropsia and color vison anomalies are provided in Tables 6 and 7. As shown in Table 4, 7 eyes (1.7%, 7/410) in the LAL group had a SSI; 3 explants, a Descemet's Stripping Endothelial Keratoplasty (DSEK) procedure, two treatments to dissolve iris adhesions to permit full pupil dilation, and a barrier retinal laser procedure as described in the table below.

TABLE 4
KEY ADVERSE EVENTS – STUDY EYE

Adverse Events - Cumulative	Safety and Performance Endpoint %	LAL (N=403)	Control (N=197)
		n (%)	n (%)
Cystoid Macular Edema (CME)[6]	3.0%	3 (0.7%)	3 (1.5%)
Hypopyon	0.3%	1 (0.2%)	0 (0.0%)
Pupillary Block	0.1%	0 (0.0%)	0 (0.0%)
Retinal Detachment	0.3%	0 (0.0%)	0 (0.0%)
Endophthalmitis	0.1%	1 (0.2%)	0 (0.0%)
Lens Dislocated From Posterior Chamber	0.1%	0 (0.0%)	0 (0.0%)
Secondary Surgical Intervention (excluding Posterior Capsulotomy)[1]	0.8%	7 (1.7%)	1 (0.5%)
Adverse Events – Persistent2	Safety and Performance Endpoint %	LAL (N=391)	Control (N=188)
		n (%)	n (%)
Corneal Edema	0.3%	0 (0.0%)	0 (0.0%)
Cystoid Macular Edema	0.5%	0 (0.0%)	0 (0.0%)
Iritis	0.3%	0 (0.0%)	0 (0.0%)
Elevated Intraocular Pressure (IOP) Requiring Treatment	0.4%	0 (0.0%)	0 (0.0%)
Adverse Events – Key Non-Standard Categories of Events[3]		LAL (N=391)	Control (N=188)
		n (%)	n (%)
Phototoxic Retinal Damage causing temporary loss of BSCVA1		1 (0.2%)	N/A
Persistent Induced Tritan Color Vision Anomaly[1]		2 (0.5%)	N/A
Persistent Induced Erythropsia		1 (0.3%)[4]	N/A
Reactivation of Ocular Herpes Simplex Infection after LDD UV treatment		1 (0.3%)[5]	N/A
Persistent Unanticipated Significant Increase in Manifest Refraction Error (≥1.0 D cylinder or MRSE)		5 (1.3%)	N/A
Premature Polymerization of the LAL Causing Visible Distortion of LAL Optic		0 (0.0%)	N/A
Intraoperative Iris Prolapse		1 (0.3%)	0 (0.0%)
Intraoperative Capsular tear during primary IOL implantation after unremarkable phacoemulsification		1 (0.3%)	0 (0.0%)
Horseshoe Retinal Tear		1 (0.3%)[7]	1 (0.5%)

[1] One subject experienced a retinal phototoxic injury that was determined to be caused by a faulty filter within the UV source of the LDD. Corrective action was taken to ensure that defective filters were not released to the market. The retinal phototoxicity was associated with loss of best spectacle corrected visual acuity to 20/150, which recovered to 20/22 approximately 5 months after surgery. This subject also experienced a tritan color vision defect that was persistent to 4 years postoperatively. The patient underwent an explant with a replacement with a monofocal IOL.

[2] The rates of persistent adverse events were calculated based on the observed population at 12 months.

[3] The rates of Key Non-Standard Categories of Events were calculated based on the observed population at any time during the clinical study.

[4] Resolved at 14 months postoperatively.

[5] Following the initial light treatment, one subject experienced a reactivation of previously undiagnosed herpes simplex virus (HSV). Following anti-HSV therapy, the subject's condition improved and remaining light treatments were administered. At the 12-month postoperative exam, BSCVA was 20/20.

[6] One case of CME required sub-Tenons kenalog injection; this caused delay of light treatment.

[7] One case included a vitreous detachment with sub-retinal fluid.

TABLE 4 CONTINUED
KEY ADVERSE EVENTS – STUDY EYE

SSI	Cause	Final Acuity at Last Visit
Explant	As described in Table 2, footnote 1, a faulty UV filter within the UV source of the LDD prevented completion of light treatments	BSCVA 20/23 with persistent tritan anomaly
Explant	Scratch on the LAL optic acquired at time of lens implant that required lens replacement at 3 weeks postop. Secondary procedure had complications.	BSCVA 20/20
Explant	Subject requested lens replacement prior to light treatment	UCVA 20/15
DSEK	Problems during delivery of LAL which led to corneal edema	BSCVA 20/26.4
Lysing of iris adhesions and sphincterotomy	Following the initial light treatment, posterior synechiae were observed which limited pupil dilation for final light treatment	BSCVA 20/17.4
Lysing of iris adhesions by YAG laser	Following the initial light treatments, posterior synechiae were observed which limited pupil dilation for final light treatment	BSCVA 20/17.4
Barrier laser treatment	Hemorrhagic posterior vitreous detachment and a horseshoe retinal tear with sub-retinal fluid 9 months postoperative.	BSCVA 20/14.5

Additional Safety Analyses

Serious ocular adverse events noted in this study are provided in Tables 5-8.

Best Spectacle Corrected Visual Acuity Change

Table 5 presents change in BSCVA at each postoperative visit compared to pre-adjustment #1 (LAL) or 17-21 day visit (Control) BSCVA. At 1 week post lock-in #2, the majority of eyes had an increase or no change in BSCVA. The mean change in BSCVA from pre-adjustment #1 to 1 week post lock-in #2 was +0.7 letters.

Overall, the distribution of eyes with gains and losses of 2 or more lines of BSCVA was similar for the LAL and the Control group at 6 and 12 months. At 6 months, only 2 eyes in the LAL group and 3 eyes in the Control group had a decrease of 2 or more lines of BSCVA. At 12 months, only 1 eye in the LAL group and 4 eyes in the Control group had a decrease of 2 or more lines of BSCVA.

TABLE 5
BSCVA CHANGE COMPARED TO PRE-ADJUSTMENT #1 (LAL)/17-21 DAYS (CONTROL)
(SUBJECTS WITH DATA AT RELEVANT TIMEPOINTS)

	Pre-Lock-in #1	Pre-Lock-in #2	1 week Post Lock-in #2
BSCVA change	**LAL (N=399)**	**LAL (N=398)**	**LAL (N=396)**
	n (%)	**n (%)**	**n (%)**
Increase in 15 letters or more (3 lines or more)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Increase in 10-14 letters (2 lines)	2 (0.5%)	3 (0.8%)	2 (0.5%)
Increase in 5-9 letters (1 line)	36 (9.0%)	42 (10.6%)	43 (10.9%)
No Change	347 (87.0%)	339 (85.2%)	330 (83.3%)
Decrease in 5-9 letters (1 line)	13 (3.3%)	13 (3.3%)	19 (4.8%)
Decrease in 10-14 letters (2 lines)	1 (0.3%)	1 (0.3%)	2 (0.5%)
Decrease in 15 letters or more (3 lines or more)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not reported	0	0	0
Mean change in number of letters	0.8 ± 2.9 (399)	0.9 ± 3.0 (398)	0.7 ± 3.2 (396)

	6 months		9 months		12 months	
BSCVA change	**LAL (N=391)**	**Control (N=193)**	**LAL (N=388)**	**Control (N=193)**	**LAL (N=391)**	**Control (N=188)**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Increase in 15 letters or more (3 lines or more)	1 (0.3%)	1 (0.5%)	1 (0.3%)	1 (0.5%)	1 (0.3%)	2 (1.1%)
Increase in 10-14 letters (2 lines)	5 (1.3%)	1 (0.5%)	4 (1.0%)	6 (3.1%)	2 (0.5%)	3 (1.6%)
Increase in 5-9 letters (1 line)	52 (13.3%)	17 (8.8%)	48 (12.4%)	15 (7.8%)	50 (12.8%)	18 (9.6%)
No Change	312 (79.8%)	150 (77.7%)	307 (79.1%)	150 (77.7%)	306 (78.3%)	142 (75.5%)
Decrease in 5-9 letters (1 line)	19 (4.9%)	21 (10.9%)	25 (6.4%)	20 (10.4%)	31 (7.9%)	19 (10.1%)
Decrease in 10-14 letters (2 lines)	2 (0.5%)	3 (1.6%)	3 (0.8%)	1 (0.5%)	1 (0.3%)	4 (2.1%)
Decrease in 15 letters or more (3 lines or more)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not reported	0	0	0	0	0	0
Mean change in number of letters	0.7 ± 4.9 (391)	-0.5 ± 3.9 (193)	0.9 ± 5.0 (388)	0.1 ± 4.2 (193)	0.6 ± 5.2 (391)	0.0 ± 4.4 (188)

Erythropsia

Erythropsia is an uncommon abnormality of vision in which objects appear to be tinged with red. It can be caused by exposure to high levels of ultraviolet (UV) light. Since the

LDD exposes the eye to higher than usual levels of UV light, the study attempted to assess the presence and severity of erythropsia experienced by the subjects . It was assumed that post-light treatment erythropsia were related to use of the LDD. At a number of study visits, subjects were asked (without occlusion of the untreated eye): "At this moment, how would you rate your color vision? Is it normal, pink, red, or dark red?" Erythropsia was graded as none for a normal response, mild for a pink response, moderate for a red response, or severe for a dark red response. It should be noted that this assessment methodology was not determined to be a psychometrically valid assessment of the concept of patient reported erythropsia.

Table 6 presents results from the erythropsia assessment. After light treatment, 233 (58.3%, 233/399) eyes in the LAL group had erythropsia of any grade. The highest rate of erythropsia was reported prior to the lock-in #2 treatment when 49.0% (195/398) of LAL subjects reported mild erythropsia. This proportion decreased significantly at 1 week post lock-in #2 (17.7%, 70/396) and was only 0.5% (2/391) at 6 months. Only 1 (0.3%, 1/389) LAL subject continued to report mild erythropsia at the 12-month exam with resolution at 14 months postoperatively. The mean duration for mild erythropsia could not be established because subjects were not required to return for interim visits with "mild" symptoms.

The highest rate of moderate erythropsia also was reported prior to the lock-in #2 treatment when 11 LAL subjects reported this level. Fourteen subjects reported moderate erythropsia at some point in the study, with none reporting severe levels. The average duration of moderate erythropsia was 11.6 days with the minimum duration of 5.0 days and a maximum duration of 22.0 days. No LAL subjects reported moderate erythropsia after the lock-in #2 visit. All but one of the reports of moderate erythropsia occurred prior to the introduction of a safety improvement to the LDD device to reduce UV exposure during the Lock-in procedure. (This device modification was instituted after about half of the subjects had received the earlier version of the LDD treatments.) However, the overall rate of subjects experiencing mild erythropsia was not substantially affected by this modification of the LDD.

TABLE 6
ERYTHROPSIA
(SUBJECTS WITH DATA AT RELEVANT TIMEPOINTS)

Degree of Erythropsia	Adj. #1	Interim	Adj. #2	Interim	Lock-In #1	Interim	Lock-In #2	Interim
LAL								
	N=400	N=9	N=262	N=8	N=399	N=24	N=398	N=9
	n (%)	n	n (%)	n	n (%)	n	n (%)	n
None	394 (98.7%)	3	223 (85.1%)	6	349 (87.5%)	3	203 (51.0%)	-
Mild (pink)	5 (1.3%)	0	38 (14.6%)	0	50 (12.5%)	6	195 (49.0%)	-
Moderate (red)	0 (0.0%)	0	1 (0.4%)	0	0 (0.0%)	11	0 (0.0%)	-
Severe (dark red)	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	-
Not assessed	1	6	0	2	0	4	0	9

Degree of Erythropsia	1 Week Post Lock-In #2	Interim	6 Months	Interim	9 Months	Interim	12 Months
LAL							
	N=396	N=57	N=391	N=18	N=388	N=23	N=391
	n (%)	n	n (%)	n	n (%)	n	n (%)
None	326 (82.3%)	11	389 (99.5%)	1	387 (99.7%)	2	388 (99.7%)
Mild (pink)	70 (17.7%)	1	2 (0.5%)	0	1 (0.3%)	0	1 (0.3%)
Moderate (red)	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
Severe (dark red)	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
Not assessed	0	45	0	17	0	21	2

Degree of Erythropsia	17-21 Days	Interim	6 Months	Interim	9 Months	Interim	12 Months
Control							
	N=197	N=21	N=193	N=8	N=193	N=13	N=188
	n (%)	n	n (%)	n	n (%)	n	n (%)
None	196 (99.5%)	2	193 (100.0%)	1	193 (100.0%)	1	188 (100.0%)
Mild (pink)	1 (0.5%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
Moderate (red)	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
Severe (dark red)	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
Not assessed	0	19	0	7	0	12	0

%=n/N(100)

Color Vision Testing

Since a high level of exposure to UV light can also affect color vision (especially causing a weakness related to perception of blue color or a tritan anomaly), the study also used color vision testing to look for defects of color vision. It was assumed that a tritan anomaly that appears only after light treatment was related to use of the LDD. The City University Color Vision Test (3rd Edition 1998) consists of a series of 11 plates, 4 for Part One and 7 for Part Two. Part One is generally used for screening for color vision defects.

The objective of Part Two is to classify color vision defects. Per the score sheet provided with the test, more than one entry for protan, deutan or tritan is considered abnormal. A protan anomaly is a color vision deficiency that affects the long wavelength sensitive cones and affects a patient's ability to distinguish blue and green colors and also red and green colors. A deutan anomaly is a color vision deficiency that affects the medium wavelength sensitive cones and affects a patient's ability to distinguish red and green colors but others may also be slighted affected. A tritan anomaly is a color vision deficiency that affects the short wavelength sensitive cones and typically affects a patient's ability to distinguish between violet, blue and green colors.

City University Test results are provided in Table 7. Any new tritan anomaly measured after the initial light treatment was considered related to the LDD UV exposure. A total of 7 (1.8%, 7/398) LAL eyes had a tritan score >1 any time after light treatment. Five eyes resolved after light treatments were complete and 2 persisted. Of the five eyes that resolved, four of the eyes were seen at consistent follow-up exams to monitor progress. The average duration of the tritan anomaly for these 4 eyes was 16 days with a minimum duration of 10 days and a maximum duration of 30 days. The fifth eye had a large time gap (557 days) from the time the eye was diagnosed with a tritan anomaly to the next clinical visit in which no tritan anomaly was observed. The two eyes with persistent tritan anomalies were measured with a tritan score >1 at the last study visit, and 1 of these eyes previously described as having an adverse device effect due to a faulty UV filter was documented as having the tritan anomaly at 4 years postoperatively. Both of the persistent and all but one of the transient tritan anomalies occurred prior to the introduction of a safety improvement to the LDD device to reduce UV exposure during the Lock-in procedure.

TABLE 7
CITY UNIVERSITY
(SUBJECTS WITH DATA AT RELEVANT TIMEPOINTS)

Part 1	Pre-Adj #1 LAL (N=400)	17-21 Days Control (N=197)	Interim Visit LAL (N=10)	Pre-Lock-in #1 LAL (N=399)	Interim Visit LAL (N=21)	Pre-Lock-in #2 LAL (N=398)	Interim Visit LAL (N=0)	1 week post Lock-in #2 LAL (N=396)	Interim Visit LAL (N=10)	Interim Visit Control (N=0)
	n (%)	n (%)	n	n (%)	n	n (%)	n	n (%)	n	n
Abnormal (<9)	12 (3.0%)	4 (2.0%)	0	8 (2.0%)	11	12 (3.0%)	0	6 (1.5%)	1	0
Not reported	1	0	0	2	0	0	0	0	0	0
Part 2										
Protan >1	2 (0.5%)	0 (0.0%)	0	2 (0.5%)	0	1 (0.3%)	0	0 (0.0%)	0	0
Deutan >1	1 (0.3%)	1 (0.5%)	0	3 (0.8%)	1	2 (0.5%)	0	1 (0.3%)	0	0
Tritan >1	0 (0.0%)	0 (0.0%)	0	1 (0.3%)	5	0 (0.0%)	0	1 (0.3%)	1	0
Not reported	1	0	0	2	0	0	0	0	0	0

Part 1	6 months LAL (N=391)	6 months Control (N=193)	Interim Visit LAL (N=1)	Interim Visit Control (N=1)	9 months LAL (N=388)	9 months Control (N=193)	Interim Visit LAL (N=1)	Interim Visit Control (N=0)	12 months LAL (N=391)	12 months Control (N=188)
	n (%)	n (%)	n	n	n (%)	n (%)	n	n	n (%)	n (%)
Abnormal (<9)	8 (2.0%)	4 (2.1%)	0	0	5 (1.3%)	2 (1.0%)	0	0	6 (1.5%)	2 (1.1%)
Not reported	0	0	0	0	0	0	0	0	0	0
Part 2										
Protan >1	1 (0.3%)	0 (0.0%)	0	0	2 (0.5%)	0 (0.0%)	0	0	1 (0.3%)	0 (0.0%)
Deutan >1	2 (0.5%)	1 (0.5%)	0	0	3 (0.8%)	1 (0.5%)	0	0	2 (0.5%)	1 (0.5%)
Tritan >1	3 (0.8%)	0 (0.0%)	0	0	0 (0.0%)	0 (0.0%)	0	0	1 (0.3%)	0 (0.0%)
Not reported	1	0	0	0	0	0	0	0	0	0

%=n/N(100)

Contrast Sensitivity

Best spectacle corrected contrast sensitivity testing was performed on a subgroup of LAL and Control eyes under photopic and mesopic test conditions, with and without glare, at pre-adjustment #1 (LAL) and 17-21 days (Control) and at 6 months postoperatively. In photopic conditions both with and without glare, there was no clinically significant difference noted between the LAL and Control groups. Mesopic results without glare show a mean improvement at each frequency for the LAL group and at each frequency except 12 cpd for the Control group. Therefore, in mesopic conditions both with and without glare, there was no clinically significant difference noted between the LAL and Control groups.

Specular Microscopy Sub-Study

As shown in Table 8, at 6 months postop, the mean endothelial cell loss (ECL) for subjects participating in the endothelial cell sub-study was 14.7% (14/99). At this time point, the minimum confirmed postoperative ECD value observed was 814 and the maximum confirmed percent loss from baseline was approximately 66%; and 21% of eyes (21/99) had losses from baseline that were greater than 25%. Results at 1 week postopertively (before light treatment) looked similar. These acute losses are greater than those typically seen in well conducted specular microscopy studies associated with cataract surgery. Since no control group was used in this substudy, it was difficult to determine causative factors.

TABLE 8
SPECULAR MICROSCOPY
ALL SPECULAR MICROSCOPY SUB-STUDY SUBJECTS WITH DATA AT RELEVANT TIMEPOINTS

	Preop	6 Months Postop	12 Months Postop
N	104	99	012
ECD			
Mean (SD)	2493.0 (318.7)	2139.8 (516.0)	2120.7 (505.5)
Percent Change in ECD			
Mean (SD)		-14.7% (15.9%)	-15.0% (15.2%)

2. Effectiveness Results

The analysis of effectiveness was based on subsets of the 584 evaluable patients at the 6-month time point. Key effectiveness outcomes are presented in Tables 9 and 10.

Table 9 presents the primary effectiveness analyses of the co-primary effectiveness endpoints that were performed based on the noted subsets of evaluable subjects at 6 months without imputation. The analyses of other key effectiveness outcomes (based on all evaluable subjects with data) are presented in Table 10.

TABLE 9
PRIMARY ANALYSES OF CO-PRIMARY EFFECTIVENESS ENDPOINTS
(EXCLUDED SUBJECTS SHOWN IN FOOTNOTES)

Endpoint		LAL (Number Implanted = 391)	Treatment Effect	Control (Number Implanted = 193)
For eyes with manifest cylinder <0.75 D at Pre-Adjustment Timepoint: Percent reduction in manifest cylinder from Pre-Adjustment (LAL) or 17-21 days post-op (control) to 6 months postop[1]				
	Number in Analysis	286		126
	Mean ± SD [95% CI]	74.6 ± 30.1) [71.1,78.1]		19.9 ± 51.1 [10.9,28.9]
	Median	83.3		20.0
	(Min, Max)	(-33, 100)		(-200, 100)
	Difference in means		54.7	
	p-value		<0.0001	
For eyes with non-zero MRSE at Pre-Adjustment Timepoint: Percent absolute reduction in MRSE from Pre-Adjustment (LAL) or 17-21 days post-op (control) to 6 months postop[2]	Number in Analysis	380		166
	Mean ± SD [95% CI]	51.5 ± 76.0 [43.8,59.1]		10.4 ± 93.1 [-3.8,24.7]
	Median	75.0		36.7
	(Min, Max)	(-500, 100)		(-400, 100)
	Difference in means		41.1	
	p-value		<0.0001	
Number (%) of eyes with axial rotation of LAL of ≤ 5 degrees from Pre-Adjustment to 6 months postop[3]	n/N (%)	344 /358 (96.1 %)		N/A
	95% Confidence Interval	[93.5%, 97.8%]		N/A

[1] Excludes subjects with <0.75 D of cylinder at Pre-Adjustment (LAL) or 17-21 days post-op (Control). 105 of LAL and 67 of Control subjects were excluded for this reason. Note that the LDD power adjustment does not treat less than 0.75 D of cylinder

[2] Excludes subjects with MRSE of 0 at Pre-Adjustment (LAL) or 17-21 days post-op (Control) since it is not possible to divide by zero (11 of LAL and 27 of Control subjects were excluded for this reason)

[3] Excludes subjects that do not have readable images at both Pre-Adjustment or 6 months (33 eyes were excluded for this reason).

Subjects were systematically excluded from the two refractive endpoint analyses above. Subjects with astigmatism <0.75 D (including 105 LAL subjects not eligible for astigmatic treatment) were not included in the main analysis of "percent reduction" of astigmatism. Subjects with zero MRSE were not included in the "percent reduction" MRSE analysis. In addition, when choosing the IOL implantatioin power, the two arms were treated differently. For LAL implantation power, subjects were targeted to +0.50 D MRSE (to compensate for the expected 0.5 D myopic shift of the lock-in), as opposed to the controls who were targeted to zero MRSE. Table10 provides key effectiveness results that were evaluated for all all implanted subjects available at 6 months. Note that the two treatment arms showed virtually the same mean magnitude of MRSE at 6 months. And the differences in the percentags of eyes with MRSE close to zero were not large. LAL implanted subjects had mean UCVA about 1 line better than control subjects and mean residual manifest cylinder 0.45 D better than control subjects.

TABLE 10
SUMMARY ADDITIONAL EFFECTIVENESS ENDPOINTS AT 6 MONTHS
(ALL SUBJECTS WITH DATA AVAILABLE AT 6 MONTHS)

	LAL (N=391)	Treatment Effect	Control (N=193)
Mean absolute MRSE ± SD (D)	0.224 ±0.225	0.089	0.313 ±0.322
Mean manifest cylinder ± SD (D)	0.299 ±0.366	0.450	0.749 ±0.620
Percent of eyes with MRSE within 0.50 D of zero n (%)	360 (92.1%)	8.7%	161 (83.4%)
Percent of eyes with MRSE within 1.00 D of zero n (%)	389 (99.5%)	2.6%	187 (96.9%)
Percent of eyes with manifest cylinder within 0.50 D of zero n (%)	322 (82.4%)	31.1%	99 (51.3%)
Percent of eyes with manifest cylinder within 1.00 D of zero	385 (98.5%)	23.9%	144 (74.6%)
Mean BSCVA LogMAR acuity (Snellen equivalent) ± SD	-0.066 (20/17.2) ± 0.084	-0.038	-0.028 (20/18.8) ± 0.091
Mean UCVA LogMAR acuity (Snellen equivalent) ± SD	0.005 (20/20) ± 0.103	0.127	0.132 (20/27) ± 0.165

%=n/N(100)

Table 11 presents the results for the secondary effectiveness endpoints. These were analyzed to demonstrate superiority in percent of subjects achieving UCVA of 20/20, superiority in "percent reduction in manifest cylinder" for two strata of cylinder at the pre-light-treatment timepoint, superiority in the "percent reduction in MRSE" for the subset of eyes with pre-light-treatment manifest cylinde < 0.75 D, and non-inferiority in BSCVA for the subset of eyes with no macular disease that would cause reduction in acuity. All of the analyses demonstrated successful results, with the exception of the "percent reduction in MRSE" analysis, which failed to show superiority.

TABLE 11
SECONDARY EFFECTIVENESS ENDPOINTS AT 6 MONTHS
(SUBJECTS WITH DATA AT RELEVANT TIMEPOINTS
(EXCLUDED SUBJECTS EXPLAINED IN FOOTNOTES)

		LAL (Number implanted=391)	Treatment Effect	Control (Number implanted=193)	p-value
UCVA 20/20 or better at 6 months[1]	n(%)	274 /391 (70.1 %)	33.8%	70 /193 (36.3 %)	< .0001
Percent reduction in manifest cylinder at 6 months in the 0.75 to 1.25 D cylinder treatment group[2]	Mean ± SD (number in analysis)	73.4 ± 33.1 **(n =203)**	54.8	18.6 ± 57.0 **(n =90)**	< .0001
Percent reduction in manifest cylinder at 6 months in the >1.25 D cylinder treatment group[3]	Mean ± SD (number in analysis)	77.5 ± 20.7 **(n=83)**	54.4	23.1 ± 32.3 **(n=36)**	< .0001
Percent absolute reduction in MRSE at 6 months for eyes with < 0.75D of cylinder at Pre-Adjustment (LAL) or 17-21 days post-op (control)[4]	Mean ± SD (number in analysis)	55.2 ± 76.3 **(n=100)**	28.0	27.2 ± 75.2 **(n=53)**	0.0318
Mean BSCVA for 'best case' cohort (no macular problems) at 6 months[5]	Mean ± SD (number in analysis)	-0.066 ± 0.083 **(n=390)**		-0.029 ± 0.090 **(n=191)**	-
	Difference in means [99% Confidence Interval]		-0.04 [-0.06,-0.02]	-	-

%=n/N(100)

[1] All eyes with UCVA data at 6 months

[2] Includes only eyes with 0.75 D to 1.25 D of cylinder at Pre-Adjustment (LAL) or 17-21 days post-op (Control); excludes eyes without data at 6 months

[3] Includes only eyes with > 1.25 D of cylinder at Pre-Adjustment (LAL) or 17-21 days post-op (Control); excludes eyes without data at 6 months

[4] Excludes subjects with MRSE of 0 at Pre-Adjustment (LAL) or 17-21 days post-op (Control) since it is not possible to divide by 0); excludes eyes without data at 6 months

[5] One LAL eye and 2 Control eyes excluded from “best case” cohort, because of macular problems

Additional Effectiveness Analysis

Table 12 characterizes the manifest cylinder and the percent reduction in cylinder at 6 and 12 months postoperative.

TABLE 12
MANIFEST CYLINDER AT 6 AND 12 MONTHS AND PERCENT REDUCTION IN CYLINDER IN EYES WITH ≥ 0.75 D CYLINDER AT PRE-ADJUSTMENT (LAL) /17-21 DAYS (CONTROL)
(SUBJECTS WITH DATA AT RELEVANT TIME POINTS)

	6 Months		12 Months	
Manifest Cylinder (D)	**LAL (N=286)**	**Control (N=126)**	**LAL (N=284)**	**Control (N=122)**
Mean ± SD (n)	0.295 ± 0.339 (286)	0.962 ± 0.626 (126)	0.370 ± 0.420 (284)	0.967 ± 0.651 (122)
Median	0.250	1.000	0.250	1.000
(Min, Max)	(0.00, 1.50)	(0.00, 2.50)	(0.00, 3.50)	(0.00, 4.50)
% Reduction in Manifest Cylinder				
Mean ± SD (n)	74.6 ± 30.1 (286)	19.9 ± 51.1 (126)	67.6 ± 36.5 (284)	19.9 ± 45.6 (122)
Median	83.3	20.0	75.0	20.0
(Min, Max)	(-33, 100)	(-200, 100)	(-133, 100)	(-125, 100)

Table 13 presents the accuracy of the cylinder correction at 6 and 12 months for all LAL eyes that had a cylinder correction attempted.

TABLE 13
CYLINDER CORRECTION ACCURACY (LAL)
(SUBJECTS WITH DATA AT RELEVANT TIME POINTS)

	6 months	12 months
Accuracy of Cylinder Correction to Intended Target	**LAL (N=286)**	**LAL (N=284)**
	n (%)	n (%)
Within 0.50 D	237 (82.9 %)	227 (79.9 %)
Within 1.00 D	283 (99.0 %)	271 (95.4 %)

%=n/N(100)

Table 14 presents the accuracy of MRSE correction for eyes in the LAL group at 6 and 12 months.

TABLE 14
ACCURACY OF MRSE CORRECTION TO INTENDED TARGET (LAL)
(SUBJECTS WITH DATA AT RELEVANT TIME POINTS)

	6 months	12 months
Accuracy of MRSE Correction to Intended Target	**LAL (N=391)**	**LAL (N=391)**
	n (%)	n (%)
Within 0.50 D	358 (91.6%)	357 (91.5%)
Within 1.00 D	387 (99.2%)	390 (100.0%)

%=n/N(100)

Refractive stability of the MRSE for the LAL and Control groups for the pairwise cohort is shown in Table 15. All 5 refractive criteria per ANSI Z80.11-2012 were met and/or exceeded at the 6-month visit. The most rigorous of these criteria, i.e., change in MRSE no greater than 0.04D/month and change per year no greater than 0.5 D, were considerably exceeded, as shown in Table 17. The mean rate of change per month for the LAL group was 0.004 D beginning at the 1 week post lock-in #2 through the 6-month visit, and the 95% confidence interval for the mean rate of change includes zero at all intervals for the LAL.

TABLE 15
MRSE REFRACTIVE STABILITY
(SUBJECTS WITH DATA AT RELEVANT TIME POINTS)

	1 week post Lock-in #2 (LAL)/17-21 days (control)to 6M		6M to 9M		9M to 12M		1 week post Lock-in #2 (LAL)/ 17-21 days (control)to 12M	
MRSE	**LAL (N=387)**	**Control (N=193)**	**LAL (N=382)**	**Control (N=191)**	**LAL (N=388)**	**Control (N=188)**	**LAL (N=387)**	**Control (N=188)**
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Eyes with ≤ 1.00 D change	385 (99.5%)	185 (95.9%)	379 (99.2%)	188 (98.4%)	387 (99.7%)	183 (97.3%)	384 (99.2%)	182 (96.8%)
Eyes with ≤ 0.50 D change	363 (93.8%)	156 (80.8%)	366 (95.8%)	170 (89.0%)	371 (95.6%)	171 (91.0%)	356 (92.0%)	157 (83.5%)
Mean Change Between Visits [95% CI]	0.021 ± 0.296 [-0.009,0.050]	0.046 ± 0.520 [-0.028,0.120]	-0.012 ± 0.302 [-0.042, 0.018]	-0.015 ± 0.384 [-0.070,0.040]	0.012 ± 0.277 [-0.016,0.040]	0.041 ± 0.391 [-0.016,0.097]	0.029 ± 0.327 [-0.003,0.062]	0.074 ± 0.458 [0.009,0.140]
Mean Change per Month	0.004	0.009	-0.004	-0.005	0.004	0.014	0.003	0.007
Mean Change per Year (Change per Month x 12)	0.050	0.110	-0.048	-0.060	0.048	0.162	0.032	0.081

%=n/N(100)

UCVA

Table 16 presents UCVA for the LAL and Control groups.

TABLE 16
UCVA BY VISIT
(SUBJECTS WITH DATA AT RELEVANT TIME POINTS)

	Pre-Adjustment (LAL) or 17-21 days post-op (control)		6 months		12 months	
UCVA	**LAL (N=400)**	**Control (N=197)**	**LAL (N=391)**	**Control (N=193)**	**LAL (N=391)**	**Control (N=188)**
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
20/12.5 or better	1 (0.3%)	2 (1.0%)	25 (6.4%)	3 (1.6%)	23 (5.9%)	5 (2.7%)
20/16 or better	12 (3.0%)	14 (7.1%)	118 (30.2%)	18 (9.3%)	104 (26.6%)	23 (12.2%)
20/20 or better	63 (15.8%)	59 (29.9%)	274 (70.1%)	70 (36.3%)	260 (66.5%)	71 (37.8%)
20/25 or better	176 (44.0%)	112 (56.9%)	358 (91.6%)	117 (60.6%)	358 (91.6%)	115 (61.2%)
20/32 or better	285 (71.3%)	149 (75.6%)	386 (98.7%)	154 (79.8%)	383 (98.0%)	144 (76.6%)
20/40 or better	352 (88.0%)	178 (90.4%)	390 (99.7%)	174 (90.2%)	391 (100.0%)	172 (91.5%)
20/80 or better	398 (99.5%)	195 (99.0%)	391 (100.0%)	192 (99.5%)	391 (100.0%)	188 (100.0%)
20/200 or better	399 (99.8%)	197 (100.0%)	391 (100.0%)	193 (100.0%)	391 (100.0%)	188 (100.0%)
Not Reported	0	0	0	0	0	0
Mean[1] ± SD (n)	0.186 (20/31.0) ± 0.154 (400)	0.150 (20/28.3) ± 0.152 (197)	0.005 (20/20.0) ± 0.103 (391)	0.132 (20/27.0) ± 0.165 (193)	0.011 (20/20.5) ± 0.101 (391)	0.122 (20/26.4) ± 0.158 (188)

%=n/N(100)
[1]LogMAR (Snellen)

Table 17 presents UCVA at 6 months stratified by manifest cylinder at the pre-light-adjustment timepoint (adjustment #1 for LAL eyes and 17-21 days postop for the control) . The difference in mean UCVA between the LAL and Control groups gets larger as the cylinder power increases. There is virtually no difference between groups for eyes with <0.75 D (levels below the cylinder treatment range of the LDD), and the difference is largest in the >1.25 D cylinder bin with a mean UCVA of 0.04 logMAR in the LAL group versus 0.30 logMAR in the Control group, a difference of about 2½ lines.

TABLE 17
UCVA AT 6 MONTHS STRATIFIED BY CYLINDER TREATMENT GROUP
(SUBJECTS WITH DATA AT 6 MONTHS)

	<0.75 D cylinder at Pre-Adjustment #1 (LAL)/ 17-21 days Post-op (control)		0.75 to 1.25 D of cylinder at Pre-Adjustment #1 (LAL)/17-21 days Post-op (control)		>1.25D of cylinder at Pre-Adjustment #1 (LAL)/17-21 days Post-op (control)	
UCVA	**LAL (N=105)**	**Control (N=67)**	**LAL (N=203)**	**Control (N=90)**	**LAL (N=83)**	**Control (N=36)**
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
20/20 or better	71 (67.6%)	37 (55.2%)	156 (76.8%)	29 (32.2%)	47 (56.6%)	4 (11.1%)
20/40 or better	104 (99.0%)	65 (97.0%)	203 (100.0%)	87 (96.7%)	83 (100.0%)	22 (61.1%)
Mean UCVA ± SD (n) at 6 months[1]	0.003 (20/20.1) ± 0.113 (105)	0.050 (20/22.4) ± 0.118 (67)	-0.011 (20/19.5) ± 0.089 (203)	0.126 (20/26.7) ± 0.136 (90)	0.044 (20/22.1) ± 0.113 (83)	0.301 (20/40.0) ± 0.184 (36)

%=n/N(100)
[1]LogMAR (Snellen)

Table 18 presents mean manifest refraction cylinder results at 6 months postop based on preoperative keratometric astigmatism to allow estimation of the astigmatic effect of treatment based on preoperative levels of astigmatism. Eyes with the highest level of preoperative keratometric cylinder showed the most significant treatment effect.

TABLE 18
MANIFEST REFRACTION CYLINDER AT 6 MONTHS
STRATIFIED BY PREOPERATIVE KERATOMETRIC CYLINDER
(SUBJECTS WITH DATA AT 6 MONTHS)

	Preoperative Keratometric Cylinder								
	0.75-1.24D			1.25 - 1.74D			≥1.75D		
	LAL (N=213)	**Control (N=118)**	**Difference**	**LAL (N=110)**	**Control (N=41)**	**Difference**	**LAL (N=68)**	**Control (N=34)**	**Difference**
Manifest Refraction Cylinder at 6 Months									
Mean	0.255	0.572	-0.317	0.298	0.835	-0.537	0.441	1.257	-0.816
SD	0.362	0.460	-	0.322	0.665	-	0.415	0.750	-

Table 19 presents the percent of LAL eyes that did not receive an astigmatic treatment by preoperative keratometric astigmatism (because postoperatively they had manifest cylinder below the treatment range of the LDD). Eyes with lower preoperative keratometric cylinder are less likely to receive an astigmatism treatment.

TABLE 19
PERCENT OF LAL EYES THAT DID NOT RECEIVE ASTIGMATISM TREATMENT BY PREOPERATIVE KERATOMETRIC CYLINDER

	Preoperative Keratometric Cylinder (LAL only)						
	0.75-0.99 (N=111)	**1.00-1.24 (N=108)**	**1.25-1.49 (N=62)**	**1.50-1.74 (N=50)**	**1.75-1.99 (N=32)**	**≥2.0 (N=37)**	**Total (N=400)**
Proportion of eyes that received NO astigmatic treatment	53 (47.7%)	34 (31.5%)	12 (19.4%)	6 (12.0%)	4 (12.5%)	1 (2.7%)	110 (27.5%)

%=n/N(100)

Figure 4 illustrates mean absolute MRSE at 6 months stratified by the pre-adjustment (LAL)/17-21 days (Control) signed MRSE. The figure shows that outcomes for the LAL are essentially independent of the initial refractive error through the 2 D treatment range while the Control eyes had a significant degradation of results with increased signed (myopic or hyperopic) MRSE at 17-21 days. In addition, subjects with an MRSE outside the range of correction are indicated by the blue dotted line.

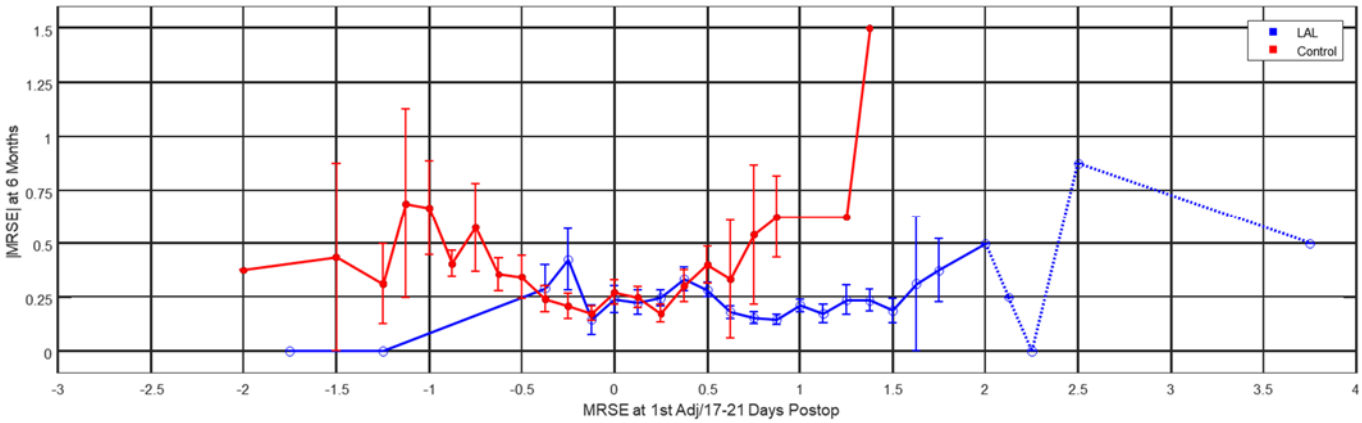


Figure 4. Absolute MRSE at 6 Months Postop Versus Pre-Adjustment/17-21 days Postop Signed

Note that the LAL and Control had different distributions of MRSE at the pre-light-treatment timepoint. This is because the IOL implantation power was chosen differently in the two arms. The LAL implantation power waschosen to achieve a target postop MRSE of +0.50 D to compensate for the 0.50 D myopic shift expected from the mandatory "lock-in" LDD treatment; the control IOL implantation power was targeted to achieve postop MRSE of zero. The pre-light-treatment MRSE for the LAL arm had a distribution with 25th , 50th and 75th percentiles of +0.375, +0.625, and +1.00 diopter respectively, while for the control the 25th, 50th and 75th percentiles for MRSE were -0.50, -0.125, and +0.1625 respectively.

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

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 included 17 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The applicant had performed a prior, much smaller, uncontrolled study on an earlier version of the device. This study did have some additional long-term (about 3 years postoperatively) safety testing on about 30 (selected) subjects using Optical Coherence Tomography (OCT) imaging, perimetry, and color vision testing. Results did not detect any obvious problems. An earlier version of the device was the subject of a published study of over 100 subjects with before and after, time-domain OCT imaging. The applicant provided the OCT images from most of the subjects in the study. Results did not show any signs of retinal phototoxicity.

An earlier version of this device has been marketed in a number of out of U.S. jurisdictions (including the EU and Mexico) since 2008, It has not been removed from the market in any jurisdiction.

FDA requested input from three external retinal specialists via a special government employee (SGE) homework assignment. They were consulted concerning the device safety with regard to the risks associated with the LDD UV light treatment on retinal health. All SGEs agreed that for use in patients with normal healthy retinas, the applicant has provided reasonable assurance of device safety in terms of risks to retinal health. However, some expressed concerns regarding the potential acceleration of existing disease processes in some special patient populations. These concerns were incorporated into the the indications for use statement as well as the professional labeling. An additional recommendation from the homework assignment was to use certain types of specialized assessments to better detect potential signs of subtle effects of UV exposure. These comments were incorporated into the final postapproval study design.

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

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Ophthalmic Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The pivotal clinical study achieved successful outcomes on all three protocol-defined co-primary effectiveness endpoints. Two of these demonstrated that the LDD achieved higher "percent reduction" in postoperative manifest cylinder and MRSE, respectively, than the control, in subsets in the range of LDD treatment for these conditions. The third demonstrated the rotational stability of the LAL IOL.

It should be noted that while all subjects received some sort of light treatment (to perform final polymerization of the plastic material), not all subjects receive a power adjustment.

Subjects were systematically excluded from the two primary refractive endpoint analyses above. When looking at results at 6 months for all eyes with available data, LAL implanted subjects had mean UCVA about 1 line better than control subjects and mean residual manifest cylinder 0.45 D better than control subjects. Larger benefits in terms of astigmatism and reduction and improved UCVA are seen in subjects needing larger levels of astigmatism treatment and this is somewhat predictable from preoperative corneal astigmatism. The two treatment arms showed virtually the same mean absolute value of MRSE at 6 months. The LDD power adjustment does reduce the likelihood that subjects at 6 months will have a clinically significant MRSE, but this outcome is not frequent in treatment with a conventional IOL and the risk of this is difficult to predict based upon preoperative assessment.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and/or animal studies as well as data collected in a clinical study conducted to support PMA approval as described above.

The submitted clinical data from the pivotal study provides a reasonable assurance of safety, in terms of conventional IOL issues. The results for the ISO safety and performance endpoints (SPE) events versus the ISO historical control did not raise significant issues. Rates for all of these categories of events, with the exception of the rate for SSIs, did not exceed the historical control rates by a clinically meaningful or statistically significant amount. Because some of these SSIs were related to product issues that have been addressed, this SSI rate does not appear to be indicative of an unacceptably high increased risk for patients who will be using the marketed device. There did not appear to be significant issues related to biocompatibility problems such as inflammation.

One unique aspect of this device is the postoperative UV treatment. The main adverse events related to the UV exposure were:

- 1 other eye had of long-lasting tritan anomaly (both persistent tritan cases were treated with pre-REL device);
- 7 eyes had a tritan anomaly at any time after light treatment (all but 1 treated with the pre-REL device);
- 1 eye with longer lasting erythropisa symptoms, persisting to 1 year;
- 14 eyes had moderate erythropsia at any time in the study (all but 1 with the pre-REL treatment; average duration (when measured) was 12 days); and
- Approximately 58% of LDD-treated eyes had at least mild erythropsia at any time in the study (not substantially decreased in the REL device). The vast majority were mild.

Also, one eye had reactivation of an ocular Herpes Simplex infection.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above.

Evaluation of the study endpoints demonstrated significant benefits of the LAL for the correction of aphakia after cataract removal, similar to conventional monofocal IOLs. Additionally, the pivotal clinical study demonstrated that the LAL and LDD system can reduce residual astigmatism and thereby improving uncorrected visual acuity. Benefits are greatest in patients with higher amounts of astigmatism. The system also reduces the likelihood of clinically significant residual spherical refractive errors.

The risks associated with use of the the device to be marketed appear to be generally of a similar level as those of more conventional marketed intraocular lenses, with the exceptions of those that are related to the LDD UV exposure. For these latter types of events, the vast majority appear to be short-lasting and mild alterations of color perceptions. There are risks of longer lasting and serious adverse events related to the UV exposure, but evidence indicates that these are likely to occur at very low rates, probably lower than those that occurred in the pivotal trial because of modifications in the device. One other risk is that of patient non-compliance with the required use of UV blocking glasses for several weeks after surgery. However, significant non-compliance was not an issue in the clinical trial.

1. Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support the conclusion that the benefits outweigh the risks for use in the indicated population.

D. 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 11/22/2017. The final conditions of approval cited in the approval order are described below.

Office of Surveillance and Biometrics (OSB) Lead PMA Post-Approval Study - LAL/LDD Postmarket Randomized Control Trial (RCT):

The LAL/LDD Postmarket RCT is designed to evaluate the following postmarket questions:
1. What is the rate of Endothelial Cell Density loss (ECL) for patients with the LAL/LDD?
2. What is the rate of retinal damage caused by UV treatment with the LDD that may not be detected by routine post-operative testing?
This is a two phased study that will include Phase A and Phase B. The primary objective of Phase A is to develop a patient reported outcome (PRO) instrument that will assess erythropsia after LDD light treatments. This part of the study is a non-interventional, qualitative research, cognitive debriefing interview study that may use patients treated using the marketed device.

Phase B is a prospective, randomized, multicenter, post approval study of the LAL and LDD to be conducted at approximately 5 clinical sites. It will begin after development of the PRO in Phase A is complete and has been accepted by FDA. This is a new enrollment study that is expected to last up to 24 months and include up to 11 study visits. 540 subjects will be randomized in a 2:1 ratio to receive either the LAL or a monofocal IOL (Control).

The following clinical examinations will be performed:
- Uncorrected visual acuity
- Manifest refraction
- Best spectacle corrected visual acuity
- Spectral Domain optical coherence tomography (SD-OCT)
  - SD-OCT scans of the macular region will be performed, covering approximately 10 degrees of eccentricity in all horizontal, vertical, and principal diagonal meridians.

- Specular microscopy
- City University Color Test
- Slit lamp exam
- Erythropsia Assessment
- Erythropsia PRO
- Fundus exam
- Fundus photos
- Multifocal electroretinogram (ERG) (if needed)
- Short-Wave Automated Perimetry (SWAP) (baseline and if needed post light treatment)

A reading center will read both the endothelial cell count images and the SD-OCT images.

ERG and SWAP will be performed in eyes that meet any of the following criteria:

- Significant erythropsia (either through in-office testing or reported by the patient),
- Has a tritan anomaly (when there was none pre-treatment), or an increase in tritan anomaly (tritan > 1) on Part II of the 3rd Edition City University Color Vision Test (CUT) at any time after light treatment,
- Any level of erythropsia or tritan anomaly at 3 months or later,
- Has an unexplained loss of acuity ≥2 lines compared to pre-light-treatment, or
- Shows changes consistent with phototoxicity on the OCT (including, e.g., evaluating outer retinal hyper or hypo reflectivity).

The primary safety endpoints are mean rate of endothelial cell density loss at postop month 6 compared to preoperatively compared between the LAL and Control group, and percent of LAL eyes with UV retinal damage at postop month 6. UV retinal damage will be diagnosed if the SD-OCT scan demonstrates disruption of the inner/outer segment junction, the outer nuclear layer, or retinal pigment epithelial layer.
Subjects will be followed for 6 months postoperatively as follows: preoperative, operative, postop day 1, postop week 1, postop week 3, adjustment #2 visit (if needed) (LAL only), lock-in #1 (LAL only), lock-in #2 (LAL only), postop months 1-2, and postop month 6. If a study eye is diagnosed with UV retinal damage, an additional follow-up exam will be added at 12 months postoperatively.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

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.