SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Ophthalmic Excimer Laser System (193 nanometer laser wavelength)
Device Trade Name:	Dishler Excimer Laser System (Model A - Serial #: DSH-99-A and Model B - Serial #: DSH-99-B)
Applicant's Name and Address:	Jon G. Dishler, M.D., F.A.C.S. DTC Eye Surgery Center/Laser Institute of the Rockies 8400 East Prentice Avenue, Suite 1200 Englewood, Colorado

Premarket Approval (PMA) Application: P970049

Date of Notice of Approval to Applicant: December 16, 1999

II. INDICATIONS FOR USE

This device is indicated to perform Laser in-situ Keratomileusis (LASIK):

1. in patients 21 years of age or older in treatments for the reduction or elimination of myopia (nearsightedness) from -0.5 to -13.0 diopters (D) MRSE (manifest refraction spherical equivalent) with or without -0.5 D to -4.0 D astigmatism; and,

2. in patients with documented evidence of changes in manifest refraction of less than or equal to 0.5 D (in both cylinder and sphere components) per year for at least one year prior to the date of preoperative examination.

III. CONTRAINDICATIONS

Do not use this device on patients with the following:

- diagnosed autoimmune disease, uncontrolled vascular disease, or immunodeficiency diseases;
- signs of keratoconus;
- Fuchs' corneal dystrophy or other significant central corneal pathology;
- lactating or who are known to be pregnant;
- history of long-term use of oral or injected steroids (such as prednisone), drugs to prevent organ transplant rejection, anti-cancer drugs, or other drugs which affect wound healing; or,
- taking one or more of the following medications: isotretinoin (Accutane™), amiodarone hydrochloride (Cordarone™), and/or sumatriptan succinate (Imitrex™).

IV. WARNINGS AND PRECAUTIONS

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

V. DEVICE DESCRIPTION

The Dishler Excimer Laser System is available in two models: A and B. Model A was technologically upgraded to the same specifications as Model B for the treatment of myopia and myopic astigmatism. The energy output and delivery mechanism for both models are the same, except that the laser beam delivery heads for the two models are designed as mirror images of each other.

Each model of the Dishler Excimer Laser system consists of a Lambda Physik COMPex 201 excimer laser, optical lens system, beam shaping apparatus, computer control system, and the patient treatment chair. The function of the device is to perform ablation of corneal tissue for correction of refractive errors. The desired lens correction information is entered into the computer, which controls the laser beam size and delivered energy density during the ablation process. When the eye is properly positioned, the operator uses a foot pedal to activate the laser and ablate the corneal tissue to achieve the desired lens correction.

The Dishler Excimer Laser System consists of the following components:

- Excimer Laser System

- Gas Management System
- Laser Beam Delivery System
- Patient Management System
- Computer Control and Software System

Each of these systems is described in more detail below and also in the Operator's Manual.

EXCIMER LASER

The commercially available embedded Lambda Physik COMPex 201 excimer laser is air-cooled and uses argon fluoride (ArF) as the halogen source to produce a beam of 193 nm in wavelength. The excimer laser beam emitted from the treatment aperture has the following specifications:

Wavelength	193 nm
Maximum Peak Power	1×10^6 W
Maximum Average Power	200 mW
Pulse Duration	10-30 ns
Pulse Rise Time	5 ns
Pulse Fall Time	7 ns
Maximum Pulse Rate Frequency	10 Hz
Integrated Radiance	12 J/(cm^2 sr)
Beam divergence	4°

Maximum voltage used to charge the laser capacitors is 30 KV. For myopia, the laser is run at 10 Hz but the voltage is reduced to 85% of maximum.

GAS MANAGEMENT SYSTEM

The laser system uses the Lambda Physik Halosafe Fluorine system as described in the Operating Manual. Compressed gases in the laser room are stored in an approved gas containment cabinet. The cabinet is vented to the outside so it cannot leak into the treatment room in the event a leak or explosion occurs.

LASER BEAM DELIVERY SYSTEM

The emission from the embedded laser passes through a safety shutter, spatial filter, image rotator, beam shaping optics, scanning optics, fluence control focusing optics, and finally is reflected downward into the working region. Beam shaping optics are used to produce a clean laser beam with the required collimation; a beam homogenizer is used to

make the ablation profile circularly symmetric; and, focusing optics are used to ensure that the energy density at the target location is at the optimum level for tissue ablation.

An operating foot pedal is depressed to allow the emission of laser radiation when proper positioning is achieved. The laser device emits its beam from the underside of a beam delivery arm and this beam is directed towards the floor. The system computer controls the operation of the laser, shutter, and beam shaping optics. An attached laser pulse energy meter is used to verify that the laser pulse energy is at the desired level and to verify that pulse to pulse variations in this energy are at an acceptable level. This pulse energy meter automatically extends into the laser beam in the working region prior to each use of the device. Failure of the system to deliver acceptable energy and stability prevents the use of the device.

PATIENT MANAGEMENT SYSTEM

Components in this category include a pair of HeNe alignment lasers which are used for proper positioning of the eye to be treated; a microscope which is used to allow the operator to view the relative position of the alignment lasers and the eye to be treated; an illumination system for proper lighting during the keratectomy and surgical procedure; a vacuum system to suction away smoke and fumes generated at the ablation site; a medical video system and a wall-mounted monitor for adequate visualization of the procedure by all personnel; and, a patient chair.

COMPUTER CONTROL AND SOFTWARE SYSTEM

The computer control system is a commercially available IBM equivalent PC. The computer board is an analog device, which provides analog to digital communications between the CPU and the controller units for laser parameter functioning. The computer control system is also used to generate the desired treatment plan.

REGULATIONS

The Dishler Excimer Laser System contains a Class IV laser. The company provided information on the device to FDA in conformance with FDA 21 CFR § 1040.10 and 1040.11 Radiologic Health requirements. Components selected for use in the system meet the following safety standards:

- DIN 57836 and VDR 0836 for electrical safety
- CE label
- GS label, indicating the following standards:
  - DIN VDE 0837 (IEC 825)
  - VBG 93
  - DIN 57836 (VDE 0836)
- C22-2 No. 125.

MICROKERATOME

The LASIK procedure requires the use of a commercially available microkeratome that has been cleared for marketing via premarket notification. The device used in this study consists of the head, a suction ring, handle, wrenches, shaft, motor, handpiece, disposable blades, and power supply with footswitches and power cords. The applanation lens set, tonometer, optical zone marker, spatula, and digital thickness gauge are provided as separate components which complete the system.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative methods for correcting nearsightedness with or without astigmatism are spectacles, contact lenses, or refractive surgery. Refractive surgery methods include: photorefractive keratectomy (PRK), automated lamellar keratoplasty (ALK), radial keratotomy (RK), and astigmatic keratotomy (AK).

VII. MARKETING HISTORY

One unit of each of the two models of the Dishler Excimer Laser System was assembled at DTC Eye Surgery Center/Laser Institute of the Rockies for use at that single site. No other units of the laser have been assembled or manufactured..

VII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse reactions associated with LASIK include: loss of best spectacle corrected visual acuity, 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, corneal erosion, problems associated with the flap including a lost, misplaced or misaligned flap, retinal detachment, and retinal vascular accidents. For information on specific adverse events observed in the study, please refer to pages 19 through 25, within the Clinical Study Section.

IX. SUMMARY OF PRECLINICAL STUDIES

Nonclinical laboratory studies were performed to evaluate the fluence, pulse stability, fluence control, beam and eye alignment systems, software validation, profilometry of acrylic test pieces, and comparability of Model A and Model B. In addition, animal studies were conducted to evaluate the effect of varying fluence on wound healing and haze formation in rabbit eyes and to accurately measure the ablation rate of corneal tissue versus fluence in bovine eyes. These studies provided evidence to support the conclusion

that the device did not present unreasonable risk to subjects and could proceed to clinical trials under an approved investigational device exemption (IDE).

FLUENCE CALIBRATIONS

Chiron Fluence Test Plates: Chiron test plates, consisting of multiple thin layers having different colors, were ablated. As the layers are ablated by the laser, a ring pattern is formed on the plate. These rings give a qualitative view of the laser beam profile.

Acrylic Test Blocks: An acrylic test piece approximately 1.5 inches square was positioned at the location where the alignment lasers cross. A treatment procedure identical to the procedure for an actual patient was applied to the test piece, using a correction of -10 diopters. The power of the lens formed in each of the acrylic test pieces was measured using a lensometer (Humphrey Instrument Inc. Model 350 Lens Analyzer). The acrylic plastic is standardized to yield 85% of the desired correction because of the difference in ablation rates between the plastic pieces and human corneal tissue. Thus, the acceptance criteria (85% of desired) is a resulting lens of between -8.25 and -8.75 diopters. The power of the lens formed in each of the acrylic test pieces was measured with a lensometer and found to be within 5% of the requested correction. The test pieces were also examined in a traveling microscope to determine the quality of the ablation pattern.

Sensor Physik Cards: The sensor cards were exposed to single laser pulses and then analyzed using a sensor card scanner to give the beam profile. The test samples subsequently were also visually inspected for any type of distortion or defect. The beam profile was found to be within acceptable limits using the Sensor Physik cards.

External Energy Meter: Energy Measurements were made by opening the beam shaping aperture to a fixed diameter and measuring three series of laser pulses delivered to the target through the aperture with the externally attached pulse energy meter. The laser was allowed to warm up with 200 pulses before the pulse energy meter extended into the target region. The laser then fired 200 pulses in 20 seconds, with the shutter set so that only every 10th pulse fired (1 pulse per second) reached the energy detector. Two additional repetitions were performed. Each set of 20 pulses was statistically analyzed and the standard deviation calculated for each set and between each of the three sets. The overall fluctuation was found to be less than 5%.

Serial Fluence Measurements: The laser system was calibrated seven times at 5 minute intervals (0, 5, 10, 15, 20, 25, and 30 minutes). During each calibration procedure, three sets of 20 pulses (60 pulses total) were measured. For each set of 20 pulses, the average and standard deviation were calculated. The value of the standard deviations and the variation between the three measurements were checked to ensure that the laser was providing energy stable pulses. The maximum and minimum average values for the seven calibration ranged between 42.1 and 43.21 mJ over the 30 minute period. Energy calibrations performed within 30 minutes of the surgery are valid for at least 30 minutes.

HOMOGENEITY TESTING

Acrylic Test Pieces: Polymethyl methacrylate (PMMA) acrylic test pieces were ablated with the laser and the ablation patterns on the test pieces were visually inspected under a slit lamp microscope. The power of the lens produced by the ablation was measured with a lensometer. The laser beam appeared to uniformly ablate the test pieces.

Chiron Test Blocks: The laser was placed in PTK (test) mode, which opens the aperture to a 7 mm zone size. The crosshairs were placed over an unused portion of the test block and pulses from the laser beam were fired into the test block until break-through occurred. The homogeneity of the beam was determined by counting the number of pulses required for breakthrough ablation between the first and last portions of the fluence plate to be ablated. At a fluence of 180 mJ/cm^2, approximately 55 laser pulses were required to break through in the center of the treatment zone. As designed, central breakthrough occurred 3 to 4 pulses before the periphery with complete breakthrough in the periphery achieved after 1 to 2 additional pulses. The ablation profile was found to be very uniform with only about 4% peak to valley variation.

PULSE STABILITY

The pulse energy of the embedded COMPex 201 Laser engine, measured at two separate excitation voltages, has a standard deviation of 2.4%. This specification includes all components of variability for the laser's output energy.

An external energy meter was used to verify that the laser pulse energy is at the desired level and to verify that pulse to pulse variations in this energy were at an acceptable level. Three sets of 20 pulses were measured by the energy detector and statistically analyzed. The standard deviation calculated for each set and between each of the three sets had an overall fluctuation of less than 5%.

The output pulse from the energy meter was also sent into a circuit which measured the peak electrical pulse height. An interface card in the computer digitized this value to give a numerical energy value. Normal operation is in the range of 20-40 mJ. Testing confirmed that the pulse energy was within this range.

FLUENCE CONTROL

Calibration testing was performed to correlate the diameter of ablation with the each position of the lenses that magnify or minimize the beam so that fluence is maintained at a constant 180 mJ/cm^2. The lenses were translated to specific positions and a series of test blocks were ablated. The diameter of the burns were accurately measured to within 0.1 mm and the fluence was calculated. The non-uniformity of the laser ablation was measured as a function of declining output energy. From these measurements, it was determined that the minimum energy required to generate a high quality ablation is 20 mJ.

BEAM AND EYE ALIGNMENT SYSTEMS

To check alignment, fluence plates were ablated with a 0.5 mm diameter laser beam focused in the center of the crosshair and with the aiming beams also centered on the crosshair. This procedure was repeated with a 4.0 mm beam to assure that there are no alignment differences between a small and large beam.

SOFTWARE VALIDATION (MODEL A AND MODEL B)

Version 9.1 (release date 1/12/99) is the current version of the software that is used in both Model A and Model B. This software underwent a comprehensive software validation, which included tests of system calibration, profile testing, and device function. No critical faults were identified during the testing. These tests verified the software requirements for the device as well as specific unit functions.

PROFILOMETRY OF ACRYLIC TEST PIECES

The ablation profiles of several plastic samples were measured using a white light interferometer (Red Cone Research) to determine the shape of corneal ablations produced by the Dishler Excimer Laser at the minimal, nominal, and maximal dioptric ranges for myopia and myopic astigmatism. These ablations in PMMA were then compared with the theoretical ablation pattern. The profilometry data obtained from the white light interferometer showed that the achieved ablation patterns in PMMA closely matched the theoretical ablation patterns across the entire dioptric range for myopia and myopic astigmatism.

COMPARABILITY TESTING OF MODEL A AND MODEL B

The following parameters were tested: (1) beam system uniformity; (2) fluence using acrylic test pieces and external energy measurements; and (3) profilometry. Using the external energy meter and acrylic test pieces, the fluence measurements for Model A and Model B were found to be equivalent and met the required specifications. Homogeneity testing showed that both Model A and Model B produced ablations in test block that were equivalent. At a fluence of 180 mJ/cm^2, both lasers show the same breakthrough pattern in Chiron test blocks. Profilometry testing was completed for the minimal, nominal, and maximal ranges of myopia and myopic astigmatism. There were no differences in any of the ablation patterns generated by Model A and Model B.

ANIMAL STUDIES

EFFECT OF VARYING FLUENCE ON WOUND HEALING AND HAZE FORMATION IN RABBIT EYES

The primary objectives of these two rabbit studies were to confirm that the laser system could produce refractive keratectomies that heal without significant corneal opacity and determine an optimum fluence.

The shape of a rabbit eye was changed with a prototype excimer laser system to show that a refractive change could be made. In a series of experiments, ablations were

performed in rabbit eyes at 3 different laser fluences to determine the effect on wound healing and corneal haze.

In the first series of rabbits, ablations in a 5 mm keratectomy were performed in 3 rabbit eyes for each of the three laser fluences tested (110, 180, and 250 mJ/cm^2). A prototype to the Dishler Excimer Laser was used to perform the ablations. Rabbits were inspected weekly for 12 weeks, then at longer intervals thereafter. In the second experiment, 8 rabbits were given 5.0 mm diameter keratectomies designed to correct myopia of either 3.0, 5.5, or 8.0 diopters using a laser fluence of either 110, 180, or 250 mJ/cm^2. Saline was instilled onto the corneal surface immediately following ablation to avoid drying. Calculated topography of the keratectomy site was performed weekly.

In the first study, the epithelium had completely recovered by 72 hours in all cases and by 48 hours in many cases. Some corneal haze developed within 1 to 2 weeks after ablation, with maximal intensity at 3 to 5 weeks and gradual complete clearing by the fifteenth week. The length of time the dry cut surface was left exposed to air influenced the density of haze formation. The fluence and ablation depth could not be correlated directly with haze formation.

In the second experiment, there appeared to be a linear improvement in haze levels with increasing fluence; however, later experiments showed that haze development was correlated with exposure to air and drying effects but not directly with fluence. The topographies for weeks 4 to 18 were very similar for each eye, with stability being achieved after 4 weeks of healing.

These experiments confirmed that the excimer laser system could create a refractive change in the cornea without significant loss of corneal transparency. The level of haze formed correlated with the length of time the ablated surface was left exposed to air but did not correlate with ablation depth or laser fluence. The refractive change appeared to be stable after four weeks of healing in the rabbits. The necessity of keeping the ablated surface moist was an important finding with regard to the surgical technique.

X. SUMMARY OF CLINICAL STUDIES

The sponsor performed a clinical study of the Dishler Excimer Laser System in the US under the auspices of an IDE G970015. The data from this study served as the basis for the approval decision. Specifically, safety and effectiveness outcomes at 6 months postoperative were assessed as stability is reached by that time. Outcomes at 12 months postoperatively were also evaluated for confirmation. The IDE study is described in detail as follows.

A. STUDY OBJECTIVES

The overall reason for the LASIK procedure was defined by this treatment goal: to evaluate the clinical efficacy and safety of the Dishler Excimer Laser in patients having LASIK for their refractive error consisting of myopia with or without astigmatism. Laser A and Laser B were both used in the clinical study.

B. STUDY DESIGN

The study was a prospective, non-randomized study where the primary control was the preoperative state of the treated eye *(i.e.*, comparison of pretreatment and post-treatment visual parameters in the same eye).

C. INCLUSION AND EXCLUSION CRITERIA

Enrollment in the Dishler Excimer Laser study was limited to patients who were at least 18 years of age; had a refractive error consisting of physiological myopia with or without astigmatism and a spherical equivalent between -1.0 to -24 D (the maximum amount of treatable astigmatism was -7 D and the amount of astigmatism could be no greater than 50% of the spherical equivalent); had a stable refraction (less than 0.50 D change in sphere and 0.50 D in cylinder) for the last 12 months, as documented by previous records or measurement of old glasses; had best spectacle corrected visual acuity (BSCVA) of at least 20/40 in both eyes; agreed to consent to undergo LASIK and signed a written informed consent form as well as return for all follow-up examinations for up to 2 years after surgery.

Patients were not permitted to enroll in the Dishler Excimer Laser study if they met any of the following exclusion criteria: a history of herpes keratitis (herpes simplex/herpes zoster) or other eye or systemic infection; any significant anterior segment pathology; ophthalmoscopic signs of progressive or unstable myopia or keratoconus; residual, recurrent, or active ocular disease; had undergone previous intraocular surgery; were blind in the fellow eye; required cataract surgery currently or in the foreseeable future; were diabetic or had diagnosed autoimmune disease, systemic connective tissue disease, or atopic syndrome; were taking chronic systemic corticosteroid or other immunosuppressive therapy, or were otherwise considered to be immunocompromised; had a history of keloid scar

formation; were allergic to any medications required during the surgical procedure or postoperatively; had unstable central keratometry readings with irregular mires; had a history of glaucoma or an intraocular pressure reading above 25 mm Hg (Patients with an intraocular pressure between 22 and 25 mm Hg were evaluated by a glaucoma specialist to confirm that the patient was not at risk for glaucoma.); or, if female, were lactating or known to be pregnant.

D. STUDY PLAN, PATIENT ASSESSMENTS, AND EFFICACY CRITERIA

All patients were expected to return for follow-up examinations: at 1 day, 1 week and 1, 3, 6, and 12 months postoperatively. Although the study plan was originally designed to include a 24 month follow-up examination, FDA approved the firm's request to modify the follow-up period to 12 months at the time of approval of the PMA application.

Patients were permitted to have bilateral treatment of their eyes. In addition, patients were eligible for retreatment if patients had an uncorrected visual acuity of 20/40 or worse; and, the eye had a stable refraction before undergoing the retreatment procedure. Retreatment was not permitted until at least 3 months after the initial treatment.

Preoperatively, the subject's medical and ocular histories were recorded. Immediately postoperative, re-epithelialization data were collected. The objective parameters measured during the study included: best spectacle corrected visual acuity (near, distance, with and without glare), uncorrected visual acuity (near and distance), manifest and cycloplegic refraction, central keratometry, intraocular pressure (by applanation), and pupil size. In addition, slit lamp and dilated fundus examinations were performed; computerized corneal topography and central pachymetry were completed. A patient questionnaire was to be administered to all patients preoperatively and postoperatively at 3, 6 and 12.

The primary efficacy variables for this study were: improvement of near or distance uncorrected visual acuity (UCVA) and best corrected visual acuity (BCVA) based on the per eye treatment goal of the procedure, and predictability of manifest refraction spherical equivalent (MRSE).

E. STUDY PERIOD, INVESTIGATIONAL SITES, AND DEMOGRAPHICS

1. STUDY PERIOD AND INVESTIGATIONAL SITES

Patients were treated between May 1, 1997 and July 31, 1999. The database for this PMA reflected data collected through January 12, 1999 and included 839 eyes: 433 first eyes and 406 second eyes. There was one investigational site.

2. DEMOGRAPHICS

The demographics of this study are typical for a contemporary refractive surgery trial performed in the US. Of the 839 treated eyes, 40.9% (343/839) were from male patients and 59.1% (496/839) from female patients. Race and contact lens histories were not recorded in the investigator's database and were not available for analysis. The right eye was treated in 50.2% (421/839) cases and the left eye was treated in 49.8% (418/839) cases. The mean age of the patients treated was 41 years with a range from 19 to 64.

Table 1: Demographic Characteristics (839 Eyes of 438 Patients)

Characteristic		Eyes Treated for Sphere Only		Eyes Treated for Spherocylinder		All Eyes	
		n/N N = 367	%	n/N N = 472	%	n/N N = 839	%
GENDER	Female	224	61.0	272		496	59.1
	Male	143	39.0	200		343	40.9
EYES	Right	195	53.1	226		421	50.2
	Left	172	46.9	246		418	49.8
AGE	Mean	40.0		41.7		41.0	
	Std. Dev.	8.8		8.5		8.7	
	Median	40.0		42.5		41.0	
	Minimum	19.0		20.0		19.0	
	Maximum	63.0		64.0		64.0	

F. DATA ANALYSIS AND RESULTS

1. PREOPERATIVE CHARACTERISTICS

Table 2 contains a summary of the preoperative acuity and refraction. Note that per protocol, monovision and intentional undercorrections were permitted. The parameters in the table below are calculated based on the actual preoperative refraction.

Table 2: Preoperative Characteristics	
UCVA 20/40 or better	0.4% (3/839)
UCVA 20/50 to 20/80	1.3% (11/839)
UCVA 20/100 or worse	98.3% (825/839)
manifest refraction cylinder	-0.94 ± 0.84 SD D; range 0.0 to -6.25 D
manifest refraction sphere	-6.11 ± 2.88 SD D; range -1.0 to -19.0 D
manifest refraction spherical equivalent	-5.65 ± 2.70 SD D; range -1.0 to -18.25 D
cycloplegic refraction cylinder	-1.09 ± 0.99 SD D; range 0.0 to - 6.75 D
cycloplegic refraction sphere	-5.65 ± 2.70 SD D; range -0.75 to -19.0 D
cycloplegic refraction spherical equivalent	-5.39 ± 2.90 SD D; range -0.75 to -18.13 D

2. POSTOPERATIVE RESULTS

a. Accountability and definition of the PMA cohort

At the stability time point of 6 months, the PMA cohort consisted of all eyes that were available for analysis (815/839; 97.1%). Of the 24 eyes not included in the 6 months analysis, 2 eyes were retreated at 3 months post-LASIK; 8 eyes missed 6-month visit but completed the later 12 month visit; and 14 eyes missed the 6 and 12 month visits. The 97.1 accountability exceeds FDA's requirement of at least 80%.

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The safety cohort included all treated eyes.

Table 3: Accountability (Number of enrolled (N) = 839)				
Status	1 months	3 months	6 months	12 months
Discontinued				
Death	0	0	0	0
Retreated	0	0	2	97
Not Eligible for Interval	0	0	0	0
Unavailable for Visit:				
Overdue	0	0	0	0
Missed Visit	81	54	8	133
Lost to Follow-up	0	6	14	27
Available for Analysis	758	779	815	582
% Accountability= Avail/(N-discont.-not eligible)	90.3%	92.8%	97.1%	81.4%

b. Stability of outcome

In the 3-6 months window, greater than 95% of eyes experienced a change of MRSE not exceeding ± 1.0D. Furthermore, the mean of the pair-difference of MRSE progressively decreased over time, and reached a change of about -0.13 D in the 3-6 months window (table 4). The changes in the 6-12 months window for the entire cohort were smaller than those observed in the previous time window; thus, stability was demonstrated by 6 months postoperative. The assessment of the efficacy was therefore performed using the outcomes of the 815 eyes evaluable at 6 months.

Table 4 :Stability Analyses (change in MRSE over time for eyes that had every exam, through stability at 6 months)			
Analysis	1 to 3 Months	3 to 6 Months	6 to 12 Months*
Change <=1 D n/N (%)	654/698 (93.7%)	671/698 (96.1%)	488/511 (95.5%)
Change (Pair-Differences)			
Mean	-0.232	-0.130	-0.0245
Std.Dev.	0.498	0.459	0.341
(95% CI)	0.037	0.034	0.030

*511 of the 698 eyes also had a 12 month exam

c. Effectiveness Outcomes

The analysis of effectiveness was based on the 815 eyes evaluable at the 6 months stability time point. Key efficacy outcomes at 6 and 12 months are presented in tables 5 and 6, respectively. The tables are stratified by preoperative manifest refraction spherical equivalent (MRSE). Refractive predictability is based on the attempted verses achieved refraction and takes into account any intentional undercorrection. Intentionally undercorrected eyes are not included in the analyses of 20/20 or better and 20/40 or better. Also, the tables exclude eyes in the unapproved diopter range of 14.0 to 18.99 D showing 810 and 579 eyes respectively for tables 5 and 6.

Table 5: Summary of Key Efficacy Variables at 6 Months by Preoperative (MRSE)

Efficacy Variables	1.0 to 1.99 D n/N (%)	2.0 to 2.99 D n/N (%)	3.0 to 3.99 D n/N (%)	4.0 to 4.99 D n/N (%)	5.0 to 5.99 D n/N (%)	6.0 to 6.99 D n/N (%)	7.0 to 7.99 D n/N (%)	8.0 to 8.99 D n/N (%)	9.0 to 9.99 D n/N (%)	10.0 to 10.99 D n/N (%)	11.0 to 11.99 D n/N (%)	12.0 to 12.99 D n/N (%)	13.0 to 13.99 D n/N (%)
UCVA 20/20 or better	29/33 87.9	67/84 79.8	71/118 60.2	59/114 51.8	49/102 48.0	39/88 44.3	29/82 35.4	12/39 30.8	12/40 30.0	5/21 23.8	2/10 20.0	1/11 9.1	1/2 50.0
UCVA 20/40 or better	33/33 100.0	84/84 100.0	110/118 93.2	97/114 85.1	86/102 84.3	78/88 88.6	70/82 85.4	32/39 82.1	30/40 75.0	15/21 71.4	8/10 80.0	6/11 54.5	2/2 100.0
MRSE +/-0.50 D	30/33 90.9	73/85 85.9	97/128 75.8	74/119 62.2	75/115 65.2	48/99 48.5	47/85 55.3	18/45 40.0	19/46 41.3	8/23 34.8	6/14 42.9	3/13 23.1	3/5 60
MRSE +/-1.00 D	33/33 100.0	82/85 96.5	122/128 95.3	98/119 82.4	92/115 80.0	82/99 82.8	65/85 76.5	30/45 66.7	28/46 60.9	14/23 60.9	10/14 71.4	7/13 53.8	5/5 100

Table 6: Summary of Key Efficacy Variables at 12 Months by Attempted Correction (MRSE)

Efficacy Variables	1.0 to 1.99 D n/N (%)	2.0 to 2.99 D n/N (%)	3.0 to 3.99 D n/N (%)	4.0 to 4.99 D n/N (%)	5.0 to 5.99 D n/N (%)	6.0 to 6.99 D n/N (%)	7.0 to 7.99 D n/N (%)	8.0 to 8.99 D n/N (%)	9.0 to 9.99 D n/N (%)	10.0 to 10.99 D n/N (%)	11.0 to 11.99 D n/N (%)	12.0 to 12.99 D n/N (%)	13.0 to 13.99 D n/N (%)
UCVA 20/20 or better	18/21 85.7	43/63 79.8	55/88 62.5	45/79 57.0	43/73 58.9	25/61 41.0	23/58 39.7	10/28 35.7	11/24 45.8	3/15 20.0	1/9 11.1	3/9 33.3	1/2 50.0
UCVA 20/40 or better	21/21 100.0	61/63 96.8	85/88 96.6	77/79 97.5	68/73 93.2	59/61 96.7	53/58 91.4	27/28 96.4	19/24 79.2	14/15 93.3	8/9 88.9	6/9 66.7	2/2 100.0
MRSE +/-0.50 D	19/21 90.5	49/64 76.6	67/94 71.3	63/83 75.9	56/79 70.9	39/71 54.9	39/61 63.9	19/31 61.3	13/29 44.8	6/17 35.3	7/13 53.8	3/11 27.3	4/5 80
MRSE +/-1.00 D	21/21 100.0	64/64 100.0	90/94 95.7	77/83 92.8	70/79 88.6	62/71 87.3	48/61 78.7	26/31 83.9	19/29 65.5	12/17 70.6	11/13 84.6	8/11 72.7	5/5 100

i. Correction of Cylindrical Component (scalar and vector analyses)

Table 7 provides an analysis of the mean percent reduction of absolute cylinder at 6 months. The Ophthalmic Devices Panel (the Panel), in the January 14, 1997 meeting in which the Panel assessed outcomes from a myopic astigmatic treatment, provided FDA with some guidance as to the acceptable effectiveness rates. The Panel considered 64% as an acceptable mean reduction in absolute cylinder at the point of stability. Therefore, the 64.8% reduction at 6 months achieved with this device is acceptable. However, 16 eyes (3.47%) out 461 eyes included in this analysis had residual postoperative cylinder that was of a greater magnitude than the preoperative cylinder.

Table 7: Mean Percent Reduction in Absolute Cylinder in Eyes Treated for SpheroCylinder

Preoperative Manifest Cylinder	Number of Eyes Evaluated (n)	Mean % Reduction of Absolute Cylinder
≤ 1.0 Diopters	178	56.9 %
>1.0 to ≤ 2.0 Diopters	222	67.8 %
>2.0 to ≤ 3.0 Diopters	45	74. 9%
>3.0 to ≤ 4.0 Diopters	16	79.8 %
Total	461	64.8%

When the data are further stratified by absolute shift in axis (table 8), 37/461 (8%) had >1.0 D of residual astigmatism with an absolute axis shift >15° and 21/461 (4.6%) had >1.0 D of residual astigmatism with an absolute axis shift >30°.

Table 8: Absolute Shift in Axis

Residual Magnitude Cylinder	Absolute Shift in Axis											
	≤5°		>5° to ≤10°		>10° to ≤15°		>15°to ≤30°		>30°		Total	
N											461	
	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
0.0											149	32.3
> 0.0 to < 0.5 D	6	1.3	9	2.0	9	2.0	14	3.0	28	6.1	66	14.3
≥ 0.5 D to < 1.0D	34	7.4	27	5.9	18	3.9	38	8.2	58	12.6	175	38.0
≥ 1.0 D to < 2.0D	9	2.0	15	3.3	8	1.7	14	3.0	19	4.1	65	14.1
≥ 2.0 D to < 3.0D	2	0.4	0	0.0	1	0.2	1	0.2	2	0.4	6	1.3
≥ 3.0 D	0	0.0	0	0.0	0	0.0	0	0.0	0	0.00	0	0.0
Total											461	

The sponsor utilized the van Saarlos method for calculating vectoral change. This method was described in the PMA.

Looking at vector magnitude, the Intended Refractive Correction ("IRC") had a mean of 1.47 D with a median of 1.25, a minimum of 0.75 D and a maximum of 6.25 D, and the Surgically Induced Refractive Correction ("SIRC") had a mean of 1.40 D, a median of 1.25 D, a minimum of 0.13 D and a maximum of 6.94 D. The results for SIRC/IRC were: 94.9% mean, median of 1.00%, minimum of 17.4% and a maximum of 234.1%. The Panel has found 82.5% acceptable for correction efficacy (SIRC/IRC) at stability. The 94.9% achieved by this device is within the same range and is therefore acceptable.

ii. Correction of Spherical Component

At 6 months, 58.9% of eyes were within +0.50 D of the intended spherical correction and 81.0 % were within +1.00 D. Although there are no specific benchmarks for only the spherical component, these results are within the benchmarks for MRSE and are therefore acceptable.

d. Safety Outcomes

The analysis of safety was based on 815 eyes that have had the 6 months exam. The key safety outcomes for this study are presented in tables 9 and 10, with all the adverse reactions reported in tables 11 and 12. Overall, the device was deemed reasonably safe. Table 10 excludes eyes in the unapproved diopter range of 14.0 to 18.99 D, showing only 810 eyes.

Table 9: Summary of Key Safety Variables by Visit

	1 Month	3 Months	6 Months	12 Months
	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Safety Variables				
Loss of ≥ 2 lines BSCVA	6/758 (0.8%)	3/779 (0.4%)	1/815 (0.1%)	1/582 (0.2%)
BSCVA worse than 20/40	2/758 (0.3%)	2/779 (0.3%)	2/815 (0.2%)	0/582 (0.0%)
BSCVA worse than 20/25 if 20/20 or better preoperatively	1/758 (0.1%)	1/779 (0.1%)	1/815 (0.1%)	0/582 (0.0%)
Not Reported	81	60	24	133

Table 10: Summary of Key Safety Variables at stability (6 Months) by Preoperative (MRSE)

	1.0 to 1.99 D n/N (%)	2.0 to 2.99 D n/N (%)	3.0 to 3.99 D n/N (%)	4.0 to 4.99 D n/N (%)	5.0 to 5.99 D n/N (%)	6.0 to 6..99 D n/N (%)	7.0 to 7.99 D n/N (%)	8.0 to 8.99 D n/N (%)	9.0 to 9.99 D n/N (%)	10.0 to 10.99 D n/N (%)	11.0 to 11.99 D n/N (%)	12.0 to 12.99 D n/N (%)	13.0 to 13.99 D n/N (%)
Safety Variables													
Loss of ≥ 2 lines BSCVA	0/33 (0.0%)	0/85 (0.0%)	0/128 (0.0%)	0/119 (0.0%)	0/115 (0.0%)	0/99 (0.0%)	0/85 (0.0%)	0/45 (0.0%)	0/46 (0.0%)	0/23 (0.0%)	0/14 (0.0%)	1/13 (7.7%)	0/5 (0.0%)
BSCVA worse than 20/40	0/33 (0.0%)	0/85 (0.0%)	0/128 (0.0%)	0/119 (0.0%)	0/115 (0.0%)	0/99 (0.0%)	0/85 (0.0%)	0/45 (0.0%)	0/46 (0.0%)	0/23 (0.0%)	0/14 (0.0%)	2/13 (15.4%)	0/5 (0.0%)
BSCVA worse than 20/25 if 20/20 or better preoperatively	0/33 (0.0%)	0/85 (0.0%)	0/128 (0.0%)	1/119 (0.8%)	0/115 (0.0%)	2/99 (2.0%)	2/85 (2.4%)	2/45 (4.4%)	1/46 (2.2%)	0/23 (0.0%)	0/14 (0.0%)	0/13 (0.0%)	1/5 (20.0%)
Not reported	3/36 (8.3%)	4/89 (4.5%)	5/133 (3.8%)	2/121 (1.7%)	4/119 (3.4%)	1/100 (1.0%)	1/86 (1.2%)	1/46 (2.2%)	1/47 (2.1%)	4/23 (17.4%)	0/14 (0.0%)	0/13 (27.8%)	0/5 (0.0%)

Table 11 presents a summary of adverse events. The benchmark for each adverse event is a rate of less than 1 % per event.

Table 11: Adverse Events at stability	
Adverse Event	**PMA cohort**
Corneal infiltrate or ulcer	0 (0.0%)
Persistent central corneal epithelial defect at 1 month or later	0 (0.0%)
Corneal edema at 1 month or later	0 (0.0%)
Uncontrolled IOP with increase of > 5 mm Hg above baseline, or any reading above 25 mm Hg	0 (0.0%)
Late onset of haze beyond 6 months with loss of 2 lines (10 letters) or more BSCVA	0 (0.0%)
Decrease in BSCVA of > 10 letters not due to irregular astigmatism as shown by hard contact lens refraction, at 6 months or later	0 (0.0%)
Retinal detachment	0 (0.0%)

All adverse reactions, measured or reported by patients, are presented in table 12. Events observed at the 6 months stability time point and at the two adjacent visits are included for comparison. In general, the rate of an adverse reaction tends to be highest immediately postoperative and tapers down over time.

Table 12: Adverse Reactions at 3, 6, and 12 months			
Adverse Events	**3 Months N = 779**	**6 Months N = 815**	**12 Months N = 582**
Corneal infiltrate or ulcer	0 (0.0%)	0 (0.0%)	0 (0.0%)
Persistent central corneal epithelial defect at 1 month or later	0 (0.0%)	0 (0.0%)	0 (0.0%)
Any corneal epithelial defect involving the keratectomy site at 1 month or later	0 (0.0%)	0 (0.0%)	0 (0.0%)
Corneal edema at 1 month or later	0 (0.0%)	0 (0.0%)	0 (0.0%)
Epithelium in the interface	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost, misplaced, or misaligned flap	0 (0.0%)	0 (0.0%)	0 (0.0%)
Melting of the flap	0 (0.0%)	0 (0.0%)	0 (0.0%)
Uncontrolled IOP with increase of > 5 mm Hg above baseline and any reading above 25 mm Hg	0 (0.0%)	0 (0.0%)	0 (0.0%)
Late onset of haze beyond 6 months with loss of 2 lines (10 letters) or more BSCVA	0 (0.0%)	0 (0.0%)	0 (0.0%)
Decrease in BSCVA of > 10 letters not due to irregular astigmatism as shown by hard contact lens refraction at 6 months or later	0 (0.0%)	0 (0.0%)	0 (0.0%)
Retinal detachment	0 (0.0%)	0 (0.0%)	0 (0.0%)
Retinal vascular accidents	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate to marked corneal haze	2 (0.3%)	1 (0.1%)	2 (0.3%)
Overcorrected by more than 1 D	24 (3.1%)	15 (1.8%)	10 (1.7%)
Overcorrected by more than 2 D	8 (1.0%)	7 (0.9%)	5 (0.9%)
Loss of more than 2 lines of BSCVA beyond 6 months	N/A	N/A	1 (0.2%)
COMPLICATION	**3 Months N = 779**	**6 Months N = 815**	**12 Months N = 582**
Corneal edema between 1 week and 1 month after the procedure	0 (0.0%)	0 (0.0%)	0 (0.0%)
Peripheral corneal epithelial defect at 1 month or later	0 (0.0%)	0 (0.0%)	0 (0.0%)
Recurrent corneal erosion at 1 month or later	0 (0.0%)	0 (0.0%)	0 (0.0%)
Foreign body sensation at 1 month or later	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pain at 1 month or later	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ghost/double images in the operative eye	0 (0.0%)	0 (0.0%)	0 (0.0%)
TOTAL	0/779 (0.0%)	0/815 (0.0%)	0/582 (0.0%)

"N" is the number of eyes evaluated at the specified visit; not all eyes were eligible for the 12 month visit.

d. Retreatment

All retreatment procedures were performed at least 3 months after the initial treatment. There were a total of 97 retreatments on the 839 eyes: 2 after 3 months, 23 after 6 months and 72 after twelve months.

All retreatments were LASIK procedures performed with the Dishler Excimer Laser System. No adverse events, or complications occurred in the 25 retreated eyes. Postoperative data for the first 25 retreatments shows that all retreated eyes (25/25; 100%) had UCVA of 20/40 or

better and that 23 (23/25; 92%) of the eyes were within +1.00D of attempted verses achieved MRSE.

e. Factors associated with outcomes

These preoperative characteristics were not evaluated for potential association with outcomes: gender, site, age, preoperative MRSE, attempted MRSE.

f. Patient Satisfaction

Patient surveys were completed on an eye-by eye basis. Information at 3 and 6 months was presented in the PMA. The most common complaints reported at 6 months postoperatively were dryness, fluctuation in vision, and those related to bright lights and dim lighting conditions. Approximately, two thirds of the patients complained of difficulty driving at night to some degree. Problems with glare, halos, or sensitivity to bright lights were reported in about half the patients who responded to the questionnaire.

g. Device Failure

There has been one case in which the laser was not functioning properly and the procedure was stopped midway through the treatment. The cause for the laser malfunction was corrected and no further problems with the laser occurred.

h. Overview of Key Safety and Efficacy Parameters

Tables 13 – 15 provide an overview of the key safety and efficacy variables for all eyes treated stratified by postoperative visits. Of the 815 evaluable eyes, 5 eyes are distributed throughout the 14 –18.99 D ranges which was not approved due to insufficient sample size.

Although the guideline targets are achieved with both lasers, it was observed that results from laser B were not as good as results from laser A. This was attributed to laser B treating more difficult cases.

Table 14: Summary of Key Safety and Efficacy Variables for all Eyes Treated

	1 Month n/N, %	3 Months n/N, %	6 Months n/N, %	12 Months
Efficacy Variables				
UCVA 20/20 or better*	408/605 58.7%	388/714 54.35	378/748 50.5%	283/538 52.6%
UCVA 20/40 or better*	648/695 93.2%	645/714 90.3%	655/748 87.6%	499/538 92.8%
MRSE ± 0.50 D	501/758 66.1%	504/779 64.75	504/815 61.8%	385/582 66.2%
MRSE ± 1.00 D	657/758 86.7%	653/779 83.8%	671/815 82.3%	512/582 88.0%
MRSE ± 2.00 D	740/758 97.6%	762/779 97.8%	795/815 97.5%	567/582 97.4%
Safety Variables				
Loss of ≥ 2 lines BSCVA	6/758 0.8%	3/779 0.4%	1/815 0.1%	1/582 0.2%
BSCVA worse than 20/40	2/758 0.3%	2/779 0.3%	2/815 0.2%	0/582 0.05
Increase > 2 D cylinder#	1/758 0.1%	1/779 0.1%	1/815 0.1%	0/582 0.0%
BSCVA worse then 20/25 if 20/20 or better preoperatively	25/758 3.3%	20/779 2.6%	9/815 1.1%	6/582 1.0%

* For all eyes minus those intentionally undercorrected
# For eyes treated for spherical correction only

Table 15: Summary of Key Safety and Efficacy Variables for Eyes Treated for Spherical Myopia Only

	1 Month n/N, %	3 Months n/N, %	6 Months n/N, %	12 Months n/N, %
Efficacy Variables				
UCVA 20/20 or better*	206/313 65.8%	183/315 58.1%	184/328 56.1%	132/232 56.95
UCVA 20/40 or better*	295/313 94.2%	284/315 90.2%	291/328 88.7%	220/232 94.8%
MRSE ± 0.50 D	247/336 73.5%	242/339 71.4%	232/353 65.7%	170/246 69.15
MRSE ± 1.00 D	305/336 90.8%	286/339 84.4%	297/353 84.1%	226/246 91.9%
MRSE ± 2.00 D	331/336 98.5%	336/339 99.1%	346/353 98.0%	242/246 98.4%
Safety Variables				
Loss of ≥ 2 lines BSCVA	2/336 0.6%	2/339 0.6%	0/353 0.0%	1/246 0.4%
BSCVA worse than 20/40	0/336 0.0%	0/339 0.0%	0/353 0.0%	0/246 0.0%
Increase > 2 D cylinder#	1/333%	1/339 0.3%	1/353 0.3%	0/246 0.0%
BSCVA worse then 20/25 if 20/20 or better preoperatively	9/336 2.7%	13/339 3.8%	5/353 1.4%	1/246 0.4%

* For all eyes minus those intentionally undercorrected
# For eyes treated for spherical correction only

Table 16: Summary of Key Safety and Efficacy Variables for All Eyes Treated for Astigmatic Myopia

	1 Month n/N, %	3 Months n/N, %	6 Months n/N, %	12 Months n/N, %
Efficacy Variables				
UCVA 20/20 or better*	202/382 52.9%	205/399 51.4%	194/420 46.2%	151/306 49.35
UCVA 20/40 or better*	353/382 92.4%	361/399 90.5%	364/420 86.7%	279/336 91.2%
MRSE ± 0.50 D	254/422 60.2%	262/440 59.5%	272/462 58.9%	215/336 64.0%
MRSE ± 1.00 D	352/422 83.4%	367/440 83.4%	374/462 81.0%	286/336 85.1%
MRSE ± 2.00 D	409/422 96.9%	426/440 96.8%	449/462 97.2%	325/336 96.7%
Safety Variables				
Loss of ≥ 2 lines BSCVA	4/422 0.9%	1/440 0.2%	1/462 0.2%	0/336 0/0%
BSCVA worse than 20/40	2/422 0.5%	2/440 0.5%	2/462 0.4%	0/336 0/0%
Increase > 2 D cylinder#	0/422 0.0%	0/440 0.0%	0/462 0.05	0/336 0/0%
BSCVA worse then 20/25 if 20/20 or better preoperatively	16/422 3.8%	7/440 1.6%	4/462 0.9%	5/336 1.5%

* For all eyes minus those intentionally undercorrected
\# For eyes treated for spherical correction only

XI. CONCLUSIONS DRAWN FROM THE CLINICAL STUDY

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

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

CDRH issued an approval order on December 16, 1999. Since the applicant does not intend to manufacture additional lasers a preapproval inspection was not warranted.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See labeling.

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

Post-approval Requirements and Restrictions: See approval order.