Summary of Safety and Effectiveness Data
For a Supplemental Premarket Approval Application

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
2800 Discovery Drive
Orlando, FL 32826

Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P970043/S5

Date of Notice of Approval to Applicant: May 9, 2000

The LADARVision® Excimer Laser System was approved on November 2, 1998 for the indication of photorefractive keratectomy for the reduction or elimination of mild to moderate myopia of between –1.00 and –10.00 D sphere and less than or equal to –4.00 D astigmatism at the spectacle plane, the combination of which must result in an attempted correction of between –0.50 and –10.00 D spherical equivalent at the spectacle plane where the sphere or cylinder is at least 1.00 D (P970043). The sponsor submitted the current supplement to further expand the indication statement. The updated pre-clinical and clinical work to support this expanded indication is provided in this summary. For more information on the data that supported the approved indication, the Summary of Safety and Effectiveness Data to that PMA application should be requested from the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857. Please identify Docket # OOM-1592. The summary can also be found on the FDA CDRH Internet Home Page located at http://www.fda.gov/cdrh/pmapage.html.

II. INDICATIONS FOR USE

The LADARVision Excimer Laser System is indicated for use:

- in Laser In-Situ Keratomileusis (LASIK) treatments for the reduction or elimination of myopia (nearsightedness) of less than –9.00D sphere and –0.50 to less than –3.00D of astigmatism at the spectacle plane;
- 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, and less than or equal to -1.00D for corrections greater than -7.00D SE; and,
- in subjects who are 21 years of age or older.

III. CONTRAINDICATIONS

LASIK 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) or amiodarone hydrochloride (Cordarone); or,
- in patients with an autoimmune disease, collagen vascular disease, or an immunodeficiency disease.

IV. WARNINGS AND PRECAUTIONS

A. WARNINGS

See the labeling.

B. PRECAUTIONS

See the labeling.

V. DEVICE DESCRIPTION

The LADARVision Excimer Laser System (henceforth, to be called LADARVision) that is the subject of this supplement has the same ablation characteristics (e.g., fluence, pulse rate, repetition rate, shot algorithm, tracker function, etc.) as the one previously approved for PRK. The changes that were

implemented were not associated with the new indications for use, but were to improve device reliability, user-friendliness, and consistency.

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

There are currently several other alternatives for the correction myopia with or without astigmatism:

Automated lamellar keratoplasty
Contact Lenses
Photorefractive Keratectomy
Radial and Astigmatic Keratotomies
Spectacles

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

VII. MARKETING HISTORY

The device has been marketed in 4 countries: USA, Canada, United Kingdom, and Italy. The LADARVision has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse 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, problems associated with the flap including a lost, misplaced or misaligned flap, retinal detachment, and retinal vascular accidents.

For adverse events and complications observed during the clinical study, please refer to tables 14, 15, and 16 presented in the clinical section of the SSED.

IX. SUMMARY OF PRECLINICAL STUDIES

No additional preclinical study was required for the use of the device in LASIK, given that device remains relatively unchanged from its design for PRK.

X. SUMMARY OF CLINICAL STUDIES

The sponsor performed a clinical study of the LADARVision in the US under the auspices of an investigational device exemptions application (IDE) G950213. The data from this study served as the basis for the approval decision. Specifically, safety and effectiveness outcomes at 3 months postoperative were assessed as stability was reached by that time. Outcomes at 6 and 9 months postoperatively were also evaluated for confirmation. The IDE study is described in detail as follows:

A. STUDY OBJECTIVES

The objective of this study was to determine the safety and effectiveness of the LADARVision for the full correction of spherical myopia ≤ -11.0 D with or without astigmatism of ≥ -0.50 D but ≤. -6.0 D at the spectacle plane using the LASIK procedure.

B. STUDY DESIGN

The study was prospective, non-randomized, unmasked, and multi-center, 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 LASIK study was limited to patients with: spherical myopia ≤ -11.0 D with or without astigmatism of ≥ -0.50 D but ≤ -6.0 D at the spectacle plane; documented stability of refraction for the prior 12 months, as demonstrated by a change of less than or equal to 0.50 D for corrections up –7.00 D SE, and less than or equal to –1.00 D for corrections greater than –7.00 D SE; both eyes correctable to 20/40 or better; and, at least 18 years of age.

Patients were not permitted to enroll in the LASIK study if they met any of the following exclusion criteria: previous intraocular or corneal surgery; history of or clinically active or visually significant ocular disease or pathology; corneal scars within the ablation zone or other corneal abnormality such as recurrent erosion; 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 nursing; use of ophthalmic medications other than artificial tears for treatment of an ocular pathology; severe dry syndrome unresolved by treatment; allergy to study medications; corneal thickness of less than 400 microns; glaucoma or glaucoma filtering surgery; or, participation in another ophthalmic clinical trial.

D. STUDY PLAN, PATIENT ASSESSMENTS, AND EFFICACY CRITERIA

All subjects were expected to return for follow-up at 1 day, 1 week, and 1, 3, 6, 9, and 12 months postoperatively.

Bilateral simultaneous treatments and retreatments were approved on August 28, 1998. Subjects were permitted to have their fellow eyes treated on the same day as the primary eye or any time thereafter provided there were no active adverse reactions for the primary eye.

Retreatments were allowed after the 1-month follow-up visit and on the approval of the Medical Director. To be retreated for undercorrection, all of the following conditions had to be met:

a) UCVA worse than 20/25 or residual myopia greater than or equal to 0.75D;
b) stable refraction, with MRSE on the two most recent consecutive visits 1 month apart within 0.50D for eyes whose primary treatment was an attempted correction up to 6D and within 1D for attempted corrections higher than 6D;
c) stable UCVA, i.e., within one line on two consecutive visits at least 1 month apart;
d) patients signed a separate informed consent document, wherein they were informed of their increased risk associated with retreatment;
e) the eligibility criteria were met and an ophthalmic evaluation (including VA, manifest refraction and slit lamp) was done to establish the preoperative condition of the eye; and,
f) prior written approval was obtained from the sponsor of the study.

Retreatment for the purpose of correcting residual refractive error was not considered a treatment failure. Results of retreated eyes were analyzed separately from the primary cohort.

No other ocular surgery procedures were allowed unless deemed medically necessary by the investigator. The sponsor had to be notified prior to any secondary surgical interventions, except in the case of an emergency.

In the event of a miscreated flap with the microkeratome, which was an adverse reaction in the study, a second cut with the microkeratome may be performed and the laser ablation procedure may be completed after a minimum of 3 months. Approval from the Medical Monitor was required prior to treating an eye with a miscreated flap.

Preoperatively, the subjects' medical and ocular histories were recorded. The objective parameters measured during the study included: uncorrected visual acuity, best spectacle corrected visual acuity, pupil size, manifest and cycloplegic refraction, intraocular pressure, and status of the cornea, conjunctiva, anterior chamber, lens, vitreous, retina, and externals. These parameters were collected preoperatively and only as needed postoperatively: corneal thickness, corneal topography, axial length, and keratometry. A patient questionnaire was administered to subjects preoperatively and at 3, 6, and 12 months postoperatively. Specular microscopy and contrast sensitivity were performed in subgroups of patients.

The primary efficacy variables for this study were improvement of UCVA based on the pre- 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

Subjects were treated between August 10, 1998 and June 14, 1999. The database for this PMA supplement reflected data collected through October 22, 1999 and included 347 eyes: 177 eyes with < -1 D of astigmatism were treated for spherical myopia only (spherical eyes), and 170 eyes with –0.50 D to –0.6 D of astigmatism were treated for spherical and cylindrical myopia (astigmatic eyes). There were 4 investigational sites with 5 lasers and 10 investigators.

It was noted that 1 site with 1 investigator and 2 lasers contributed 72% of the eyes in the PMA cohort. The sponsor performed statistical analyses to show that the demographics and outcomes from this site were not statistically different from the other sites, in order to justify pooling the data.

2. Demographics

The demographics of this study population are very typical of a contemporary refractive surgery trial performed in the US. The cohort consists primarily of Caucasians. Preoperative patient

characteristics that were found to associate with outcomes are discussed in section X.F.2.f.

Table 1: DEMOGRAPHICS			
	All Eyes (N= 347)	Spherical Eyes (N=177)	Astigmatic Eyes (N=170)
Gender			
Female	182 (52.4%)	86 (48.6%)	96 (56.5%)
Male	165 (47.6%)	91 (51.4%)	74 (43.5%)
Race			
Caucasian	327 (94.2%)	172 (97.2%)	155 (91.2%)
Hispanic	14 (4.0%)	2 (1.1%)	12 (7.1%)
Asian	4 (1.2%)	1 (0.6%)	3 (1.8%)
Black	2 (0.6%)	2 (1.1%)	0
Eye			
Right	177 (51.0%)	91 (51.4%)	86 (50.6%)
Left	170 (49.0%)	86 (48.6%)	84 (49.4%)
Age (Years)			
Average	42.8	42.5	43.1
Standard Deviation	9.3	9.4	9.3
Minimum	21	21	21
Maximum	65	65	62
Contact Lens History			
None	85 (24.5%)	34 (19.2%)	51 (30.0%)
Soft	238 (68.6%)	136 (76.8%)	102 (60.0%)
RGP	24 (6.9%)	7 (4.0%)	17 (10.0%)
PMMA	0	0	0

F. DATA ANALYSIS AND RESULTS

1. Preoperative Characteristics

Tables 2 and 3 contain the number of eyes enrolled stratified by the preoperative refraction. Note that per the protocol, the attempted correction corresponds with a subject's preoperative refractive error except for eyes undercorrected for monovision therapy. These eyes are excluded from the UCVA analysis, but are included in the remaining analyses.

TABLE 2 : Spherical Eyes
Stratified by Preop Sphere And Cylinder
Components of Manifest Refraction

	CYLINDER				
SPHERE	0.00	-0.25	-0.50	-0.75	TOTAL
0.0 to -0.99	0 0.0%	0 0.0%	0 0.0%	1 0.6%	1 0.6%
-1.0 to -1.99	5 2.8%	1 0.6%	11 6.2%	3 1.7%	20 11.3%
-2.0 to -2.99	14 7.9%	4 2.2%	13 7.3%	4 2.2%	35 19.8%
-3.0 to -3.99	13 7.3%	8 4.5%	11 6.2%	3 1.7%	35 19.8%
-4.0 to -4.99	14 7.9%	7 4.0%	10 5.6%	4 2.2%	35 19.8%
-5.0 to –5.99	8 4.5%	4 2.2%	6 3.4%	0 0.0%	18 10.1%
-6.0 to –6.99	4 2.2%	1 0.6%	1 0.6%	3 1.7%	9 5.1%
-7.0 to –7.99	4 2.2%	2 1.1%	4 2.2%	1 0.6%	11 6.2%
-8.0 to –8.99	2 1.1%	1 0.6%	5 2.8%	1 0.6%	9 5.1%
-9.0 to –9.99	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%
-10 to -11	1 0.6%	1 0.6%	1 0.6%	1 0.6%	4 2.2%
TOTAL	65 36.7%	29 16.4%	62 35.0%	21 11.8%	177 100%

TABLE 3: Astigmatic Eyes
Stratified by Preop Sphere And Cylinder
Components of Manifest Refraction

SPHERE	CYLINDER						
	-0.50 to -0.99	-1.0 to -1.99	-2.0 to -2.99	-3.0 to -3.99	-4.0 to -4.99	-5.0 to -6.0	TOTAL
0.0 to -0.99	0 0.0%	5 2.9%	3 1.8%	4 2.4%	1 0.6%	1 0.6%	14 8.2%
-1.0 to -1.99	4 2.4%	12 7.1%	8 4.7%	1 0.6%	0 0.0%	1 0.6%	26 15.3%
-2.0 to -2.99	4 2.4%	9 5.3%	6 3.5%	1 0.6%	1 0.6%	1 0.6%	22 12.9%
-3.0 to -3.99	6 3.5%	19 11.2%	7 4.1%	0 0.0%	1 0.6%	0 0.0%	33 19.4%
-4.0 to -4.99	2 1.2%	12 7.1%	6 3.5%	0 0.0%	0 0.0%	0 0.0%	20 11.8%
-5.0 to –5.99	4 2.4%	10 5.9%	3 1.8%	0 0.0%	0 0.0%	0 0.0%	17 10.0%
-6.0 to –6.99	3 1.8%	7 4.1%	4 2.4%	1 0.6%	0 0.0%	0 0.0%	15 8.8%
-7.0 to –7.99	4 2.4%	9 5.3%	0 0.0%	1 0.6%	0 0.0%	0 0.0%	14 8.2%
-8.0 to –8.99	1 0.6%	3 1.8%	1 0.6%	0 0.0%	0 0.0%	0 0.0%	5 2.9%
-9.0 to –9.99	1 0.6%	2 1.2%	1 0.6%	0 0.0%	0 0.0%	0 0.0%	4 2.4%
-10 to -11	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%
TOTAL	29 17.1%	88 51.8%	39 22.9%	8 4.7%	3 1.8%	3 1.8%	170 100.0%

2. Postoperative results

a. Accountability

The percent of enrolled eyes accounted for at each visit is acceptable.

Table 4: Accountability of Spherical Eyes					
		1 Month	3 Months	6 Months	9 Months
Enrolled	Primary	92	92	92	92
	Fellow	85	85	85	85
	N	177	177	177	177
Available for Analysis	n	171	169	157	72
	n/N (%)	96.6%	95.5%	88.7%	40.7%
Discontinued	n				
	Deceased	0	0	0	0
	Retreated	0	1	4	16
	n/N(%)	0.0%	0.6%	2.3%	9.0%
Missed visit	n	3	4	5	9
	n/N (%)	1.7%	2.3%	2.8%	5.1%
Not yet eligible for the interval Or Still eligible for interval when database closed	n	0	0	8	77
	n/N (%)	0%	0%	4.5%	43.5%
Lost to Follow-up	n	3	3	3	3
	n/N (%)	1.7%	1.7%	1.7%	1.7%
% Accountability = Available for Analysis / (Enrolled – Discontinued – Not yet eligible)		96.6%	96.0%	95.2%	85.7%

Table 5: Accountability of Astigmatic Eyes					
		1 Month	3 Months	6 Months	9 Months
Enrolled	Primary	94	94	94	94
	Fellow	76	76	76	76
	N	170	170	170	170
Available for Analysis	n	167	161	113	43
	n/N (%)	98.2%	94.7%	66.5%	25.3%
Discontinued	n				
	Deceased	0	0	0	0
	Retreated	0	2	13	16
	n/N (%)	0.0%	1.7%	7.6%	9.4%
Missed visit	n	3	4	5	6
	n/N (%)	1.8%	2.4%	2.9%	3.5%
Not yet eligible for the interval Or Still eligible for interval when database closed	n	0	0	36	102
	n/N (%)	0%	0%	21.2%	60.0%
Lost to Follow-up	n	0	3	3	3
	n/N (%)	0.0%	1.8%	1.8%	1.8%
% Accountability = Available for Analysis / (Enrolled – Discontinued – Not yet eligible)		98.2%	95.8%	93.4%	82.7%

b. Stability of outcome

In the 1-3 month window, greater than 95% of eyes experienced a change of MRSE not exceeding ± 1.0D.

Furthermore, the mean of the paired-difference of MRSE progressively decreased over time, and reached a change of less than |0.10| D in the 1-3 months window (Tables 6 to 9). The changes in the 3-6 months window for the entire cohort remained at less than |0.10| D; thus, stability was demonstrated by 3 months postoperative.

TABLE 6: Spherical Eyes
Stability Of MRSE
(Eyes that had every exam through 6 Months)

Change in Spherical Equivalent Between		1 and 3 Months (n=146)	3 and 6 Months (n=146)
≤1.00	n	143	146
	%	98.0%	100.0%
Mean Difference		-0.07	-0.09
SD		0.36	0.30
95% CI		(-0.13, -0.01)	(-0.14, -0.04)

TABLE 7: Spherical Eyes Stability Of MRSE (eyes that had 2 consecutive but not every exam)				
Change in Spherical Equivalent Between		1 and 3 Months (n=160)	3 and 6 Months (n=152)	6 and 9 Months (n=71)
≤1.00	n %	156 97.5%	152 100.0%	70 98.6%
Mean Difference		-0.07	-0.08	+0.03
SD		0.38	0.31	0.32
95% CI		(-0.13, -0.01)	(-0.13, -0.03)	(-0.04, 0.11)

TABLE 8: Astigmatic Eyes Stability Of MRSE (Eyes that had every exam through 6 Months)			
Change in Spherical Equivalent Between		1 and 3 Months (n=108)	3 and 6 Months (n=108)
≤1.00	n %	108 100.0%	108 100.0%
Mean Difference		-0.08	+0.02
SD		0.32	0.34
95% CI		(-0.14, -0.02)	(-0.05, 0.08)

TABLE 9: Astigmatic Eyes Stability Of MRSE (eyes that had 2 consecutive exams but not every exam)				
Change in Spherical Equivalent Between		1 and 3 Months (n=155)	3 and 6 Months (n=111)	6 and 9 Months (n=41)
≤1.00	n %	154 99.4%	110 99.1%	40 97.6%
Mean Difference		-0.07	+0.04	-0.05
SD		0.32	0.41	0.40
95% CI		(-0.12, -0.02)	(-0.04, 0.12)	(-0.18, 0.07)

c. Effectiveness Outcomes

The analysis of UCVA effectiveness was based on the158 spherical and 143 astigmatic eyes and MRSE effectiveness was based on 167 spherical and 160 astigmatic eyes available at the 3-month stability time point. There were 3 eyes that had no MRSE reported, but did have UCVA reported.

TABLE 10: SPHERICAL EYES AT STABILITY
SUMMARY OF KEY EFFECTIVENESS VARIABLES STRATIFIED BY DIOPTERS

Efficacy Variables		-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	**Total <7D**	-7.0 to -7.99	-8.0 to -8.99	-9.0 to -9.99	-10.0 to -11.0	**Total ≥7D**	**Cum Total**
BSCVA ≥ 20/20 Preop*		**n=13**	**n=38**	**n=28**	**n=29**	**n=16**	**n=8**	**n=132**	**n=9**	**n=6**	**n=2**	**n=4**	**n=21**	**n=153**
UCVA 20/20 or better if BSCVA 20/20 or better Preop*	n	7	33	17	20	9	2	**88**	7	5	0	3	**15**	103
	%	53.8%	86.8%	60.7%	69.0%	56.3%	25.0%	**66.7%**	77.8%	83.3%	0.0%	75.0%	**71.4%**	67.3%
		n=13	**n=38**	**n=30**	**n=29**	**n=17**	**n=10**	**n=137**	**n=9**	**n=6**	**n=2**	**n=4**	**n=21**	**n=158**
UCVA 20/20 or better*	n	7	33	17	20	9	2	**88**	7	5	0	3	**15**	103
	%	53.8%	86.8%	56.7%	69.0%	52.9%	20.0%	**64.2%**	77.8%	83.3%	0.0%	75.0%	**71.4%**	65.2%
UCVA 20/25 or better*	n	10	34	25	22	12	6	**109**	7	6	2	3	**18**	127
	%	76.9%	89.5%	83.3%	75.9%	70.6%	60.0%	**79.6%**	77.8%	100.0%	100.0%	75.0%	**85.7%**	80.4%
UCVA 20/40 or better*	n	12	37	28	27	15	9	**128**	9	6	2	4	**21**	149
	%	92.3%	97.4%	93.3%	93.1%	88.2%	90.0%	**93.4%**	100.0%	100.0%	100.0%	100.0%	**100.0%**	94.3%
		n=13	**n=39**	**n=34**	**n=31**	**n=18**	**n=10**	**n=145**	**n=8**	**n=8**	**n=2**	**n=4**	**n=22**	**n=167**
MRSE ±0.50D of intended	n	12	34	28	25	15	4	**118**	6	7	2	4	**19**	137
	%	92.3%	87.2%	82.4%	80.6%	83.3%	40.0%	**81.3%**	75.0%	87.5%	100.0%	100.0%	**86.4%**	82.0%
MRSE ±1.00D of intended	n	13	39	32	26	17	10	**137**	6	7	2	4	**19**	156
	%	100.0%	100.0%	94.1%	83.9%	94.4%	100.0%	**94.5%**	75.0%	87.5%	100.0%	100.0%	**86.4%**	93.4%
MRSE ±2.00D of intended	n	13	39	34	31	18	10	**145**	8	8	2	4	**22**	167
	%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	**100.0%**	100.0%	100.0%	100.0%	100.0%	**100.0%**	100.0%

*Excludes monovision eyes

TABLE 11: ASTIGMATIC EYES AT STABILITY
SUMMARY OF KEY EFFECTIVENESS VARIABLES STRATIFIED BY DIOPTERS

Efficacy Variables		-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	**Total <7D**	-7.0 to -7.99	-8.0 to -8.99	-9.0 to -9.99	-10.0 to -11.0	**Total ≥7D**	**Cum Total**
BSCVA ≥ 20/20 Preop*		**n=16**	**n=25**	**n=16**	**n=23**	**N=20**	**n=8**	**n=108**	**n=11**	**n=11**	**n=3**	**n=2**	**n=27**	**n=135**
UCVA 20/20 or better if BSCVA 20/20 or better Preop*	n	11	14	6	11	6	3	**51**	2	5	2	1	**10**	61
	%	68.8%	56.0%	37.5%	47.8%	30.0%	37.5%	**47.2%**	18.2%	45.5%	66.7%	50.0%	**37.0%**	45.2%
		n=16	**n=26**	**n=17**	**n=24**	**N=20**	**n=8**	**n=111**	**n=14**	**n=12**	**n=3**	**n=3**	**n=32**	**n=143**
UCVA 20/20 or better*	n	11	14	6	11	6	3	**51**	3	5	2	1	**11**	62
	%	68.8%	53.8%	35.3%	45.8%	30.0%	37.5%	**45.9%**	21.4%	41.7%	66.7%	33.3%	**34.4%**	43.4%
UCVA 20/25 or better*	n	11	16	13	18	9	5	**72**	8	7	3	1	**19**	91
	%	68.8%	61.5%	76.5%	75.0%	45.0%	62.5%	**64.9%**	57.1%	58.3%	100.0%	33.3%	**59.4%**	63.6%
UCVA 20/40 or better*	n	16	23	17	21	14	7	**98**	13	8	3	3	**27**	125
	%	100.0%	88.5%	100.0%	87.5%	70.0%	87.5%	**88.3%**	92.9%	66.7%	100.0%	100.0%	**84.4%**	87.4%
		n=16	**n=26**	**n=24**	**n=29**	**n=21**	**n=9**	**n=125**	**n=15**	**n=14**	**n=3**	**n=3**	**n=35**	**n=160**
MRSE ±0.50D of intended	n	15	17	18	22	13	7	**92**	9	7	3	2	**21**	113
	%	93.8%	65.4%	75.0%	75.9%	61.9%	77.8%	**73.6%**	60.0%	50.0%	100.0%	66.7%	**60.0%**	70.6%
MRSE ±1.00D of intended	n	16	24	24	27	18	8	**117**	14	10	3	3	**30**	147
	%	100.0%	92.3%	100.0%	93.1%	85.7%	88.9%	**93.6%**	93.3%	71.4%	100.0%	100.0%	**85.7%**	91.9%
MRSE ±2.00D of intended	n	16	26	24	29	21	9	**125**	15	11	3	3	**32**	157
	%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	**100.0%**	100.0%	78.6%	100.0%	100.0%	**91.4%**	98.1%

*Excludes monovision eyes

Key effectiveness outcomes are presented in Tables 10 and 11. The data indicate that the device is reasonably effective for the treatment range studied. It is noted, however, that the data are very limited data in the higher range.

Analysis of the correction of the cylindrical component of the astigmatic eyes is presented in Tables 12 and 13. The Ophthalmic Devices Panel (the Panel), at the January 14, 1997 meeting, assessed outcomes from a myopic astigmatic treatment and provided FDA with recommendations as to acceptable effectiveness rates. The Panel considered 64% an acceptable mean reduction in absolute cylinder at the point of stability. Therefore, the 76% reduction at 3 months achieved with this device is considered acceptable.

TABLE 12: Scalar Astigmatism – Achieved Correction

CYLINDER	1 Month (n=165)	3 Months (n=160)	6 Months (n=113)	9 Months (n=43)
Mean ± SD	-0.42 ± 0.48	-0.43 ± 0.52	-0.31 ± 0.41	-0.27 ± 0.35
Attempted	-1.66 ± 0.94	-1.63 ± 0.90	-1.48 ± 0.67	-1.53 ± 0.56
Achieved	-1.28 ± 0.84	-1.24 ± 0.77	-1.22 ± 0.70	-1.26 ± 0.60
% Achieved	76 ± 29	76 ± 29	81 ± 27	81 ± 24
≤0.50D	120 72.7%	111 69.4%	95 84.1%	35 81.4%
≤1.00D	152 92.1%	146 91.3%	106 93.8%	42 97.7%

The sponsor utilized the Alpins method for calculating vectoral change. This method was described in Alpins, N., "A new method of analyzing vectors for changes in astigmatism." *Journal of Cataract and Refractive Surgery*, Vol 19, July 1993.

At the same meeting, the Panel found 82.5% acceptable for correction efficacy (SIRC/IRC) at stability. The overall 95% achieved by this device is therefore acceptable. It is noted, however, that at 1, 3, and 6 months, small astigmatic errors were consistently overcorrected and large errors were consistently undercorrected. Although these deviations from intended correction are not serious, they appear to be inherent to this device.

TABLE 13:VECTOR ANALYSIS OF ASTIGMATISM

Baseline Cylinder	n	Intended Vector (A)	Achieved Vector (B)	Difference Vector (C)	% Achieved (B/A)	Angle of error (a)	Index of Success (C/A)
1 MONTH							
ALL	165	1.66 ± 0.94 (1.51, 1.80)	1.50 ± 0.85 (1.37, 1.63)	0.42 ± 0.48 (0.34, 0.49)	94 ± 35 (89, 99)	5.9 ± 9.4 (4.4, 7.3)	0.29 ± 0.40 (0.23, 0.35)
0.0 to 0.9	29	0.69 ± 0.11 (0.65, 0.73)	0.70 ± 0.27 (0.60, 0.81)	0.28 ± 0.32 (0.15, 0.40)	104 ± 44 (87, 120)	10.2 ± 14.2 (4.8, 15.6)	0.42 ± 0.54 (0.22, 0.62)
1.0 to 1.9	85	1.33 ± 0.30 (1.26, 1.39)	1.26 ± 0.50 (1.15, 1.37)	0.36 ± 0.48 (0.25, 0.46)	96 ± 39 (87, 104)	5.9 ± 9.5 (3.8, 7.9)	0.29 ± 0.44 (0.20, 0.39)
2.0 to 2.9	37	2.32 ± 0.29 (2.22, 2.42)	1.97 ± 0.45 (1.82, 2.12)	0.52 ± 0.44 (0.37, 0.67)	85 ± 19 (79, 92)	3.4 ± 3.2 (2.3, 4.4)	0.22 ± 0.17 (0.16, 0.28)
≥3.0	14	3.93 ± 0.82 NA**	3.34 ± 0.85 NA**	0.80 ± 0.62 NA**	86 ± 14 NA**	3.3 ± 2.7 NA**	0.19 ± 0.14 NA**
3 MONTHS							
ALL	160	1.63 ± 0.90 (1.49, 1.77)	1.47 ± 0.77 (1.35, 1.59)	0.43 ± 0.52 (0.35, 0.52)	95 ± 36 (89, 101)	6.2 ± 10.7 (4.6, 7.9)	0.29 ± 0.41 (0.23, 0.35)
0.0 to 0.9	28	0.69 ± 0.11 (0.64, 0.73)	0.70 ± 0.27 (0.60, 0.81)	0.26 ± 0.37 (0.12, 0.40)	104 ± 49 (85, 123)	10.4 ± 18.7 (3.2, 17.7)	0.41 ± 0.62 (0.17, 0.65)
1.0 to 1.9	85	1.33 ± 0.30 (1.27, 1.40)	1.29 ± 0.48 (1.18, 1.39)	0.38 ± 0.50 (0.27, 0.49)	98 ± 37 (90, 106)	6.4 ± 9.3 (4.4, 8.3)	0.29 ± 0.41 (0.20, 0.38)
2.0 to 2.9	35	2.32 ± 0.29 (2.22, 2.42)	2.01 ± 0.41 (1.86, 2.15)	0.49 ± 0.46 (0.33, 0.65)	87 ± 18 (81, 93)	3.4 ± 4.0 (2.1, 4.8)	0.21 ± 0.19 (0.14, 0.27)
≥3.0	12	3.90 ± 0.80 NA**	2.99 ± 0.95 NA**	1.06 ± 0.72 NA**	77 ± 18 NA**	3.6 ± 2.6 NA**	0.27 ± 0.17 NA**
6 MONTHS							
ALL	113	1.48 ± 0.67 (1.36, 1.61)	1.43 ± 0.66 (1.31, 1.55)	0.31 ± 0.41 (0.23, 0.38)	99 ± 36 (92, 106)	4.2 ± 7.0 (2.9, 5.5)	0.25 ± 0.39 (0.17, 0.32)
0.0 to 0.9	20	0.68 ± 0.12 NA**	0.75 ± 0.47 NA**	0.30 ± 0.44 NA**	113 ± 74 NA**	5.1 ± 7.6 NA**	0.45 ± 0.70 NA**
1.0 to 1.9	63	1.31 ± 0.29 (1.24, 1.38)	1.27 ± 0.38 (1.18, 1.37)	0.32 ± 0.42 (0.21, 0.42)	98 ± 22 (92, 103)	5.3 ± 7.9 (3.3, 7.3)	0.25 ± 0.31 (0.17, 0.32)
2.0 to 2.9	26	2.27 ± 0.28 (2.16, 2.38)	2.12 ± 0.46 (1.93, 2.30)	0.26 ± 0.40 (0.10, 0.42)	93 ± 17 (86, 100)	1.4 ± 2.6 (0.3, 2.4)	0.11 ± 0.18 (0.04, 0.18)
≥3.0	4	3.19 ± 0.38 NA**	2.79 ± 0.25 NA**	0.44 ± 0.32 NA**	88 ± 9 NA**	1.1 ± 1.7 NA**	0.13 ± 0.09 NA**
9 MONTHS							
ALL	43	1.53 ± 0.56 (1.36, 1.70)	1.47 ± 0.72 (1.24, 1.69)	0.27 ± 0.35 (0.17, 0.38)	93 ± 25 (85, 101)	3.4 ± 5.7 (1.7, 5.2)	0.19 ± 0.24 (0.11, 0.26)
0.0 to 0.9	5	0.75 ± 0.00 NA**	0.46 ± 0.32 NA**	0.30 ± 0.33 NA**	61 ± 43 NA**	7.3 ± 10.6 NA**	0.40 ± 0.44 NA**
1.0 to 1.9	27	1.35 ± 0.25 (1.25, 1.45)	1.29 ± 0.31 (1.16, 1.41)	0.24 ± 0.28 (0.13, 0.35)	96 ± 17 (89, 102)	3.4 ± 5.1 (1.3, 5.4)	0.17 ± 0.20 (0.09, 0.25)
2.0 to 2.9	11	2.32 ± 0.28 NA**	2.37 ± 0.65 NA**	0.34 ± 0.50 NA**	101 ± 22 NA**	1.8 ± 3.3 NA**	0.14 ± 0.21 NA**
≥3.0	0						

*95% confidence interval **Sample size too small to calculate confidence interval (n<25) ***no eyes available

At 6 months, 75.2% (85/113) of eyes were within +0.50 D of the intended spherical correction and 93.8% (106/113) 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 the combined spherical and astigmatic eyes available at each exam. The key safety outcomes for this study are presented in Table 14, with all the adverse reactions noted at each exam reported in Table 15. The benchmark for each adverse event is a rate of less than 1 % per event. Overall, the device was deemed reasonably safe.

TABLE 14: KEY SAFETY EVENTS

Event	Combined	Spherical		Astigmatic	
		<7 D MRSE	≥7 D MRSE	<7 D MRSE	≥7 D MRSE
Intra-operative flap complications	2/347 0.6%	0/153	0/24	2/134 1.5%	0/36
Postoperative flap complications	4/347 1.2%	1/153 0.7%	0/24	3/134 2.2%	0/36
BSCVA worse than 20/25 at stability, if 20/20 or better preop *(None worse than 20/40)*	1/310 0.3%	0/140	0/22	1/120 8.3%	0/28
Lost of 2 lines of BSCVA at stability (*None lost > 2 lines*)	4/327 1.2%	0/145	1/22 4.5%	2/125 1.6%	1/35 2.9%
Induced manifest refractive astigmatism of > 2 D absolute cylinder at stability	0/327	0/145	0/22	0/125	0/35
Unintended under-corrections > 2 D MRSE at stability	3/327 0.9%	0/145	0/22	0/125	3/35 8.6%
Unintended over-corrections > 2 D MRSE at stability	0/327	0/145	0/22	0/125	0/35

TABLE 15: ADVERSE REACTIONS BY VISIT								
Event	**1 Month (n=338)**		**3 Months (n=330)**		**6 Months (n=270)**		**9 Months (n=115)**	
	n/N	%	n/N	%	n/N	%	n/N	%
Conjunctival injection	0/338	0	0/330	0	2/270	0.7	0/115	0
Corneal Folds/Striae/Wrinkle	7/338	2.1	3/330	0.9	2/270	0.7	0/115	0
Double/ghost images	2/338	0.6	1/330	0.3	1/270	0.4	0/115	0
Epithelial defect	0/338	0	0/330	0	1/270	0.4	0/115	0
Epithelium in the interface	3/338	0.9	3/330	0.9	1/270	0.4	0/115	0
Feeling of something in the eye	1/338	0.3	0/330	0	0/270	0	0/115	0
Fibrotic healing at flap edge	0/338	0	3/330	0.9	2/270	0.7	0/115	0
Flap distortion	1/338	0.3	0/330	0	0/270	0	0/115	0
Induced astigmatism –flap decentration	1/338	0.3	1/330	0.3	0/270	0	0/115	0
Interface debris	12/338	3.6	13/330	3.9	11/270	4.1	0/115	0
Interface haze/opacity	10/338	3.0	10/330	3.0	1/270	0.4	1/115	0.9
Oil droplets/sheen	5/338	1.5	0/330	0	2/270	0.7	0/115	0
Serous Macular Edema	0/338	0	0/330	0	0/270	0	1/115	0.9
Sterile Interface Inflammation	2/338	0.6	2/330	0.6	0/270	0	0/115	0
Superficial punctate keratitis (SPK)	17/338	5.0	10/330	3.0	7/270	2.6	3/115	2.6

In addition, the following adverse reactions were reported at unscheduled visits that occurred at 1 month or later:

- increase in intraocular pressure >10mmHg above baseline (3 eyes);
- HSV dendrite (1 eye);
- corneal folds/striae/wrinkle (2 eyes);
- interface haze/opacity (4 eyes);
- superficial punctate keratitis (15 eyes);
- peau d' orange (2 eyes);
- flap distortion (1 eye); vacuoles (1 eye); and,
- conjunctival injection (2 eyes).

Each of the following ocular events were reported at 6 months (n=270) at a rate of 0.7%: blepharitis, retinal vessel tortuosity, and lattice degeneration with floaters.

The events reported on the patient questionnaire are listed in Table 16. These events came from the self-evaluations performed at the 6-month visit in the majority of eyes (243 eyes), with the remaining responses at 3 months or later.

TABLE 16:
CHANGE IN SYMPTOMS POSTOPERATIVE FROM PREOP

n %	Significantly Better	Better	No Change	Worse	Significantly Worse	Question NR*	No QE**	Total
Light Sensitivity	36 10.6%	43 12.7%	183 54.0%	67 19.8%	10 3.0%	0	8	347
Headache	30 8.9%	41 12.1%	244 72.0%	23 6.8%	1 0.3%	0	8	347
Pain	46 13.7%	36 10.7%	247 73.3%	8 2.4%	0 0.0%	2	8	347
Redness	41 12.1%	52 15.3%	227 67.0%	15 4.4%	4 1.2%	0	8	347
Excessive Tearing	40 11.8%	32 9.5%	258 76.3%	8 2.4%	0 0.0%	1	8	347
Burning	37 11.0%	42 12.4%	246 72.8%	13 3.9%	0 0.0%	1	8	347
Gritty Feeling	46 13.6%	43 12.7%	231 68.1%	19 5.6%	0 0.0%	0	8	347
Glare	24 7.1%	46 13.6%	161 47.5%	88 26.0%	20 5.9%	0	8	347
Halos	18 5.3%	48 14.2%	173 51.0%	84 24.8%	16 4.7%	0	8	347
Dryness	20 5.9%	62 18.3%	175 51.6%	69 20.4%	13 3.8%	0	8	347
Night Driving Difficulty	29 8.6%	73 21.6%	128 37.9%	76 22.5%	32 9.5%	1	8	347
Blurring of Vision	56 16.5%	55 16.2%	169 49.9%	52 15.3	7 2.1%	0	8	347
Double Vision	36 10.7%	25 7.4%	254 75.2%	19 5.6%	4 1.2%	1	8	347
Fluctuation of Vision	36 10.7%	48 14.2%	178 52.7%	67 19.8%	9 2.7%	1	8	347

*NR= No response to question; ** No QE= Questionnaire not performed

A subgroup study on contrast sensitivity testing was performed at 2 sites. Preoperative and 6-month postoperative data from 212 myopic eyes was analyzed. However, results were unreliable and no conclusions could be made.

A subgroup study on central endothelial cell density was performed at 1 site. Endothelial cell density was determined pre-operatively, and at 1, 3, and 6 months postoperatively. Data was available for 205 eyes at 1 month, 231 eyes at 3 months, and 211 eyes at 6 months. A clinically significant change in endothelial cell density was considered to be $\geq$ 10 % due to the inherent error in the measurements. There was no significant change in endothelial cell density at any time point from preoperative density for the subgroup of eyes studied.

e. Retreatments

Thirty-seven eyes were retreated with the study laser due to undercorrection and/or regression. Four eyes with slight hyperopic sphere (+0.25 to +0.75) postoperatively were treated for undercorrection or induction of cylinder only. Six eyes were treated immediately prior to the database closing, so no data were available on these eyes post-retreatment. Tables 17 and 18 summarize the outcomes of the retreated eyes. There were insufficient data to form any definitive conclusions regarding retreatment outcomes with this device.

TABLE 17:
SUMMARY OF KEY SAFETY AND EFFICACY VARIABLES FOR RETREATED EYES

Efficacy Variables		**1 Month**	**3 Months**	**6 Months**	**Last Reported****
		n=25	**n=20**	**n=9**	**n=31**
UCVA 20/20 or better*	n	19	12	6	24
	%	76.0%	60.0%	66.7%	77.4%
UCVA 20/25 or better*	n	22	17	7	27
	%	88.0%	85.0%	77.8%	87.1%
UCVA 20/32 or better*	n	25	20	9	31
	%	100.0%	100.0%	100.0%	100.0%
UCVA 20/40 or better*	n	25	20	9	31
	%	100.0%	100.0%	100.0%	100.0%
		n=25	**n=20**	**n=9**	**n=31**
MRSE ±0.50D of intended	n	23	20	9	30
	%	92.0%	100.0%	100.0%	96.8%
MRSE ±1.00D of intended	n	25	20	9	31
	%	100.0%	100.0%	100.0%	100.0%
Safety Variables		**n=25**	**n=20**	**n=9**	**n=31**
Loss of >2 Lines BSCVA^{+}	n	0	0	0	0
	%	0.0%	0.0%	0.0%	0.0%
Loss of 2 Lines BSCVA^{+}	n	0	1	1	1
	%	0.0%	5.0%	11.1%	3.2%
BSCVA worse than 20/40	n	0	0	0	0

TABLE 17:
SUMMARY OF KEY SAFETY AND EFFICACY VARIABLES
FOR RETREATED EYES

Efficacy Variables		1 Month	3 Months	6 Months	Last Reported**
	%	0.0%	0.0%	0.0%	0.0%
Increase >2D cylinder	n %	0 0.0%	0 0.0%	0 0.0%	0 0.0%
BSCVA ≥ 20/20 Preop		**n=25**	**n=20**	**n=9**	**n=31**
BSCVA worse than 20/25 if 20/20 or better preoperatively	n %	0 0.0%	1 5.0%	1 11.1%	1 3.2%

*Not including monovision eyes **1 Week to 9 Months †From preop prior to any treatment

TABLE 18:
CHANGE IN SYMPTOMS POSTOPERATIVE FROM PREOP
FOR RETREATED EYES AS PER PATIENT QUESTIONNAIRE

n %	Significantly Better	Better	No Change	Worse	Significantly Worse	Question NR*	Total ‡
Light Sensitivity	4 19.1%	2 9.5%	8 38.1%	3 14.3%	4 19.1%	0	21
Headache	3 14.3%	2 9.5%	10 47.6%	6 28.6%	0 0.0%	0	21
Pain	4 19.1%	1 4.8%	13 61.9%	3 14.3%	0 0.0%	0	21
Redness	2 9.5%	3 14.3%	15 71.4%	1 4.8%	0 0.0%	0	21
Excessive Tearing	3 14.3%	1 4.8%	15 71.4%	1 4.8%	1 4.8%	0	21
Burning	3 14.3%	4 19.1%	12 57.1%	2 9.5%	0 0.0%	0	21
Gritty Feeling	2 19.1%	1 4.8%	14 66.7%	2 9.5%	0 0.0%	0	21
Glare	3 14.3%	4 19.1%	9 42.9%	3 14.3%	2 9.5%	0	21
Halos	3 14.3%	2 9.5%	10 47.6%	3 14.3%	3 14.3%	0	21
Dryness	4 19.1%	2 9.5%	7 33.3%	6 28.6%	2 9.5%	0	21
Night Driving Difficulty	2 9.5%	6 28.6%	5 23.8%	5 23.8%	3 14.3%	0	21
Blurring of Vision	5 23.8%	2 9.5%	10 47.6%	2 9.5%	2 9.5%	0	21
Double Vision	3 14.3%	1 4.8%	14 66.7%	1 4.8%	2 9.5%	0	21
Fluctuation of Vision	3 14.3%	1 4.8%	13 61.9%	2 9.5%	2 9.5%	0	21

* NR: Answer to question not reported by patient ‡ Total: Total number of eyes available for 3M or 6M

f. Factors associated with outcomes

Several associations were noted between various preoperative factors and outcomes at 6 months postoperatively. A strong association showed that females above the median age of 43 were less likely to have UCVA of 20/20 or better compared to the men above that median age. There was no association with respect to the use of hormone replacement therapy in older females. An association was also found between female gender and under-correction, although only 12 eyes total were under-corrected by >1 D of MRSE and 10 eyes were under-corrected by >1 D of sphere. Female subjects treated for spherical myopia only were more likely to be under-corrected by >1 D of MRSE and sphere. A comparison of 31 eyes of females on oral contraceptives versus 239 eyes of females not on oral contraceptives showed that those on contraceptives were less likely to have MRSE within $\pm$ 0.50 of intended.

Subjects older than 43 years and treated with a volume per pulse greater than the median of 481, were less likely to have UCVA of 20/20 or better compared to their younger counterparts. However, this association with outcome is more likely due to age than volume per pulse because of noise in its measurement.

Subjects who did not wear soft contact lenses prior to spherical treatment were less likely to have UCVA of 20/20 or better and MRSE within $\pm$ 0.5 D of intended, than those not wearing contact lenses. Inversely, subjects who wore soft contact lenses prior to astigmatic treatment were less likely to have UCVA of 20/20 or better and MRSE within $\pm$ 0.5 D of intended.

Subjects treated under humidity conditions above the median of 46% were less likely to have UCVA of 20/20 or better and MRSE within $\pm$ 0.5 D of intended compared to subjects treated under humidity conditions below the median.

g. Patient Satisfaction

Reported in Table 19 are the assessments made at the 6 month visit in the majority of eyes (243 eyes), with the remaining 104 eyes at 3 months or later.

TABLE 19: PATIENT SATISFACTION			
Quality Of Vision		**Satisfaction**	
Significantly Better	155 45.7%	Extremely Satisfied	175 51.6%
Better	77 22.7%	Satisfied	94 27.7%
No Change	64 18.9%	Not Sure	31 9.1%
Worse	39 11.5%	Unsatisfied	34 10.0%
Significantly Worse	4 1.2%	Extremely Unsatisfied	5 1.5%
Not Reported		8	
Total		347	

h. Device failures

Six eyes experienced interruptions during the surgical procedure due to laser system failures: a faulty on/off switch (1); internal timing error (3); double pressing of footswitch by operator (1); and, failure to track due to simultaneous activation of tracking and printing (1). There was no loss of BSCVA in any of these eyes. Five eyes achieved UCVA of 20/40 or better at the last reported visit. One eye was slightly undercorrected with a UCVA of 20/50. The causes of the interruptions were fixed.

XI. CONCLUSIONS DRAWN FROM THE CLINICAL STUDY

The data in this application support reasonable assurance of safety and effectiveness of the LADARVision® Excimer Laser System 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. FDA DECISION

The applicant satisfactorily addressed FDA's remaining deficiencies. CDRH issued an approval order on May 9, 2000.

XIV. APPROVAL SPECIFICATIONS

Labeling: Data in the labeling are to be limited to the approved treatment range.

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.