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

I. GENERAL INFORMATION

Device Generic Name:	Ophthalmic Medical Laser System (193 nanometer laser wavelength)
Device Trade Name:	VISX STAR S2 and S3 Excimer Laser Systems
Applicant's Name and Address:	VISX, Incorporated 3400 Central Expressway Santa Clara, CA 95051-0703 408-733-2020
Date of Panel Recommendation:	May 11, 2000
Premarket Approval (PMA) Application Number:	P930016/S10
Date of Notice of Approval to Applicant:	October 18, 2000
Expedited Review:	Expedited review was granted on July 27, 1999 based on the potential public health benefit from reducing the number of patients being treated using the device off-label in a two-step process employing two VisionKey™ cards and a break in the treatment course which ultimately resulted in a thinner cornea than is necessary to accomplish the correction.

This device was originally approved on March 27, 1996, under PMA P930016, for the limited indication for myopic photorefractive keratectomy (PRK) using a 6.0 mm ablation zone in patients 18 years of age or older with 1.0 to 6.0 diopters (D) of myopia with astigmatism of ≤ 1.0 D whose refractive change for one year prior to treatment is within ± 0.5 D.

This clinical indication was expanded in supplements 3 (approved on April 24, 1997), 5 (approved on January 29, 1998) and 7 (approved November 2, 1998) to include PRK in patients 21 years of age or older in PRK treatments for the reduction or elimination of myopia (nearsightedness) of between 0 and -12.0 D spherical myopia at the spectacle plane and up to -4.0 D of astigmatism and hyperopia (sphere only) of between +1.0 and +6.0 D

spherical equivalent with no more than 1.0 D of refractive astigmatism. On November 19, 1999 (P990010), the clinical indication was further expanded to include laser in-situ keratomileusis (LASIK) treatments in patients 18 years of age or older for the reduction or elimination of myopia (nearsightedness) from 0 to -14.0 D with or without -0.50 to -5.0 D of astigmatism.

The sponsor submitted this supplement to further expand the clinical indications. The updated clinical data to support the expanded indication is provided in this summary. The preclinical test results were presented in the original PMA application. For more information on the data which supported the approved indications, the summaries of safety and effectiveness data (SSED) for P930016 and P990010 should be referenced. Written requests for copies of the SSED can be obtained from the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857 under Docket # 97M-0084 (original PMA and S3), Docket # 99M-0293 (S5), Docket # 00M-1391 (S7), and Docket # 00M-1447 (LASIK) or you may download the files from the internet sites http://www.fda.gov/cdrh/pdf/p930016.pdf and http://www.fda.gov/cdrh/pdf/p990010.pdf.

II. INDICATIONS FOR USE

Photorefractive Keratectomy (PRK) procedure using the VISX STAR S2 and S3 Excimer Laser Systems is intended for use:

- in patients with documented evidence of a change in manifest refraction of less than or equal to 0.5 D (in both cylinder and sphere components) per year for at least one year prior to the date of pre-operative examination; and

- in patients 21 years of age or older for the reduction or elimination of naturally occurring hyperopia between +0.5 and +5.0 D sphere at the spectacle plane with refractive astigmatism from +0.5 to +4.0 D with a maximum manifest refraction spherical equivalent (MRSE) of +6.0 D.

III. CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

A. Contraindications:

PRK surgery is contraindicated:

- In patients with collagen vascular, autoimmune or immunodeficiency diseases.

- In pregnant or nursing women.

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- In patients with signs of keratoconus.

- In patients who are taking one or both of the following medications:
  - isotretinoin (Accutane)
  - amiodarone hydrochloride (Cordarone)

B. Warnings: see the labeling

C. Precautions: see the labeling

IV. DEVICE DESCRIPTION

The device used in the clinical study was the VISX STAR S2 Excimer Laser System for which a full description can be found in the SSED for supplement 7. The excimer is an argon-fluoride laser that generates pulses at 193 nm wavelength. The output of the excimer laser also has the following characteristics: fluence of 160 mJ/cm^2; 20 nanoseconds pulse duration; and, pulse repetition rate of up to 10 Hz.

The STAR S3 with Eyetracker was approved on April 20, 2000 for all of the above indications. The eye tracker pauses treatment when an eye movement >0.2 mm occurs between two sampled positions, or when it detects significant non-circularity of the pupil. The operator can turn the tracker on or off at any time. The delay between the tracker acquisition of a positional signal and the beam positional response is about 67 msec, less than the interpulse interval of the laser beam. Based on engineering reviews of this application, the use of the VISX active eyetracker incorporated in the VISX STAR S3 Excimer Laser System should not introduce new safety or effectiveness problems regarding the PRK treatment of hyperopia with astigmatism. Therefore the STAR S3 is considered comparable to the STAR S2 model (without the eyetracker) for this indication for use, and PMA approval includes both models.

V. ALTERNATIVE PRACTICES OR PROCEDURES

Conventional methods in correcting farsightedness with astigmatism are: spectacles, contact lenses, LASIK, or other types of refractive surgery.

VI. MARKETING HISTORY

VISX has over 1000 Excimer Systems located in approximately 44 countries (Argentina, Aruba, Australia, Bolivia, Brazil, Bulgaria, Canada, Chile, China, Colombia, Cyprus, Czech Republic, Ecuador, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Israel, Italy, Japan, Korea, Mexico, Netherlands, New Zealand, Norway, Pakistan, Paraguay, Peru, Philippines, Portugal, Russia, Russia-Kazakhstan, Slovak Republic, Spain,

Sweden, Switzerland, Taiwan, Turkey, United Kingdom, United States, Uruguay). The VISX Excimer System has not been withdrawn from any country or market for reasons of safety or effectiveness.

VII. ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse reactions associated with PRK include: loss of best spectacle corrected visual acuity, worsening of patient complaints such as double vision, sensitivity to bright lights, increased difficulty with night vision, fluctuations in vision, increase in intraocular pressure, corneal haze, and secondary surgical intervention.

Please refer to the complete listing of adverse events and complication observed during the clinical study which are presented on pages 13-15 of the clinical study section.

VIII. SUMMARY OF PRECLINICAL STUDIES

Please refer to the SSED of the original PMA P930016.

IX. SUMMARY OF CLINICAL STUDIES

A prospective study with 172 patients was conducted at seven investigation sites in the United States.

A. Study Objective

The clinical study reported here evaluated the safety and efficacy of the VISX Excimer Laser to treat naturally occurring hyperopia between +0.5 and +6.0 D sphere (spectacle plane) with refractive astigmatism between +0.5 and +4.0 D (spectacle plane).

B. Study Design

This was a prospective, non-randomized, unmasked, multi-center clinical study where the primary control was the pre-operative state of the treated eye (i.e., comparison of pretreatment and post-treatment visual parameters in the same eye).

C. Inclusion and Exclusion Criteria

Study subjects were 21 years or older and must have signed an informed consent form. Enrollment occurred if the subject met these conditions: naturally occurring refractive hyperopia between +0.5 and +6.0 diopters sphere (spectacle plane), with between +0.5 and +4.0 diopters of refractive astigmatism; best corrected visual acuity of 20/40 or better in both eyes; the difference between the manifest and cyclopegic refractions (sphere or

cylinder) may be no more than 0.75 D and no more than 15 degrees axis. Refractive error of fellow eyes may not exceed +6.0 D sphere (spectacle plane) with more than +4.0 D refractive cylinder (spectacle plane). Stable spherical or cylindrical portion of manifest refraction as documented by ≤0.5 D change within the previous twelve months, astigmatic axis may not vary by more than 15 degrees. Contact lens wearers had to abstain from contact lens use prior to baseline examination (2 weeks for soft lenses, 3 weeks for hard lenses) and have 3 central keratometry readings and manifest refractions taken at one week intervals, the last two of which must not differ by more than 0.50 diopter in either meridian; mires regular. Patients must be willing and capable to return for all schedules follow-up visits for a period of at least 12 months.

Subjects not meeting the above inclusion criteria were excluded from the study. In addition, subjects who exhibited any of the following conditions were excluded: keratoconus, active ocular disease or corneal abnormality, patent corneal neovascularization within 1 mm of the intended ablation zone, previous corneal surgery or trauma within the intended ablation zone, systemic disease likely to affect wound healing, unstable central keratometry readings with irregularly shaped mires or corneascope photographs with broken central rings, use of systemic medications likely to affect wound healing or immunodeficiency, under 21 years of age, spherical or cylindrical portion of manifest refractive has progressed at a rate of more than 0.50 diopter per year from date of baseline exam, females who are pregnant or breast-feeding.

D. Study Plan, Patient Assessments and Efficacy Criteria

Subjects were evaluated preoperatively, every 24 hours post-operatively until re-epithelialization, and at 1, 3, 6, 9 and 12 months post-treatment.

Pre-operatively the subject's medical and ocular histories were recorded. Post-operatively, subjects were questioned about any visual symptoms and their satisfaction with the procedure at 6 and 12 months for primary eyes only. Objective measurements included: distance and near uncorrected and best corrected visual acuity, manifest refraction, keratometry, intraocular pressure, pachymetry, clinical assessment of corneal clarity, clinical assessment of anterior chamber, vitreal, retinal and lens status, assessment of complications or adverse reactions.

Procedure effectiveness was evaluated based on improvement in uncorrected visual acuity, the ability of eyes to attain the targeted correction, and achieve stability of manifest refraction spherical equivalent and patient acceptance of the procedure. The stability of the procedure was defined in terms of the change in manifest refraction over time, starting one month after treatment.

E. Study Period, Investigational Sites and Demographic Data

1. Study Period and Investigational Sites

This study was conducted at 7 centers in the United States. A total of 172 subjects (276 eyes) were enrolled and treated between August 7, 1998 and August 8, 1999.

2. Demographics

Demographic characteristics with respect to patient age, race, sex, and contact lens history are shown in Table 1.

Table 1
Demographic Information
(N=276)

Category	Classification	n	% Eyes
Gender	Male	139	50.4
	Female	137	49.6
Race	Caucasian	258	93.5
	Asian/Pacific Islander	1	0.4
	African American	7	2.5
	American Indian/Aleut Eskimo	0	0.0
	Other: Hispanic	8	2.9
	Other: Latino	2	0.7
Eyes	Right	139	50.4
	Left	137	49.6
CL History	None	103	60.6
	Soft	50	29.4
	RGP/PMMA	17	10.0
Age (in Years)	Average	51.3	
	Standard Deviation	± 11.2	
	Minimum	24	
	Maximum	77	

F. Data Analysis and Results

1. Pre-operative Characteristics

The pre-operative refractive error of subjects ranged from between +0.50 and +6.00 diopters of sphere with between +0.50 and +4.00 diopters of refractive astigmatism. Table 2 presents pre-operative refractive error stratified by diopter of sphere and cylinder.

Table 2 Pre-Operative Refractive Error Stratified by Sphere and Cylinder (N=276)										
	Cylinder								Total	
	>0 to ≤ 1 D		>1 to ≤ 2 D		>2 to ≤ 3 D		>3 to ≤ 4 D			
Sphere	n	%	n	%	n	%	n	%	n	%
>0 to ≤ 1 D	11	8.5	11	11.8	4	12.9	8	36.4	34	12.3
>1 to ≤ 2 D	50	38.5	26	28.0	3	9.7	5	22.7	84	30.4
>2 to ≤ 3 D	25	19.2	24	25.8	10	32.3	3	13.6	62	22.5
>3 to ≤ 4 D	21	16.2	16	17.2	8	25.8	1	4.5	46	16.7
>4 to ≤ 5 D	15	11.5	7	7.5	1	3.2	3	13.6	26	9.4
>5 to ≤ 6 D	8	6.2	9	9.7	5	16.1	2	9.1	24	8.7
Total	130	47.1	93	33.7	31	11.2	22	8.0	276	100

2. Post-operative Characteristics and Results

a. Patient Accountability

Follow-up accountability exceeded 95% at every visit. All eyes treated are included in Table 3. (Please note: The efficacy cohort excluded subjects with sphere >5.0 D.)

Table 3 Updated Subject Accountability: All Eyes (N=276)										
	1 Month		3 Months		6 Months		9 Months		12 Months	
	n	%	n	%	N	%	n	%	N	%
Available for Analysis	275	99.6	272	98.6	272	98.6	254	92.0	237	85.9
Discontinued	0	0.0	0	0.0	2	0.7	2	0.7	2	0.7
Missed Visit	1	0.4	3	1.1	1	0.4	11	4.0	17	7.2
Not yet eligible	0	0.0	0	0.0	0	0.0	0	0.0	5	1.8
Lost to Follow-Up	0	0.0	1	0.4	1	0.4	9	3.3	15	6.3
% Accountability: Available for Analysis (enrolled – discontinued – not yet eligible)	275/276 99.6%		272/276 98.6%		272/274 99.3%		254/274 92.7%		237/269 88.1%	

*Two eyes are excluded from analyses because treatment departed significantly from protocol.
Available for Analysis [completed, evaluable]: total number of eyes that have reached the post-operative interval being reported and have also undergone the examination specified for that interval.
Discontinued: total number of eyes that are no longer continuing under the treatment; e.g., eyes in subjects who have deceased and the retreated eyes.
Enrolled (N): total number of eyes that have received treatment.
Lost to follow-up [Incomplete]: total number of eyes that failed to undergo the examination specified for a post-operative interval and all subsequent examination intervals; e.g., eyes of subjects who have moved or have informed the investigator that they do not plan to come back for any future exam.
Missed Visit: total number of eyes that failed to undergo the examination required for the visit being reported but were examined at a subsequent visit.
Not yet eligible for the Interval [active]: total number of eyes that have not yet reached the post-operative interval being reported.
Percent Accountability: total number of eyes available for analysis divided by the quantity of total enrolled, minus total discontinued, and minus total not yet eligible for the interval.

b. Early Post-Operative Symptoms

Patients were seen daily for post-operative visits until the epithelium was healed completely. More than half the eyes were healed within 4 days and over 75% were healed by Day 5. Within 1 week, over 95% of eyes were healed. There were 12 eyes that took longer than 7 days to heal completely, and 2/3 of these were healed by Day 9. A total of 4 eyes took more than 9 days to heal, and all had epithelialized by Day 13 (1 each on day 10, 11, 12, and 13). Uncorrected acuity was measured on the day of epithelialization. Almost half the eyes had a UCVA of 20/40 or better on the day the cornea wound healed and over 90% saw 20/80 or better uncorrected. As anticipated, those eyes that were targeted for emmetropia had slightly better uncorrected visual acuity on the day of epithelialization. Post-operative symptoms were reported each day following treatment until healing was complete. Specifically, the following symptoms were reported: pain, tearing, photophobia, discomfort, blurry vision, swollen lids, itching, dryness, and burning sensation. The most common symptom reported after Day 4 was dryness. By the day that epithelialization was complete, most symptoms had resolved. The only other symptoms reported on the day of healing were dryness and swollen lids, both at an incidence of < 1%.

c. Effectiveness Outcomes

(1) Stability

To evaluate mean manifest refractive spherical equivalent (MRSE) over time it is important to consider only those eyes targeted for emmetropia at each visit. From the 9 months to the 12 month visit, the mean MRSE changed 0.13 D, or 0.04 D per month. Table 4 presents the mean MRSE over time.

Table 4
Mean MRSE Over Time
(Eyes Targeted for Emmetropia, N=234)

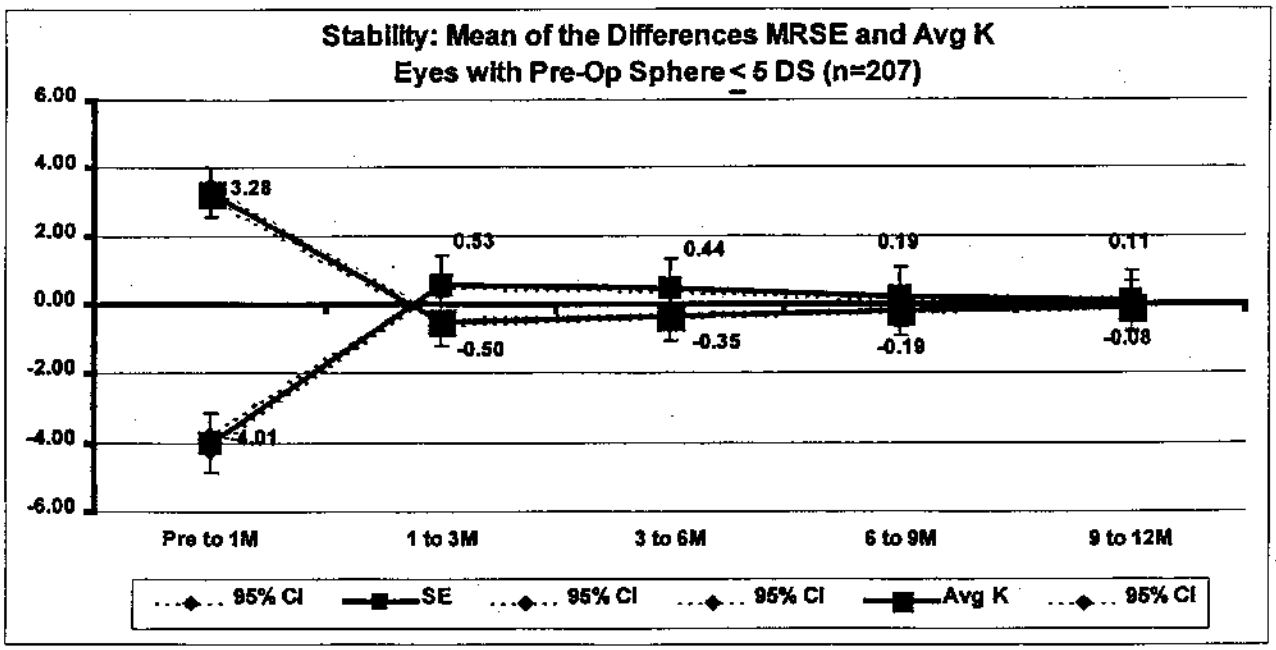
	1 Month (n=233)	3 Months (n=230)	6 Month (n=231)	9 Months (n=218)	12 Months (n=205)
MRSE (D)					
Mean	-0.75	-0.18	0.20	0.38	0.50
SD	0.81	0.64	0.61	0.67	0.70
95% CI for Mean	(-0.87, -0.65)	(-0.26, -0.09)	(0.12, 0.28)	(0.29, 0.47)	(0.40, 0.59)

Between 9 and 12 months 95.7% of eyes changed not more than one diopter of MRSE with a mean of 0.11 D. From the 9 month visit to the 12 month visit, the mean MRSE changed 0.03 D per month. Between 9 and 12 months 98% of eyes changed not more than one diopter of Average Keratometry with a mean of -0.08 D. From the 9 month visit to the 12 month visit the mean MRSE changed 0.04 D per month.

Table 5 Stability: Mean of the Differences (Eyes with 1, 3, 6, 9 and 12-Month Visits, N=207)								
	1 and 3 Months		3 and 6 Months		6 and 9 Months		9 and 12 Months	
Change ≤ 1.00 D	n	%	n	%	n	%	n	%
MRSE	165	79.7	176	85.0	196	94.7	198	95.7
95% CI for %	(74.2, 85.2)		(80.2, 89.9)		(91.6, 97.7)		(92.9, 98.4)	
Mean	0.53		0.44		0.19		0.11	
SD	0.74		0.58		0.51		0.49	
95% CI for Mean	(0.43, 0.63)		(0.36, 0.52)		(0.12, 0.26)		(0.04, 0.18)	
Avg K	161	77.8	187	91.2	188	92.6	201	98.0
95% CI for %	(72.1, 83.4)		(86.3, 94.4)		(86.9, 94.8)		(94.8, 99.4)	
Mean	-0.50		-0.35		-0.19		-0.08	
SD	0.86		0.51		0.50		0.41	
95% CI for Mean	(-0.62, -0.38)		(-0.42, -0.28)		(-0.26, -0.12)		(-0.13, -0.02)	

When plotted over time, the mean of the differences in manifest refraction spherical further supported by almost no change between the 9 and 12-month visits. Figure 1 presents a plot of the mean of the differences in MRSE and Avg K over the course of the study.

Figure 1: Plot of Stability Over Time



The target outcome for refractive stability is the point at which 95% of eyes experience a change of not more than one diopter between two visits at least 3 months apart. Based on this definition, stability of refractive cylinder is achieved between 3 and 6 months post-operatively and is maintained through 12 months. Table 6 presents stability of refractive cylinder.

Table 6 Stability of Refractive Cylinder (Eyes with 1, 3, 6, 9 and 12-Month Visits, N=207)								
	1 and 3 Months		3 and 6 Months		6 and 9 Months		9 and 12 Months	
Change in Cyl	n	%	n	%	n	%	n	%
≤ 1.00 D	198	95.7	203	98.1	203	98.1	202	97.6
95% CI for %	(92.9, 98.4)		(96.2, 99.9)		(96.2, 99.9)		(95.5, 99.7)	
Mean	-0.11		-0.05		0.05		0.03	
SD	0.53		0.47		0.51		0.45	
95% CI for Mean	(-0.04, -0.19)		(0.02, -0.11)		(0.12, -0.02)		(0.09, -0.03)	

The surgically induced refractive change (SIRC) was assessed by vector analysis and compared to the intended refractive change (IRC) to produce a mean vector axis and magnitude of error.

Table 7a Cylinder Vector Magnitude at 12 Months (N=207)					
	Pre	Post	IRC	SIRC	SIRC/IRC
Mean	1.46	0.45	-1.59	-1.55	0.97
Median	1.25	0.50	-1.30	-1.30	1.00
SD	0.92	0.48	1.02	0.99	
Min	0.50	0.00	-4.71	-4.97	
Max	4.00	3.25	-0.52	-0.02	

SIRC=Surgically Induced Refractive Change
IRC=Intended Refractive Change

Table 7b Cylinder Correction Efficacy Stratified by Pre-Operative Cylinder at 12 Months (N=207)		
Pre-Operative Cylinder	Percent Reduction of Absolute Cylinder (Not a Vector)	Achieved vs Intended Vector Magnitude Ratio (SIRC/IRC)
≤ 1.0 D	52% (0.36/0.75)	112% (-0.91/-0.81)
> 1.0 to ≤ 2.0 D	72% (0.45/1.61)	90% (-1.59/-1.76)
> 2.0 to ≤ 3.0 D	76% (0.63/2.58)	95% (-2.71/-2.86)
> 3.0 to ≤ 4.0 D	78% (0.78/3.57)	92% (-3.57/-3.89)
Total	69% (0.45/1.46)	98% (-1.55/-1.59)

Table 8
Residual Astigmatic Error at 12 Months
(N=217)

Residual Cylinder Magnitude	Absolute Shift in Axis						
	0 n % 95% CI	≤5° n % 95% CI	>5 to ≤10° n % 95% CI	>10 to ≤15° n % 95% CI	>15 to ≤30° n % 95% CI	>30° n % 95% CI	Total n % 95% CI
0 D	77 100 (88.8, 100)	0 0.0 (0.0, 10.9)	0 0.0 (0.0, 56.6)	0 0.0 (0.0, 29.5)	0 0.0 (0.0, 27.2)	0 0.0 (0.0, 17.3)	77 35.5 (29.1, 41.9)
> 0 to < 0.5 D	0 0.0 (0.0, 11.2)	19 23.5 (14.2, 32.7)	1 33.3 (0.0, 86.7)	0 0.0 (0.0, 29.5)	2 15.4 (0.0, 35.0)	6 18.8 (5.2, 32.3)	28 12.9 (8.4, 17.4)
≥ 0.5 to < 1.0 D	0 0.0 (0.0, 11.2)	39 48.1 (37.3, 59.0)	2 66.7 (13.3, 100)	7 63.6 (35.2, 92.1)	6 46.2 (19.1, 73.3)	21 65.6 (49.2, 82.1)	75 34.6 (28.2, 40.9)
≥ 1.0 to < 2.0 D	0 0.0 (0.0, 11.2)	21 25.9 (16.4, 35.5)	0 0.0 (0.0, 56.6)	3 27.3 (1.0, 53.6)	5 38.5 (12.0, 64.9)	5 15.6 (3.0, 28.2)	34 15.7 (10.8, 20.5)
≥ 2.0 to < 3.0 D	0 0.0 (0.0, 11.2)	2 2.5 (0.0, 5.8)	0 0.0 (0.0, 56.6)	0 0.0 (0.0, 29.5)	0 0.0 (0.0, 27.2)	0 0.0 (0.0, 17.3)	2 0.9 (0.0, 2.2)
≥ 3.0 D	0 0.0 (0.0, 11.2)	0 0.0 (0.0, 10.9)	0 0.0 (0.0, 56.6)	1 9.1 (0.0, 26.1)	0 0.0 (0.0, 27.2)	0 0.0 (0.0, 17.3)	1 0.5 (0.0, 1.4)
Total	77 35.5	81 37.3	3 1.4	11 5.1	13 6.0	32 14.7	217 100

(2) Uncorrected Visual Acuity (UCVA)

Table 9 presents the distance uncorrected visual acuity of eyes targeted for emmetropia over time.

Table 9
UCVA Over Time
(Eyes Targeted for Emmetropia, N=234)

	Pre-Op (n=234) n % (95% CI)	1 Month (n=233) n % (95% CI)	3 Months (n=230) n % (95% CI)	6 Months (n=231) n % (95% CI)	9 Months (n=218) n % (95% CI)	12 Months (n=205) n % (95% CI)
20/20 or better	1 0.4 (0.0, 1.3)	31 13.3 (8.9, 17.7)	87 37.8 (31.6, 44.1)	116 50.2 (43.8, 56.7)	113 51.8 (45.2, 58.5)	100 48.8 (41.9, 55.6)
20/25 or better	2 0.9 (0.0, 2.0)	70 30.0 (24.2, 35.9)	140 60.9 (54.6, 67.2)	164 71.0 (65.1, 76.8)	158 72.5 (66.5, 78.4)	140 68.3 (61.9, 74.7)
20/32 or better	5 2.1 (0.3, 4.0)	124 53.2 (46.8, 59.6)	178 77.4 (72.0, 82.8)	203 87.9 (83.7, 92.1)	188 86.2 (81.7, 90.8)	173 84.4 (79.4, 89.4)
20/40 or better	17 7.3 (3.9, 10.6)	160 68.7 (62.7, 74.6)	205 89.1 (85.1, 93.2)	223 96.5 (94.2, 98.9)	208 95.4 (92.6, 98.2)	195 95.1 (92.2, 98.1)
20/80 or better	97 41.5 (35.1, 47.8)	229 98.3 (96.6, 100)	229 99.6 (98.7, 100)	231 100 (93.6, 100)	218 100 (93.4, 100)	205 100 (93.2, 100)
20/200 or better	209 89.3 (85.4, 93.3)	233 100 (93.6, 100)	230 100 (93.5, 100)	231 100 (93.6, 100)	218 100 (93.4, 100)	205 100 (93.2, 100)
Worse than 20/200	25 10.7 (6.7, 14.6)	0 0.0 (0.0, 6.4)	0 0.0 (0.0, 6.5)	0 0.0 (0.0, 6.4)	0 0.0 (0.0, 6.6)	0 0.0 (0.0, 6.8)
Not Reported	0	0	0	0	0	0
Total	234 100	233 100	230 100	231 100	218 100	205 100

(3) Predictability of Outcome

Table 10 presents the accuracy of sphere and cylinder over time.

Table 10
Accuracy of Sphere (to Target) and Cylinder (to Zero) Component
(N=252)

	1 Month (n=251) n % (95% CI)	3 Months (n=248) n % (95% CI)	6 Months (n=249) n % (95% CI)	9 Months (n=231) n % (95% CI)	12 Months (n=217) n % (95% CI)
Sphere					
± 0.50 D	68 27.1 (21.6, 32.6)	149 60.1 (54.0, 66.2)	173 69.5 (63.8, 75.2)	162 70.1 (64.2, 76.0)	146 67.3 (61.0, 73.5)
± 1.00 D	148 59.0 (52.9, 65.0)	208 83.9 (79.3, 88.4)	227 91.2 (87.6, 94.7)	198 85.7 (81.2, 90.2)	184 84.8 (80.0, 89.6)
Cylinder					
± 0.50 D	156 62.2 (56.2, 68.2)	174 70.2 (64.5, 75.9)	191 76.7 (71.5, 82.0)	169 73.2 (67.4, 78.9)	143 65.9 (59.6, 72.2)
± 1.00 D	223 88.8 (84.9, 92.7)	231 93.1 (90.0, 96.3)	232 93.2 (90.0, 96.3)	215 93.1 (89.8, 96.3)	202 93.1 (89.7, 96.5)

At 6 months or later no eye was overcorrected by more than two diopters while 2.0% of eyes were undercorrected by more than two diopters. The target outcomes for accuracy of MRSE (50% within 0.50 D and 75% within 1.00 D of attempted correction) are exceeded at 3 months and later. Table 11 presents the accuracy of MRSE over time.

Table 11
Accuracy of MRSE: Attempted versus Achieved
(N=252)

MRSE	Pre-Op (n=252) n % (95% CI)	1 Month (n=251) n % (95% CI)	3 Months (n=248) n % (95% CI)	6 Months (n=249) n % (95% CI)	9 Months (n=231) n % (95% CI)	12 Months (n=217) n % (95% CI)
± 0.50 D	0 0.0 (0.0, 6.2)	84 33.5 (27.6, 39.3)	157 63.3 (57.3, 69.3)	159 63.9 (57.9, 69.8)	144 62.3 (56.1, 68.6)	132 60.8 (54.3, 67.3)
± 1.00 D	1 0.4 (0.0, 1.2)	178 70.9 (65.3, 76.5)	215 86.7 (82.5, 90.9)	217 87.1 (83.0, 91.3)	187 81.0 (75.9, 86.0)	166 76.5 (70.9, 82.1)
± 2.00 D	59 23.4 (18.2, 28.6)	231 92.0 (88.7, 95.4)	242 97.6 (95.7, 99.5)	244 98.0 (96.2, 99.7)	226 97.8 (96.0, 99.7)	210 96.8 (94.4, 99.1)
Total	252 100	251 100	248 100	249 100	231 100	217 100
Overcorrected			(Myopic)			
< -1.00 D		65 25.9 (20.5, 31.3)	21 8.5 (5.0, 11.9)	4 1.6 (0.0, 3.2)	3 1.3 (0.0, 2.8)	4 1.8 (0.1, 3.6)
< -2.00 D		18 7.2 (4.0, 10.4)	2 0.8 (0.0, 1.9)	0 0.0 (0.0, 6.2)	0 0.0 (0.0, 6.4)	0 0.0 (0.0, 6.7)
Undercorrected			(Hyperopic)			
> +1.00 D		8 3.2 (1.0, 5.4)	12 4.8 (2.2, 7.5)	28 11.2 (7.3, 15.2)	41 17.7 (12.8, 22.7)	47 21.7 (16.2, 27.1)
> +2.00 D		2 0.8 (0.0, 1.9)	4 1.6 (0.0, 3.2)	5 2.0 (0.3, 3.8)	5 2.2 (0.3, 4.0)	7 3.2 (0.9, 5.6)

d. Safety Outcomes

(1) Loss of Best Spectacle Corrected Visual Acuity (BSCVA)

BSCVA was not reduced to clinically significant levels beyond the 1-month visit.

Table 12
Change in BSCVA Over Time
(All Eyes, N=276)

	1 Month (n=275) n % (95% CI)	3 Months (n=272) n % (95% CI)	6 Months (n=272) n % (95% CI)	9 Months (n=254) n % (95% CI)	12 Months (n=237) n % (95% CI)
Decrease > 2 Lines	22 8.0 (4.8, 11.2)	5 1.8 (0.2, 3.4)	4 1.5 (0.0, 2.9)	0 0.0 (0.0, 6.1)	0 0.0 (0.0, 6.4)
Decrease > 1 to ≤ 2 Lines	30* 10.9 (7.2, 14.6)	25* 9.2 (5.8, 12.6)	14* 5.1 (2.5, 7.8)	19* 7.5 (4.2, 10.7)	12* 5.1 (2.3, 7.9)
Decrease > 0 to ≤ 1 Line	127 46.2 (40.3, 52.1)	101 37.1 (31.4, 42.9)	97 35.7 (30.0, 41.4)	68 26.8 (21.3, 32.2)	64 27.0 (21.4, 32.7)
No Change	51 18.5 (14.0, 23.1)	80 29.4 (24.0, 34.8)	66 24.3 (19.2, 29.4)	68 26.8 (21.3, 32.2)	81 34.2 (28.1, 40.2)
Increase >0 to ≤ 1 Line	29 10.5 (6.9, 14.2)	55 20.2 (15.4, 25.0)	82 30.1 (24.7, 35.6)	89 35.0 (29.2, 40.9)	70 29.5 (23.7, 35.3)
Increase > 1 to ≤ 2 Lines	1 0.4 (0.0, 1.1)	3 1.1 (0.0, 2.3)	7 2.6 (0.7, 4.5)	7 2.8 (0.7, 4.8)	9 3.8 (1.4, 6.2)
Increase > 2 Lines	0 0.0 (0.0, 5.9)	0 0.0 (0.0, 5.9)	0 0.0 (0.0, 5.9)	0 0.0 (0.0, 6.1)	0 0.0 (0.0, 6.4)
Not Reported	0 0.0	0 0.0	0 0.0	0 0.0	0 0.0
Total	275 100	272 100	272 100	254 100	237 100

*Loss of 2 lines of BSCVA: 1M=15, 3M=3, 6M=2, 9M=3, and 12M=1

(2) Adverse Events and Complications

Table 13 presents the summary of complications reported during this trial at the 1, 3, 6, 9 and 12-month visits.

Table 13 Complications (All Eyes, N=276)										
	1 Month (n=275)		3 Months (n=272)		6 Months (n=272)		9 Months (n=255)		12 Months (n=237)	
	n	%	n	%	n	%	n	%	n	%
Corneal edema between 1 week and 1 month after the procedure	1	0.4	0	0.0	0	0.0	0	0.0	0	0.0
Peripheral corneal epithelial defect at 1 month or later	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Recurrent corneal erosion at 1 month or later	0	0.0	1	0.4	0	0.0	0	0.0	0	0.0
Foreign body sensation at 1 month or later	0	0.0	1*	0.4	0	0.0	1	0.4	1	0.4
Pain at 1 month or later	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Ghost/double images in the operative eye	0	0.0	0	0.0	2	0.7	2	0.8	0	0.0

*This eye (#212003) reported a foreign body sensation at 3 months that was diagnosed initially as viral keratoconjunctivitis and later developed dendritiform disease consistent with herpes simplex keratitis. This eye was treated with topical antiviral medications and resolution occurred without sequelae within 2 weeks.

Table 14 presents the summary of adverse events reported during this trial at the 1, 3, 6, 9 and 12-month visits.

Table 14 Summary of Adverse Events (All Eyes, N=276)										
	1 Month (n=275)		3 Months (n=272)		6 Months (n=272)		9 Months (n=255)		12 Months (n=237)	
	n	%	n	%	n	%	n	%	n	%
Corneal Infiltrate/Ulcer	3*	1.1	0	0.0	0	0.0	0	0.0	0	0.0
Persistent Epithelial Defect at 1 month or later	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Uncontrolled IOP >5mm Hg or any reading above 25 mm Hg	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Late onset of haze beyond 6 months with loss of 2 lines or more of BSCVA	n/a		n/a		0	0.0	0	0.0	0^	0.0
Decrease in BSCVA of > 10 letter not due to irregular astigmatism as shown by hard contact lens refraction, at 6 months or later	n/a		n/a		0	0.0	0	0.0	0	0.0
Retinal Detachment	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Retinal Vascular Accidents	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

*Three eyes developed corneal infiltrates that were associated with the immediate post-operative period with a contact lens in place and all resolved without clinically significant sequelae.
^While there was 1 eye that had a 2 line loss of BSCVA at the 12 month visit, this was not considered an adverse event because it was noted to resolve after discontinuation of serzone medication.

e. Patient Survey

Table 15 reflects the responses to a patient questionnaire on a scale of 1 (poor) to 5 (excellent). Responses at 6 and 12 months were compared to the pre-operative responses. The results presented reflect changes in response from baseline.

Table 15
Patient Symptoms: Comparison of Vision After Surgery
(All Eyes with a Pre-Operative Sphere ≤ 5.00 and Questionnaire, N=206)

	6 Months (N=203)				12 Months (N=180)			
	Improve (+ ≥ 2)	No Change (0 ± 1)	Worsen (- ≥ 2)	NR	Improve (+≥ 2)	No Change (0 ± 1)	Worsen (- ≥ 2)	NR
	n %	n %	n %	n	n %	n %	n %	n
Sharpness and Clarity	39 19.2	157 77.3	7 3.4	0	34 18.9	135 75.0	11 6.1	0
Consistency of Vision	68 33.5	131 64.5	4 2.0	0	54 30.0	123 68.3	3 1.7	0
Sustained Close Work	26 12.9	162 80.6	13 6.5	2	23 12.8	137 76.5	19 10.6	1
Daylight Driving	55 27.4	140 69.7	6 3.0	2	56 31.3	114 63.7	9 5.0	1
Night Driving	63 31.2	133 65.8	6 3.0	1	57 32.0	115 64.6	6 3.4	2
Night Vision with Glare	74 36.8	122 60.7	5 2.5	2	62 34.8	109 61.2	7 3.9	2
Reading in Dim Light	36 17.9	157 78.1	8 4.0	2	28 15.7	134 75.3	16 9.0	1
General Vision in Dim Light	17 8.5	165 82.9	17 8.5	4	18 10.1	135 75.8	25 14.0	2
Overall Visual Comfort	178 88.6	23 11.4	0 0.0	2	148 82.7	31 17.3	0 0.0	1

f. Retreatments

Eyes were eligible for retreatments no sooner than 1 month after the primary procedure and must have had a UCVA of 20/32 or worse with concomitant refractive error and no significant loss of BSCVA. Two eyes (0.7%) were retreated during the course of the study. Although these two eyes presented no major safety concerns, there are not enough data to form any definitive conclusions regarding retreatment outcomes with this procedure.

g. Conclusions

The key safety and effectiveness criteria are summarized in Tables 16 and 17.

Table 16
Summary of Key Safety and Effectiveness Variables Over Time

Criteria	1 Month n/N, % (%CI)	3 Months n/N, % (%CI)	6 Months n/N, % (%CI)	9 Months n/N, % (%CI)	12 Months n/N, % (%CI)
[illegible]					
N=191* **	N=191	N=188	N=190	N=178	N=167
UCVA 20/20 or better	30 15.7 (10.5, 20.9)	85 45.2 (38.1, 52.3)	114 60.6 (53.0, 67.1)	109 61.2 (54.1, 68.4)	98 58.7 (51.2, 66.2)
UCVA 20/40 or better	136 71.2 (64.8, 77.6)	171 91.0 (86.9, 95.1)	187 98.4 (96.6, 100)	174 97.8 (95.6, 99.9)	163 97.6 (95.3, 99.9)
N=234* ***	N=233	N=230	N=231	N=218	N=205
UCVA 20/20 or better	31 13.3 (8.9, 17.7)	87 37.8 (31.6, 44.1)	116 50.2 (43.8, 56.7)	113 51.8 (45.2, 58.5)	100 48.8 (41.9, 55.6)
UCVA 20/40 or better	160 68.7 (62.7, 74.6))	205 89.1 (85.1, 93.2)	223 96.5 (94.2, 98.9)	208 95.4 (92.6, 98.2)	195 95.1 (92.2, 98.1)
N=252	N=251	N=248	N=249	N=231	N=217
MRSE ± 0.50 D	84 33.5 (27.6, 39.3)	157 63.3 (57.3, 69.3)	159 63.9 (57.9, 69.8)	144 62.3 (56.1, 68.6)	132 60.8 (54.3, 67.3)
MRSE ± 1.00 D	178 70.9 (65.3, 76.5)	215 86.7 (82.5, 90.9)	217 87.1 (83.0, 91.3)	187 81.0 (75.9, 86.0)	166 76.5 (70.9, 82.1)
MRSE ± 2.00 D	231 92.0 (88.7, 95.4)	242 97.6 (95.7, 99.5)	244 98.0 (96.2, 99.7)	226 97.8 (96.0, 99.7)	210 96.8 (94.4, 99.1)
[illegible]					
N=207♦		N=207	N=207	N=207	N=207
Change ≤ 1.00 D		167 80.7 (75.3, 86.1)	176 85.0 (80.2, 89.9)	196 94.7 (91.6, 97.7)	198 95.7 (92.9, 98.4)
Mean		0.53	0.44	0.19	0.11
[illegible]					
N=275	N=275	N=272	N=272	N=254	N=237
Loss of ≥ 2 lines BSCVA	37 13.5 (9.4, 17.5)	8 2.9 (0.9, 4.9)	6 2.2 (0.5, 4.0)	3 1.2 (0.0, 2.5)	1 0.4 (0.0, 1.2)
Loss of > 2 lines BSCVA	22 8.0 (4.8, 11.2)	5 1.8 (0.2, 3.4)	4 1.5 (0.0, 2.9)	0 0.0 (0.0, 6.1)	0 0.0 (0.0, 6.4)
BSCVA worse than 20/40	6 2.2 (0.5, 3.9)	1 0.4 (0.0, 1.1)	2 0.7 (0.0, 1.8)	2 0.8 (0.0, 1.9)	1 0.4 (0.0, 1.2)
Increase > 2 D Cylinder	0 0.0 (0.0, 5.9)	0 0.0 (0.0, 5.9)	0 0.0 (0.0, 5.9)	0 0.0 (0.0, 61.)	0 0.0 (0.0, 6.4)
N=220**	N=219	N=216	N=217	N=201	N=188
BSCVA worse than 20/40	1 0.5 (0.0, 1.3)	0 0.0 (0.0, 6.7)	0 0.0 (0.0, 6.7)	0 0.0 (0.0, 6.9)	0 0.0 (0.0, 7.1)

*Excluding eyes intentionally overcorrected for monovision.
**BSCVA 20/20 or better pre-operatively.
***Includes eyes with a pre-operative BSCVA worse than 20/20.
♦Includes only eyes with all visits.

Table 17
Summary of Key Safety and Effectiveness Variables Stratified by Pre-Op MRSE
12 Months

Criteria	1 to 1.99 n/N, % (%CI)	2 to 2.99 n/N, % (%CI)	3 to 3.99 n/N, % (%CI)	4 to 4.99 n/N, % (%CI)	5 to 5.99 n/N, % (%CI)	6 to 6.99 n/N, % (%CI)	7 to 7.99 n/N, % (%CI)	Cum Total n/N, % (%CI)
N=167	N=37	N=53	N=37	N=26	N=12	N=2		N=167
UCVA 20/40 or better * ***	36 97.3 (92.1, 100)	52 98.1 (94.5, 100)	35 94.6 (87.3, 100)	26 100 (80.8, 100)	12 100 (71.7, 100)	2 100 (30.7, 100)		163 97.6 (95.3, 99.9)
N=205	N=40	N=59	N=48	N=34	N=20	N=4		N=205
UCVA 20/40 or better* **	39 97.5 (92.7, 100)	57 96.6 (92.0, 100)	44 91.7 (83.8, 99.5)	33 97.1 (91.4, 100)	18 90.0 (76.9, 100)	4 100 (51.0, 100)		195 95.1 (92.2, 98.1)
N=217	N=41	N=63	N=53	N=34	N=22	N=4		N=217
MRSE ± 0.50 D	32 78.0 (65.4, 90.7)	40 63.5 (51.6, 75.4)	30 56.6 (43.3, 69.9)	18 52.9 (36.2, 69.7)	9 40.9 (20.4, 61.5)	3 75.0 (32.6, 100)		132 60.8 (54.3, 67.3)
MRSE ± 1.00 D	39 95.1 (88.5, 100)	52 82.5 (73.2, 91.9)	38 71.7 (59.6, 83.8)	24 70.6 (55.3, 85.9)	10 45.5 (24.6, 66.3)	3 75.0 (32.6, 100)		166 76.5 (70.9, 82.1)
N=237	N=41	N=63	N=53	N=34	N=28	N=12	N=6	N=237
Loss of ≥ 2 lines BSCVA	0 0.0 (0.0, 15.3)	0 0.0 (0.0, 12.3)	0 0.0 (0.0, 13.5)	0 0.0 (0.0, 16.8)	0 0.0 (0.0, 18.5)	0 0.0 (0.0, 28.3)	1 16.7 (0.0, 46.5)	1 0.4 (0.0, 1.2)
Loss of > 2 lines BSCVA	0 0.0 (0.0, 15.3)	0 0.0 (0.0, 12.3)	0 0.0 (0.0, 13.5)	0 0.0 (0.0, 16.8)	0 0.0 (0.0, 18.5)	0 0.0 (0.0, 28.3)	0 0.0 (0.0, 40.0)	0 0.0 (0.0, 6.4)
BSCVA worse than 20/40	0 0.0 (0.0, 15.3)	0 0.0 (0.0, 12.3)	1 1.9 (0.0, 5.5)	0 0.0 (0.0, 16.8)	0 0.0 (0.0, 18.5)	0 0.0 (0.0, 28.3)	0 0.0 (0.0, 40.0)	1 0.4 (0.0, 1.2)
N=188	N=38	N=57	N=41	N=26	N=17	N=6	N=3	N=188
BSCVA worse than 20/40***	0 0.0 (0.0, 15.9)	0 0.0 (0.0, 13.0)	0 0.0 (0.0, 15.3)	0 0.0 (0.0, 19.2)	0 0.0 (0.0, 23.8)	0 0.0 (0.0, 40.0)	0 0.0 (0.0, 56.6)	0 0.0 (0.0, 7.1)

*Excluding eyes intentionally overcorrected for monovision
**Includes eyes with a pre-operative BSCVA worse than 20/20.
***BSCVA 20/20 or better pre-operatively.

h. Device Failures

In one case a keyboard locked up and the system had to be rebooted to continue with the procedure. A service engineer inspected, calibrated, and tested full operation of the laser system to factory specifications. The keyboard assembly was replaced although the intermittent problem was not duplicated. No further action was required.

X. CONCLUSIONS DRAWN FROM THE CLINICAL STUDIES

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

XI. PANEL RECOMMENDATIONS

On May 11,2000, the Ophthalmic Devices Advisory Panel recommended that the premarket approval application for the VISX Excimer Laser for the PRK procedure in the treatment of hyperopia with astigmatism be considered approvable with conditions. The conditions recommended by the panel were to:

- modify the refractive ranges for approval;
- stratify effectiveness data (predictability/stability) by attempted correction presenting all statistically significant findings;
- add cautionary language regarding stability;
- where appropriate, state that there is no data on retreatment, pupil diameter or monovision;
- if appropriate, add labeling regarding epithelial healing, pain, photophobia, visual acuity recovery, spectacle wear (near and distance), visual function under dim illumination and presbyopia; and
- develop a separate patient information booklet for hyperopia with astigmatism.

XII. CDRH DECISION

Following the panel meeting on May 11, 2000, CDRH issued a major deficiency letter to VISX, Inc. on June 30, 2000 requesting full analysis of the updated 12-month cohort. In amendments received by FDA on July 17 and September 25, 2000, VISX submitted the required changes, clarification and information.

CDRH concurred with the Ophthalmic Devices Panel's recommendation. The applicant addressed all the labeling concerns raised by the Panel and FDA. CDRH issued an approval order on October 18, 2000.

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