SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Ophthalmic Excimer Laser System

Device Trade Name: LADARVision® Excimer Laser System

Applicant's Name and Address: Autonomous Technologies Corporation
2501 Discovery Drive, Suite 500
Orlando, FL 32826

Date of Panel Recommendation: February 13, 1998

Premarket Approval (PMA) Application: P970043

Date of Notice of Approval to Applicant: November 2, 1998

II. INDICATION FOR USE

The LADARVision® Excimer Laser System is indicated for use:

- In photorefractive keratectomy (PRK) treatments for the reduction or elimination of mild to moderate myopia (near-sightedness) of between -1.00 and -10.00D of sphere and less than or equal to -4.00D of astigmatism at the spectacle plane, the combination of which must result in an attempted correction between -0.50 and -10.00D spherical equivalent (SE) at the spectacle plane where sphere or cylinder is at least 1.00D.

- In subjects with documented stability of refraction for the prior 12 months, as demonstrated by a change of less than or equal to 0.50D for corrections up to -7.00D SE, and less than or equal to -1.00D for corrections greater than -7.00D SE.

- In subjects who are 21 years of age or older.

III. CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

A. Contraindications

PRK is contraindicated:

- In patients with signs of keratoconus
- In pregnant or nursing women
- In patients who are taking one or both of the following medications: isotretinoin (Accutane); amiodarone hydrochloride (Cordarone)

B. Warnings: See the labeling

C. Precautions: See the labeling

IV. DEVICE DESCRIPTION

Two configurations of the LADARVision® Excimer Laser System were used in clinical trials. These are designated as the "Alpha" and "Beta" models. The material provided in this section specifically pertains to the Beta configuration.

A. Theory of Operation

The LADARVision® Excimer Laser System uses a small diameter pulsed ultraviolet laser beam to reshape the cornea. Refractive correction is achieved by delivering hundreds to thousands of ablative laser pulses to the eye in a predetermined spatial pattern. The system also incorporates an infrared eye-tracking system to maximize accuracy of the corneal reshaping. The eye tracker compensates for patient eye motion during procedures, so that each excimer laser pulse is delivered to the appropriate corneal location.

B. Excimer Laser Characteristics

The ultraviolet laser used in the LADARVision® Excimer Laser System is an argon fluoride excimer laser. Each laser pulse is 10 nanoseconds in duration, at a wavelength of 193 nanometers. The laser repetition rate is between 40 and 100 pulses per second. The characteristics of the laser beam at the corneal treatment plane are shown below.

Treatment Plane Characteristics of the LADARVision® Excimer Laser Beam

Pulse energy (mJ)	2.4 - 3.0
Beam diameter (mm) [a]	0.80 - 0.90
Average fluence per Pulse (mJ/cm^2) [b]	180-240

Note (a): This beam diameter is the width of the beam at the 1/e points in the Gaussian fluence distribution.

Note (b): This is the average value per pulse laser fluence over the ablated area.

C. Excimer Laser Optical Transmission System

The ultraviolet output from the excimer laser first passes through an optical telescope, which produces an expanded, slowly converging laser beam. This is done to reduce the peak fluence striking downstream excimer optics and still provide a small laser spot size at the treatment plane.

The excimer laser beam next reflects off several mirrors in the beam translation assembly. Linear movements of these mirrors position the excimer laser pulses in the correct locations at the treatment plane.

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The excimer laser next reflects off several mirrors that convey the beam to the upper optics module (above the patient). In the upper optics module the excimer laser beam is reflected off two tracking mirrors. Rotation of these mirrors compensates for patient eye motion, as detected by the LADARVision® eye tracking system. The excimer laser beam finally exits the system through the output window.

D. Excimer Laser Energy Monitoring/Control

An energy monitor is mounted at the output of the LADARVision® Excimer Laser System. Prior to treatment this energy monitor is used to ensure that the laser pulse energy delivered to the eye will be between 2.4 and 3.0 mJ. During treatment the detector monitors laser operation.

E. Excimer Gas Handling

The excimer laser enclosure box holds the laser, gas bottle, and gas plumbing manifold. The gas bottle contains the pre-mixed excimer laser gas, which contains neon as the buffer gas, in addition to argon and fluorine. The initial pressure in the gas bottle is 2000 PSI. The outlet nozzle of the gas bottle contains a flow restrictor valve. Gas from the bottle flows to a fluorine-compatible gas regulator, which reduces the line pressure to 55 PSI. Two gas lines exit the regulator. One leads directly to the outlet line of the laser enclosure. In the event of a diaphragm failure, excimer gas will flow from the regulator down this line and out of the enclosure. Outside the laser enclosure the gas flows through a charcoal-based filter (to remove the F_2) before venting into the room. The second gas line exiting the regulator leads to the excimer laser cavity. At the line connection to the cavity there is a solenoid valve, which responds to commands from the laser control electronics board. A second solenoid valve exists at the gas outlet port of the laser cavity. The outlet gas line also leads out of the laser enclosure, and through the charcoal filter.

F. Eye Tracking System

The LADARVision® Excimer Laser System eye tracker employs an infrared laser operating at a wavelength of 905 nm. The output beam of this laser is directed toward the patient eye by a series of optical elements. The infrared laser radiation reaching the treatment plane is "eye safe." That is, the potential patient exposure during a procedure is well below the Class I limit, as described in ANSI Z136.1-1986, ANSI Z136.1-1993, and FDA CFR 21 Part 1040. Specific characteristics of the laser radiation signal returning from the eye are used to determine eye position. The LADARVision® system repositions tracking mirrors in the upper optical module to compensate for detected eye motion.

G. 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. This is effectively a stereo operating microscope with adjustable magnification that is co-axial with the treatment excimer laser beam. Two halogen lamps are mounted on either side of the system output window to provide visible illumination of the treatment plane. The operating microscope optical system is completely independent from the eye tracking optical system and does not provide "tracked" imagery of the patient eye.

H. Fixation Target

A visible fixation target is mounted in the system to facilitate the patient's looking in the direction of the treatment excimer beam. The fixation target assembly consists of a yellow light emitting diode (LED), a pinhole aperture, an edge-illuminated reticule, and two lenses. These lenses in combination with a 300mm focal length achromat in the operating microscope optical path place the focal plane of the pinhole aperture at infinite distance from the patient's perspective. The edge-illuminated reticule is a clear glass flat etched with two sets of horizontal lines. These lines are also visible to the patient, at an effective focal length of approximately 18 inches. For proper eye alignment the patient is instructed to shift position until the LED pinhole light is centered within the parallel lines, and then to maintain that fixation during treatment.

I. System Software

All LADARVision® systems utilizing the proprietary excimer laser employ an Intel Pentium-based personal computer. The LADARVision® system software runs under the Microsoft Windows operating system.

J. Excimer Laser Shot Patterns

The LADARVision® system software calculates the "laser shot pattern," i.e., the number of excimer laser pulses to deliver to the eye and the required position of each pulse on the cornea, based on the desired refractive correction and the current laser calibration. The laser shot pattern consists of hundreds to thousands of individual pulses that partially overlap on the corneal surface. The system software also calculates a sequence to fire the pulses in the shot pattern such that no corneal site is revisited by the excimer beam for a finite interval. The laser firing sequence is designed to provide a gradually changing corneal curvature from the starting surface shape to the corrected final profile.

K. Safety

The LADARVision® Excimer Laser System contains a Class IV laser. The company provided information on the device to FDA in conformance with the US FDA 21 CFR 1040 Radiological Health requirements. The laser system was designed to meet the following safety requirements:

UL 544	EN601-1-1-2
CSA 22.2	EN61000-4-2
IEC 825:1993	EN61000-4-3
EN55011	EN61000-4-4
EN601-2-22	EN61000-4-5

V. ALTERNATE PRACTICES AND PROCEDURES

Alternative methods for correcting nearsightedness with or without astigmatism are spectacles, contact lenses, and surgical procedures such as radial keratotomy (RK), automated lamellar keratoplasty (ALK), and astigmatic keratotomy (AK).

VI. MARKETING HISTORY

Units have recently been placed in Italy and the United Kingdom for commercial use. The device has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VII. POTENTIAL ADVERSE EFFECTS ON HEALTH

Potential adverse effects associated with PRK include: loss of best spectacle corrected visual acuity (BSCVA), worsening of BSCVA, increase in intraocular pressure (IOP), corneal haze, and secondary surgical intervention. Adverse reactions and complications that occurred in the study are given on page 11.

VIII. SUMMARY OF PRECLINICAL STUDIES

- Ablation calibrations (volume per pulse) performed on a synthetic laminate target

  These tests characterized the ablation behavior of the synthetic material used to calibrate the clinical device prior to patient treatment. The calibration characteristics of the plastic were found to be predictable and unaffected over a large range (i.e., a 40% change) in incident laser pulse energies.

- Beam profile and pulse stability

  These measurements were used to assess the stability of the laser beam energy distribution at the treatment plane for repetitive excimer laser firing. Laser pulses were sampled periodically during a 160,000 train using a single fill of the argon/fluorine laser gas mixture. The average pulse energy (for 20 consecutive pulses) did not vary by more than 3% over the 160,000-pulse train. The standard deviation in pulse energy for each 20 pulse sample was also 3%.

- Beam alignment stability

  These tests established the optical alignment stability of the beam during extensive firing of the excimer laser. Over 18 simulated 8-diopter myopic surgeries, the maximum pointing error in the excimer laser beam (prior to any software correction) was 0.3 mm. This was well within the compensation range of the automated "geometry adjust" software algorithm.

- Excimer laser pulse (energy and peak fluence) control

  These experiments validated the requirement that the LADARVision® system keep the excimer pulse energy at the eye plane within the acceptable range for surgery. For 18 simulated 8-diopter myopic surgeries, the variation in laser pulse energy was less than 0.1 mJ (i.e., 4% of the 2.7 mJ target energy).

- Beam positioning system accuracy (beam positioning translators and tracker performance)

  These tests characterized the laser pointing accuracy of the LADARVision® system during operation of the beam translation and the eye tracking subsystems. Grid patterns ablated on both stationary and oscillating plastic targets were analyzed using surface profilometry. Results indicated that the laser placement accuracy was within 40 microns.

- Eye alignment with respect to ablation position

  These measurements were used to determine the accuracy of the LADARVision® system "centration" process. All tests of repeatability and accuracy showed that the maximum error in realigning the pupil center using the software limbus reticle was less than 100 microns.

- Ablation profile testing for software validation using PMMA targets

  These tests validated the ability of the LADARVision® system to ablate refractive craters of predefined shapes. Ablative treatment profiles of various prescriptions were ablated into flat PMMA slides and examined using surface profilometry. Measured profile curvatures were in good agreement with intended shapes, and profile depths were a direct linear function of prescription magnitude.

- Electrical safety and electromagnetic compatibility validation

  These measurements determined the compliance of the LADARVision® system with regulatory standards for electrical safety and electromagnetic compatibility. The LADARVision® system was evaluated as specified in Section VII and in accordance with both the Canadian and U.S. National Electrical Codes, as well as Standards CSA 22.2 No. 125-1984 and UL 544 for Product Safety.

- Non-human primate eye study of epithelialization, flattening and histopathology

  Twelve eyes of nine Rhesus monkeys were ablated for 3D or 6D of attempted myopic PRK correction. These animal trials assessed the corneal healing response and degree of corneal flattening achieved following LADARVision® treatment. The results showed rapid postoperative healing, minimal haze and no recurrent corneal erosions. Retinoscopy indicated that although undercorrections were obtained in all eyes, the 6D attempted corrections resulted in approximately twice the dioptric change as compared to the 3D attempted corrections. Consistent with the retinoscopic data, keratometric measurements indicated that there was minimal corneal flattening. Serial corneal topography showed that no irregular astigmatism was induced.. Histological specimens from immediately postoperative to 6 months showed minimal tissue damage to non-ablated areas, and a smooth well-tapered ablation that healed well without fibrosis.

IX. SUMMARY OF CLINICAL STUDIES

Autonomous Technologies has conducted both foreign and domestic clinical trials using the LADARVision® Excimer Laser System. At one foreign site, an evaluation of the LADARVision® laser in non-sighted and sighted eyes was conducted to establish the safety and relative calibration of the LADARVision® laser for use in correction of myopia. Thereafter, a study was initiated on 102 low myopia (-1 to -6D) patients at the same site. The results in this foreign study demonstrated conformance to all FDA performance guidelines for laser refractive correction. These data provided the basis for initiation of the U.S. clinical trials under IDE G950213. A summary of the U.S. clinical trials is presented below.

A. Study Objective

The objective of the multi-center, clinical investigation of the LADARVision® Excimer Laser System for Photorefractive Keratectomy, conducted under IDE G950213, was to assess the ability of the product to safely improve uncorrected visual acuity and to predictably reduce refractive error in healthy eyes. Treatments were performed for the reduction or elimination of mild to moderate myopia (near-sightedness) of between -1.00 and -10.00D of sphere and less than or equal to -6.00D of astigmatism at the spectacle plane, the combination of which resulted in an attempted correction between -0.50 and -10.00D spherical equivalent (SE) at the spectacle plane where sphere or cylinder was at least 1.00D.

B. Study Design

This was a prospective, non-randomized, unmasked multi-center clinical 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. Subject Selection And Exclusion Criteria

Recruited patients had the study details and follow-up requirements explained to them and were asked to sign an Informed Consent Document. A preoperative screening evaluation was conducted within 60 days of surgery to determine eligibility.

To be eligible for inclusion into the U.S. IDE studies, the manifest refraction at the spectacle plane in both eyes must have been a sphere of up to -10D and a cylinder of up to -6D, the combination of which resulted in a spherical equivalent between -1D and -10D.

The eye to be treated could not have had any previous corneal or intraocular corneal surgery. However, the fellow eye could have had prior corneal surgery including excimer laser surgery with an FDA approved laser. In this case, the fellow eye could not be treated in this study.

Patients must have been at least 18 years of age and both eyes correctable to 20/40 or better visual acuity.

Patients who were contact lens wearers were requested to discontinue contact lens wear in both eyes at least 3 weeks prior to the preoperative examination. Patients who had worn rigid gas permeable (RGP) and polymethylmethacrylate (PMMA) lenses were required to have two examinations conducted 2-3 weeks apart which showed stability of refraction without lens wear.

Stability of refraction for at least the previous 12 months must have been established and documented using previous clinical records or measurement of spectacles worn over this period. In addition, the manifest and cycloplegic refraction measured at the preoperative examination must have been within 0.50D of each other in the sphere and cylinder components for eyes with a manifest refraction of up to -7D and within 0.75D for eyes with greater than 7D of myopia.

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

- history of or active clinically or visually significant ocular disease or pathology
- corneal scars within the ablation zone or other corneal abnormality such as recurrent erosion
- signs of progressive or unstable myopia or keratoconus
- irregular corneal astigmatism
- history of herpes keratitis
- autoimmune disease, connective tissue disease, clinically significant atopic syndrome or insulin dependent diabetes
- use of chronic systemic corticosteroids or other immunosuppressive therapy
- pregnant or lactating females
- use of ophthalmic medications for treatment of an ocular pathology other than artificial tears
- history of keloid formation
- severe dry syndrome unresolved by treatment
- allergy to study medications
- corneal thickness of less than 400 microns
- glaucoma or prior glaucoma filtering surgery
- participation in another ophthalmic clinical trial

On discussion with their surgeon, patients were given the option of having an intentional under-correction in the eye to be treated if a monovision outcome was desired. All surgeries performed in the study were subject to approval by the Sponsor.

D. Pre and Postoperative Evaluations and Follow-up

Preoperative examinations could be performed a maximum of 60 days prior to the surgery day. Follow-up visits were conducted daily until unreepithelialized and then at 1, 3, 6, 9, 12 and 18 months. All procedures were performed with no correction or best spectacle correction in place (no contact lenses). The following procedures were performed at all sites using comparable pieces of equipment:

- Uncorrected visual acuity
- Best spectacle corrected visual acuity
- Pupil diameter
- Manifest refraction
- Cycloplegic refraction
- Applanation tonometry
- Pachymetry*
- Slit lamp exam
- Fundus exam
- Corneal topography*
- Axial length*
- Keratometry*
- Patient Satisfaction
- Specular Microscopy (Subgroup Study)

*assessed on all eyes preoperatively and if required to assess anomalous results postoperatively.

E. Surgical Parameters

To receive a spherical treatment, refractive astigmatism had to be less than 1.00D. For the astigmatism algorithm to be used, at least 0.50D of spectacle astigmatism was required. Therefore the surgeon had the choice as to whether to treat 0.50D or 0.75D of cylinder or to treat the spherical equivalent instead. The spherical and cylindrical components of the ablation were applied simultaneously. The ablation zone diameter for spherical treatments was 6.0mm and for astigmatic treatments was 5.5mm x 7.5mm. De-epithelialization was performed using either a rotating brush or manual scrape technique. The pupil was dilated prior to surgery to optimize the tracker performance. The laser was calibrated prior to each patient.

F. Postoperative Medications

Postoperative pharmaceutical treatment consisted of one drop each of diclofenac sodium 0.1% (Voltaren, CIBAVision Ophthalmics, Atlanta, GA) for the first 2 days and a combination of an antibiotic and a corticosteroid drop three to four times daily until healed. A bandage contact lens was applied to all eyes treated for up to 4 days.

Following cessation of this immediate postoperative drug therapy, no other corticosteroids were prescribed routinely unless indicated by the refractive error at the 1-month visit. Patients who had a spherical equivalent refractive error of ≥+0.50D were not prescribed steroids. Patients who had a spherical equivalent refractive error of <+0.50D were prescribed fluoromethalone qid for one month. At the 2 month follow-up visits, the steroid regimen was continued if further regression occurred or tapered if refraction was within 0.50D of target. If greater than 1.00D of regression occurred in the first 3 months, dexamethasone was prescribed.

Prednisolone acetate 1% could be prescribed for late regression at any time after the 3-month visit. Later regression was defined as a myopic change of ≥0.50D from the previous visit and a spherical equivalent more myopic than the desired outcome.

Patients with significant over-correction could be managed on the advice of the Medical Director with Voltaren drops and/or an extended wear soft contact lens over a one-month period. If this action did not improve the over-correction, epithelial scraping from the ablation bed could be considered.

G. Adverse Reactions and Complications

Adverse reactions were reported to the Sponsor immediately following their occurrence. Adverse reactions were reported to the FDA and the Institutional Review Board (IRB) within 10 days of their occurrence. Adverse reactions and complications were defined in the protocol as listed below.

- Corneal infiltrate or ulcer
- Persistent central corneal epithelial defect at one month or later
- Corneal edema at one month or later
- IOP increase of >10mm Hg above baseline or any reading above 25mm Hg
- Late onset of haze beyond six months with loss of ≥ 2 lines of BSCVA

- Decrease in BSCVA of greater than 10 letters not due to irregular astigmatism as shown by hard contact lens refraction at six months or later
- Retinal detachment
- Retinal vascular accidents

Complications were defined as:

- Corneal edema between one week and one month after the procedure
- Peripheral corneal epithelial defect at 1 month or later, including but not limited to recurrent corneal erosion
- Foreign body sensation at 1 month or later
- Pain at 1 month or later
- Double/ghost images in the operative eye

Adverse events and complications that occurred in the clinical study are shown below.

Summary of Adverse Events[1] and Complications[2]

	Spherical Myopia* **(n=467)**	**Myopia with Astigmatism**** **(n=211)**
Corneal Infiltrates[1]	1.5%	1.9%
IOP increase above 25 mmHg[1]	0.2%	1.4%
Feeling of something in the eye[2]	3.0%	2.4%
Double/ghost images[2]	2.6%	6.2%
Peripheral epithelial defect[2]	1.3%	0.5%
Pain[2]	1.3%	1.9%
Halos/starbursts[2]	0.6%	0.5%

*Other findings that occurred at a rate of <0.3% included corneal ulcer, corneal erosion, corneal abrasion, scratchiness, pain, epithelial irregularity, corneal swelling, subconjunctival hemorrhage, light sensitivity, epithelial dots, iritis and ocular hypertension.

** Other findings that occurred at a rate of <0.5% included retinal vascular accident, corneal abrasion and iritis.

Other events that did not occur in this study that could occur following PRK include significant corneal haze and loss of best-corrected visual acuity.

Subjects were asked to rate their conditions compared to before surgery. The percentage of patients that rated each condition as "significantly worse" than preoperative are listed below:

	Spherical Myopia (n=358)	**Myopia with Astigmatism (n=187)**
Difficulty with night driving	4.3%	9.4%
Glare	1.7%	4.4%
Halos	2.3%	6.1%
Feeling of something in eye	1.4%	0.0%
Fluctuation of vision	1.1%	3.8%
Blurring of vision	0.9%	2.2%
Light sensitivity	0.9%	0.5%
Headache	0.3%	0.5%
Double vision	0.3%	0.5%
Pain	0.3%	0.0%
Excessive tearing	0.3%	0.0%
Burning	0.3%	0.0%

Corneal infiltrates occurred in the immediate postoperative period at a rate of 1.6%. The infiltrates were aggressively treated and monitored. No impact to any clinical outcome has been shown (BSCVA 20/20 or better in 82% at 1 month). All eyes treated had prescribed use of non-steroid anti-inflammatory drugs (NSAIDs) and contact lenses for the first several days postop for pain management. Several actions were taken to mitigate the incidence level of infiltrate development, including reduction in the duration and frequency of NSAID use, increased warnings to the patient to minimize such use, and ensuring equal dosage of steroid drops with the NSAID drop. In addition, the method of epithelial removal was evaluated for its potential contribution to the infiltrate incidence. There was no statistically significant difference in the rate of infiltrates between the brush and scrape de-epithelialization techniques (p=.3406; Fisher exact test).

Increases in IOP were all associated with concomitant steroid use. The incidents of retinal tear, death of a patient by suicide and the brain aneurysm were not related to the refractive surgery procedure.

H. Study Period

In the U.S. clinical trial, the patients were entered into the clinical trial between the dates of March 12, 1996, and May 30, 1997. Low myopia patients were entered throughout the trial; patients having between –7.00D and –10.00D sphere and all astigmatic patients having cylinder -0.50D or greater were entered between February 21 and May 30, 1997.

I. Investigational Sites

The study was conducted in 6 locations throughout the U.S.A. Enrollment in each site is shown in Table 1.

TABLE 1
INVESTIGATIONAL SITES

Site Number	Spherical Myopia		Myopia with Astigmatism	
	n	%	n	%
1	72	15.4	3	1.4
2	174	37.3	90	42.7
3	101	21.6	50	23.7
4	27	5.8	11	5.2
5	56	12.0	26	12.3
6	37	7.0	31	14.7
Total	**467**	**100**	**211**	**100**

J. Demographics

TABLE 2
DEMOGRAPHICS

	Spherical Myopia n=467	Myopia with Astigmatism n=211
Age		
Mean ± SD	40.3 ± 9.6	42.0 ± 9.0
Range	19-72	20-64
Gender		
Male	38.7%	42.8%
Female	61.3%	57.2%
Race		
Caucasian	92.4%	92.3%
Black	2.5%	2.6%
Asian	3.3%	5.2%
Other	1.8%	0.0%
Contact Lens History		
None	22.5%	29.9%
Soft	69.4%	50.5%
RGP/PMMA)Hard	7.8%	18.5%
Other	0.3%	1.0%

K. Baseline Characteristics

TABLE 3 BASELINE CHARACTERISTICS				
	Spherical Myopia (n=467)		**Myopia with Astigmatism (n=211)**	
Refractive Parameters	Mean ± SD	Range	Mean ± SD	Range
Spherical Equivalent	-4.05 ± 1.85	-1.00 to -9.75	-5.03 ± 2.05	-1.00 to -10.25
Sphere	-3.90 ± 1.85	-0.75 to -9.50	-4.32 ± 2.06	0.00 to -9.50
Cylinder	-0.30 ± 0.28	0.00 to -0.75	-1.42 ± 0.73	-0.50 to -5.50
Preoperative UCVA	n	%	n	%
20/100 or worse	365	83.9	186	92.5
20/50 to20/80	54	12.4	10	5.0
20/25 to 20/40	16	3.7	5	2.5
≤ 20/20	0	0.0	0	0.0
Preoperative BSCVA	n	%	n	%
20/25 to 20/40	22	4.7	23	10.9
≤20/20	445	95.3	188	89.1

L. ACCOUNTABILITY

Table 4 shows the accountability for the spherical myopia cohort (n=467). There were 417 eyes (95.6% of those available for follow-up) analyzed at 6 months for safety and effectiveness.

TABLE 4 ACCOUNTABILITY: SPHERICAL MYOPIA						
Follow-up (Months)	**1**	**3**	**6**	**9**	**12**	**18**
Available for Refractive Analysis	460	450	417	171	75	26
% Accountability (available/[available + overdue])	98.5	96.6	95.6	85.5	92.6	100.0
Monovision eyes	32	31	38	12	6	1
Available for UCVA Analysis	428	419	389	159	69	25

Table 5 shows the accountability for the myopia with astigmatism cohort (n=211). There were 187 eyes (99.5% of those available for follow-up) analyzed at 6 months for safety and effectiveness.

TABLE 5 ACCOUNTABILITY: MYOPIA WITH ASTIGMATISM			
Follow-up (Months)	**1**	**3**	**6**
Available for Refractive Analysis	210	208	187
% Accountability (available/[available + overdue])	99.5	98.6	99.5
Monovision eyes	10	9	10
Available for UCVA Analysis	200	199	177

Nine month data was acquired on 112 eyes at the time of the FDA Panel review which represented 100% accountability of those eligible.

M. DATA ANALYSIS AND RESULTS

1. Stability of Refraction

Stability of Refraction is defined as the key effectiveness variable to permit analysis of results for safety and effectiveness in the treatment of refractive error. Stability is defined as a change of spherical equivalent of less than or equal to 1.00D between two refractions taken 3 months apart. The FDA Guidance Document states that this percentage should be at least 95%.

Paired difference analysis of manifest refraction spherical equivalent (MRSE) was performed to assess stability. Only subjects who had every follow-up exam were included in this analysis. Stability (Table 6) was achieved between 3 and 6 months in 96.5% of the spherical myopia population and in 97.3% of the myopia with astigmatism population.

TABLE 6 STABILITY OF MANIFEST REFRACTION		
Change in Spherical Equivalent ≤1.00 Between	1 and 3 Months	3 and 6 Months
Spherical Myopia (n=403)		
n	362	389
% stable	89.8	96.5
Mean Difference	0.49D	0.30D
SD	0.56	0.34
95% CI	(0.437; 0.547)	(0.269; 0.336)
Myopia with Astigmatism (n=185)		
n	161	180
% stable	87.0	97.3
Mean Difference	0.52	0.31
SD	0.53	0.33
95% CI	(0.439; 0.590)	(0.261; 0.357)

Between 6 and 9 months, 98.2% (n=164) had a change in MRSE of ≤1 Diopter for spherical myopia and 98.3% (n=118) had a change of ≤1 Diopter for myopia with astigmatism.

2. Spherical Myopia Cohort

a) Key Safety and Effectiveness Outcomes

A summary of the key safety and efficacy results for all eyes is shown in Table 7. At 6 months, uncorrected visual acuity was better than preoperative best corrected visual acuity in 19% of eyes. Table 8 shows the same results at 6 months stratified by diopter.

TABLE 7
SUMMARY OF KEY SAFETY AND EFFICACY VARIABLES
SPHERICAL MYOPIA -1 TO -10D

EFFICACY VARIABLES	1 Month	3 Months	6 Months	9 Months	12 Months	18 Months
	n=428	n=419	n=389	n=159	n=69	n=25
UCVA 20/20 or better*	58.9%	69.2%	69.7%	67.9%	87.0%	92.0%
UCVA 20/25 or better*	78.3%	83.3%	84.8%	83.6%	95.7%	96.0%
UCVA 20/40 or better*	95.6%	96.4%	95.9%	97.5%	100%	96.0%
	n=460	n=450	n=417	n=171	n=75	n=26
MRSE ±0.50D of intended	62.4%	74.8%	77.5%	81.3%	72.0%	84.6%
MRSE ±1.00D of intended	84.1%	91.5%	92.6%	95.9%	97.3%	96.2%
SAFETY VARIABLES	n=460	n=450	n=417	n=171	n=75	n=26
Loss of >2 Lines BSCVA	1.1%	0.9%	0.5%	0.0%	0.0%	0.0%
Loss of 2 Lines BSCVA	2.8%	2.9%	1.0%	1.8%	1.3%	0.0%
BSCVA worse than 20/40	0.2%	0.0%	0.2%	0.0%	0.0%	0.0%
Increase >2D cylinder	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
BSCVA 20/20 Preop	n=438	n=428	n=396	n=161	n=74	n=26
BSCVA worse than 20/25 if 20/20 or better preop	2.1%	1.9%	0.5%	0.0%	0.0%	0.0%

*not including monovision eyes

TABLE 8
SUMMARY OF KEY SAFETY AND EFFICACY VARIABLES
SPHERICAL MYOPIA -1 TO -10D STRATIFIED BY DIOPTERS
6 MONTHS

Efficacy		1.0 to 1.99	2.0 to 2.99	3.0 to 3.99	4.0 to 4.99	5.0 to 5.99	6.0 to 6.99	**Cum <7D**	7.0 to 7.99	8.0 to 8.99	9.0 to 9.99	**Cum ≥7D**
		n=57	**n=69**	**n=82**	**n=62**	**n=51**	**n=39**	**n=360**	**n=19**	**n=8**	**n=2**	**n=29**
UCVA 20/20 or better*	n	45	49	72	43	28	20	**257**	11	3	0	**14**
	%	78.9	71.0	87.8	69.4	54.9	51.3	**71.4**	57.9	37.5	0.0	**48.3**
UCVA 20/40 or better*	n	56	68	82	56	49	37	**348**	17	7	1	**25**
	%	98.2	98.6	100	90.3	96.1	94.9	**96.7**	89.5	87.5	50.0	**86.2**
		n=57	**n=72**	**n=88**	**n=69**	**n=56**	**n=45**	**n=387**	**n=20**	**n=8**	**n=2**	**n=30**
MRSE ±0.50D	n	51	59	78	47	39	31	**305**	16	1	1	**18**
	%	89.5	81.9	88.6	68.1	69.6	68.9	**78.8**	80.0	12.5	50.0	**60.0**
MRSE ±1.00D	n	57	71	87	60	48	40	**362**	18	4	1	**23**
	%	100	98.6	98.9	87.0	85.7	88.9	**93.5**	90.0	50.0	50.0	**76.7**
Safety		**n=57**	**n=72**	**n=88**	**n=69**	**n=56**	**n=45**	**n=387**	**n=20**	**n=8**	**n=2**	**n=30**
Loss of >2 Lines BSCVA	n	0	0	0	0	0	0	**0**	0	1	1	**2**
	%	0.0	0.0	0.0	0.0	0.0	0.0	**0.0**	0.0	12.5	50.0	**6.7**
Loss of 2 Lines BSCVA	n	1	1	0	0	1	1	**4**	0	0	0	**0**
	%	1.8%	1.4%	0.0%	0.0%	1.8%	2.2%	**1.0%**	0.0%	0.0%	0.0%	**0.0%**
BSCVA worse than 20/40	n	0	0	0	0	0	0	**0**	0	1	0	**1**
	%	0.0	0.0	0.0	0.0	0.0	0.0	**0.0**	0.0	12.5	0.0	**3.3**
Increase >2D cyl	n	0	0	0	0	0	0	**0**	0	0	0	**0**
	%	0.0	0.0	0.0	0.0	0.0	0.0	**0.0**	0.0	0.0	0.0	**0.0**
BSCVA 20/20 preop		**n=57**	**n=64**	**n=87**	**n=69**	**n=52**	**n=40**	**n=369**	**n=18**	**n=8**	**n=1**	**n=27**
BSCVA worse than 20/25 if 20/20 or better preop	n	0	0	0	0	0	1	**1**	0	1	0	**1**
	%	0.0	0.0	0.0	0.0	0.0	2.5	**0.3**	0.0	12.5	0.0	**3.7**

*not including monovision eyes

b) MRSE as a Function of Postoperative Time

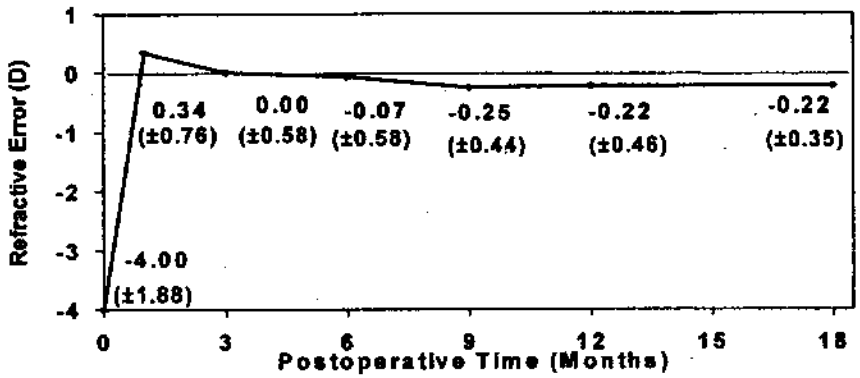

Fig. 1. Spherical Myopia Study : MRSE as a Function of Postoperative Time (±SD)

c) Additional Safety Outcomes

In the spherical cohort at 6 months, corneal haze was trace or less in 94% of eyes. At 6 months, there was one eye with Grade 3 haze that resolved by 9 months. This grade of haze was associated with loss of BSCVA of more than 2 lines (from 20/20 to 20/50). On resolution of the haze, the BSCVA returned to the preoperative level of 20/20. No fundus or crystalline lens abnormalities occurred due to the procedure. None of the eyes had an IOP of greater than 25mm Hg or a change in IOP of greater than 10mm Hg reported at a scheduled follow-up visit. One eye had an IOP of greater than 25mm Hg at an unscheduled visit that was reported as an adverse reaction.

d) Statistical Analysis Outcomes

Statistical analysis showed that younger patients had better UCVA and BSCVA than older patients, and Asians as a group had more overcorrection at one month than other races. This difference was not significant at later intervals, however. More males than females achieved 20/20 UCVA. Previous hard/RGP lens wearers had a lower chance of obtaining 20/20 UCVA and had a worse refractive outcome than soft or non-wearers. Overcorrection was significantly associated with older patient age, higher attempted corrections, lower laser room humidity and longer deepithelialization times. Eyes with larger pupils read fewer letters uncorrected and had more negative spherical equivalents postoperatively. Lower myopes had a better outcome overall than moderate myopes.

e) Patient Questionnaire Responses

Responses to the patient satisfaction questionnaire at 6 months indicated that the quality of vision was improved in 93.5% of eyes and 88.6% were satisfied or extremely satisfied with the results. There was no need for distance correction by 95.2% of patients.

3. Myopia With Astigmatism

a) Key Safety and Effectiveness Outcomes

e) Patient Questionnaire Responses

Responses to the patient satisfaction questionnaire at 6 months indicated that the quality of vision was improved in 93.5% of eyes and 88.6% were satisfied or extremely satisfied with the results. There was no need for distance correction by 95.2% of patients.

3. Myopia With Astigmatism

a) Key Safety and Effectiveness Outcomes

A summary of the key safety and efficacy results for all eyes is shown in Table 9. At 6 months, uncorrected visual acuity was better than preoperative best corrected visual acuity in 23% of eyes. Table 10 shows the same results at 6 months stratified by diopter of spherical equivalent correction.

Following submission of the final PMA to FDA, nine month data was acquired on 112 eyes which provided longer term safety and effectiveness results as follows: UCVA 20/20 or better 61.6%; UCVA 20/25 or better 76.8%; UCVA 20/40 or better 99.1%; MRSE ±0.50D 79.0%; MRSE ±1.00D 93.3%; Loss of >2 lines BSCVA 0.8%.

TABLE 9
SUMMARY OF KEY SAFETY AND EFFICACY VARIABLES
ASTIGMATIC TREATMENTS

Efficacy Variables	**1 Month**	**3 Months**	**6 Months**
	n=200	**n=199**	**n=177**
UCVA 20/20 or better *	48.0%	55.3%	59.3%
UCVA 20/25 or better*	72.0%	76.9%	80.8%
UCVA 20/40 or better *	92.5%	92.5%	93.2%
	n=210	**n=208**	**n=187**
MRSE ±0.50D	58.1%	71.6%	74.3%
MRSE ±1.00D	86.2%	89.9%	92.0%
Safety Variables	**n=210**	**n=208**	**n=187**
Loss of >2 Lines BSCVA	0.5%	0.5%	0.0%
Loss of 2 Lines BSCVA	3.3%	2.9%	2.1%
BSCVA worse than 20/40	0.5%	0.0%	0.0%
Increase >2D Cylinder	0.0%	0.0%	0.0%
BSCVA 20/20 Preop	**n=187**	**n=185**	**n=168**
BSCVA worse than 20/25 if 20/20 or better Preop	1.1%	2.2%	0.0%

*Not including monovision eyes

TABLE 10
SUMMARY OF KEY SAFETY AND EFFICACY VARIABLES
ASTIGMATIC TREATMENTS STRATIFIED BY DIOPTERS
(SPHERICAL EQUIVALENT)
6 MONTHS

Efficacy Variables	SE	1.0 to 1.99	2.0 to 2.99	3.0 to 3.99	4.0 to 4.99	5.0 to 5.99	6.0 to 6.99	Cum <7D	7.0 to 7.99	8.0 to 8.99	9.0 to 9.99	Cum ≥7D
		n=12	n=15	n=36	n=36	n=24	n=18	n=141	n=22	n=9	n=5	n=36
UCVA 20/20* or better	N	9	14	22	20	16	8	89	9	5	2	16
	%	75.0	93.3	61.1	55.6	66.7	44.4	63.1	40.9	55.6	40.0	44.4
UCVA 20/40* or better	N	11	15	35	33	23	16	133	20	7	5	32
	%	91.7	100	97.2	91.7	95.8	88.9	94.3	90.9	77.8	100	88.9
		n=12	n=15	n=36	n=36	n=28	n=20	n=147	n=24	n=10	n=6	n=40
MRSE ±0.50D	N	11	14	33	27	16	15	116	13	6	4	23
	%	91.7	93.3	91.7	75.0	57.1	75.0	78.9	54.2	60.0	66.7	57.5
MRSE ±1.00D	N	12	14	35	34	24	17	136	22	8	6	36
	%	100	93.3	97.2	94.4	85.7	85.0	92.5	91.7	80.0	100	90
Safety Variables		n=12	n=15	n=36	n=36	n=28	n=20	n=147	n=24	n=10	n=6	n=40
Loss of >2 Lines BSCVA	N	0	0	0	0	0	0	0	0	0	0	0
	%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Loss of 2 Lines BSCVA	N	0	0	0	0	1	1	2	2	0	0	2
	%	0.0	0.0	0.0	0.0	3.6	5.0	1.4	8.3	0.0	0.0	5.0
BSCVA worse than 20/40	0	0	0	0	0	0	0	0	0	0	0	0
	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Increase >2D Cylinder	N	0	0	0	0	0	0	0	0	0	0	0
	%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BSCVA 20/20 Preop		n=11	n=14	n=35	n=36	n=27	n=14	n=137	n=20	n=8	n=3	n=31
BSCVA worse than 20/25 if 20/20 or better Preop	N	0	0	0	0	0	0	0	0	0	0	0
	%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

*Not including monovision eyes

b) MRSE as a Function of Postoperative Time

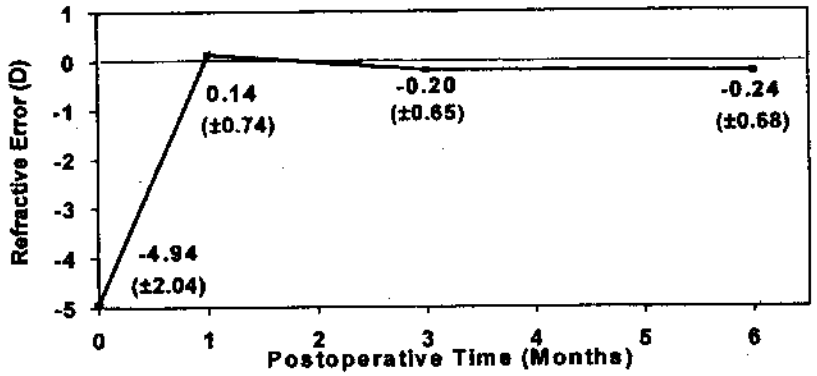

Fig. 2. Myopia with Astigmatism: MRSE as a Function of Postoperative Time (±SD)

c) Cylinder Correction: Scalar and Vector Analysis

Astigmatism correction was assessed based on the magnitude of cylinder and vector analysis (Table 11). Vector analysis showed that 96% of the intended cylinder correction was achieved. At 6 months, 81.3% of eyes had ≤0.50D and 94.7% of eyes had ≤1.00D of residual cylinder.

TABLE 11
SUMMARY OF CYLINDER CORRECTION
6 MONTHS

Absolute Magnitude		Vector Analysis	
Preoperative	1.42 ± 0.69	Intended Vector	1.42 ± 0.69
Postoperative	0.30 ± 0.43	Difference Vector	0.30 ± 0.43
Achieved Magnitude	1.15 ± 0.71	Achieved Vector	1.36 ± 0.72
% Achieved	79 ± 29	% Achieved	96 ± 32
Axis Shift*	31.7 ± 27.3	Angle of Error	4.9 ± 11.0

*eyes with residual cylinder >0

d) Additional Safety Outcomes

At 6 months, there was no corneal haze greater than grade 2 and no cases of significant corneal haze resulting in a loss of BSCVA of greater than 2 lines. There were no significant fundus abnormalities that were not reported preoperatively. One patient developed posterior subcapsular cataract in both the treated and untreated eye postoperatively. Three eyes had an IOP of greater than 25mm Hg and more than 10mm Hg higher than baseline. All 3 eyes were reported as adverse reactions.

e) Statistical Analysis Outcomes

Statistical analysis showed that younger patients had better UCVA than older patients and lower myopes had a better outcome than higher myopes. There was no difference in outcome based on the amount of cylinder correction. More overcorrection was associated with higher attempted corrections, lower laser room humidity and longer deepithelialization times.

f) Patient Questionnaire Responses

Responses to the patient satisfaction questionnaire at 6 months indicated that the quality of vision was improved in 93.4% of eyes and 87.4% were satisfied or extremely satisfied with the results. Distance correction was not required by 93.4% of patients postoperatively.

4. Moderate Myopia

Data has been gathered on 48 eyes to demonstrate safety and effectiveness of the laser for the moderate myopic group. This group incorporates eyes from the Primary and Continuing Cases Cohort with myopia (with and without astigmatism) with a spherical equivalent correction between -8.01 and -10.00D. Data from the Primary Cohort only has been reported in the remainder of this document and represents results of primary and fellow eyes treated prior to May 30, 1997. The Continuing Cases Cohort consists of fellow eyes of patients enrolled in the Primary Cohort and these treatments were performed after May 30, 1997. Table 12 shows the key safety and efficacy parameters for these eyes.

TABLE 12
SUMMARY OF KEY SAFETY AND EFFICACY VARIABLES
-8.01 TO -10D SE MYOPIA ± ASTIGMATISM

Efficacy Variables	1 Month	3 Months	6 Months	9 Months
	n=40	n=39	n=39	n=27
UCVA 20/20 or better *	12 30.0%	20 51.3%	18 46.2%	16 59.3%
UCVA 20/25 or better*	19 47.5%	28 71.8%	25 64.1%	19 70.4%
UCVA 20/40 or better *	36 90.0%	35 89.7%	32 82.1%	24 88.9%
	n=48	n=47	n=47	n=28
MRSE ±0.50D	11 22.9%	24 51.1%	22 46.8%	16 57.1%
MRSE ±1.00D	25 52.1%	37 78.7%	31 66.0%	23 82.1%
Safety Variables	**n=48**	**n=47**	**n=47**	**n=28**
Loss of >2 Lines BSCVA	1 2.1%	0 0.0%	3 ** 6.4%	1 3.6%
Loss of 2 Lines BSCVA	2 4.2%	3 6.4%	1 2.1%	0 0.0%
BSCVA worse than 20/40	1 2.1%	0 0.0%	1 2.1%	0 0.0%
Increase >2D Cylinder	0 0.0%	0 0.0%	0 0.0%	0 0.0%

*not including monovision eyes ** two eyes recovered to no loss of lines by 9 months
Note: 10 eyes were not 20/20 or better BSCVA preoperatively

5. Combined Cohort

a) Patient Satisfaction

Responses to the patient satisfaction questionnaire at 6 months indicated that in the spherical myopia cohort, the quality of vision was improved in 93.5% of eyes and 88.6% were satisfied or extremely satisfied with the results. There was no need for distance correction in 95.2% of eyes. In the myopia with astigmatism group, the quality of vision was improved in 93.4% of eyes and 87.4% were satisfied or extremely satisfied with the results. Distance correction was not required in 93.4% of eyes postoperatively.

b) Subgroup Study - Endothelial Cell Density

Two clinical sites contributed eyes to the subgroup analysis of endothelial cell density. Data was available on 135 eyes at 1 month, 120 eyes at 3 months and 112 eyes at 6 months. There was no statistically significant difference in cell density for all eyes combined or low myopes. There was no clinically significant difference in cell density (<10%) for moderate myopes. A further analysis was performed comparing previous contact lens wearers to non-wearers and no significant difference was found.

c) Retreatments

Retreatments occurred in 1.9% (9 eyes) of the spherical myopia population and 3.8% (8 eyes) of the myopia with astigmatism population. In the spherical cohort, at the last visit 89% of the eyes were 20/40 or better uncorrected and 78% were within 0.50D of intended correction. Corneal haze was grade 1 or less in all eyes. In the astigmatic cohort, at the last visit 87% of the eyes were 20/40 or better uncorrected and 87% were within 0.50D of intended correction. Corneal haze was graded as trace or less in all eyes.

X. CONCLUSIONS DRAWN FROM THE CLINICAL STUDIES

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

XI. PANEL RECOMMENDATIONS

On February 13, 1998, the Ophthalmic Devices Panel recommended that the premarket approval application for the excimer laser be approved with the following conditions:

- Change the age limitation statement in the indications for use and inclusion criteria from 18 years of age to 21 years of age because too few eyes were studied between the ages of 18 and 21.

- Modify the patient and physician labeling and summary of safety and effectiveness data to reflect the specific dioptric limits: the correction of -1.00 D to -10.00 D of myopia and less than or equal to -4.00 D of astigmatism at the spectacle plane, the combination of which must result in an attempted correction between -0.50 D and -10.00 D spherical equivalent (SE) at the spectacle plane where sphere or cylinder is at least -1.00 D.

- Add statements to the labeling addressing the following concerns:

    a. No refractive treatment should be performed on patients in whom the residual corneal thickness at the completion of ablation would be less than 250 microns.

    b. The risk of sterile infiltrates associated observed during the clinical study needs to be included in the Precautions.

    c. A minimum pre-operative pupillary dilation of 7 mm must be achieved and maintained in all potential patients throughout the refractive procedure.

    d. All parameters associated with overcorrections should be clearly stated in the Precautions.

XII. FDA DECISION

CDRH concurred with the Panel's recommendation of February 13, 1998. However, a letter was issued to Autonomous Technologies Corporation on April 6, 1998 advising that the PMA was not approvable due to the additional questions raised pertaining to the comparability of the initial laser head (alpha unit) to a faster replacement laser head (beta unit). This second unit was to be used with the excimer laser system. The applicant satisfactorily addressed the Panel's and FDA's remaining deficiencies. FDA issued an approval order on November 3, 1998. The applicant's manufacturing facility was inspected from August 24 through September 4, 1998 and was found to be in compliance with the device quality system regulations (QSR) regulations.

XIII. APPROVAL SPECIFICATIONS

- Post approval Requirements and Restrictions: see Approval Order
- Hazards to Health from Use of the Device: see Indications, Contraindications, Warnings, Precautions, and Adverse Events in the labeling
- Directions for Use: see the labeling