SUMMARY OF SAFETY AND EFFECTIVENESS DATA
SUPPLEMENTAL PREMARKET APPROVAL APPLICATION

I. GENERAL INFORMATION

Device Generic Name: Ophthalmic Excimer Laser System
(193 nanometer laser wavelength)

Device Trade Name: Nidek EC-5000 Excimer Laser System

Applicant's Name and Address: Nidek Technologies, Inc.
675 South Arroyo Parkway
Suite 330
Pasadena, California 91105

Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P970053/S002

Date of Notice of Approval to Applicant: April 14, 2000

This device was originally approved on December 17, 1998 for Photorefractive Keratectomy (PRK) for the reduction or elimination of myopia ranging from -0.75 D to -13.00 D (P970053). On September 29, 1999 (P970053/S1), the indications for use were further expanded to include PRK treatment of -1.00 to -8.00 MRSE with refractive astigmatism ranging from -0.50 to -4.00 D absolute cylinder by manifest refraction. The sponsor submitted this current supplement (P970053/S002) to further expand the indications to include Laser in-situ Keratomileusis (LASIK) treatment of myopia and myopic astigmatism. 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 indications, the Summary of Safety and Effectiveness Data to that PMA application should be referenced. Written requests for copies of the SSED can be obtained from the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857. Please identify Docket # (OOM-1640 for the original application and OOM-1664 for P970053/S1). 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

This device is indicated to perform LASIK in:

- Treatments for the reduction or elimination of myopia with or without astigmatism ranging in severity from -1.00 to -14.00 diopters (D), in terms of manifest refraction spherical equivalent (MRSE), with refractive astigmatism ranging in severity from 0.00 D to -4.00 D cylinder by manifest refraction. Due to cylinder coupling effects on sphere, some combinations of cylinder and sphere are not possible in the lower range of the indication for use. A nomogram lookup table must be used for the entire refractive range for specific treatment combinations;

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- Patients who have a stable history of pretreatment myopia with or without astigmatism (i.e., a magnitude change in manifest refraction of ≤ 0.50 D per year in terms of MRSE for at least one year preceding treatment);

- For myopic astigmatism, in patients who have a stable history of pretreatment astigmatism ≤ -4.00 D (i.e., a magnitude change of ≤ 0.50 D per year in cylinder for at least one year preceding treatment); and,

- Patients who are over 21 years of age.

III. CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

A. CONTRAINDICATIONS:

LASIK surgery is contraindicated:

- In patients who have a systemic disease that would influence corneal wound healing, particularly autoimmune or immunodeficiency diseases and collagen vascular diseases, including rheumatoid arthritis, systemic lupus, and Sjögren's syndrome.

- In patients who have current signs, early signs, or clinical indications of keratoconus.

- In patients who are pregnant or nursing.

- In patients with systemic conditions which would stimulate excessive scar tissue (keloid formation).

- In patients whose current medications include ocular or systemic steroid regimens that would affect their refractive correction.

- In patients who have irregular astigmatism as evidenced in topographical analysis.

B. WARNINGS: see the labeling

C. PRECAUTIONS: see the labeling

IV. DEVICE DESCRIPTION

A. Laser System

The device used in this clinical study was the Nidek EC-5000 Excimer Laser System. A full description of this laser system can be found in the SSED for the original PMA approved on December 17, 1998.

With the following exceptions, the EC-5000 device used in LASIK treatment is the same as the approved EC-5000 device used in PRK treatment:

- The procedure-specific software for cylinder corrections (used for LASIK) that was disabled for the PRK approval is enabled.
- The slit apertures utilized to control the laser beam width and angle for cylinder correction were present, but disabled, in the approved EC-5000 device. These apertures are now enabled for LASIK.

B. Microkeratome

The LASIK procedure requires the use of a commercially available microkeratome that has been cleared for marketing that has been cleared for marketing via premarket notification. The devices used in this study consist of an instrument tray which includes the shaper head, an adjustable height suction ring, handle, wrenches and test shaft. The left/right adapter, instrument motor, handpiece, disposable blades, power supply with footswitches and power cords, applanation lens set, tonometer, optical zone marker, spatula, stop attachment, sterilization tray, accessory stand, digital thickness gauge, and equipment suitcase are provided as separate components which complete the system.

V. ALTERNATIVE PRACTICES AND PROCEDURES

Conventional methods for correcting myopia and astigmatism are: spectacles, contact lenses, and refractive surgery (such as radial keratotomy and PRK).

VI. MARKETING HISTORY

The EC-5000 Excimer Laser System has been distributed worldwide in more than 50 countries including Germany, France, UK, South Africa, Brazil, Chile, Mexico, Canada, Australia, Taiwan and Japan. The first units were shipped in 1992 and 1993. To date, in excess of 250 units have been shipped to countries outside of the United States.

The Nidek EC-5000 has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

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

Please refer to Tables 14, 15 and 16 of the Clinical Section for specific adverse event information observed in the clinical study.

VIII. SUMMARY OF PRECLINICAL STUDIES

Please refer to the SSED for the original PMA for PRK (P970053).

IX. SUMMARY OF CLINICAL STUDIES

The sponsor performed a clinical study of the Nidek EC-5000 Excimer Laser System in the United States under the auspices of IDE G940084 for LASIK treatment of myopia and myopic astigmatism. The data from this study served as the basis of the approval decision. Specifically, safety and effectiveness outcomes at 3 months postoperative were assessed as stability is reached by that time. Outcomes at 6 months postoperatively were also evaluated for confirmation.

A total of 622 subjects at 8 investigational sites had a primary eye or both eyes treated (N=1126 total eyes consisting of 622 primary treated eyes and 504 secondary eyes) during the initial and expanded parts of the Nidek EC-5000 excimer laser study for LASIK therapy for myopia and astigmatism. There were 277 males and 344 females (gender not reported for one subject). The median age for all treated subjects at the time of first treatment was 42.6 years (range, 19 to 70 years). All subjects were treated between November 1996 and August 27, 1999.

The IDE study is described in detail as follows.

A. STUDY OBJECTIVE

The objective of the U.S. clinical investigation of the Nidek EC-5000 Excimer Laser System was to correct myopia with or without astigmatism by LASIK for refractive errors in the range of -1.00 D to -20.00 D spherical equivalent and cylinder 0.00 to -4.00 D.

B. STUDY DESIGN

This study was an open, prospective, stratified multi-center (8 sites) 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

Subjects who were included into the initial and expanded portions of the study met specific criteria, had stable myopia or myopic astigmatism, and overall good health. Subjects entering the study met common selection criteria within the desired refractive range. Fellow (secondary) eyes had additional criteria generally based on initial results from the first eye.

Subjects meeting the following criteria were to be admitted into the investigation:

Inclusion criteria

Subjects over 18 years of age, with myopia or myopic astigmatism by manifest refraction in the first treated eye from -1.0 to -20.0 D, with ≤ 4.0 D astigmatism; a stable history of pre-treatment myopia and astigmatism, and a clear cornea.

Subjects were excluded from enrolling in the study if they possessed any one of the following at pre-treatment: less than 20/40 best spectacle corrected visual acuity (BSCVA) in either eye; systemic disease that would influence corneal wound healing; any active ocular disease, including but not limited to uncontrolled glaucoma, uveitis, uncontrolled blepharitis, iritis, severe dry eye; kerataconus; prior ocular surgery; corneal epithelial, stromal, or endothelial dystrophy.

D. STUDY PLAN, PATIENT ASSESSMENTS. AND EFFICACY CRITERIA

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

Subjects were permitted to have their fellow-eyes treated after the optional one week evaluation. The primary efficacy variables for this study were improvement of near or distance UCVA based on the per eye treatment goal of the procedure, and predictability of manifest refraction spherical equivalent (MRSE).

Table 1

Clinical Test Schedule for LASIK Study

(X indicates exam for treated eyes; C untreated eyes; □ data collection through all visits.)

Test/Information	Pre-op	1+d	1 w**	1 m	3 m	6 m	12 m
Demographics, consent, history	X						
Medications or devices	XC	□	□	□	□	□	□
Slit Lamp Examination	XC	X	X	X	XC	XC*	XC*
Uncorrected Visual Acuity	XC	XI	X	X	XC	XC*	XC*
Best Spectacle Corrected VA	XC		X	X	XC	XC*	XC*
Manifest Refraction, pupil size	XC		X	X	XC	XC*	XC*
Intraocular Pressure	XC			X&	XC	XC*	XC*
Corneal Topography	XC				'	'	'
Keratometry	XC				XC	XC*	XC*
Vitreal Status	XC					XC*	XC*
Fundoscopic Exam	XC					XC*	XC*
Cycloplegic Refraction	XC						XC*
Questionnaire	XC						XC*
H Subset Studies							
Specular Microscopy "	XC					XC*	
Pachymetry	XC					XC*	XC*

* = Long-term follow-up exams for untreated eyes were done if they had not undergone disqualifying ocular procedures by that date (i.e., surgery).

& = Special care was taken for any contact IOP measures during the flap healing process. If the examiner believed the flap was not secure at the 1 month exam, the IOP test may have been omitted.

H = Specialized tests were conducted at selected centers or to supplement previous data, as needed.

I = Immediate post-operative exams prior to 1 month did not require use of ETDRS visual acuity charts.

' = Testing required only for subjects meeting requirements for follow-up tests or serious complaints.

" = Subjects in this study were used only if insufficient numbers were obtained from other protocol(s) or for cases of attempted correction greater than 7 D S.E.

** = This qualifying evaluation, as early as 1 week after treatment, was needed to precede a fellow eye treatment if the fellow eye is to be treated before the 1 month evaluation of the first eye. This exam period was added for the expansion of the LASIK protocol when fellow eye treatments were permitted before the one-month exam.

Note: During the initial portion of the study with the first 50 subjects, 9, 18, and 24-month evaluations were scheduled. However, with the FDA approval for expansion of the study to 700 subjects, these exam periods were eliminated from the approved protocol.

E. STUDY PERIOD, INVESTIGATIONAL SITES, AND DEMOGRAPHICS

1. Study Period and Investigational Sites

Subjects were treated between November 1996 and July 1999 and consisted of 622 primary eyes and 504 secondary (fellow) eyes. There were 8 investigational sites.

2. Demographics

The demographics of this study were typical of a contemporary refractive surgery trial in the U.S.

Demographics

Table 2a: All Treated Eyes
(available information for 1125 Eyes Treated of 622 Subjects)

	Number	Percentage
Gender		
Female	344	55.4
Male	277	44.4
Not reported	1	0.2
Race		
Caucasian	529	85.0
Hispanic	42	6.8
Asian	27	4.3
Black	5	0.8
American Indian	17	2.7
Eye		
Right	573	50.9
Left	552	49.1
Age at First Surgery(in years)		
Average	42.6	
Standard Deviation	9.2	
Minimum	19.0	
Maximum	70.0	
Contact Lens History		
None	19	3.1
Soft	213	34.3
Hard	114	18.4

Table 2b: Astigmatic Myopia Treatment
(available information for 722 Eyes Treated of 444 Subjects)

		Percentages
Gender		
Female	251	56.5
Male	192	43.3
Not reported	1	0.2
Race		
Caucasian	377	84.8
Hispanic	32	7.3
Asian	22	5.0
Black	0	0
American Indian	12	2.7
Eye		
Right	356	49.4
Left	366	50.6
Age at First Surgery(in years)		
Average	42.9	
Standard Deviation	9.1	
Minimum	19.0	
Maximum	70.0	
Contact Lens History		
None	12	2.7
Soft	131	29.7
Hard	100	22.7

Table 2c: Spherical Myopia Only Treatment
(available information for 403 Eyes Treated of 266 Subjects)

	Number	Percentage
Gender		
Female	142	53.6
Male	124	46.4
Race		
Caucasian	230	86.4
Hispanic	14	5.3
Asian	8	3.0
Black	5	1.9
American Indian	8	3.0
Eye		
Right	217	541
Left	186	459
Age at First Surgery(in years)		
Average	42.4	
Standard Deviation	9.4	
Minimum	19.0	
Maximum	63.0	
Contact Lens History		
None	9	3.4
Soft	112	42.3
Hard	32	12.1

F. DATA ANALYSIS AND RESULTS

1. Preoperative Characteristics

Table 3 is a summary table of preoperative acuity and refraction.

Table 3: Preoperative Visual Acuity Characteristics
(primary and secondary eyes)

Pre-op UCVA	
UCVA 20/40 or better	<1% (8/1016*)
UCVA 20/50 to 20/80	2.8% (28/1016)
UCVA 20/100 or worse	96.5% (980/1016)
Pre-op BSCVA	
BSCVA 20/20 or better	95.4% (969/1016**)
BSCVA 20/25 to 20/40	14.5% (147/1016)
BSCVA 20/50 or worse	<1.0% (1/1016)

*110 eyes were missing a preoperative component for their UCVA or had values that were so poor that no suitable logMAR value could be assigned.
** 9 enrolled eyes in the LASIK study had missing preoperative BSCVA values.

The pre-operative stratification of myopia and myopic astigmatism for the treated primary and secondary eyes in this study was based on pre-operative manifest refraction in terms of spherical equivalence (MRSE). Low was defined in the LASIK protocol as -1.00 D to -5.99 D S.E., moderate was defined as -6.00 D to -9.99 D S.E., and high was defined as -10.00 D to -20.00 D S.E. Each of these strata could include a pre-operative cylinder component of

0 to -4.00 D. For purposes of analysis, the strata were re-defined in accordance with the FDA guidance as follows:

- Low : ≤-7.00 D S.E.
- High: >-7.00 D S.E.

Table 4: Pre-Operative Myopic Stratification for Treated Primary and Secondary Eyes

	# Eyes with ≤-7.00 D S.E	# Eyes with >7.00 D S.E.	Total Eyes
Primary Eye	344	278	622
Secondary Eyes	270	231	501
Total Eyes	614	509	1123*

*Three secondary eyes enrolled in the study had missing preoperative SE values.

2. POSTOPERATIVE RESULTS

a. Accountability and definition of the PMA cohort

Accountability, calculated in accordance with FDA suggested Refractive Laser Guidance (October, 1996) is represented in the table below:

Table 5: Overall Accountability for Treated Primary and Secondary Eyes

	1 Month	3 Months	6 Months*	12 Months
All Eyes N=1126	88%	88.3%	82.5%	78.1%
1° Eyes N=622	92.4%	91.0%	83.2%	80.2%
2°Eyes N=504	82.7%	84.9%	81.6%	75.6%

*Time Point of Stability

Table 6: Subject Accountability – Primary Eyes (all)

	1 month	3 months	6 months	12 months
No. of Eyes in Cohort	622	622	622	622
Available for Analysis	573/620 (92.4%)	549/603 (91.0%)	423/508 (83.3%)	288/360 (80%)
Discontinued/ Retreated	2/622 (0.3%)	14/617 (2.3%)	103/611 (16.9%)	124/484 (25.6%)
Not yet eligible for the interval	0/622 (0%)	5/622 (0.8%)	11/622 (1.8%)	138/622 (22.2%)
Lost to follow-up	4/620 (0.6%)	5/603 (0.8%)	9/508 (1.8%)	14/360 (3.9%)
Missed Visit	43/620 (6.9%)	49/603 (8.1%)	76/508 (1.8%)	58/360 (16.1%)
% Accountability	573/620 (92.4%)	549/603 (91%)	423/508 (83.3%)	288/360 (80%)

Table 7: Subject Accountability – Secondary Eyes (all)

	1 month	3 months	6 months	12 months
No. of Eyes in Cohort	504	504	504	504
Available for Analysis	415/502 (82.7%)	417/492 (84.8%)	351/430 (81.6%)	266/299 (75.6%)
Discontinued/ Retreated	1/503 (0.2%)	6/498 (1.2%)	60/490 (12.2%)	73/372 (19.6%)
Not yet eligible for the interval	1/504 (0.2%)	6/504 (1.2%)	14/504 (2.8%)	132/504 (26.2%)
Lost to follow-up	3/502 (0.6%)	5/492 (1.0%)	10/430 (2.3%)	12/299 (4.0%)
Missed Visit	21/502 (4.2%)	24/492 (4.9%)	23/430 (5.3%)	5/299 (1.7%)
% Accountability	415/502 (82.7%)	417/492 (84.8%)	351/430 (81.6%)	226/299 (75.6%)

The percent accountability at 6 months is 82.5%. As can also be seen from these tables, using FDA's guidance, out of 1126 treated eyes, there were a total of 938 eyes or 83% that could have potentially been seen at 6 months (total eyes treated less eyes discontinued/retreated and those not yet eligible). Of these 938 eyes, 774 eyes or 82.5% were available for analysis.

The number of subjects available at each interval varied. Variability was caused by several factors, including subjects who were lost to follow-up or who missed visits (i.e., the subject did not report as scheduled), or who were considered discontinued from the study at each interval. Discontinued subjects included those who were deceased (there were none) and, as denoted by the FDA guidance, those with re-treated eyes.

Secondary eyes were not required to have the same follow-up exam schedule as primary eyes, and were seen only when a primary eye was examined beginning after the secondary eye surgery.

In addition, a consistent cohort was created for analysis of refractive stability, comprised of all subjects who were present at all of their visits through 6 months. This cohort was then analyzed similarly to the population of all eyes.

As defined by the FDA, the Discontinued/Re-treated category included deceased subjects or those who had their eyes re-treated. During the course of this study, there were no deaths.

b. Stability of Outcome

It was observed that except for those subjects with myopia >7.0D in the 3-6 month window, greater than 95% of eyes experienced a change of MRSE not exceeding ± 1D. For those subjects with myopia >7.0D, the change was 92.9%

Furthermore, the mean of the pair-difference of MRSE for the entire cohort progressively decreased over time, and reached a change of about -0.05D in the 3-6 month window (Tables 8 and 9). The changes in the 6-12 month 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 612 eyes evaluable at 6 months.

Table 8: Stability Analyses for All Eyes Treated

(change in MRSE over time for eyes
that had every exam, through 6 months)

	1 to 3 Months	3 to 6 Months	6 to 12 Months
Change <=1 D n/N (%) (95% CI)	579/608 (95.2%) [93.5-96.9%]	590/612 (96.4%) [94.9-97.9%]	351/368 (95.4%) [93.2-97.5%]
Change (Pair-Differences) Mean Std.Dev. (95% CI)	-0.16 0.50 [-0.19 to -0.12]	-0.05 0.45 [-0.09 to -0.01]	-0.08 0.50 [-0.13 to -0.03]

Table 9: Stability of MRSE

Sphere and Spherocylinder Stability Presented Separately	**3 to 6 Months n/N (%)**	**6 to 12 Months n/N (%)**
All Treated Eyes (Total Cohort)	590/612 (96.4%)	351/368 (95.4%)
Sphere Only (≤7D)	155/157 (98.7%)	103/104 (99.0%)
Sphere Only (>7D)	59/63 (93.7%)	32/33 (97.0%)
Spherocylinders (≤7D)	185/186 (99.5%)	106/110 (96.4%)
Spherocylinders (>7D)	191/206 (92.7%)	110/121 (90.9%)

c. Effectiveness Outcomes

Key effectiveness variables are defined for two areas: uncorrected visual acuity (UCVA) and accuracy and precision of refractive outcome for manifest refraction spherical equivalent (MRSE). UCVA is reported for the proportions of eyes that achieve uncorrected distance visual acuity levels of 20/20 or better, 20/25 or better, and 20/40 or better. For predictability of MRSE outcome, the precision is reported for the proportions within ±0.50, ±1.00, and ±2.00 D of the desired outcome. These levels are important in describing the ability of the laser system, in conjunction with the LASIK technique and the individual patient response, to achieve the intended refractive outcome. Accuracy of MRSE is also reported by observing the

attempted versus achieved refractive outcome. Table 10 summarizes the target outcome levels as percentages for certain key effectiveness variables. FDA provided a guidance document specifying these outcome levels for several variables. The FDA targets were stratified by pre-operative MRSE (with or without astigmatism) for low and high levels and specifically related to those eyes that had 20/20 or better best corrected visual acuity before laser surgery. Table V.D.1 also shows the related targets as they were specified in the Nidek LASIK protocol. The Nidek LASIK protocol used different pre-operative strata to distinguish low, moderate, and high levels of refractive error.

Table 10
FDA Guidance and Protocol Targets for Key Effectiveness Variables

Effectiveness Variable	FDA Guidance Strata		Nidek Protocol Strata		
	Myopia ≤ 7 D	Myopia > 7 D	Myopia < 6 D	Myopia 6-9.9 D	Myopia ≥ 10 D
UCVA 20/20 or better	---	---	---	---	---
UCVA 20/25 or better	---	---	50%	50%	40%
UCVA 20/40 or better	**85%**	**75%**	**80%**	**80%**	**65%**
Precision ±0.50 MRSE	50%	30%	---	---	---
Precision ±1.00 MRSE	**75%**	**60%**	**85%**	**75%**	**65%**
Precision ±2.00 MRSE	---	90%	---	---	---

--- = Target proportion not specified.

Comment: *These are the target values that the sponsor used in their protocol, not their results.*

The refractive predictability data was organized to show that the achieved refractive outcome is directly proportional to the attempted correction. This is referred to as the "attempted versus achieved" refractive result. The "attempted" correction is the difference between the preoperative MRSE and the target MRSE indicated at the time of surgery. The "target" MRSE is the refractive outcome expected after surgery and stabilization of the refraction. The target MRSE is not necessarily emmetropia, and 32% (362/1125) of eyes in this analysis had specified a target MRSE below emmetropia. The majority of eyes that were not targeted for emmetropia were expected to have a small amount of residual myopia after treatment. The "achieved" correction is the actual change in MRSE from the preoperative value to the follow-up value. For this evaluation at 6 months (after refractive stability had been reached), eyes that received more than one laser treatment before this period were excluded from the analysis.

Table 11: Summary of Key Efficacy Variables (all treated eyes)
(988 subjects available for analysis)

	1 month	3 months	6 months	12 months
UCVA 20/20 or better	441/970 (45.5%)	396/943 (42.0%)	359/758 (47.4%)	247/505 (48.9%)
UCVA 20/40 or better	800/970 (82.5%)	724/943 (76.8%)	640/758 (84.4%)	433/505 (85.7%)
MRSE ± 0.50 D	566/962 (58.8%)	530/944 (56.1%)	455/755 (60.3%)	321/512 (62.7%)
MRSE ± 1.00 D	771/962 (80.1%)	733/944 (77.6%)	643/755 (85.2%)	446/512 (87.1%)
MRSE ± 2.00 D	915/962 (95.1%)	882/944 (93.4%)	733/755 (97.1%)	503/512 (98.2%)

UCVA not reported: 18 subjects at 1 month, 23 at 3 months, 16 at 6 months, and 9 at 12 months
MRSE not reported: 16 subjects at 1 and 3 months, 15 at 3 months, and 2 at 12 months.

Table 12: Summary of Key Efficacy Variables at the Point of Stability (6 months)
(Stratified by preoperative spherical equivalent for all treated eyes)

Efficacy Variables	< -2.00	-2.00 to - 3.99	-4.00 to -5.99	-6.00 to -7.99	-8.00 to -9.99	-10.00 to -11.99	-12.00 to -13.99	≥ -14.00
UCVA 20/20 or better	15/17 (88.2%)	93/152 (61.2%)	89/164 (54.3%)	77/179 (43%)	52/145 (35.9%)	23/77 (29.9%)	9/20 (45%)	1/4 (25%)
UCVA 20/40 or better	16/17 (94.1%)	131/152 (86.2%)	142/164 (86.6%)	154/179 (86.0%)	113/145 (77.9%)	64/77 (83.1%)	17/20 (85%)	3/4 (75%)
MRSE ±0.50D of intended	11/17 (64.7%)	121/150 (80.7%)	110/163 (67.5%)	110/179 (55.9%)	71/145 (49%)	39/77 (50.6%)	3/20 (15%)	0/4 (0%)
MRSE ±1.00D of intended	16/17 (94.1%)	144/150 (96.0%)	150/163 (92.0%)	152/179 (84.9%)	112/145 (77.2%)	58/77 (75.3%)	11/20 (55%)	0/4 (0%)
MRSE ±2.00D of intended	17/17 (100%)	150/150 (100.0%)	163/163 (100.0%)	175/179 (97.8%)	137/145 (94.5%)	72/77 (93.5%)	16/20 (80%)	3/4 (75%)

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Accuracy Of Manifest Refraction

Astigmatic Myopia Treatment

Myopia <= 7.0D

Difference from Intended Outcome	SE at 3 mo	SE at 6 mo	SE at 12 mo
± 0.50 D	175/292 (59.9%) [54.3-65.6%]	155/231(67.1%) [61.0-73.2%]	100/155(64.5%) [57.0-72.0%]
± 1.00 D	39/292 (81.8%) [77.4-86.3%]	208/231(90.0%) [86.2-93.9%]	139/155(89.7%) [84.9-94.5%]
± 2.00 D	283/292 (96.9%) [94.9-98.9%]	230/231(99.6%) [98.7-100.0%]	155/155(100.0) [100.0-100.0%]
> ± 2.00 D	9/292 (3.1%) [1.1-5.1%]	1/231(0.4%) [0.0-1.3%]	0/155 (0.0%) [0.0-0.0%]
Not Reported	13	12	2
Total	**305**	**243**	**157**

Accuracy Of Manifest Refraction
Astigmatic Myopia Treatment

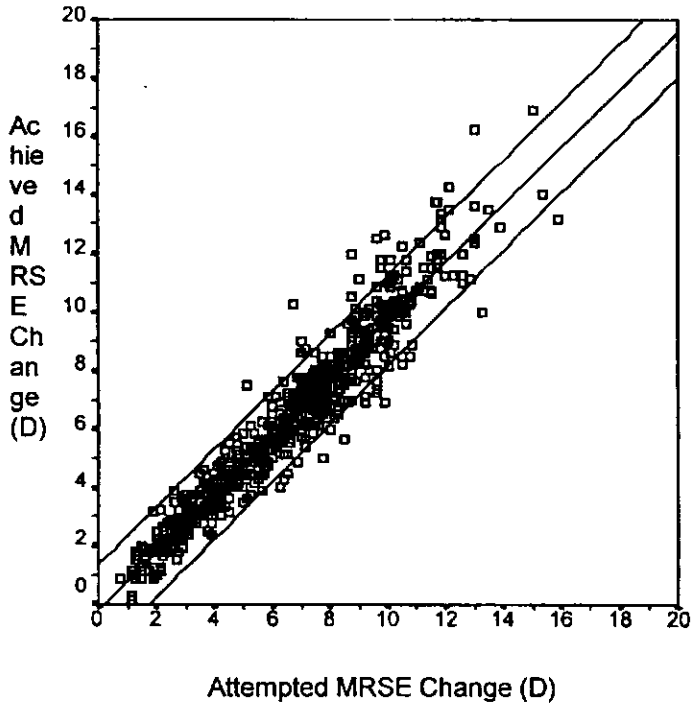
Myopia > 7.0D

Difference from Intended Outcome	SE at 3 mo	SE at 6 mo	SE at 12 mo
± 0.50 D	144/ 320 (45.0%) [39.5-50.5%]	107/ 247 (43.3% [37.1-49.5%]	78/ 162 (48.1%) [40.5-55.8%]
± 1.00 D	217/ 320 (67.8%) [62.7-72.9%]	181/ 247 (73.3%) [67.8-78.8%]	125/162 (77.2%) [70.7-83.6%]
± 2.00 D	285/ 320 (89.1%) [85.6-92.5%]	229/ 247 (92.7%) [89.5-96.0%]	153/ 162 (94.4%) [90.9-98.0%]
> ± 2.00 D	35/ 320(10.9%) [7.5-14.4%]	18/ 247 (7.3%) [4.0-10.5%]	9/ 162 (5.6%) [2.0-9.1%]
Not Reported	3	5	0
Total	**323**	**252**	**162**

Refractive predictability for the spherical equivalent refraction is shown in Figure 1. Data from the available paired refractions for preop and 6 months are used in this linear regression analysis (95% confidence intervals are also shown).

Figure 1

Attempted versus Achieved S.E. at 6 Months after LASIK (n=755)
The average attempted correction was 6.30 ± 2.87 D, while the average achieved MRSE change was 6.05 ± 2.95 D.



These results were achieved through the use of a preliminary nomogram that adjusts device settings as a function of the attempted correction for sphere and cylinder. Details regarding the nomogram used in this study are included as part of the device labeling.

The refractive predictability (as a precision measure) is determined by examining the proportion of eyes within certain ranges of the desired outcome. Achieving a high proportion of refractive outcomes within a narrow range of the target MRSE is used to establish precision. The results at 6 months follow-up are shown in Table 13.

Table 13
Refractive Accuracy Summary for Outcome Proportions (%)
at 6 Months after LASIK (n=753)[1]

Effectiveness Variable	FDA Guidance Strata		Nidek Protocol Strata			
	Myopia ≤ 7 D	Myopia > 7 D	Myopia < 6 D	Myopia 6-9.9 D	Myopia ≥ 10 D	All Strata
Precision ±0.50 MRSE	70.4	47.4	73.8	52.8	41.6	60.4
Precision ±1.00 MRSE	92.7	75.8	94.5	81.5	68.3	85.4
Precision ±2.00 MRSE	99.3	94.2	100.0	96.3	90.1	97.1
N =	426	327	328	324	101	753

[1]The count of observations (n) between tables for different variables (e.g., UCVA and refraction) may differ slightly from the visit accountability reports due to missing or invalid preoperative or follow-up data for the respective variables.

d. Safety Outcomes:

The analysis of safety was based on all eyes that have had the 6 months exam. The key safety outcomes for this study are presented below, with all adverse reactions reported in Tables 15 and 16. Overall, the device was deemed reasonably safe.

BSCVA was obtained from primary eyes pre-operatively and at 1, 3, 6, and 12 months. For secondary eyes in the analyses, examinations coincided with the primary eye visit schedule, so the follow-up period does not necessarily align with primary eyes. In these cases, the period closest to the actual visit date in relation to the secondary eye treatment is used. LogMAR values are used to allow for a linear system for calculations.

Safety results for all eyes at 6 months follow-up indicate only 0.6% had a loss of more than 2 lines of BSCVA, 0.5% had follow-up BSCVA worse than 20/40 (if 20/20 or better pre-op), no eyes lost vision due to haze, no eyes with sphere-only treatments had induced cylinder greater than 2 diopters, and adverse events by type remained below 1% at or beyond 6 months follow-up.

Change in Best Spectacle Corrected Visual Acuity

All Eyes Treated

Myopia <= 7.0D

BSCVA	1 Month	3 Month	6 Month	12 Month
Decrease > 2	2 /523 (0.4%) [0.0-0.9%]	2 /515 (0.4%) [0.0-0.9%]	2 /430 (0.5%) [0.0-1.1%]	1/ 300 (0.3%) [0.0-1.0%]
Decrease 2 lines	6 /523 (1.1%) [0.2-2.1%]	2 /515 (0.4%) [0.0-0.9%]	3 /430 (0.7%) [0.0-1.5%]	1 /300 (0.3%) [0.0-1.0%]
Decrease 1 line	68 /523 (13.0%) [10.1-15.9%]	48 /515 (9.3%) [6.8-11.8%]	46 /430 (10.7%) [7.8-13.6%]	38 /300 (12.7%) [8.9-16.4%]
No Change	314 /523 (60.0%) [55.8-64.2%]	320 /515 (62.1%) [57 9-66.3%]	263 /430 (61.2%) [56.6-65.8%]	181 /300 (60.3%) [54.8-65.9%]
Increase 1 line	126 /523 (24.1%) [20.4-27.8%]	130 /515 (25.2%) [21 5-29.0%]	107 /430 (24.9%) [20.8-29.0%]	72 /300 (24.0%) [19.2-28.8%]
Increase 2 lines	6 /523 (1.1%) [0.2-2.1%]	7 /515 (1.4%) [0.4-2.4%]	5 /430 (1.2%) [0.1-2.2%]	6 /300 (2.0%) [0.4-3.6%]
Increase > 2	1 /523 (0.2%) [0.0-0.6%]	6 /515 (1.2%) [0.2-2.1%]	4 /430 (0.9%) [0.0-1.8%]	1 /300 (0.3%) [0.0-1.0%]
Total Reported	**523**	**515**	**430**	**300**
Not reported	13	18	12	6
All Records	**536**	**533**	**442**	**306**

Change in Best Spectacle Corrected Visual Acuity
All Eyes Treated

Myopia > 7.0D

BSCVA	1 Month	3 Month	6 Month	12 Month
Decrease > 2	10 /439 (2.3%) [0.9-3.7%]	4 /424 (0.9%) [0.0-1.9%]	3 /322 (0.9%) [0.0-2.0%]	2 /199 (1.0%) [0.0-2.4%]
Decrease 2 lines	2 /439 (0.5%) [0.0-1.1%]	1 /424 (0.2%) [0.0-0.7%]	3 /322 (0.9%) [0.0-2.0%]	4 /199 (2.0%) [0.1-4.0%]
Decrease 1 line	55 /439 (12.5%) [9.4-15.6%]	44 /424 (10.4%) [7.5-13.3%]	29 /322 (9.0%) [5.9-12.1%]	21 /199 (10.6%) [6.3-14.8%]
No Change	256 /439 (58.3%) [53.7-62.9%]	263 /424 (62.0%) [57.4-66.6%]	201 /322 (62.4%) [57.1-67.7%]	127 /199 (63.8%) [57.1-70.5%]
Increase 1 line	100 /439 (22.8%) [18.9-26.7%]	98 /424 (23.1%) [19.1-27.1%]	72 /322 (22.4%) [17.8-26.9%]	36 /199 (18.1%) [12.7-23.4%]
Increase 2 lines	7 /439 (1.6%) [0.4-2.8%]	8 /424 (1.9%) [0.6-3.2%]	5 /322 (1.6%) [0.2-2.9%]	6 /199 (3.0%) [0.6-5.4%]
Increase > 2	9 /439 (2.1%) [0.7-3.4%]	6 /424 (1.4%) [0.3-2.5%]	9 /322 (2.8%) [1.0-4.6%]	3 /199 (1.5%) [0.0-3.2%]
Total Reported	**439**	**424**	**322**	**199**
Not reported	11	7	10	9
All Records	**450**	**431**	**332**	**208**

The highest rate of loss of BSCVA of greater than 2 lines from preoperative levels was greatest in the >7.0D spherical equivalent group with rates of 0.9% at 6 months and 1.0% at 12 months. Additionally, this same dioptric group had the greater losses of 2 lines with 0.9% at 6 months and 2.0% at 12 months. Loss of 2 lines or more had a rate of 1.8% at 6 months and 3.0% at 12 months. Loss of 1 line or more of BSCVA at 6 months in this category totaled 10.8% at 6 months and 13.6% at 12 months.

In contrast, the <7.0D spherical equivalent group showed rates of loss of BSCVA of >2 lines from the preoperative level of 0.5% at 6 months and 0.3% at 12 months. For 2 lines of BSCVA lost, the rates were 0.7% at 6 months and 0.3% at 12 months. Decreases of 2 or more lines showed rates of 1.2% at 6 months and 0.6% at 12 months. For losses of one line or more of BSCVA for the <7.0D dioptric group the rates were 11.9% at 6 months and 13.3% at 12 months.

Table 14: Summary of Key Safety Variables at the Point of Stability (6 months)
(Stratified by preoperative spherical equivalent for all treated eyes)

Efficacy Variables	< -2.00	-2.00 to - 3.99	-4.00 to -5.99	-6.00 to -7.99	-8.00 to -9.99	-10.00 to -11.99	-12.00 to -13.99	≥ -14.00
BSCVA worse than 20/40	0/17 (0%)	0/152 (0%)	1/164 (0.6%)	0/178 (0%)	0/143 (0%)	0/76 (0%)	0/20 (0%)	0/4 (0%)
Loss of 2 lines BSCVA	0/17 (0%)	1/152 (0.7%)	1/163 (0.6%)	1/177 (0.6%)	2/143 (1.4%)	1/76 (1.3%)	0/20 (0%)	0/4 (0%)
Loss of > 2 lines BSCVA	0/17 (0%)	1/152 (0.7%)	1/163 (0.6%)	0/177 (0.0%)	1/143 (0.7%)	2/76 (2.6%)	0/20 (0%)	0/4 (0%)
BSCVA worse than 20/25 with 20/20 or better pre-op	0/17 (0%)	1/152 (0.7%)	1/163 (0.6%)	0/177 (0.0%)	1/143 (0.7%)	2/76 (2.6%)	0/20 (0%)	0/4 (0%)
Increase > 2 cylinder	0/17 (0%)	0/150 (0%)	1/163 (0.6%)	0/179 (0.0%)	0/145 (0%)	0/77 (0%)	1/20 (5.0%)	0/4 (0%)
BSCVA not reported	2	5	1	7	4	1	0	0

Table 15 presents a summary of adverse events. The benchmark for each adverse event is a rate of less than 1% per event.

Table 15: Adverse Events at stability (6 months) – All Eyes Treated
(based on 938 eyes available for analysis)

Adverse Event	Percentage
Corneal or stromal infiltrate or ulcer (2+ or above)	0/938 (0.0%)
Persistent central corneal epithelial defect at 1 month or later (2+ or above)	0/938 (0.0%)
Uncontrolled IOP with increase of > 10 mm Hg above baseline	0/938 (0.0%)
IOP reading above 25 mm Hg	0/938 (0.0%)
Late onset of haze beyond 6 months with loss of 2 lines (10 letters) or more BSCVA	0/938 (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	5/938 (0.5%)
Retinal detachment	0/938 (0.0%)
Retinal vascular accidents	0/938 (0.0%)

All adverse reactions, measured or reported by patients, are presented in Table 16. 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 tended to be highest immediately postoperative and tapers down over time.

Table 16: Adverse Reactions at 3, 6, and 12 months
N= number of eyes

Adverse Reactions	3 months N=1095	6 months N=938	12 months N=659
Peripheral corneal defect at 1 month or later	0/1095 (0%)	2/938 (0.2%)	0/659 (0%)
Epithelium in the interface	1/1095 (0.1%)	1/938 (0.1%)	1/659 (0.2%)
Ghosts/Double images	21/1095 (1.9%)	12/938 (1.3%)	7/659 (1.1%)
Foreign body sensation	8/1095 (0.7%)	5/938 (0.5%)	0/659 (0.0%)
Pain	4/1095 (0.4%)	0/938 (0.0%)	0/659 (0.0%)
Flap is not the size and shape as initially intended or microkeratome stopped in mid-cut	0/1095 (0.0%)	0/938 (0.0%)	0/659 (0.0%)

e. Retreatment

All retreatment procedures were performed at least 3 months after the initial treatment. Retreatments could be performed for under-correction and regression of refractive effect for myopia and/or astigmatism, or for haze, decentration, or interrupted treatments. There were a total of 197 retreatments performed on 197 eyes through August 27, 1999 (197/1126 = 17.5%).

All of these eyes received retreatment for residual myopia, astigmatism, or regression of refractive effect. Of these 197 eyes, 15 cases did not specify a reason for retreatment on the surgery page, but had treatable myopia or astigmatism under the protocol at the preoperative evaluation. No eyes were retreated with the laser in response to an adverse event. Only 2 cases (0.18%) were reported for performing more than one enhancement. All retreatment cases were also analyzed separately and removed from the main analysis cohort after their respective date of retreatment.

Compared to eyes receiving only one treatment, retreated eyes did not differ remarkably at the 1-month period after retreatment, where the most available data exist. The proportion of eyes within ±1.00 D of the intended MRSE outcome was 96.1%. This is not clinically different than the proportion observed for ≤ 7 D myopic eyes. The relative rates of uncorrected vision at follow-up for 20/20 (68.8%) and 20/40 or better (94.8%) also appear satisfactory. For the key safety variables, only 1 eye (1.3%) had a loss of BSCVA of 2 or more lines. Average BSCVA was unchanged. No eyes after retreatment were worse than 20/40 or had significant increases in cylinder.

No adverse events associated with these retreated eyes have been reported.

X. 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 labeling.

XI. 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.

XII. CDRH DECISION

CDRH issued an approval order for this supplement to Nidek Technologies, Inc. on April 14, 2000.

XIII. 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.