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

I. GENERAL INFORMATION

Device Generic Name:	Ophthalmic Medical Laser System (193 nanometer wavelength)
Device Trade Name:	VISX STAR Excimer Laser System Models S2 and S3
Applicant's Name and Address:	VISX, Incorporated 3400 Central Expressway Santa Clara, CA 95051-0703
Date of Panel Recommendation:	None
Premarket Approval (PMA) Application Number:	P930016/S12
Date of Notice of Approval to Applicant:	April 27, 2001
Expedited Review:	Expedited review was granted on August 24, 2000 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. Expedited review status was withdrawn on January 10, 2001 because a legally marketed therapeutic modality became available for the intended patient population.

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), 7 (approved November 2, 1998), and 10 (approved October

18, 2000) 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, hyperopia (sphere only) of between +1.0 and +6.0 D spherical equivalent with no more than 1.0 D of refractive astigmatism, and 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. 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 (P930016 and S3), Docket # 99M-0293 (S5), Docket # 00M-1391 (S7), Docket # 01M-0015 (S10), and Docket # 00M-1447 (P990010) 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

The Laser in situ Keratomileusis (LASIK) 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 no more than 0.5 D (in both cylinder and sphere components) for at least one year prior to the date of preoperative-examination; and

- in patients 21 years of age or older in treatments for the reduction or elimination of naturally occurring hyperopia between +0.5 D and +5.0 D sphere at the spectacle plane with or without refractive astigmatism up to +3.0 D with a maximum manifest refraction spherical equivalent (MRSE) of +6.0 D.

III. CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

A. Contraindications:

LASIK surgery is contraindicated:

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

- In pregnant or nursing women.
- 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

A. Laser System

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 previously approved 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 LASIK 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.

B. Microkeratome

The LASIK procedure requires the use of a commercially available microkeratome that has been cleared for marketing via premarket notification. The device used in this study consists of a sterilization/storage tray which includes the shaper head, a left/right eye adapter, suction ring, suction handle, blade handling pin, and corneal reference marker. The instrument motor, tonometer, cleaning brush, disposable blades, power/suction supply unit with vacuum and motor footswitches and power cords are provided as separate components in an accessory stand and equipment suitcase which complete the system.

V. ALTERNATIVE PRACTICES AND PROCEDURES

Conventional methods in correcting farsightedness with astigmatism are: spectacles, contact lenses, PRK, 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 LASIK include: loss of best spectacle corrected visual acuity, worsening of patient complaints such as double vision, sensitivity to bright lights, increased difficulty with night vision, fluctuations in vision, increase in intraocular pressure, corneal haze, secondary surgical intervention, corneal infiltrate or ulcer, corneal epithelial defect, corneal edema, problems associated with the flap including a lost, misplaced or misaligned flap, retinal detachment, and retinal vascular accidents.

Please refer to the complete listing of adverse events and complications observed during the clinical study which are presented on pages 15-16 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

The sponsor performed a clinical study of the VISX STAR Excimer Laser System in the US under the auspices of an IDE G930017 Substudy B. The data from this study served as the basis for the approval decision. Specifically, safety and effectiveness outcomes at 3 months postoperative were assessed as stability is reached by that time. Outcomes at 6 months postoperatively were also evaluated for confirmation. The IDE study is described in detail as follows.

A. Study Objective

The overall reason for the LASIK procedure was defined by this treatment goal: to assess the ability of the VISX STAR Excimer Laser System to produce clinically acceptable results for the treatment of hyperopia with or without refractive astigmatism.

B. Study Design

This was a prospective, multi-center, open-label 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 VISX LASIK for Hyperopia with or without Refractive Astigmatism study was limited to:

- Male or female subjects of any race, and at least 21 years old at the time of the pre-operative examination.
- Operative eye(s) that required treatment of refractive hyperopia from +0.50 to +6.00 diopters sphere with or without refractive astigmatism $\leq$ +6.00 diopters as determined by manifest refraction (12.5 mm vertex distance).
- Eyes with a difference between the manifest and cycloplegic refractions (sphere or cylinder) of no more than 0.75 diopters and no more than 15 degrees (axis).
- Eyes where the planned treatment was not closer than 250 microns from the corneal endothelium based on pachymetric measurement and the maximal depth ablated as described by the VISX software added to flap thickness.
- Subjects who had a best spectacle corrected visual acuity of at least 20/40 in both eyes.
- Operative eye(s) with demonstrated refractive stability, confirmed by clinical records. Refractive stability was documented by a change of not more than 0.50 diopters (sphere and cylinder) at an exam at least 12 months prior to the baseline examination. The astigmatic axis may not have varied by more than 15 degrees.
- Contact lens wearers who removed soft lenses at least 1 week prior and rigid (Gas permeable and PMMA) lenses at least 2 weeks prior to baseline measurements. At that baseline exam manual keratometry, cycloplegic and manifest refractions, as well as corneal topography were obtained on both eyes. If the investigator determined that the topography was within normal limits, surgery was scheduled at least one week after the initial exam, with no contact lens wear permitted prior to the surgery. If on the day of scheduled surgery, for the operative eye, central keratometry readings and manifest refraction spherical equivalents did not differ significantly from the initial exam measurements (by more than 0.50 diopter), surgery proceeded. If the refractive change exceeded this criterion, the surgery was rescheduled after refractive stability was achieved.
- Subjects were willing and capable of returning for follow-up examinations for the duration of the study.

Patients were not permitted to enroll in the study if they met any of the following exclusion criteria:

- Subjects with a fellow eye that did not meet all inclusion criteria.
- Female subjects who were pregnant, breast-feeding or intended to become pregnant over the course of the study.
- Subjects who used concurrent topical or systemic medications which may impair healing, including but not limited to: antimetabolites, isotretinoin (Accutane®) within 6 months of treatment, amiodarone hydrochloride (Cordarone®) within 12 months of treatment, and sumatripin (Imitrex®) within 1 month of treatment.
  NOTE: The use of topical or systemic corticosteroids, whether chronic or acute, was deemed to adversely affect healing and subjects using such medication specifically excluded from eligibility.
- Subjects with a history of any of the following medical conditions, or any other condition that could affect wound healing: collagen vascular disease, autoimmune disease, immunodeficiency diseases, ocular herpes zoster or simplex, endocrine disorders (including, but not limited to active thyroid disorders and diabetes), lupus, and rheumatoid arthritis.
  NOTE: The presence of diabetes (either type 1 or 2), regardless of disease duration, severity or control, specifically excluded subjects from eligibility.
- Subjects with a history of prior intraocular or corneal surgery (including cataract extraction), active ophthalmic disease or abnormality (including, but not limited to, blepharitis, recurrent corneal erosion, dry eye syndrome, neovascularization > 1mm from limbus), clinically significant lens opacity, clinical evidence of trauma (including scarring), or with evidence of glaucoma or propensity for narrow angle glaucoma as determined by gonioscopic examination in either eye.
  NOTE: This included any subject with open angle glaucoma, regardless of medication regimen or control. Additionally, any subject with an IOP greater than 21 mm Hg at baseline was specifically excluded from eligibility.
- Subjects with evidence of keratoconus, corneal irregularity, or abnormal videokeratography in either eye.
- Subjects with known sensitivity or inappropriate responsiveness to any of the medications used in the post-operative course.
- Subjects who were participating in any other clinical trial.

D. Study Plan, Patient Assessments, and Efficacy Criteria

All subjects were expected to return for follow-up examinations at 1 and 7 days, and 1, 3, and 6 months postoperatively.

Subjects were permitted to have second eyes (fellow eyes) treated at the same time as the first eye (primary eyes). In addition, subjects were eligible for enhancement no sooner than 1 month after treatment. To qualify for enhancement, eyes must have had a UCVA of 20/32 (or worse) with no significant loss of BSCVA (2 lines or less) with concomitant refractive error. Subjects were eligible for retreatment no sooner than 1 month after surgery. To qualify for retreatment, subjects must have had a BSCVA loss of 2 or more lines and a UCVA of equal to or worse than 20/32 due to decentered ablation, central island, irregular

astigmatism or other remediable corneal abnormality. Videokeratography shall be used to document the status of the cornea in advance of retreatment.

Preoperatively, the subject's medical and ocular histories were recorded. Immediately postoperative data were collected. The objective parameters measured during the study were:

At 1 and 3 months - distance visual acuity (uncorrected and best spectacle corrected), manifest refraction, keratometry, videokeratography, applanation tonometry, and slit lamp examination. A subjective questionnaire was administered to each patient at the 3-month examination. Adverse events, complications, medications and other clinical findings were noted as appropriate.

At 6 months - distance visual acuity (uncorrected and best spectacle corrected), manifest refraction, keratometry, corneal videokeratography, applanation tonometry, slit lamp examination, specular microscopy, and a subjective questionnaire. After cycloplegia, a refraction, dilated media and fundoscopic examination were performed. Adverse events, complications, medications, and other clinical findings were noted as appropriate.

The primary efficacy variables for this study were: improvement of distance UCVA and predictability of manifest refraction spherical equivalent (MRSE).]

E. Study Period, Investigational Sites, and Demographic Data

1. Study period and investigational sites

   Eighty nine subjects were treated between 26 Aug 99 and 6 Dec 99. The database for this PMA supplement reflected data collected through 2 Jun 99 and included 169 eyes: 89 first eyes and 80 second eyes. There were 6 investigational sites.

2. Demographics

   The demographics of this study are very typical for a contemporary refractive surgery trial performed in the US. Of the 169 treated eyes, 49.7% (84/169) were from male subjects and 50.3% (85/169) from female subjects. Furthermore, 96.4% (163/169) were from Caucasians, 1.2% (2/169) were from Blacks, and 2.4% (4/169) were of other races. The right eye was treated in 48.5% (82/169) cases and the left eye was treated in 51.5% (87/169) cases. The mean age of the subjects treated was 50.6 years with a range from 23 to 79. Preoperative patient characteristics that were found to associate with outcomes are discussed in section 2f.

Table 1 Demographic Information (N=169)			
Category	**CLASSIFICATION**	**n**	*% Eyes*
Gender	Male	84	49.7
	Female	85	50.3
Race	Caucasian	163	96.4
	Asian/Pacific Islander	0	0
	African American	2	1.2
	American Indian/Aleut Eskimo	2	1.2
	Other: Hispanic	2	1.2
Eyes	Right	82	48.5
	Left	87	51.5
CL History	None	109	64.5
	Soft	49	29.0
	RGP/PMMA	11	6.5
Age (in Years)	Average	50.6	
	Standard Deviation	10.7	
	Minimum	23	
	Maximum	79	

F. Data Analysis and Results

1. Preoperative characteristics

Table 2 contains a summary of the preoperative refractive errors of the entire cohort. Note that evaluation of effectiveness was voluntarily truncated to a subset of eyes with a spherical component of treatment that did not exceed 5 diopters.

Table 2 SAFETY COHORT Stratified by Treatment Sphere and Cylinder (N=169)																
	Cylinder															
	0 D		**>0 to ≤ 1 D**		**>1 to ≤ 2 D**		**>2 to ≤ 3 D**		**>3 to ≤ 4 D**		**>4 to ≤ 5D**		**>5 to ≤ 6D**		**Total**	
Tx Sphere	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
>0 to ≤ 1 D	0	0.0	4	5.7	5	11.6	5	21.7	4	36.4	0	0.0	1	25.0	19	11.2
>1 to ≤ 2 D	5	33.3	25	35.7	6	14.0	4	17.4	1	9.1	0	0.0	3	75.0	44	26.0
>2 to ≤ 3 D	4	26.7	10	14.3	5	11.6	3^	13.0	0	0.0	2	66.7	0	0.0	24	14.2
>3 to ≤ 4 D	5♦	33.3	16	22.9	11	25.6	2	8.7	4	36.4	1	33.3	0	0.0	39	23.1
>4 to ≤ 5 D	1	6.7	10	14.3	12	27.9	7	30.4	1	9.1	0	0.0	0	0.0	31	18.3
>5 to ≤ 6 D	0	0.0	5	7.1	4	9.3	2	8.7	1	9.1	0	0.0	0	0.0	12	7.1
Total	15	8.9	70	41.4	43	25.4	23	13.6	11	6.5	3	1.8	4	2.4	169	100

^1 eye (45162) is included in the safety cohort but was excluded from the effectiveness cohort due to lack of refractive stability pre-operatively.

♦1 eye (43102) had pre-operative cylinder (0.25) that was not treated. Table 3 of the original submission (S12) presented these data stratified by pre-operative refractive error; therefore, this eye was reflected in the >0 to ≤ 1 DC column accounting for the difference in 'n' from 14 to 15.

2. Post-operative Characteristics and Results

a. Patient Accountability

Accountability was excellent, exceeding 96% at all visits and yielding no fewer than 93% of eyes available for analysis. This surpasses the 80% benchmark. The following cohorts were used for analysis:

- Safety—all eyes (n=169)
- Effectiveness—eyes with a spherical treatment that did not exceed 5 diopters (n=156)
- Stability—subset of effectiveness cohort, eyes with visits at 1, 3, and 6 months (n=140)

Table 3
Subject Accountability: All Eyes
(N=169*)

	1 Month		3 Months		6 Months	
	n	%	n	%	n	%
Available for Analysis	169	100	163	96.4	158	93.5
Discontinued	0	0.0	0	0.0	4	2.4
Missed Visit	0	0.0	6	3.6	2	1.2
Not yet eligible	0	0.0	0	0.0	5	3.0
Lost to Follow-Up	0	0.0	0	0.0	0	0.0
% Accountability: Available for Analysis (enrolled – discontinued – not yet eligible)	100% 169/169		96.4% 163/169		98.8% 158/160	

*Two eyes are excluded from analyses because treatment departed significantly from protocol.

b. Stability of Outcome

In the 3-6 months window, greater than 95% of eyes experienced a change of MRSE not exceeding ± 1.0D. Furthermore, the mean of the pair-difference of MRSE progressively decreased over time, and reached a change of about 0.07 D in the 1-3 months window (table 4). The changes in the 3-6 months window for the cohort were smaller (0.06 D) than those observed in the previous time window; thus, stability was demonstrated by 3 months postoperative. The assessment of the stability was therefore performed using the outcomes of the 140 eyes evaluable at 3 months.

Table 4
Refractive Stability
(Eyes with 1, 3, and 6-month visits, N=140)

Change in MRSE	1 and 3 Months n % 95% CI	3 and 6 Months n % 95% CI
≤ 1.00 D	137 97.9	134 95.7
95% CI for %	(95.5, 100)	(92.4, 99.1)
MRSE (D)		
Mean	0.07	0.06
SD	0.46	0.45
95% CI for Mean	(0.14, -0.01)	(0.14, -0.01)

c. Effectiveness Outcomes

The analysis of effectiveness was based on the 150 eyes evaluable at the 3-month stability time point. Key efficacy outcomes over the course of the study and at the point of stability stratified by diopter of MRSE are presented in tables 5 and 6.

Table 5
Summary of Key Effectiveness Variables Over Time

CRITERIA	1 Month n % (95% CI)	3 Months n % (95% CI)	6 Months n % (95% CI)
N=141*	n=141	n=135	n=133
UCVA 20/20 or better	61 43.3 (35.1, 51.4)	62 45.9 (37.5, 54.3)	64 48.1 (39.6, 56.6)
UCVA 20/40 or better	128 90.8 (86.0, 95.6)	131 97.0 (94.2, 99.9)	129 97.0 (94.1, 99.9)
N=156	n=156	n=150	n=144
MRSE ± 0.50 D	113 72.4 (65.4, 79.4)	106 70.7 (63.4, 78.0)	110 76.4 (69.5, 83.3)
MRSE ± 1.00 D	144 92.3 (88.1, 96.5)	142 94.7 (91.1, 98.3)	131 91.0 (86.3, 95.7)

*Excluding eyes intentionally overcorrected for monovision

Table 6
Summary of Key Effectiveness Variables at Stability Endpoint of 3 Months (Stratified by Treatment MRSE)

CRITERIA	Up to 2.00 n/N, % (%CI)	>2 to 3.00 n/N, % (%CI)	>3 to 4.00 n/N, % (%CI)	>4 to 5.00 n/N, % (%CI)	>5 to 6.00 n/N, % (%CI)	>6 to 7.00 n/N, % (%CI)	>7 to 8.00 n/N, % (%CI)	Cum Total n/N, % (%CI)
N=113	n=29	n=31	n=21	n=15	n=17	n=0		N=113
UCVA 20/20 or better * ***	18 62.1 (44.4, 79.7)	20 64.5 (47.7, 83.4)	11 52.4 (31.0, 73.7)	8 53.3 (28.1, 78.6)	4 23.5 (3.4, 43.7)	n/a		61 54.0 (44.8, 63.2)
UCVA 20/40 or better * ***	29 100 (81.8, 100)	31 100 (82.4, 100)	20 95.2 (86.1, 100)	15 100 (74.7, 100)	17 100 (76.2, 100)	n/a		112 99.1 (97.4, 100)
N=150	n=30	n=39	n=34	n=20	n=26	n=1		N=150
MRSE ± 0.50 D	23 76.7 (61.5, 91.8)	31 79.5 (66.8, 92.2)	22 64.7 (48.6, 80.8)	13 65.0 (44.1, 85.9)	16 61.5 (42.8, 80.2)	1 100 (2.0, 100)		106 70.7 (63.4, 78.0)
MRSE ± 1.00 D	29 96.7 (90.2, 100)	38 97.4 (92.5, 100	31 91.2 (81.6, 100)	18 90.0 (76.9, 100)	25 96.2 (88.8, 100)	1 100 (2.0, 100)		142 94.7 (91.1, 98.3)

*Excluding eyes intentionally overcorrected for monovision
***BSCVA 20/20 or better pre-operatively

i. Correction of Cylindrical Component (scalar and vector analyses)

The sponsor utilized the VectorInspector™ method for calculating vectoral change. This method was described in the PMA Supplement. Table 7 provides an analysis of scalar astigmatism - the amount of correction achieved in terms of its absolute reduction. The Ophthalmic Devices Panel (the Panel), in the January 14, 1997 meeting in which the Panel assessed outcomes from a myopic astigmatic treatment, provided FDA with some guidance as to the acceptable effectiveness rates. The Panel considered 64% as an acceptable mean reduction in absolute cylinder at the point of stability. Therefore, the 66.7% reduction at 3 months achieved with this device is acceptable.

Table 7
Cylinder Correction Efficacy Stratified by Pre-Operative Cylinder
(N=136)

	3 Months	
Pre-Operative Cylinder	**% Reduction of Absolute Cylinder (Not a Vector)**	
≤ 1.0 D	29.2%	(0.5/0.7)
> 1.0 to ≤ 2.0 D	74.0%	(0.4/1.6)
> 2.0 to ≤ 3.0 D	76.4%	(0.6/2.6)
> 3.0 to ≤ 4.0 D	70.1%	(1.1/3.5)
> 4.0 to ≤ 5.0 D	100%	(0.0/5.0)
> 5.0 to ≤ 6.0 D	93.1%	(0.4/5.4)
Total	66.7%	(0.5/1.5)

Looking at intended versus achieved vector magnitude cylinder, the Intended Refractive Correction ("IRC") had a mean of –1.7 D with a median of –1.3 (range –6.8 D to 0.0 D). The Surgically Induced Refractive Correction ("SIRC") had a mean of –1.8 D with a median of –1.5 D (range (–7.2 D to -0.1 D). The vector magnitude ratio (SIRC/IRC) was 106% at 3 months. The Panel has found 82.5% acceptable for correction efficacy (SIRC/IRC) at stability. The result achieved is certainly within this range and is therefore acceptable.

Table 8 Cylinder Correction Efficacy Stratified by Pre-Operative Cylinder (N=136)		
	3 Months	
Pre-Operative Cylinder	Achieved vs Intended Vector Magnitude Ratio (SIRC/IRC)	
≤ 1.0 D	129%	(-0.9/-0.7)
> 1.0 to ≤ 2.0 D	106%	(-1.9/-1.8)
> 2.0 to ≤ 3.0 D	100%	(-2.8/-2.8)
> 3.0 to ≤ 4.0 D	100%	(-3.9/-3.9)
> 4.0 to ≤ 5.0 D	100%	(-5.7/-5.7)
> 5.0 to ≤ 6.0 D	100%	(-6.0/-6.0)
Total	106%	(-1.8/-1.7)

ii. Correction of Spherical Component

At 3 months, 74.0% of eyes were within ±0.50 D of the intended spherical correction and 93.3% were within ±1.00 D. Although there are no specific benchmarks for only the spherical component, these results are within the benchmarks for MRSE and are therefore acceptable.

d. Safety Outcomes

The analysis of safety was based on the 163 eyes that have had the 3-month exam. The key safety outcomes for this study are presented in tables 9 and 10, with all the adverse reactions reported in tables 11a, 11b and 12. Overall, the device was deemed reasonably safe.

Table 9 Summary of Key Safety Variables Over Time			
CRITERIA	1 Month n % (95% CI)	3 Months n % (95% CI)	6 Months n % (95% CI)
N=169	n=169	n=163	n=156
Loss of ≥ 2 lines BSCVA	8 4.7 (1.5, 7.9)	6 3.7 (0.8, 6.6)	6 3.8 (0.8, 6.8)
Loss of > 2 lines BSCVA	2 1.2 (0.0, 2.8)	0 0.0 (0.0, 7.7)	0 0.0 (0.0, 7.8)
BSCVA worse than 20/40	3 1.8 (0.0, 3.8)	2 1.2 (0.0, 2.9)	1 0.6 (0.0, 1.9)
N=134**	n=134	n=132	n=124
BSCVA worse than 20/40	0 0.0 (0.0, 8.5)	0 0.0 (0.0, 8.5)	0 0.0 (0.0, 8.8)

**BSCVA 20/20 or better pre-operatively.

Table 10
Summary of Key Safety Variables at Stability Endpoint of 3 Months (Stratified by Treatment MRSE)

CRITERIA	Up to 2.00 n/N, % (%CI)	>2 to 3.00 n/N, % (%CI)	>3 to 4.00 n/N, % (%CI)	>4 to 5.00 n/N, % (%CI)	>5 to 6.00 n/N, % (%CI)	>6 to 7.00 n/N, % (%CI)	>7 to 8.00 n/N, % (%CI)	Cum Total n/N, % (%CI)
N=163	n=30	n=39	n=34	n=21	n=29	n=7	n=3	N=163
Loss of ≥ 2 lines BSCVA	0 0.0 (0.0, 17.9)	0 0.0 (0.0, 15.7)	0 0.0 (0.0, 16.8)	3 14.3 (0.0, 29.3)	2 6.9 (0.0, 16.1)	0 0.0 (0.0, 37.0)	1 33.3 (0.0, 86.7)	6 3.7 (0.8, 6.6)
Loss of > 2 lines BSCVA	0 0.0 (0.0, 17.9)	0 0.0 (0.0, 15.7)	0 0.0 (0.0, 16.8)	0 0.0 (0.0, 21.4)	0 0.0 (0.0, 18.2)	0 0.0 (0.0, 37.0)	0 0.0 (0.0, 56.6)	0 0.0 (0.0, 7.7)
Increase > 2 D cylinder	0 0.0 (0.0, 17.9)	0 0.0 (0.0, 15.7)	0 0.0 (0.0, 16.8)	0 0.0 (0.0, 21.4)	0 0.0 (0.0, 18.2)	0 0.0 (0.0, 37.0)	0 0.0 (0.0, 56.6)	0 0.0 (0.0, 7.7)
N=132	n=30	n=32	n=28	n=16	n=21	n=3	n=2	N=132
BSCVA worse than 20/40***	0 0.0 (0.0, 17.9)	0 0.0 (0.0, 17.3)	0 0.0 (0.0, 18.5)	0 0.0 (0.0, 24.5)	0 0.0 (0.0, 21.4)	0 0.0 (0.0, 56.6)	0 0.0 (0.0, 69.3)	0 0.0 (0.0, 8.5)

***BSCVA 20/20 or better pre-operatively

Table 11a presents a summary of adverse events. The benchmark for each adverse event is a rate of less than 1 % per event.

Table 11a
Summary of Adverse Events
(All Eyes, N=169)

	1 Month (n=169)		3 Months (n=163)		6 Months (n=158)	
	n	%	n	%	n	%
Corneal Infiltrate/Ulcer	0^	0.0	0	0.0	0	0.0
Corneal epithelial defect involving the keratectomy at 1 month or later	0	0.0	0	0.0	0	0.0
Corneal edema at 1 month or later (specify "flap" or "bed" or both)	0	0.0	0	0.0	0	0.0
Epithelium in the interface with loss of 2 or more lines of BSCVA	0	0.0	0	0.0	0	0.0
Lost, misplaced or misaligned flap	0	0.0	0	0.0	0	0.0
Melting of the flap (LASIK only)	0	0.0	0	0.0	0	0.0
Uncontrolled IOP >10 mm Hg	0	0.0	0	0.0	0	0.0
Any reading > 25 mm Hg	0	0.0	0	0.0	0	0.0
Late onset of haze beyond 6 months with loss of 2 lines (10 letters) or more BSCVA					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					0	0.0
Retinal Detachment	0	0.0	0	0.0	0	0.0
Retinal Vascular Accidents	0	0.0	0	0.0	0	0.0

^two cases of ILK (intrastromal lamellar keratitis) were reported in the immediate post-operative period. Both cases resolved without sequelae within 1 week of onset.

Table 11b presents a summary of complications reported during the course of the trial.

Table 11b
Summary of Complications
(All Eyes, N=169)

	1 Month (n=169)		3 Months (n=163)		6 Months (n=158)	
	n	%	n	%	n	%
Corneal edema between 1 week and 1 month after the procedure	0	0.0	0	0.0	0	0.0
Peripheral corneal epithelial defect at 1 month or later	1	0.6	0	0.0	0	0.0
Epithelium in the interface	5	3.0	2	1.2	0	0.0
Foreign body sensation at 1 month or later	0	0.0	0	0.0	0	0.0
Pain at 1 month or later	0	0.0	0	0.0	0	0.0
Ghost/double images in the operative eye	0	0.0	3	1.8	0	0.0
Flap not size and shape as intended or microkeratome stopped in mid-cut	0	0.0	0	0.0	0	0.0

In addition to Adverse Events and Complications that met defined criteria, all other adverse reactions reported are presented in Table 12. Events observed at the 3 months stability time point and at the two adjacent visits are included for comparison. In general, the rate of an adverse reaction tends to be highest immediately postoperative and tapers down over time.

Table 12
Other Adverse Reactions at 1, 3, and 6 months

Adverse Reaction	1 months N=169		3 months N=163		6 months N=158	
Blurry vision	2	1.2%	0	0.0%	0	0.0%
Conjunctivitis	2	1.2%	2	1.2%	0	0.0%
Epithelial irregularity	0	0.0%	1	0.6%	0	0.0%
Glare	0	0.0%	0	0.0%	2	1.3%
Interface debris	0	0.0%	1	0.6%	0	0.0%
Map dot dystrophy	0	0.0%	2	1.3%	0	0.0%
SPK	5	2.9%	0	0.0%	0	0.0%
Thickened flap edge	0	0.0%	1	0.6%	0	0.0%

e. Retreatment

1. Procedures performed to achieve resolution of an adverse event:

   None

2. Procedures performed to improve refractive outcome:

   Four eyes underwent LASIK enhancement (4/169 or 2.4%) during the study, mostly due to initial over-correction. Post-operatively, 2 of these eyes had significant residual refractive error and the other 2 had no residual refractive error (plano).

   The small number of enhancements is insufficient to yield clinically useful information, however caution should be taken to assure refractive stability before performing additional procedures.

Table 13
Summary of Key Safety and Effectiveness Variables Over Time
All Eyes (N=169)

CRITERIA	1 Month n % (95% CI)	3 Months n % (95% CI)	6 Months n % (95% CI)
EFFECTIVENESS VARIABLES			
N=115* ***	n=115	n=113	n=108
UCVA 20/20 or better	58 50.4 (41.3, 59.6)	61 54.0 (44.8, 63.2)	61 56.5 (47.1, 65.8)
UCVA 20/40 or better	108 93.9 (89.5, 98.3)	112 99.1 (97.4, 100)	108 100 (90.6, 100)
N=156	n=156	n=150	n=144
MRSE ± 0.50 D	113 72.4 (65.4, 79.4)	106 70.7 (63.4, 78.0)	110 76.4 (69.5, 83.3)
MRSE ± 1.00 D	144 92.3 (88.1, 96.5)	142 94.7 (91.1, 98.3)	131 91.0 (86.3, 95.7)
MRSE ± 2.00 D	156 100 (92.2, 100)	148 98.7 (96.8, 100)	143 99.3 (97.9, 100)
SAFETY VARIABLES			
N=169	n=169	n=163	n=156
Loss of ≥ 2 lines BSCVA	8 4.7 (1.5, 7.9)	6 3.7 (0.8, 6.6)	6 3.8 (0.8, 6.8)
Loss of > 2 lines BSCVA	2 1.2 (0.0, 2.8)	0 0.0 (0.0, 7.7)	0 0.0 (0.0, 7.8)
BSCVA worse than 20/40	3 1.8 (0.0, 3.8)	2 1.2 (0.0, 2.9)	1 0.6 (0.0, 1.9)
Increase > 2 D cylinder	0 0.0 (0.0, 7.5)	0 0.0 (0.0, 7.7)	0 0.0 (0.0, 7.8)
N=134***	n=134	n=132	n=124
BSCVA worse than 20/40	0 0.0 (0.0, 8.5)	0 0.0 (0.0, 8.5)	0 0.0 (0.0, 8.8)

*Excluding eyes intentionally overcorrected
***BSCVA 20/20 or better pre-operatively.

f. Factors Associated with Outcomes

To evaluate the consistency of results and effect of treatment by study site and baseline characteristics, results at 6 months post-operatively were analyzed. The key safety and effectiveness variables were compared to FDA target percentages to determine if the results were significantly different. Since no eye had a BSCVA loss of > 2 lines, analysis of safety outcomes was limited to evaluating outcomes based upon a BSCVA worse than 20/40 at 6 months. For each criterion, comparisons between the actual and target outcomes (MRSE ± 0.50, MRSE ± 1.00, UCVA 20/40 or better) were made using a Mantel-Haenszel chi-square test to obtain p-values and determine the statistical confidence of any difference noted.

In these analyses, statistically significant differences in outcome were identified. One site had a significantly lower percentage of eyes with a

UCVA of 20/40 or better (72%, p=0.001). This is likely due to a higher percentage of monovision treatments (21%, 8/38) at this site as it was the highest percentage when compared to the other sites (range 2.6% to 17.6%). There was no statistically significant effect of contact lens wear history on outcome noted, however those eyes with a history of soft contact lens wear pre-operatively had a lower percentage of eyes with a UCVA of 20/40 or better (85%, p=0.068). There was statistically significant evidence that those eyes with a lower pre-operative MRSE had better effectiveness outcomes (MRSE ± 0.50, p=0.001; MRSE ± 1.00, p=0.036; UCVA 20/40 or better, p=0.038). Room temperature had no effect on outcome, however the effect of laser room humidity did produce statistically significant evidence that those procedures performed at lower humidity had better outcomes (p=0.019).

g. Patient Satisfaction

In this study, at the point of stability, patients were asked a series of questions about their vision post-operatively, including clarity, consistency, sustained close work, driving in day and night lighting, reading and vision in dim light, and visual comfort. For those subjects with a pre-operative MRSE > 2.00 D, an average of 3.7% responded that they preferred their vision prior to the LASIK treatment (range 0 - 7.1% for each condition of vision). This average was significantly higher (11.5%) among subjects with a pre-operative MRSE < 2.00 D (range 0 - 21.2%).

Table 14 reflects responses to a patient questionnaire on a scale of 1 (poor) to 5 (excellent). Reponses at 3 and 6 months were compared to pre-operative responses. The results presented reflect changes in uncorrected vision compared to baseline.

Table 14
Patient Symptoms: Comparison of Vision After Surgery
(All Eyes with a Pre-Operative Sphere ≤ 5.00 and Questionnaire, N=206)

	3 Months N=147				6 Months N=144			
	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	24 16.3	116 78.9	7 4.8	0	22 15.3	112 77.8	10 6.9	0
Consistency of Vision	19 12.9	122 83.0	6 4.1	0	19 13.2	115 79.9	10 6.9	0
Sustained Close Work	21 14.3	121 82.3	5 3.4	0	22 15.3	118 81.9	4 2.8	0
Daylight Driving	18 12.2	123 83.7	6 4.1	0	18 12.5	120 83.3	6 4.2	0
Night Driving	18 12.2	123 83.7	6 4.1	0	23 16.0	114 79.2	7 4.9	0
Night Vision with Glare	22 15.0	117 79.6	8 5.4	0	26 18.1	112 77.8	6 4.2	0
Reading in Dim Light	14 9.5	123 83.7	10 6.8	0	15 10.5	119 83.2	9 6.3	1
General Vision in Dim Light	19 12.9	118 80.3	10 6.8	0	19 13.2	116 80.6	9 6.3	0
Overall Visual Comfort	23 15.6	116 78.9	8 5.4	0	24 16.8	116 81.1	3 2.1	1

X. CONCLUSIONS DRAWN FROM THE CLINICAL STUDY

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 RECOMMENDATION

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

XII. CDRH DECISION

CDRH issued a major deficiency letter to VISX, Inc. on September 15, 2000. In an amendment received by FDA on November 22, 2000, VISX submitted the required changes, clarification and information. The applicant addressed all the labeling concerns raised by FDA. CDRH issued an approval order on April 27, 2001.

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.