

## SUMMARY OF SAFETY AND EFFECTIVENESS DATA

### I. GENERAL INFORMATION

Device Generic Name:	Ophthalmic Excimer Laser System
Device Trade Name:	LADARVision <sup>®</sup> 4000 Excimer Laser System and the LADAR6000 <sup>™</sup> Excimer Laser System
Applicant's Name and Address:	Alcon, Inc. 2501 Discovery Drive, Suite 500 Orlando, FL 32826
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P970043/S022
Date of Notice of Approval to Applicant:	May 2, 2006

The LADARVision<sup>®</sup> 4000 Excimer Laser System was approved on November 2, 1998 for the indication of photorefractive keratectomy (PRK) for the reduction or elimination of mild to moderate myopia of between -1.00 and -10.00D sphere and less than or equal to -4.00D astigmatism at the spectacle plane, the combination of which must result in an attempted correction of between -0.50D and -10.00D spherical equivalent (SE) at the spectacle plane where the sphere or cylinder is at least 1.00D (P970043). On May 9, 2000, the device was approved for the indication of laser in-situ keratomileusis (LASIK) for the reduction or elimination of myopia of less than -9.00D sphere and -0.50D to less than -3.00D astigmatism at the spectacle plane (P970043/S5). On September 22, 2000, the device was approved for the indication of LASIK for the reduction or elimination of refractive error of less than or equal to +6.00D sphere and -6.00D astigmatism at the spectacle plane (hyperopia with or without astigmatism and mixed astigmatism) (P970043/S7).

On October 18, 2002, the LADARVision<sup>®</sup> 4000 System was approved for wavefront-guided LASIK for the reduction or elimination of myopia up to -7.00D sphere with less than -0.50D astigmatism at the spectacle plane (P970043/S10). On June 29, 2004, the device was approved for wavefront-guided LASIK for the reduction or elimination of myopic astigmatism up to -8.00D sphere with -0.50D to -4.00D cylinder and up to -8.00D spherical equivalent at the spectacle plane (P970043/S15). On May 26, 2005, the sponsor submitted a supplement for wavefront-guided LASIK for the reduction or elimination of hyperopia and hyperopic astigmatism of +0.75D to less than +5.00D sphere with up to -3.00D cylinder and up to +5.00D spherical equivalent (SE) at the spectacle plane (P970043/S020).

The LADAR6000<sup>™</sup> Excimer Laser System was approved on May 1, 2006 in P970043/S19. Because this laser was found comparable to the LADARVision<sup>®</sup> 4000 Excimer Laser System based on preclinical and testing data, approval of this supplement (S22) allows the use of both laser systems for the mixed astigmatism indication.

On May 1, 2006, FDA issued an approval order for PMA P970043/S23 for an increase in the laser repetition rate from 60 Hz to 92 Hz in the LADAR6000™ Excimer Laser System.

The sponsor submitted this supplement to further expand the clinical indications to include wavefront-guided CustomCornea® LASIK for mixed astigmatism. The updated clinical data to support the expanded indication is provided in this summary. The pre-clinical test results were provided in the original PMA and prior PMA supplements. Written requests for copies of the SED can be obtained from the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20857 under Docket #02M-0487 or you may download these files from the internet site <http://www.fda.gov/cdrh/pdf/p970043.pdf>.

## II. INDICATIONS FOR USE

The LADARVision®4000 and LADAR6000™ Excimer Laser Systems are indicated for wavefront-guided Laser Assisted In-Situ Keratomileusis (LASIK):

- for the reduction or elimination of mixed astigmatism of 1.00D to less than 5.00D cycloplegic cylinder magnitude at the spectacle plane, which is greater than the sphere magnitude, and the cylinder and sphere have opposite signs;
- in patients who are 21 years of age or older; and
- in patients with documented stability of refraction for the prior 12 months, as demonstrated by a change in sphere and cylinder of less than or equal to 0.50D.

## III. CONTRAINDICATIONS

Wavefront-guided LASIK is contraindicated in:

- pregnant or nursing women.
- patients with autoimmune, collagen vascular, or immunodeficiency diseases.
- patients with signs of keratoconus.
- patients who are taking one or both of the following medications: isotretinoin (Accutane<sup>1</sup>) or amiodarone hydrochloride (Cordarone<sup>2</sup>).

## IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the device labeling.

## V. DEVICE DESCRIPTION

### A. Wavefront Measurement Device (WMD)

The first step in performing CustomCornea® LASIK surgery is to perform a wavefront examination on the patient using a wavefront measurement device (WMD) compatible with the LADARVision®4000 and the LADAR6000™ Excimer Laser Systems. At the present time, the only compatible WMD is the Alcon®

<sup>1</sup> Accutane Reg. TM of Hoffman-La Roche Inc.

<sup>2</sup> Cordarone Reg. TM of Sanofi-Synthelabo Inc.

LADARWave® CustomCornea® Wavefront System, the wavefront measurement device used in the clinical trial.

The LADARWave® CustomCornea® Wavefront System is indicated for measuring, recording, and analyzing visual aberrations (such as myopia, hyperopia, astigmatism, coma and spherical aberration) and for displaying refractive error maps of the eye to assist in prescribing refractive corrections. This device is enabled to export wavefront data and associated anatomical registration information to a compatible treatment laser with an indication for wavefront-guided refractive surgery.

Essential features of the compatible WMD are as follows:

1. *Patient Fixation and Fogging*

The WMD includes a fixation optical subsystem that provides the patient with an unambiguous fixation point. In addition, the fixation subsystem includes adjustable optics to compensate for the patient's inherent refractive error. The optics are used to "fog" the eye, first clarifying the fixation target and then it optically adjusts beyond the patient's far point to minimize accommodation.

2. *Centration*

Prior to dilation, the WMD is used to record the geometric relationship between the natural daytime pupil center and the limbus of the eye. This information is then used to center the wavefront measurement and subsequent ablative treatment on the natural line of sight.

3. *Wavefront Measurement*

The WMD measures the wavefront profile of the eye with a high degree of accuracy and characterizes the profile using Zernike polynomials. The pupil must be large enough so that valid wavefront data can be obtained over a large area. Higher-order aberrations are more significant at night when the pupil is naturally larger. Therefore, when treating these aberrations, measurement over a large pupil provides the greatest utility.

4. *Registration*

The WMD uses synchronized video imagery and on-screen software reticules to record the relationship of the wavefront data to the limbus of the eye and to ink marks applied to the sclera just before the wavefront exam. This registration information is used to position the excimer ablation profile at the correct corneal location and cyclotorsional angle.

5. *Data Export*

The WMD has the ability to export the wavefront examination data as an electronic file to removable media for transfer to the LADARVision®4000 and LADAR6000™ Systems. The electronic file is structured in a specific format and contains essential patient information, centration/registration information, and the detailed aberration data. In addition, the electronic file is encrypted in a manner that can only be deciphered by the LADARVision®4000 and LADAR6000™ Systems.

## B. Microkeratome

The LASIK procedure requires the use of a commercially available microkeratome that has been cleared for marketing via a premarket notification. The device used in this study consists of a head, plates, ring, handle, wrenches, shaft, motor, hand-piece, disposable blades, and power supply with footswitches and power cords. The system is completed with the appplanation lens set, tonometer, corneal storage jar, optical zone marker, spatula, stop attachment, and digital thickness gauge.

The microkeratomes used in the clinical trial included the BD K-4000<sup>3</sup> (manufactured by Becton-Dickinson), Hansatome<sup>4</sup> (manufactured by Bausch & Lomb), and the Moria<sup>5</sup> CB and LSK (manufactured by Moria).

## C. CustomCornea<sup>®</sup> Surgery Planning Software

The CustomCornea<sup>®</sup> Surgery Planning Software is a stand-alone computer application linking the diagnostic wavefront data with the surgical treatment on the LADARVision<sup>®</sup>4000 and LADAR6000<sup>™</sup> Excimer Laser Systems. The planning software allows refinement of surgical parameters within the approved wavefront-guided indication for the LADARVision<sup>®</sup>4000 and LADAR6000<sup>™</sup> Systems, and calculation of ablation depth.

System. calculates ablation depth, checks for treatment eligibility, and exports all messages and warnings to the excimer laser system.

After completing the surgery planning tasks, the planned treatment file is transferred to the LADARVision<sup>®</sup>4000 and LADAR6000<sup>™</sup> Systems. The LADARVision<sup>®</sup>4000 and LADAR6000<sup>™</sup> Systems software imports the treatment file, calculates the excimer treatment pattern, and performs the surgery.

Software version 1.0 was used in the clinical trial. Software version 1.4 is the commercial release version.

## D. LADARVision<sup>®</sup>4000 Excimer Laser System

The LADARVision<sup>®</sup>4000 excimer laser beam is of Gaussian profile and small in diameter (<0.90mm). Corneal sculpting is achieved by delivering hundreds to thousands of excimer laser pulses to the eye in a complex pattern of spatially overlapping spots, and precision of this process depends on accurate placement of the laser pulses. The LADARVision<sup>®</sup>4000 Excimer Laser System incorporates the LADARTracker<sup>®</sup> closed-loop eye-tracking system to track and compensate for patient eye motion, including saccadic movements, during procedures so that each excimer laser pulse is delivered to the appropriate location on the cornea.

Rather than the refractive correction being entered manually by the physician based on phoropter refraction, the CustomCornea<sup>®</sup> treatment requires that the pre-operative aberrations in the eye be measured with a wavefront measurement device. The treatment is based on Zernike data derived from a wavefront measurement device.

<sup>3</sup> *BD K-4000* TM of Becton, Dickinson and Company

<sup>4</sup> *Hansatome* Reg. TM of Bausch & Lomb Incorporated

<sup>5</sup> *Moria* Reg. TM of Moria SA

including treatment of lower-order sphere and astigmatism components and higher-order components, such as coma and spherical aberration.

The electronic file that the LADARVision®4000 System receives from the wavefront measurement device includes the following information:

- Patient information, including name, identification number, and clinical prescription.
- Eye information, including OD/OS and the geometric relationship of the wavefront data to the limbus and to the pupil center.
- Wavefront information, including a Zernike polynomial representation of the wavefront and the physical radius of that description.

The excimer laser beam characteristics (i.e., pulse energy, firing rate, fluence distribution at the treatment plane) are the same for Conventional and CustomCornea® treatment modalities. The Conventional LADARVision®4000 System treatment utilizes sphere, cylinder and axis components entered manually by the operator to generate the ablation profile. The CustomCornea® LASIK shaping algorithm utilizes aberration information unique to a given eye that is obtained from the WMD to guide the ablation of the cornea. The wavefront information is registered to the anatomical geometry of the eye using the WMD while the patient is sitting upright. This registered alignment information is passed to the LADARVision®4000 System, which allows for the compensation of this alignment information due to the natural cyclotorsion incurred when the patient assumes a prone position and uses the geometry information to accurately position the customized ablation profile on the eye.

The approved CustomCornea® ablation zone parameters, as used in the clinical trial, include a 6.5mm optical zone with a 1.25mm blend zone for a 9.0mm total ablation zone.

CustomCornea® mixed astigmatism corrections are locked out for greater than 6.00D cycloplegic cylinder magnitude. A flag warning will appear when a correction above the approved indication is selected.

Features and components of the LADARVision®4000 Excimer Laser System include:

1. *Excimer laser*

This argon fluoride excimer laser produces 10 nanosecond pulses of ultraviolet radiation at a wavelength of 193 nanometers. The laser repetition rate is approximately 60 pulses per second for the LADARVision®4000 Excimer Laser System and approximately 92 pulses per second for the LADAR6000™ System. The characteristics of the laser beam at the corneal treatment plane include: a pulse energy of 2.4 to 3.0mJ; a beam diameter of less than 0.90mm; and average fluence of 180 to 240 mJ/cm<sup>2</sup>.

2. *Optical transmission system*

The excimer laser passes through an optical telescope, followed by reflection off a series of mirrors, which position the excimer laser pulses in the correct locations at the treatment plane.

### 3. *Energy monitoring and control*

The laser pulse energy is monitored to ensure delivery of 2.4 to 3.0 mJ to the eye prior to surgery and during ablation.

### 4. *Gas handling system*

The excimer laser enclosure holds the laser, gas bottle, and gas-plumbing manifold. The gas bottle contains the pre-mixed gas, including argon, fluorine, and neon as the buffer gas. Gas flow is regulated through the system, responding to commands from the laser control electronics board.

### 5. *Active Closed-Loop Eye Tracking System*

The LADARTracker® System actively tracks the position of the eye by irradiating it with pulses of 905 nm infrared “eye-safe” energy and analyzing characteristics of the returning laser radiation. This measurement occurs 4000 times each second to detect even rapid eye motion before significant movement of the cornea has occurred. The LADARTracker® System actively compensates for the detected motion, rather than simply disabling the laser when the eye position exceeds some tolerated error range.

### 6. *Operating microscope*

The stereo viewing operating microscope is located in the optics head. The dual optical paths are independent of the excimer beam path and the tracker mirrors.

### 7. *Fixation target*

A visible fixation target is mounted in the system to facilitate the patient looking in the direction of the excimer beam. The fixation target consists of a light emitting diode (LED), a pinhole aperture, an edge-illuminated reticule, and a lens.

### 8. *Motorized Bed and Cross Beam Patient Positioning*

A motorized patient bed, which moves on X, Y and Z axes, smoothly and rapidly positions the patient and facilitates bilateral procedures. Cross beam Class I lasers are used to place the cornea at a predetermined height for proper ablation.

### 9. *Plume Removal System*

The plume removal system is housed within the calibration stage. During surgery, the plume removal system is deployed to a pre-determined height and provides a constant level of plume removal during ablation.

### 10. *System Software Control*

The LADARVision®4000 System software enables the user to: properly center the treatment; make adjustments in the X and Y axes; adjust for cyclotorsion and correctly reference astigmatism; place a hinge guard to protect the flap during surgery; and properly match the alignment of the wavefront map to the ablation.

Software versions 5.09, 5.11, 5.13 and 5.13 (Build 7) were used in the clinical trial for the Primary Cohort. Software version 5.4 is the commercial release version.

### E. LADAR6000™ Excimer Laser System

The LADAR6000™ Excimer Laser System was approved on May 1, 2006. The LADAR6000™ laser is functionally equivalent to the LADARVision® 4000 in that:

1. The excimer laser engine has not changed;
2. The excimer laser beam characteristics at the eye plane are unchanged;
3. Infrared LADAR eye tracking remains unchanged;
4. The shot pattern algorithms are unchanged (for a given treatment, identical shot patterns are generated and the sequence and timing of these shots are identical); and,
5. Treatment procedures are the same.

The differences between the two laser systems are:

1. Design changes in the LADAR6000™ Illumination System (2 new light sources for illumination during surgery: one to improve visualization of blood vessels, and the other to improve visualization of the pupil-iris boundary);
2. Tighter calibration controls to the LADAR6000™ with the addition of a software parameter to establish and monitor a Volume-Per-Shot (VPS) band to ensure the laser energy is within the acceptable energy levels;
3. Changes to the device labeling (name change to LADAR6000™); and,
4. Modifications to the user interface in the LADAR6000™ System Operation Manual.

The LADAR6000™ Excimer Laser System had only minor ergonomic and obsolescence changes to the LADARVision® 4000 Excimer Laser System. Additionally, an increase in the laser repetition rate from 60 Hz to 92 Hz was approved on May 1, 2006 for just the LADAR6000™ Excimer Laser System. All specs for beam shape, fluence, and wavelength were unchanged in the LADAR6000™. The shot pattern, algorithms, and frequency of operation were unchanged. The design changes were illumination and ergonomic features that affected some labeling. The complete system had validation and verification testing. Based on engineering reviews of this application, the use of the LADAR6000™ Excimer Laser System should not introduce any new safety or effectiveness problems regarding wavefront-guided LASIK treatment of mixed astigmatism. Therefore, the LADAR6000™ Excimer Laser System is considered comparable to the LADARVision® 4000 Excimer Laser System for this indication for use, and PMA approval includes both models.

## VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are currently several other alternatives for the correction of mixed astigmatism:

Automated Lamellar Keratoplasty (ALK)

Contact Lenses

Conventional Laser Assisted In-Situ Keratomileusis (LASIK)-based on phoropter refraction

Radial Keratotomy (RK)

Spectacles

Each alternative has its own advantages and disadvantages. A prospective patient should fully discuss with his/her care provider these alternatives in order to select the correction method that best meets his/her expectation and lifestyle.

## VII. MARKETING HISTORY

The LADARVision®4000 and LADAR6000™ Excimer Laser Systems have been marketed in the following countries: Argentina, Australia, Belgium, Brazil, Canada, China, Colombia, Cyprus, Czech Republic, France, Germany, Greece, Hong Kong, India, Italy, Korea, Malaysia, Mexico, Netherlands, Norway, Peru, Philippines, Portugal, Puerto Rico, Singapore, Spain, Sweden, Switzerland, Taiwan, Thailand, United Kingdom, United States, and Vietnam. The LADARVision®4000 and LADAR6000™ Excimer Laser Systems have not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

## VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse effects associated with LASIK include: loss of best spectacle corrected visual acuity (BSCVA); worsening of patient complaints such as double vision, sensitivity to bright lights, increased difficulty with night vision, fluctuations in vision; increase in intraocular pressure; corneal haze; secondary surgical intervention; corneal infiltrate or ulcer; corneal epithelial defect; corneal edema; problems associated with the flap including a lost, misplaced or misaligned flap; retinal detachment; and retinal vascular accidents.

Refer to Section X.F.2.e (Safety Outcomes) for a complete listing of adverse events and complications observed during the clinical study.

## IX. SUMMARY OF PRECLINICAL STUDIES

A series of pre-clinical tests were conducted upon initial development for conventional refractive surgery procedures prior to entry into human clinical trials. Those tests included algorithm simulations and ablation profiles using plastic blocks, as well as animal testing. Please refer to the SSED for the original PMA (P970043) for a summary of the pre-clinical testing.

A series of pre-clinical tests were conducted on the CustomCornea® algorithms prior to entering human clinical trials. These tests included algorithm validation, which tested the ablation shot pattern in both an ablation simulation program and actual PMMA substrate (surrogate) ablation experiments. Excellent agreement was demonstrated between the results obtained from PMMA substrate and simulated ablations. The CustomCornea® algorithm reproduced the results obtained with the existing conventional algorithm and demonstrated accuracy in performing more complex ablations. This algorithm validation provided sufficient evidence to proceed to human clinical trials.

## X. SUMMARY OF CLINICAL STUDIES

The Sponsor performed a clinical study of wavefront-guided CustomCornea<sup>®</sup> LASIK correction of mixed astigmatism using the LADARVision<sup>®</sup>4000 System in the U.S. under an investigational device exemption application (IDE G950213). In addition, one foreign site collected data under an investigational device application in Canada using a protocol that was the same as the U.S. protocol in terms of the inclusion and exclusion criteria, study procedures, patient measurements, and the treatment applied to the eye. Therefore, data from the U.S. and Canadian centers were pooled for the analysis of safety and effectiveness. A summary of the clinical trial is presented below.

### A. Study Objective

The primary objective of the clinical investigation of the LADARVision<sup>®</sup>4000 Excimer Laser System for wavefront-guided CustomCornea<sup>®</sup> LASIK correction of mixed astigmatism was to establish safety and effectiveness. Secondary study objectives included 1) to obtain preoperative and postoperative wavefront data to aid in the understanding of refractive and corneal shape changes as a result of the surgery and postoperative healing; and 2) to analyze the relationship between quality of vision indicators calculated from the wavefront data and clinical outcomes.

### B. Study Design

The initial study design in the U.S. protocol began as a prospective, randomized, unmasked multi-center trial, where one eye of each patient was randomly assigned CustomCornea<sup>®</sup> treatment based on data from the wavefront system and the fellow eye was assigned conventional treatment based on cycloplegic phoropter refraction. For this initial subgroup of patients, the fellow eye served as a contralateral control.

The U.S. study was changed to a prospective, non-randomized, unmasked, multi-center trial, where one or both eyes of a patient received wavefront-guided CustomCornea<sup>®</sup> treatment. An equivalent study design was also in progress under a Canadian protocol. In this case, the primary control was the preoperative state of the treated eye for comparison with postoperative outcomes.

### C. Inclusion and Exclusion Criteria

Recruited patients had the study details and follow-up requirements explained to them and were asked to sign an Informed Consent Document preoperatively. To be eligible for the study, mixed astigmatic patients must have had a preoperative cycloplegic refraction at the spectacle plane of  $> 0.00\text{D}$  to  $+6.00\text{D}$  sphere with  $< 0.00\text{D}$  to  $-6.00\text{D}$  astigmatism (in minus cylinder convention) with an absolute cylinder magnitude greater than the sphere magnitude. Enrollment of mixed astigmatic eyes in the study occurred over the preoperative cycloplegic refractive range of  $+0.25\text{D}$  to  $+4.25\text{D}$  sphere with  $-1.00\text{D}$  to  $-6.00\text{D}$  astigmatism and  $-1.38\text{D}$  to  $+1.63\text{D}$  spherical equivalent (SE).

Stability of refraction must have been established and documented using previous clinical records or measurement of spectacles. Stability was demonstrated by a change in the manifest sphere and cylinder over the prior 12 months of less than or equal to  $0.50\text{D}$ . If a year-old refraction was not available, the change in refraction

must have been 0.50D or less per year since the last documented refraction in both the manifest sphere and cylinder to a 1.00D maximum SE change. The manifest and cycloplegic refraction measured at the preoperative examination must have been within 1.00D of each other in the sphere and cylinder components. In addition, the cycloplegic refraction could not differ by more than 1.00D in sphere or cylinder from the attempted correction determined by the wavefront system.

For the contralateral treatment group, the cycloplegic refraction between the patient's two eyes could not differ by more than 1.00D in sphere or cylinder. In addition, patients must have been willing to have LASIK correction in both eyes within a 2-week period. These two criteria were not applicable to patients treated under the bilateral CustomCornea<sup>®</sup> treatment study design.

Patients must have been at least 18 years of age and had a BSCVA of 20/25 or better in the operative eye(s). Patients must have been willing to return for scheduled follow-up examinations for 9 months after surgery and have their eyes pharmacologically dilated at the required visits.

Patients who were contact lens wearers were requested to discontinue contact lens wear for a minimum of 2 weeks for soft contact lenses and 3 weeks for hard contact lenses (RGP/PMMA) prior to the preoperative examination. Patients who had previously worn hard lenses were required to have two examinations conducted 2 to 3 weeks apart to show stability of refraction without lens wear. Prior to surgery, patients were not to wear their contact lenses in the operative eye(s) for 2 to 3 weeks for soft and hard contact lenses, respectively.

Patients who exhibited any of the following conditions were excluded from the study:

- previous corneal, intraocular, or strabismus surgery in the operative eye(s)
- history of active clinically significant or visually threatening ocular disease or pathology
- clinically significant corneal scar within the ablation zone or other corneal abnormality such as recurrent erosion or severe basement membrane disease
- signs of keratoconus
- irregular corneal astigmatism
- history of herpes keratitis
- autoimmune disease, connective tissue disease, clinically significant atopic syndrome or diabetes
- use of chronic systemic corticosteroids or other immunosuppressive therapy
- use of systemic medication with significant ocular side effects
- pregnant or lactating females
- use of ophthalmic medications other than artificial tears for treatment of an ocular pathology
- severe dry eye syndrome unresolved by treatment
- known allergy to study medications
- glaucoma or glaucoma filtering surgery
- participation in another ophthalmic clinical trial
- calculated residual posterior stromal thickness of less than 250 microns
- unable to achieve a pupillary dilation of  $\geq 7$ mm
- at risk for angle closure

- an inability to obtain a clear and complete wavefront image

#### D. Study Plan, Patient Assessments, and Effectiveness Criteria

All patients were expected to return for follow-up at 1 day, 1 week, and 1, 3, 6 and 9 months postoperatively. All CustomCornea<sup>®</sup> treatments in the study were conducted using an optical zone of 6.5mm with a blend zone of 1.25mm for a total ablation zone of 9.0mm. All eyes were required to be treated for a target of emmetropia. All surgeries performed in the study were subject to approval by the Sponsor.

Under the contralateral treatment study design, patients were required to have their fellow eye treated with Conventional LASIK on the same day or within 2 weeks of the CustomCornea<sup>®</sup> treatment in the primary eye.

Under the bilateral CustomCornea<sup>®</sup> treatment study design, patients were permitted to have the fellow eye treated on the same day as the primary eye or any time thereafter provided there was no active complication or adverse event for the primary eye.

Retreatments were permitted after the 3-month follow-up visit based on these criteria:

1. An uncorrected visual acuity (UCVA) worse than 20/25 or residual sphere or cylinder greater than or equal to 0.50D at both of the two most recent consecutive visits that are at least one month apart.
2. Stable refraction with the sphere and cylinder components within 0.50D on two most recent consecutive visits that are at least one month apart.
3. Stable UCVA (i.e., within one line) on two consecutive visits at least one month apart.
4. Patient's signature on a separate Retreatment Informed Consent document, wherein the patient is informed of the risks associated with retreatment.
5. The eligibility criteria are met and an ophthalmic evaluation (including visual acuity, manifest refraction, and slit lamp) is done to establish the preoperative condition of the eye.
6. Prior written approval from the Sponsor of the study.

Retreatment for the purpose of correcting residual refractive error was not considered a treatment failure. Retreated patients were exited from the study and re-entered as a retreatment case. Results of retreated eyes were analyzed separately from the primary treatment population.

No other ocular surgery procedures were allowed unless deemed medically necessary by the Investigator. The Investigator was required to notify the Sponsor prior to any secondary surgical intervention, except in the case of an emergency in which case notification must occur as soon as possible.

In the event of a miscreated flap with the microkeratome, considered an adverse event in the study, a second cut with the microkeratome with completion of the laser ablation procedure was allowed after a minimum of 3 months. Approval from the Medical Monitor was required prior to treating an eye with a miscreated flap.

Preoperatively, the patient's medical and ocular histories were recorded. The objective parameters measured during the study included: uncorrected visual acuity, best spectacle corrected visual acuity, pupil size, vertex distance, manifest and

cycloplegic refraction, wavefront measurement, contrast sensitivity, intraocular pressure, angle assessment, slit lamp and dilated fundus examination.

The following objective parameters were collected preoperatively and only as needed postoperatively: corneal thickness, corneal topography, and keratometry. The subjective parameters measured during the study included a patient questionnaire.

The primary effectiveness parameters for this study were: improvement of UCVA; predictability and stability of manifest refraction spherical equivalent (MRSE) and manifest cylinder; reduction of wavefront error, including higher-order aberrations; and patient satisfaction. The safety parameters were: preservation of BSCVA; absence of significant findings in slit lamp and fundus examination; absence of significant intraocular pressure (IOP) elevation; and incidence of complications and adverse events.

#### E. Study Period, Investigational Sites, and Demographics

##### 1. Study Period and Investigational Sites

The Primary Cohort enrollment of 110 eyes of 63 subjects in the CustomCornea<sup>®</sup> wavefront-guided mixed astigmatism LASIK study occurred between December 11, 2002 and December 28, 2004. All eyes were treated based on the Zernike data from the wavefront measurement system including lower-order aberrations, such as sphere and cylinder and higher-order aberrations, such as spherical aberration and coma. Nine investigational sites enrolled patients in the Primary Cohort, including eight U.S. sites and one Canadian site.

##### 2. Demographics

The demographics of the study population (Table 1) were typical for a refractive surgery trial performed in the U.S. The mean  $\pm$  standard deviation patient age was  $40.6 \pm 10.7$  years with a range from 20 to 60 years. The majority of patients were Caucasian (94.5%) and the remaining patients were Hispanic (3.6%) and Indian (1.8%). Slightly more females (53.6%) than males (46.4%) participated in the study. The distribution of right and left eyes that received treatment was approximately equal (49.1% vs. 50.9%). While most patients (64.5%) did not wear contact lenses prior to surgery, 32.7% wore soft contact lenses and 2.7% wore rigid gas permeable (RGP) lenses. Preoperative patient characteristics that were found to associate with outcomes are discussed in Section X.F.2.j. (Statistical Analysis Outcomes).

<b>Table 1. Demographics</b>			
110 Eyes of 63 Enrolled Patients			
<b>Age (In Years)</b>			
Average ± Standard Deviation		40.6 ± 10.7	
Minimum to Maximum		20 to 60	
<b>Race</b>	Caucasian	N 104	% Eyes 94.5%
	Hispanic	4	3.6%
	Indian	2	1.8%
<b>Gender</b>	Female	59	53.6%
	Male	51	46.4%
<b>Eye</b>	Left	56	50.9%
	Right	54	49.1%
<b>Contact Lens History</b>	None	71	64.5%
	Soft	36	32.7%
	Rigid Gas Permeable (RGP)	3	2.7%

F. Data Analysis and Results

1. Preoperative Characteristics

The study population of mixed astigmatic eyes had a preoperative cycloplegic cylinder magnitude greater than the sphere in minus cylinder convention. Preoperative cycloplegic refractive range was +0.25D to +4.25D sphere with -1.00D to -6.00D cylinder and -1.38D to +1.63D spherical equivalent. The mean ± standard deviation for the preoperative cycloplegic refraction was +1.50D ± 0.94D sphere, -2.90D ± 1.20D cylinder and +0.06D ± 0.65D spherical equivalent. Table 2 displays the number of eyes stratified by preoperative cycloplegic sphere and cylinder. Table 3 displays the number of eyes stratified by preoperative cycloplegic spherical equivalent and cylinder.

<b>Table 2. Preoperative Cycloplegic Refraction Stratified by Sphere and Cylinder</b>							
<b>CYLINDER MAGNITUDE (D) IN MINUS CYLINDER CONVENTION</b>							
<b>SPHERE (D)</b>		<b>-1.00 to -1.99</b>	<b>-2.00 to -2.99</b>	<b>-3.00 to -3.99</b>	<b>-4.00 to -4.99</b>	<b>-5.00 to -6.00</b>	<b>TOTAL</b>
<b>&gt; 0.00 to +0.99</b>	n/N	15/110	14/110	7/110	0/110	0/110	36/110
	%	13.6%	12.7%	6.4%	0.0%	0.0%	32.7%
<b>+1.00 to +1.99</b>	n/N	9/110	19/110	10/110	3/110	0/110	41/110
	%	8.2%	17.3%	9.1%	2.7%	0.0%	37.3%
<b>+2.00 to +2.99</b>	n/N	0/110	4/110	6/110	9/110	4/110	23/110
	%	0.0%	3.6%	5.5%	8.2%	3.6%	20.9%
<b>+3.00 to +3.99</b>	n/N	0/110	0/110	2/110	5/110	2/110	9/110
	%	0.0%	0.0%	1.8%	4.5%	1.8%	8.2%
<b>+4.00 to +5.00</b>	n/N	0/110	0/110	0/110	0/110	1/110	1/110
	%	0.0%	0.0%	0.0%	0.0%	0.9%	0.9%
<b>TOTAL</b>	n/N	24/110	37/110	25/110	17/110	7/110	110/110
	%	21.8%	33.6%	22.7%	15.5%	6.4%	100.0%

D = Diopter

CYLINDER MAGNITUDE (D) IN MINUS CYLINDER CONVENTION							
SPHERICAL EQUIVALENT (D)		-1.00 to -1.99	-2.00 to -2.99	-3.00 to -3.99	-4.00 to -4.99	-5.00 to -6.00	TOTAL
-1.00 to -2.00	n/N %	0/110 0.0%	1/110 0.9%	5/110 4.5%	2/110 1.8%	0/110 0.0%	8/110 7.3%
0.00 to -0.99	n/N %	9/110 8.2%	19/110 17.3%	11/110 10.0%	3/110 2.7%	3/110 2.7%	45/110 40.9%
+0.01 to +0.99	n/N %	15/110 13.6%	15/110 13.6%	4/110 3.6%	9/110 8.2%	2/110 1.8%	45/110 40.9%
+1.00 to +2.00	n/N %	0/110 0.0%	2/110 1.8%	5/110 4.5%	3/110 2.7%	2/110 1.8%	12/110 10.9%
<b>TOTAL</b>	n/N %	24/110 21.8%	37/110 33.6%	25/110 22.7%	17/110 15.5%	7/110 6.4%	110/110 100.0%

(D) = Diopter

## 2. Postoperative Results

## a. Accountability

Accountability for this study was  $\geq 98.2\%$  at all postoperative intervals (Table 4). Postoperative data were available for 110 eyes (100%) up to 6 months and for 108 eyes (98.2%) at 9 months. One patient (2 eyes) missed the 9-month visit because the patient moved out of the country prior to the opening of the 9-month visit window.

			1 MONTH	3 MONTHS	6 MONTHS	9 MONTHS
Total Eyes Enrolled		N	110	110	110	110
Available for Analysis		N %	110 100.0%	110 100.0%	110 100.0%	108 98.2%
Unavailable	Missed Visit	N %	0 0.0%	0 0.0%	0 0.0%	2 1.8%
% Accountability= [available/(available + unavailable)]		%	100.0%	100.0%	100.0%	98.2%

## b. Stability of Outcome

Refractive stability was analyzed as paired differences in the non-vector manifest cylinder magnitude between consecutive visits (Table 5). Eyes with data available at each postoperative interval were evaluated in a 6-month consistent cohort of 110 eyes and a 9-month cohort of 108 eyes.

Cylinder stability was achieved between 1 and 3 months with 100% of eyes demonstrating  $\leq 1.00D$  magnitude change and a mean change of  $-0.05D \pm 0.29D$  at a rate of  $-0.03D$  change per month for the 6-month consistent cohort. Cylinder stability was confirmed between 3 and 6 months with 100%

of eyes demonstrating  $\leq 1.00D$  magnitude change and a decrease in the mean change over time to  $0.02D \pm 0.24D$  at a rate of  $0.01D$  change per month. The 95% confidence interval of the mean change in cylinder magnitude overlapped between postoperative intervals with a narrow range ( $\leq 0.11D$ ) between the upper and lower limits.

The 9-month consistent cohort supported the overall trends in cylinder stability observed among the 6-month cohort. Between all consecutive postoperative intervals, at least 99.1% of eyes showed  $\leq 1.00D$  of cylinder magnitude change. The mean change in cylinder magnitude was  $0.05D \pm 0.25D$  between 6 and 9 months at a rate of  $0.02D$  change per month.

6-Month Cohort (N=110)	Change in Cylinder Magnitude Between		1 and 3 Months	3 and 6 Months		
	$\leq 1.00D$	n/N %	110/110 100.0%	110/110 100.0%		
	Mean Change* $\pm$ Standard Deviation		-0.05 $\pm$ 0.29	0.02 $\pm$ 0.24		
	95% Confidence Interval of Mean Change		(-0.11, 0.00)	(-0.03, 0.06)		
	Mean Change* per Month		-0.03	0.01		
9-Month Cohort (N=108)	Change in Cylinder Magnitude Between		1 and 3 Months	3 and 6 Months	6 and 9 Months	
	$\leq 1.00D$	n/N %	108/108 100.0%	108/108 100.0%	107/108 99.1%	
		Mean Change* $\pm$ Standard Deviation		-0.05 $\pm$ 0.29	0.01 $\pm$ 0.23	0.05 $\pm$ 0.25
		95% Confidence Interval of Mean Change		(-0.11, 0.00)	(-0.03, 0.05)	(0.00, 0.10)
		Mean Change* per Month		-0.03	0.003	0.02

D = Diopter

\* Positive value reflects an increase in magnitude and a negative value reflects a decrease in magnitude between visits.

Similarly, refractive stability was analyzed as paired differences in MRSE between consecutive visits for the 6-month and 9-month consistent cohorts of eyes with data available at each postoperative interval (Table 6).

Stability of MRSE was achieved between 1 and 3 months with 100% of eyes demonstrating a change in MRSE  $\leq 1.00D$  and a mean change of  $0.06D \pm 0.29D$  at a rate of  $0.03D$  change per month for the 6-month consistent cohort. Stability was confirmed between 3 and 6 months with 100% of eyes demonstrating a change in MRSE  $\leq 1.00D$  and a decrease in the mean change over time to  $0.03D \pm 0.25D$  at a rate of  $0.01D$  change per month. The 95% confidence interval of the mean change in MRSE overlapped between postoperative intervals with a narrow range ( $\leq 0.11D$ ) between the upper and lower limits.

The 9-month consistent cohort showed similar MRSE stability trends to the 6-month cohort. All eyes demonstrated a change in MRSE  $\leq 1.00D$  between postoperative visits. Between 6 and 9 months, the mean MRSE change was  $-0.04D \pm 0.26D$  at a rate of  $-0.01D$  change per month.

<b>Table 6. Stability of Manifest Refraction Spherical Equivalent</b>					
<b>6-Month Cohort (N=110)</b>	<b>Change in MRSE Between</b>		<b>1 and 3 Months</b>	<b>3 and 6 Months</b>	
	≤ 1.00D	n/N %	110/110 100.0%	110/110 100.0%	
	Mean Change ± Standard Deviation		0.06 ± 0.29	0.03 ± 0.25	
	95% Confidence Interval of Mean Change		(0.00, 0.11)	(-0.01, 0.08)	
	Mean Change per Month		0.03	0.01	
<b>9-Month Cohort (N=108)</b>	<b>Change in MRSE Between</b>		<b>1 and 3 Months</b>	<b>3 and 6 Months</b>	<b>6 and 9 Months</b>
	≤ 1.00D	n/N %	108/108 100.0%	108/108 100.0%	108/108 100.0%
	Mean Change ± Standard Deviation		0.06 ± 0.29	0.03 ± 0.25	-0.04 ± 0.26
	95% Confidence Interval of Mean Change		(0.00, 0.11)	(-0.02, 0.07)	(-0.09, 0.01)
	Mean Change per Month		0.03	0.01	-0.01

D = Diopter

c. Effectiveness Outcomes

The key effectiveness outcomes for UCVA and accuracy of MRSE and manifest cylinder are shown in Table 7. These parameters at 3 and 6 months are also shown stratified by preoperative cycloplegic cylinder in Table 8 and by preoperative cycloplegic refraction spherical equivalent (CRSE) in Table 9.

The effectiveness data meet the criteria established in the FDA Guidance Document for at least 85% of eyes achieving a UCVA of 20/40 or better and accuracy of MRSE within 0.50D in at least 50% of eyes and within 1.00D in 75% of eyes at all postoperative intervals.



**Table 8. Summary of Key Effectiveness Parameters at 3 and 6 Months Stratified by Diopter (D) of Preoperative Cycloplegic Cylinder**

3 MONTHS							
Effectiveness Parameters		-1.00 to -1.99	-2.00 to -2.99	-3.00 to -3.99	-4.00 to -4.99	-5.00 to -6.00	Total
UCVA 20/20 or better if Preop BSCVA 20/20 or better	n/N %	16/22 72.7%	20/36 55.6%	18/23 78.3%	5/9 55.6%	1/4 25.0%	60/94 63.8%
UCVA 20/20 or better	n/N %	16/24 66.7%	21/37 56.8%	18/25 72.0%	6/17 35.3%	1/7 14.3%	62/110 56.4%
UCVA 20/25 or better	n/N %	24/24 100.0%	28/37 75.7%	23/25 92.0%	12/17 70.6%	2/7 28.6%	89/110 80.9%
UCVA 20/40 or better	n/N %	24/24 100.0%	33/37 89.2%	25/25 100.0%	17/17 100.0%	6/7 85.7%	105/110 95.5%
MRSE ± 0.50D of intended	n/N %	23/24 95.8%	25/37 67.6%	17/25 68.0%	9/17 52.9%	4/7 57.1%	78/110 70.9%
MRSE ± 1.00D of intended	n/N %	24/24 100.0%	35/37 94.6%	23/25 92.0%	14/17 82.4%	6/7 85.7%	102/110 92.7%
RSE ± 2.00D of intended	n/N %	24/24 100.0%	37/37 100.0%	25/25 100.0%	16/17 94.1%	7/7 100.0%	109/110 99.1%
Cylinder magnitude ≤ 0.50D of intended	n/N %	20/24 83.3%	25/37 67.6%	14/25 56.0%	13/17 76.5%	1/7 14.3%	73/110 66.4%
Cylinder magnitude ≤ 1.00D of intended	n/N %	24/24 100.0%	36/37 97.3%	23/25 92.0%	14/17 82.4%	3/7 42.9%	100/110 90.9%
Cylinder magnitude ≤ 2.00D of intended	n/N %	24/24 100.0%	37/37 100.0%	25/25 100.0%	17/17 100.0%	6/7 85.7%	109/110 99.1%
6 MONTHS							
Effectiveness Parameters		-1.00 to -1.99	-2.00 to -2.99	-3.00 to -3.99	-4.00 to -4.99	-5.00 to -6.00	Total
UCVA 20/20 or better if Preop BSCVA 20/20 or better	n/N %	21/22 95.5%	19/36 52.8%	20/23 87.0%	7/9 77.8%	0/4 0.0%	67/94 71.3%
UCVA 20/20 or better	n/N %	21/24 87.5%	20/37 54.1%	20/25 80.0%	9/17 52.9%	0/7 0.0%	70/110 63.6%
UCVA 20/25 or better	n/N %	24/24 100.0%	29/37 78.4%	25/25 100.0%	14/17 82.4%	4/7 57.1%	96/110 87.3%
UCVA 20/40 or better	n/N %	24/24 100.0%	35/37 94.6%	25/25 100.0%	17/17 100.0%	7/7 100.0%	108/110 98.2%
MRSE ± 0.50D of intended	n/N %	24/24 100.0%	28/37 75.7%	18/25 72.0%	10/17 58.8%	4/7 57.1%	84/110 76.4%
MRSE ± 1.00D of intended	n/N %	24/24 100.0%	34/37 91.9%	22/25 88.0%	14/17 82.4%	6/7 85.7%	100/110 90.9%
MRSE ± 2.00D of intended	n/N %	24/24 100.0%	37/37 100.0%	25/25 100.0%	17/17 100.0%	7/7 100.0%	110/110 100.0%
Cylinder magnitude ≤ 0.50D of intended	n/N %	19/24 79.2%	24/37 64.9%	15/25 60.0%	11/17 64.7%	2/7 28.6%	71/110 64.5%
Cylinder magnitude ≤ 1.00D of intended	n/N %	23/24 95.8%	35/37 94.6%	24/25 96.0%	14/17 82.4%	2/7 28.6%	98/110 89.1%
Cylinder magnitude ≤ 2.00D of intended	n/N %	24/24 100.0%	37/37 100.0%	25/25 100.0%	17/17 100.0%	6/7 85.7%	109/110 99.1%

UCVA = Uncorrected Visual Acuity  
MRSE = Manifest Refraction Spherical Equivalent

BSCVA = Best Spectacle Corrected Visual Acuity  
D = Diopter

<b>Table 9. Summary of Key Effectiveness Parameters at 3 and 6 Months Stratified by Diopter (D) of Preoperative Cycloplegic Refraction Spherical Equivalent</b>						
<b>3 MONTHS</b>						
<b>Effectiveness Parameters</b>		<b>-1.00 to -2.00</b>	<b>0.00 to -0.99</b>	<b>+0.01 to +0.99</b>	<b>+1.00 to +2.00</b>	<b>Total</b>
UCVA 20/20 or better if Preop BSCVA 20/20 or better	n/N %	5/6 83.3%	24/41 58.5%	24/36 66.7%	7/11 63.6%	60/94 63.8%
UCVA 20/20 or better	n/N %	5/8 62.5%	24/45 53.3%	26/45 57.8%	7/12 58.3%	62/110 56.4%
UCVA 20/25 or better	n/N %	7/8 87.5%	39/45 86.7%	34/45 75.6%	9/12 75.0%	89/110 80.9%
UCVA 20/40 or better	n/N %	8/8 100.0%	43/45 95.6%	43/45 95.6%	11/12 91.7%	105/110 95.5%
MRSE ± 0.50D of intended	n/N %	7/8 87.5%	35/45 77.8%	27/45 60.0%	9/12 75.0%	78/110 70.9%
MRSE ± 1.00D of intended	n/N %	8/8 100.0%	42/45 93.3%	41/45 91.1%	11/12 91.7%	102/110 92.7%
MRSE ± 2.00D of intended	n/N %	8/8 100.0%	45/45 100.0%	44/45 97.8%	12/12 100.0%	109/110 99.1%
Cylinder magnitude ≤ 0.50D of intended	n/N %	4/8 50.0%	30/45 66.7%	32/45 71.1%	7/12 58.3%	73/110 66.4%
Cylinder magnitude ≤ 1.00D of intended	n/N %	8/8 100.0%	40/45 88.9%	42/45 93.3%	10/12 83.3%	100/110 90.9%
Cylinder magnitude ≤ 2.00D of intended	n/N %	8/8 100.0%	44/45 97.8%	45/45 100.0%	12/12 100.0%	109/110 99.1%
<b>6 MONTHS</b>						
<b>Effectiveness Parameters</b>		<b>-1.00 to -2.00</b>	<b>0.00 to -0.99</b>	<b>+0.01 to +0.99</b>	<b>+1.00 to +2.00</b>	<b>Total</b>
UCVA 20/20 or better if Preop BSCVA 20/20 or better	n/N %	5/6 83.3%	29/41 70.7%	27/36 75.0%	6/11 54.5%	67/94 71.3%
UCVA 20/20 or better	n/N %	6/8 75.0%	29/45 64.4%	29/45 64.4%	6/12 50.0%	70/110 63.6%
UCVA 20/25 or better	n/N %	8/8 100.0%	41/45 91.1%	36/45 80.0%	11/12 91.7%	96/110 87.3%
UCVA 20/40 or better	n/N %	8/8 100.0%	44/45 97.8%	45/45 100.0%	11/12 91.7%	108/110 98.2%
MRSE ± 0.50D of intended	n/N %	7/8 87.5%	34/45 75.6%	34/45 75.6%	9/12 75.0%	84/110 76.4%
MRSE ± 1.00D of intended	n/N %	8/8 100.0%	42/45 93.3%	39/45 86.7%	11/12 91.7%	100/110 90.9%
MRSE ± 2.00D of intended	n/N %	8/8 100.0%	45/45 100.0%	45/45 100.0%	12/12 100.0%	110/110 100.0%
Cylinder magnitude ≤ 0.50D of intended	n/N %	4/8 50.0%	27/45 60.0%	33/45 73.3%	7/12 58.3%	71/110 64.5%
Cylinder magnitude ≤ 1.00D of intended	n/N %	8/8 100.0%	39/45 86.7%	42/45 93.3%	9/12 75.0%	98/110 89.1%
Cylinder magnitude ≤ 2.00D of intended	n/N %	8/8 100.0%	44/45 97.8%	45/45 100.0%	12/12 100.0%	109/110 99.1%

UCVA = Uncorrected Visual Acuity  
MRSE = Manifest Refraction Spherical Equivalent

BSCVA – Best Spectacle Corrected Visual Acuity  
D = Diopter

Uncorrected visual acuity is displayed in Table 10. Preoperatively, 35.5% of eyes had a UCVA of 20/40 or better. At 3 months, the UCVA was 20/20 or better in 56.4% of eyes, 20/25 or better in 80.9% and 20/40 or better in 95.5%. At 6 months, the UCVA was 20/20 or better in 63.6% of eyes, 20/25 or better in 87.3% and 20/40 or better in 98.2%. For those eyes with a preoperative BSCVA of 20/20 or better, a UCVA of 20/20 or better was achieved in 63.8% and 71.3% of eyes at 3 and 6 months, respectively.

		<b>PREOP</b>	<b>1 MONTH</b>	<b>3 MONTHS</b>	<b>6 MONTHS</b>	<b>9 MONTHS</b>
20/10	n/N %	0/110 0.0%	1/110 0.9%	2/110 1.8%	3/110 2.7%	3/108 2.8%
20/12.5 or better	n/N %	0/110 0.0%	8/110 7.3%	11/110 10.0%	11/110 10.0%	9/108 8.3%
20/16 or better	n/N %	0/110 0.0%	33/110 30.0%	33/110 30.0%	39/110 35.5%	40/108 37.0%
20/20 or better	n/N %	1/110 0.9%	70/110 63.6%	62/110 56.4%	70/110 63.6%	66/108 61.1%
20/25 or better	n/N %	4/110 3.6%	95/110 86.4%	89/110 80.9%	96/110 87.3%	91/108 84.3%
20/32 or better	n/N %	17/110 15.5%	104/110 94.5%	98/110 89.1%	104/110 94.5%	99/108 91.7%
20/40 or better	n/N %	39/110 35.5%	106/110 96.4%	105/110 95.5%	108/110 98.2%	101/108 93.5%
20/50 or better	n/N %	53/110 48.2%	109/110 99.1%	110/110 100.0%	109/110 99.1%	107/108 99.1%
20/63 or better	n/N %	68/110 61.8%	110/110 100.0%	110/110 100.0%	110/110 100.0%	107/108 99.1%
20/80 or better	n/N %	84/110 76.4%	110/110 100.0%	110/110 100.0%	110/110 100.0%	108/108 100.0%
20/100 or better	n/N %	98/110 89.1%	110/110 100.0%	110/110 100.0%	110/110 100.0%	108/108 100.0%
Worse than 20/100	n/N %	12/110 10.9%	0/110 0.0%	0/110 0.0%	0/110 0.0%	0/108 0.0%

A comparison of **postoperative UCVA** to **preoperative BSCVA** after CustomCornea<sup>®</sup> LASIK surgery is presented in Table 11 with differences based on lines of visual acuity. A postoperative UCVA equal to or better than the preoperative BSCVA was achieved in 56.4% and 60.0% of eyes at 3 and 6 months, respectively.

**Table 11. Postoperative Uncorrected Visual Acuity Compared to Preoperative Best Spectacle Corrected Visual Acuity**

		1 MONTH	3 MONTHS	6 MONTHS	9 MONTHS
UCVA 2 Lines Better Than Preop BSCVA	n/N %	0/110 0.0%	0/110 0.0%	2/110 1.8%	2/108 1.9%
UCVA 1 Line Better Than Preop BSCVA	n/N %	13/110 11.8%	18/110 16.4%	19/110 17.3%	20/108 18.5%
UCVA Equal* to Preop BSCVA	n/N %	53/110 48.2%	44/110 40.0%	45/110 40.9%	43/108 39.8%
UCVA 1 Line Worse Than Preop BSCVA	n/N %	26/110 23.6%	21/110 19.1%	29/110 26.4%	21/108 19.4%
UCVA 2 Lines Worse Than Preop BSCVA	n/N %	9/110 8.2%	13/110 11.8%	7/110 6.4%	11/108 10.2%
UCVA >2 Lines Worse Than Preop BSCVA	n/N %	9/110 8.2%	14/110 12.7%	8/110 7.3%	11/108 10.2%

UCVA = Uncorrected Visual Acuity      BSCVA = Best Spectacle Corrected Visual Acuity

\* Equal visual acuity is within 2 or 3 letters on the same line of a visual acuity chart

As shown in Table 12, accuracy of MRSE was within 0.50D of emmetropia in 70.9% of eyes, within 1.00D in 92.7% and within 2.00D in 99.1% at 3 months. At 6 months, the MRSE was within 0.50D of emmetropia in 76.4% of eyes, within 1.00D in 90.9% and within 2.00D in 100%. Of the eyes that did not achieve an MRSE within 1.00D of emmetropia, 5.5% at 3 months and 7.3% at 6 months had more than +1.00D of hyperopia, whereas 1.8% at 3 and 6 months had more than -1.00D of myopia. One eye (0.9%) had more than +2.00D of hyperopia by MRSE at 3 months.

**Table 12. Accuracy of Manifest Refraction Spherical Equivalent**

		1 MONTH	3 MONTHS	6 MONTHS	9 MONTHS
± 0.50D	n/N %	79/110 71.8%	78/110 70.9%	84/110 76.4%	81/108 75.0%
± 1.00D	n/N %	104/110 94.5%	102/110 92.7%	100/110 90.9%	96/108 88.9%
± 2.00D	n/N %	109/110 99.1%	109/110 99.1%	110/110 100.0%	108/108 100.0%
> ± 2.00D	n/N %	1/110 0.9%	1/110 0.9%	0/110 0.0%	0/108 0.0%
Postop Hyperopic MRSE > +1.00D	n/N %	5/110 4.5%	6/110 5.5%	8/110 7.3%	9/108 8.3%
Postop Hyperopic MRSE > +2.00D	n/N %	1/110 0.9%	1/110 0.9%	0/110 0.0%	0/108 0.0%
Postop Myopic MRSE < -1.00D	n/N %	1/110 0.9%	2/110 1.8%	2/110 1.8%	3/108 2.8%
Postop Myopic MRSE < -2.00D	n/N %	0/110 0.0%	0/110 0.0%	0/110 0.0%	0/108 0.0%

MRSE = Manifest Refraction Spherical Equivalent

D = Diopter

Accuracy of manifest refraction is displayed for the preoperative hyperopic meridian in Table 13 and preoperative myopic meridian in Table 14. Slight undercorrection along the preoperative hyperopic meridian was observed based on a mean correction error of  $+0.15D \pm 0.69D$  at 3 months and  $+0.20D \pm 0.63D$  at 6 months. Along the preoperative myopic meridian, slight undercorrection was observed based on a mean correction error of  $-0.09D \pm 0.67D$  at 3 months and  $-0.07D \pm 0.61D$  at 6 months.

<b>Table 13. Accuracy of Manifest Refraction in Preoperative Hyperopic Meridian</b>					
<b>Correction Error</b>		<b>1 MONTH</b>	<b>3 MONTHS</b>	<b>6 MONTHS</b>	<b>9 MONTHS</b>
Mean $\pm$ SD (D)		$+0.07 \pm 0.68$	$+0.15 \pm 0.69$	$+0.20 \pm 0.63$	$+0.17 \pm 0.63$
$0.00 \pm 0.50D$	n/N	79/110	74/110	77/110	73/108
	%	71.8%	67.3%	70.0%	67.6%
<b>Undercorrected (Postoperative Hyperopia)</b>					
$> 0.50$ to $1.00D$	n/N	10/110	18/110	16/110	15/108
	%	9.1%	16.4%	14.5%	13.9%
$> 1.00$ to $2.00D$	n/N	4/110	7/110	8/110	7/108
	%	3.6%	6.4%	7.3%	6.5%
$> 2.00D$	n/N	2/110	2/110	2/110	2/108
	%	1.8%	1.8%	1.8%	1.9%
<b>Overcorrected (Postoperative Myopia)</b>					
$> 0.50$ to $1.00D$	n/N	10/110	5/110	5/110	10/108
	%	9.1%	4.5%	4.5%	9.3%
$> 1.00$ to $2.00D$	n/N	5/110	4/110	2/110	1/108
	%	4.5%	3.6%	1.8%	0.9%
$> 2.00D$	n/N	0/110	0/110	0/110	0/108
	%	0.0%	0.0%	0.0%	0.0%

<b>Table 14. Accuracy of Manifest Refraction in Preoperative Myopic Meridian</b>					
<b>Correction Error</b>		<b>1 MONTH</b>	<b>3 MONTHS</b>	<b>6 MONTHS</b>	<b>9 MONTHS</b>
Mean $\pm$ SD (D)		$-0.12 \pm 0.64$	$-0.09 \pm 0.67$	$-0.07 \pm 0.61$	$-0.13 \pm 0.66$
$0.00 \pm 0.50D$	n/N	73/110	67/110	71/110	66/108
	%	66.4%	60.9%	64.5%	61.1%
<b>Undercorrected (Postoperative Myopia)</b>					
$> 0.50$ to $1.00D$	n/N	17/110	20/110	17/110	19/108
	%	15.5%	18.2%	15.5%	17.6%
$> 1.00$ to $2.00D$	n/N	6/110	5/110	5/110	6/108
	%	5.5%	4.5%	4.5%	5.6%
$> 2.00D$	n/N	1/110	0/110	0/110	0/108
	%	0.9%	0.0%	0.0%	0.0%
<b>Overcorrected (Postoperative Hyperopia)</b>					
$> 0.50$ to $1.00D$	n/N	9/110	11/110	8/110	10/108
	%	8.2%	10.0%	7.3%	9.3%
$> 1.00$ to $2.00D$	n/N	4/110	7/110	9/110	7/108
	%	3.6%	6.4%	8.2%	6.5%
$> 2.00D$	n/N	0/110	0/110	0/110	0/108
	%	0.0%	0.0%	0.0%	0.0%

SD = Standard Deviation

D = Diopter

Table 15 displays the accuracy of manifest sphere and cylinder magnitude. Postoperative manifest sphere was within 0.50D of emmetropia in 71.3% of eyes, within 1.00D in 87.0% and within 2.00D in 98.1% at 3 months. Manifest sphere was within 0.50D of emmetropia in 70.4% of eyes, within 1.00D in 88.0% and within 2.00D in 98.1% at 6 months.

Postoperative manifest cylinder magnitude was  $\leq 0.50$ D of emmetropia in 66.4% of eyes,  $\leq 1.00$ D in 90.9% and  $\leq 2.00$ D in 99.1% at 3 months. Cylinder magnitude was  $\leq 0.50$ D in 64.5% of eyes,  $\leq 1.00$ D in 89.1% and  $\leq 2.00$ D in 99.1% at 6 months.

<b>Table 15. Accuracy of Manifest Sphere and Cylinder Magnitude</b>					
<b>Sphere*</b>		<b>1 MONTH (N=108)</b>	<b>3 MONTHS (N=108)</b>	<b>6 MONTHS (N=108)</b>	<b>9 MONTHS (N=106)</b>
Postop Mean $\pm$ SD (D)		+0.27 $\pm$ 0.65	+0.31 $\pm$ 0.68	+0.35 $\pm$ 0.62	+0.33 $\pm$ 0.64
Attempted Mean $\pm$ SD (D)		+1.20 $\pm$ 0.88	+1.20 $\pm$ 0.88	+1.20 $\pm$ 0.88	+1.19 $\pm$ 0.89
Achieved Mean $\pm$ SD (D)		+0.92 $\pm$ 0.98	+0.89 $\pm$ 1.03	+0.85 $\pm$ 1.00	+0.87 $\pm$ 1.04
% Achieved		69 $\pm$ 85	64 $\pm$ 79	61 $\pm$ 85	60 $\pm$ 91
$\pm 0.50$ D	n/N	81/108	77/108	76/108	77/106
	%	75.0%	71.3%	70.4%	72.6%
$\pm 1.00$ D	n/N	99/108	94/108	95/108	94/106
	%	91.7%	87.0%	88.0%	88.7%
$\pm 2.00$ D	n/N	106/108	106/108	106/108	104/106
	%	98.1%	98.1%	98.1%	98.1%
<b>Cylinder</b>		<b>1 MONTH (N=110)</b>	<b>3 MONTHS (N=110)</b>	<b>6 MONTHS (N=110)</b>	<b>9 MONTHS (N=108)</b>
Postop Mean $\pm$ SD (D)		-0.58 $\pm$ 0.55	-0.53 $\pm$ 0.53	-0.55 $\pm$ 0.47	-0.59 $\pm$ 0.46
Attempted Mean $\pm$ SD (D)		-2.89 $\pm$ 1.21	-2.89 $\pm$ 1.21	-2.89 $\pm$ 1.21	-2.90 $\pm$ 1.21
Achieved Mean $\pm$ SD (D)		-2.30 $\pm$ 1.12	-2.36 $\pm$ 1.12	-2.34 $\pm$ 1.15	-2.31 $\pm$ 1.17
% Achieved		78 $\pm$ 20	81 $\pm$ 18	79 $\pm$ 18	77 $\pm$ 20
$\leq 0.50$ D	n/N	71/110	73/110	71/110	66/108
	%	64.5%	66.4%	64.5%	61.1%
$\leq 1.00$ D	n/N	96/110	100/110	98/110	95/108
	%	87.3%	90.9%	89.1%	88.0%
$\leq 2.00$ D	n/N	108/110	109/110	109/110	107/108
	%	98.2%	99.1%	99.1%	99.1%

\* Excludes two eyes with a preoperative manifest sphere of 0D.

Effectiveness of astigmatism correction at 3 and 6 months was evaluated based on the percentage reduction in cylinder magnitude and by vector analysis (Table 16). The mean percentage reduction in absolute manifest cylinder was 80.6% at 3 months and 79.1% at 6 months with an overall trend for a greater percentage reduction in eyes with higher preoperative cylinder. The mean correction ratio based on vector analysis of manifest cylinder was 0.92 at 3 months and 0.91 at 6 months.

<b>3 MONTHS</b>			
<b>Preoperative Cylinder</b>	<b>N</b>	<b>Mean Percentage Reduction in Cylinder Magnitude</b>	<b>Vector Analysis Mean <math>\pm</math> SD Correction Ratio</b>
All	110	80.6%	0.92 $\pm$ 0.18
1.00 to < 2.00D	26	75.9%	0.86 $\pm$ 0.21
2.00 to < 3.00D	34	79.9%	0.94 $\pm$ 0.17
3.00 to < 4.00D	26	84.1%	0.93 $\pm$ 0.14
4.00 to < 5.00D	16	87.1%	1.01 $\pm$ 0.12
5.00 to 6.00D	8	74.4%	0.83 $\pm$ 0.24
<b>6 MONTHS</b>			
<b>Preoperative Cylinder</b>	<b>N</b>	<b>Mean Percentage Reduction in Cylinder Magnitude</b>	<b>Vector Analysis Mean <math>\pm</math> SD Correction Ratio</b>
All	110	79.1%	0.91 $\pm$ 0.17
1.00 to < 2.00D	26	72.3%	0.84 $\pm$ 0.20
2.00 to < 3.00D	34	77.3%	0.92 $\pm$ 0.17
3.00 to < 4.00D	26	83.9%	0.93 $\pm$ 0.16
4.00 to < 5.00D	16	87.0%	0.98 $\pm$ 0.12
5.00 to 6.00D	8	78.0%	0.86 $\pm$ 0.20

SD = Standard Deviation

D = Diopter

Correction Ratio is the ratio of achieved vs. intended vector magnitude

Table 17 presents the manifest and cycloplegic phoropter refraction over time and the wavefront refraction from the wavefront measurement under cycloplegic conditions.

The mean manifest spherical equivalent was  $+0.03D \pm 0.62D$  at 3 months and  $+0.06D \pm 0.57D$  at 6 months. The mean cycloplegic and wavefront spherical equivalents were similar over time. As expected under cycloplegic conditions, the cycloplegic and wavefront spherical equivalents reflected more hyperopia that was within 0.50D of the manifest spherical equivalent preoperatively and postoperatively.

The mean manifest cylinder was  $-0.53D \pm 0.53D$  at 3 months and  $-0.55D \pm 0.47D$  at 6 months. The mean cycloplegic cylinder was similar to the manifest cylinder over time. The mean wavefront cylinder was within 0.25D of the manifest and cycloplegic refractions postoperatively.

**Table 17. Mean Refraction Over Time**

Mean ± Standard Deviation	PREOP	1 MONTH	3 MONTHS	6 MONTHS	9 MONTHS
<b>Manifest Refraction (D)</b>	N=110	N=110	N=110	N=110	N=108
Spherical Equivalent	-0.27 ± 0.67	-0.03 ± 0.59	0.03 ± 0.62	0.06 ± 0.57	0.02 ± 0.59
Cylinder	-2.89 ± 1.21	-0.58 ± 0.55	-0.53 ± 0.53	-0.55 ± 0.47	-0.59 ± 0.46
<b>Cycloplegic Refraction (D)*</b>	N=110	--	N=110	N=108	--
Spherical Equivalent	0.06 ± 0.65	--	0.49 ± 0.56	0.44 ± 0.56	--
Cylinder	-2.90 ± 1.20	--	-0.49 ± 0.51	-0.52 ± 0.49	--
<b>Wavefront Refraction (D)**</b>	N=110	N=103	N=100	N=103	N=100
Spherical Equivalent	0.04 ± 0.71	0.35 ± 0.45	0.44 ± 0.46	0.31 ± 0.46	0.39 ± 0.52
Cylinder	-2.91 ± 1.25	-0.71 ± 0.49	-0.69 ± 0.47	-0.65 ± 0.35	-0.74 ± 0.52

Refractions at the spectacle plane

D = Diopter

\* Cycloplegic refraction not required at 1 month and 9 months

\*\*Wavefront measurement under cycloplegic conditions with refraction analyzed over 3.5mm diameter

d. Wavefront Outcomes

Table 18 displays the mean change from preoperative in total root mean square (RMS) wavefront error and in higher-order aberrations through 6<sup>th</sup>-order. The mean change in total RMS wavefront error decreased by 64.1% at 3 months and 67.2% at 6 months from preoperative. Higher-order aberrations were not significantly changed from preoperative on average with an increase of 2.3% at 3 months and 2.2% at 6 months. Spherical aberration decreased in magnitude at 3 and 6 months from preoperative with a mean directional shift from positive spherical aberration preoperatively (0.233µm) towards slightly negative spherical aberration at 3 months (-0.003µm) and 6 months (-0.007µm).

**Table 18. Mean Change in Aberrations Up to 6<sup>th</sup>-Order From Preoperative\***

Aberration	3 MONTHS (N=100)		6 MONTHS (N=103)	
	Mean Change (µm)	Mean Change (%)	Mean Change (µm)	Mean Change (%)
Total RMS Error	-1.905	-64.1	-1.998	-67.2
Higher-Order	0.010	2.3	0.010	2.2
Coma	0.030	12.5	0.034	13.9
Trefoil	0.008	4.0	0.005	2.7
Spherical Aberration Magnitude †	-0.114	-48.4	-0.101	-42.8
Spherical Aberration Value ‡	-0.236	-101.2	-0.240	-102.9
Secondary Astigmatism	0.073	92.8	0.066	84.3
Tetrafoil	0.023	30.4	0.027	35.3
Combined 5 <sup>th</sup> and 6 <sup>th</sup> Order	0.037	49.5	0.035	46.6

RMS = Root Mean Square

Wavefront Analysis Diameter = 6.0mm

\* Positive change represents increase from preop; Negative change represents decrease from preop

† Based on absolute spherical aberration magnitude    ‡ Based on signed spherical aberration value

At 3 and 6 months, 100% of eyes had a reduction in total RMS error from preoperative. A reduction in higher-order aberrations from preoperative was observed in 55.0% of eyes at 3 months and 54.4% at 6 months (Table 19).

	<b>3 MONTHS (N=100)</b>	<b>6 MONTHS (N=103)</b>
<b>Aberration</b>	<b>% Eyes with Reduction in Aberrations</b>	
Total RMS Error	100.0%	100.0%
Higher-Order	55.0%	54.4%
Coma	48.0%	49.5%
Trefoil	49.0%	45.6%
Spherical Aberration Magnitude †	80.0%	78.6%
Secondary Astigmatism	18.0%	17.5%
Tetrafoil	32.0%	32.0%
Combined 5 <sup>th</sup> and 6 <sup>th</sup> Order	18.0%	17.5%

RMS = Root Mean Square

Wavefront Analysis Diameter = 6.0mm

† Reduction in absolute spherical aberration magnitude

Wavefront-guided CustomCornea<sup>®</sup> LASIK was compared to the baseline established for Conventional LASIK correction of mixed astigmatism using phoropter refraction for eyes treated under the same study protocol over the same preoperative cycloplegic refractive range of -1.00D to -3.50D cylinder. Wavefront aberrations at 3 and 6 months were analyzed up to 4<sup>th</sup>-order for the Comparison Cohort (Table 20).

Compared to Conventional eyes, CustomCornea<sup>®</sup> eyes showed:

- statistically significantly lower mean amplitudes of total RMS error, higher-order aberrations, trefoil, spherical aberration magnitude, secondary astigmatism and tetrafoil at 3 and 6 months postoperatively (t-test with unequal variance;  $p < 0.05$ ).
- greater mean decrease in total RMS error from preoperative at 3 and 6 months.
- a mean decrease in higher-order aberrations from preoperative compared to a mean increase for Conventional eyes at 3 and 6 months.

Spherical aberration value for the CustomCornea<sup>®</sup> eyes was positive preoperatively (0.235 $\mu$ m) and at 3 months (0.041 $\mu$ m) and 6 months (0.029 $\mu$ m). Similarly for the Conventional eyes, spherical aberration value was positive preoperatively (0.176 $\mu$ m) and at 3 months (0.099 $\mu$ m) and 6 months (0.112 $\mu$ m).

<b>Table 20. Mean Change in Aberrations Up to 4<sup>th</sup>-Order from Preoperative*: CustomCornea<sup>®</sup> vs. Conventional Comparison Cohort</b>					
<b>3 MONTHS</b>					
<b>Aberration</b>	<b>CustomCornea<sup>®</sup> (N=74)</b>		<b>Conventional (N=26)</b>		<b>p- Value §</b>
	<b>µm</b>	<b>%</b>	<b>µm</b>	<b>%</b>	
Total RMS Error	-1.509	-62.2	-0.990	-39.8	<b>&lt;0.0001</b>
Higher-Order	-0.060	-13.7	0.199	51.3	<b>&lt;0.0001</b>
Coma	-0.008	-3.3	0.108	55.7	0.1542
Trefoil	-0.021	-11.1	0.167	91.6	<b>&lt;0.0001</b>
Spherical Aberration Magnitude †	-0.132	-56.0	-0.016	-8.9	<b>0.0167</b>
Spherical Aberration Value ‡	-0.195	-82.8	-0.076	-43.4	0.1332
Secondary Astigmatism	0.046	62.3	0.086	98.8	<b>0.0142</b>
Tetrafoil	0.021	30.3	0.048	51.9	<b>0.0029</b>
<b>6 MONTHS</b>					
<b>Aberration</b>	<b>CustomCornea<sup>®</sup> (N=81)</b>		<b>Conventional (N=25)</b>		<b>p- Value §</b>
	<b>µm</b>	<b>%</b>	<b>µm</b>	<b>%</b>	
Total RMS Error	-1.534	-63.2	-0.985	-39.6	<b>&lt;0.0001</b>
Higher-Order	-0.053	-12.0	0.232	59.8	<b>&lt;0.0001</b>
Coma	-0.010	-3.9	0.135	69.5	0.0905
Trefoil	-0.014	-7.7	0.160	88.1	<b>0.0001</b>
Spherical Aberration Magnitude †	-0.120	-51.1	-0.008	-4.6	<b>0.0224</b>
Spherical Aberration Value ‡	-0.206	-87.5	-0.064	-36.4	<b>0.0421</b>
Secondary Astigmatism	0.047	63.4	0.091	104.3	<b>0.0272</b>
Tetrafoil	0.027	38.3	0.066	72.3	<b>0.0004</b>

RMS = Root Mean Square

Wavefront Analysis Diameter = 6.0mm

\* Positive change represents increase from preop; Negative change represents decrease from preop

† Based on absolute spherical aberration magnitude ‡ Based on signed spherical aberration value

§ t-test with unequal variance for postoperative comparison between treatment types;

p &lt; 0.05 statistically significant, shown in bold

As shown in Table 21, more eyes had a reduction in higher-order aberrations after CustomCornea<sup>®</sup> LASIK compared to after Conventional LASIK at 3 months (66.2% vs. 7.7%) and 6 months (61.7% vs. 8.0%).

Aberration	3 MONTHS		6 MONTHS	
	CustomCornea <sup>®</sup> (N=74)	Conventional (N=26)	CustomCornea <sup>®</sup> (N=81)	Conventional (N=25)
Total RMS Error	100.0%	92.3%	100.0%	96.0%
Higher-Order	66.2%	7.7%	61.7%	8.0%
Coma	55.4%	19.2%	55.6%	28.0%
Trefoil	55.4%	7.7%	51.9%	20.0%
Spherical Aberration Magnitude †	86.5%	57.7%	85.2%	52.0%
Secondary Astigmatism	21.6%	19.2%	19.8%	16.0%
Tetrafoil	32.4%	23.1%	30.9%	20.0%

RMS = Root Mean Square

Wavefront Analysis Diameter = 6.0mm

† Reduction in absolute spherical aberration magnitude

#### e. Safety Outcomes

The key safety outcomes by visit are presented in Table 22. These parameters at 3 and 6 months are also shown stratified by preoperative cycloplegic cylinder in Table 23 and by preoperative CRSE in Table 24.

No eyes had a loss of more than 2 lines of BSCVA and one eye (0.9%) had a loss of 2 lines at 1 month. All eyes had a BSCVA within 1 line of preoperative BSCVA at 3 months or later. Preoperative BSCVA was 20/25 or better for all eyes. Postoperative BSCVA was 20/32 or better at all postoperative intervals and 20/25 or better at 3 months or later.

The safety data meet the criteria established in the FDA Guidance Document of less than 5% of eyes with a loss of more than 2 lines of BSCVA, less than 1% having a BSCVA of worse than 20/40, and less than 5% having an increase in cylinder magnitude of more than 2D at all postoperative intervals.

Safety Parameters		1 MONTH	3 MONTHS	6 MONTHS	9 MONTHS
Loss of > 2 Lines BSCVA	n/N	0/110	0/110	0/110	0/108
	%	0.0%	0.0%	0.0%	0.0%
	CI	(0.0, 3.3)	(0.0, 3.3)	(0.0, 3.3)	(0.0, 3.4)
Loss of 2 Lines BSCVA	n/N	1/110	0/110	0/110	0/108
	%	0.9%	0.0%	0.0%	0.0%
	CI	(0.0, 5.0)	(0.0, 3.3)	(0.0, 3.3)	(0.0, 3.4)
BSCVA worse than 20/40	n/N	0/110	0/110	0/110	0/108
	%	0.0%	0.0%	0.0%	0.0%
	CI	(0.0, 3.3)	(0.0, 3.3)	(0.0, 3.3)	(0.0, 3.4)
Increase > 2D cylinder magnitude	n/N	0/110	0/110	0/110	0/108
	%	0.0%	0.0%	0.0%	0.0%
	CI	(0.0, 3.3)	(0.0, 3.3)	(0.0, 3.3)	(0.0, 3.4)
BSCVA worse than 20/25 if 20/20 or better preoperatively	n/N	1/94	0/94	0/94	0/92
	%	1.1%	0.0%	0.0%	0.0%
	CI	(0.0, 5.8)	(0.0, 3.8)	(0.0, 3.8)	(0.0, 3.9)

BSCVA = Best Spectacle Corrected Visual Acuity    CI = 95% Confidence Interval    D = Diopter

3 MONTHS							
Safety Parameters		-1.00 to -1.99	-2.00 to -2.99	-3.00 to -3.99	-4.00 to -4.99	-5.00 to -6.00	Total
Loss of > 2 Lines BSCVA	n/N	0/24	0/37	0/25	0/17	0/7	0/110
	%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Loss of 2 Lines BSCVA	n/N	0/24	0/37	0/25	0/17	0/7	0/110
	%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
BSCVA worse than 20/40	n/N	0/24	0/37	0/25	0/17	0/7	0/110
	%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Increase > 2D cylinder magnitude	n/N	0/24	0/37	0/25	0/17	0/7	0/110
	%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
BSCVA worse than 20/25 if 20/20 or better preoperative	n/N	0/22	0/36	0/23	0/9	0/4	0/94
	%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
6 MONTHS							
Safety Parameters		-1.00 to -1.99	-2.00 to -2.99	-3.00 to -3.99	-4.00 to -4.99	-5.00 to -6.00	Total
Loss of > 2 Lines BSCVA	n/N	0/24	0/37	0/25	0/17	0/7	0/110
	%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Loss of 2 Lines BSCVA	n/N	0/24	0/37	0/25	0/17	0/7	0/110
	%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
BSCVA worse than 20/40	n/N	0/24	0/37	0/25	0/17	0/7	0/110
	%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Increase > 2D cylinder magnitude	n/N	0/24	0/37	0/25	0/17	0/7	0/110
	%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
BSCVA worse than 20/25 if 20/20 or better preoperative	n/N	0/22	0/36	0/23	0/9	0/4	0/94
	%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

BSCVA = Best Spectacle Corrected Visual Acuity

D = Diopter

<b>Table 24. Summary of Key Safety Parameters at 3 and 6 Months Stratified by Diopter (D) of Preoperative Cycloplegic Refraction Spherical Equivalent</b>						
<b>3 MONTHS</b>						
<b>Safety Parameters</b>		<b>-1.00 to -2.00</b>	<b>0.00 to -0.99</b>	<b>+0.01 to +0.99</b>	<b>+1.00 to +2.00</b>	<b>Total</b>
Loss of > 2 Lines BSCVA	n/N %	0/8 0.0%	0/45 0.0%	0/45 0.0%	0/12 0.0%	0/110 0.0%
Loss of 2 Lines BSCVA	n/N %	0/8 0.0%	0/45 0.0%	0/45 0.0%	0/12 0.0%	0/110 0.0%
BSCVA worse than 20/40	n/N %	0/8 0.0%	0/45 0.0%	0/45 0.0%	0/12 0.0%	0/110 0.0%
Increase > 2D cylinder magnitude	n/N %	0/8 0.0%	0/45 0.0%	0/45 0.0%	0/12 0.0%	0/110 0.0%
BSCVA worse than 20/25 if 20/20 or better preoperative	n/N %	0/6 0.0%	0/41 0.0%	0/36 0.0%	0/11 0.0%	0/94 0.0%
<b>6 MONTHS</b>						
<b>Safety Parameters</b>		<b>-1.00 to -2.00</b>	<b>0.00 to -0.99</b>	<b>+0.01 to +0.99</b>	<b>+1.00 to +2.00</b>	<b>Total</b>
Loss of > 2 Lines BSCVA	n/N %	0/8 0.0%	0/45 0.0%	0/45 0.0%	0/12 0.0%	0/110 0.0%
Loss of 2 Lines BSCVA	n/N %	0/8 0.0%	0/45 0.0%	0/45 0.0%	0/12 0.0%	0/110 0.0%
BSCVA worse than 20/40	n/N %	0/8 0.0%	0/45 0.0%	0/45 0.0%	0/12 0.0%	0/110 0.0%
Increase > 2D cylinder magnitude	n/N %	0/8 0.0%	0/45 0.0%	0/45 0.0%	0/12 0.0%	0/110 0.0%
BSCVA worse than 20/25 if 20/20 or better preoperative	n/N %	0/6 0.0%	0/41 0.0%	0/36 0.0%	0/11 0.0%	0/94 0.0%

BSCVA = Best Spectacle Corrected Visual Acuity

D = Diopter

Using a standard (high-contrast) visual acuity chart, BSCVA was measured under dim room illumination (10-12 cd/m<sup>2</sup>). At least 90.9% of eyes had a gain or no change in BSCVA from preoperative at all postoperative intervals (Table 25). A trend for postoperative BSCVA gain of 1 line was observed compared to a loss of 1 line at 3 months (39.1% vs. 6.4%) and at 6 months (38.2% vs. 3.6%). While a small percentage of eyes had a BSCVA gain of 2 lines at 3 months (0.9%) and at 6 months (3.6%), no eyes had a BSCVA loss of 2 lines at 3 months or later.

		<b>1 MONTH</b>	<b>3 MONTHS</b>	<b>6 MONTHS</b>	<b>9 MONTHS</b>
Decrease > 2 Lines	n/N	0/110	0/110	0/110	0/108
	%	0.0%	0.0%	0.0%	0.0%
Decrease 2 Lines	n/N	1/110	0/110	0/110	0/108
	%	0.9%	0.0%	0.0%	0.0%
Decrease 1 Line	n/N	9/110	7/110	4/110	6/108
	%	8.2%	6.4%	3.6%	5.6%
No change	n/N	68/110	59/110	60/110	51/108
	%	61.8%	53.6%	54.5%	47.2%
Increase 1 Line	n/N	29/110	43/110	42/110	48/108
	%	26.4%	39.1%	38.2%	44.4%
Increase 2 Lines	n/N	3/110	1/110	4/110	3/108
	%	2.7%	0.9%	3.6%	2.8%
Increase > 2 Lines	n/N	0/110	0/110	0/110	0/108
	%	0.0%	0.0%	0.0%	0.0%

Low contrast BSCVA was measured using a 10% low contrast visual acuity chart under dim room illumination (Table 26). Slightly more eyes had a gain than loss of 1 line of low contrast BSCVA at 3 months (30.6% vs. 17.6%) and at 6 months (33.6% vs. 19.1%). In addition, more eyes had a gain than loss of  $\geq 2$  lines of low contrast BSCVA at 3 months (7.4% vs. 4.6%) and 6 months (8.2% vs. 2.7%).

		<b>3 MONTHS</b>	<b>6 MONTHS</b>
Decrease > 2 Lines	n/N	1/108	0/110
	%	0.9%	0.0%
Decrease 2 Lines	n/N	4/108	3/110
	%	3.7%	2.7%
Decrease 1 Line	n/N	19/108	21/110
	%	17.6%	19.1%
No change	n/N	43/108	40/110
	%	39.8%	36.4%
Increase 1 Line	n/N	33/108	37/110
	%	30.6%	33.6%
Increase 2 Lines	n/N	7/108	8/110
	%	6.5%	7.3%
Increase > 2 Lines	n/N	1/108	1/110
	%	0.9%	0.9%

Cumulative adverse events and complications reported at any postoperative visit up to 9 months in the clinical study for CustomCornea® LASIK correction of mixed astigmatism are summarized in Table 27. The data meet the safety criteria established in the FDA Guidance Document of less than 1% occurrence of each type of adverse event and less than 5% overall.

<b>Table 27. Summary of Adverse Events and Complications At Any Postoperative Visit</b>		
<b>ADVERSE EVENTS</b>	<b>n/N</b>	<b>%</b>
Miscreated flap (related to microkeratome)	2/111†	1.8%
Corneal infiltrate (related to viral epidemic keratoconjunctivitis)	1/110	0.9%
<b>COMPLICATIONS</b>		
Grade $\geq$ 1 Superficial Punctate Keratitis (SPK) at one month or later	11/110	10.0%
Epithelium in the interface	6/111†	5.4%
Diffuse lamellar keratitis (DLK)	5/110	4.5%
Pain at one month or later	2/110	1.8%
Foreign body sensation at one month or later	1/110	0.9%

† One eye did not receive laser ablation after the miscreated flap and was not included in the analysis of eyes receiving laser treatment (N=111).

There were no reports of the following adverse events and complications in the clinical study:

- corneal edema at one week or later;
- corneal epithelial defect (central or peripheral) at one month or later;
- decrease in BSCVA of more than 10 letters (> 2 lines) not due to irregular astigmatism, as shown by hard contact lens refraction at six months or later;
- epithelium in the interface with a loss of BSCVA of 2 or more lines;
- intraocular pressure increase of more than 10 mmHg above baseline;
- intraocular pressure of more than 25 mmHg;
- late onset of corneal haze at six months or later with a loss of BSCVA of 2 or more lines;
- melting of the flap;
- misaligned flap;
- retinal detachment; and
- retinal vascular accident.

f. Additional Safety Outcomes

All eyes had an IOP of  $\leq$  22 mmHg preoperatively and at all postoperative visits. There was no postoperative increase in IOP > 6 mmHg from preoperative. No corneal haze greater than mild was observed at any postoperative interval and there was no BSCVA loss of  $\geq$  2 lines associated with haze. Grade  $\geq$  1 superficial punctate keratitis or punctate erosion was reported in 10.0% of eyes at 1 month or later. No other clinically significant slit lamp findings were noted at 1 month or later that were not reported preoperatively or as an adverse event or complication. There were no clinically significant crystalline lens, vitreous or fundus findings noted postoperatively that were not present preoperatively.

## g. Contrast Sensitivity

Contrast sensitivity was measured under photopic and mesopic conditions using CSV-1000 (VectorVision<sup>6</sup>). A clinically significant change from preoperative was defined as > 2 levels (> 0.3 log units) at  $\geq 2$  spatial frequencies (Table 28).

The majority of eyes did not have a clinically significant change in contrast sensitivity from preoperative to postoperative. Of the eyes with a change in photopic contrast sensitivity, slightly fewer eyes showed a gain than loss at 3 months (2.7% vs. 6.4%) and an equal percentage of eyes (5.5%) had a gain or loss at 6 months. Under mesopic conditions, a trend for more eyes with a gain than loss of contrast sensitivity was observed at 3 months (22.4% vs. 11.2%) and at 6 months (26.2% vs. 10.3%).

In addition, a gain from preoperative was observed in the mean contrast sensitivity log at each spatial frequency under photopic and mesopic conditions at 3 and 6 months (Table 29). While no statistically significant change was observed at 3 months, statistically significant ( $p < 0.05$ ) gains were noted at 6 cycles per degree (cpd) under photopic conditions and for all spatial frequencies under mesopic conditions at 6 months.

		Photopic		Mesopic*	
		3 MONTHS	6 MONTHS	3 MONTHS	6 MONTHS
<b>Loss</b>	n/N	7/110	6/110	12/107	11/107
	%	6.4%	5.5%	11.2%	10.3%
<b>No Change</b>	n/N	100/110	98/110	71/107	68/107
	%	90.9%	89.1%	66.4%	63.6%
<b>Gain</b>	n/N	3/110	6/110	24/107	28/107
	%	2.7%	5.5%	22.4%	26.2%

Spatial Frequency (cpd)	Preop Mean $\pm$ SD	3-Month Mean $\pm$ SD	p-value <sup>†</sup>	6-Month Mean $\pm$ SD	p-value <sup>†</sup>
<b>Photopic</b>	(N=110)	(N=110)		(N=110)	
3	1.73 $\pm$ 0.15	1.75 $\pm$ 0.19	0.156	1.75 $\pm$ 0.17	0.115
6	1.92 $\pm$ 0.19	1.94 $\pm$ 0.25	0.204	1.96 $\pm$ 0.22	<b>0.018</b>
12	1.56 $\pm$ 0.25	1.56 $\pm$ 0.28	0.986	1.57 $\pm$ 0.31	0.748
18	1.09 $\pm$ 0.26	1.08 $\pm$ 0.31	0.764	1.08 $\pm$ 0.32	0.892
<b>Mesopic*</b>	(N=107)	(N=107)		(N=107)	
3	1.51 $\pm$ 0.23	1.55 $\pm$ 0.26	0.134	1.56 $\pm$ 0.24	<b>0.036</b>
6	1.48 $\pm$ 0.25	1.52 $\pm$ 0.28	0.238	1.56 $\pm$ 0.27	<b>0.009</b>
12	0.91 $\pm$ 0.32	0.98 $\pm$ 0.31	0.086	1.00 $\pm$ 0.33	<b>0.048</b>
18	0.41 $\pm$ 0.34	0.42 $\pm$ 0.36	0.749	0.50 $\pm$ 0.36	<b>0.016</b>

\*Mesopic illumination with neutral density filters in front of eyes.

† p-value from paired t-test of differences between preoperative and postoperative means;  $p < 0.05$  is statistically significant, shown in bold.

<sup>6</sup> VectorVision™ of Brain Lab AG

## h. Patient Questionnaire

Patients were asked to rate symptoms without glasses or contact lenses after surgery as compared to their recollection of symptoms before surgery, as shown in Table 30. The symptoms reported as “worse” or “significantly worse” in >10% of eyes at 6 months were dryness, light sensitivity, blurring of vision, fluctuation of vision, glare, halos, and night driving difficulty.

<b>Table 30. Postoperative Change in Subjective Symptoms without Correction vs. Preoperative*</b>					
<b>3 MONTHS (N=110)</b>					
<b>Comfort Symptoms</b>	<b>Significantly Better</b>	<b>Better</b>	<b>No Change</b>	<b>Worse</b>	<b>Significantly Worse</b>
Burning	0.0%	10.0%	86.4%	2.7%	0.9%
Dryness	3.6%	7.3%	47.3%	40.0%	1.8%
Excessive Tearing	1.8%	2.7%	95.5%	0.0%	0.0%
Gritty Feeling	3.6%	5.5%	83.6%	6.4%	0.9%
Headache	7.3%	17.3%	70.9%	4.5%	0.0%
Light Sensitivity	10.9%	7.3%	54.5%	27.3%	0.0%
Pain	4.5%	5.5%	81.8%	6.4%	1.8%
Redness	0.0%	11.8%	81.8%	4.5%	1.8%
<b>Visual Symptoms</b>					
Blurring of Vision	14.5%	17.3%	46.4%	20.0%	1.8%
Double Vision	11.8%	8.2%	71.8%	8.2%	0.0%
Fluctuation of Vision	5.5%	8.2%	62.7%	20.0%	3.6%
Glare	10.9%	10.0%	52.7%	26.4%	0.0%
Halos	8.2%	5.5%	59.1%	27.3%	0.0%
Night Driving Difficulty	21.8%	10.0%	48.2%	20.0%	0.0%
<b>6 MONTHS (N=110)</b>					
<b>Comfort Symptoms</b>	<b>Significantly Better</b>	<b>Better</b>	<b>No Change</b>	<b>Worse</b>	<b>Significantly Worse</b>
Burning	4.5%	9.1%	79.1%	6.4%	0.9%
Dryness	5.5%	6.4%	49.1%	36.4%	2.7%
Excessive Tearing	2.7%	4.5%	90.0%	2.7%	0.0%
Gritty Feeling	2.7%	5.5%	84.5%	6.4%	0.9%
Headache	9.1%	10.0%	76.4%	4.5%	0.0%
Light Sensitivity	10.9%	11.8%	54.5%	20.9%	1.8%
Pain	6.4%	4.5%	84.5%	4.5%	0.0%
Redness	3.6%	7.3%	81.8%	7.3%	0.0%
<b>Visual Symptoms</b>					
Blurring of Vision	13.6%	15.5%	49.1%	13.6%	8.2%
Double Vision	7.3%	12.7%	73.6%	4.5%	1.8%
Fluctuation of Vision	8.2%	10.0%	55.5%	21.8%	4.5%
Glare	10.0%	8.2%	68.2%	13.6%	0.0%
Halos	10.0%	3.6%	63.6%	19.1%	3.6%
Night Driving Difficulty	19.1%	19.1%	47.3%	10.9%	3.6%

\* Based on the patients' comparison of symptom severity after surgery as better or worse compared to their recollection of symptom severity before surgery.

Compared to preoperative, uncorrected quality of vision at 6 months was reported as better or significantly better in 86.3% of eyes, same in 4.5% and worse or significantly worse in 9.1% (Table 31). Satisfaction with surgery at 6 months was reported as satisfied or extremely satisfied in 73.7% of eyes, unsure in 10.9%, and unsatisfied or extremely unsatisfied in 15.4% (Table 32). Frequency of wearing distance correction at 6 months was reported as never in 81.8% of eyes and at least some of the time in 18.2% with frequent or constant use in 11.8% (Table 33).

<b>Table 31. Postoperative Quality of Vision without Correction vs. Preoperative*</b>		
	<b>3 MONTHS (N=108)</b>	<b>6 MONTHS (N=110)</b>
Significantly Better	54.6%	52.7%
Better	28.7%	33.6%
Same	7.4%	4.5%
Worse	7.4%	5.5%
Significantly Worse	1.9%	3.6%

\* Based on the patients' comparison of quality of vision after surgery as better or worse compared to their recollection of quality of vision before surgery.

<b>Table 32. Postoperative Satisfaction with Surgery</b>		
	<b>3 MONTHS (N=108)</b>	<b>6 MONTHS (N=110)</b>
Extremely Satisfied	47.2%	48.2%
Satisfied	26.9%	25.5%
Not Sure	15.7%	10.9%
Unsatisfied	6.5%	11.8%
Extremely Unsatisfied	3.7%	3.6%

<b>Table 33. Postoperative Frequency of Distance Correction</b>		
	<b>3 MONTHS (N=108)</b>	<b>6 MONTHS (N=110)</b>
Never	85.2%	81.8%
Seldom	3.7%	6.4%
Frequently	1.9%	1.8%
Constantly	9.3%	10.0%

i. Retreatment

There are insufficient data for retreatment to establish safety and effectiveness.

## j. Statistical Analysis Outcomes

Statistical analysis was performed to assess for potential associations between demographic and baseline characteristics and clinical outcomes. Age, gender, race, preoperative cycloplegic cylinder, preoperative CRSE, operative room humidity and temperature were the characteristics considered to have the most potential for clinical relevance to the procedure. Outcomes evaluated at refractive stability (3 months) and at 6 months included: BSCVA loss of  $\geq 2$  lines; UCVA of 20/20 or better and 20/40 or better; and accuracy of MRSE, manifest sphere and manifest cylinder magnitude within 0.50D and 1.00D of emmetropia.

One-sided exact binomial tests ( $\alpha=0.05$ ) were used to support the observed overall rates of safety and effectiveness outcomes to the FDA Guidance Document targets. There was no BSCVA loss of  $\geq 2$  lines at 3 and 6 months, thereby meeting the FDA target rate of  $< 5\%$  of eyes with BSCVA loss of  $> 2$  lines for safety. FDA targets were met or exceeded for effectiveness outcomes overall, including UCVA 20/40 or better and accuracy of MRSE within 0.50D and within 1.00D of emmetropia. For each baseline subgroup, the observed rate either met the target or the 95% confidence interval (CI) contained the FDA target.

To assess the consistency of outcomes across characteristics, differences in rates among subgroups were assessed using the Cochran-Mantel-Haenszel (CMH) test. No statistical significance was observed among subgroups of preoperative CRSE for any outcome. Statistically significant ( $p<0.05$ ) trends among subgroups are listed below by characteristic.

Among age subgroups by decade over a range of 20 to 60 years, higher rates were observed in younger patients as compared to older patients for the following outcomes:

- UCVA 20/20 or better at 3 months ( $p=0.0129$ ). The observed rate was  $\geq 60.0\%$  for subgroups between 20 to 49 years vs. 33.3% for 50 to 60 years. At 6 months, no statistical significance remained among age subgroups for UCVA 20/20 or better.
- UCVA of 20/40 or better at 3 months ( $p=0.0020$ ). The observed rate was 100% for subgroups between 20 to 49 years vs. 81.5% for 50 to 60 years, although the 95% CI contained the FDA target of 85%. At 6 months, no statistical significance by age remained and all age subgroups exceeded the FDA target for UCVA of 20/40 or better.
- MRSE within 0.50D at 3 and 6 months ( $p=0.0114$  and  $p=0.0056$ ). The observed rate was  $\geq 76.2\%$  at 3 and 6 months for subgroups between 20 to 49 years vs. 40.7% at 3 months and 51.9% at 6 months for 50 to 60 years with the FDA target of 50% included in the 95% CI. All age subgroups met or exceeded the FDA target for MRSE within 0.50D at 6 months.
- No statistical significance by age was observed for accuracy of MRSE within 1.00D and all age subgroups met or exceeded the FDA target for MRSE within 1.00D at 3 and 6 months. However, older patients, primarily between 40 and 60 years, were more likely to have a hyperopic MRSE of more than +1.00D at 3 and 6 months ( $p=0.0108$  and  $p=0.0013$ ). Younger patients were more likely to have a myopic MRSE of more than -1.00D at 3 and 6 months ( $p=0.0391$ ), which was observed in two eyes of a 20 year-old patient.

- Manifest sphere within 0.50D at 3 and 6 months ( $p=0.0005$  and  $p=0.0027$ ). The observed rate was  $\geq 71.4\%$  for subgroups between 20 to 49 years vs. 37.0% for 50 to 60 years.
- Manifest sphere within 1.00D at 6 months ( $p=0.0005$ ). The observed rate was  $\geq 91.4\%$  for subgroups between 20 to 49 years vs. 66.7% for 50 to 60 years. Older patients, primarily between 40 and 60 years, were more likely to have a hyperopic manifest sphere of more than +1.00D at 3 and 6 months ( $p=0.0042$  and  $p=0.0005$ ). Younger patients were more likely to have a myopic manifest sphere of more than -1.00D at 3 months ( $p=0.0391$ ), which was observed in two eyes of a 20 year-old patient.

Preoperative astigmatism was measured in subgroups by diopter of cycloplegic cylinder over a range from -1.00D to -6.00D. Eyes with lower preoperative astigmatism showed higher rates as compared to eyes with higher preoperative astigmatism for the following outcomes (observed rates at 3 and 6 months by preoperative cycloplegic cylinder are shown in Table 7):

- At 3 and 6 months, UCVA 20/20 or better ( $p=0.0404$  and  $p=0.0060$ ). All preoperative cylinder subgroups met or exceeded the FDA target for UCVA of 20/40 or better at 3 and 6 months.
- MRSE within 0.50D ( $p=0.0038$  and  $p=0.0011$ ). All preoperative cylinder subgroups met or exceeded the FDA target for MRSE within 0.50D at 3 and 6 months.
- MRSE within 1.00D ( $p=0.0304$  and  $p=0.0433$ ). All preoperative cylinder subgroups met or exceeded the FDA target for MRSE within 1.00D at 3 and 6 months.
- Manifest sphere within 1.00D at 3 months ( $p=0.0082$ ). No statistical significance based on preoperative cylinder remained for manifest sphere outcomes at 6 months. In addition, eyes with higher preoperative astigmatism were more likely to have a hyperopic manifest sphere of more than +1.00D at 3 months compared to eyes with lower preoperative astigmatism ( $p=0.0412$ ).
- Manifest cylinder magnitude  $\leq 0.50D$  at 3 months ( $p=0.0227$ ).
- Manifest cylinder magnitude  $\leq 1.00D$  at 3 and 6 months ( $p=0.0002$  and  $p=0.0012$ ).

Race was analyzed in two subgroups, 94.5% Caucasians and 5.5% other races, including Hispanic (3.6%) and Indian (1.8%). Note that apparent associations by race should be interpreted with caution because of the small sample size of six eyes in the other races subgroup. Caucasians had higher rates than other races for the following outcomes:

- MRSE within 0.50D at 3 months ( $p=0.0380$ ). The observed rate was 73.1% for Caucasians vs. two of six eyes (33.3%) in the other races subgroup, although the 95% CI contained the FDA target of 50%. At 6 months, no statistically significant difference remained by race for MRSE within 0.50D. Both subgroups met or exceeded the FDA target for MRSE within 0.50D at 6 months and for MRSE within 1.00D at 3 and 6 months.
- Manifest sphere within 0.50D at 6 months ( $p=0.0380$ ). The observed rate was 73.1% for Caucasians vs. two of six eyes (33.3%) in the other races subgroup.

- Manifest cylinder magnitude  $\leq 1.00D$  at 3 months ( $p=0.0345$ ). The observed rate was 92.3% for Caucasians vs. four of six eyes (66.7%) in the other races subgroup. At 6 months, no statistically significant difference based on race remained for manifest cylinder outcomes.

Room temperature, room humidity and gender each showed one statistically significant association with postoperative manifest sphere or manifest cylinder magnitude, as follows:

- Eyes treated in a room with a lower temperature between 65.0°F and 69.9°F showed higher rates than eyes treated in a room between 70.0°F and 74.9°F for manifest sphere within 1.00D at 3 months (97.0% vs. 83.1%;  $p=0.0467$ ).
- Eyes treated in a lower room humidity showed higher rates as compared to eyes treated in higher room humidity for manifest cylinder magnitude  $\leq 1.00D$  at 6 months ( $p=0.0450$ ). The observed rate was  $\geq 81.3\%$  for room humidity subgroups between 18% to 59% vs. 0.0% for the two eyes of one patient treated in a room humidity of 63%.
- Females showed higher rates as compared to males for manifest cylinder magnitude  $\leq 1.00D$  at 3 months (96.6% vs. 84.3%;  $p=0.0260$ ) and at 6 months (96.6% vs. 80.4%;  $p=0.0068$ ).

k. Comparative Analysis by Defocus Type

To optimize the CustomCornea<sup>®</sup> wavefront-guided LASIK treatment of mixed astigmatism, eyes were categorized as myopic or hyperopic based on the preoperative wavefront defocus error. Myopic or hyperopic components of the algorithm were used as determined by the preoperative wavefront defocus. The study included 85 eyes with a myopic defocus and 25 eyes with a hyperopic defocus based on the preoperative wavefront.

Clinical outcomes at 3 and 6 months for each preoperative wavefront defocus type were compared to established target rates for refractive surgery. In addition, outcomes were compared between myopic and hyperopic defocus types. Outcomes evaluated at refractive stability (3 months) and at 6 months included: BSCVA loss of  $\geq 2$  lines; UCVA of 20/20 or better and 20/40 or better; and accuracy of MRSE, manifest sphere and manifest cylinder magnitude within 0.50D and 1.00D of emmetropia. Postoperative outcomes of myopia or hyperopia of more than 1.00D by MRSE and manifest sphere were also evaluated.

One-sided exact binomial tests ( $\alpha=0.05$ ) were used to compare the observed overall rates of eyes meeting safety and effectiveness criteria to the FDA Guidance Document target rates. There was no BSCVA loss of  $\geq 2$  lines at 3 and 6 months for both subgroups, thereby meeting the FDA target rate of  $< 5\%$  of eyes with BSCVA loss of  $> 2$  lines for safety. Both defocus types of mixed astigmatic eyes exceeded FDA targets overall for effectiveness including for UCVA of 20/40 or better and accuracy of MRSE within 0.50D and 1.00D of emmetropia at 3 and 6 months.

To compare clinical outcomes of mixed astigmatic eyes by preoperative defocus type, the Cochran-Mantel-Haenszel (CMH) test was used to assess for differences. A  $p$ -value  $< 0.05$  would indicate a statistically significant difference in outcomes between defocus types.

Myopic and hyperopic defocus groups had outcomes that were not significantly different. Tables 34 and 35 display the comparative analysis by defocus type at 3 and 6 months.

<b>Table 34. Comparative Analysis of Mixed Astigmatic Eyes by Defocus Type at 3 Months</b>						
<b>Criteria</b>	<b>CMH P-Value*</b>		<b>Myopic Defocus</b>	<b>Hyperopic Defocus</b>	<b>Total</b>	<b>FDA Target P-Value**</b>
<b>Key Effectiveness Parameters</b>						
UCVA 20/20 or better	0.6183	n/N % CI	49/85 57.6% (46.4, 68.3)	13/25 52.0% (31.3, 72.2)	62/110 56.4% (46.6, 65.8)	--
UCVA 20/40 or better	0.2166	n/N % CI	80/85 94.1% (86.8, 98.1)	25/25 100.0% (86.3, 100.0)	105/110 95.5% (89.7, 98.5)	≥ 85% 0.9999
MRSE ± 0.50D	0.7169	n/N % CI	61/85 71.8% (61.0, 81.0)	17/25 68.0% (46.5, 85.1)	78/110 70.9% (61.5, 79.2)	≥ 50% 1.0000
MRSE ± 1.00D	0.8740	n/N % CI	79/85 92.9% (85.3, 97.4)	23/25 92.0% (74.0, 99.0)	102/110 92.7% (86.2, 96.8)	≥ 75% 1.0000
<b>Accuracy of Manifest Sphere and Cylinder</b>						
Manifest Sphere ± 0.50D	0.0417	n/N % CI	57/85 67.1% (56.0, 76.9)	22/25 88.0% (68.8, 97.5)	79/110 71.8% (62.4, 80.0)	--
Manifest Sphere ± 1.00D	0.9017	n/N % CI	74/85 87.1% (78.0, 93.4)	22/25 88.0% (68.8, 97.5)	96/110 87.3% (79.6, 92.9)	--
Manifest Cylinder Magnitude ≤ 0.50D	0.4994	n/N % CI	55/85 64.7% (53.6, 74.8)	18/25 72.0% (50.6, 87.9)	73/110 66.4% (56.7, 75.1)	--
Manifest Cylinder Magnitude ≤ 1.00D	0.1736	n/N % CI	79/85 92.9% (85.3, 97.4)	21/25 84.0% (63.9, 95.5)	100/110 90.9% (83.9, 95.6)	--
<b>Postoperative Manifest Spherical Equivalent and Manifest Sphere</b>						
Postoperative MRSE > +1.00D (Hyperopic)	0.1738	n/N % CI	6/85 7.1% (2.6, 14.7)	0/25 0.0% (0.0, 13.7)	6/110 5.5% (2.0, 11.5)	--
Postoperative MRSE < -1.00D (Myopic)	0.0088	n/N % CI	0/85 0.0% (0.0, 4.2)	2/25 8.0% (1.0, 26.0)	2/110 1.8% (0.2, 6.4)	--
Postoperative Manifest Sphere > +1.00D (Hyperopic)	0.2095	n/N % CI	11/85 12.9% (6.6, 22.0)	1/25 4.0% (0.1, 20.4)	12/110 10.9% (5.8, 18.3)	--
Postoperative Manifest Sphere < -1.00D (Myopic)	0.0088	n/N % CI	0/85 0.0% (0.0, 4.2)	2/25 8.0% (1.0, 26.0)	2/110 1.8% (0.2, 6.4)	--

\* Cochran-Mantel-Haenszel (CMH) Test with rank scores

\*\* One-sided exact binomial test comparison to the FDA target

CI = 95% Confidence Interval

UCVA = Uncorrected Visual Acuity

D = Diopter

p < 0.05 is statistically significant

MRSE = Manifest Refraction Spherical Equivalent

BSCVA = Best Spectacle Corrected Visual Acuity

<b>Table 35. Comparative Analysis of Mixed Astigmatic Eyes by Defocus Type at 6 Months</b>						
<b>Criteria</b>	<b>CMH P-Value*</b>		<b>Myopic Defocus</b>	<b>Hyperopic Defocus</b>	<b>Total</b>	<b>FDA Target P-Value**</b>
<b>Key Effectiveness Parameters</b>						
UCVA 20/20 or better	0.3687	n/N % CI	56/85 65.9% (54.8, 75.8)	14/25 56.0% (34.9, 75.6)	70/110 63.6% (53.9, 72.6)	--
UCVA 20/40 or better	0.4410	n/N % CI	83/85 97.6% (91.8, 99.7)	25/25 100.0% (86.3, 100.0)	108/110 98.2% (93.6, 99.8)	≥ 85% 1.0000
MRSE ± 0.50D	0.6279	n/N % CI	64/85 75.3% (64.7, 84.0)	20/25 80.0% (59.3, 93.2)	84/110 76.4% (67.3, 83.9)	≥ 50% 1.0000
MRSE ± 1.00D	0.8299	n/N % CI	77/85 90.6% (82.3, 95.8)	23/25 92.0% (74.0, 99.0)	100/110 90.9% (83.9, 95.6)	≥ 75% 1.0000
<b>Accuracy of Manifest Sphere and Cylinder</b>						
Manifest Sphere ± 0.50D	0.5257	n/N % CI	59/85 69.4% (58.5, 79.0)	19/25 76.0% (54.9, 90.6)	78/110 70.9% (61.5, 79.2)	--
Manifest Sphere ± 1.00D	0.1703	n/N % CI	73/85 85.9% (76.6, 92.5)	24/25 96.0% (79.6, 99.9)	97/110 88.2% (80.6, 93.6)	--
Manifest Cylinder Magnitude ≤ 0.50D	0.9485	n/N % CI	55/85 64.7% (53.6, 74.8)	16/25 64.0% (42.5, 82.0)	71/110 64.5% (54.9, 73.4)	--
Manifest Cylinder Magnitude ≤ 1.00D	0.0987	n/N % CI	78/85 91.8% (83.8, 96.6)	20/25 80.0% (59.3, 93.2)	98/110 89.1% (81.7, 94.2)	--
<b>Postoperative Manifest Spherical Equivalent and Manifest Sphere</b>						
Postoperative MRSE > +1.00D (Hyperopic)	0.1128	n/N % CI	8/85 9.4% (4.2, 17.7)	0/25 0.0% (0.0, 13.7)	8/110 7.3% (3.2, 13.8)	--
Postoperative MRSE < -1.00D (Myopic)	0.0088	n/N % CI	0/85 0.0% (0.0, 4.2)	2/25 8.0% (1.0, 26.0)	2/110 1.8% (0.2, 6.4)	--
Postoperative Manifest Sphere > +1.00D (Hyperopic)	0.1703	n/N % CI	12/85 14.1% (7.5, 23.4)	1/25 4.0% (0.1, 20.4)	13/110 11.8% (6.4, 19.4)	--
Postoperative Manifest Sphere < -1.00D (Myopic)	NA	n/N % CI	0/85 0.0% (0.0, 4.2)	0/25 0.0% (0.0, 13.7)	0/110 0.0% (0.0, 3.3)	--

\* Cochran-Mantel-Haenszel (CMH) Test with rank scores

NA = Not Applicable

\*\* One-sided exact binomial test comparison to the FDA target

CI = 95% Confidence Interval

p < 0.05 is statistically significant

UCVA = Uncorrected Visual Acuity

MRSE = Manifest Refraction Spherical Equivalent

D = Diopter

BSCVA = Best Spectacle Corrected Visual Acuity

## 1. Device Failures

There were no device failures reported for this study of mixed astigmatism. All 110 treated eyes in the Primary Cohort had complete laser ablation and were tracked throughout the ablation. There were no problems during surgery for the Primary Cohort reported related to the LADARVision®4000 System.

Two eyes had a reported problem during surgery of miscreated flap related to the microkeratome and were reported as adverse events. In both cases, the microkeratome lost suction resulting in an incomplete flap. Laser ablation was not applied to either eye at the time. One patient elected not to receive creation of a new flap and laser ablation in the study. The other patient was followed for 3 months after the miscreated flap to allow the cornea to heal and then underwent creation of a new flap and laser ablation. This patient had a routine postoperative course following the laser treatment.

## XI. CONCLUSIONS DRAWN FROM THE STUDIES

Clinical studies demonstrated that safety and effectiveness parameters fell within acceptable FDA criteria providing reasonable assurance that the device is safe and effective when used in accordance with the indications and directions for use.

The LADAR 6000™ Excimer Laser System was approved on May 1, 2006. Because this laser was found comparable to the LADARVision® 4000 Excimer Laser System based on preclinical and testing data, approval of this supplement (S22) allows the use of both laser systems for the mixed astigmatism indication.

## XII. PANEL RECOMMENDATION

In accordance with the provisions of section 515(c)(2) 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. CDRH DECISION

FDA issued an approval order on May 2, 2006.

The applicant's manufacturing facility was inspected and found to be in compliance with the Quality System Regulation (21 CFR 820).

## XIV. APPROVAL SPECIFICATIONS

- Direction for use: see labeling.
- Hazard to Health from Use of the Device: see Indications, Contraindications, Warning, Precautions, and Adverse Events in the labeling.
- Postapproval Requirements and Restriction: see Approval Order