SUMMARY OF SAFETY AND EFFECTIVENESS DATA
FOR A SUPPLEMENTAL PREMARKET APPROVAL (PMA) APPLICATION

I. GENERAL INFORMATION

Device Generic Name:	OPHTHALMIC EXCIMER LASER SYSTEM (193 nanometer laser wavelength)
Device Trade Name:	NIDEK EC-5000 EXCIMER LASER SYSTEM for Photorefractive Keratectomy for Moderate Myopia with Astigmatism
Applicant's Name and Address:	Nidek Technologies, Inc. 675 South Arroyo Parkway Suite 330 Pasadena, California 91105 (626) 578-1351 Fax: (626) 578-1327
Date(s) of Panel Recommendation:	None
PMA Supplement Number:	P970053/S1
Date of Notice of Approval to Applicant:	September 29, 1999

The Nidek EC-5000 Excimer Laser System was approved on December 17, 1998 under P970053. That approval is for the limited indication for Myopic Photorefractive Keratectomy (PRK). The approved PRK treatments are for the reduction or elimination of myopia in the range of –0.75 Diopters (D) to –13.00 D spherical equivalent (S.E.) in patients over 21years of age and with a stable history of pretreatment myopia, that is a change of $\leq$ 0.50 D in sphere or cylinder in the 12 month period preceding treatment for correction of myopia $\leq$ -7.00 S.E., or a change of $\leq$ 1.00 D in sphere or cylinder for correction of myopia > -7.00 D S.E. 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 under Docket # 00M-1640. The summary can also be found on the FDA CDRH Internet Home Page located at http://www.fda.gov/cdrh/pmapage.html.

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II. INDICATIONS FOR USE

The Nidek EC-5000 Excimer Laser System is intended for use in:

- the reduction or elimination of myopia with astigmatism ranging in severity from –1.00 to -8.00 diopters (D), in terms of manifest refraction spherical equivalent (MRSE), with refractive astigmatism ranging in severity from –0.5 to –4.00 D cylinder by manifest refraction. Due to cylinder coupling effects on sphere, the lower range of the intended use must be restricted in a step-wise fashion. A nomogram lookup table is provided for specific treatment combinations.

- patients who have a stable history of both pretreatment myopic astigmatism (i.e., a magnitude of change in manifest refraction of $\leq$ 0.5 D per year in terms of MRSE for at least one year preceding treatment) and pretreatment astigmatism (i.e., a magnitude of change of $\leq$ 0.5 D per year in cylinder for at least one year preceding treatment); and

- patients who are over 21 years of age.

NOTE: You should be aware that the treatment ranges for PRK for myopia without astigmatism and PRK for myopia with astigmatism are different. Refer to the EC-5000 Operator's Manual as needed for specific treatment ranges.

III. CONTRAINDICATIONS

The Nidek EC-5000 Excimer Laser System should not be used to perform laser surgery:

- 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 Sjogren'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 regimenthat would affect their refractive correction.

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

IV. WARNINGS AND PRECAUTIONS

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

V. DEVICE DESCRIPTION

The Nidek EC-5000 Excimer Laser System for Photorefractive Keratectomy for Moderate Myopia with Astigmatism is intended to perform keratectomy on exposed corneal tissue to modify curvature for vision correction of both myopia and astigmatism.

The Excimer laser output is produced by electronically exciting a gas mixture of argon and fluorine. This produces radiation at a far-ultraviolet wavelength of 193nm which causes photo-decomposition of molecular bonds. The optical correction is achieved by re-contouring the anterior surface of the cornea with photo-ablative decomposition.

The Nidek EC-5000 Excimer Laser System is composed of an Excimer laser generator, a beam delivery optical system, an optical system for observation, a gas system, and a computer control system.

With the following exceptions, the Nidek EC-5000 Excimer Laser System for Photorefractive Keratectomy for Moderate Myopia with Astigmatism is the same as the Nidek EC-5000 Excimer Laser System approved in the original P970053 for the treatment of myopia:

a. Myopia with astigmatism treatment procedure specific software that was disabled for the myopic PRK approval is enabled. A Nidek EC-5000 Surface PRK for Moderate Myopia with Astigmatism Nomogram Lookup Table is provided for using software version 2.25e for specific treatment combinations. Due to cylinder coupling effects on sphere, the lower range of the intended use must be restricted in a step-wise fashion.

b. The slit apertures utilized to control the laser beam width and angle for cylinder correction that were also disabled in the approved EC-5000 are now enabled.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The currently other alternatives and procedures for the correction of mild to moderate myopic astigmatism include: spectacles, contact lenses, radial keratotomy, and other surgical procedures.

VII. 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.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The potential adverse reactions include: corneal edema, persistent central corneal epithelial defect, increase in IOP, retinal detachment, vitreal cells, vitreal hemorrhage, late onset of corneal haze, decrease in best spectacle corrected visual acuity (BSCVA), increases in fluctuation of vision, glare and difficulty in night driving.

The rates of these adverse reactions are found in the Summary of Clinical Studies of this document (Section X).

IX. SUMMARY OF PRECLINICAL STUDIES

Please refer to the SSED for the original PMA, i.e., P970053, for the preclinical studies applicable to PRK in general. In addition to these general studies, specific profilometry testing was conducted to verify the accuracy and precision of the spherical and cylindrical correction on PMMA with theoretical profiles, the results indicate that the actual PMMA profiles closely match the theoretical PMMA profiles expected during the operation of the EC-5000. Also, software/hardware validations were expanded and redone as necessary with a system level validation of the revised version of the EC-5000 hardware and software to verify that the EC-5000 meets the revised system specifications for performance and accuracy.

X. SUMMARY OF CLINICAL STUDIES

The sponsor performed a clinical study of the Nidek EC-5000 Excimer Laser System for Photorefractive Keratectomy for Moderate Myopia with Astigmatism in the US under the auspices of IDE G940084. The data from this study served as the basis for the approval decision. Specifically, safety and effectiveness outcomes at 6 months postoperative were assessed as stability is reached by that time. Outcomes at 9 to 24 months postoperatively were also evaluated for confirmation. The IDE study is described in detail as follows.

A. STUDY OBJECTIVES

The study objective for the Nidek EC-5000 Excimer Laser System for Photorefractive Keratectomy for Moderate Myopia with Astigmatism treatment procedure was defined by this goal: to assess the safety and effectiveness of the EC-5000 Excimer Laser System for the treatment of low and moderate myopia with astigmatism.

B. STUDY DESIGN

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

C. INCLUSION AND EXCLUSION CRITERIA

1. INCLUSION CRITERIA

Enrollment in this protocol was limited to patients who were over the age of 21 years; were healthy and free from major systemic and cardiovascular disease; have myopia with astigmatism in the range of –1.00 to –8.00D myopia with astigmatism ranging from –0.50 to –4.00D; exhibit a stable preoperative refraction of $\leq$ 1.0D change in spherical equivalent for the previous year documented by clinical testing and/or prescription history; have a clear cornea in the area to receive laser treatment; and discontinue contact lens wear (3 weeks for hard lenses and 2 weeks for soft lenses).

2. EXCLUSION CRITERIA

Patients were not permitted to enroll in this investigation if they had less than 20/40 BSCVA in either eye; a variable astigmatic axis (no agreement within $\pm$ 15° among the manifest cylinder, cycloplegic, and keratometric axes); systemic disease influencing corneal wound healing; active ocular disease; keratoconus (current, early signs, or clinical indications); previous penetrating ocular or corneal surgery; previous corneal scarring in the treatment zone; irregular astigmatism as seen in topographical analysis; nystagmus or any other condition which would prevent a steady gaze, or if they were taking medications including steroids (ocular or systemic that would affect their refractive correction); pregnant or lactating; participating or planning to participate in other clinical trial.

D. STUDY PLAN, PATIENT ASSESSMENTS, AND EFFICACY CRITERIA

All subjects were expected to return for follow-up examinations: at 1, 2 (optional), 3 days, and at least three times a week starting 3 day until the epithelium has healed, and then 1, 3, 6, 9, 12, 18 and 24 months postoperatively.

Subjects were permitted to have second eyes (fellow eyes) treated a minimum of 3 months after treatment of the first eye. In addition, subjects were eligible for retreatment if they meet the following inclusion criteria after the first laser treatment:

- A resulting myopia > 1.0 D from the intended correction for sphere due to under correction or regression, and/or an induced astigmatism which is > 1.0 D from the intended cylinder correction;
- Post-op refractive stability defined by a $\leq$ 1.0 D S.E. change at 2 consecutive visits which are at least 2 months apart;
- Subjects meet the health requirements of the inclusion criteria for the primary surgery.

Re-treatment was not permitted until at least 6 months after the initial treatment.

Preoperatively, the subject's medical and ocular histories were recorded. Immediately postoperative, re-epithelialization data were collected. The objective parameters measured during the study included best spectacle corrected visual acuity (near and distance), uncorrected visual acuity (near and distance), manifest and cycloplegic refraction, intraocular pressure, pupil size, slit lamp examination, corneal topography, fundoscopic examination and retinal status, vitreal status, and keratometry. A patient questionnaire was to be administered to all subjects preoperatively and postoperatively at 6, 12, and 24 months. Glare, contrast sensitivity, specular microscopy, and pachymetry are included for subset studies only.

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 (MRSE).

The key safety variable is BSCVA measured in terms of Snellen lines of acuity following PRK treatment.

E. STUDY PERIOD, INVESTIGATIONAL SITES, AND DEMOGRAPHICS

1. STUDY PERIOD AND INVESTIGATIONAL SITES

Subjects were treated between January 1996 and June 1998. The database for this PMA supplement are for subjects with a minimum of 6 months follow-up as of December 31, 1998, and included 749 eyes: 486 first eyes and 363 second eyes. There were eight investigational sites. The data were analyzed for site factors which would prevent poolability of data and no bias were detected.

2. DEMOGRAPHICS

The population characteristics are presented in Table 1 for all eyes treated.

Table 1: Demographics

(749 Eyes of 486 Enrolled Subjects)

	Number	Percentage
Gender		
Female	241	49.6
Male	245	50.4
Race		
Caucasian	442	90.9
Hispanic	22	4.5
Asian	15	3.1
Black	4	0.8
American Indian	3	0.6
Eye		
Right	384	51.3
Left	365	48.7
Age at First Surgery(in years)		
Average	43.0	
Standard Deviation	9.0	
Minimum	21.0	
Maximum	67.0	
Contact Lens History		
None	352	72.4
Soft	126	25.9
RGP	125	25.7

F. DATA ANALYSIS AND RESULTS

1. PREOPERATIVE CHARACTERISTICS

Table 2 is a summary table of preoperative visual acuity.
Table 3 presents the number and proportion for the treated eyes stratified by pre-operative MRSE and refractive cylinder.

Table 2: Preoperative Visual Acuity Characteristics

Pre-op UCVA	
UCVA 20/40 or better	1.4% (10/720*)
UCVA 20/50 to 20/80	5.8% (42/720)
UCVA 20/100 or worse	92.7% (668/720)
Pre-op BSCVA	
BSCVA 20/20	89.8% (672/748**)
BSCVA 20/25	9.8% (73/748)
BSCVA 20/40 or worse	0.4% (3/748)

*29 eyes are not reported because of missing preoperative UCVA value
**One eye was missing the preoperative BSCVA value

Table 3: Pre-Operative MRSE/Cylinder Strata

Pre-op Stratum	LOW S.E./LOW CYL	LOW S.E./MOD CYL	MOD S.E./LOW CYL	MOD S.E./LOW CYL
Manifest Refraction Limits	<-5.00 D S.E. ≤-2.00 D CYL	<-5.00 D S.E. >-2.00 D CYL	≥-5.00 D S.E. ≤2.00 D CYL	≥-5.00 D S.E. >-2.00 CYL
Treated Count (%)	320/749 (42.7%)	70/749 (9.3%)	273/749 (36.4%)	86/749 (11.5%)

2. POSTOPERATIVE RESULTS

a. Accountability and definition of the PMA cohort

The investigation was conducted in two phases: Phase II and Phase III. A total of 749 eyes were treated. The two phases were statistically and clinically comparable. All treated eyes in the two phases were combined into one cohort.

Accountability was determined for all treated eyes (both primary and secondary) with at least 6 months of postoperative follow-up. While there were a total of 486 subjects and 749 eyes available for analysis, the number available at each interval varied. The variability was caused by

several factors, including subjects missed visits, discontinued, and lost to follow-up.

In the following table, percent accountability is calculated by:

$$\% \text{ Accountability} = \frac{(\#\text{ Available for analysis})}{(\#\text{ Enrolled} - \#\text{ Discontinued} - \#\text{ Not yet eligible})}.$$

Table 4: Accountability

	1 month	3 months	6 months	12 months	18 months	24 months
No. of Eyes in Cohort	749	749	749	749	749	749
Available for Analysis	564/749 (75.3%)	663/749 (88.5%)	635/749 (84.8%)	483/749 (64.5%)	350/749 (46.7%)	140/749 (18.7%)
Discontinued	0/749 (0.0%)	0/749 (0.0%)	1/749 (0.1%)	6/749 (0.8%)	19/749 (2.5%)	19/749 (2.5%)
Not yet eligible for the interval	0/749 (0.0%)	0/749 (0.0%)	0/749 (0.0%)	65/749 (8.7%)	239/749 (31.9%)	531/749 (70.9%)
Lost to follow-up	6/749 (0.8%)	7/749 (0.9%)	16/749 (2.1%)	29/749 (3.9%)	31/749 (4.1%)	31/749 (4.1%)
Missed Visit	179/749 (23.9%)	79/749 (10.5%)	97/749 (13.0%)	166/749 (22.2%)	110/749 (14.7%)	28/749 (3.7%)
% Accountability	564/749 (75.3%)	663/749 (88.5%)	635/748 (84.9%)	483/678 (71.2%)	350/491 (71.3%)	140/199 (70.4%)

A total of 50 subjects exited the study early. Of the subjects who exited the study early, 19 subjects were discontinued from the study and 31 subjects were lost to follow-up.

b. Stability of outcome

Tables 5 and 6 provide the results of stability analyses.
In the 3-6 months window, 95.5% of eyes experienced a change of MRSE not exceeding ± 1.0D. The assessment of the efficacy was therefore performed using the outcomes of the eyes evaluable at 6 months.

Table 5: Stability Analyses

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

	1 to 3 Months	3 to 6 Months	6 to 9 Months	9 to 12 Months
Change <=1 D n/N (%) (95% CI)	377/449 (84.0%) [80.6-87.4%]	429/449 (95.5%) [93.6-97.5%]	357/370 (96.5%) [94.6-98.4%]	299/306 (97.7%) [96.0-99.4%]
Change (Pair-Differences) Mean Std.Dev. (95% CI)	-0.44 0.97 [-0.53 to -0.35]	-0.03 0.93 [-0.11 to 0.06]	0.22 0.62 [-0.05 to 0.08]	-0.05 0.39 [-0.10 to –0.01]

Table 6: Stability Analyses
(change in MRSE over time for eyes that
had 2 consecutive exams, through 12 months)

	1 to 3 Months	3 to 6 Months	6 to 9 Months	9 to 12 Months
Change <=1 D n/N (%) (95% CI)	430/513 (83.8%) [80.6-87.0%]	539/562 (95.9%) [94.3-97.5%]	464/478 (97.1%) [95.6-98.6%]	368/377 (97.6%) [96.1-99.2%]
Change (Pair-Differences) Mean Std.Dev. (95% CI)	-0.43 0.98 [-0.51 to – 0.34]	-0.03 0.85 [-0.10 to 0.04]	0.02 0.58 [-0.04 to 0.07]	-0.05 0.42 [-0.09 to –0.01]

c. Effectiveness Outcomes

i. Key efficacy outcome

A summary of the key efficacy variable for all treated eyes is presented in Table 7.

Table 8 is a summary of UCVA results stratified by pre-operative MRSE and refractive cylinder.

Table 9 demonstrates the accuracy of manifest refraction in spherical equivalent (MRSE, attempted vs. achieved) for treated eyes across all pre-operative strata.

Table 7: Summary of Key Efficacy Variables

Efficacy Variables	1 month	3 months	6 months	12 months	18 months	24 months
UCVA 20/20 OR BETTER	249/561 (44.4%)	405/662 (61.2%)	406/631 (64.3%)	320/477 (67.1%)	232/344 (67.4%)	86/133 (64.7%)
UCVA 20/40 or better	491/561 (87.5%)	623/662 (94.1%)	590/631 (93.5%)	446/477 (93.5%)	328/344 (95.3%)	128/133 (96.2%)
MRSE ± 0.50 D	286/561 (51.0%)	419/661 (63.4%)	394/632 (62.3%)	297/474 (62.7%)	218/339 (64.3%)	86/133 (64.7%)
MRSE ± 1.00 D	416/561 (74.2%)	556/661 (84.1%)	544/632 (86.1%)	397/474 (83.8%)	280/339 (82.6%)	122/133 (91.7%)
MRSE ± 2.00 D	515/561 (91.8%)	642/661 (97.1%)	617/632 (97.6%)	457/474 (96.4%)	326/339 (96.2%)	128/133 (96.2%)

N = 749 total eyes treated; data is shown for all subject eyes present at each visit.
UCVA not reported: 3 subjects at 1 month, 1 at 3 months, 4 at 6 months, 6 each at 12 and 18 months, and 7 at 24 months.
MRSE not reported: 3 subjects at 1 and 6 months, 2 at 3 months, 9 at 12 months, 11 at 18 months, and 7 at 24 months.

Table 8: Summary of Accuracy Results for All Treated Eyes and for Each Pre-operative S.E./Cylinder Stratum

	Pre-op N/N (%)	6 Months n/N (%)	12 Months n/N (%)
20/20 or better			
All Treated Eyes	2/720 (0.3%)	406/631 (64.3%)	320/477 (67.1%)
Low S.E./Low Cyl	1/313 (0.3%)	204/271 (75.3%)	148/182 (81.3%)
Low S.E./ Mod Cyl	0/69 (0.0%)	36/53 (67.9%)	32/48 (66.7%)
Mod S.E./Low Cyl	1/254 (0.4%)	130/233 (55.8%)	105/187 (56.1%)
Mod S.E./Mod Cyl	0/84 (0%)	36/74 (48.6%)	35/60 (58.3%)
20/40 or better			
All Treated Eyes	10/720 (1.4%)	590/631 (93.5%)	446/477 (93.5%)
Low S.E./Low Cyl	5/313 (1.6%)	259/271 (95.6%)	178/182 (97.8%)
Low S.E./ Mod Cyl	4/69 (5.8%)	52/53 (98.1%)	47/48 (97.9%)
Mod S.E./Low Cyl	1/254 (0.4%)	212/233 (91.0%)	167/187 (89.3%)
Mod S.E./Mod Cyl	0/84 (0.0%)	67/74 (90.5%)	54/60 (90.0%)

Table 9: Accuracy of Manifest Refraction (Predictability of Outcome)

Difference from Intended Outcome	1 month	3 months	6 months	12 months	18 months	24 months
± 0.50 D	286/561 (51.0%)	419/661 (63.4%)	394/632 (62.3%)	297/474 (62.7%)	218/339 (64.3%)	86/133 (64.7%)
± 1.00 D	416/561 (74.2%)	556/661 (84.1%)	544/632 (86.1%)	397/474 (83.8%)	280/339 (82.6%)	122/133 (91.7%)
± 2.00 D	515/561 (91.8%)	642/661 (97.1%)	617/632 (97.6%)	457/474 (96.4%)	326/339 (96.2%)	128/133 (96.2%)
> ± 2.00 D	46/561 (8.2%)	19/661 (2.9%)	15/632 (2.4%)	17/474 (3.6%)	13/339 (3.8%)	5/133 (3.8%)
Under-corrected < –1.00 D	7/561 (1.2%)	23/661 (3.5%)	20/632 (3.2%)	20/474 (4.2%)	16/339 (4.7%)	3/133 (2.3%)
Under-corrected < –2.00 D	2/561 (0.4%)	5/661 (0.8%)	2/632 (0.3%)	5/474 1.1(%)	4/339 (1.2%)	0/133 (0.0%)
Over-corrected > +1.00 D	138/561 (24.6%)	82/661 (12.4%)	68/632 (10.8%)	57/474 (12.0%)	43/339 (12.7%)	8/133 (6.0%)
Over-corrected > +2.00 D	44/561 (7.8%)	14/661 (2.1%)	13/632 (2.1%)	12/474 (2.5%)	9/339 (2.7%)	5/133 (3.8%)

Analysis of over- and under-correction was also performed for the treated eyes stratified by pre-operative MRSE and refractive cylinder. Table 10 and 11 show the numbers and proportions of treated eyes in each S.E./cylinder strata, which fall into the given predictability bins at 6 and 12 months post-treatment, respectively.

Table 10: Proportion of Pre-operative S.E./Cylinder Results Expressed as Difference from Intended Refraction for All Treated Eyes at 6 Months

Strata:	Low S.E./Low Cyl		Low S.E./Mod Cyl		Mod S.E./Low Cyl		Mod S.E./Mod Cyl	
SE bin (D)	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
<-3.00	0/271	0.0	0/53	0.0	1/234	0.4	0/74	0.0
-3.00 to <-2.00	0/271	0.0	0/53	0.0	1/234	0.4	0/74	0.0
-2.00 to <-1.00	1/271	0.4	1/53	1.9	13/234	5.6	3/74	4.1
±1.00	257/271	94.8	46/53	86.8	178/234	76.1	63/74	85.1
>+1.00 to +2.00	12/271	4.4	5/53	9.4	32/234	13.7	6/74	8.1
>+2.00 to +3.00	1/271	0.4	1/53	1.9	6/234	2.5	1/74	1.4
>+3.00	0/271	0.0	0/53	0.0	3/234	1.3	0/74	1.4

Table 11: Proportion of Pre-operative S.E./Cylinder Results Expressed as Difference from Intended Refraction for All Treated Eyes at 12 Months

Strata:	Low S.E./Low Cyl		Low S.E./Mod Cyl		Mod S.E./Low Cyl		Mod S.E./Mod Cyl	
SE bin (D)	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
<-3.00	0/182	0.0	0/47	0.0	1/185	0.5	0/60	0.0
-3.00 to <-2.00	1/182	0.5	0/47	0.0	1/185	0.5	2/60	3.3
-2.00 to <-1.00	1/182	0.5	0/47	0.0	13/185	7.0	1/60	1.7
±1.00	168/182	92.3	42/47	89.4	138/185	74.6	49/60	81.7
>+1.00 to +2.00	12/182	6.6	5/47	10.6	23/185	12.4	5/60	8.3
>+2.00 to +3.00	0/182	0.0	0/47	0.0	7/185	3.8	2/60	3.3
>+3.00	0/182	0.0	0/47	0.0	2/185	1.1	1/60	1.7

At 12 months, over-correction of more than +2.00 D occurred 0% (0/182) in the low MRSE/low cylinder group, 0.0% (0/47) in the low MRSE/moderate cylinder group, 4.9% (9/185) in the moderate MRSE/low cylinder group, and 5.0% (3/60) in the moderate MRSE/moderate cylinder group. At 12 months, under-correction of more than –2.00 D occurred 0.5% (1/182) in the low MRSE/low cylinder group, 0.0% (0/47) in the low MRSE/moderate cylinder group, 1.1% (2/185) in the moderate MRSE/low cylinder group, and 3.3% (2/60) in the moderate MRSE/moderate cylinder group.

ii. Correction of Cylindrical and Spherical Components

Table 12 is a vector analysis summary comparing pre-operative and 6 month post-op manifest refractions. For those treated eyes with both preoperative and 6-month follow up refraction data available, the average preoperatrive cylinder mangnitude was –1.59 ± 0.74 D. The average value at 6 months was reduced to -0.44 ± 0.4 D (n=632). Average reduction of cylinder magnitude at 6 months is 72.3%. The Ophthalmic Devices Panel (the Panel), in the January 14, 1997 meeting in which the Panel assessed outcomes from a myopic astigmatic treatment, provided FDA with some guidance as to the acceptable effectiveness rates. The Panel considered 64% as an acceptable mean reduction in absolute cylinder at the point of stability. Therefore, the 72.3% reduction at 6 months achieved with this device is acceptable.

Table 12: Vector Analysis Summary Comparing Pre-operative and 6 Month Manifest Refractions

	Pre-op		Target (Desired)		6 Mo. Post-op			Induced Change		Error Vector		Axis Delta
	Sph	Cyl	Sph	Cyl	Sph	Cyl	SE	Sph	Cyl	Magn	Angle	
Avg	-4.11	-1.59	-0.21	0.00	0.18	-0.44	-0.04	4.29	1.55	-0.04	1	26
SD	1.75	0.74	0.42	0.00	0.87	0.40	0.85	2.01	0.85	0.48	10	31
Min	-8.00	-5.25	-2.00	0.00	-7.50	-2.00	-7.50	-0.50	0.00	-1.67	-80	0
Max	0.00	-0.25	0.50	0.00	4.50	0.00	3.75	11.00	5.12	1.93	90	90
n	632	632	632	632	632	632	632	632	632	632	632	632

Vector analysis according to the method of Alpins [see Alpins, NA: A new method of analyzing vectors for changes in astigmatism. *J Caqtaract Refrat Surg* **19**: 524-533 (1993).] showed that at 6 months follow-up, the average targeted induced astigmatism (TIA) was -1.59 ± 0.74 D at 103° ± 69° while the average surgically induced astigmatism (SIA) was 1.55 ± 0.85 D at 94° ± 67°. The analyses indicated that the observed error vectors averaging 1 ± 10°, with 92% (582/632) of error vectors within ±15° of the desired axis value of zero error. 97.6 % (617/632) of the error vector axes were within ±30°, and 99.4% (628/632) were within ±45°. The analysis also indicated that the magnitude of the error vectors at 6 months follow-up averaged – 0.04 ± 0.48 D, with 81.3% (514/632) of the error vector magnitudes within ±0.5 D and 95.1% (601/632) within ±1.0 D. Under-correction of cylinder was strongly associated with small changes in refractive axis, while over-corrections in cylinder magnitude were associated with large axis changes. Cylinder over-corrections by more than 1.00 D occurred in 2.8% (18/632) of eyes by vector analysis, while cylinder under-corrections by more than 1.00 D occurred in 2.1% (13/632) of eyes. Over- and under-corrections by ≥ 2.00 D combined occurred in 0.0% (0/632) of cases, according to the vector analysis method. The vector analysis results indicated that the EC-5000 reliably corrected cylinder as intended.

d. Safety Outcomes

The analysis of safety was based on all subject eyes present at each visit. The summary of key safety varibles for this study are presented in Tables 13 and 14.

Table 13: Summary of Key Safety Variables by Visit

Safety Variables	1 month	3 months	6 months	12 months	18 months	24 months
BSCVA worse than 20/40	6/559 (1.1%)	1/658 (0.2%)	0/630 (0.0%)	0/474 (0.0%)	0/341 (0.0%)	0/133 (0.0%)
Loss of 2 lines BSCVA	7/558 (1.3%)	9/657 (1.4%)	7/629 (1.1%)	3/473 (0.6%)	3/341 (0.9%)	1/133 (0.8%)
Loss of >2 lines BSCVA	17/558 (3.0%)	9/657 (1.4%)	3/629 (0.5%)	3/473 (0.6%)	3/341 (0.9%)	0/133 (0.0%)
BSCVA worse than 20/25; 20/20 or better pre-op	14/558 (2.5%)	12/657 (1.8%)	4/629 (0.6%)	3/473 (0.6%)	3/341 (0.9%)	0/133 (0.0%)

N = 749 total eyes treated; data is shown for all subject eyes present at each visit.
BSCVA was not reported for 5 subjects each at 1, 3, and 6 months, 9 subjects each at 12 and 18 months, and 7 subjects at 24 months. In determining loss of lines of BSCVA, values were missing pre-operatively or post-operatively for 6 subjects each at 1, 3, and 6 months, 10 subjects at 12 months, 9 subjects at 18 months, and 7 subjects at 24 months.

Table 14: Summary of Key Safety Variables at stability Stratified by Preoperative Spherical Equivalent

	Low S.E./Low CYL	Low S.E./Mod CYL	Mod S.E./Low CYL	Mod S.E./Mod CYL
Available for Analysis	272	53	236	74
Safety Variables	n/N (%)	n/N (%)	n/N (%)	n/N (%)
BSCVA worse than 20/40	0/271 (0.0%)	0/53 (0.0%)	0/233 (0.0%)	0/73 (0%)
BSCVA not reported	1	0	3	1
Loss of 2 lines BSCVA	2/270 (0.7%)	0/53 (0.0%)	3/233 . (1.3%)	2/73 (2.7%)
Loss of > 2 lines BSCVA	1/270 (0.4%)	0/53 (0.0%)	2/233 (0.9%)	0/73 (0.0%)
BSCVA worse than 20/25 if 20/20 or better preop	1/270 (0.4%)	0/53 (0.0%)	3/233 (1.3%)	0/73 (0.0%)
BSCVA value missing preop or postop	2	0	3	1

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

Adverse Event	Available for analysis n=635
Corneal or stromal infiltrate or ulcer (2+ or above)	0/635 (0.0%)
Persistent central corneal epithelial defect at 1 month or later (2+ or above)	1/635 (0.2%)
Uncontrolled IOP with increase of > 10 mm Hg above baseline	0/635 (0.0%)
IOP reading above 25 mm Hg	3/635 (0.4%)
Late onset of haze beyond 6 months with loss of 2 lines (10 letters) or more BSCVA	0/635 (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	3/635 (0.5%)
Retinal detachment	1/635 (0.2%)
Retinal vascular accidents	0/635 (0.0%)

Significant corneal haze beyond 6 months occurs in less than 1% of treated eyes. 0.9% (6/634) of eyes had mild or moderate haze at 6 months after surgery, 0.3% (2/634) had mild to moderate haze with significant loss of vision. 0.6% of patients continue to experience a small amount of haze over 1-2 years, i.e., 0.6% (3/480) at 12 months, 0.6% (2/345) at 18 months.

Table 16 presents the incidence of complications reported in this study for eyes available for analysis by visits.

The following additional complications were reported at 6 months post final treatment from the subject questionnaires used in the study: an increase in fluctuation of vision (40.5% pre-operatively vs. 45.7% post-operatively); glare (27.7% pre-operatively vs. 31.4% post-operatively); and difficulty in night driving (24.3% pre-operatively vs. 43.9% post-operatively).

Table 16: Complications

	1 month	3 month	6 month
Available for analysis	564	663	635
Complications			
Corneal Edema	2 / 564 (0.4%)		
Foreign body sensation at one month or later	0 / 564 (0%)	0 / 663 (0%)	0 / 635 (0%)
Pain at one month or later	0 / 564 (0%)	0 / 663 (0%)	0 / 635 (0%)
Vitreal Cell	0/564 (0.0%)	0/663 (0.0%)	1/635 (0.2%)
Vitreal Hemorrhage	0/564 (0.0%)	0/663 (0.0%)	1/635 (0.2%)
Cystoid Macular Edema	0/564 (0.0%)	0/663 (0.0%)	0/635 (0.0%)
Retinal Hemorrhage	0/564 (0.0%)	0/663(0.0%)	0/635 (0.0%)

d. Retreatment

All retreatment procedures were performed at least 6 months after the initial treatment. There were a total of 10 retreatments on the 10 eyes. These eyes were retreated to enhance the refraction result. No adverse events associated with these re-treated eyes have been reported.

We do not have enough data to form any definitive conclusions regarding retreatment outcomes with this device. Because of this low number of re-treated eyes, the proportions for each outcome variable will not likely to be statistically relevant when extrapolated to larger population.

XI. CONCLUSIONS DRAWN FROM THE CLINICAL STUDY

The data in this application supports reasonable assurance of safety and efficacy of this device for the reduction or elimination of myopia with astigmatism ranging in severity from –1.00 to -8.00 diopters (D), in terms of manifest refraction spherical equivalent (MRSE), with refractive astigmatism ranging in severity from –0.5 to –4.00 D cylinder by manifest refraction.

XII. PANEL RECOMMENDATION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Ophthalmic Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CDRH DECISION

CDRH issued an approval order for this supplement to Nidek Technologies, Inc. on September 29, 1999.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See labeling.

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

Post-approval Requirements and Restrictions: See approval order.