SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Ophthalmic Excimer Laser System

Device Trade Name: Nidek EC-5000 Excimer Laser System

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

Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P970053

Date of Notice of Approval to Applicant: December 17, 1998

II. INDICATIONS FOR USE

This device is indicated for photorefractive keratectomy (PRK) for the reduction or elimination of mild to moderate myopia in patients with the following three characteristics:

1. In PRK treatments for the reduction or elimination of myopia in the low, moderate, or high ranges (-0.75 Diopters (D) to –13.0 D) spherical equivalent (S.E.) at the spectacle plane, uncomplicated by refractive astigmatism (i.e., ≤ 0.75 D in any meridian).

2. In patients who have a stable history of pretreatment myopia, that is a change of ≤0.50 D in sphere or cylinder in the 12 months period preceding treatment for correction of myopia ≤-7.0D S.E., or a change of ≤1.00 D in sphere or cylinder for correction of myopia >-7.0 D S.E.

3. In patients who are over 21 years of age.

III. CONTRAINDICATIONS

The 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 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 regimen that would affect their refractive correction.

IV. WARNINGS AND PRECAUTIONS

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

V. DEVICE DESCRIPTION

The EC-5000 Excimer Laser System is an ophthalmic laser system used for corneal refractive correction and ablation of the corneal surface.

The system is composed of an excimer laser (193nm) generator, a beam delivery optical system, an optical system for observation, a gas system, and a computer control system. The EC-5000 Excimer Laser System requires periodic maintenance and care, particularly for the gas system.

Refer to the Operator's Manual for care instructions and precautions.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Eyeglasses, contact lenses, and different kinds of refractive surgery such as radial keratotomy (RK), and automated lamellar keratoplasty.

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 EC-5000 Excimer Laser System 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 events of this device include: corneal infiltrate or ulcer; uncontrolled intraocular pressure (IOP); late onset of haze > 6 months, with loss of ≥ 2 lines best spectacle corrected visual acuity (BSCVA); decrease in BSCVA of > 10 letters not due to irregular astigmatism as shown by hard contact lens refraction, at 6 months or later; retinal vascular accidents; retinal detachment.

Adverse events and complications noted during this study are presented on pages 19 and 20.

IX. SUMMARY OF PRECLINICAL STUDIES

Nonclinical laboratory studies were performed to evaluate the achieved profiles (depth, width, and radius of curvature) in polymethylmethacrylate (PMMA). Various correction levels were tested in PMMA to verify that their profiles follow an expected linear relationship of curvature (inverse radius) versus diopter.

A. Summary of animal testing

Preclinical laboratory animal studies were performed using the 193 nm EC-5000 excimer laser system on pig eyes and rabbit eyes to provide information on temperature elevation, corneal clinical observations, histological and ultrastructural observations, and the effects of laser energy and pulse rate on these measures.

These preclinical animal studies indicate that the Nidek EC-5000 excimer laser appears to safely deliver predictable ablative energy pulses, properly aimed and capable of forming the optically corrective changes required for corneal photorefractive keratectomy. Details of each of the four reports follow their respective summaries below.

1. Nidek No. 005 - Temperature Elevation on Ablated Pig Eye

A laboratory investigation on the 193 nm EC-5000 system was conducted to examine the temperature rise expected to occur during corneal refractive laser surgery on enucleated pig eyes. Measurements of cornea surface temperature were made using a NEC thermotracer model 6T62 set obliquely above the pig eye. Calibrated color thermographs were generated which recorded the actual surface temperature at a linear spatial resolution of ≥ 0.25 mm per pixel and temperature resolution of 0.1°C. The system was set to provide an ablation rate of 0.20-0.25 μm/scan to an optical zone diameter of 4.5 mm at varying frequencies from 10-50 Hz. The change in temperature from baseline (Δt) was tabulated for various numbers of scans delivered at each of the selected frequencies. Four pig eyes were used for each experimental setting.

The results of these experiments showed that Δt was a function of scan frequency (50 Hz > 40 Hz > 30 Hz > 20 Hz > 10 Hz) which leveled off when scan numbers exceeded about 100 and had achieved an ablation depth of about 25 μm. When additional scans continued to be made, the ablation continued to proceed in a linear fashion but Δt did not rise significantly further. The maximum Δt at 50 Hz was 12.6 ± 2.21°C (occurring after about 700 scans), while the maximum Δt after about 1100 scans was 7.9 ± 0.7°C and 3.0 ± 0.2°C for 30 Hz and 10 Hz, respectively.

2. Nidek No. 006 - Excimer Laser for Corneal Refractive Change: Clinical Observation After Excimer Laser Photoablation in Rabbit Eyes

A laboratory investigation using the 193 nm EC-5000 excimer laser system was conducted to examine corneal surface change and clinical observations following corneal refractive laser surgery on albino rabbits. The study was conducted in conformance with the ARVO Resolutions on the Use of Animals in Research. The study evaluated the effect on corneal thickness, endothelial cell density and epithelial healing for up to one month following surgery in eight eyes. The EC-5000 was set to provide an ablation depth of 140 μm using 130 mJ at 30 Hz on the right eyes and 100 mJ at 30 Hz on the left eyes to an optical zone diameter of 4.5 mm. Measurements at various followup periods included ultrasonic pachymetry, endothelial cell counts and slit-lamp examinations. Postoperative medications included only ofloxacine ointment immediately after surgery and ofloxacine eye drops one daily thereafter.

Immediately following surgery, the surfaces of the corneas were very smooth throughout the circular ablation zone with sharp margins. Pachymetry measurements indicate that the depth of ablation was uniform and accurate. By three days following surgery, the epithelium had covered the entire surface of the ablated cornea, and some corneal edema was present at the superficial stroma. Mean endothelial cell counts were apparently slightly reduced, but were not analyzed statistically because of the small sample number. By slit-lamp examination, no differences in wound healing were observed between left (100 mJ) and right (130 mJ) eyes. By 5 days, corneal edema had cleared and slight subepithelial haze began to appear. At 7 days, very mild subepithelial haze was observed, but no difference between the left (100 mJ) and right (130 mJ) eyes could be seen. At 2 weeks, the epithelium remained intact and mild haze was observed in all eyes, which remained or was slightly increased by 4 weeks.

These results indicate that the EC-5000 excimer system can ablate rabbit cornea in a uniform fashion and that corneal healing begins immediately following the surgery. Very mild or mild subepithelial haze is observed during follow-up, with only topical ofloxacine treatment being used.

3. Nidek No. 007 - Excimer Laser for Corneal Refractive Change: Histological and Ultrastructural Study of Nidek EC-5000 Excimer Laser Keratectomy in Rabbits

A laboratory investigation using the 193 nm EC-5000 excimer laser system was conducted to examine the cornea for the presence of damage and/or ultrastructural changes following corneal refractive laser surgery on albino rabbits. The study was conducted in conformance with the ARVO Resolutions on the Use of Animals in Research. Observations were made using optical, transmission and scanning electron microscopy on corneas prepared following enucleation either immediately or 2 weeks after surgery. The EC-5000 was set to deliver 130 mJ at 30 Hz to an optical zone diameter of 4.5 mm. Four eyes were used for these experiments.

Results immediately following surgery revealed a smooth ablation surface by light microscopy, more evident at the center than the margins. Transmission electron microscopy (TEM) revealed electron-dense material (pseudomembrane) on the surface of the ablated area. Stromal collagen adjacent to the pseudomembrane showed normal structure. No changes were observed in endothelial cells, except for very slight swelling of mitochondria. Scanning electron microscopy (SEM) also showed the smooth central portion of the ablation area, with a wave-like pattern observed at the periphery.

By 2 weeks following surgery, the corneas showed complete migration of peripheral epithelial cells over the ablated area by light microscopy. The epithelium was thickened and in a state of hyperplasia. At the subepithelial level, fibrous tissue with many activated keratocytes (fibroblasts) was observed. With TEM, no significant changes in endothelial cells were observed except for very slight swelling of mitochondria.

4. Nidek No. 008 - Relationship of Laser Energy, Scan Frequency, Ablation Depth and Temperature Rise on Pig Eyes

A laboratory investigation using the 193 nm EC-5000 excimer laser system was conducted to examine the relationship of laser energy, scan frequency, ablation depth and temperature rise following corneal refractive laser surgery on enucleated pig eyes. The study was conducted in conformance with the ARVO Resolutions on the Use of Animals in Research. The EC-5000 was set to deliver 50-150 mJ at 10, 30 and 50 Hz to an optical zone diameter of 5.0 mm yielding an ablation depth of 100 μm. Observations of temperature

on the cornea during the ablation were made using the infrared Nihondenki-Sanei Thermograph. Central corneal thickness was measured immediately before and immediately after the ablation. Thirty-six eyes were used in this study.

Results indicated that increasing laser energy (from 50-150 mJ/scan) increased the ablation rate from 0.38 μm/scan to 1.09 μm/scan at 30 Hz. This reflects results similar to the laboratory study noted above using PMMA test plates for ablation rate *vs.* fluence. Ablation rate did not seem to be affected by the scan frequency. Temperature rise (Δt) was observed to be related to both laser energy and frequency, with Δt ranging from 11.6°C for 10 Hz, 130 mJ to 17.6°C for 50 Hz, 130 mJ.

The in vitro and animal studies provided evidence to support the conclusion that the device did not present an unreasonable risk to subjects and could proceed to clinical trials under an approved investigational device exemptions (IDE).

X. SUMMARY OF CLINICAL STUDIES

The sponsor performed a clinical study of EC-5000 Excimer Laser System in the US under the auspices of an 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 12-months postoperatively were also evaluated for confirmation. The IDE study is described in detail as follows.

A. STUDY OBJECTIVES

The overall reason for the EC-5000 Excimer Laser System procedure was defined by this treatment goal: to assess the safety and efficacy of the EC-5000 Excimer Laser System for spherical correction of myopia.

B. STUDY DESIGN

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

C. INCLUSION AND EXCLUSION CRITERIA

Enrollment in the EC-5000 Excimer Laser System study was limited to patients with: low to high myopia (-0.75 to –13.00 D) in one or both eyes, uncomplicated by refractive astigmatism (i.e., ≤ 0.75 D in any meridian);

over 21 years of age; stable history of pretreatment myopia including documented test and prescription history (i.e., for ≤ -7.00 D S.E., a change of ≤ 0.50 D in sphere or cylinder in the 12 month period preceding treatment or for > -7.00 D S.E., a change of ≤ 1.0 D in sphere or cylinder in the 12 month period preceding treatment); stable history of pretreatment astigmatism of 0.75 D as determined by manifest refraction (≤ 0.75 D change in cylinder correction in the 12 month period preceding treatment); clear cornea in the area to receive laser energy; where applicable, discontinuation of contact lens use prior to final enrollment evaluation where soft contact lenses were removed for at least two (2) weeks, and hard contact lenses for at least three (3) weeks; and best spectacle corrected visual acuity of 20/40 or better.

Patients were not permitted to enroll in EC-5000 Excimer Laser System study if they met any of the following exclusion criteria: functionally monocular (i.e., BSCVA of fellow eye worse than 20/40); difference of more than 1.00 D between preoperative MRSE and cycloplegic refraction spherical equivalent; more than 1.00 D of corneal astigmatism, history of glaucoma or a preoperative intraocular pressure of 21 mm Hg or greater; irregular astigmatism; progressive retinal pathology, such as diabetic retinopathy; clinically significant cataract; signs of keratoconus; previous intraocular or corneal surgery; any systemic autoimmune disease or disseminated vasculopathies; herpes simplex or herpes zoster; or are pregnant or nursing.

D. STUDY PLAN, PATIENT ASSESSMENTS, AND EFFICACY CRITERIA

All subjects were expected to return for follow-up examinations: at 1, 3, and 7 days (only required at 7 days if not re-epithelialized at 3 days), and 1, 3, 6, 12, 18 and 24 months postoperatively.

In addition to having a primary eye treated, under the protocol a subject could have the contralateral eye treated, provided that the primary (or first eye) had a certain improved visual outcome and that sufficient time had elapsed between the time of the surgery on the primary eye and the time of surgery for the second eye.

Preoperatively, the subject's medical and ocular histories were recorded. Immediately postoperative, re-epithelialization data were collected. The objective parameters measured during the study included: best spectacle corrected visual acuity (near, distance, with and without glare), uncorrected visual acuity (near and distance), manifest and cycloplegic refraction, intraocular pressure, corneal topography, keratometry, fundoscopic exam, pupil size and status of the cornea, conjunctiva, anterior chamber, lens, vitreous, retina, and externals. A patient

questionnaire was to be administered to all subjects preoperatively and postoperatively.

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).

E. STUDY PERIOD, INVESTIGATIONAL SITES, AND DEMOGRAPHICS

1. STUDY PERIOD AND INVESTIGATIONAL SITES

Subjects were treated between December 1994 and April 1997. The database for this PMA reflected data collected through April 1997 and included 611 subjects. There were eight (8) investigational sites. A total of 611 subjects had a primary eye or both eyes treated (N=940 total eyes consisting of 611 primary eyes and 329 secondary eyes) at eight clinical centers (Table 1) during the two phases of the Nidek EC-5000 excimer laser study for PRK therapy for myopia under an FDA Investigational Device Exemption (IDE). These subjects were treated between December 1994 and April 1997 and had at least six months follow-up.

During this study, data was collected pre-operatively and post-operatively every two to three days until re-epithelialization and then at 1, 3, 6, 12, 18, and 24 months. The "point of stability" was found to be between 3 and 6 months (i.e., by the 6 month visit). Of the 940 total treated eyes, 587 eyes were evaluated at each of the following visits: pre-operative, 1 month, 3 months, and 6 months. These 587 eyes are considered the "consistent cohort" for the following clinical study results, unless otherwise stated.

2. DEMOGRAPHICS

The demographics of this study are typical for a contemporary refractive surgery trial performed in the US. Of the 611 subjects, 49.9% (305/611) were from male subjects and 49.6% (303/611) from female subjects.

TABLE 1. EC-5000 CLINICAL STUDY POPULATION DEMOGRAPHICS

	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6	Site 7	Site 8	Total Subjects
# Males	45	110	31	42	31	20	9	17	305
Median Age	*39*	*43*	*41*	*41*	*36*	*44*	*41*	*44*	*41*
# Females	53	88	49	52	38	11	3	9	303

Median Age	*38*	*42*	*39*	*40*	*36*	*41*	*43*	*41*	*40*
Sex Not Given	–	1	–	–	–	1	–	1	3
Total *(by Site)*	98	199	80	94	69	32	12	27	611

F. DATA ANALYSIS AND RESULTS

1. PREOPERATIVE CHARACTERISTICS

Table 2 summarizes key safety and efficacy variables for the consistent cohort stratified by pre-operative manifest refraction spherical equivalent (MRSE). 364 subjects were treated in the low myopia range (< –6.00 D); 202 were treated in the moderate myopia range (–6.00 D to –9.99 D), and 21 subjects were treated in the high myopia range (≥ –10.00 D). Tables 3-5 show preoperative characteristics for the entire 587 eyes in the consistent cohort.

TABLE 2. KEY SAFETY AND EFFICACY VARIABLES BY PRE-OPERATIVE MRSE RANGE

A: Low Myopia: Pre-Operative MRSE < –6.00 D

	1 month		3 months		6 months	
EFFICACY VARIABLES*	**n / N**	**%**	**n / N**	**%**	**n / N**	**%**
UCVA 20/20 or better	190 / 364	52.2%	232 / 362	64.1%	245 / 364	67.3%
UCVA 20/40 or better	337 / 364	92.6%	338 / 362	93.4%	345 / 364	94.8%
MRSE ± 0.50 D	201 / 364	55.2%	260 / 364	71.4%	253 / 363	69.7%
MRSE ± 1.00 D	288 / 364	79.1%	325 / 364	89.3%	330 / 363	90.9%
MRSE ± 2.00 D	354 / 364	97.3%	358 / 364	98.4%	358 / 363	98.6%
SAFETY VARIABLES**						
BsCVA worse than 20/40	1 / 364	0.3%	1 / 363	0.3%	0 / 364	0.0%
Loss of 2 lines BsCVA	12 / 364	3.3%	3 / 363	0.8%	8 / 364	2.2%
Loss of >2 lines BsCVA	6 / 364	1.6%	6 / 363	1.7%	1 / 364	0.3%
BsCVA worse than 20/25; 20/20 or better pre-op	10 / 364	2.7%	7 / 363	1.9%	3 / 364	0.8%
Increase >2 D cylinder	1 / 364	0.3%	1 / 364	0.3%	0 / 363	0.0%

N = 364 subjects with pre-operative MRSE < –6.00 D in the combined consistent cohort.
* UCVA was not reported for 2 subjects at 3 months. MRSE was not reported for 1 subject at 6 months.
** BsCVA was not reported for 1 subject at 3 months. In determining loss of lines of BsCVA, values were missing pre-operatively or post-operatively for 1 subject at 3 months. In determining change in cylinder, values were missing for 1 subject at 6 months.

B: Moderate Myopia: Pre-Operative MRSE –6.00 D to –9.99 D

	1 month		3 months		6 months	
EFFICACY VARIABLES*	**n / N**	**%**	**n / N**	**%**	**n / N**	**%**

UCVA 20/20 or better	69 / 202	34.2%	87 / 202	43.1%	102 / 201	50.7%
UCVA 20/40 or better	156 / 202	77.2%	171 / 202	84.7%	175 / 201	87.1%
MRSE ± 0.50 D	83 / 202	41.1%	96 / 202	47.5%	106 / 201	52.7%
MRSE ± 1.00 D	124 / 202	61.4%	150 / 202	74.3%	155 / 201	77.1%
MRSE ± 2.00 D	173 / 202	85.6%	188 / 202	93.1%	184 / 201	91.5%
SAFETY VARIABLES**						
BsCVA worse than 20/40	3 / 202	1.5%	2 / 202	1.0%	3 / 201	1.5%
Loss of 2 lines BsCVA	6 / 201	3.0%	6 / 201	3.0%	5 / 200	2.5%
Loss of >2 lines BsCVA	11 / 201	5.5%	9 / 201	4.5%	6 / 200	3.0%
BsCVA worse than 20/25; 20/20 or better pre-op	11 / 201	5.5%	9 / 201	4.5%	8 / 200	4.0%
Increase >2 D cylinder	1 / 202	0.5%	0 / 202	0.0%	1 / 201	0.5%

N = 202 subjects with pre-operative MRSE –6.00 D to –9.99 D in the combined consistent cohort.
* UCVA and MRSE were not reported for 1 subject at 6 months.
** BsCVA was not reported for 1 subject at 6 months. In determining loss of lines of BsCVA, values were missing pre-operatively or post-operatively for 1 subject each at 1 month and 3 months, and 2 subjects at 6 months. In determining change in cylinder, values were missing for 1 subject at 6 months.

C: High Myopia: Pre-Operative MRSE ≥ –10.00 D

	1 month		3 months		6 months	
EFFICACY VARIABLES	n / N	%	n / N	%	n / N	%
UCVA 20/20 or better	0 / 21	0.0%	5 / 21	23.8%	8 / 21	38.1%
UCVA 20/40 or better	14 / 21	66.7%	14 / 21	66.7%	15 / 21	71.4%
MRSE ± 0.50 D	5 / 21	23.8%	5 / 21	23.8%	5 / 21	23.8%
MRSE ± 1.00 D	10 / 21	47.6%	7 / 21	33.3%	11 / 21	52.4%
MRSE ± 2.00 D	10 / 21	47.6%	14 / 21	66.7%	15 / 21	71.4%
SAFETY VARIABLES						
BsCVA worse than 20/40	2 / 21	9.5%	2 / 21	9.5%	0 / 21	0.0%
Loss of 2 lines BsCVA	3 / 21	14.3%	1 / 21	4.8%	0 / 21	0.0%
Loss of >2 lines BsCVA	3 / 21	14.3%	2 / 21	9.5%	0 / 21	0.0%
BsCVA worse than 20/25; 20/20 or better pre-op	5 / 21	23.8%	3 / 21	14.3%	1 / 21	4.8%
Increase >2 D cylinder	1 / 21	4.8%	0 / 21	0.0%	0 / 21	0.0%

N = 21 subjects with pre-operative MRSE ≥ –10.00 D in the combined consistent cohort.

TABLE 3. PRE-OPERATIVE UCVA (n=587)*

20/100 or worse		20/50 to 20/80		20/25 to 20/40		20/20 or better	
n/N	%	n/N	%	n/N	%	n/N	%
552/582	94.8%	25/582	4.3%	4/582	0.7%	1/582	0.2%

* N = 587 eyes in the consistent cohort; UCVA was reported for 582 eyes and not reported for 5 eyes at the pre-operative visit.

TABLE 4. PRE-OPERATIVE BSCVA (n=587)*

20/40 or worse		20/25 to 20/30		20/20 or better	
n/N	%	n/N	%	n/N	%
4/586	0.7%	28/586	4.8%	554/586	94.5%

* N = 586 eyes with BsCVA reported and 1 eye with BsCVA not reported at pre-operative visit=587 eyes.

TABLE 5. PRE-OPERATIVE MYOPIA/SPHERICAL EQUIVALENT (n=587)*

< –6.00 D		–6.00 D to –9.99 D		> –10.00 D	
n/N	%	n/N	%	n/N	%
364/587	62.0%	202/587	34.4%	21/587	3.6%

* N = 587 eyes with MRSE reported at pre-operative visit.

2. POSTOPERATIVE RESULTS

a. Accountability and definition of the PMA cohort

Of the 940 total treated eyes, 587 eyes were evaluated at each of the following visits: pre-operative, 1 month, 3 months, and 6 months. These 587 eyes are considered the "consistent cohort" for the following clinical study results, unless otherwise stated. Table 6 – Patient Accountability.

TABLE 6. PATIENT ACCOUNTABILITY—PRIMARY EYES

	1 month	3 months	6 months
Available for Analysis (Consistent Cohort)	556/611 (90.1%)	556/611 (90.1%)	556/611 (90.1%)
Discontinued	0	2/611 (0.3%)	0
Not yet Eligible for the Interval	0	0	0
Lost to Follow-up	0	1/611 (0.2%)	0
Missed Visit	7/611 (1.1%)	16/611 (2.6%)	39/611 (6.4%)
Visits Available but not in Consistent Cohort	48/611 (7.9%)	36/611 (5.9%)	16/611 (2.6%)

* N = total primary eyes enrolled

b. Stability of Visual Outcome

The "consistent" cohort data are divided below into the strata for comparison of MRSE changes between the two periods 3-6 months and 6-12 months (Table 7). The first

three tables below (A, B, and C) compare these changes for each of the myopia ranges: low myopia (pre-operative MRSE < –6.00 D), moderate myopia (MRSE –6.00 D to –9.99 D), and high myopia (MRSE ≥ –10.00 D). The fourth and fifth tables (D and E) compare these changes across two myopia strata: < –7.00 D and ≥ –7.00 D. The final table (F) compares these changes for the combined consistent cohort.

Confidence intervals (CI_{95}) for proportions are calculated by exact methods according to Fisher and Yates, 1963, and the confidence intervals for mean of MRSE change (Δ) are calculated as 1.96 times the $SD/n^{0.5}$ for the data.

TABLE 7. STABILITY OF MANIFEST REFRACTION AFTER PRK (BY PRE-OPERATIVE MRSE STRATA)

A: Low Myopia: Pre-Operative MRSE Stratum < –6.00 D

Period	**Proportion ±1.00** [95% CI for %]	**Mean Δ ± SD** [95%CI for mean Δ]
3-6 Months	**351 / 363 (97%)** [94.3, 98.3]	**–0.04 ± 0.47** [–0.08, +0.01]
6-12 Months	**310 / 321 (97%)** [94.0, 98.3]	**–0.08 ± 0.49** [–0.13, –0.03]

B: Moderate Myopia: Pre-Operative MRSE Stratum –6.00 D to –9.99 D

Period	**Proportion ±1.00** [95% CI for %]	**Mean Δ ± SD** [95%CI for mean Δ]
3-6 Months	**175 / 201 (87%)** [81.6, 91.4]	**–0.08 ± 0.80** [–0.19, +0.03]
6-12 Months	**158 / 180 (88%)** [82.1, 92.2]	**–0.16 ± 0.84** [–0.28, –0.04]

C: High Myopia: Pre-Operative MRSE Stratum ≥ –10.00 D

Period	**Proportion ±1.00** [95% CI for %]	**Mean Δ ± SD** [95%CI for mean Δ]
3-6 Months	**18 / 21 (86%)** [63.7, 96.6]	**–0.14 ± 0.89** [–0.52, +0.24]
6-12 Months	**15 / 20 (75%)** [50.9, 91.3]	**–0.41 ± 0.95** [–0.83, +0.01]

D: Pre-Operative MRSE < –7.00 D

Period	**Proportion ±1.00** [95% CI for %]	**Mean Δ ± SD** [95%CI for mean Δ]
3-6 Months	**422 / 440 (96%)** [93.6, 97.6]	**–0.05 ± 0.51** [–0.09, +0.00]
6-12 Months	**377 / 393 (96%)** [93.5, 97.7]	**–0.07 ± 0.52** [–0.12, –0.02]

E: Pre-Operative MRSE ≥ –7.00 D

Period	Proportion ±1.00 [95% CI for %]	Mean Δ ± SD [95%CI for mean Δ]
3-6 Months	**122 / 145 (84%)** [77.2, 89.7]	**–0.08 ± 0.87** [–0.22, +0.06]
6-12 Months	**106 / 128 (83%)** [75.1, 88.9]	**–0.27 ± 0.94** [–0.43, –0.10]

F: All Pre-Operative MRSE Stratum Combined (0.00 D to –15.00 D)

Period	Proportion ±1.00 [95% CI for %]	Mean Δ ± SD [95%CI for mean Δ]
3-6 Months	**544 / 585 (93%)** [90.6, 94.9]	**–0.05 ± 0.62** [–0.10, +0.00]
6-12 Months	**483 / 521 (93%)** [90.1, 94.8]	**–0.12 ± 0.65** [–0.17, +0.06]

For the n=587 "consistent" cohort, 2 eyes did not have recorded refraction data though they appeared for their 6 month visit. The 6-12 month data uses the eyes from the consistent cohort for which both 6 and 12 month data are available (n=521), even though the 12 month follow-up visit was not required for inclusion in the consistent cohort.

c. Efficacy Results

Efficacy data are presented for 587 eyes in the consistent cohort. Table 8 presents a summary of efficacy results stratified by pre-operative MRSE (i.e., < –7.00 D and ≥ –7.00 D strata).

This data is presented on initial treatment only (i.e., excluding retreatment procedures).

TABLE 8. SUMMARY OF KEY EFFICACY VARIABLES BY PRE-OPERATIVE MRSE STRATA

Efficacy Variables	Pre-Operative MRSE < –7.00 D*			Pre-Operative MRSE ≥ –7.00 D		
	1 month	3 months	6 months	1 month	3 months	6 months
UCVA 20/20 or better	219 / 442 (49.5%)	270 / 440 (61.4%)	289 / 441 (65.5%)	40 / 145 (27.6%)	54 / 145 (37.2%)	66 / 145 (45.5%)
UCVA 20/40 or better	405 / 442 (91.6%)	410 / 440 (93.2%)	418 / 441 (94.8%)	102 / 145 (70.3%)	113 / 145 (77.9%)	117 / 145 (80.7%)
MRSE ± 0.50 D	235 / 442 (53.2%)	299 / 442 (67.6%)	302 / 440 (68.6%)	54 / 145 (37.2%)	62 / 145 (42.8%)	62 / 145 (42.8%)
MRSE ± 1.00 D	341 / 442 (77.1%)	388 / 442 (87.8%)	397 / 440 (90.2%)	81 / 145 (55.9%)	94 / 145 (64.8%)	99 / 145 (68.3%)
MRSE ± 2.00 D	422 / 442 (95.5%)	435 / 442 (98.4%)	432 / 440 (98.2%)	115 / 145 (79.3%)	125 / 145 (86.2%)	125 / 145 (86.2%)

N = 587 subjects in the consistent cohort; 442 subjects had a pre-operative MRSE strata < –7.00 D; 145 subjects had a pre-operative strata ≥ –7.00 D.

* For subjects with pre-operative MRSE < –7.00 D, UCVA was not reported for 2 subjects at 3 months and 1 subject at 6 months; and MRSE was not reported for 2 subject at 6 months.

(1) Uncorrected Visual Acuity (UCVA)

Table 9 summarizes the distribution of uncorrected visual acuity pre- and post-operatively. At the point of stability (6 months after treatment), 91.3% (535/586) of patients tested at 20/40 or better; 85.8% (503/586) tested at 20/32 or better; 78.0% (457/586) tested at 20/25 or better; and 60.6% (355/586) of patients tested at 20/20 or better.

TABLE 9. UNCORRECTED VISUAL ACUITY (UCVA PRE- AND POST-OPERATIVELY)

Distance UCVA	Pre-operative		1 month		3 months		6 months	
	n / N	%	n / N	%	n / N	%	n / N	%
20/20 or better	1 / 582	0.2%	259 / 587	44.1%	324 / 585	55.4%	355 / 586	60.6%
20/25 or better	2 / 582	0.3%	375 / 587	63.9%	437 / 585	74.7%	457 / 586	78.0%
20/32 or better	3 / 582	0.5%	457 / 587	77.9%	493 / 585	84.3%	503 / 586	85.8%
20/40 or better	5 / 582	0.9%	507 / 587	86.4%	523 / 585	89.4%	535 / 586	91.3%
20/80 or better	30 / 582	5.2%	574 / 587	97.8%	567 / 585	96.9%	572 / 586	97.6%
20/200 or better	275 / 582	47.3%	585 / 587	99.7%	583 / 585	99.7%	586 / 586	100.0%

* N = 587 subjects in the consistent cohort. Distance UCVA was not reported for 5 subjects pre-operatively, 2 subjects at 3 months, and 1 subject at 6 months.

(2) Accuracy Of Manifest Refraction (Predictability Of Outcome)

Table 10 summarizes the accuracy of manifest refraction in terms of difference from intended outcome for the combined consistent cohort.

TABLE 10. ACCURACY OF MANIFEST REFRACTION (PREDICTABILITY OF OUTCOME) FOR THE COMBINED CONSISTENT COHORT (n=587)

Difference from Intended Outcome	SE at 1 month		SE at 3 months		SE at 6 months	
	n / N	%	n / N	%	n / N	%
± 0.50 D	289 / 587	49%	361 / 587	61%	364 / 585	62%
± 1.00 D	422 / 587	72%	482 / 587	82%	496 / 585	85%
± 2.00 D	537 / 587	91%	560 / 587	95%	557 / 585	95%
> ± 2.00 D	50 / 587	9%	27 / 587	5%	28 / 585	5%
Under-corrected < –2.00 D	7 / 587	1%	11 / 587	2%	15 / 585	3%
Under-corrected < –1.00 D	20 / 587	3%	49 / 587	8%	42 / 585	7%
Over-corrected > +1.00 D	145 / 587	25%	56 / 587	10%	47 / 585	8%
Over-corrected > +2.00 D	43 / 587	7%	16 / 587	3%	13 / 585	2%

* N = 587 subjects in the consistent cohort. Spherical Equivalent not reported for 2 subjects at 6 months.

Table 11 demonstrates the predictability of outcome stratified by MRSE of < –7.00 D and ≥ –7.00 D.

TABLE 11. ACCURACY OF MANIFEST REFRACTION (PREDICTABILITY OF OUTCOME) (STRATIFIED BY DIOPTRIC GROUP)

Difference from Intended Outcome	Pre-Operative MRSE < –7.00 D*			Pre-Operative MRSE ≥ –7.00 D		
S.E. at Visit:	1 month	3 months	6 months	1 month	3 months	6 months
± 0.50 D	235 / 442 (53.2%)	299 / 442 (67.6%)	302 / 440 (68.6%)	54 / 145 (37.2%)	62 / 145 (42.8%)	62 / 145 (42.8%)
± 1.00 D	341 / 442 (77.1%)	388 / 442 (87.8%)	397 / 440 (90.2%)	81 / 145 (55.9%)	94 / 145 (64.8%)	99 / 145 (68.3%)
± 2.00 D	422 / 442 (95.5%)	435 / 442 (98.4%)	432 / 440 (98.2%)	115 / 145 (79.3%)	125 / 145 (86.2%)	125 / 145 (86.2%)
> ± 2.00 D	20 / 442 (4.5%)	7 / 442 (1.6%)	8 / 440 (1.8%)	30 / 145 (20.7%)	20 / 145 (13.8%)	20 / 145 (13.8%)
Under-corrected < –2.00 D	2 / 442 (0.5%)	2 / 442 (0.5%)	4 / 440 (0.9%)	5 / 145 (3.4%)	9 / 145 (6.2%)	11 / 145 (7.6%)
Under-corrected < –1.00 D	9 / 442 (2.0%)	24 / 442 (5.4%)	20 / 440 (4.5%)	11 / 145 (7.6%)	25 / 145 (17.2%)	22 / 145 (15.2%)
Over-corrected > +1.00 D	92 / 442 (20.8%)	30 / 442 (6.8%)	23 / 440 (5.2%)	53 / 145 (36.6%)	26 / 145 (17.9%)	24 / 145 (16.6%)
Over-corrected > +2.00 D	18 / 442 (4.1%)	5 / 442 (1.1%)	4 / 440 (0.9%)	25 / 145 (17.2%)	11 / 145 (7.6%)	9 / 145 (6.2%)

N = 587 subjects in the consistent cohort; 442 subjects had a pre-operative MRSE strata < –7.00 D; 145 subjects had a pre-operative strata ≥ –7.00 D.

*For subjects with pre-operative MRSE < –7.00 D, SE was not reported for 2 subjects at 6 months

d. Safety Outcomes

The analysis of safety was based on the entire 587 eyes that had the 6 months exam. The key safety outcomes for this study are presented in tables 12 and 13, with all the adverse reactions reported in tables 14 and 15.

TABLE 12. KEY SAFETY AND EFFICACY VARIABLES BY PRE-OPERATIVE MRSE RANGE

A: Low Myopia: Pre-Operative MRSE < –6.00 D

	1 month		3 months		6 months	
EFFICACY VARIABLES*	n / N	%	n / N	%	n / N	%
UCVA 20/20 or better	190 / 364	52.2%	232 / 362	64.1%	245 / 364	67.3%
UCVA 20/40 or better	337 / 364	92.6%	338 / 362	93.4%	345 / 364	94.8%
MRSE ± 0.50 D	201 / 364	55.2%	260 / 364	71.4%	253 / 363	69.7%
MRSE ± 1.00 D	288 / 364	79.1%	325 / 364	89.3%	330 / 363	90.9%
MRSE ± 2.00 D	354 / 364	97.3%	358 / 364	98.4%	358 / 363	98.6%
SAFETY VARIABLES**						
BsCVA worse than 20/40	1 / 364	0.3%	1 / 363	0.3%	0 / 364	0.0%
Loss of 2 lines BsCVA	12 / 364	3.3%	3 / 363	0.8%	8 / 364	2.2%
Loss of >2 lines BsCVA	6 / 364	1.6%	6 / 363	1.7%	1 / 364	0.3%
BsCVA worse than 20/25; 20/20 or better pre-op	10 / 364	2.7%	7 / 363	1.9%	3 / 364	0.8%
Increase >2 D cylinder	1 / 364	0.3%	1 / 364	0.3%	0 / 363	0.0%

N = 364 subjects with pre-operative MRSE < –6.00 D in the combined consistent cohort.
* UCVA was not reported for 2 subjects at 3 months. MRSE was not reported for 1 subject at 6 months.
** BsCVA was not reported for 1 subject at 3 months. In determining loss of lines of BsCVA, values were missing pre-operatively or post-operatively for 1 subject at 3 months. In determining change in cylinder, values were missing for 1 subject at 6 months.

B: Moderate Myopia: Pre-Operative MRSE –6.00 D to –9.99 D

	1 month		3 months		6 months	
EFFICACY VARIABLES*	n / N	%	n / N	%	n / N	%
UCVA 20/20 or better	69 / 202	34.2%	87 / 202	43.1%	102 / 201	50.7%
UCVA 20/40 or better	156 / 202	77.2%	171 / 202	84.7%	175 / 201	87.1%
MRSE ± 0.50 D	83 / 202	41.1%	96 / 202	47.5%	106 / 201	52.7%
MRSE ± 1.00 D	124 / 202	61.4%	150 / 202	74.3%	155 / 201	77.1%
MRSE ± 2.00 D	173 / 202	85.6%	188 / 202	93.1%	184 / 201	91.5%
SAFETY VARIABLES**						
BsCVA worse than 20/40	3 / 202	1.5%	2 / 202	1.0%	3 / 201	1.5%
Loss of 2 lines BsCVA	6 / 201	3.0%	6 / 201	3.0%	5 / 200	2.5%
Loss of >2 lines BsCVA	11 / 201	5.5%	9 / 201	4.5%	6 / 200	3.0%
BsCVA worse than 20/25; 20/20 or better pre-op	11 / 201	5.5%	9 / 201	4.5%	8 / 200	4.0%
Increase >2 D cylinder	1 / 202	0.5%	0 / 202	0.0%	1 / 201	0.5%

N = 202 subjects with pre-operative MRSE –6.00 D to –9.99 D in the combined consistent cohort.
* UCVA and MRSE were not reported for 1 subject at 6 months.
** BsCVA was not reported for 1 subject at 6 months. In determining loss of lines of BsCVA, values were missing pre-operatively or post-operatively for 1 subject each at 1 month and 3 months,

and 2 subjects at 6 months. In determining change in cylinder, values were missing for 1 subject at 6 months.

C: High Myopia: Pre-Operative MRSE ≥ –10.00 D

	1 month		3 months		6 months	
EFFICACY VARIABLES	n / N	%	n / N	%	n / N	%
UCVA 20/20 or better	0 / 21	0.0%	5 / 21	23.8%	8 / 21	38.1%
UCVA 20/40 or better	14 / 21	66.7%	14 / 21	66.7%	15 / 21	71.4%
MRSE ± 0.50 D	5 / 21	23.8%	5 / 21	23.8%	5 / 21	23.8%
MRSE ± 1.00 D	10 / 21	47.6%	7 / 21	33.3%	11 / 21	52.4%
MRSE ± 2.00 D	10 / 21	47.6%	14 / 21	66.7%	15 / 21	71.4%
SAFETY VARIABLES						
BsCVA worse than 20/40	2 / 21	9.5%	2 / 21	9.5%	0 / 21	0.0%
Loss of 2 lines BsCVA	3 / 21	14.3%	1 / 21	4.8%	0 / 21	0.0%
Loss of >2 lines BsCVA	3 / 21	14.3%	2 / 21	9.5%	0 / 21	0.0%
BsCVA worse than 20/25; 20/20 or better pre-op	5 / 21	23.8%	3 / 21	14.3%	1 / 21	4.8%
Increase >2 D cylinder	1 / 21	4.8%	0 / 21	0.0%	0 / 21	0.0%

N = 21 subjects with pre-operative MRSE ≥ –10.00 D in the combined consistent cohort.

TABLE 13. SUMMARY OF KEY SAFETY VARIABLES BY PRE-OPERATIVE MRSE STRATA

	Pre-Operative MRSE < –7.00 D*			Pre-Operative MRSE ≥ –7.00 D**		
Safety Variables	1 month	3 months	6 months	1 month	3 months	6 months
BsCVA worse than 20/40	2 / 442 (0.5%)	1 / 441 (0.2%)	1 / 441 (0.2%)	4 / 145 (2.8%)	4 / 145 (2.8%)	2 / 145 (1.4%)
Loss of 2 lines BsCVA	13 / 442 (2.9%)	5 / 441 (1.1%)	9 / 441 (2.0%)	8 / 144 (5.6%)	5 / 144 (3.5%)	4 / 144 (2.8%)
Loss of >2 lines BsCVA	8 / 442 (1.8%)	9 / 441 (2.0%)	2 / 441 (0.5%)	12 / 144 (8.3%)	8 / 144 (5.6%)	5 / 144 (3.5%)
BsCVA worse than 20/25; 20/20 or better pre-op	12 / 442 (2.7%)	9 / 441 (2.0%)	5 / 441 (1.1%)	14 / 144 (9.7%)	10 / 144 (6.9%)	7 / 144 (4.9%)
Increase >2 D Cylinder	1 / 442 (0.2%)	1 / 442 (0.2%)	0 / 440 (0.0%)	2 / 145 (1.4%)	0 / 145 (0.0%)	1 / 145 (0.7%)

N = 587 subjects in the consistent cohort; 442 subjects had a pre-operative MRSE strata < –7.00 D; 145 subjects had a pre-operative strata ≥ –7.00 D.

* For subjects with pre-operative MRSE < –7.00 D, BsCVA was not reported for 1 subject at 3 months and 1 subject at 6 months. In determining loss of lines of BsCVA, values were missing pre-operatively or post-operatively for 1 subject each at 3 months and 6 months. In determining change in cylinder, values were missing pre-operatively or post-operatively for 2 subjects at 6 months.

** For subjects with pre-operative MRSE ≥ –7.00 D, BsCVA was reported for all subjects. In determining loss of lines of BsCVA, values were missing pre-operatively or post-operatively for 1 subject each at 1 month, 3 months and 6 months.

G. ADVERSE EVENTS

This analysis of safety includes data collected on 587 eyes in the consistent cohort. Results are summarized in Table 14.

Tables 15 and 16 below summarize the incidences of complications reported in this study.

Potential adverse effects of ophthalmologic laser surgery can occur at any time during the recovery period. During the Nidek clinical study, a small number of adverse events were observed through 6 months as noted in Table 14.

Some potential adverse effects are reported every time they occur during the recovery period; others resolve themselves during the recovery period and are reported only if the condition is present 6 months post-operatively.

Adverse effects that are reported only if present 6 months or more post-operatively can include loss of more than 2 lines in best spectacle corrected visual acuity (1.2% [7 of 585 eyes]), moderate or marked haze (0.5% [3 of 587 eyes]), induced astigmatism of greater than 2.00 D (0.2% [1 of 585 eyes]), over-correction > +2.00 D (2.0% [13 of 585 eyes]), under-correction < –2.00 D (3.0% [15 of 585 eyes]).

TABLE 14. ADVERSE EVENTS

Adverse Event	1 month	3 months	6 months
Corneal or stromal infiltrate or ulcer (2+ or above)	3/940 (0.3%)	0/940	0/940
Persistent central corneal epithelial defect at 1 month or later (2+ or above)	4/940 (0.4%)	0/940	0/940
Uncontrolled IOP with increase of >10 mm Hg above baseline	1/940 (0.1%)	5/940 (0.5%)	3/940 (0.3%)
IOP reading above 25 mm Hg	1/940 (0.1%)	5/940 (0.5%)	4/940 (0.4%)
Late onset of haze beyond 6 months with loss of 2 lines (10 letters) or more BsCVA	----	----	0/940
Decrease in BsCVA of >10 letters not due to irregular astigmatism as shown by hard contact lens refraction, at 6 months or later	----	----	11/940 (1.2%)
Retinal detachment	0/940	0/940	0/940
Retinal vascular accidents	0/940	0/940	0/940

TABLE 15. COMPLICATIONS

Complications	Immediate Post-Op	1 month	3 months	6 months
Corneal edema between 1 week and 1 month after the procedure	1/556 (0.2%)	0	0	0
Recurrent corneal erosion at 1 month or later	0	0	0	0
Foreign body sensation (including itching and scratchiness)	431/556 * (77.5%)	0	0	0
Pain (including discomfort, pressure, etc.)	634/556* (114%)	0	1/556 (0.2%)	0

Ghost or double images in the operative eye	7/556* (1.3%)	0	0	0

*Incidence in immediate post-operative period is inflated and may exceed 100% due to multiple reports from the same individual during the period.

TABLE 16. OTHER LASER RELATED COMPLICATIONS

Laser-Related Complications	Immediate Post-Op	1 month	3 months	6 months
Blurred / cloudy vision	50/556 (9%)	1/556 (0.2%)	0	0
Tearing / watery eyes	61/556 (11%)	0	0	0
Photophobia	51/556 (9%)	0	0	0
Dry eye (including irritation and redness)	52/556 (9%)	0	0	0

(1) VISUAL ACUITY

In terms of safety, BsCVA safety targets for the overall proportion of cases (n=587) with significant loss of >2 lines of BsCVA and proportion 20/40 or better were met and exceeded. Reduction in BsCVA of >2 lines was observed in 1.2% (7/585) of subject eyes at 6 months. In addition, 0.5% (3/586) of subject eyes were found to have BsCVA worse than 20/40 at 6 months post-treatment.

Table 17 illustrates the change in BsCVA over time. At six months 3.4% (20/585) of eyes had lost 2 or more lines of BsCVA.

TABLE 17. CHANGE IN BEST SPECTACLE CORRECTED VISUAL ACUITY IN THE COMBINED CONSISTENT COHORT (n=587)*

BsCVA	1 month		3 months		6 months	
	n / N	%	n / N	%	n / N	%
Decrease >2 lines	20 / 586	3.4%	17 / 585	2.9%	7 / 585	1.2%
Decrease 2 lines	21 / 586	3.6%	10 / 585	1.7%	13 / 585	2.2%
Decrease 1 line	126 / 586	21.5%	114 / 585	19.5%	72 / 585	12.3%
No change	326 / 586	55.6%	297 / 585	50.8%	305 / 585	52.1%
Increase 1 line	87 / 586	14.8%	135 / 585	23.1%	168 / 585	28.7%
Increase 2 lines	4 / 586	0.7%	8 / 585	1.4%	11 / 585	1.9%
Increase >2 lines	2 / 586	0.3%	4 / 585	0.7%	9 / 585	1.5%

* N = 587 subjects in the consistent cohort. BsCVA was not reported for 1 subject at 1 month, 2 subjects at 3 months, and 2 subjects at 6 months.

(2) OVER-CORRECTION AND UNDER-CORRECTION

Over-correction of more than +1.00 D at 6 months occurred in 8% (47/585) of eyes (Table 18). Under-correction of more than –1.00 D at 6 months occurred in 7% (42/585) of eyes. Therefore, the distribution of over- and under-correction at 6 months was closely balanced around 0.0 D. To assess any clinical or environmental variables that may be related to a risk of over-correction or under-correction, a series of chi-square, t-test, and ANOVA analyses were performed.

The first analysis evaluated the effect that pre-operative dioptric range (i.e., attempted correction range) may have on the chance of over- or under-correction. Using three pre-operative MRSE ranges, as shown in Table 18, there appears to be a significant relationship between pre-operative dioptric (MRSE) group and the occurrence of over- and under-correction. Chi-square analysis supported this relationship ($p < 0.001$). An ANOVA to assess any statistical difference in the dioptric group means of the "differences from intended outcome" showed no differences between the groups ($p = 0.098$). As expected from the ANOVA, t-tests between each pair of dioptric groups revealed no significant differences (p range = 0.276 to 0.522).

In conclusion, a chi-square analysis of the clinical data supports a statistically significant increase in the chance of both over- and under-correction as the pre-operative dioptric (MRSE) range increases. Since the over-correction and under-correction were balanced for each dioptric group, no statistical differences between the average "difference from intended outcome" in each group were found. These results point toward higher variability in refractive outcomes as attempted correction increases. Since patients tend to tolerate slight myopia (e.g., –0.50 D to –1.00 D) better than slight hyperopia, a slightly myopic target outcome should be considered.

TABLE 18. OVER-CORRECTION AND UNDER-CORRECTION

Difference from Intended Outcome by SE at 6 months	Pre-operative MRSE Range < –6.00 D	Pre-operative MRSE Range –6.00 D to –9.99 D	Pre-operative MRSE Range ≥ –10.00 D	All Subjects Combined*
Under-corrected < –2.00 D	3 / 363 (0.8%)	9 / 201 (4.5%)	3 / 21 (14.3%)	15 / 585 (3%)
Under-corrected < –1.00 D	14 / 363 (3.9%)	24 / 201 (11.9%)	4 / 21 (19.0%)	42 / 585 (7%)
Over-corrected > +1.00 D	19 / 363 (5.2%)	22 / 201 (10.9%)	6 / 21 (28.6%)	47 / 585 (8%)
Over-corrected > +2.00 D	2 / 363 (0.6%)	8 / 201 (4.0%)	3 / 21 (14.3%)	13 / 585 (2%)

* N = 587 subjects in the consistent cohort. For subjects with pre-operative MRSE < –6.00 D, SE was not report for 1 subject at 6 months. For subjects with pre-operative MRSE –6.00 D to –9.99 D, SE was not reported for 1 subject at 6 months.

The next analysis evaluated the effect of age on the risk of over- and under-correction. A chi-square analysis revealed that there was a statistically significant difference between age groups (i.e., 20-29, 30-39, 40-49, 50-59, ≥ 60) with regard to over-correction ($p < 0.001$). An ANOVA to assess any difference in age group means of the "difference from intended outcome" also revealed a statistically significant difference ($p < 0.001$).

T-tests between age group pairs showed no significant differences between some age group pairs: 20-29 vs. 30-39 ($p = 0.807$), 20-29 vs. 40-49 ($p = 0.323$), and 50-59 vs. ≥ 60 ($p = 0.061$). However, t-tests between the following age group pairs yielded statistically significant outcomes: 20-29 vs. 50-59 ($p < 0.001$), 20-29 vs. ≥ 60 ($p < 0.001$), 30-39 vs. 50-59 ($p < 0.001$), and 40-49

vs. 50-59 ($p < 0.001$). The means and standard deviations of the "difference from intended outcome" for the 20-29, 50-59, and ≥ 60 age groups were –0.18 ± 0.78 D, +0.42 ± 0.88 D, and +1.00 ± 1.11 D, respectively.

The chi-square results and the means support over-correction, as opposed to under-correction, increasing with age. These results support choosing a slightly myopic target outcome (e.g., –0.50 D to –1.00 D) for patients who are 50 years of age or older.

In conclusion, statistical analyses of the effect of age on the chance of over-correction or under-correction indicate that a statistically significant increase occurs in the proportion of over-correction with patients age 50 years of age and above.

The final analysis evaluated the effect of environmental conditions in the operative suite (i.e., temperature, humidity) on over- and under-correction. Temperature groupings (e.g., subjects treated with operating room temperature of 67°, 71°, 74°, or 81°) showed no relationship to over- or under-correction ($p = 0.680$) in chi-square and ANOVA analyses.

Humidity groupings (e.g., subjects treated with operating room humidity of 10%, 30%, 50%, or 70%) showed slightly significant differences between groups in both chi-square ($p = 0.043$) and ANOVA ($p = 0.027$) analyses for over- and under-correction rates. T-tests of humidity group pairs revealed a statistical difference in the means between 30% and 50% ($p = 0.026$) and 50% and 70% ($p = 0.040$), but no significant differences between the other pairs. The means and standard deviations of the "difference from intended outcome" for the 30%, 50%, and 70% groups were +0.07 ± 1.02 D, –0.13 ± 0.78 D, and +0.13 ± 1.01 D, respectively, with the means balanced around 0.00 D. Therefore, although a slight statistical difference was observed at 50% humidity, it does not appear to result in a clinically relevant change in the risk of over- or under-correction.

(3) INCREASE IN REFRACTIVE CYLINDER

Manifest refraction measurements, including refractive cylinder, were gathered at the 1, 3, and 6 month post-operative visits. At the point of stability at 6 months post-operatively, an increase in refractive cylinder was observed in 0.2% (1/585) of eyes.

(4) EFFECT OF GLARE CONDITIONS ON VISUAL ACUITY

Glare effects were assessed in this study using the Brightness Acuity Testing (BAT) instrument at the mid-level setting in conjunction with ETDRS vision charts under two different glare conditions (standard and dilated pupil). The average change in BsCVA under glare conditions for the total substudy group (n=100) showed an approximately 1 ETDRS letter average improvement under both standard and dilated conditions. These assessments of the effect of glare conditions on visual acuity (BsCVA) demonstrate that there are no apparent systematic deleterious changes in BsCVA under standard glare conditions.

(5) CHANGE IN CONTRAST SENSITIVITY

A substudy was conducted on 100 subjects to analyze the correlation of contrast sensitivity pre-operatively and 6 months post-operatively and loss in visual acuity (BsCVA), and difficulty with night vision. Contrast sensitivity was assessed using the Vector Vision automated contrast sensitivity test systems (Model #CSV-1000) before and after PRK treatment.

When examining the change in contrast sensitivity from the pre-operative measurement to 6 months post-operatively for the substudy population, a slight reduction in contrast sensitivity was observed. For the same interval, the change in BsCVA showed a slight improvement in visual acuity. Comparing the change in contrast sensitivity to the change in BsCVA, these results appear to be slightly inconsistent, but the results do not appear to be clinically significant for this subgroup of patients.

The correlation between contrast sensitivity and perceived change in night vision was analyzed by reviewing subject responses to pre- and post-operative questionnaires administered to the study participants. The average change for the entire substudy group was a slight improvement in night vision. When comparing the change in contrast sensitivity to the questionnaire responses on night vision, these results were also slightly inconsistent with the slight reduction in contrast sensitivity observed, but these results did not appear to be clinically significant.

In conclusion, the analyses of contrast sensitivity revealed that there were no apparent systematic deleterious changes in contrast sensitivity in the substudy population 6 months after PRK treatment. No correlation was found between a change in contrast sensitivity at 6 months post-treatment (compared to baseline) and any loss in visual acuity (BsCVA) and/or difficulty with night vision.

(6) INTRAOCULAR PRESSURE (IOP)

Topical steroids were not required as part of post-operative regime during this study. However, about 1/3 of eyes were treated with topical steroids. A majority of eyes with higher myopic corrections were placed on steroids, either prophylactically or in response to the appearance of subepithelial haze.

Therefore, IOP was monitored pre-operatively and at each post-operative visit. The number of subjects who experienced a change in IOP of >10 mm Hg at any follow-up visit (compared to the pre-operative IOP value) and any subjects who had a post-laser surgery value of >25 mm Hg were reported.

At 1 month after treatment, 0.2% (1/535) of eyes had a change in IOP of >10 mm Hg, and at the 3 month visit, 0.7% (4/558) of eyes had this change in IOP. At the point of stability at 6 months post-operatively, 0.5% (3/561) of eyes experienced a change in IOP of >10 mm Hg.

In terms of absolute IOP level, at the 1 month post-operative visit, no IOP values greater than 25 mm Hg were reported. At the 3 month visit, 0.9% (5/558) of eyes had an IOP value >25 mm Hg. At the point of stability at 6 months post-

operatively, 0.7% (4/561) of eyes experience an IOP value of >25 mm Hg. For all cases of elevated pressures, appropriate tension-lowering medications were prescribed and pressures were subsequently reduced at later follow-up periods.

(7) CORNEAL HAZE

Subepithelial haze data was assessed at each follow-up visit using a standardized graded severity scale. The scale was graded from 0 (clear) to 4+ (marked). Table 19 summarizes the incidence of corneal haze. At 6 months, 12 of 587 eyes (2.0%) reported mild haze (grade 2+), and 3 of 587 eyes (0.5%) eyes reported moderate haze (grade 3+). No cases of marked haze (grade 4+) were reported for any post-operative visit in the study group through 6 months.

TABLE 19. CORNEAL HAZE

Haze	Pre-operative	1 month	3 months	6 months
Clear (0)	586 / 587 (99.8%)	57 / 587 (9.7%)	64 / 587 (10.9%)	197 / 587 (33.6%)
Minimal (½)	1 / 587 (0.2%)	421 / 587 (71.7%)	427 / 587 (72.7%)	328 / 587 (55.9%)
Trace (1)	0 / 587 (0%)	90 / 587 (15.3%)	80 / 587 (13.6%)	47 / 587 (8.0%)
Mild (2)	0 / 587 (0%)	17 / 587 (2.9%)	8 / 587 (1.4%)	12 / 587 (2.0%)
Moderate (3)	0 / 587 (0%)	2 / 587 (0.3%)	8 / 587 (1.4%)	3 / 587 (0.5%)
Marked (4)	0 / 587 (0%)	0 / 587 (0%)	0 / 587 (0%)	0 / 587 (0%)

N= 587 subjects in the consistent cohort.

(8) LENS ABNORMALITIES

Significant cataracts did not develop during this short study, even though the median age was above 40 years. No cases of lens dislocations or other abnormalities were reported.

H. RETREATMENT

Retreatment or "enhancement" procedures with the EC-5000 Excimer Laser System were performed on 28 eyes under the protocol through October 15, 1997. This reflects a retreatment or enhancement rate of 3.0% (28/940) for the overall study. This enhancement rate may be artificially low due to earlier retreatment restrictions under the investigational protocol. Primary (first-treated) eyes were retreated in 24 cases and secondary (fellow) eyes were retreated in 4 cases. No cases of more than one retreatment to an eye have been recorded.

At the last examination prior to retreatment or enhancement, all 28 eyes were myopic, having ≥ 1.00 D S.E. of residual myopia. Additionally, all 28 retreated eyes had ≤ Trace (grade 1) haze prior to retreatment. For 27 of 28 eyes, the reason for retreatment was to enhance the refraction due to under-correction or regression of myopia. Two of these were given cylinder treatment only for residual myopic cylinder as allowed under the protocol. One eye was retreated for the combination of residual myopia and an apparent central island formation.

Uncorrected visual acuities for the 28 eyes prior to treatment ranged from 20/32 (45 letters read) to 20/200 (5 letters read), averaging 20/80 (25 letters read). Following retreatment, the UCVA average improved to 20/32 (45 letters read). Average BsCVA levels remained unchanged at 20/20. No adverse events associated with these retreated eyes have been reported.

I. RE-EPITHELIALIZATION

Re-epithelialization was completed for the vast majority of eyes by Day 4. Delay in re-epithelialization almost always could be attributed to interference from an underlying systemic condition or concomitant medication. Although not studied during this investigation, published reports for patients using loratadine (Claritan™) or hormone replacement therapy (HRT) indicate the practitioner should proceed with caution. These medications are associated with a prolonged time to re-epithelialization after corneal laser surgery. Patients on loratadine or HRT should consider choosing different vision correction methods or temporarily discontinuing these medications in preparation for the procedure and pending re-epithelialization.

J. TOPOGRAPHICAL ANALYSIS

The objective of analysis of corneal surface topographic changes between the pre-operative and post-PRK corneal surface in the same eye was to evaluate any non-uniform topographic changes due to PRK treatment in a substudy population of 100 subjects and to assess the degree that these changes correlate with any significant loss in visual acuity (> 2 lines lost in BsCVA). Pre-operative and 6 month follow-up corneal topographies were combined to create a difference map to evaluate the frequencies of homogeneous and inhomogeneous topographic findings and to evaluate apparent correlations with visual outcomes.

Differences were categorized using topographic patterns. At the 6-month follow-up visit, the following inhomogeneous pattern proportions were observed in the difference maps: Keyhole/Semicircular (5%), Central Island (4%), Focal Topographic Variants (4%), Decentration (3%), Irregularly Irregular (1%), and Smooth Toric Bowtie vs. Axis Pattern (1%). The remaining patterns were homogenous in appearance. All of the individual inhomogeneous categories had very small sample size (n ≤ 5) which prevent meaningful conclusions about statistical significance.

The data from the corneal topography substudy with 6-month follow-up on 100 first-treated eyes indicated that the large majority of eyes (81%) have a homogeneous type of corneal topographic difference map after treatment with the Nidek EC-5000 excimer laser.

K. ENDOTHELIAL CELLS

Specular photographs of the central corneal endothelium were taken in a substudy group of first-treated eyes of patients at two selected centers using a Keeler-Konan specular contact microscope at the pre-operative and 6 month post-operative visits. From the same group of patients, additional photographs were made of the untreated contralateral eyes to provide a comparison dataset. All photographs were sent to a central reading site, and were coded and masked prior to evaluation.

Analysis of endothelial cell photographs included mean cell area, coefficient of variation (CV) for cell area, cell density, and the frequency of hexagons. The measurement objective was to obtain cell corner data for a contiguous group of cells representative of the field of view in each photograph. This information was analyzed by validated software.

For the treated eyes in the matched cohort (82 subjects), the change from the pretreatment values to 6 months was not statistically significant (paired Student's *t*-test) for cell density, mean cell area, or frequency of hexagons. The decrease in the coefficient of variation was statistically significant ($p < 0.05$). Results observed for the untreated contralateral eyes indicate very little change from the pre-operative to the 6 months follow-up. None of the differences between the pre-operative and 6 months visits are statistically significant for these untreated contralateral eyes.

These results indicate that corneal endothelial cells are not significantly affected by PRK treatment with the Nidek EC-5000 excimer laser.

L. PRINCIPAL EFFECTIVENESS AND SAFETY RESULTS

A total of 611 subjects had a primary eye or both eyes treated (N=940 total eyes consisting of 611 primary eyes and 329 secondary eyes). Of the 940 total treated eyes, 587 eyes were evaluated at teach of the following visits: pre-operative, 1 month, 3 months and 6 months. These 587 eyes are considered the "consistent cohort." Table 20 summarizes key safety and efficacy variables for the consistent cohort. Note: The sub-sample of subjects treated for myopia exceeding –10.00 D (n=21) may be too low to detect other complications and/or adverse events in this refractive error range.

TABLE 20. KEY SAFETY AND EFFICACY VARIABLES

	1 month		3 months		6 months	
EFFICACY VARIABLES*	n / N	%	n / N	%	n / N	%
UCVA 20/20 or better	259 / 587	44.1%	324 / 585	55.4%	355 / 586	60.6%
UCVA 20/40 or better	507 / 587	86.4%	523 / 585	89.4%	535 / 586	91.3%
MRSE ± 0.50 D	289 / 587	49.2%	361 / 587	61.5%	364 / 585	62.2%
MRSE ± 1.00 D	422 / 587	71.9%	482 / 587	82.1%	496 / 585	84.8%
MRSE ± 2.00 D	537 / 587	91.5%	560 / 587	95.4%	557 / 585	95.2%
SAFETY VARIABLES**						
BsCVA worse than 20/40	6 / 587	1.0%	5 / 586	0.9%	3 / 586	0.5%
Loss of 2 lines BsCVA	21 / 586	3.6%	10 / 585	1.7%	13 / 585	2.2%
Loss of >2 lines BsCVA	20 / 586	3.4%	17 / 585	2.9%	7 / 585	1.2%
BsCVA worse than 20/25; 20/20 or better pre-op	26 / 586	4.4%	19 / 585	3.2%	12 / 585	2.1%
Increase >2 D cylinder	3 / 587	0.5%	1 / 587	0.2%	1 / 585	0.2%

N = 587 subjects in the combined consistent cohort.

* UCVA was not reported for 2 subjects at 3 months and 1 subject at 6 months. MRSE was not reported for 2 subjects at 6 months.

** BsCVA was not reported for 1 subject at 3 months and 1 subject at 6 months. In determining loss of lines of BsCVA, values were missing pre-operatively or post-operatively for 1 subject at 1 month, and 2 subjects each at 3 months and 6 months. In determining change in cylinder, values were missing pre-operatively or post-operatively for 1 subject at 6 months.

XI. CONCLUSIONS DRAWN FROM THE CLINICAL STUDY

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

XII. PANEL RECOMMENDATION

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

XIII. CDRH DECISION

CDRH issued an approval order on December 17, 1998. The applicant's manufacturing facility was inspected on April 17, 1998 and was found to be in compliance with the device Quality System Regulation.

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.