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
Dates of Panel Recommendation:	None (see Section XII.)
Premarket Approval (PMA) Application Number:	P930016/S14
Date of Notice of Approval to Applicant:	November 6, 2001

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. Supplement 12 (approved April 27, 2001) expanded the indication to include patients 21 years of age or older in treatments for the reduction or elimination of naturally 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.

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 mixed astigmatism where the magnitude of cylinder (≤ 6.0 D at the spectacle plane) is greater than the magnitude of sphere and the cylinder and sphere have opposite signs.

III. CONTRAINDICATIONS

Laser refractive surgery is contraindicated:

- in patients with collagen vascular, autoimmune or immunodeficincy 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®) or amiodarone hydrochloride (Cordarone®).

IV. WARNINGS AND PRECAUTIONS

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

V. 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.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Conventional methods in correcting mixed astigmatism are: spectacles and contact lenses.

VII. 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.

VIII. POTENTIAL 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 17-18 of the clinical study section.

IX. SUMMARY OF PRECLINICAL STUDIES

Refer to the original PMA (#P930016) for description of preclinical studies.

X. SUMMARY OF CLINICAL STUDIES

The sponsor performed a clinical study of the VISX STAR Excimer Laser System in the U.S. under the auspices of an IDE G000037. 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 mixed 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 Mixed 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 mixed astigmatism where the magnitude of cylinder ($\leq$ 6.0 D at the spectacle plane) is greater than the magnitude of sphere and the cylinder and sphere have opposite signs.
- Operative fellow eyes that have mixed astigmatism as defined above or hyperopia with refractive astigmatism ($\leq$ +6.0 D sphere with $\leq$ +6.0 D cylinder).
- 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 diopter (sphere and cylinder) at an examination at least 12 months prior to the baseline examination. The astigmatic axis may not vary 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 examination, 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 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 or did not fall within approved indications for treatment using the VISX STAR S2 Excimer Laser.
- 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 might impair healing, including but not limited to: antimetabolites, isotretinoin (Accutane®) within 6 months of treatment, and amiodarone hydrochloride (Cordarone®) within 12 months 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 were 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 unstable 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 is 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 was 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. Contrast sensitivity (at designated centers) and 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, contrast sensitivity (at designated centers) 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 refraction [manifest refraction spherical equivalent (MRSE) and cylinder].

E. Study Period, Investigational Sites, and Demographics

1. Study period and investigational sites

Sixty eight subjects were treated between June 13, 2000 and December 15, 2000. The database for this PMA supplement reflected data collected through December 28, 2000 and included 122 eyes: 68 first eyes and 54 second eyes. There were 7 investigational sites, 6 of which provided eligible data for analysis.

Of the 122 eyes, the data from seven eyes were removed from all analyses. Four eyes of two subjects were excluded due to protocol violations. Additionally, three eyes of three subjects were removed because their

treatment fell within current approved indications and, per the requirements set in the protocol (section 2.2.3), were not included in the analyses. Therefore, 115 eyes were eligible for analysis of mixed astigmatism by the LASIK procedure.

2. Demographics

The demographics of this study are very typical for a contemporary refractive surgery trial performed in the U.S. Of the 115 treated eyes, 64.3% (74/115) were from male subjects and 35.7% (41/115) from female subjects. Furthermore, 88.7% (102/115) were from Caucasians, 1.7% (2/115) were from Blacks, 1.7% (2/115) were from American Indian/Aleut Eskimo, and 7.8% (9/115) were of other races. The right eye was treated in 49.6% (57/115) cases and the left eye was treated in 50.4% (58/115) cases. The mean age of the subjects treated was 41.3 years with a range from 21 to 68. Preoperative patient characteristics that were found to associate with outcomes are discussed in section F2f. Table 1 presents demographic information for the 115 eyes eligible for analysis.

Table 1
Demographic Information
(N=115)

Category	CLASSIFICATION	n	% Eyes
Gender	Male	74	64.3
	Female	41	35.7
Race	Caucasian	102	88.7
	Asian/Pacific Islander	0	0
	African American	2	1.7
	American Indian/Aleut Eskimo	2	1.7
	Other: Hispanic	9	7.8
Eyes	Right	57	49.6
	Left	58	50.4
CL History	None	91	79.1
	Soft	16	13.9
	RGP/PMMA	8	7.0
Age (in Years)	Average	41.3	
	Standard Deviation	11.3	
	Minimum	21	
	Maximum	68	

F. Data Analysis and Results

1. Preoperative characteristics

Table 2 contains a summary of the preoperative refractive errors of the entire cohort.

Table 2 Pre-Operative Refractive Error Stratified by Sphere and Cylinder (N=115)														
	Cylinder													
	0 to ≤1 D		>1 to ≤ 2 D		>2 to ≤ 3 D		>3 to ≤ 4 D		>4 to ≤ 5D		>5 to ≤ 6D		Total	
Sphere	n	%	n	%	n	%	n	%	n	%	n	%	n	%
<0 to ≤ -1 D	4	3.5	21	18.3	7	6.1	1	0.9	9	7.8	2	1.7	44	38.3
<-1 to ≤ -2 D	0	0.0	6	5.2	25	21.7	3	2.6	5	4.3	2	1.7	41	35.7
<-2 to ≤ -3 D	0	0.0	0	0.0	5	4.3	6	5.2	8	7.0	0	0.0	19	16.5
<-3 to ≤ -4 D	0	0.0	0	0.0	0	0.0	2	1.7	5	4.3	1	0.9	8	7.0
<-4 to ≤ -5 D	0	0.0	0	0.0	0	0.0	0	0.0	1	0.9	2	1.7	3	2.6
Total	4	3.5	27	23.5	37	32.2	12	10.4	28	24.3	7	6.1	115	100

2. Postoperative results

a. Patient Accountability

Accountability was excellent, exceeding 95% at all visits and yielding no fewer than 95% of eyes available for analysis. The following cohorts were used for analysis:

- Safety and Effectiveness - (n=115)
- Stability - subset of safety and effectiveness cohort, eyes with visits at 1, 3, and 6 months (n=105)

Table 3 Subject Accountability (N=115*)						
	1 Month		3 Months		6 Months	
	n	%	n	%	n	%
Available for Analysis	110	95.7	115	100	110	95.7
Discontinued	0	0.0	0	0.0	1	0.9
Missed Visit	5	4.3	0	0.0	3	2.6
Not yet eligible	0	0.0	0	0.0	1	0.9
Lost to Follow-Up	0	0.0	0	0.0	0	0.0
% Accountability: Available for Analysis (enrolled – discontinued – not yet eligible)	95.7% 110/115		100% 115/115		97.3% 110/113^	

*Seven eyes were excluded from all analyses (See Section E, 1)

^This denominator (113) was derived from the 115 eyes enrolled minus one eye that underwent enhancement (discontinued) and one eye that was not yet due for examination.

b. Stability of Outcome

In the 3-6 months window, 99% of eyes experienced a change of MRSE not exceeding ± 1.0 D and 98% of eyes experienced a change of cylinder not exceeding ± 1.0 D. The assessment of stability was performed using the outcomes of the 105 eyes with 1, 3, and 6-month visits.

Table 4
Refractive Stability-MRSE and Cylinder
(Eyes with 1, 3, and 6-month visits, N=105)

Change in Refraction	1 and 3 Months n % 95% CI	3 and 6 Months n % 95% CI
≤ 1.00 D (MRSE) 95% CI for %	105 100 (97.2, 100)	104 99.0 (94.8, 100)
≤ 1.00 D (Cylinder) 95% CI for %	105 100 (97.2, 100)	103 98.1 (93.3, 99.8)
Mean MRSE (D) SD 95% CI for Mean	-0.05 0.32 (-0.12, 0.01)	0.11 0.33 (0.05, 0.18)
Mean Cylinder (D) SD 95% CI for Mean	-0.03 0.34 (-0.09, 0.04)	0.03 0.36 (-0.04, 0.10)

c. Effectiveness Outcomes

The analysis of effectiveness was based on the 115 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 pre-operative cylinder are presented in tables 5 and 6 respectively.

Table 5
Summary of Key Effectiveness Variables Over Time
(N=115)

CRITERIA	1 Month n % (95% CI)	3 Months n % (95% CI)	6 Months n % (95% CI)
N=115*	n=110	n=115	n=110
UCVA 20/20 or better	60 54.5 (44.8, 64.1)	67 58.3 (48.7, 67.4)	68 61.8 (52.1, 70.9)
UCVA 20/40 or better	106 96.4 (91.0, 99.0)	113 98.3 (93.9, 99.8)	109 99.1 (95.0, 100)
MRSE: ± 0.50 D	84 76.4 (67.3, 83.9)	91 79.1 (70.6, 86.1)	85 77.3 (68.3, 84.7)
± 1.00 D	107 97.3 (92.2, 99.4)	112 97.4 (92.6, 99.5)	105 95.5 (89.7, 98.5)
Cylinder: ± 0.50 D	71 64.5 (54.9, 73.4)	76 66.1 (56.7, 74.7)	70 63.6 (53.9, 72.6)
± 1.00 D	99 90.0 (82.8, 94.9)	97 84.3 (76.4, 90.5)	98 89.1 (81.7, 94.2)

*Includes eyes with a pre-operative BSCVA worse than 20/20.

Table 6
Summary of Key Effectiveness Variables at Stability Endpoint of 3 Months (Stratified by Pre-Operative Cylinder)

CRITERIA	0.00 to 1.00 n/N, % (%CI)	>1 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)	Cum Total n/N, % (%CI)
N=115*	n=4	n=27	n=37	n=12	n=28	n=7	n=115
UCVA 20/20 or better	3 75.0 (19.4, 99.4)	23 85.2 (66.3, 95.8)	24 64.9 (47.5, 79.8)	7 58.3 (27.7, 84.8)	9 32.1 (15.9, 52.4)	1 14.3 (0.4, 57.9)	67 58.3 (48.7, 67.4)
UCVA 20/40 or better	4 100 (47.3, 100)	27 100 (89.5, 100)	36 97.3 (85.8, 99.9)	12 100 (77.9, 100)	27 96.4 (81.7, 99.9)	7 100 (65.2, 100)	113 98.3 (93.9, 99.8)
N=115	n=4	n=27	n=37	n=12	n=28	n=7	n=115
MRSE: ± 0.50 D	3 75.0 (19.4, 99.4)	23 85.2 (66.3, 95.8)	29 78.4 (61.8, 90.2)	9 75.0 (42.8, 94.5)	20 71.4 (51.3, 86.8)	7 100 (65.2, 100)	91 79.1 (70.6, 86.1)
± 1.00 D	4 100 (47.3, 100)	27 100 (89.5, 100)	35 94.6 (81.8, 99.3)	12 100 (77.9, 100)	27 96.4 (81.7, 99.9)	7 100 (65.2, 100)	112 97.4 (92.6, 99.5)

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 83.2% reduction at 3 months achieved with this device is acceptable.

Table 7
Cylinder Correction Efficacy Stratified by Pre-Operative Cylinder (N=115)

	3 Months
Pre-Operative Cylinder	**% Reduction of Absolute Cylinder (Not a Vector)**
≤ 1.0 D	85.2%
> 1.0 to ≤ 2.0 D	87.5%
> 2.0 to ≤ 3.0 D	79.2%
> 3.0 to ≤ 4.0 D	84.9%
> 4.0 to ≤ 5.0 D	82.9%
> 5.0 to ≤ 6.0 D	86.8%
Total	83.2%

Looking at intended versus achieved vector magnitude cylinder, the Intended Refractive Correction ("IRC") had a mean of -3.1 D with a median of -2.8 (range -0.8 D to -6.3 D). The Surgically Induced Refractive Correction ("SIRC") had a mean of -2.9 D with a median of -2.7 D (range (-0.7 D to -6.8 D). The vector magnitude ratio (SIRC/IRC) was 93.2% at 3 months. The Panel has found 82.5% acceptable for correction efficacy (SIRC/IRC) at stability. The result achieved is within this range and is therefore acceptable.

Table 8a Cylinder Correction Efficacy Stratified by Pre-Operative Cylinder (N=115)	
	3 Months
Pre-Operative Cylinder	Achieved vs Intended Vector Magnitude Ratio (SIRC/IRC)
≤ 1.0 D	90.9%
> 1.0 to ≤ 2.0 D	93.1%
> 2.0 to ≤ 3.0 D	89.7%
> 3.0 to ≤ 4.0 D	92.1%
> 4.0 to ≤ 5.0 D	97.2%
> 5.0 to ≤ 6.0 D	90.8%
Total	93.2%

Tables 8b, 8c, and 8d reflect the manifest refractive cylinder and axis change from baseline and the accuracy of manifest refraction in the pre-operative Hyperopic and Myopic meridians for eyes with ≤ 15° axis change from baseline.

Table 8b Manifest Refractive Cylinder and Axis Change from Baseline						
	1 Month		3 Months		6 Months	
	n	%	n	%	n	%
Number of eyes with ≤15° axis change from baseline	55	50.0	67	58.3	64	58.2
Number of eyes with >15° axis change from baseline	55^	50.0	48~	41.7	46*	41.8
Available for analysis	N=110		N=115		N=110	

^34 of these eyes (61.8%) had a post-op cylinder of 0.50 D or less
~24 of these eyes (50.0%) had a post-op cylinder of 0.50 D or less
*20 of these eyes (43.5%) had a post-op cylinder of 0.50 D or less

Table 8c
Accuracy of Manifest Refraction in Pre-Op HYPEROPIC Meridian Mixed Astigmatism Cohort
(For eyes with ≤15° axis change from baseline)

Correction Error	1 Month		3 Months		6 Months	
	n	%	n	%	n	%
0.00 to ± 0.50 D	38	69.1	53	79.1	48	75.0
Under-corrected (Hyperopic)						
> 0.50 - 0.99 D	8	14.5	4	6.0	7	10.9
1.00 – 1.99 D	8	14.5	9	13.4	9	14.1
≥ 2.00	1	1.8	1	1.5	0	0.0
Over-corrected (Myopic)						
> 0.50 - 0.99 D	0	0.0	0	0.0	0	0.0
1.00 – 1.99 D	0	0.0	0	0.0	0	0.0
≥ 2.00 D	0	0.0	0	0.0	0	0.0
Total	N=55		N=67		N=64	

Table 8d
Accuracy of Manifest Refraction in Pre-Op MYOPIC Meridian Mixed Astigmatism Cohort
(For eyes with ≤15° axis change from baseline)

Correction Error	1 Month		3 Months		6 Months	
	n	%	n	%	n	%
0.00 to ± 0.50 D	49	89.1	59	88.1	61	95.3
Under-corrected (Myopic)						
> 0.50 - 0.99 D	2	3.6	2	3.0	0	0.0
1.00 – 1.99 D	1	1.8	3	4.5	2	3.1
≥ 2.00	0	0.0	0	0.0	0	0.0
Over-corrected (Hyperopic)						
> 0.50 - 0.99 D	2	3.6	1	1.5	0	0.0
1.00 – 1.99 D	1	1.8	2	3.0	1	1.6
≥ 2.00 D	0	0.0	0	0.0	0	0.0
Total	N=55		N=67		N=64	

d. Safety Outcomes

The analysis of safety was based on all 115 eyes. The key safety outcomes for this study are presented in tables 9 and 10, with all the adverse reactions reported in tables 11-13. Overall, the device was deemed reasonably safe.

Table 9
Summary of Key Safety Variables Over Time
(N=115)

CRITERIA	1 Month n % (95% CI)	3 Months n % (95% CI)	6 Months n % (95% CI)	FDA Targets
N=115	**n=110**	**n=115**	**n=110**	
Loss of ≥ 2 lines BSCVA	1 0.9 (0.0, 5.0)	1 0.9 (0.0, 4.7)	0 0.0 (0.0, 2.7)	
Loss of > 2 lines BSCVA	0 0.0 (0.0, 2.7)	0 0.0 (0.0, 2.6)	0 0.0 (0.0, 2.7)	<5
Increase > 2 D cylinder	0 0.0 (0.0, 2.7)	0 0.0 (0.0, 2.6)	0 0.0 (0.0, 2.7)	<5
N=94^	**n=90**	**n=94**	**n=90**	
BSCVA worse than 20/40	0 0.0 (0.0, 3.3)	0 0.0 (0.0, 3.1)	0 0.0 (0.0, 3.3)	<1

^BSCVA 20/20 or better pre-operatively.

Table 10
Summary of Key Safety Variables at Stability Endpoint of 3 Months (Stratified by Pre-Operative Cylinder)

CRITERIA	0.00 to 1.00 n/N, % (%CI)	>1 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)	Cum Total n/N, % (%CI)
N=115	**n=4**	**n=27**	**n=37**	**n=12**	**n=28**	**n=7**	**n=115**
Loss of ≥ 2 lines BSCVA	0 0.0 (0.0, 52.7)	0 0.0 (0.0, 10.5)	0 0.0 (0.0, 7.8)	0 0.0 (0.0, 22.1)	0 0.0 (0.0, 10.1)	1 14.3 (0.4, 57.9)	1 0.9 (0.0, 4.7)
Loss of > 2 lines BSCVA	0 0.0 (0.0, 52.7)	0 0.0 (0.0, 10.5)	0 0.0 (0.0, 7.8)	0 0.0 (0.0, 22.1)	0 0.0 (0.0, 10.1)	0 0.0 (0.0, 34.8)	0 0.0 (0.0, 2.6)
Increase > 2 D cylinder	0 0.0 (0.0, 52.7)	0 0.0 (0.0, 10.5)	0 0.0 (0.0, 7.8)	0 0.0 (0.0, 22.1)	0 0.0 (0.0, 10.1)	0 0.0 (0.0, 34.8)	0 0.0 (0.0, 2.6)
N=94^	**n=4**	**n=26**	**n=32**	**n=9**	**n=17**	**n=6**	**n=94**
BSCVA worse than 20/40	0 0.0 (0.0, 52.7)	0 0.0 (0.0, 10.9)	0 0.0 (0.0, 8.9)	0 0.0 (0.0, 28.3)	0 0.0 (0.0, 16.2)	0 0.0 (0.0, 39.3)	0 0.0 (0.0, 3.1)

^BSCVA 20/20 or better pre-operatively.

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

Table 11
Summary of Adverse Events
(N=115)

	1 Month (n=110)		3 Months (n=115)		6 Months (n=110)	
	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 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

There were no protocol defined adverse events reported in this study, however, three subjects experienced 'other' adverse events that were reported to both FDA and all reviewing IRBs. The 'other' adverse reactions reported at the postoperative examinations included two eyes of one subject who formed a bullous epithelial reaction during the microkeratome pass of each treatment, two eyes of another subject who developed diffuse lamellar keratitis (DLK), and one subject who experienced a seizure (unrelated to the LASIK procedure) in between the three and 6 month visits.

Table 12 presents a summary of complications reported during the course of the trial.

Table 12
Summary of Complications
(N=115)

	1 Month (n=110)		3 Months (n=115)		6 Months (n=110)	
	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	0	0.0	0	0.0	0	0.0
Epithelium in the interface	1	0.9	0	0.0	0	0.0
Foreign body sensation at 1 month or later	3	2.7	1	0.9	0	0.0
Pain at 1 month or later	1	0.9	1	0.9	0	0.0
Ghost/double images in the operative eye	0	0.0	2	1.7	0	0.0
Flap is not of the size and shape as initially 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 13. 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 13
Other Adverse Reactions at 1, 3, and 6 months

Adverse Reaction	1 months N=110		3 months N=115		6 months N=110	
Chemical Toxicity from use of non-preservative free Artificial Tears	2	1.8%	2	1.7%	0	0.0%
Debris under flap	3	2.7%	0	0.0%	0	0.0%
Filament	1	0.9%	0	0.0%	0	0.0%
Blood in the Interface	1	0.9%	0	0.0%	0	0.0%
Irregular epithelium	3	2.7%	1	0.9%	0	0.0%
Glare and/or Halos	3	2.7%	6	5.2%	4	3.6%
Allergic conjunctivitis	0	0.0%	4	3.5%	0	0.0%

e. Retreatment

One eye underwent LASIK retreatment (1/115 or 0.9%) during the study, mostly due to initial over-correction. One retreatment is an insufficient number to yield clinically useful information, however caution should be taken to assure refractive stability before performing additional procedures.

Table 14
Summary of Key Safety and Effectiveness Variables (N=115)

CRITERIA	1 Month n % (95% CI)	3 Months n % (95% CI)	6 Months n % (95% CI)	FDA Targets
EFFECTIVENESS VARIABLES				
N=94^	n=90	n=94	n=90	%
UCVA 20/20 or better	59 65.6 (54.8, 75.3)	65 69.1 (58.8, 78.3)	63 70.0 (59.4, 79.2)	
UCVA 20/25 or better	74 82.2 (72.7, 89.5)	84 89.4 (81.3, 94.8)	84 93.3 (86.1, 97.5)	
UCVA 20/40 or better	89 98.9 (94.0, 100)	93 98.9 (94.2, 100)	90 100 (96.7, 100)	≥85
N=115*	n=110	n=115	n=110	
UCVA 20/20 or better	60 54.5 (44.8, 64.1)	67 58.3 (48.7, 67.4)	68 61.8 (52.1, 70.9)	
UCVA 20/25 or better	84 76.4 (67.3, 83.9)	96 83.5 (75.4, 89.7)	92 83.6 (75.4, 90)	
UCVA 20/40 or better	106 96.4 (91.0, 99.0)	113 98.3 (93.9, 99.8)	109 99.1 (95.0, 100)	
N=115	n=110	n=115	n=110	
MRSE: ± 0.50 D	84 76.4 (67.3, 83.9)	91 79.1 (70.6, 86.1)	85 77.3 (68.3, 84.7)	≥50
± 1.00 D	107 97.3 (92.2, 99.4)	112 97.4 (92.6, 99.5)	105 95.5 (89.7, 98.5)	≥75
± 2.00 D	109 99.1 (95.0, 100)	115 100 (97.4, 100)	110 100 (97.3, 100)	
Cylinder: ± 0.50 D	71 64.5 (54.9, 73.4)	76 66.1 (56.7, 74.7)	70 63.6 (53.9, 72.6)	
± 1.00 D	99 90.0 (82.8, 94.9)	97 84.3 (76.4, 90.5)	98 89.1 (81.7, 94.2)	
± 2.00 D	108 98.2 (93.6, 99.8)	114 99.1 (95.3, 100)	110 100 (97.3, 100)	
STABILITY				
N=105♦	[redacted]	1-3 Months n=105	3-6 Months n=105	
Change in MRSE ≤ 1.00 D	[redacted]	105 100 (97.2, 100)	104 99.0 (94.8, 100)	≥95
Mean Change in MRSE	[redacted]	-0.05 ± 0.32 (-0.12, 0.01)	0.11 ± 0.33 (0.05, 0.18)	
Change in Cylinder ≤ 1.00 D	[redacted]	105 100 (97.2, 100)	103 98.1 (93.3, 99.8)	
Mean Change in Cylinder	[redacted]	-0.03 ± 0.34 (-0.09, 0.04)	0.03 ± 0.36 (-0.04, 0.10)	
SAFETY VARIABLES				
N=115	n=110	n=115	n=110	
Loss of ≥ 2 lines BSCVA	1 0.9 (0.0, 5.0)	1 0.9 (0.0, 4.7)	0 0.0 (0.0, 2.7)	
Loss of > 2 lines BSCVA	0 0.0 (0.0, 2.7)	0 0.0 (0.0, 2.6)	0 0.0 (0.0, 2.7)	<5
Increase > 2 D cylinder	0 0.0 (0.0, 2.7)	0 0.0 (0.0, 2.6)	0 0.0 (0.0, 2.7)	<5
N=94^	n=90	n=94	n=90	
BSCVA worse than 20/40	0 0.0 (0.0, 3.3)	0 0.0 (0.0, 3.1)	0 0.0 (0.0, 3.3)	<1

^BSCVA 20/20 or better pre-operatively.
*Includes eyes with a pre-operative BSCVA worse than 20/20.
♦Includes only eyes with all visits.

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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 using a chi-square test to obtain p-values. In all cases the observed safety values were less than the target threshold and in some cases the sample size was sufficient to demonstrate that the observed level was significantly better.

In all cases the observed effectiveness values either met or exceeded the target percentage, with the exception of two groups with small sample sizes [temperature between 74-76° (n=3) and humidity 35-39% (n=5)], which could not be considered representative samples for target percentages or confidence intervals.

There is no evidence that there were any subgroups that were significantly worse than the target. All significant p-values indicated that the group was superior to the target. There also did not appear to be any differences in outcome for the various temperature or humidity categories.

g. Patient Satisfaction

In this study, at the point of stability, patients were asked a series of questions about their vision. VISX recommends that all patients be counseled carefully to establish realistic expectations before they proceed with the surgical correction of refractive error.

Table 15 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 best corrected vision.

Table 15
Patient Symptoms: Comparison of Pre-Operative Best-Corrected Vision to Post-Operative Uncorrected Vision
(N=115)

	3 Months N=115				6 Months N=110			
	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	2 1.8	104 92.0	7 6.2	2	3 2.7	101 91.8	6 5.5	0
Consistency of Vision	4 3.5	103 91.2	6 5.3	2	1 0.9	100 90.9	9 8.2	0
Daylight Driving	2 1.8	105 92.9	6 5.3	2	3 2.7	102 92.7	5 4.5	0
Night Driving	9 8.0	94 83.2	10 8.8	2	15 13.6	92 83.6	3 2.7	0
Night Vision with Glare	11 9.7	94 83.2	8 7.1	2	13 11.8	94 85.5	3 2.7	0
General Vision in Dim Light	6 5.3	101 89.4	6 5.3	2	6 5.5	99 90.0	5 4.5	0
Overall Visual Comfort	12 10.6	92 81.4	9 8.0	2	7 6.4	94 85.5	9 8.2	0

h. Device failure

There was only one reported problem during treatment in this study. A monitor displayed characters broken on lettering. Technical service checked the connection on back of the monitor to ensure connection was tight. No further action was required.

XI. CONCLUSIONS DRAWN FROM THE CLINICAL STUDY

The data in this application supports reasonable assurance of safety and efficacy of this device for the treatment of LASIK in patients with naturally occurring mixed astigmatism where the magnitude of cylinder (≤ 6.0 D at the spectacle plane) is greater than the magnitude of sphere and cylinder and have opposite signs.

XII. PANEL RECOMMENDATION

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

XIII. CDRH DECISION

CDRH issued a minor deficiency letter to VISX, Inc. on September 5, 2001. In an amendment received by FDA on September 20, 2001, VISX submitted the required changes, clarification and information. The applicant addressed all labeling concerns raised by FDA. CDRH issued an approval order on November 6, 2001.

XIV. 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 labeling.