SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Ophthalmic Medical Laser System (193 nanometer wavelength)
Device Trade Name:	Kremer Excimer Laser Serial No. KEA940202
Applicant's Name and Address:	Photomed, Inc. Frederic B. Kremer, M.D. 200 Mall Boulevard King of Prussia, PA 19406 (610) 337-1580
Date of Panel Recommendation:	February 13, 1998
Premarket Approval (PMA) Application Number:	P970005
Date of Notification of Approval to Applicant:	July 30, 1998

II. INDICATIONS FOR USE

The Kremer Excimer Laser Serial No. KEA940202, using a 6.0 mm ablation zone, is indicated for myopic and astigmatic laser assisted in-situ keratomilieusis (LASIK) in patients:

- with myopia ranging between -1.0 and -15.0 diopters (D) with or without astigmatism ranging from 0.0 D to 5.00 D;
- who are 18 years of age or older; and,
- with stable refraction over the 1-year period prior to surgery. Note: Patients between 18 and 20 years old should not demonstrate a shift in refraction greater than 0.5 D. Patients 21 years and older should not demonstrate a shift greater than 1.0 D.

III. CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

CONTRAINDICATIONS - Patients with the following conditions should not be considered for this procedure:

- Active ocular / systemic infection
- Fuchs' corneal dystrophy
- Keratoconus

- Central corneal scars affecting visual acuity
- Cornea too thin to achieve the desired correction
- Pregnant or nursing women

WARNINGS - Patients presenting with the following condition(s) should be considered for this treatment only after careful assessment of the potential risk and benefit to the specific patient:

- Previous herpetic keratitis[1]
- Collagen vascular disorders[2]
- Ablation of corneal stroma to less than 200µm from the endothelium
- Ablation depths within less than 250 microns from the endothelium may result in the loss of two or more lines of BSCVA.

PRECAUTIONS - The safety and effectiveness of this procedure has not been established in patients presenting with the following conditions:

- Severe dry eye syndrome
- Glaucoma
- Uveitis
- Blepharitis
- Psoriasis
- Immunosuppression
- Systemic or topical use of steroids
- History of keloid formation

- Due to the small sample of eyes treated in the investigational device exemptions (IDE) study with myopia of -13.0 D or more (1%, 6/665) or astigmatism of -4.0 D or more (1.8%, 13/720), the reported safety and effectiveness for this refractive range is less reliable than for eyes with less severe myopia or astigmatism.
- Patients with high myopia greater than -7.0 D whose BSCVA was 20/20 preoperatively have a 9% chance of being worse than 20/25 postoperatively at the 6 month postoperative interval.
- The effects of the LASIK procedure on visual performance under poor lighting conditions have not been determined. It is possible, following LASIK treatment, that patients may find it difficult to see in conditions such as very dim light, rain, snow, fog or glare from bright lights at night.
- Patients may still need glasses or contact lenses.
- There is no safety and effectiveness data for surface ablation performed with this laser.

---

1. Patient needs to understand risks associated with corneal trauma and possible re-activation of herpetic keratitis.
2. Patient needs to understand the risks associated with collagen vascular disorders and their associated corneal involvement. The patient may be included if sufficient understanding of possible complications is demonstrated. Consideration should be given to treatment on a monocular basis.

IV. DEVICE DESCRIPTION

A. The KEA940202 consists of the following system components:

Excimer Laser: An argon-fluorine excimer laser provides the following characteristics:

Laser wavelength:	193 nm
Laser pulse duration:	8-30 ns (FWHM)
Repetition rate:	10 Hz
Fluence (at the eye):	134 mJ/cm2
Ablation zone:	6.0 mm diameter
Composition of gases:	
ArF Premix	Argon (97.73%)
	Fluorine (2.17%)
Buffer:	Helium (99.999% purity)
For internal purging:	Helium

Laser Beam Delivery System:

Before reaching the eye, the raw rectangular beam of the excimer laser is directed sequentially through homogenizing optics that condense the long beam axis and modify the short axis to reduce effects of the Gaussian distribution.

The laser beam is continually monitored by an automatic fail-safe energy detector which evaluates each pulse to determine if it falls within predetermined energy limits.

Gas Management System:

The laser automatically mixes the correct proportion of halogen and buffer gases in the laser cavity to produce the 193 nm laser wavelength.

Patient Management System:

Patient management components include an operating microscope that allows the physician to view the eye; a fiber optic light source that illuminates the patient's eye; a fixation light source upon which the patient focuses during the procedure; a patient operating table with an adjustable V-shaped headrest to stabilize the patient's head; and a video camera and monitor for recording and viewing the procedure.

Computer Control System:

The KEA 940202 Laser has two PC-based computer systems with monitors and keyboards. The first system is the calibration computer which is used for daily calibration of the laser and to calculate an adjusted refractive correction. The second system is the laser computer. Its function is to accept the adjusted refractive correction and convert it into corresponding ablation profile

tables, and thereafter manage treatment by controlling the number of laser pulses and aperture size and shape for each ablation layer.

Note: Details regarding the operation of Kremer Excimer Laser Serial No. KEA940202 can be found in the operator's manual.

B. Microkeratome:

The complete system consists of an instrument tray which includes the shaper head, an adjustable height suction ring, handle, wrenches and test shaft. The instrument motor, handpiece, disposable blades, power supply with footswitches and power cords, applanation lens set, tonometer, optical zone marker, spatula, stop attachment, and digital thickness gauge are provided as separate components which complete the system

V. ALTERNATIVE PRACTICES

Conventional methods of correcting nearsightedness are: spectacles, contact lenses, or refractive surgery involving radial keratotomy (RK), or laser photorefractive keratotomy (PRK).

VI. MARKETING HISTORY

The Kremer Excimer Laser Serial No. KEA940202 is a single laser unit.

VII. ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse reactions associated with LASIK include: loss of best spectacle-corrected visual acuity, overcorrection, undercorrection, increase in refractive cylinder, abnormal glare, halos, double vision, difficulty with night vision, corneal haze, epithelial ingrowth, corneal infection/ulcer/infiltrate, corneal decompensation/edema, lens abnormality, anxiety, and possible need for secondary surgical intervention.

VIII. SUMMARY OF PRECLINICAL STUDIES

Prior to clinical investigation, photoablations were performed in plastic materials, animal eyes, and human cadaver eyes with the Kremer Excimer Laser. The shape and surface of the ablations were analyzed under the electron microscope.

The laser was bench tested to assess the stability and reliability of the laser emissions and beam quality. Testing in plastic (PMMA) was performed to established reliability and predictability of the shape and depth of the ablation for given beam settings and pulse sequences.

Test results showed that the laser could make smooth and reproducible ablations, primarily perpendicular to the surface, which were of controlled depth and geometry. Photoablation of the plastics showed that refractive correction were reproducible and predictable.

IX. SUMMARY OF CLINICAL STUDIES

A. Study Objectives

The objectives of this clinical investigation of the LASER-K^{sm} LASIK procedure using the Kremer Excimer Laser were to:

- Reduce myopia and myopic astigmatism predictably and safely in eyes with myopia ranging between -1.0 D and -15.0 D, with or without astigmatism up to 5.0 D;

- Improve uncorrected visual acuity to reduce patients' dependence on spectacles and/or contact lenses.

B. Study Design

This was a prospective, non-randomized, unmasked, single-center clinical study performed by two surgeons, with the participants acting as their own controls.

C. Inclusion/Exclusion Criteria

Participants were eligible for the study if they met the following inclusion criteria:

- ≥18 years old;
- primary myopia between -1.0 D and -15.0 D with or without astigmatism up to 5.0 D;
- stable refraction defined as <1.0 D shift over the one year prior to surgery;
- demonstrated desire for independence from spectacles or contact lenses;
- no soft contact lens wear for 2 weeks prior to surgery or no hard contact lens wear for 3 weeks prior to surgery;
- willingness to comply with all postoperative follow-up visits.

All patients were required to sign an informed consent form, were instructed about the risks associated with LASIK, and were clearly informed of all alternatives for the correction of their refractive error.

Patients who did not meet all of the above inclusion criteria were excluded from the study. Patients with any of the following conditions were also excluded: active ocular or systemic infection; severe dry eye syndrome; Fuchs' dystrophy; anterior basement membrane dystrophy; keratoconus associated with thinning; and chronic topical steroid use. Patients who had central corneal scars that affected visual acuity or whose corneas were too thin to permit the desired correction were also excluded.

D. Study Plan, Patient Assessments, and Efficacy Criteria

From May 1, 1993 through June 30, 1996, the study was conducted under Institutional Review Board approval. This study population is known as Cohort 1. Beginning July 1, 1996, the study was conducted under a slightly modified, FDA-approved protocol (IDE G960101). This study

group is known as the Cohort 2 population. A second investigator joined the study during this IDE phase.

In essence, the protocols for both cohorts were the same, with one notable exception. Initially, the intended correction was typically calculated by subtracting 20% from the ideal correction. With time and experience, this 'safety factor' was progressively reduced. As a result, some patients in the Cohort 1 population were intentionally undercorrected by some degree. All patients in the Cohort 2 population, however, were treated using an intended correction that was equivalent to the ideal correction, with no safety factor included. The only other protocol change was a slight verbiage modification of the informed consent form. It should also be noted that, with time and experience, the primary operating surgeon improved the centering strategy and the operating technique.

Patients were evaluated preoperatively; 1 day postoperatively; 1 week postoperatively; 1, 3, and 6 months postoperatively, and 1 year postoperatively. Whenever an enhancement was performed, the follow-up schedule started over from the date of the retreatment.

Preoperatively, complete ocular and medical histories were taken, and visual acuity measurements, brightness acuity testing, cycloplegic refraction, and pupil examinations were performed. Refractive and ocular stability was documented.

Objective postoperative measurements performed at the 1-week visit and each visit thereafter included keratometry, uncorrected and best spectacle-corrected visual acuities, manifest refraction, and a thorough slit lamp examination for assessment of corneal clarity, anterior chamber, and lens status. All patient complaints, complications, and adverse reactions were recorded. Additional evaluations were performed at the 6-month and 1-year visits as outlined in the protocol. Cycloplegic refractions were performed at the 1-year visit.

The effectiveness of the procedure was based on uncorrected visual acuity (UCVA) improvement, reduction in the spherical equivalent (SE) [including independent analyses of both the spherical and cylindrical components], and accuracy of the achieved SE (as compared with the intended SE). The predictability of the procedure and device was evaluated by assessing the proportion of eyes experiencing a deviation from intended correction within ± 0.5 D, ± 1 D, and ± 2 D. Stability was defined as a change of less than or equal to 1 D for two consecutive visits three months apart. Stability evaluation also included analysis of the mean differences between the two visits.

Safety was evaluated in terms of loss of >2 lines of best spectacle-corrected visual acuity (BSCVA), BSCVA worse than 20/40, increase in cylinder of >2 D (eyes treated for myopia only), BSCVA worse than 20/25 in eyes that were 20/20 or better preoperatively, and all patient symptoms/complaints and adverse events.

All safety and efficacy analyses were performed on the population following a single treatment, and after retreatment (final result). Retreatment results were also evaluated separately.

Statistical analyses were performed at the 0.05 significance level at the point of stability (defined as the 6-month interval) for the key safety and efficacy variables. The following between-group comparisons were conducted for all of these key variables: Cohort 1 versus Cohort 2; myopes versus astigmatic myopes; eyes with <7 D versus eyes with ≥7 D preoperative SE; and eyes receiving a single treatment versus those that received at least one enhancement.

E. Study Period, Investigational Site, and Demographic Data/Baseline Characteristics

Study period

A total of 2,482 eyes were treated under both protocols, beginning on May 1, 1993. The database was closed for purposes of this analysis on November 20, 1997.

Investigational site

All procedures were performed at the Kremer Laser Eye Center. Patients were evaluated postoperatively at the Kremer Laser Eye Center and at co-managing sites, provided the referring caregiver was qualified as a co-managing investigator.

Demographics

Demographics of both cohorts were quite similar. Slightly fewer females than males were treated, and mean age was in the upper 30s for both cohorts. Slightly more eyes for myopic astigmatism were treated than for myopia only. Table 1 summarizes these key demographic characteristics.

Table 1. Summary of Key Demographic Characteristics

	Male	Female	Mean Age (years)	Myopia (eyes)	Myopic Astigmatic (eyes)
Cohort 1 Population	329/616 (53.4%)	285/616 (46.3%)	38.1	487/1140 (42.7%)	653/1140 (57.3%)
Cohort 2 Population	359/704 (51.0%)	342/704 (48.6%)	36.3	630/1342 (46.9%)	712/1342 (53.1%)

Baseline characteristics

The majority of eyes treated in both cohorts for spherical myopia had moderate myopia from -2 D to -7 D spherical equivalent with no astigmatism, although some eyes did require spherical corrections up to just under -15 D.

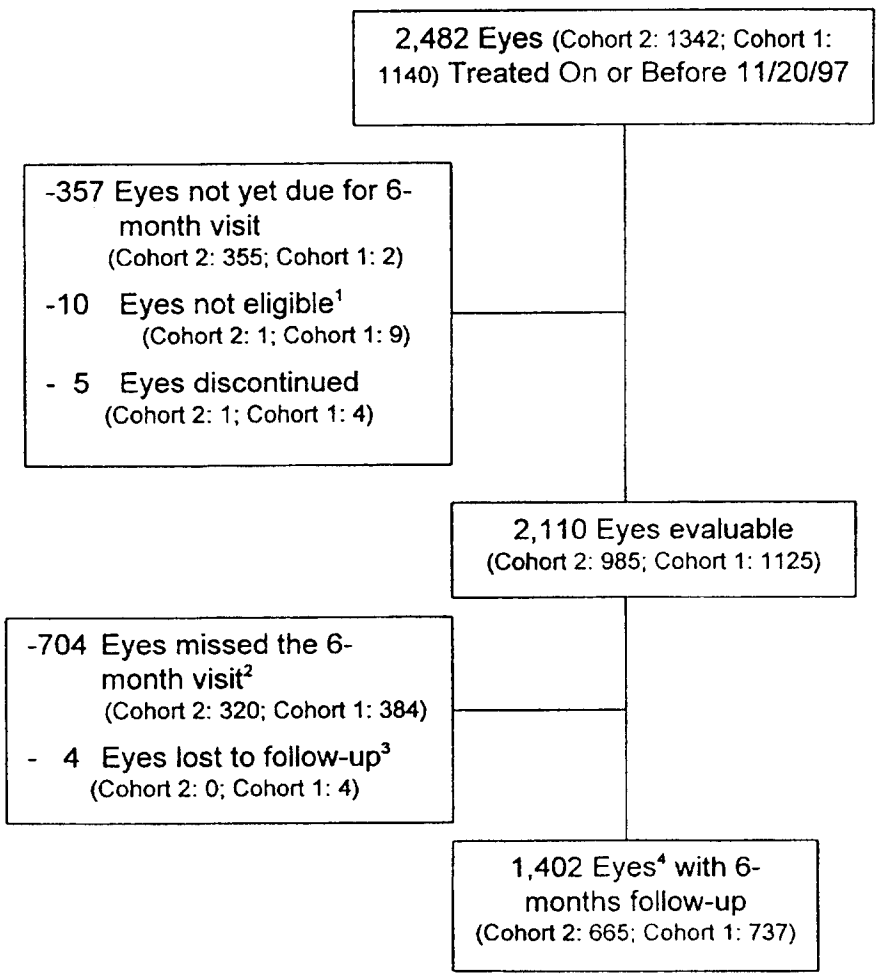
The majority of eyes treated for myopic astigmatism had low to moderate myopia with low to moderate astigmatism. Nearly 72% of eyes in Cohort 2 had preoperative sphere < -7 D; 58.5% of eyes in the Cohort 1 had preoperative sphere < -7 D. The remaining eyes had preoperative sphere ranging from ≥-7 D to just under -15 D. Approximately 94% and 96% of eyes in the Cohort 2 and Cohort 1 populations, respectively, had preoperative cylinder < 3 D.

F. Data Analysis and Results

Patient accountability

Primary data analysis was performed using 6-month follow-up, as recommended by the October 10, 1996 CDRH FDA guidance for refractive surgery lasers performing LASIK. There were 2,482 enrolled eyes in the study on the cutoff date of November 20, 1997. There were 1,402 eyes with one or more LASIK treatments available for analysis at 6 months. Table 1 shows the 6-month status of all eyes that entered the study.

Table 1. Status of All Eyes at 6 Months



1. Not eligible due to non-myopic enhancement.
2. Note that 403 of these eyes (Cohort 2: 235; Cohort 1: 168) missed the 6-month visit *and* were not yet due for the 12-month visit or missed the 12-month visit. Also, 301 of these eyes (Cohort 2: 85; Cohort 1: 216) were seen after 6-months.
3. Patients considered lost to follow-up 18 months after their last visit.
4. Following one or more LASIK treatments.

Data validity was verified by twenty-four separate intra-data-set statistical comparisons. Overall accountability at the 6-month visit was 77.5% (Cohort 2: 81.1%; Cohort 1: 73.9%), with a total of 1,402 eyes seen at 6-months (i.e., 1402/1809). Accountability was calculated by dividing the eyes available at 6-months (1,402) by the total eyes enrolled (2,482) after adjusting the denominator for discontinued eyes (5), eyes not yet due for the interval (357), eyes not eligible for analysis (10), and eyes that missed the interval but were seen subsequently (301). Additional data validity analyses were performed. Safety and efficacy variables of eyes (a) seen at 6-months, and (b) last status of eyes seen prior to 6-months were compared to (c) eyes seen at 6-months, and (d) eyes not yet due for 6-month follow-up. Similar comparisons were performed at the 12-month interval as well (24 comparisons in all). As a result of these analyses, it was determined that the data presented in the PMA application are reliable, unbiased, and therefore constitute valid scientific evidence.

Key efficacy variables

Table 2(a) presents a summary of efficacy results at the 6-and 12-month visits, stratified by protocol, for eyes having one or more LASIK treatments, and Table 2(b) for eyes after initial LASIK treatment only. Six-month UCVA was 20/40 or better in 88.4% of all eyes after the final LASIK treatment, and 84.1% following initial treatment only without regard to further enhancement. When the 6-month UCVA results were compared between cohorts 1 and 2, there was a statistically significant between-group difference. A greater proportion of eyes in the Cohort 2 population had UCVA of 20/40 or better and 20/20 or better. This is due to the intentional undercorrection performed in some of the Cohort 1 eyes. None of the other efficacy variables were significantly different when the two populations were compared.

Table 2(a). Summary of Key Efficacy Results After Final[1] Treatment at 6 and 12 Months

	Cohort 2 (%)		Cohort 1 (%)		
Efficacy Variable	6 months	12 months	6 months	12 months	P value[2]
UCVA:[3]					
20/20 or better	199/491 (40.5)	87/218 (39.9)	212/668 (31.7)	202/612 (32.7)	0.840
20/40 or better	446/491 (90.3)	201/218 (92.2)	579/668 (86.7)	535/612 (87.4)	0.523
MRSE:[4]					
±0.5 D	472/665 (71.0)	199/269 (74.0)	494/737 (67.0)	431/688 (62.6)	0.401
±1 D	584/665 (87.8)	249/269 (92.6)	631/737 (85.6)	588/688 (85.5)	0.231
±2 D	650/665 (97.7)	266/269 (98.9)	710/737 (96.3)	669/688 (97.2)	0.091

1. Final treatment includes all eyes treated after their last LASIK procedure.
2. Cochran-Mantel-Haenszel statistic comparing 6 and 12 months, controlling for protocol.
3. All eyes treated for monovision were excluded from this analysis, since undercorrection is intentional in this sub-population
4. Manifest refraction spherical equivalent.

Table 2(b). Summary of Key Efficacy Results After Initial[1] Treatment at 6 and 12 Months

	Cohort 2 (%)		Cohort 1 (%)		
Efficacy Variable	6 months	12 months	6 months	12 months	P value[2]
UCVA:[3]					
20/20 or better	195/493 (39.6)	87/219 (39.7)	192/657 (29.2)	185/563 (32.9)	0.262
20/40 or better	440/493 (89.3)	201/219 (91.8)	527/657 (80.2)	481/563 (85.4)	0.009
MRSE:[4]					
±0.5 D	461/670 (68.8)	199/271 (73.4)	421/724 (58.2)	387/637 (60.8)	0.102
±1 D	579/670 (86.4)	249/271 (91.9)	556/724 (76.8)	530/637 (83.2)	0.001
±2 D	655/670 (97.8)	268/271 (98.9)	675/724 (93.2)	614/637 (96.4)	0.003

1. Initial treatment includes all eyes after their first LASIK treatment without regard to further enhancement.
2. Cochran-Mantel-Haenszel statistic comparing 6 and 12 months, controlling for protocol.

3. All eyes treated for monovision were excluded from this analysis, since undercorrection is intentional in this sub-population
4. Manifest refraction spherical equivalent.

There was a statistically significant difference between all key efficacy variables when eyes with preoperative SE <7 D were compared with those with preoperative SE ≥7 D, thus indicating that the LASIK procedure produced better results in eyes with low to moderate preoperative myopia. Table 3(a) summarizes the key efficacy variables and statistical comparisons for patient eyes after their final LASIK treatment, and Table 3(b) summarizes key efficacy variables and statistical comparisons for patient eyes after their initial LASIK treatment without regard to further enhancement.

Table 3(a). Summary of Key Efficacy Results After Final[1] Treatment at 6 Months Stratified by Preoperative SE

	Cohort 2 (%)		Cohort 1 (%)		
Efficacy Variable	<7 D	≥7 D	<7 D	≥7 D	P value[2]
UCVA:[3]					
20/20 or better	185/371 (49.9)	14/120 (11.7)	176/447 (39.4)	36/221 (16.3)	0.001
20/40 or better	358/371 (96.5)	88/120 (73.3)	407/447 (91.1)	172/221 (77.8)	0.001
MRSE:[4]					
±0.5 D	374/477 (78.4)	98/188 (52.1)	356/483 (73.7)	138/254 (54.3)	0.001
±1 D	446/477 (93.5)	138/188 (73.4)	439/483 (90.9)	192/254 (75.6)	0.001
±2 D	475/477 (99.6)	175/188 (93.1)	480/483 (99.4)	230/254 (90.6)	0.001

1. Final treatment includes all eyes treated after their last LASIK procedure.
2. Cochran-Mantel-Haenszel statistic comparing preoperative SE (<7 D vs. ≥7D), controlling for protocol.
3. All eyes treated for monovision were excluded from this analysis, since undercorrection is intentional in this sub-population.
4. Manifest refraction spherical equivalent.

Table 3(b). Summary of Key Efficacy Results After Initial[1] Treatment at 6 Months Stratified by Preoperative SE

	Cohort 2 (%)		Cohort 1 (%)		
Efficacy Variable	<7 D	≥7 D	<7 D	≥7 D	P value[2]
UCVA:[3]					
20/20 or better	181/371 (48.8)	14/122 (11.4)	160/441 (36.3)	32/216 (14.8)	0.001
20/40 or better	356/371 (96.8)	84/122 (68.9)	382/441 (86.6)	145/216 (67.1)	0.001
MRSE:[4]					
±0.5 D	367/479 (76.6)	94/191 (49.2)	316/476 (66.4)	105/248 (42.3)	0.001
±1 D	445/479 (92.9)	134/191 (70.2)	401/476 (84.2)	155/248 (62.5)	0.001
±2 D	477/479 (99.6)	178/191 (93.2)	467/476 (98.1)	208/248 (83.9)	0.001

1. Initial treatment includes all eyes after their first LASIK treatment without regard to further enhancement.
2. Cochran-Mantel-Haenszel statistic comparing preoperative SE (<7 D vs. ≥7D), controlling for protocol.
3. All eyes treated for monovision were excluded from this analysis, since undercorrection is intentional in this sub-population.
4. Manifest refraction spherical equivalent.

Table 4 summarizes the key efficacy variables and statistical comparisons for myopic eyes versus myopic astigmatic eyes at 6-months after the final LASIK treatment in the Cohort 2 study. When controlling for high vs. low myopia, a comparison of efficacy results between eyes treated for myopia only and eyes treated for both myopia and astigmatism showed no statistically significant differences, with the lone exception being a reduction in the number of high myopic astigmatic eyes achieving UCVA of 20/20 or better.

Table 4. Summary of Key Efficacy Results[1] at 6 Months Stratified by Spherical vs. Astigmatic Myopia Controlling for Preoperative SER

	< 7 D		≥ 7 D		
Efficacy Variable	Spherical Myopia	Astigmatic Myopia	Spherical Myopia	Astigmatic Myopia	P value[2]
UCVA:[3]					
20/20 or better	111/213 (52.1)	74/158 (46.8)	12/61 (19.7)	2/59 (3.4)	0.057
20/40 or better	204/213 (95.8)	154/158 (97.5)	47/61 (77.1)	41/59 (69.5)	0.808
MRSE:[4]					
±0.5 D	192/243 (79.0)	182/234 (77.8)	36/76 (47.4)	62/112 (55.4)	0.703
±1 D	228/243 (93.8)	218/234 (93.2)	52/76 (68.4)	86/112 (76.8)	0.456
±2 D	242/243 (99.6)	233/234 (99.6)	68/76 (89.5)	107/113 (95.4)	0.141

1. Includes all eyes in the IDE study after the last LASIK treatment.
2. Cochran-Mantel-Haenszel statistic comparing spherical and astigmatic myopia, controlling for Preoperative SER group.
3. All eyes treated for monovision were excluded from this analysis, since undercorrection is intentional in this sub-population.
4. Manifest refraction spherical equivalent.

Other efficacy results after final LASIK treatment:

- Stability of manifest refraction. A total of 451 eyes were examined at three (3) consecutive visits (1, 3 & 6 months) in Cohort 2, of which 89.3% achieved stability (defined as a change in SE of ≤1.00 D across consecutive visits) between the month-1 and month-3 visits, increasing to 93.3% stability between the 3-month and 6-month visits. When analyzing those eyes evaluated at all four (4) consecutive visits in the Cohort 2 study, (n=139) 90.6% achieved stability between the 1- and 3-month visits, 95.0% between the 3- and 6-month visits, and 96.4% between the 6- and 12-month visits. Between 6 and 12 months the mean difference in refractive error was 0.05 D per month.

Table 4(a). Stability of Manifest Refraction - Cohort 2 - All Eyes Treated

Change in Spherical Equivalent Between	1 and 3 Months n/N (%)	3 and 6 Months n/N (%)	6 and 12 Months n/N (%)
≤ 1.00 D	126/139 (90.6)	132/139 (95.0)	134/139 (96.4)
Mean Difference	0.45	0.38	0.31
SD	0.44	0.38	0.34
95% CI	(0.42 - 0.48)	(0.36 - 0.40)	(0.29 - 0.33)

Only those subjects with all 1,3,6, and 12 months visits are included in the analysis.

- Accuracy of sphere and cylinder for astigmatic myopes.

Sphere. For all eyes treated under Cohort 2, mean intended spherical correction was -4.95 D and mean actual correction at the sixth postoperative month was -4.94 D. For eyes treated under the Cohort 1, mean intended spherical correction was -5.58 D and mean actual correction at month 6 was -5.34 D.

Over 80% of those eyes treated for myopic astigmatism achieved correction within ±1 D of intended sphere at 1 month. This level of accuracy was maintained throughout the 1-year study period.

Cylinder. Over 80% of all eyes treated for myopic astigmatism achieved cylinder correction within ±1 D of zero cylinder at 1 month. This level of accuracy was maintained throughout the 1-year study period. For myopic astigmatism, there was a mean undercorrection of just 0.1 D in Cohort 2. The procedure most effectively reduced cylinder magnitude in eyes with >1 D preoperative cylinder. Table 5 presents the accuracy of cylinder correction (to zero) for eyes in Cohort 2, stratified by high versus low dioptric group.

Table 5. Accuracy of Cylinder Correction (to Zero) for Eyes Treated in IDE Study

Sphere	Preoperative SER[1] < -7 D			
	1 Month n/N (%)	3 Months n/N (%)	6 Months n/N (%)	12 Months n/N (%)
≤ 0.50 D	252/365 (69.0)	208/327 (63.6)	153/234 (65.4)	63/95 (66.3)
≤ 1.00 D	329/365 (90.1)	287/327 (87.8)	209/234 (89.3)	84/95 (88.4)
Sphere	Preoperative SER ≥ -7 D			
	1 Month n/N (%)	3 Months n/N (%)	6 Months n/N (%)	12 Months n/N (%)
≤ 0.50 D	58/149 (38.9)	53/135 (39.3)	43/112 (38.4)	18/43 (41.9)
≤ 1.00 D	105/149 (70.5)	94/135 (69.9)	77/112 (68.8)	25/43 (58.1)

1. Spherical Equivalent Refraction.

Manifest versus Cycloplegic Refraction: Table 6 compares manifest refraction and cycloplegic refraction at 12 months for the Cohort 2 study group. There were no statistical differences in the proportion of eyes within 0.5 D or 2.0 D of target correction. There was a statistical difference between manifest and cycloplegic refractions when looking at proportions of eyes within 1.0 D of target. This is attributed to a higher proportion of hyperopic overcorrections in the ± 1.0 D group than in the ± 0.5 D group. However, 89% of eyes within 1.0 D of target correction meets current FDA guidelines for this parameter.

Table 6. Comparison of Manifest and Cycloplegic Refractions at 12 Months

Spherical Equivalent	Manifest Refraction	Cycloplegic Refraction	p-value[1]
SE ± 0.5 D	158/224 (70.5)	160/224 (71.4)	0.7440
SE ± 1.0 D	221/224 (94.2)	199/224 (88.8)	0.0075
SE ± 2.0 D	222/224 (99.1)	221/224 (98.7)	1.000

1. P-value for proportions derived from McNemar's test.

- Stability of cylinder. The manifest cylinder refraction was considered stable when cylinder did not change by more than 1 D between any two postoperative visits. Stability of cylinder was achieved in approximately 93.5% of all eyes between the month 1 and 3 visits, increasing to 94.7% between the 3 and 6 month visits, and 95.5% had a stable cylinder between 6 and 12 months.

Key safety variables

Table 7(a) presents a summary of key safety variables for all eyes after their final LASIK treatment at the 6- and 12-month visits, stratified by protocol. Table 7(b) summarizes key safety variables for all eyes after their initial LASIK treatment without regard to further enhancement. The overall proportion of eyes for both studies combined losing ≥2 lines of BSCVA at 12-months was 2.3% after final LASIK treatment, and 1.4% after initial LASIK treatment. When these key safety results are compared between Cohorts 1 and 2, there are no statistically significant differences.

Table 7(a). Summary of Key Safety Results After Final[1] Treatment at 6 and 12 Months

	Cohort 2 (%)		Cohort 1 (%)		
Safety Variable	6 months	12 months	6 months	12 months	P value[2]
BSCVA:					
Loss of >2 lines	14/665 (2.1)	2/269 (0.7)	20/737 (2.7)	20/688 (2.9)	0.593
Worse than 20/40	4/665 (0.6)	3/269 (1.1)	11/737 (1.5)	12/688 (1.7)	0.480
Worse than 20/25 with 20/20 or better preop	26/665 (3.9)	10/269 (3.7)	33/737 (4.5)	28/688 (4.1)	0.696
Increase of >2D cylinder[3]	2/319 (0.6)	2/131 (1.5)	1/315 (0.3)	2/283 (0.7)	0.258

1. Final treatment includes all eyes treated after their last LASIK procedure.
2. Cochran-Mantel-Haenszel statistic comparing 6 and 12 months, controlling for protocol.
3. Eyes treated for spherical correction only.

Table 7(b). Summary of Key Safety Results After Initial[1] Treatment at 6 and 12 Months

Safety Variable	Cohort 2 (%) 6 months	Cohort 2 (%) 12 months	Cohort 1 (%) 6 months	Cohort 1 (%) 12 months	P value[2]
BSCVA:					
Loss of >2 lines	14/670 (2.1)	2/271 (0.7)	16/724 (2.2)	11/637 (1.7)	0.754
Worse than 20/40	5/670 (0.8)	3/271 (1.1)	9/724 (1.2)	10/637 (1.6)	0.472
Worse than 20/25 with 20/20 or better preop	27/670 (6.6)	10/271 (3.7)	29/724 (4.0)	20/637 (3.1)	0.411
Increase of >2D cylinder[3]	2/319 (0.6)	2/131 (1.5)	1/306 (0.3)	3/264 (0.7)	0.140

1. Initial treatment includes all eyes after their first LASIK treatment without regard to further enhancement.
2. Cochran-Mantel-Haenszel statistic comparing 6 and 12 months, controlling for protocol.
3. Eyes treated for spherical correction only.

There was a statistically significant difference in favor of SE <7 D in several of the key safety variables when eyes with preoperative SE <7 D were compared with those with preoperative SE ≥7 D. Table 8(a) summarizes the key safety variables and statistical comparisons for patient eyes after final LASIK treatment, and Table 8(b) summarizes key safety variables after initial LASIK treatment.

Table 8(a). Summary of Key Safety Variables After Final[1] Treatment at 6 Months Stratified by Preoperative SE

Safety Variable	Cohort 2 (%) <7 D	Cohort 2 (%) ≥7 D	Cohort 1 (%) <7 D	Cohort 1 (%) ≥7 D	P value[2]
BSCVA:					
Loss of >2 lines	2/477 (0.4)	12/188 (6.3)	2/483 (0.4)	18/254 (7.1)	0.001
Worse than 20/40	1/477 (0.2)	3/188 (1.6)	0/483 (0)	11/254 (4.3)	0.001
Worse than 20/25 with 20/20 or better preop	9/477 (2.0)	17/188 (9.0)	8/469 (2.0)	17/183 (9.0)	0.001
Increase of >2D cylinder[3]	0/243 (0)	2/76 (2.6)	0/252 (0)	1/63 (1.6)	0.001

1. Final treatment includes all eyes treated after their last LASIK procedure.
2. Cochran-Mantel-Haenszel statistic comparing preoperative SE (<7D vs. ≥7D), controlling for protocol.
3. Eyes treated for spherical correction only.

Table 8(b). Summary of Key Safety Variables After Initial[1] Treatment at 6 Months Stratified by Preoperative SE

	Cohort 2 (%)		Cohort 1 (%)		
Safety Variable	<7 D	≥7 D	<7 D	≥7 D	P value[2]
BSCVA:					
Loss of >2 lines	2/479 (0.4)	12/191 (6.3)	0/476 (0)	16/248 (6.5)	0.001
Worse than 20/40	1/479 (0.2)	4/191 (2.1)	0/476 (0)	9/248 (3.6)	0.001
Worse than 20/25 with 20/20 or better preop	9/479 (1.9)	18/191 (9.4)	8/476 (1.7)	21/248 (8.5)	0.001
Increase of >2D cylinder[3]	0/242 (0)	2/77 (2.6)	0/247 (0)	1/59 (1.7)	0.001

1. Initial treatment includes all eyes after their first LASIK treatment without regard to further enhancement.
2. Cochran-Mantel-Haenszel statistic comparing preoperative SE (<7D vs. ≥7D), controlling for protocol.
3. Eyes treated for spherical correction only.

Adverse events/complications after final LASIK treatment:

Adverse events / Complications

Adverse events included corneal infiltrate (1 eye in Cohort 1 population), 1 case of cap malalignment (repositioned without sequelae), 1 retinal detachment in each cohort, and several early cataracts. The retinal detachments occurred at 11 months and >1 year postoperatively, indicating that these detachments were unrelated to surgery. The early cataracts were noted prior to surgery and were not induced. There were no corneal infections, lost or melted caps, or retinal vascular accidents recorded.

Corneal edema was noted between 1 week and 1 month in 5.3% of the Cohort 1 population and 3.4% of the Cohort 2 population. These cases resolved with further healing. The following complications - transient corneal central and peripheral epithelial defects, epithelium in the central interface that required removal, aborted procedures due to an incomplete cap, and cap striae - each occurred with ≤ 1% incidence. Epithelium in the periphery, which did not influence vision and did not require removal, occurred somewhat more frequently in the Cohort 1 population, as compared with the Cohort 2 population. Hingeless flap, an intraoperative complication, occurred in 1.8% of cases in the Cohort 1 population and 0.7% of cases in the Cohort 2 population. There were no associated sequelae with a hingeless flap. Interface foreign bodies at each interval which were observed under slit-lamp, but had no clinical sequelae, ranged between 14.5% and 8.8%.

Recorded patient complaints included glare, halos, trouble with night driving, double vision/ghosting, foreign body sensation, anxiety, and pain. The incidence of complaints considered by patients to be bothersome ranged from 0% to 4.1% for both protocol populations. Difficulty with night driving that was of a bothersome nature occurred at a rate of 4.1% in the Cohort 1 population and 1.1% in the Cohort 2 population. Complaints of a similar nature but not considered bothersome by the patients occurred at a somewhat higher incidence.

All of these complaints tended to be less prevalent in the Cohort 2 population than in the earlier Cohort 1 population, likely because of improvements in centering strategy and surgical technique. As expected, complaints were also less prevalent in the <7 D group as compared with the ≥7 D group in both protocol populations. Eyes with residual refractive errors also had a higher incidence of symptoms than those with SEs within ±0.5 D. The study did not measure the extent to which the complaints may have resolved in the presence of spectacle correction, as would be expected. Tables 9(a) and (b) summarize the bothersome complaints reported by patients in both studies.

Table 9(a). Summary of Adverse Events and Complications Experienced in Cohort 2.

	Cohort 2 (%)				
Adverse Events / Complicati	Operative[1]	1 month	3 months	6 months	12 months
Corneal infiltrate		0/873 (0)	0/814 (0)	0/657 (0)	0/308 (0)
Corneal edema ≥ 1 mo		2/873 (0.2)	1/814 (0.1)	0/657 (0)	0/308 (0)
Flap misalignment		1/873 (0.1)	0/814 (0)	0/657 (0)	0/308 (0)
Retinal detachment		0/873 (0)	0/814 (0)	0/657 (0)	1/308 (0.3)
Corneal Edema < 1 mo	30/873 (3.4)				
Incomplete cap-abort procedur	4/1342 (0.3)				
No hinge on flap	9/1342 (0.7)				
Epithelial defect - Central		1/873 (0.1)	1/814 (0.1)	0/657 (0)	0/308 (0)
Epithelial defect - Peripheral		1/873 (0.1)	0/814 (0)	1/657 (0.2)	0/308 (0)
Epithelium in interface-Central		1/873 (0.1)	0/814 (0)	1/657 (0.2)	0/308 (0)
Epithelium in interface-Periph.		8/873 (0.9)	10/814 (1.2)	8/657 (1.2)	1/308 (0.3)
Interface foreign bodies		126/873 (14)	128/814 (14)	95/657 (15)	27/308 (9)
Cap striae		9/873 (1.0)	6/814 (0.7)	5/657 (0.8)	1/308 (0.3)
Pain		4/873 (0.5)	4/814 (0.5)	3/657 (0.5)	2/308 (0.7)
Glare[2]				5/661 (0.8)	4/269 (1.5)
Halos[2]				7/661 (1)	0/269 (0)
Night Driving Problems[2]				7/661 (1)	2/269 (0.7)
Double Vision / Ghosts[2]				10/661 (1.5)	2/269 (0.7)
Foreign Body Sensation[2]				5/661 (0.8)	0/269 (0)
Anxiety[2]				0/661 (0)	0/269 (0)

1. Adverse events occurring operatively and up to 1 month postoperatively.
2. These events were reported 6 and 12 months after final treatment.

Table 9(b). Summary of Adverse Events and Complications Experienced in Cohort 1.

Cohort 1 (%)					
Adverse Events	Operative[1]	1 month	3 months	6 months	12 months
Corneal infiltrate		0/804 (0)	0/910 (0)	1/788 (0.1)	0/752 (0)
Corneal edema ≥ 1 mo		14/804 (1.7)	4/910 (0.4)	0/788 (0)	0/752 (0)
Flap misalignment		0/804 (0.1)	0/910 (0)	0/788 (0)	0/752 (0)
Retinal detachment		0/804 (0)	0/910 (0)	0/788 (0)	1/752 (0.1)
Complications					
Corneal Edema < 1 mo	43/741 (5.8				
Incomplete cap-abort procedur	1/1141 (0.1				
No hinge on flap	20/1141 (1.8				
Epithelial defect - Central		2/741 (0.3)	1/859 (0.1)	2/750 (0.3)	0/687 (0)
Epithelial defect - Peripheral		1/741 (0.1)	1/859 (0.1)	0/750 (0)	2/687 (0.3)
Epithelium in interface-Central		2/741 (0.3)	0/859 (0)	1/750 (0.1)	0/687 (0)
Epithelium in interface-Periph.		8/741 (1.1)	12/859 (1.4)	15/750 (2)	10/687 (1.5)
Interface foreign bodies		71/741 (9.6)	78/859 (9.1)	50/750 (6.7)	43/687 (6.3)
Cap striae		3/741 (0.4)	7/859 (0.8)	5/750 (0.7)	3/687 (0.4)
Pain		4/741 (0.5)	1/859 (0.1)	3/750 (0.4)	2/687 (0.3)
Glare[2]				23/726 (3.2)	16/678 (2.4)
Halos[2]				14/726 (1.9)	6/678 (0.9)
Night Driving Problems[2]				30/726 (4.1)	15/678 (2.2)
Double Vision / Ghosts[2]				6/726 (0.8)	5/678 (0.7)
Foreign Body Sensation[2]				1/726 (0.1)	0/678 (0)
Anxiety[2]				1/726 (0.1)	1/678 (0.1)

1. Adverse events occurring operatively and up to 1 month postoperatively.
2. These events were reported 6 and 12 months after final treatment.

Other safety results after final LASIK treatment

- Residual cylinder. Both Cohort 2 and 1 populations had slight cylindrical overcorrections when the intended correction was taken into consideration (mean overcorrections: 0.18 D and 0.21 D, respectively). These overcorrections, or surgically induced residual astigmatism, were greater in eyes treated for myopia only. The mean cylinder overcorrection was approximately one-half of a diopter among eyes treated for myopia only in both populations.

  Of eyes treated for myopic astigmatism, 68.8% of those treated under the Cohort 2 and 70.9% of those treated under the Cohort 1 had residual cylinder <1 D at the point of stability (6 months postoperatively). The number of these eyes with residual cylinder >2 D is low (n=15/346 [4.3%]for the Cohort 2 population and n=21/422 [4.9%] for the Cohort 1 population). Table 11 summarizes the residual astigmatic error observed at 6-months postoperatively in eyes treated for astigmatic myopia.

Table 10. Summary of Residual Astigmatic Error at 6 Months Postoperative in Eyes Treated for Myopic Astigmatism

Residual Cylinder Magnitude	Cohort 2 (%)	Cohort 1 (%)
0.0 D to < 0.5 D	148/346 (42.8)	156/422 (37)
≥ 0.5 D to < 1.0 D	90/346 (26)	141/422 (33.4)
≥ 1.0 D to < 2.0 D	90/346 (26)	87/422 (20.6)
≥ 2.0 D to < 3.0 D	11/346 (3.2)	15/422 (3.6)
>3.0 D	4/346 (1.2)	6/422 (1.4)
Unknown	3/346 (0.8)	17/422 (4.0)

- Change in cylinder axis. The median shift in cylinder axis among all eyes treated was 25° for the Cohort 2 population and 35° for the Cohort 1 population. The highest shifts in astigmatic axes tended to occur in eyes with the lowest degrees of residual cylinder. A shift in axis has no clinical significance, and is analogous to a compass needle showing multiple directions at the North Pole. Table 12 summarizes the observed shift in axis.

Table 11. Summary Statistics of Shift in Cylinder Axis in Eyes Treated for Myopic Astigmatism

	Cohort 2 Shift in Axis	Cohort 1 Shift in Axis
N	655	712
Mean	42.55	46.64
Median	25.00	35.99
Std Dev	40.27	40.32
Min	0.00	0.00
Max	147.00	149.00

Retreatments

Under Cohort 2, 47 eyes were retreated for undercorrection, for an overall enhancement rate of 3.5% (n=47/1342) under this protocol. In Cohort 2, 1 of 13 eyes that had a BSCVA of 20/20 or better preoperatively exhibited a BSCVA of worse than 20/25 at 6-months postoperative.

Under Cohort 1, 162 eyes were retreated for undercorrection, for an overall enhancement rate of 14.2% (n=162/1140). The higher retreatment rate in this earlier population is attributable to the earlier Cohort 1 requirement of intentional undercorrection. Four (4) retreated eyes had a decrease of BSCVA greater than 2 lines at 3 months which persisted out to 12 months postoperatively. Two eyes (2.1%) at 6 months and 3 eyes (3.9%) at 12 months had a BSCVA worse than 20/40. Eight eyes (8.3%) at 6 months and 8 eyes (10.4%) at 12 months that had a BSCVA of 20/20 or better preoperatively exhibited a BSCVA of 20/25 or worse.

X. CONCLUSIONS

The laboratory and clinical results based on 665 eyes treated and followed for six months provide reasonable assurance that the Kremer Excimer Laser is safe and effective for LASIK procedures when used as indicated and in accordance with the directions for use. The results of this study have been complemented and supported by safety and effectiveness information from an additional 737 eyes also followed for six months and 957 eyes followed for 12 months.

XI. PANEL RECOMMENDATIONS

On February 13, 1998, the Ophthalmic Devices Panel recommended that the premarket approval application for this excimer laser be considered not approvable. The major concerns raised by the panel related to:

- accountability;
- use of Snellen charts;
- hyperopic retreatments;
- induced cylinder;
- cycloplegic refraction;
- stability of cylinder;
- clarification of 250μ versus 200μ residual thickness; and,
- labeling (retreatments, indications, contraindications and precautions)

XII. FDA DECISION

This laser was originally developed for the use of Dr. Kremer for his patients. It was developed to perform what has come to be referred to as the Laser K^{SM} LASIK procedure. The device was first used for the LASIK treatment of patients in 1993 and until 1996 under studies approved by an Investigational Review Board (IRB). In late 1995, FDA requested that an IDE be submitted to, and approved by, the Agency if Dr. Kremer was to continue to study human subjects with his laser. Dr. Kremer received approval for his IDE on June 7, 1996. This PMA was filed on January 31, 1997.

Following the February 13, 1998 panel meeting, CDRH met with the sponsor on February 24, 1998 to discuss clinical issues and on March 10, 1998 to discuss engineering and software concerns. Subsequently, CDRH issued a major deficiency letter on March 12, 1998 which requested the information and clarifications specified by the panel and FDA.

The sponsor provided FDA with detailed responses to each of the deficiencies in subsequent amendments to the PMA. The major concerns raised by the panel were resolved in the following manner:

Accountability: The sponsor performed the required analyses and demonstrated that those patients not available at 6 months are no different in their safety when compared to those that were available. Also, they had a somewhat better effectiveness outcome.

Use of Snellen charts: FDA accepted the sponsor's explanation of the constant error introduced by the use of the Snellen charts instead of ETDRS charts. The sponsor re-calculated the key safety variables using the conventional definition of lines lost with respect to loss of >2 lines of visual acuity. Moreover, FDA acknowledges that the IDE study was approved by FDA using Snellen charts so that there would be comparability with the IRB protocol.

Hyperopic retreatments: All key safety and effectiveness variables were recalculated by the sponsor after eliminating hyperopic retreatments. The outcomes are satisfactory. Dataline listings of retreated eyes were provided by the sponsor. These data did not reveal a problem with the device.

Induced cylinder: The sponsor demonstrated that after correcting for decentration early in the clinical trial, there was minimal induction of cylinder.

Cycloplegic refraction: The sponsor compared cycloplegic refraction with manifest refraction at one year and found minimal overcorrection when cyclopleged.

Stability of cylinder: The sponsor reanalyzed the residual cylinder in a manner requested by FDA. There is reasonable assurance of effectiveness of the laser with regard to cylinder correction.

Clarification of 250μ versus 200μ residual thickness: Only six eyes were treated with a residual depth of 200μ. FDA expressed its concerns to the sponsor about future ectasia in these eyes. This issue was addressed in the Warnings section of the labeling.

Labeling: Labeling revisions concerning retreatment, indications, contraindications and precautions were recommended by FDA and agreed to in a meeting with the sponsor held on May 26, 1998 and in subsequent facsimile correspondence.

This PMA approval is for a single device and does not authorize the PMA applicant to manufacture or distribute any additional units. Therefore, no preapproval Good Manufacturing Practices (GMP) inspection was required. However, the Office of Compliance did recommend a postmarket approval inspection.

XIII. APPROVAL SPECIFICATIONS

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