SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Ophthalmic Excimer Laser System
Device Trade Name:	LADARVision®4000 Excimer Laser System and the LADAR*6000*™ 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/S20
Date of Notice of Approval to Applicant:	May 1, 2006

The LADARVision®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 -0.50 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 -0.50 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®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). The sponsor submitted this supplement to further expand the clinical indications to include wavefront-guided CustomCornea® LASIK for hyperopia and hyperopic 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 SSED 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.

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II. INDICATIONS FOR USE

The LADARVision®4000 Excimer Laser System and LADAR*6000*™ Excimer Laser System are indicated for wavefront-guided Laser Assisted In-Situ Keratomileusis (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 (which has a magnitude less than or equal to the sphere in minus cylinder convention) and a cycloplegic spherical equivalent up to +5.00D at the spectacle plane;
- 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[1]) or amiodarone hydrochloride (Cordarone[2]).

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® 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.

[1] Accutane Reg. TM of Hoffman-La Roche Inc.
[2] Cordarone Reg. TM of Sanofi-Synthelabo Inc.

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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 LADAR*6000*™ 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 the LADAR*6000*™ 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 applanation 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[3] (manufactured by Becton-Dickinson), Hansatome[4] (manufactured by Bausch & Lomb), and the Moria[5] CB and LSK (manufactured by Moria).

C. CustomCornea® Surgery Planning Software

The CustomCornea® Surgery Planning Software is a stand-alone computer application linking the diagnostic wavefront data with the surgical treatment on the LADARVision®4000 and LADAR*6000*™ Excimer Laser Systems. The planning software allows refinement of surgical parameters within the approved wavefront-guided indication for the LADARVision®4000 and LADAR*6000*™ Excimer Laser Systems and calculation of ablation depth.

After completing the surgery planning tasks, the planned treatment file is transferred to the LADARVision®4000 and LADAR*6000*™ Excimer Laser Systems. The LADARVision®4000 and LADAR*6000*™ Excimer Laser Systems software imports the treatment file, enforces the eligibility, calculates the excimer treatment pattern, and performs the surgery.

Software version 1.0 was used in the clinical trial. Software version 1.1 is the commercial release version.

D. LADARVision®4000 Excimer Laser System

The LADARVision®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®4000 Excimer Laser System incorporates the LADARTracker® closed-loop laser radar 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® 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, 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.

[3] *BD K-4000* TM of Becton, Dickinson and Company
[4] *Hansatome* Reg. TM of Bausch & Lomb Incorporated
[5] *Moria* Reg. TM of Moria SA

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- 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® hyperopia and hyperopic astigmatism corrections are locked out for greater than +5.00D cycloplegic spherical equivalent and greater than -3.00D cylinder. 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 LADAR*6000*™ 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^2.

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 Laser Radar 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. *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. Software version 5.2 is the commercial release version.

10. *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.

E. LADAR*6000*™ Excimer Laser System

The LADAR*6000*™ Excimer Laser System was approved on May 1, 2006. The LADAR*6000*™ 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 LADAR*6000*™ 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 LADAR*6000*™ 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 LADAR*6000*™); and,
4. Modifications to the user interface in the LADAR*6000*™ System Operation Manual.

The LADAR*6000*™ 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 LADAR*6000*™ Excimer Laser System. All specs for beam shape, fluence, and wavelength were unchanged in the LADAR*6000*™. 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 LADAR*6000*™ Excimer Laser System should not introduce any new safety or effectiveness problems regarding wavefront-guided LASIK treatment of mixed astigmatism. Therefore, the LADAR*6000*™ 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 hyperopia and hyperopic astigmatism:

Automated Lamellar Keratoplasty (ALK)
Conductive Keratoplasty (CK)
Contact Lenses
Conventional Laser In-Situ Keratomileusis (LASIK - based on phoropter refraction)
Conventional Photorefractive Keratectomy (PRK - based on phoropter refraction)
Laser Thermal Keratoplasty (LTK)
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

In general, the device has 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 LADAR*6000*™ System 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.

Please 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® LASIK correction of hyperopia and hyperopic astigmatism using the LADARVision®4000 Excimer Laser 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®4000 Excimer Laser System for wavefront-guided CustomCornea® LASIK correction of hyperopia and hyperopic 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 subject was randomly assigned CustomCornea® 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 subjects, 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 subject received wavefront-guided CustomCornea® 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 subjects 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 inclusion into the study, hyperopic subjects must have had a preoperative cycloplegic refraction at the spectacle plane of up to +6.00D sphere with up to -6.00D astigmatism (in minus cylinder convention) and up to +6.00D spherical equivalent (SE). Enrollment of hyperopic and hyperopic astigmatic eyes in the study occurred over the preoperative cycloplegic refractive range of +0.75D to +6.00D sphere with up to -5.00D astigmatism and up to +5.75D SE, where the absolute cycloplegic cylinder in minus cylinder convention was less than or equal to the sphere.

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 0.50D. 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 subject's two eyes could not differ by more than 1.00D in sphere or cylinder. In addition, subjects must have been willing to have LASIK correction in both eyes within a 2-week period. These two criteria were not applicable to subjects treated under the bilateral CustomCornea® treatment study design.

Subjects must have been at least 18 years of age and had a best-spectacle corrected visual acuity (BSCVA) of 20/25 or better in the operative eye(s). Subjects 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.

Subjects 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. Subjects 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, subjects were not to wear their contact lenses in the operative eye(s) for 2 to 3 weeks for soft and hard contact lenses, respectively.

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.

Patients with the following conditions could not be included in the study:

- previous corneal, intraocular, or strabismus surgery in the operative eye(s)
- history of or active clinically significant or vision 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 ≥7mm
- 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® treatments in the study were conducted with use of an optical zone of 6.5mm with a blend zone of 1.25mm for a total ablation zone of 9.0mm.

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® treatment in the primary eye. Under the bilateral CustomCornea® 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 is 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. Subject's signature on a separate Retreatment Informed Consent document, wherein the subject 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 subjects 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 subjective questionnaire. 21

The primary effectiveness variables for this study were improvement of uncorrected visual acuity (UCVA), predictability and stability of manifest refraction spherical equivalent (MRSE) and manifest cylinder, reduction of wavefront error, including higher-order aberrations and subject 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 for the CustomCornea® wavefront-guided hyperopia and hyperopic astigmatism LASIK study occurred between December 11, 2002 and October 14, 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. Eleven investigational sites enrolled subjects in the Primary Cohort, including ten U.S. sites and one Canadian site.

2. Demographics

The demographics of the CustomCornea® study (Table 1) were typical for a refractive surgery trial performed in the U.S. The mean subject age was 49.8 ± 9.2 years with a range from 19 to 70 years. The majority of subjects were Caucasian (95.4%) and the remaining subjects were Hispanic (2.9%) and Black (1.7%). Slightly more males (54.0%) than females (46.0%) participated in the study. The distribution of right and left eyes that received treatment was approximately equal (51.2% vs. 48.8%). While most subjects (59.5%) did not wear contact lenses prior to surgery, 37.6% wore soft contact lenses and 2.9% 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).

Table 1. Demographics

346 Eyes of 202 Enrolled Subjects

Age (In Years)			
Average ± Standard Deviation		49.8 ± 9.2	
Minimum to Maximum		19 to 70	
Race:		**N**	**% Eyes**
Black		6	1.7%
Caucasian		330	95.4%
Hispanic		10	2.9%
Gender:	Female	159	46.0%
Male		187	54.0%
Eye:	Left	169	48.8%
Right		177	51.2%
Contact Lens History:	None	206	59.5%
Rigid Gas Permeable (RGP)		10	2.9%
Soft		130	37.6%

F. Data Analysis and Results

The Primary Safety Cohort consisted of 346 eyes with a preoperative cycloplegic refractive range of +0.75D to +6.00D sphere with up to -5.00D cylinder and up to +5.75D spherical equivalent. The Primary Effectiveness Cohort consisted of 297 eyes with a preoperative cycloplegic refractive range of +0.75D to +6.00D sphere with up to -3.00D cylinder and up to +5.00D spherical equivalent (Table 2). A spherical eye was defined as having less than -0.50D preoperative cycloplegic cylinder and an astigmatic eye was defined as having at least -0.50D preoperative cycloplegic cylinder.

Table 2. Primary Safety and Effectiveness Cohorts

Cohort	N Enrolled	Preoperative Cycloplegic Refractive Range (D)		
		Sphere	Cylinder	Spherical Equivalent
Safety	346	+0.75 to +6.00	0.00 to -5.00	+0.50 to +5.75
Spherical Hyperopia	90	+0.75 to +5.00	0.00 to -0.25	+0.63 to +4.88
Hyperopic Astigmatism	256	+1.00 to +6.00	-0.50 to -5.00	+0.50 to +5.75
Effectiveness	297	+0.75 to +6.00	0.00 to -3.00	+0.50 to +5.00
Spherical Hyperopia	85	+0.75 to +5.00	0.00 to -0.25	+0.63 to +4.88
Hyperopic Astigmatism	212	+1.00 to +6.00	-0.50 to -3.00	+0.50 to +5.00

(D) = Diopter

1. Preoperative Characteristics

For the Primary Safety Cohort, the number of eyes is shown stratified by preoperative cycloplegic sphere and cylinder in Table 3 and by preoperative cycloplegic spherical equivalent and cylinder in Table 4.

Table 3. Preoperative Cycloplegic Refraction Stratified by Sphere and Cylinder: Safety Cohort

SPHERE (D)		CYLINDER MAGNITUDE (D) IN MINUS CYLINDER CONVENTION						
		0.00 to -0.49	-0.50 to -0.99	-1.00 to -1.99	-2.00 to -3.00	-3.01 to -4.00	-4.01 to -5.00	TOTAL
+0.75 to +1.99	n/N	35/346	45/346	29/346	0/346	0/346	0/346	109/346
	%	10.1%	13.0%	8.4%	0.0%	0.0%	0.0%	31.5%
+2.00 to +2.99	n/N	33/346	34/346	28/346	7/346	0/346	0/346	102/346
	%	9.5%	9.8%	8.1%	2.0%	0.0%	0.0%	29.5%
+3.00 to +3.99	n/N	10/346	25/346	18/346	6/346	0/346	0/346	59/346
	%	2.9%	7.2%	5.2%	1.7%	0.0%	0.0%	17.1%
+4.00 to +4.99	n/N	11/346	23/346	8/346	6/346	0/346	0/346	48/346
	%	3.2%	6.6%	2.3%	1.7%	0.0%	0.0%	13.9%
+5.00 to +6.00	n/N	1/346	5/346	9/346	8/346	3/346	2/346	28/346
	%	0.3%	1.4%	2.6%	2.3%	0.9%	0.6%	8.1%
TOTAL	n/N	90/346	132/346	92/346	27/346	3/346	2/346	346/346
	%	26.0%	38.2%	26.6%	7.8%	0.9%	0.6%	100.0%

(D) = Diopter

Table 4. Preoperative Cycloplegic Refraction Stratified by Spherical Equivalent and Cylinder: Safety Cohort

SPHERICAL EQUIVALENT (D)		CYLINDER MAGNITUDE (D) IN MINUS CYLINDER CONVENTION						
		0.00 to -0.49	-0.50 to -0.99	-1.00 to -1.99	-2.00 to -3.00	-3.01 to -4.00	-4.01 to -5.00	TOTAL
0.00 to +0.99	n/N	6/346	4/346	19/346	0/346	0/346	0/346	29/346
	%	1.7%	1.2%	5.5%	0.0%	0.0%	0.0%	8.4%
+1.00 to +1.99	n/N	30/346	53/346	31/346	9/346	0/346	0/346	123/346
	%	8.7%	15.3%	9.0%	2.6%	0.0%	0.0%	35.5%
+2.00 to +2.99	n/N	33/346	37/346	22/346	6/346	0/346	1/346	99/346
	%	9.5%	10.7%	6.4%	1.7%	0.0%	0.3%	28.6%
+3.00 to +3.99	n/N	9/346	21/346	10/346	5/346	2/346	1/346	48/346
	%	2.6%	6.1%	2.9%	1.4%	0.6%	0.3%	13.9%
+4.00 to +5.00	n/N	12/346	14/346	6/346	7/346	1/346	0/346	40/346
	%	3.5%	4.0%	1.7%	2.0%	0.3%	0.0%	11.6%
+5.01 to +6.00	n/N	0/346	3/346	4/346	0/346	0/346	0/346	7/346
	%	0.0%	0.9%	1.2%	0.0%	0.0%	0.0%	2.0%
TOTAL	n/N	90/346	132/346	92/346	27/346	3/346	2/346	346/346
	%	26.0%	38.2%	26.6%	7.8%	0.9%	0.6%	100.0%

(D) = Diopter

For the Primary Effectiveness Cohort, the number of eyes is shown stratified by preoperative cycloplegic sphere and cylinder in Table 5 and by preoperative cycloplegic spherical equivalent and cylinder in Table 6.

Table 5. Preoperative Cycloplegic Refraction Stratified by Sphere and Cylinder: Effectiveness Cohort

SPHERE (D)		CYLINDER MAGNITUDE (D) IN MINUS CYLINDER CONVENTION				
		0.00 to -0.49	-0.50 to -0.99	-1.00 to -1.99	-2.00 to-3.00	TOTAL
+0.75 to +1.99	n/N %	35/297 11.8%	35/297 11.8%	18/297 6.1%	0/297 0.0%	88/297 29.6%
+2.00 to +2.99	n/N %	29/297 9.8%	31/297 10.4%	22/297 7.4%	7/297 2.4%	89/297 30.0%
+3.00 to +3.99	n/N %	9/297 3.0%	25/297 8.4%	18/297 6.1%	5/297 1.7%	57/297 19.2%
+4.00 to +4.99	n/N %	11/297 3.7%	23/297 7.7%	7/297 2.4%	6/297 2.0%	47/297 15.8%
+5.00 to +6.00	n/N %	1/297 0.3%	2/297 0.7%	5/297 1.7%	8/297 2.7%	16/297 5.4%
TOTAL	n/N %	85/297 28.6%	116/297 39.1%	70/297 23.6%	26/297 8.8%	297/297 100.0%

(D) = Diopter

Table 6. Preoperative Cycloplegic Refraction Stratified by Spherical Equivalent and Cylinder: Effectiveness Cohort

SPHERICAL EQUIVALENT (D)		CYLINDER MAGNITUDE (D) IN MINUS CYLINDER CONVENTION				
		0.00 to -0.49	-0.50 to -0.99	-1.00 to -1.99	-2.00 to -3.00	TOTAL
0.00 to +0.99	n/N %	6/297 2.0%	0/297 0.0%	9/297 3.0%	0/297 0.0%	15/297 5.1%
+1.00 to +1.99	n/N %	30/297 10.1%	46/297 15.5%	26/297 8.8%	8/297 2.7%	110/297 37.0%
+2.00 to +2.99	n/N %	29/297 9.8%	35/297 11.8%	20/297 6.7%	6/297 2.0%	90/297 30.3%
+3.00 to +3.99	n/N %	8/297 2.7%	21/297 7.1%	9/297 3.0%	5/297 1.7%	43/297 14.5%
+4.00 to +5.00	n/N %	12/297 4.0%	14/297 4.7%	6/297 2.0%	7/297 2.4%	39/297 13.1%
TOTAL	n/N %	85/297 28.6%	116/297 39.1%	70/297 23.6%	26/297 8.8%	297/297 100.0%

(D) = Diopter

2. Postoperative Results

a. Accountability

Tables 7 and 8 show the accountability of the Primary Safety and Effectiveness Cohorts for this study, which was greater than 99% at all postoperative intervals.

Table 7. Accountability at Each Visit: Safety Cohort

		1 Month	3 Months	6 Months	9 Months
Total Eyes Enrolled: Primary	n	202	202	202	202
Fellow	n	144	144	144	144
Total	N	346	346	346	346
Available for Analysis:	**n**	**346**	**346**	**320**	**161**
	%	**100.0%**	**100.0%**	**92.5%**	**46.5%**
Not Eligible for Interval:	n	0	0	24	185
	%	0.0%	0.0%	6.9%	53.5%
Unavailable: Missed Visit	n	0	0	2	0
	%	0.0%	0.0%	0.6%	0.0%
Lost to Follow-up	n	0	0	0	0
	%	0.0%	0.0%	0.0%	0.0%
% Accountability= [available/(available +unavailable)]	**%**	**100.0%**	**100.0%**	**99.4%**	**100.0%**

Table 8. Accountability at Each Visit: Effectiveness Cohort

		1 Month	3 Months	6 Months	9 Months
Total Eyes Enrolled: Primary	n	175	175	175	175
Fellow	n	122	122	122	122
Total	N	297	297	297	297
Available for Analysis:	**n**	**297**	**297**	**276**	**138**
	%	**100.0%**	**100.0%**	**92.9%**	**46.5%**
Not Eligible for Interval:	n	0	0	19	159
	%	0.0%	0.0%	6.4%	53.5%
Unavailable Missed Visit	n	0	0	2	0
	%	0.0%	0.0%	0.7%	0.0%
Lost to Follow-up	n	0	0	0	0
	%	0.0%	0.0%	0.0%	0.0%
% Accountability= [available/(available + unavailable)]	**%**	**100.0%**	**100.0%**	**99.3%**	**100.0%**

b. Stability of Outcome

Stability of MRSE was analyzed as paired differences in MRSE between 1 and 3 months, between 3 and 6 months, and between 6 and 9 months. Analyses were performed for the entire Primary Effectiveness Cohort with data available at any interval and for consistent cohorts with data available at each interval over time (Table 9).

The data meet the FDA guidance document criterion of at least 95% having a change in MRSE of ≤ 1.00D between all intervals. Refractive stability was reached between 3 and 6 months with 99.6% of the eyes demonstrating a change ≤ 1.00D of MRSE; a mean change in MRSE of 0.04D ± 0.29D between 3 and 6 months with a rate of 0.01D per month; a decrease in the mean change in MRSE from 1 month to 6 months; and a 95% confidence interval (0.00, 0.07) that includes zero for the mean change between 3 and 6 months. Stability was confirmed between 6 and 9 months.

Table 9. Stability of Manifest Refraction Spherical Equivalent

Entire Cohort	**Change in MRSE Between**		**1 and 3 Months**	**3 and 6 Months**	**6 and 9 Months**
	≤ 1.00D	n/N %	294/297 99.0%	275/276 99.6%	137/138 99.3%
	Mean ± SD Change		0.09 ± 0.33	0.04 ± 0.29	0.07 ± 0.32
	95% Confidence Interval		(0.05, 0.13)	(0.00, 0.07)	(0.01, 0.12)
	Mean Change per Month		0.04	0.01	0.02
6-Month Cohort	**Change in MRSE Between**		**1 and 3 Months**	**3 and 6 Months**	
	≤ 1.00D	n/N %	274/276 99.3%	275/276 99.6%	
	Mean ± SD Change		0.09 ± 0.32	0.04 ± 0.29	
	95% Confidence Interval		(0.05, 0.13)	(0.00, 0.07)	
	Mean Change per Month		0.04	0.01	
9-Month Cohort	**Change in MRSE Between**		**1 and 3 Months**	**3 and 6 Months**	**6 and 9 Months**
	≤ 1.00D	n/N %	137/138 99.3%	137/138 99.3%	137/138 99.3%
	Mean ± SD Change		0.07 ± 0.31	0.02 ± 0.29	0.07 ± 0.32
	95% Confidence Interval		(0.02, 0.12)	(-0.02, 0.07)	(0.01, 0.12)
	Mean Change per Month		0.03	0.008	0.02

MRSE = Manifest Refraction Spherical Equivalent SD = Standard Deviation

c. Effectiveness Outcomes

The outcomes for UCVA and MRSE by visit are shown for all eyes in the Primary Effectiveness Cohort (Table 10) and by refractive type (Table 11). The effectiveness parameters are further stratified by preoperative cycloplegic refraction spherical equivalent (CRSE) at 6 months (Table 12).

Preoperatively, 33.3% of eyes had a UCVA of 20/40 or better. At 6 months, the UCVA was 20/20 or better in 59.1% of eyes, 20/25 or better in 80.8% and 20/40 or better in 95.3%. For those eyes with a preoperative best spectacle corrected visual acuity (BSCVA) of 20/20 or better, a UCVA of 20/20 or better was achieved in 62.9% of eyes at 6 months.

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Accuracy of MRSE was within 0.50D of emmetropia in 70.7% of eyes, within 1.00D in 88.4% and within 2.00D in 98.6% at 6 months. Of the eyes that did not achieve an MRSE within 1.00D of emmetropia at 6 months, 3.3% of eyes were undercorrected by >1.00D of MRSE and 8.3% of eyes were overcorrected.

Whereas the mean MRSE (-0.09D ± 0.69D) was slightly myopic at 6 months, the mean CRSE (+0.13D ± 0.64D) was slightly hyperopic but within 0.25D of the mean MRSE. Accuracy of CRSE at 6 months was within 0.50D of emmetropia in 65.6% of eyes, within 1.00D in 89.1% and within 2.00D in 99.6%. At 6 months, 6.9% of eyes were undercorrected by >1.00D of CRSE and 4.0% of eyes were overcorrected.

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 10. Summary of Key Effectiveness Parameters Over Time

All Eyes: Effectiveness Cohort		1 Month	3 Months	6 Months	9 Months
UCVA 20/20 or better if Preop BSCVA 20/20 or better	n/N	162/273	167/273	161/256	79/128
	%	59.3%	61.2%	62.9%	61.7%
	CI	(53.3, 65.2)	(55.1, 67.0)	(56.7, 68.8)	(52.7, 70.2)
UCVA 20/20 or better	n/N	162/297	168/297	163/276	81/138
	%	54.5%	56.6%	59.1%	58.7%
	CI	(48.7, 60.3)	(50.7, 62.3)	(53.0, 64.9)	(50.0, 67.0)
UCVA 20/25 or better	n/N	239/297	241/297	223/276	112/138
	%	80.5%	81.1%	80.8%	81.2%
	CI	(75.5, 84.8)	(76.2, 85.4)	(75.6, 85.3)	(73.6, 87.3)
UCVA 20/40 or better	n/N	283/297	282/297	263/276	130/138
	%	95.3%	94.9%	95.3%	94.2%
	CI	(92.2, 97.4)	(91.8, 97.1)	(92.1, 97.5)	(88.9, 97.5)
MRSE ± 0.50D of intended	n/N	191/297	193/297	195/276	90/138
	%	64.3%	65.0%	70.7%	65.2%
	CI	(58.6, 69.8)	(59.3, 70.4)	(64.9, 76.0)	(56.6, 73.1)
MRSE ± 1.00D of intended	n/N	267/297	264/297	244/276	123/138
	%	89.9%	88.9%	88.4%	89.1%
	CI	(85.9, 93.1)	(84.8, 92.2)	(84.0, 91.9)	(82.7, 93.8)
MRSE ± 2.00D of intended	n/N	293/297	294/297	272/276	137/138
	%	98.7%	99.0%	98.6%	99.3%
	CI	(96.6, 99.6)	(97.1, 99.8)	(96.3, 99.6)	(96.0, 100.0)

UCVA = Uncorrected Visual Acuity
BSCVA = Best Spectacle Corrected Visual Acuity
MRSE = Manifest Refraction Spherical Equivalent
CI = 95% Confidence Interval
D = Diopter

Table 11. Summary of Key Effectiveness Parameters Over Time: Spherical Hyperopia and Hyperopic Astigmatism

Spherical Hyperopia: Effectiveness Cohort		**1 Month**	**3 Months**	**6 Months**	**9 Months**
UCVA 20/20 or better if Preop BSCVA 20/20 or better	n/N	47/81	50/81	47/73	24/41
	%	58.0%	61.7%	64.4%	58.5%
	CI	(46.5, 68.9)	(50.3, 72.3)	(52.3, 75.3)	(42.1, 73.7)
UCVA 20/20 or better	n/N	47/85	50/85	47/76	25/44
	%	55.3%	58.8%	61.8%	56.8%
	CI	(44.1, 66.1)	(47.6, 69.4)	(50.0, 72.8)	(41.0, 71.7)
UCVA 20/25 or better	n/N	72/85	72/85	65/76	37/44
	%	84.7%	84.7%	85.5%	84.1%
	CI	(75.3, 91.6)	(75.3, 91.6)	(75.6, 92.5)	(69.9, 93.4)
UCVA 20/40 or better	n/N	85/85	83/85	75/76	44/44
	%	100.0%	97.6%	98.7%	100.0%
	CI	(95.8, 100.0)	(91.8, 99.7)	(92.9, 100.0)	(92.0, 100.0)
MRSE ± 0.50D of intended	n/N	55/85	56/85	50/76	27/44
	%	64.7%	65.9%	65.8%	61.4%
	CI	(53.6, 74.8)	(54.8, 75.8)	(54.0, 76.3)	(45.5, 75.6)
MRSE ± 1.00D of intended	n/N	79/85	79/85	70/76	42/44
	%	92.9%	92.9%	92.1%	95.5%
	CI	(85.3, 97.4)	(85.3, 97.4)	(83.6, 97.0)	(84.5, 99.4)
MRSE ± 2.00D of intended	n/N	83/85	84/85	74/76	44/44
	%	97.6%	98.8%	97.4%	100.0%
	CI	(91.8, 99.7)	(93.6, 100.0)	(90.8, 99.7)	(92.0, 100.0)
Hyperopic Astigmatism: Effectiveness Cohort		**1 Month**	**3 Months**	**6 Months**	**9 Months**
UCVA 20/20 or better if Preop BSCVA 20/20 or better	n/N	115/192	117/192	114/183	55/87
	%	59.9%	60.9%	62.3%	63.2%
	CI	(52.6, 66.9)	(53.7, 67.9)	(54.8, 69.3)	(52.2, 73.3)
UCVA 20/20 or better	n/N	115/212	118/212	116/200	56/94
	%	54.2%	55.7%	58.0%	59.6%
	CI	(47.3, 61.1)	(48.7, 62.5)	(50.8, 64.9)	(49.0, 69.6)
UCVA 20/25 or better	n/N	167/212	169/212	158/200	75/94
	%	78.8%	79.7%	79.0%	79.8%
	CI	(72.6, 84.1)	(73.7, 84.9)	(72.7, 84.4)	(70.2, 87.4)
UCVA 20/40 or better	n/N	198/212	199/212	188/200	86/94
	%	93.4%	93.9%	94.0%	91.5%
	CI	(89.2, 96.3)	(89.7, 96.7)	(89.8, 96.9)	(83.9, 96.3)
MRSE ± 0.50D of intended	n/N	136/212	137/212	145/200	63/94
	%	64.2%	64.6%	72.5%	67.0%
	CI	(57.3, 70.6)	(57.8, 71.0)	(65.8, 78.6)	(56.6, 76.4)
MRSE ± 1.00D of intended	n/N	188/212	185/212	174/200	81/94
	%	88.7%	87.3%	87.0%	86.2%
	CI	(83.6, 92.6)	(82.0, 91.4)	(81.5, 91.3)	(77.5, 92.4)
MRSE ± 2.00D of intended	n/N	210/212	210/212	198/200	93/94
	%	99.1%	99.1%	99.0%	98.9%
	CI	(96.6, 99.9)	(96.6, 99.9)	(96.4, 99.9)	(94.2, 100.0)

UCVA = Uncorrected Visual Acuity BSCVA = Best Spectacle Corrected Visual Acuity
MRSE = Manifest Refraction Spherical Equivalent CI = 95% Confidence Interval D = Diopter

Table 12. Summary of Key Effectiveness Parameters at 6 Months Stratified by Diopter (D) of Preoperative Cycloplegic Refraction Spherical Equivalent

All Eyes: Effectiveness Cohort		**0.0 to 0.99D**	**1.0 to 1.99D**	**2.0 to 2.99D**	**3.0 to 3.99D**	**4.0 to 5.0D**	**Total**
UCVA 20/20 or better if Preop BSCVA 20/20 or better	n/N	14/15	75/102	49/76	13/34	10/29	161/256
	%	93.3%	73.5%	64.5%	38.2%	34.5%	62.9%
UCVA 20/20 or better	n/N	14/15	76/106	49/80	14/39	10/36	163/276
	%	93.3%	71.7%	61.3%	35.9%	27.8%	59.1%
UCVA 20/25 or better	n/N	15/15	96/106	62/80	28/39	22/36	223/276
	%	100.0%	90.6%	77.5%	71.8%	61.1%	80.8%
UCVA 20/40 or better	n/N	15/15	105/106	76/80	34/39	33/36	263/276
	%	100.0%	99.1%	95.0%	87.2%	91.7%	95.3%
MRSE ± 0.50D of intended	n/N	15/15	89/106	52/80	20/39	19/36	195/276
	%	100.0%	84.0%	65.0%	51.3%	52.8%	70.7%
MRSE ± 1.00D of intended	n/N	15/15	103/106	71/80	29/39	26/36	244/276
	%	100.0%	97.2%	88.8%	74.4%	72.2%	88.4%
MRSE ± 2.00D of intended	n/N	15/15	106/106	79/80	39/39	33/36	272/276
	%	100.0%	100.0%	98.8%	100.0%	91.7%	98.6%
Spherical Hyperopia: Effectiveness Cohort		**0.0 to 0.99D**	**1.0 to 1.99D**	**2.0 to 2.99D**	**3.0 to 3.99D**	**4.0 to 5.0D**	**Total**
UCVA 20/20 or better if Preop BSCVA 20/20 or better	n/N	6/6	19/27	16/23	1/6	5/11	47/73
	%	100.0%	70.4%	69.6%	16.7%	45.5%	64.4%
UCVA 20/20 or better	n/N	6/6	19/29	16/23	1/6	5/12	47/76
	%	100.0%	65.5%	69.6%	16.7%	41.7%	61.8%
UCVA 20/25 or better	n/N	6/6	26/29	20/23	6/6	7/12	65/76
	%	100.0%	89.7%	87.0%	100.0%	58.3%	85.5%
UCVA 20/40 or better	n/N	6/6	29/29	23/23	6/6	11/12	75/76
	%	100.0%	100.0%	100.0%	100.0%	91.7%	98.7%
MRSE ± 0.50D of intended	n/N	6/6	24/29	15/23	1/6	4/12	50/76
	%	100.0%	82.8%	65.2%	16.7%	33.3%	65.8%
MRSE ± 1.00D of intended	n/N	6/6	29/29	23/23	4/6	8/12	70/76
	%	100.0%	100.0%	100.0%	66.7%	66.7%	92.1%
MRSE ± 2.00D of intended	n/N	6/6	29/29	23/23	6/6	10/12	74/76
	%	100.0%	100.0%	100.0%	100.0%	83.3%	97.4%
Hyperopic Astigmatism: Effectiveness Cohort		**0.0 to 0.99D**	**1.0 to 1.99D**	**2.0 to 2.99D**	**3.0 to 3.99D**	**4.0 to 5.0D**	**Total**
UCVA 20/20 or better if Preop BSCVA 20/20 or better	n/N	8/9	56/75	33/53	12/28	5/18	114/183
	%	88.9%	74.7%	62.3%	42.9%	27.8%	62.3%
UCVA 20/20 or better	n/N	8/9	57/77	33/57	13/33	5/24	116/200
	%	88.9%	74.0%	57.9%	39.4%	20.8%	58.0%
UCVA 20/25 or better	n/N	9/9	70/77	42/57	22/33	15/24	158/200
	%	100.0%	90.9%	73.7%	66.7%	62.5%	79.0%
UCVA 20/40 or better	n/N	9/9	76/77	53/57	28/33	22/24	188/200
	%	100.0%	98.7%	93.0%	84.8%	91.7%	94.0%
MRSE ± 0.50D of intended	n/N	9/9	65/77	37/57	19/33	15/24	145/200
	%	100.0%	84.4%	64.9%	57.6%	62.5%	72.5%
MRSE ± 1.00D of intended	n/N	9/9	74/77	48/57	25/33	18/24	174/200
	%	100.0%	96.1%	84.2%	75.8%	75.0%	87.0%
MRSE ± 2.00D of intended	n/N	9/9	77/77	56/57	33/33	23/24	198/200
	%	100.0%	100.0%	98.2%	100.0%	95.8%	99.0%

UCVA = Uncorrected Visual Acuity BSCVA = Best Spectacle Corrected Visual Acuity
MRSE = Manifest Refraction Spherical Equivalent CI = 95% Confidence Interval D = Diopter

A comparison of **postoperative** uncorrected visual acuity (UCVA) to **preoperative** best spectacle corrected visual acuity (BSCVA) after CustomCornea® LASIK surgery is presented in Table 13. A postoperative UCVA equal to or better than the preoperative BSCVA was achieved in 41.7% of eyes at 6 months.

Table 13. 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	0/297	1/297	0/276	0/138
	%	0.0%	0.3%	0.0%	0.0%
UCVA **1 Line Better** Than Preop BSCVA	n/N	18/297	28/297	24/276	13/138
	%	6.1%	9.4%	8.7%	9.4%
UCVA **Equal to** Preop BSCVA	n/N	93/297	86/297	91/276	49/138
	%	31.3%	29.0%	33.0%	35.5%
UCVA **1 Line Worse** Than Preop BSCVA	n/N	88/297	90/297	80/276	32/138
	%	29.6%	30.3%	29.0%	23.2%
UCVA **2 Lines Worse** Than Preop BSCVA	n/N	54/297	43/297	34/276	21/138
	%	18.2%	14.5%	12.3%	15.2%
UCVA **>2 Lines Worse** Than Preop BSCVA	n/N	44/297	49/297	47/276	23/138
	%	14.8%	16.5%	17.0%	16.7%

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

Effectiveness of astigmatic correction was evaluated at the 6-month point of stability for hyperopic astigmatic eyes. The mean percentage reduction in absolute manifest cylinder was 53.3% for all eyes with a greater percentage reduction in eyes with higher preoperative cylinder (Table 14). The mean correction ratio based on vector analysis of manifest cylinder was 1.13 for all astigmatic eyes and approximately 1.00 for eyes with -1.00D to -3.00D preoperative manifest cylinder (Table 15). Astigmatic correction by cycloplegic cylinder reflected similar trends to manifest cylinder.

Table 14. Mean Percentage Reduction of Absolute (Non-Vector) Cylinder for Hyperopic Astigmatic Eyes

6 MONTHS

Preoperative Cylinder	Manifest Cylinder		Cycloplegic Cylinder	
	N	Mean %	N	Mean %
All	198	53.3%	200	53.5%
>0.00 to < 0.50D *	7	0.0%	0	--
0.50 to < 1.00D	106	45.4%	110	41.2%
1.00 to < 2.00D	61	64.7%	67	65.6%
2.00 to 3.00D	24	74.8%	23	77.1%

* By preoperative manifest refraction, two eyes had no cylinder and seven eyes had -0.25D cylinder; by preoperative cycloplegic refraction, these 9 eyes had -0.50D or -0.75D cylinder.

Table 15. Vector Analysis for Hyperopic Astigmatic Eyes

6 MONTHS

Preoperative Cylinder	Manifest Cylinder		Cycloplegic Cylinder	
	N	Mean ± SD Correction Ratio	N	Mean ± SD Correction Ratio
ALL	198	1.13 ± 0.57	200	1.12 ± 0.47
>0.00 to < 0.50D *	7	2.39 ± 1.44	0	--
0.50 to < 1.00D	106	1.15 ± 0.56	110	1.20 ± 0.57
1.00 to < 2.00D	61	1.00 ± 0.31	67	1.02 ± 0.32
2.00 to 3.00D	24	0.99 ± 0.18	23	1.00 ± 0.14

* By preoperative manifest refraction, two eyes had no cylinder and seven eyes had -0.25D cylinder; by preoperative cycloplegic refraction, these 9 eyes had -0.50D or -0.75D cylinder.

d. Wavefront Outcomes

At 6 months, there was an average reduction in total RMS wavefront error by 63.9% and an average increase in higher-order aberrations by 23.6% from preoperative for all eyes in the Primary Effectiveness Cohort with data available at 6 months (N=261). Table 16 displays the preoperative and 6-month total wavefront error and higher-order aberrations through 6th-order for eyes with data at preoperative, 1, 3 and 6 months (6-month consistent cohort; N=256). Spherical aberration decreased in magnitude at 6 months from preoperative with a mean directional shift from positive spherical aberration (0.249µm) preoperatively towards negative spherical aberration (-0.147µm) postoperatively, as expected from a hyperopic ablation profile.

Table 16. Mean Aberrations Up to 6th-Order: 6-Month Consistent Cohort

Aberration (µm)	PREOP N = 256	6 MONTHS N = 256
Total RMS Error	2.677	1.000
Higher-Order	0.460	0.554
Coma	0.237	0.343
Trefoil	0.203	0.214
Spherical Aberration Magnitude*	0.249	0.219
Spherical Aberration Value**	0.249	-0.147
Secondary Astigmatism	0.072	0.111
Tetrafoil	0.080	0.120
Combined 5th and 6th Order	0.082	0.125

RMS = Root Mean Square Wavefront Analysis Diameter = 6.0mm

* Average based on the absolute spherical aberration magnitude

** Average based on the signed spherical aberration, reflecting a *positive* or *negative* direction

At 6 months, 99.6% of all eyes had a decrease in total RMS from preoperative and 49.0% had a decrease in higher-order aberrations, as shown in Table 17.

Table 17. Percentage of Eyes with Reduced Aberrations Up to 6th-Order From Preoperative

6 MONTHS N = 261	
Aberration	**% Eyes with Reduction in Aberrations**
Total RMS Error	99.6%
Higher-Order	49.0%
Coma	38.7%
Trefoil	47.9%
Spherical Aberration Magnitude*	61.7%
Secondary Astigmatism	29.5%
Tetrafoil	31.0%
Combined 5th and 6th Order	21.8%

RMS = Root Mean Square Wavefront Analysis Diameter = 6.0mm

* Reduction in absolute spherical aberration magnitude

Wavefront-guided CustomCornea® LASIK was compared to the baseline established for Conventional LASIK using preoperative cycloplegic phoropter refraction treated under the same study protocol. Wavefront aberrations at 6 months were analyzed up to 4th-order for comparison.

In a Comparison Cohort, CustomCornea® and Conventional eyes were analyzed over the same preoperative refractive range of +0.75D to +4.25D sphere, up to -3.00D cylinder and up to +4.00D SE. Compared to Conventional eyes, CustomCornea® eyes showed statistically significantly lower mean amplitudes of total root mean square (RMS), higher-order aberrations, coma, and trefoil postoperatively with adjustment of baseline differences (ANCOVA, $p<0.05$). Table 18 shows that on average, CustomCornea® LASIK resulted in a greater mean reduction in total RMS error (62.3% vs. 46.1%) and less induction of higher-order aberrations (8.0% vs. 29.2%) from preoperative compared to Conventional LASIK.
On average, both CustomCornea® and Conventional eyes showed a mean directional shift from positive spherical aberration preoperatively towards negative spherical aberration postoperatively, which was not statistically significant between the treatment groups.

A vision simulation program was used to model the effect of mean higher-order aberration magnitudes at 6 months after CustomCornea® LASIK versus Conventional LASIK in the Matched Cohort. The difference in image blurring is comparable to a defocus error difference of approximately one tenth of a diopter (i.e., ~0.1D for the CustomCornea® simulation and ~0.2D for the Conventional simulation).

Table 18. Mean Aberrations Up to 4th-Order from Preoperative: CustomCornea® vs. Conventional Comparison Cohort

Aberration (µm)	PREOP		6 MONTHS		p-Value†
	CustomCornea® Eyes N = 258	Conventional All Eyes N = 95	CustomCornea® Eyes N = 229	Conventional All Eyes N = 94	
Total RMS Error	2.350	2.424	0.887	1.307	**<0.0001**
Higher-Order	0.451	0.497	0.487	0.642	**<0.0001**
Coma	0.236	0.264	0.307	0.402	**0.0061**
Trefoil	0.204	0.217	0.206	0.322	**<0.0001**
Spherical Aberration Magnitude*	0.251	0.276	0.188	0.201	0.3298
Spherical Aberration Value**	0.250	0.275	-0.108	-0.127	0.1325
Secondary Astigmatism	0.071	0.086	0.106	0.122	0.2566
Tetrafoil	0.081	0.098	0.119	0.159	**0.0045**

RMS – Root Mean Square Wavefront Analysis Diameter 6.0mm

* Average based on the absolute spherical aberration magnitude

** Average based on the signed spherical aberration, reflecting a *positive* or *negative* direction

† ANCOVA for postoperative comparison between treatment types, adjusting for preoperative aberration differences; $p<0.05$ is statistically significant, shown in bold

The percentage of patients with reduced higher-order aberrations was 55.9% for CustomCornea® LASIK compared to 33.0% for Conventional LASIK (Table 19).

Table 19. Percentage of Eyes with Reduced Aberrations Up to 4th-Order from Preoperative: CustomCornea® vs. Conventional Comparison Cohort

6 MONTHS

Aberration	CustomCornea® Eyes N = 229	Conventional All Eyes N = 94
Total RMS Error	99.6%	89.4%
Higher-Order	55.9%	33.0%
Coma	42.4%	26.6%
Trefoil	49.8%	27.7%
Spherical Aberration Magnitude*	67.7%	68.1%
Secondary Astigmatism	31.4%	41.5%
Tetrafoil	32.3%	30.9%

RMS = Root Mean Square Wavefront Analysis Diameter = 6.0mm

* Reduction in absolute spherical aberration magnitude

To further evaluate the treatment types, a subgroup of subjects who underwent contralateral treatment of CustomCornea® LASIK in the primary eye and Conventional LASIK in the fellow eye were analyzed. This Contralateral Cohort had a preoperative cycloplegic refractive range of +0.75D to +4.25D sphere, up to -2.25D cylinder and up to +3.88D SE. Compared to Conventional eyes, CustomCornea® eyes in the Contralateral Cohort showed statistically significantly lower mean amplitudes of total RMS, higher-order aberrations, and trefoil postoperatively (ANCOVA, $p<0.05$). Table 20 shows that on average, CustomCornea® LASIK resulted in a greater mean reduction in total RMS error (62.2% vs. 51.2%) and less induction of higher-order aberrations (5.2% vs. 20.7%) from preoperative compared to Conventional LASIK. On average, both CustomCornea® and Conventional eyes showed a mean directional shift from positive spherical aberration preoperatively towards negative spherical aberration postoperatively, which was not statistically significant between the treatment groups.

Table 20. Mean Aberrations Up to 4th-Order from Preoperative: CustomCornea® vs. Conventional Contralateral Cohort

Aberration (µm)	PREOP		6 MONTHS		p-Value†
	CustomCornea® Eyes N = 42	Conventional Fellow Eyes N = 42	CustomCornea® Eyes N = 41	Conventional Fellow Eyes N = 41	
Total RMS Error	2.127	2.178	0.803	1.062	**0.0012**
Higher-Order	0.420	0.445	0.442	0.537	**0.0089**
Coma	0.210	0.267	0.269	0.318	0.1663
Trefoil	0.201	0.192	0.203	0.249	**0.0389**
Spherical Aberration Magnitude*	0.239	0.226	0.180	0.213	0.3158
Spherical Aberration Value**	0.237	0.223	-0.102	-0.182	0.0590
Secondary Astigmatism	0.056	0.079	0.078	0.084	0.7101
Tetrafoil	0.074	0.081	0.122	0.132	0.6563

RMS = Root Mean Square Wavefront Analysis Diameter = 6.0mm

* Average based on the absolute spherical aberration magnitude

** Average based on the signed spherical aberration, reflecting a *positive* or *negative* direction

† ANCOVA for postoperative comparison between treatment types, adjusting for preoperative aberration differences; $p<0.05$ is statistically significant, shown in bold

The percentage of patients in the Contralateral Cohort with reduced higher-order aberrations at 6 months after surgery compared to before surgery was 46.3% for CustomCornea® LASIK compared to 36.6% for Conventional LASIK (Table 21).

Table 21. Percentage of Eyes with Reduced Aberrations Up to 4th-Order from Preoperative: CustomCornea® vs. Conventional Contralateral Cohort

6 MONTHS		
Aberration	**CustomCornea® Eyes** N = 41	**Conventional Fellow Eyes** N = 41
Total RMS Error	100.0%	90.2%
Higher-Order	46.3%	36.6%
Coma	43.9%	36.6%
Trefoil	46.3%	36.6%
Spherical Aberration Magnitude*	63.4%	58.5%
Secondary Astigmatism	29.3%	43.9%
Tetrafoil	26.8%	36.6%

RMS = Root Mean Square Wavefront Analysis Diameter = 6.0mm

* Reduction in absolute spherical aberration magnitude

c. Safety Outcomes

The key safety outcomes for all 346 eyes in the Primary Safety Cohort are presented for all eyes in Table 22 and by refractive type in Table 23. These parameters are stratified by preoperative CRSE at 6 months in Table 24.

The safety data meet the criteria established in the FDA guidance document of less than 5% of eyes with a loss of >2 lines of BSCVA, less than 1% having a BSCVA of worse than 20/40, and less than 5% having induced astigmatism >2D.

A trend for early postoperative loss of ≥ 2 lines of BSCVA at 1 month with recovery over time was observed, which is consistent with trends observed previously after Conventional hyperopic LASIK surgery. All eyes except two have shown resolution of the BSCVA to within 1 line of preoperative BSCVA at a later follow-up examination. Of the two eyes with unresolved loss at 9 months, one eye improved with RGP contact lens refraction to preoperative level and the other eye had idiopathic choroidal neovascularization at 9 months, which was an adverse event unrelated to the device.

Table 22. Summary of Key Safety Parameters Over Time

All Eyes: Safety Cohort		1 Month	3 Months	6 Months	9 Months
Loss of >2 Lines BSCVA	n/N	3/346	1/346	0/320	0/161
	%	0.9%	0.3%	0.0%	0.0%
	CI	(0.2, 2.5)	(0.0, 1.6)	(0.0, 1.1)	(0.0, 2.3)
Loss of 2 Lines BSCVA	n/N	16/346	6/346	3/320	5/161
	%	4.6%	1.7%	0.9%	3.1%
	CI	(2.7, 7.4)	(0.6, 3.7)	(0.2, 2.7)	(1.0, 7.1)
BSCVA worse than 20/40	n/N	1/346	1/346	0/320	0/161
	%	0.3%	0.3%	0.0%	0.0%
	CI	(0.0, 1.6)	(0.0, 1.6)	(0.0, 1.1)	(0.0, 2.3)
Increase >2D cylinder magnitude	n/N	0/346	0/346	0/320	0/161
	%	0.0%	0.0%	0.0%	0.0%
	CI	(0.0, 1.1)	(0.0, 1.1)	(0.0, 1.1)	(0.0, 2.3)
BSCVA worse than 20/25 if 20/20 or better preoperatively	n/N	3/315	0/315	1/294	2/148
	%	1.0%	0.0%	0.3%	1.4%
	CI	(0.2, 2.8)	(0.0, 1.2)	(0.0, 1.9)	(0.2, 4.8)

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

Table 23. Summary of Key Safety Parameters Over Time: Spherical Hyperopia and Hyperopic Astigmatism

Spherical Hyperopia: Safety Cohort		1 Month	3 Months	6 Months	9 Months
Loss of >2 Lines BSCVA	n/N	0/90	0/90	0/79	0/46
	%	0.0%	0.0%	0.0%	0.0%
	CI	(0.0, 4.0)	(0.0, 4.0)	(0.0, 4.6)	(0.0, 7.7)
Loss of 2 Lines BSCVA	n/N	4/90	3/90	1/79	1/46
	%	4.4%	3.3%	1.3%	2.2%
	CI	(1.2, 11.0)	(0.7, 9.4)	(0.0, 6.9)	(0.1, 11.5)
BSCVA worse than 20/40	n/N	0/90	0/90	0/79	0/46
	%	0.0%	0.0%	0.0%	0.0%
	CI	(0.0, 4.0)	(0.0, 4.0)	(0.0, 4.6)	(0.0, 7.7)
Increase >2D cylinder magnitude	n/N	0/90	0/90	0/79	0/46
	%	0.0%	0.0%	0.0%	0.0%
	CI	(0.0, 4.0)	(0.0, 4.0)	(0.0, 4.6)	(0.0, 7.7)
BSCVA worse than 20/25 if 20/20 or better preoperatively	n/N	0/85	0/85	0/76	0/43
	%	0.0%	0.0%	0.0%	0.0%
	CI	(0.0, 4.2)	(0.0, 4.2)	(0.0, 4.7)	(0.0, 8.2)
Hyperopic Astigmatism: Safety Cohort		**1 Month**	**3 Months**	**6 Months**	**9 Months**
Loss of >2 Lines BSCVA	n/N	3/256	1/256	0/241	0/115
	%	1.2%	0.4%	0.0%	0.0%
	CI	(0.2, 3.4)	(0.0, 2.2)	(0.0, 1.5)	(0.0, 3.2)
Loss of 2 Lines BSCVA	n/N	12/256	3/256	2/241	4/115
	%	4.7%	1.2%	0.8%	3.5%
	CI	(2.4, 8.0)	(0.2, 3.4)	(0.1, 3.0)	(1.0, 8.7)
BSCVA worse than 20/40	n/N	1/256	1/256	0/241	0/115
	%	0.4%	0.4%	0.0%	0.0%
	CI	(0.0, 2.2)	(0.0, 2.2)	(0.0, 1.5)	(0.0, 3.2)
Increase >2D cylinder magnitude	n/N	0/256	0/256	0/241	0/115
	%	0.0%	0.0%	0.0%	0.0%
	CI	(0.0, 1.4)	(0.0, 1.4)	(0.0, 1.5)	(0.0, 3.2)
BSCVA worse than 20/25 if 20/20 or better preoperatively	n/N	3/230	0/230	1/218	2/105
	%	1.3%	0.0%	0.5%	1.9%
	CI	(0.3, 3.8)	(0.0, 1.6)	(0.0, 2.5)	(0.2, 6.7)

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

Table 24. Summary of Key Safety Parameters at 6 Months Stratified by Diopter (D) of Preoperative Cycloplegic Refraction Spherical Equivalent

All Eyes: Safety Cohort		**0.0 to 0.99D**	**1.0 to 1.99D**	**2.0 to 2.99D**	**3.0 to 3.99D**	**4.0 to 5.0D**	**>5.0 to 6.0D**	**Total**
Loss of >2 Lines BSCVA	n/N %	0/28 0.0%	0/117 0.0%	0/87 0.0%	0/44 0.0%	0/37 0.0%	0/7 0.0%	0/320 0.0%
Loss of 2 Lines BSCVA	n/N %	0/28 0.0%	1/117 0.9%	0/87 0.0%	1/44 2.3%	0/37 0.0%	1/7 14.3%	3/320 0.9%
BSCVA worse than 20/40	n/N %	0/28 0.0%	0/117 0.0%	0/87 0.0%	0/44 0.0%	0/37 0.0%	0/7 0.0%	0/320 0.0%
Increase >2D cylinder magnitude	n/N %	0/28 0.0%	0/117 0.0%	0/87 0.0%	0/44 0.0%	0/37 0.0%	0/7 0.0%	0/320 0.0%
BSCVA worse than 20/25 if 20/20 or better preoperative	n/N %	0/27 0.0%	0/113 0.0%	0/82 0.0%	0/38 0.0%	0/29 0.0%	1/5 20.0%	1/294 0.3%
Spherical Hyperopia: Safety Cohort		**0.0 to 0.99D**	**1.0 to 1.99D**	**2.0 to 2.99D**	**3.0 to 3.99D**	**4.0 to 5.0D**	**>5.0 to 6.0D**	**Total**
Loss of >2 Lines BSCVA	n/N %	0/6 0.0%	0/29 0.0%	0/25 0.0%	0/7 0.0%	0/12 0.0%	--	0/79 0.0%
Loss of 2 Lines BSCVA	n/N %	0/6 0.0%	0/29 0.0%	0/25 0.0%	1/7 14.3%	0/12 0.0%	--	1/79 1.3%
BSCVA worse than 20/40	n/N %	0/6 0.0%	0/29 0.0%	0/25 0.0%	0/7 0.0%	0/12 0.0%	--	0/79 0.0%
Increase >2D cylinder magnitude	n/N %	0/6 0.0%	0/29 0.0%	0/25 0.0%	0/7 0.0%	0/12 0.0%	--	0/79 0.0%
BSCVA worse than 20/25 if 20/20 or better preoperative	n/N %	0/6 0.0%	0/27 0.0%	0/25 0.0%	0/7 0.0%	0/11 0.0%	--	0/76 0.0%
Hyperopic Astigmatism: Safety Cohort		**0.0 to 0.99D**	**1.0 to 1.99D**	**2.0 to 2.99D**	**3.0 to 3.99D**	**4.0 to 5.0D**	**>5.0 to 6.0D**	**Total**
Loss of >2 Lines BSCVA	n/N %	0/22 0.0%	0/88 0.0%	0/62 0.0%	0/37 0.0%	0/25 0.0%	0/7 0.0%	0/241 0.0%
Loss of 2 Lines BSCVA	n/N %	0/22 0.0%	1/88 1.1%	0/62 0.0%	0/37 0.0%	0/25 0.0%	1/7 14.3%	2/241 0.8%
BSCVA worse than 20/40	n/N %	0/22 0.0%	0/88 0.0%	0/62 0.0%	0/37 0.0%	0/25 0.0%	0/7 0.0%	0/241 0.0%
Increase >2D cylinder magnitude	n/N %	0/22 0.0%	0/88 0.0%	0/62 0.0%	0/37 0.0%	0/25 0.0%	0/7 0.0%	0/241 0.0%
BSCVA worse than 20/25 if 20/20 or better preoperative	n/N %	0/21 0.0%	0/86 0.0%	0/57. 0.0%	0/31 0.0%	0/18 0.0%	1/5 20.0%	1/218 0.5%

BSCVA = Best Spectacle Corrected Visual Acuity D = Diopter

Best spectacle corrected visual acuity (BSCVA) was measured using a standard (high-contrast) visual acuity chart under dim room illumination (10-12 cd/m^2). All eyes had a BSCVA of 20/32 or better at 6 months. At least 73.7% of eyes at all postoperative intervals and 81.6% of eyes at 6 months had no change or a gain in BSCVA from preoperative (Table 25).

Table 25. Change in Best Spectacle Corrected Visual Acuity

		1 MONTH	3 MONTHS	6 MONTHS	9 MONTHS
Decrease >2 Lines	n/N %	3/346 0.9%	1/346 0.3%	0/320 0.0%	0/161 0.0%
Decrease 2 Lines	n/N %	16/346 4.6%	6/346 1.7%	3/320 0.9%	5/161 3.1%
Decrease 1 Line	n/N %	72/346 20.8%	63/346 18.2%	56/320 17.5%	16/161 9.9%
No change	n/N %	185/346 53.5%	184/346 53.2%	183/320 57.2%	88/161 54.7%
Increase 1 Line	n/N %	66/346 19.1%	89/346 25.7%	77/320 24.1%	50/161 31.1%
Increase 2 Lines	n/N %	4/346 1.2%	3/346 0.9%	1/320 0.3%	2/161 1.2%
Increase >2 Lines	n/N %	0/346 0.0%	0/346 0.0%	0/320 0.0%	0/161 0.0%

Low contrast BSCVA was measured using a 10% low contrast visual acuity chart under dim room illumination (Table 26). While 38.1% of eyes had no change in low contrast BSCVA from preoperative to 6 months, slightly more eyes showed a gain than loss of 1 line (25.6% vs. 22.8%) and of ≥ 2 lines (7.8% vs. 5.6%).

Table 26. Change in Low Contrast Best Spectacle Corrected Visual Acuity

		3 MONTHS	6 MONTHS
Decrease >2 Lines	n/N %	13/346 3.8%	7/320 2.2%
Decrease 2 Lines	n/N %	19/346 5.5%	11/320 3.4%
Decrease 1 Line	n/N %	71/346 20.5%	73/320 22.8%
No change	n/N %	136/346 39.3%	122/320 38.1%
Increase 1 Line	n/N %	80/346 23.1%	82/320 25.6%
Increase 2 Lines	n/N %	25/346 7.2%	22/320 6.9%
Increase >2 Lines	n/N %	2/346 0.6%	3/320 0.9%

A summary of cumulative adverse events and complications reported at any postoperative visit up to 9 months for the Primary Safety Cohort is shown 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 <5% overall.

Table 27. Summary of Adverse Events and Complications At Any Postoperative Visit

ADVERSE EVENTS	n/N	%
Corneal subepithelial infiltrate (related to viral keratoconjunctivitis)	2/346	0.6%
Follicular conjunctivitis with associated loss of > 10 letters of BSCVA	2/346	0.6%
Decrease in BSCVA >10 letters not due to irregular astigmatism as shown by hard contact lens refraction at 6 months or later	1/346	0.3%
Idiopathic choroidal neovascular membrane (unrelated to device)	1/346	0.3%
COMPLICATIONS	**n/N**	**%**
Epithelium in the interface	11/346	3.2%
Diffuse lamellar keratitis (DLK)	5/346	1.4%
Foreign body sensation at one month or later	3/346	0.9%
Filamentary keratitis	2/346	0.6%
Superficial punctate keratitis (SPK) (with medical management)	2/346	0.6%
Pain at one month or later	1/346	0.3%
Peripheral corneal epithelial defect at one month or later across keratectomy or off flap	1/346	0.3%

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

- corneal edema
- double or ghost images
- corneal epithelial defect involving the keratectomy at one month or later
- late onset of corneal haze at six months with a loss of 2 or more lines of best spectacle corrected visual acuity (BSCVA)
- epithelium in the interface with a loss of 2 or more lines of BSCVA
- melting of the flap
- miscreated flap
- misaligned flap
- intraocular pressure (IOP) of more than 25 mmHg
- IOP increase of more than 10 mmHg above baseline
- retinal detachment
- retinal vascular accident.

f. Additional Safety Outcomes

All eyes had an IOP of ≤ 23 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 ≥ 2 lines associated with haze.

Corneal and anterior segment findings that were reported at 1 month or later and were not reported preoperatively or as an adverse event or complication included: 10.1% of eyes with Grade ≥ 1 superficial punctate keratitis (SPK) or trace SPK requiring insertion of punctal plugs, and 1.2% of eyes with conjunctivitis, including viral (0.6%), bacterial (0.3%) and allergic (0.3%). There were no clinically significant crystalline lens, vitreous or fundus findings noted postoperatively that were not present preoperatively or reported as an adverse event.

g. Contrast Sensitivity

Contrast sensitivity was measured under both photopic and mesopic conditions using CSV-1000 (VectorVision[6]) (Table 28). A clinically significant change from preoperative was defined as >2 levels (>0.3 log) at two or more spatial frequencies.

Under photopic conditions, the majority of eyes (85.3%) did not have a clinically significant change from preoperative to 6 months. In addition, the percentage of eyes with a clinically significant gain or loss of photopic contrast sensitivity was approximately equal (7.2% vs. 7.5%) at 6 months. Under mesopic conditions, 67.0% of subjects had no clinically significant change at 6 months. A clinically significant gain was observed in 20.1% of eyes at 6 months, while a loss was observed in 12.9% of eyes, showing a trend for more gain than loss under mesopic conditions.

In addition, the mean log at each spatial frequency was compared for eyes with data at preoperative, 3 months and 6 months (consistent 6-month cohort, Table 29). The data reflect a mean gain in all spatial frequencies postoperatively under photopic and mesopic conditions. Statistically significant gains were noted at 6 months for all photopic spatial frequencies and for all mesopic spatial frequencies except 6 cycles per degree (cpd).

Table 28. Change of >2 Levels (> 0.3 Log) at 2 or More Spatial Frequencies

		Photopic		Mesopic*	
		3 Months	6 Months	3 Months	6 Months
Loss	n/N %	25/344 7.3%	24/319 7.5%	52/327 15.9%	40/309 12.9%
No Change	n/N %	282/344 82.0%	272/319 85.3%	198/327 60.6%	207/309 67.0%
Gain	n/N %	37/344 10.8%	23/319 7.2%	77/327 23.5%	62/309 20.1%

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

[6] *VectorVision* TM of Brain Lab AG

Table 29. Comparison of Mean Contrast Sensitivity Log by Spatial Frequency: 6-Month Consistent Cohort

Spatial Frequency (cpd)	Preop Mean ± SD	3-Month Mean ± SD	p-value†	6-Month Mean ± SD	p-value†
Photopic	N = 317	N = 317		N = 317	
3	1.70 ± 0.17	1.73 ± 0.18	**0.008**	1.76 ± 0.17	**<0.0001**
6	1.91 ± 0.18	1.94 ± 0.24	**0.042**	1.94 ± 0.21	**0.019**
12	1.53 ± 0.26	1.56 ± 0.29	0.149	1.57 ± 0.29	**0.023**
18	1.04 ± 0.29	1.06 ± 0.31	0.220	1.09 ± 0.29	**0.004**
Mesopic	N = 305	N = 305		N = 305	
3	1.48 ± 0.23	1.54 ± 0.24	**<0.0001**	1.52 ± 0.22	**0.004**
6	1.49 ± 0.28	1.51 ± 0.31	0.372	1.52 ± 0.30	0.211
12	0.89 ± 0.33	0.93 ± 0.38	0.052	0.93 ± 0.37	**0.048**
18	0.34 ± 0.35	0.38 ± 0.40	0.097	0.40 ± 0.36	**0.008**

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

h. Patient Self-Evaluation

Patients were also 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 for the Primary Effectiveness Cohort.

Table 30. Postoperative Change in Subjective Symptoms without Correction vs. Preoperative*

6 MONTHS						
Comfort Symptoms	**N**	**Significantly Better**	**Better**	**No Change**	**Worse**	**Significantly Worse**
Burning	276	9.4%	6.5%	79.3%	4.7%	0.0%
Dryness	276	9.1%	8.3%	58.0%	23.6%	1.1%
Excessive Tearing	274	4.0%	6.6%	85.8%	3.6%	0.0%
Gritty Feeling	276	6.9%	4.3%	78.3%	9.8%	0.7%
Headache	275	10.2%	10.2%	75.3%	4.4%	0.0%
Light Sensitivity	275	5.5%	16.4%	54.2%	20.0%	4.0%
Pain	276	7.2%	3.6%	85.1%	4.0%	0.0%
Redness	276	7.2%	7.2%	76.4%	8.3%	0.7%
Visual Symptoms						
Blurring of Vision	276	14.1%	16.3%	51.4%	15.2%	2.9%
Double Vision	276	7.2%	3.3%	76.1%	10.5%	2.9%
Fluctuation of Vision	276	6.9%	15.2%	56.2%	17.8%	4.0%
Glare	276	8.3%	12.3%	58.3%	18.5%	2.5%
Halos	275	9.1%	5.1%	70.2%	12.0%	3.6%
Night Driving Difficulty	276	17.0%	23.2%	46.4%	10.5%	2.9%

* Based on the patients' comparison of symptom severity after surgery to their recollection of symptom severity before surgery.

Uncorrected quality of vision at 6 months was unchanged, better or significantly better than preoperative quality of vision in 92.8% of subjects, worse in 6.5%, and significantly worse in 0.7% (Table 31). In addition, 79.7% of subjects were extremely satisfied or satisfied, 12.0% were not sure, 5.4% were unsatisfied and 2.9% were extremely unsatisfied with surgery results at 6 months (Table 32). At 6 months, 85.5% of subjects reported never wearing any distance correction (Table 33).

Table 31. Postoperative Quality of Vision without Correction vs. Preoperative

6 MONTHS N = 276	
Significantly Better	56.9%
Better	30.8%
Same	5.1%
Worse	6.5%
Significantly Worse	0.7%

Table 32. Postoperative Satisfaction with Surgery

6 MONTHS N = 276	
Extremely Satisfied	47.8%
Satisfied	31.9%
Not Sure	12.0%
Unsatisfied	5.4%
Extremely Unsatisfied	2.9%

Table 33. Postoperative Frequency of Distance Correction

6 MONTHS N = 276	
Never	85.5%
Seldom	7.6%
Frequently	2.2%
Constantly	4.7%

i. Retreatments

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. Demographic and baseline characteristics that were considered to have the most potential for clinical relevance to the procedure included age, gender, race, preoperative cycloplegic sphere, cylinder and CRSE, operative room humidity and temperature. Outcomes evaluated at refractive stability (6 months) included loss of BSCVA, UCVA and accuracy of MRSE.

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

To assess the consistency of outcomes across demographic and baseline subcategories, differences in rates among the subcategories were assessed using the Cochran-Mantel-Haenszel (CMH) test. A p-value of < 0.05 indicates statistically significant differences between demographic and baseline categories. For a loss of 2 or more lines of BSCVA at 6 months, no statistically significant differences among the demographic and baseline categories were found.

Statistically significant differences in the rates of subjects achieving a UCVA of 20/20 or better at 6 months were noted based on room temperature (p=0.0160), preoperative cycloplegic sphere (p<0.0001) and preoperative CRSE (p<0.0001). Eyes treated in a lower room temperature and eyes with lower preoperative cycloplegic sphere or lower preoperative CRSE were more likely to achieve a UCVA of 20/20 or better. No FDA target is established for UCVA 20/20 or better.

For the outcome of UCVA 20/40 or better at 6 months, statistically significant differences in the rates of subjects were observed for preoperative cycloplegic sphere (p=0.0005), cylinder (p=0.0054), and CRSE (p=0.0031). Subjects with lower preoperative cycloplegic sphere, lower preoperative cycloplegic cylinder and lower preoperative CRSE were more likely to achieve a UCVA of 20/40 or better. However, all preoperative sphere, cylinder and CRSE subgroups met or exceeded the FDA target of ≥ 85% of eyes achieving a UCVA 20/40 or better at 6 months.

Baseline categories that showed statistically significant differences in the rates of subjects achieving an accuracy of MRSE within 0.50D of emmetropia were room humidity (p=0.0433), temperature (p=0.0480), preoperative cycloplegic sphere (p<0.0001) and preoperative CRSE (p<0.0001). While there was no consistent trend in MRSE based on room humidity, subjects treated in lower room temperature were more likely to have an MRSE within 0.50D at 6 months.

Accuracy of MRSE within 0.50D was more likely in subjects with lower preoperative cycloplegic sphere and lower preoperative CRSE. In addition, all room humidity, temperature, preoperative sphere and preoperative CRSE subgroups met or exceeded the FDA target for MRSE within 0.50D at 6 months.

At 6 months, statistically significant differences were observed for an MRSE outcome within 1.00D based on room humidity ($p=0.0113$), age ($p=0.0061$), preoperative cycloplegic sphere ($p<0.0001$) and preoperative CRSE ($p<0.0001$). As noted for an MRSE within 0.50D, there was no consistent trend based on room humidity for MRSE within 1.00D and all humidity subgroups met or exceeded the FDA target. A higher percentage of older subjects were within 1.00D MRSE at 6 months compared to younger subjects; however, at least 75% of eyes within each age subgroup had an MRSE within 1.00D, meeting or exceeding the FDA target.

Preoperative latent hyperopia, particularly in younger subjects with greater accommodative reserve, may be a contributing factor to the postoperative MRSE outcome. All eyes enrolled were required to have a difference in preoperative cycloplegic and manifest sphere and cylinder of $\leq$ 1.00D. However, subjects with a difference between preoperative CRSE and MRSE of $\leq$ 0.50D were more likely to have an MRSE within 1.00D at 6 months compared to subjects with more than +0.50D of hyperopia by preoperative CRSE ($p=0.0158$). At 6 months, $\geq$ 75% of eyes with a difference of $\geq$ 0.50 or more than +0.50D had an MRSE within 1.00D, meeting or exceeding the FDA target.

Accuracy of MRSE within 1.00D was more likely in subjects with lower preoperative cycloplegic sphere and lower preoperative CRSE. For the +4.00D to +4.99D preoperative sphere range, 69.0% of eyes had an MRSE within 1.00D; however, the 95% confidence interval (52.9%, 82.4%) included the FDA target rate of at least 75% of eyes. All other preoperative sphere subcategories, including the highest sphere range of +5.00D to +6.00D, met or exceeded the FDA targets. For the +3.00D to +3.99D and +4.00D to +5.00D preoperative CRSE ranges, the observed rates for MRSE within 1.00D were 74.4% (57.9%, 87.0% CI) and 72.2% (54.8%, 85.8% CI), respectively, with 95% confidence intervals that included the FDA target. As noted for cycloplegic sphere, all other CRSE subcategories met or exceeded the FDA targets for accuracy of MRSE.

Similar associations were found between overcorrection of the MRSE by >1.00D at 6 months and baseline characteristics such as room humidity ($p=0.0057$), age ($p=0.0001$), preoperative cycloplegic sphere ($p<0.0001$) and preoperative CRSE ($p<0.0001$). Higher rates of overcorrection by more than 1.00D tended to occur in subjects treated in lower room humidity. Younger subjects, primarily less than 50 years of age, were more likely to be overcorrected than older subjects. Subjects with a difference of more than +0.50D between preoperative CRSE and MRSE were more likely to have MRSE overcorrection by more than 1.00D at 6 months ($p=0.0004$). Overcorrection was also more likely in subjects with higher preoperative cycloplegic sphere and CRSE.

Considering subjects who were undercorrected by more than 1.00D in MRSE at 6 months, statistically significant differences were noted for preoperative cycloplegic sphere (p=0.0281) and preoperative cycloplegic cylinder (p=0.0033). While undercorrection was more likely to occur in eyes with higher preoperative sphere, a trend for a greater percentage of eyes with overcorrection than undercorrection was observed with higher preoperative sphere. Higher rates of MRSE undercorrection were observed for subjects with more preoperative cylinder.

k. Surgical Issues

There were three eyes with reported problems during surgery that were unrelated to the LADARVision®4000 System, including a microkeratome-related issue during flap creation and insufficient dilation requiring administration of additional dilating drops prior to ablation. LADARVision®4000 system-related messages were recorded during the surgery for two eyes, which had no impact on the surgical treatment and no safety risk to the subject. In addition, there were seven eyes treated with a single laser system over a period of time when the video was not correctly calibrated, but there was no safety or effectiveness impact observed. At the last reported visit, all eyes had an uncorrected visual acuity (UCVA) of 20/25 or better and a BSCVA of 20/20 or better, which was equal to or better than the preoperative BSCVA. Postoperatively, none of the eyes had a loss of 2 or more lines of BSCVA or a reported complication or adverse event.

No device malfunctions were reported.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

Clinical studies provided reasonable assurance of safety and effectiveness of the LADARVision®4000 Excimer Laser System for wavefront-guided Laser In-Situ Keratomileusis (LASIK) correction of hyperopia and hyperopic astigmatism 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 bench testing data, approval of this supplement (S20) allows the use of both laser systems for the hyperopia and hyperopic astigmatism indications.

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 was found to be in compliance with the Quality System Regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

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