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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

**Memorandum**

P910062

**Date** SEP 29 1995

**From** Director, Office of Device Evaluation (HFZ-400)
Center for Devices and Radiological Health (CDRH)

**Subject** Premarket Approval of VISX,Inc.
Excimer Laser System (Models B and C)

**To** The Director, CDRH
Through: ORA ____

ISSUE. Publication of a notice announcing approval of the subject PMA.

FACTS. Tab A contains a FEDERAL REGISTER notice announcing:

(1) a premarket approval order for the above referenced medical device (Tab B); and

(2) the availability of a summary of safety and effectiveness data for the device (Tab C).

RECOMMENDATION. I recommend that the notice be signed and published.

Susan Alpert, Ph.D., M.D.

Attachments
Tab A - Notice
Tab B - Order
Tab C - S & E Summary

DECISION

Approved ___ Disapproved ___ Date _____

Prepared by Mark Stern, M.D. and Quynh Hoang, CDRH, HFZ-460, 9/29/95, 594-2018.

DRAFT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

[DOCKET NO. _____]

VISX, Inc.; PREMARKET APPROVAL OF VISX Excimer Laser System (Models B and C)

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its approval of the application by VISX, Inc. of Santa Clara, CA, for premarket approval, under the Federal Food, Drug, and Cosmetic Act (the act), of the VISX Excimer Laser System (Models B and C). After reviewing the recommendation of the Ophthalmic Devices Panel, FDA's Center for Devices and Radiological Health (CDRH) notified the applicant, by letter on September 29, 1995, of the approval of the application.

DATES: Petitions for administrative review by (insert date 30 days after date of publication in the FEDERAL REGISTER); Written comments by (insert date 30 days after date of publication in the FEDERAL REGISTER).

ADDRESSES: Written requests for copies of the summary of safety and effectiveness data and petitions for administrative review, to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Morris Waxler, Ph.D.,
Center for Devices and Radiological Health (HFZ-460),
Food and Drug Administration,
9200 Corporate Blvd.,
Rockville, MD 20850,
301-594-2018.

SUPPLEMENTARY INFORMATION: On December 24, 1991, VISX, Inc., Santa Clara, CA, submitted to CDRH an application for premarket approval of the VISX Excimer Laser System (Models B and C). The VISX Excimer Laser System delivers pulses at 193 nanometers wavelength. The device is indicated for phototherapeutic keratectomy (PTK) in subjects with decreased best corrected visual acuity and/or with disabling pain that are the result of superficial corneal epithelial irregularities or stromal scars in the anterior one-third of the cornea. The subjects must have failed with alternative treatment options. For safety, the immediate

postoperative corneal thickness must not be less than 250 microns.

Examples of those conditions that warrant PTK are:

- corneal scars and opacity (from trauma and inactive infections),
- dystrophies (Reis-Buckler's, granular and lattice),
- Thygeson's superficial keratitis,
- irregular corneal surfaces associated with filamentary keratitis and Salzmann's nodular degeneration,
- residual band keratopathy after unsuccessful EDTA treatment, and,
- scars subsequent to previous (not concurrent) pterygium excision.

On March 21, 1994, the Ophthalmic Devices Panel of the Medical Devices Advisory Committee, an FDA advisory committee, reviewed and recommended approval of the application.

On September 29, 1995, CDRH approved the application by a letter to the applicant from the Director of the Office of Device Evaluation, CDRH.

A summary of the safety and effectiveness data on which

CDRH based its approval is on file in the Dockets Management Branch (address above) and is available from that office upon written request. Requests should be identified with the name of the device and the docket number found in brackets in the heading of this document.

Opportunity for Administrative Review

Section 515(d)(3) of the act (21 U.S.C. 360e(d)(3)) authorizes any interested person to petition, under section 515(g) of the act, for administrative review of CDRH's decision to approve this application. A petitioner may request either a formal hearing under part 12 (21 CFR part 12) of FDA's administrative practices and regulations or a review of the application and CDRH's action by an independent advisory committee of experts. A petition is to be in the form of a petition for reconsideration under 10.33(b) (21 CFR 10.33(b)). A petitioner shall identify the form of review requested (hearing or independent advisory committee) and shall submit with the petition supporting data and information showing that there is a genuine and substantial issue of material fact for resolution through administrative review. After reviewing the petition, FDA will decide whether to grant or deny the petition and will

publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issue to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

Petitioners may, at any time on or before (insert date 30 days after date of publication in the FEDERAL REGISTER), file with the Dockets Management Branch (address above) two copies of each petition and supporting data and information, identified with the name of the device and the docket number found in brackets in the heading of this document. Received petitions may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act secs. 515(d) 520(h) (21 U.S.C. 360e(d), 360j(h))) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Director, Center for Devices and Radiological Health (21 CFR 5.53).

Dated:_____.

_____

P910062

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

SEP 29 1995

Jordan D. Haller, M.D.
Vice President Clinical and Regulatory Affairs
VISX, Incorporated
3400 Central Expressway
Santa Clara, CA 95051-0703

RE: P910062
VISX Excimer Laser System (Models B and C) for Phototherapeutic Keratectomy
Filed: December 24, 1991
Amended: January 29, March 5 and 24, April 2 and 6, and September 3, 1992; April 19, July 8, September 1, October 12, and December 22, 1993; January 13 and 21, February 2 and 24, March 11, May 19, June 8, August 22 and 30, September 6 and 24, October 31, November 21 and 28, and December 22, 1994; January 24, February 6 and 8, March 20, April 5, 11, and 17, July 6, 11, and 25, August 18 and 30, and September 25, 1995

Dear Dr. Haller:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the VISX Excimer Laser System (Models B and C). The Excimer Laser System is indicated for phototherapeutic keratectomy (PTK) in subjects with decreased best-corrected visual acuity and/or with disabling pain that are the result of superficial corneal epithelial irregularities or stromal scars in the anterior one-third of the cornea. The subjects must have failed with alternative treatment options. For safety, the immediate postoperative corneal thickness must not be less than 250 microns.

Examples of those conditions that may warrant PTK are:

- corneal scars and opacity (from trauma and inactive infections),
- dystrophies (Reis-Buckler's, granular and lattice),
- Thygeson's superficial keratitis,
- irregular corneal surfaces associated with filamentary keratitis and Salzmann's nodular degeneration,

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- residual band keratopathy after unsuccessful EDTA treatment, and,
- scars subsequent to previous (not concurrent) pterygium excision.

We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

In addition to the postapproval requirements in the enclosure, VISX must also report the following to the Agency if the information becomes available to VISX:

1. any instances of device tampering (such as the removal of the PRK lockout mechanisms) or device usage outside of the approved indications;

2. any excimer systems that were exported under an 801(e) order, but are now back in the U.S.; and,

3. all complications as part of your annual reporting.

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the act.

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

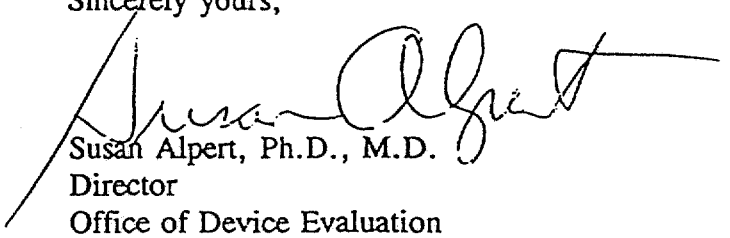
You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit a supplement to this PMA submission with copies of all approved labeling in final printed form. For your reference, enclosed is a copy of the finalized indication, contraindication, warning, and precaution statements.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Quynh Hoang at (301) 594-2018.

Sincerely yours,



Susan Alpert, Ph.D., M.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures

## CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. **This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.**

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

(1) Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

(2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

(a) unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

(b) reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

(1) A mixup of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

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REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984, and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to FDA whenever they receive or otherwise became aware of information that reasonably suggests that one of its marketed devices

(1) may have caused or contributed to a death or serious injury or

(2) has malfunctioned and that the device or any other device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for this PMA, you shall submit the appropriate reports required by the MDR Regulation and identified with the PMA reference number to the following office:

Division of Surveillance Systems (HFZ-531)
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Drive, Room 240
Rockville, Maryland 20850
Telephone (301) 594-2735

Events included in periodic reports to the PMA that have also been reported under the MDR Regulation must be so identified in the periodic report to the PMA to prevent duplicative entry into FDA information systems.

Copies of the MDR Regulation and an FDA publication entitled, "An Overview of the Medical Device Reporting Regulation," are available by written request to the address below or by telephoning 1-800-638-2041.

Division of Small Manufacturers Assistance (HFZ-220)
Center for Devices and Radiological Health
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

## SUMMARY OF SAFETY AND EFFECTIVENESS

I. GENERAL INFORMATION

Device Generic Name: Ophthalmic Medical Laser System (193 nanometer laser wavelength)

Device Trade Name: VISX Excimer Laser System, Models B and C

Applicant's Name and Address: VISX Incorporated
3400 Central Expressway
Santa Clara, CA 95051-0703
(408) 733-2020

Date of Panel Recommendation: Conditional Approval on March 21, 1994

Premarket Approval (PMA) Application Number: P910062

Date of Notice of Approval to Applicant: September 29, 1995

II. INDICATIONS FOR USE

Phototherapeutic Keratectomy (PTK) procedures using the VISX Excimer Laser System (hereinafter called the excimer system) are primarily indicated for subjects with decreased best corrected visual acuity and/or with disabling pain that are the result of superficial corneal epithelial irregularities or stromal scars in the anterior one-third of the cornea. The subjects must have failed with alternative treatment options. For safety, the immediate postoperative corneal thickness must not be less than 250 microns.

Examples of those conditions that may warrant PTK are:

- corneal scars and opacity (from trauma and inactive infections),
- dystrophies (Reis-Buckler's, granular and lattice),
- Thygeson's superficial keratitis,
- irregular corneal surfaces associated with filamentary keratitis and Salzmann's nodular degeneration,
- residual band keratopathy after unsuccessful EDTA treatment, and,
- scars subsequent to previous (not concurrent) pterygium excision.

## III. CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

### A. Contraindications

The Phototherapeutic Keratectomy procedure should not be performed if the post-operative thickness would be less than 250 microns (excluding the epithelium and Bowman's layer), or if a deep scar is present which is not contained in the anterior one-third of the cornea.

### B. Warnings

1. Hyperopic shift has been a major complication following PTK. It is advisable to ablate only to a depth that is necessary to improve vision and/or relieve symptoms, and not to attempt to remove all scar tissue. Aggressive attempts to ablate all visible scar tissue risk hyperopic shift and corneal ectasia. Subjects should be informed concerning the possibility of hyperopia and of subsequently induced anisometropia.

2. Reactivation of herpes simplex keratitis has occurred after PTK. A course of oral acyclovir is recommended if there is a history of herpetic infection.

3. If topical steroids are used post-operatively, subjects must be monitored for possible steroid side-effects, such as ocular hypertension, and/or glaucoma with subsequent damage to the optic nerve, or development of posterior subcapsular cataract.

4. Subjects with systemic diseases likely to affect wound healing, such as connective tissue disease, diabetes, severe atopic disease, or immunocompromised status should be approached very cautiously, as the safety and effectiveness of the excimer system has not been established in patients with these conditions.

### c. Precautions

1. The safety and effectiveness of the VISX Excimer Laser System has not been established in:

   - the treatment of recurrent corneal erosions;
   - the treatment of corneal pathology in the presence of recurrent or active ocular disease such as iritis, uveitis, keratitis sicca, or severe blepharitis;

- the treatment of scars and irregularities in patients with keratoconus;
- subjects with corneal neovascularization near the ablation zone;
- subjects with previous corneal surgery;
- pregnant women; or,
- subjects under 18 years of age.

2. Considerations should be given to the following in determining the appropriate subjects for PTK:

   - the potential induced refractive error would result in significant uncorrectable anisometropia and/or induced astigmatism;
   - the subject should have the ability to tolerate local or topical anesthesia; and,
   - the subject should have the ability to lie flat without difficulty.

3. During the PTK procedure,

   1. The output of the laser is potentially hazardous only to the skin and the surface layers of the cornea. This radiation has not been shown to pose a threat to retinal structures or the crystalline lens. Analysis of the Nominal Hazard Zone (Ref. D. Sliney and T. Clapham, Safety of Medical Excimer Lasers with an Emphasis on Compressed Gases, Data on File at VISX, Inc.) within which the Maximum Permissible Exposure (MPE) may be exceeded shows that the area of potential hazard (Nominal Hazard Zone) for production of a photochemical keratitis is less than 40 cm. It is recommended that direct exposure to the skin or eye by the primary beam be avoided by all health care personnel. While no hazard exists beyond 40 cm from the patient, the use of protective eyewear is recommended if the possibility exists that health care personnel will approach closer than this distance.

   2. While the estimated depth and size of the abnormal pathologic tissue are the necessary starting points for the PTK procedure, the pre-treatment slit-lamp examination can only estimate the depth and size of the abnormal pathologic tissue and not the clinically important issue of tissue ablation rate.

3. It must be recognized that ablation rates of pathologic corneal tissues can be unpredictable. Only at the time of treatment can the tissue ablation rate be determined that will in turn be the key piece of information upon which the treatment depends.

4. The main therapeutic endpoint should always be the production or maintenance of a smooth corneal treatment bed upon which an appropriate healing response is dependent. In addition in opacified corneal tissue, a sufficient ablation depth should be reached to provide for the adequate transmission of light.

5. In order to achieve a smooth corneal treatment bed, a necessary prerequisite for a predictable healing response upon which optical performance is ultimately dependent, one must compensate for the differential rate of ablation among normal, diseased corneal tissue and within the diseased tissue itself.

6. The use of a smoothing agent is to avoid producing an uneven corneal treatment bed that would occur if the differential rate of ablation were not compensated for among normal, diseased corneal tissue and within the diseased tissue itself.

7. When using smoothing agents in treating pathologic corneal tissue, the surgical plan should be flexible, responding in real time to the way the corneal tissue is behaving in relation to the tissue ablation rate per laser pulse which cannot be known until the laser treatment is underway.

8. Therefore, the laser treatment should be periodically interrupted for a slit-lamp examination to determine corneal surface smoothness and/or estimate treatment depth since examination through the operating microscope alone may not provide this information.

## IV. DEVICE DESCRIPTION

The VISX Excimer Laser System is available in two models: B and C. Although the model C is a technological upgrade of the model B, the energy output and the delivery mechanism from both models remain the same.

Each model combines a 193 nm laser with a computer controlled optics system. Srinivasan was the first to describe the unique non-thermal chemical bond breaking properties of the newly developed excimer lasers.[1] He pointed out the potential of the

193 nm laser for sculpting organic materials and with Trokel and Braren applied this new technology to ophthalmic surgery, specifically to the cornea in 1983.[2] VISX, in cooperation Srinivasan, Trokel, and L'Esperance, developed the Excimer Laser System. The laser system produces its surgical effect by ablative photodecomposition. Short intense pulses of laser energy allows precise control of the depth of the corneal incision. The first clinical application of the laser system was for the treatment of corneal pathology through a process called phototherapeutic keratectomy, and is the subject of this PMA.

A. The VISX Excimer Laser System consists of the following components:

1. Excimer Laser:

| | |
|---|---|
| Laser wavelength: | 193 nanometers |
| Laser pulse duration: | 20 nanoseconds (Full Wave Half Max) |
| Repetition rate: | 5 Hertz |
| Fluence (at the eye): | 160 mJ/cm$^2$ |
| PTK ablation zones: | |
| slit | width from 0.6 to 6.0 mm in 0.1 mm increments, and must be ≤ length |
| | length from 0.6 to 6.0 mm in 0.1 mm increments, and must be ≥ width |
| | axis is 0° to 180° in 1° increments |
| circle | overall diameter of 2.0 to 6.0 mm in 0.1 mm increments, with a transition zone width from 0.0 to 2.7 mm in 0.1 mm increments, and meeting the constraint that (overall diameter - 2(transition zone width)) ≥ 0.6 mm |
| Laser head output: | > 400 mJ |
| Composition of gases: | |
| ArF Premix | Argon<br>Fluorine ( < 1.0%)<br>Helium<br>Neon |
| For internal purging | Helium (99.9995% purity) |
| For purifying (model B) | Liquid Nitrogen |

2. Gas Management System: This system includes the housing for gas cylinders, a gas alarm for fluorine, a gas discharge system that uses an activated charcoal filter to ensure that no fluorine is exhausted into the atmosphere, and an emergency safety system that automatically seals the ArF Premix cylinder in the event of a natural disaster or power failure.

3. Laser Beam Delivery System: Before reaching the eye, the raw rectangular beam of an excimer laser is directed by mirrors to pass sequentially through: homogenizing optics that convert the raw beam into a uniform and coaxial profile beam; a spatial and temporal integrator that minimizes variations in the average treatment beam profile; and, a beam shaping module (iris diaphragm and rotatable slit blades) that controls the size and shape of the exiting beam.

4. Patient Management System: Components under this category include an operating microscope that allows the physician to view the eye; a halogen illuminator that illuminates the patient's eye; a blinking fixation LED upon which the patient focuses during the procedure; a reticle for aligning the eye to the system; a patient chair and a vacuum pillow; and a video camera and monitor for recording and viewing a procedure.

5. Computer Control and Software System: Provided with the laser is an IBM or equivalent PC system that contains a monitor, a keyboard, a trackball and a printer. The PC drives the excimer system's components, calculates ablation algorithms, and prompts the user through the surgical procedure. Additionally, the PC is equipped with the VISX VisionKey optical memory cards. Each card stores patient information and treatment data, provides standardization of ablations, and controls treatment selection.

   The VisionKey cards available to U.S. users will allow only PTK treatments.

B. Regulations

The excimer system contains a Class IV laser that conforms with US/FDA 21 CFR 1040.10 and 1040.11 Radiological Health requirements. The laser system was designed to meet the following safety standards:

UL544
CSA C22.2 No. 125M1984
IEC 601-1: 1988
IEC 601-2-22: 1991

IEC 825: 1984
EN 60601-1-2
EN 55011
IEC 801-2,3,4,5

## V. ALTERNATIVE PRACTICES OR PROCEDURES

Conventional procedures used in the treatment or mitigation of superficial corneal epithelial irregularities or stromal scars include penetrating keratoplasty, lamellar keratoplasty, stromal micropuncture, superficial keratectomy, chemical chelation, contact lens therapy, patching and medical therapy.

## VI. MARKETING HISTORY

VISX has over 140 excimer systems located in approximately 28 countries. The 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

Adverse reactions/complications associated with PTK include hyperopic shift greater than +3.0 D, induced anisometropia greater than 3.0 D at ≥ 1 year, delayed reepithelialization, loss of best corrected visual acuity, corneal haze and scarring, transient increase in intraocular pressure secondary to steroid use, herpes simplex virus reactivation.

## VIII. SUMMARY OF PRECLINICAL STUDIES

### A. Laboratory Studies

#### 1. Beam Rotator Test

The objective of the beam rotator test was to determine the effect of beam rotation on PMMA ablations. The test involved ablating samples of PMMA plastic with the VISX Excimer Laser System set at 160 mJ/cm$^2$, 6 mm iris, and 300 pulses. Samples were ablated, at the iris plane, to a 50 $\mu$m depth with the beam rotator rotating normally, and with the rotator stopped. The samples were then examined with a phase contrast microscope to assess any changes in surface smoothness.

Visual and phase contrast microscope examination of the PMMA samples consistently showed significant linear ridges on the samples ablated with the beam rotator stopped. The samples of PMMA that were ablated with the beam rotator rotating normally had a surface that was consistently smoother, with no striations or ridges. The absence of linear ridges or striations in the samples ablated with normal beam rotation suggested that the beam rotator was in fact acting as a temporal integrator and contributed significantly to the smoothness of the ablated surface.

2. Reliability Testing of the Model B and Model C Lasers

a. Laser module

A modified (external cooled) laser module was fired continuously until breakdown, repaired when necessary, and then fired until 97 million shots were delivered (estimated to be 24 years of maximum service given that in very heavy use, the laser would be used to treat no more than 4000 eyes per year or deliver less than 4 million shots per year). When components failed they were redesigned, if possible, to increase their longevity. Based on these tests, the following factory service intervals were determined: (1) the laser chamber dust filter needs to be cleaned or replaced every 15 to 20 million shots, and (2) the optics needs to be cleaned at least every 7 million shots, and its service life is about 20 million shots.

b. Integrator

The Beam Integrator Module performs the function of temporal and spatial beam integration. It is operating only during the time of actual laser light delivery. Two integrators were tested. Each was run for 720 continuous hours with no discernible wear or failure. Life expectancy of the Beam Integrator should exceed 15,000 patient treatments.

c. Shutters

There are three shutters in the optics delivery system. The first two shutters are actuated with every ablation, including calibration, and the third shutter is opened after the treatment beam calibration. During this test all shutters were cycled at 1 second interval for 106 continuous hours. At the conclusion of the test,

the shutters were examined for wear. Based on the results of this test, the life expectancy of the shutter assemblies should exceed 150,000 patients.

d. Beam shaping module

The Beam shaping module uses three different mechanisms to control the shape of the laser beam (iris drive, slit drive and axis drive). In this test all functions of the three Beam Shaping module mechanisms were cycled respectively through full motion. At the conclusion of the test, the mechanism was disassembled and inspected for wear. The iris and slit drives were run continuously for 60 hours each. The axis drive was run for 50 hours. Life expectancy of the Beam Integrator Module was estimated to exceed 250,000 patient treatments.

3. Software validation

a. Model B software (V 4.10)

V 4.10 is the current version of the software in Model B. This software underwent a comprehensive set of tests which exercised boundary conditions, extreme values, and nominal data entry fields. Also included were extensive tests for system calibration, safety interlocks, and motor movement. Ablations were created and tested for accuracy in a number of different ways. No critical faults were identified during the testing. These tests verified the software requirements for the product as well as specific unit functions.

b. Model C software (V 1.00 and V 1.01)

Two software test procedures were performed for V 1.00. The first was a complete test, including all ablations tests (similar to that done for Model B). The second was an abbreviated test, with only selected ablation tests. The tests were performed on different Model C units. The purpose of performing two tests was to determine whether there were any machine-dependent software problems. None were identified. During a field test of the Model C, a problem in the calculation of the astigmatic angle was identified. V 1.01 was prepared to correct this problem and it was subjected to a test which focused on this parameter. No faults were identified in this test. V 1.01 is the current version of the software in the Model C.

4. Comparability testing of Model B and Model C

The following parameters were tested: (1) raw laser beam profiles, (2) laser temporal pulse width, (3) system beam uniformity, and (4) comparable plastic ablations. Measurements were made on the beams from three Model B and three Model C lasers, and from three Model B and three Model C finished systems. Each unit was evaluated five times for a specific parameter. The resulting data were subjected to an Analysis of Variance to test for differences between Models. There were no significant differences ($p<0.05$) in the above parameters between the two Models. Unit to unit variation is greater in Model B.

B. Animal Studies

1. Autorefractor Scans Of Ablated Animal Eyes

a. Objective

The objective of this test was to determine if a modified autorefractor could be used to measure the refractive change in an animal cornea after excimer laser ablation.

b. Test

The shape of the cornea of an animal eye was changed with an excimer laser system, and attempt was made to measure the refractive change using a modified autorefractor.

c. Test Setup

A CooperVision, Inc. Dioptron IV autorefractor was modified so that an analog signal representing focal quality was available. An albino rabbit was ablated with an attempted -3 diopter ablation with a VISX Excimer Laser System prototype. An African Green monkey was ablated with an attempted -6 diopter correction. Measurements of the eyes were made pre and post operatively. The eyes were aligned to the autorefractor, and focal scans were made. The autorefractor output consisted of a graph of focal quality vs. scan position. The position at which the focal quality was the highest represented the dioptric power of the eye.

d. Results

For the rabbit eye, the post-op focal peak minus the pre-op focal peak showed 1.5 diopters of flattening, which was 50% of the targeted correction. For the monkey eye, the post-op minus pre-op scans showed 3.5 diopters of flattening, which was 58% of the targeted correction. The eyes were scanned multiple times, with repeatable results within +/- 0.2 diopters in most cases.

e. Conclusion

The autorefractor was able to measure a refractive change in the eye. The differences in the achieved vs. targeted results were probably due to an overestimation of how much tissue was removed for each laser pulse. The excimer laser was able to flatten the eyes by about 50% of the targeted amount.

2. Effect of Excimer Laser on Keratocytes

a. Objective

The study was designed to test whether exposure to the radiation from the excimer laser resulted in the oncogenic transformation of cornea cells.

b. Test

Cultured keratocytes and whole corneas from rats were exposed to excimer laser radiation. Following exposure, the growth patterns of cultured cells were monitored. Cultured cells and exposed corneas were also implanted subcutaneously in the rats to assess potential tumor growth.

c. Test Setup

Keratocytes and corneas were exposed at 80 and 160 $mJ/cm^2$ fluence, and at a repetition rate of 5 Hz.

d. Results

No effects on cultured cell growth patterns were observed. No tumors were induced following subcutaneous implantation of laser exposed cells or corneas. As a positive control, treatment of keratocytes with a known carcinogen did result in altered cell growth, and an incidence of tumors in the implanted rats.

e. Conclusions

Exposed cells appear to be either killed by laser exposure, or are unaltered. There is no evidence of oncogenic transformation.

f. Publication

Gebhardt et al. Effect of excimer laser energy on the growth potential of corneal keratocytes. *Cornea* 9(3): 205-210, 1990.

3. Effect of Nitrogen Blowing on Corneal Smoothness

a. Objective

To test the effect of blowing nitrogen gas across the cornea during ablation on corneal smoothness

b. Test

Scanning and transmission electron microscopy were used to evaluate corneal smoothness after excimer laser photo ablation of bovine corneas.

c. Test Set Up

Fresh bovine corneas obtained from a local abattoir were ablated with an excimer system using clinical laser settings. Varying amounts of nitrogen were blown across the corneas (0 to 20 SCFH), and one group of eyes was ablated with hydrated nitrogen ( 90% relative humidity) blown across the cornea.

d. Results

Corneas ablated with dry nitrogen during the ablation process were rougher than those which were not blown or were blown with moist nitrogen. The corneas blown with dry nitrogen had a jagged

ablated surface by transmission microscopy. The roughness increased with ablation depth, and the undulations were about 20% of the ablation depth. Corneas blown with moist nitrogen were indistinguishable from those which were not blown.

e. Conclusion

Blowing dry nitrogen across the corneal surface during excimer laser photo ablation increases surface roughness.

4. Effect of Nitrogen Blowing on Corneal Ablation Rates

a. Objective

To determine the effect of hydration on corneal ablation rates.

b. Test

Ablation rates were determined using corneal perforation for corneas ablated with dry nitrogen, moist nitrogen and no blown nitrogen.

c. Test Set Up

Fresh bovine corneas obtained from a local abattoir were ablated with a VISX /Twenty Excimer Laser using clinical laser settings. Varying amounts of nitrogen were blown across the corneas (0 to 20 SCFH), and one group of eyes was ablated with hydrated nitrogen (90% relative humidity) blown across the cornea. By determining the thickness of a cornea using an ultrasonic pachymeter and counting the number of pulses used to perforate the cornea, the average ablation rate of corneal tissue could be determined.

d. Results

Ablation rates for corneas which were not blown with nitrogen or blown with moist nitrogen were 0.27 $\mu$m/pulse, while those ablated with dry nitrogen blowing at 20 SCFH had ablation rates of 0.5 $\mu$m/pulse.

e. Conclusion

Blowing dry nitrogen across the corneal surface during excimer laser photo ablation increases ablation rates.

5. Effluent Removal Measurements

a. Objective

The measurements were performed to determine whether the effluent removal system of the VISX Excimer Laser System fully removed debris caused by ablation during the time between laser pulses, and to determine the optimal settings for the effluent removal system.

b. Test

A video camera was used to record the images of bovine corneas during excimer laser ablation. Single frame viewing of the tape demonstrated the effectiveness of the ablation removal.

c. Test Setup

The eye was illuminated from the side, so light scattered by the effluent could be viewed against a black background. The Excimer Laser System was operated at 6 Hz, ablating bovine eyes with constant diameter treatments. The video camera recorded images at 30 frames per second. The effluent removal system was operated at various settings from off up to the maximum.

d. Results

There is a rapidly ejected component of the effluent in addition to a hovering, cloudlike component of the effluent. The rapidly ejected component is completely removed within about 100 msec using any setting from one to ten of the effluent removal system, with a fresh filter and the nozzle in its standard position. The hovering component is not removed at any setting of the effluent removal system unless the nozzle is moved very close to the eye. This component can be blown away with an extremely gentle flow across the eye, suggesting that the effluent removal system does not cause much airflow across the eye.

e. Conclusions

For removal of the rapidly ejected effluent component, a mid-range setting of the effluent removal system is optimal. Higher settings have no advantage in removal, and lower settings may be inadequate once some clogging of the filter has occurred. The system does not remove the hovering component at any setting.

6. Profilometry of Corneal Ablations

a. Objective

To determine the shape of corneal ablations at different diameters and ablation depths using an excimer laser beam with a uniform irradiance profile.

b. Test

Ablation shapes of various diameters and depths in porcine corneas were measured with a custom optical profilometer.

c. Test Set Up

Fresh porcine corneas obtained from a local abattoir were ablated with an excimer system using clinical laser settings. Prior to ablating tissue, the laser was tested to ensure a uniform laser beam profile by measuring ablations in plastic. Subtracting post from pre ablation corneal elevations as determined by video images provided a measure of ablation shape. Ablations at depths of 10, 20, 40 and 80 $\mu$m and diameter of 6 mm diameter were measured. Also, -6 D PRK ablations of varying diameter were measured.

d. Results

The ablated corneas consistently showed ablation rates which were greater peripherally than centrally. This effect was more pronounced at large diameters. When measured at different intended ablation depths, the percent variation in ablation rates relative to the intended ablation was the same.

e. Conclusion

Even with a uniform laser beam profile, the cornea does not ablate evenly. This effect is dependent upon the ablation diameter and does not change significantly with ablation depth.

f. Publication

Shimmick et al., Cornea Ablation Profilometry and Factors Associated with Central Island Formation. *Invest Oph & Vis Sci*, Mar 15, 1995, 36(4), p. S1.

7. Corneal Healing Following Laser Refractive Keratectomy

a. Objective

To study the effect of edge profile and wound depth on reepithelialization and stromal healing.

b. Test

Ablated rabbit corneas are evaluated for reepithelialization and clarity.

c. Test Setup

A 193 nm excimer laser system was used to ablate 4.5-mm optically contoured zones in the corneal stroma of rabbits to achieve optical flattening of 2, 4, 8, and 16 diopters. Dichlorotriazinyl aminofluorescein, a vital dye that covalently binds the stromal bed and delineates the boundaries of new collagen synthesis, was placed in each eye post surgery.

d. Results

All the corneas reepithelialized; no subsequent recurrent erosions occurred. All seven corneas that received an ablation of less than 50 $\mu$m were clear centrally at 8 weeks. No evidence of new collagen formation or epithelial hyperplasia was found in any of these seven corneas. At an ablation depth of approximately 100 $\mu$m, opacification and scarring were observed biomicroscopically and histopathologically in two specimens. Stromal remodeling was observed in the two corneas that exhibited scarring.

e. Conclusion

For ablations that are less than 50 $\mu$m, no scarring, collagen regrowth, or epithelial hyperplasia was observed.

f. Publication

Good GL, et al., Corneal healing following laser refractive keratectomy. *Arch Ophthal* 107:1799-1803, 1989.

8. One-Year Refractive Results of Central Photorefractive Keratectomy for Myopia in the Nonhuman Primate Cornea

a. Objective

To determine the effects of PRK on nonhuman primate corneas.

b. Test

Predictability, stability and complications are evaluated.

c. Test Setup

Thirty-two eyes of 16 adult green monkeys underwent myopic PRK. Each eyes is randomly assigned to receive either a 42 pulse ablation (1.5 D flattening) or a 84 pulse ablation (3 D flattening). Eight monkeys were chosen randomly to receive mechanical debridement while the other eight had laser removal of the epithelium.

d. Results

The corneas healed satisfactorily, with normal formation of basal lamina and hemidesmosomal attachments visible in 14-week histologic specimens. No recurrent erosions were observed clinically. After a transient period of faint haze, all corneas were clear at 17 weeks and remained clear through the 1-year follow-up. In terms of accuracy, all corneas demonstrated a significant flattening compared with preoperative values, but no significant difference was seen between the groups with different intended corrections (1.5 and 3 diopters). The changes in corneal shape stabilized by 17 weeks, as measured by keratometry. The clinical results suggest that mechanical removal of the epithelium is preferable to laser ablation of the epithelium.

e. Conclusion

The results suggest that excimer laser ablation of the corneal stroma can produce a stable dioptric change in the primate cornea with good healing and long-term corneal clarity.

f. Publication

McDonald MB, et al., One year refractive results of central photorefractive keratectomy for myopia in the nonhuman primate cornea. *Arch Ophthal.* 108:40-47, 1990)

C. Additional Studies-- Electrical Safety and Electromagnetic Compatibility Testing

Model B was tested by Technischer Überwachungs Verein (TÜV) Rheinland of North America, Inc and CKC Laboratories Inc., and found to be in compliance with:

IEC 601-1 (1977)
IEC 601-1 (1988)
IEC 601-2-22 (1991)
IEC 825 (1984)
VDE Vfg 1046 Class B Requirements

Model C was tested by TÜV Rheinland of North America, Inc. and found to be in compliance with:

EN 60601-1
EN 60601-1-2
IEC 601-2-22
EN 55011
IEC 801-2,3,4,5

## IX. SUMMARY OF CLINICAL STUDIES

### A. Study Objectives

The objectives of the multicenter clinical investigation of the VISX excimer system for PTK, conducted under investigation device exemptions (IDE) application G890122, were to assess the safety and efficacy of PTK in improving vision and/or symptoms of pain that were caused by superficial corneal epithelial irregularities or stromal scars.

### B. Study Design

This was a prospective, nonrandomized, uncontrolled, unmasked multicenter clinical study.

### C. Inclusion and Exclusion Criteria

Study subjects were of any age; those under 18 must have parental/guardian consent. Enrollment occurred if the subject met these conditions: best corrected visual acuity not better than 20/40, pathology in the anterior one-third of the cornea, and the expected immediate post-treatment corneal thickness of at least 250 microns.

Subjects not meeting the above inclusion criteria were excluded from the study. In addition, subjects who exhibited any of the following conditions were also excluded: immunocompromised, uncontrolled uveitis, severe blepharitis, lagophthalmos, dry eyes, inability to tolerate procedure under local or topical anesthesia, unable to lie flat without difficulty, and inability to comply with preop medical therapy.

### D. Study Plan, Patient Assessments, and Efficacy Criteria

Subjects were evaluated preoperatively, every 24 to 48 hours postop until re-epithelialization, and at 1 and 3 months postoperatively. Although not provided for in the original protocol, additional follow-up was performed at 6, 12, and beyond 12 months postop.

Preoperatively, the subject's medical and ocular history were recorded. Postoperatively, subjects were asked about their tolerance for contact lenses and/or spectacles, and their comfort level. Objective measurements included: uncorrected visual acuity, manifest or cycloplegic refraction, keratometry, intraocular pressure, pachymetry, slit lamp examination of cornea and anterior segment, and dilated fundus examination.

Success or failure of the clinical procedure was determined by an improvement in comfort or best vision.

E. Study Period, Investigational Sites and Demographic Data

1. Study Period

The PTK study was conducted under an approved investigational device exemptions application G890122. A total of 291 eyes in 269 subjects were treated across 17 participating centers in the three phases of the study. Twenty-two subjects had both eyes treated. The 269 first eyes were included in the analysis and represent the basis for the safety and efficacy determination. The 22 fellow eyes were excluded from this analysis.

| Phase | Treatment Dates | Number of eyes |
|---|---|---|
| 1 | 7/1/89 to 9/11/89 | 10 |
| 2 | 12/11/89 to 8/10/90 | 30 |
| 3 | 8/20/90 to 5/18/93 | 229 |
| | TOTAL EYES* | 269 |

Of the 269 PMA cohort, 56 (21%) were considered as candidates for penetrating keratoplasty (PKP), 89 (33%) as candidates for lamellar keratectomy, and 124 (46%) could be considered as candidates for either surgery.

2. Investigational Sites

The following roster is the 17 sites that participated in the clinical investigation:

| Site | Number of Eyes |
|---|---|
| Doheney Medical Group, CA | 17 |
| LSU Eye Center, LA | 35 |
| Piedmont Ophthalmic Specialties, NC | 18 |
| Mericos Eye Center, CA | 9 |
| Wills Eye Hospital, PA | 20 |
| Wilmer Institute, MD | 33 |
| Saint Francis Medical Center, MO | 2 |
| Ellis Eye Center, CA | 7 |
| Massachusetts Eye and Ear Infirmary, MA | 5 |
| Manhattan Eye, Ear, and Throat Hospital, NY | 26 |
| New Jersey Eye Center, NJ | 1 |
| Genesee Valley Eye Care, NY | 44 |
| OshKosh Surgery Center, Ltd., WI | 16 |
| Dallas Eye Institute, TX | 5 |
| Kraff Eye Institute, IL | 14 |
| Eye Foundation of Kansas City, MO | 14 |
| O'Donnell Eye Institute, MO | 3 |
| Total | 269 |

3. Demographics

Within the 269 cases, there were 149 (55%) with scars and leukomas, 106 (39%) with corneal dystrophies, and 14 (5%) with corneal surface irregularities without scars or leukomas.

| Characteristics | Number of Subjects N=269 |
|---|---|
| Sex | |
| Male | 123 (46%) |
| Female | 146 (54%) |
| Race | |
| Caucasian | 245 (91%) |
| African American | 19 (7%) |
| Asian | 5 (2%) |
| Eye Treated | |
| Right | 151 (56%) |
| Left | 118 (44%) |
| Age (years) | |
| Mean (SD) | 54.4 (± 19) |
| Range | 5 to 90 |

F. Data Analysis and Results

1. Preoperative characteristics

Baseline characteristics for the 269 were as follows:

a Best corrected visual acuity (BCVA) with spectacles

Forty nine eyes (18%) had a preoperative BCVA of 20/40 or better. An additional 113 eyes (42%) were between 20/50 and 20/100, while 107 eyes (40%) had a baseline acuity worse than 20/100.

b. Uncorrected visual acuity (UCVA)

Six (2%) eyes had a preoperative UCVA better than 20/40. These underwent PTK, despite their good acuity, in order to improve comfort. An additional 56 (21%) eyes had preop UCVA between 20/50 and 20/100, and 207 (77%) eyes were worse than 20/100.

c. Comfort

Subjects were asked to assess the degree to which they experienced pain, tearing, photophobia, conjunctival erythema and foreign body sensation in the target eye. The grading scale was: none, mild, moderate and severe.

These conditions were rated preoperatively as moderate or severe by the indicated number of subjects: pain - 23 (10%), tearing - 19 (8%), photophobia - 68 (29%), erythema - 22 (10%), and foreign body sensation - 27 (11%)

d. Corneal clarity

These various layers of the cornea directly affected by the excimer ablation were graded independently: superficial epithelium, deep epithelium and anterior stroma. The scores were as follows: none/mild if refraction was not affected, moderate if refraction was affected but still possible, and severe if unable to refract.

In the 260 reported superficial epithelium scores, 158 (61%) were none/mild, 50 (19%) were moderate, and 52 (20%) were severe. For the 263 reported deep epithelium scores, 119 (45%) were none/mild, 78 (30%) were moderate, and 66 (25%) were severe. The 266 reported anterior stroma scores were: 55 (21%) none/mild, 123 (46%) moderate, and 88 (33%) severe.

e. Medical and Ophthalmic History

The 269 patients treated in this study had these pre-existing conditions. Many had multiple conditions so the percentages do not equal 100%.

| Condition | Number of subjects |
|---|---|
| Hypertension | 71 (26%) |
| Diabetes | 16 (6%) |
| Collagen vascular disease | 4 (1%) |
| Prior corneal trauma | 130 (48%) |
| Prior ocular surgery | 95 (35%) |
| Pathological condition | 65 (24%) |
| PKP | 35 (13%) |
| Glaucoma | 33 (12%) |
| Dry eye | 14 (5%) |
| Blepharitis | 2 (1%) |

2. Operative Characteristics

The excimer system was set at the following operating conditions:

| | | |
|---|---|---|
| Pulse Rate | | 5 Hz |
| Pulse Duration | | 20 nsec |
| Mean number of pulses | | 353 pulses |
| Fluence | | 160 ± 8 mJ/cm$^2$ |
| Ablation zone | Mean ± SD | 4.9 ± 1.2 mm |
| | Range | 0.6 to 6.0 mm |

Preoperatively, 109 patients received analgesic or sedative.

In the 265 cases where epithelium removal was required, 150 (56%) were performed with the laser and 115 (44%) were by mechanical scraping. No mechanical treatment was allowed beyond epithelium removal.

3. Postoperative Characteristics and Results

a. Patient Accountability

The study period was extended from 3 months as described in the original protocol to one year or more. At 1 year or later, 222 (83%) of 269 eyes were examined.

| Status | Preop | 3 M | 6 M | 1 Yr | ≥ 1 Yr |
|---|---|---|---|---|---|
| Eligible for visit | 269 | 261 (97% or 261/269) | 244 (91%) | 229 (85%) | 222 (83%) |
| Evaluated at visit* | 269 (100%) | 240 (92% or 240/261) | 146 (60%) | 138 (60%) | 222 (100%) |
| Not evaluated at visit (#/269 %) | | | | | |
| Missed visit | 0 | 21 (8%) | 98 (40%) | 91 (40%) | 0 |
| Removed from study prior to visit** | 0 | 1 (0%) | 2 (1%) | 2 (1%) | 2 (1%) |
| Retreated prior to visit | 0 | 1 (0%) | 1 (0%) | 8 (3%) | 9 (3%) |
| Died or terminally ill before visit | 0 | 1 (0%) | 2 (1%) | 3 (1%) | 9 (3%) |
| Lost to follow-up | 0 | 5 (2%) | 20 (7%) | 27 (10%) | 27 (10%) |

* Include cases with PKP before visit: 3 (3 months), 7 (6 months), 12 (1 year), and 15 (≥ 1 year).

** One subject with herpetic keratitis scar with pre-treatment history of recurrent epithelial breakdown failed to re-epithelialize after 16 days. Subject moved to another study for persistent epithelial defect.
One subject had radial keratotomy performed.

b. Re-epithelialization

Seventy percent (188/269) of subjects were re-epithelialized or discharged with a small defect (predicted by the investigator to heal without difficulty within 24 hours) by 4 days post treatment, 240/269 (89%) by 7 days post treatment, and 261/269 (97%) by 30 days post treatment.

Of the remaining 8 (2%, 8/269) subjects who had not re-epithelialized within the first 30 days, four re-epithelialized by the next visit at day 31, 35, 89, and 99 respectively. The other four failed to re-epithelialize due to pre-existing ocular pathology: one subject had a herpetic scar with pre-treatment history of recurrent epithelial breakdown, and was removed from the current study after 16 days and placed in a clinical study for persistent epithelial defects; two subjects, one with neurotrophic keratitis and the other with an alkali burn, had failed PKP prior to PTK and then underwent a repeat PKP after PTK; and, one subject with previous alkali burn, was re-treated 3 weeks after initial PTK because of failure to re-epithelialize, and was finally treated with a temporary tarsorrhaphy.

c. BCVA with spectacles

| BCVA | PREOP n = 269 | 3M n = 238 | 6M n= 130 | 1 Yr n = 127 | ≥ 1 Yr n = 205 |
|---|---|---|---|---|---|
| | | | | | |
| 20/40 or Better | 49 (18%) | 97 (41%) | 53 (41%) | 60 (47%) | 96 (47%) |
| 20/50 - 20/100 | 113 (42%) | 93 (39%) | 52 (40%) | 47 (37%) | 72 (35%) |
| Worse than 20/100 | 107 (40%) | 48 (20%) | 25 (19%) | 20 (16%) | 37 (18%) |
| | | | | | |
| Not tested | 0 | 2 | 16 | 11 | 17 |

The percent of post-op cases with a spectacle BCVA of 20/40 or better, at each visit, shows a statistically significant improvement from preop ($p<0.01$).

d. Changes in BCVA from preop

| Lines | 3 M n = 238 | 6 M n = 130 | 1 Yr n = 127 | ≥ 1 Yr n = 205 |
|---|---|---|---|---|
| No Change ± 1* | 114 (48%) | 57 (44%) | 48 (38%) | 80 (39%) |
| Increase 2 | 22 (9%) | 18 (14%) | 13 (10%) | 24 (12%) |
| 3 | 23 (10%) | 14 (11%) | 24 (19%) | 30 (15%) |
| 4 | 16 (7%) | 5 (4%) | 6 (%%) | 10 (5%) |
| 5 | 18 (8%) | 5 (4%) | 8 (6%) | 15 (7%) |
| 6 | 4 (2%) | 9 (7%) | 8 (6%) | 11 (5%) |
| 7 | 12 (5%) | 4 (3%) | 3 (2%) | 6 (3%) |
| 8 | 5 (2%) | 1 (<1%) | 1 (<1%) | 5 (2%) |
| 9 | 1 (<1%) | 0 | 3 (2%) | 4 (2%) |
| 10 or more | 2 (1%) | 4 (3%) | 3 (2%) | 3 (2%) |
| Total increase | 103 (43%) | 60 (46%) | 69 (54%) | 108 (53%) |
| Decrease 2 | 10 (4%) | 4 (31%) | 3 (2%) | 3 (2%) |
| 3 | 4 (2%) | 4 (3%) | 4 (3%) | 6 (3%) |
| 4 | 2 (<1%) | 0 | 1 (<1%) | 2 (1%) |
| 5 | 2 (<1%) | 2 (2%) | 2 (2%) | 2 (1%) |
| 6 | 2 (<1%) | 2 (2%) | 0 | 1 (<1%) |
| 7 | 1 (<1%) | 1 (<1%) | 0 | 2 (1%) |
| 8 | 0 | 0 | 0 | 0 |
| 9 | 0 | 0 | 0 | 1 (<1%) |
| total decrease | 21 (9%) | 13 (10%) | 10 (8%) | 17 (8%) |
| | | | | |
| Not tested at visit | 2 | 16 | 11 | 17 |

*NO CHANGE ≡ ± 1 lines as defined by Kremer et al., Radial Keratotomy: Prospective evaluation of safety and efficacy, Ophth. Surg. 14:925-930, 1983.

The mean line was a statistically significant gain of 1.8 ± 0.2 (SEM) lines at 3 months ($p<0.0001$) and 2.2 ± 0.2 (SEM) at the later than one year visit ($p<0.0001$ with sign test).

There were 3 possible reasons for decreased vision at ≥ 1 year. In 5 (1.8%, 5/269) the visual loss was possibly related to some corneal surface irregularity induced by the PTK procedure itself. In 7 (2.6%, 7/269) cases, other unrelated pre-existing disease or a recurrence of the underlying corneal pathology resulted in a visual loss. In 2 (0.7%,2/269) cases, the vision fluctuated from visit to visit possibly as a result of pre-existing corneal or other pathology. In the remaining 3 (1.1%, 3/269) cases, PKP was performed before the 1 year visit. Prior to PKP, their visual acuity was decreased from pre-treatment.

e. Changes in Uncorrected Visual Acuity

| UCVA Change | 3 M<br>n = 234 | 6 M<br>n = 136 | 1 Yr<br>n = 128 | ≥ 1 Yr<br>n = 198 |
|---|---|---|---|---|
| | | | | |
| Gain ≥ 2 lines | 97 (42%) | 50 (37%) | 59 (46%) | 91 (46%) |
| No change ≤1 line | 94 (40%) | 61 (45%) | 48 (38%) | 78 (39%) |
| Loss ≥ 2 lines | 43 (18%) | 25 (18%) | 21 (16%) | 29 (15%) |
| | | | | |
| Data not available | 6 | 10 | 10 | 24 |

Spontaneous improvement in visual acuity is virtually unknown in this group of subjects. The mean line was a statistically significant gain of 1.13± 0.24 (SEM) lines ($p<0.0002$ with sign test) at 3 months and 1.73 ± 0.27 (SEM) lines ($p<0.0001$ with sign test) at 1 year or later.

f. Manifest Refraction (spherical equivalent)

Because of the corneal pathology, refraction was unobtainable at some time periods and thus the total number of cases evaluated refractively from one time period to another is markedly decreased when compared to the other studied variables.

| Manifest Refraction (spherical equivalent) | Preop n = 165[1] | 3M n = 184[2] | 6M n = 102[3] | 1 Yr n = 101[4] | ≥ 1 Yr n = 158[5] |
|---|---|---|---|---|---|
| | | | | | |
| Myopic ≥ 5.0 | 17 (10%) | 10 (5%) | 3 (3%) | 4 (4%) | 9 (6%) |
| 4.0-4.99 | 6 (4%) | 6 (3%) | 1 (1%) | 1 (1%) | 2 (1%) |
| 3.0-3.99 | 8(5%) | 5 (3%) | 1 (1%) | 0 | 3 (2%) |
| 2.0-2.99 | 7 (4%) | 8 (4%) | 5 (5%) | 7 (7%) | 7 (4%) |
| 1.01-1.99 | 20 (12%) | 7 (4%) | 4 (4%) | 6 (6%) | 11 (7%) |
| | | | | | |
| Emmetropic ± 1.00 | 61 (37%) | 48 (26%) | 32 (31%) | 27 (27%) | 44 (28%) |
| | | | | | |
| Hyperopic 1.01-1.99 | 18 (11%) | 15 (8%) | 7 (7%) | 11 (11%) | 20 (13%) |
| 2.0-2.99 | 14 (8%) | 14 (8%) | 10 (10%) | 9 (9%) | 12 (8%) |
| 3.0-3.99 | 7 (4%) | 19 (10%) | 11 (10%) | 10 (10%) | 16 (10%) |
| 4.0-4.99 | 0 | 12 (7%) | 9 (9%) | 4 (4%) | 6 (4%) |
| >5.0 | 7 (4%) | 40 (22%) | 19 (19%) | 22 (22%) | 28 (18%) |

Percentages do not add up to 100% due to rounding error.

Legends:

| | |
|---|---|
| refrac = | manifect refraction was measured |
| eligible = | number of eyes eligible for this visit |
| unable = | testing could not be performed because of the underlying pathology |
| not measured = | parameter was not measured at visit |
| others = | unknown |

1. refrac = 165; total = 269; unable = 57; not measured = 28; and, others = 19
2. refrac = 184; total = 240; unable = 32; not measured = 22; and, others = 2
3. refrac = 102; total = 146; unable = 21; not measured = 21; and, others = 2
4. refrac = 101; total = 138; unable = 18; not measured = 17; and, others = 2
5. refrac = 158; total = 222; unable = 35; not measured = 25; and, others = 4

The average refractive change was 2.4 D at 3 months and 2.3 D at > 1 year post-treatment. At each post-op visit, the percent of eyes that are more myopic than 1.0 D showed a statistically significantly decrease from preop ($p < 0.02$). Conversely, the percent of eyes that are more hyperopic than 1.0 D at each post-op visit shows a statistically significantly increase from preop. While only 14/165 (8%) of cases were hyperopic by ≥ 3D pre-treatment, 71/184 (39%) at 3 months and 50/158 (32%) at ≥ 1 year post-treatment were this hyperopic. A shift in the hyperopic direction occurs

between pre-treatment and post-treatment. Hyperopic shift is discussed in detail in section "e. Analysis of Hyperopic Shift" below.

d. Stability of Manifest Refraction

The table below demonstrates refractive stability between 3 and 6 months, 3 months to ≥ 1 year, and 6 months to ≥ 1 year. Manifest refraction was reported to be stable over time with no statistically significant differences in the frequency of cases within ± 1 D between the various time periods.

| | 3M to 6M<br>n = 89 | 3M to ≥ 1 Yr<br>n = 137 | 6M to ≥ 1 Yr<br>n = 81 |
|---|---|---|---|
| | | | |
| Myopic > 5.0 | 2 (2%) | 9 (7%) | 3 (4%) |
| 4.0 - 4.99 | 2 (2%) | 2 (1%) | 2 (2%) |
| 3.0 - 3.99 | 4 (4%) | 6 (4%) | 2 (2%) |
| 2.0 - 2.99 | 4 (4%) | 7 (5%) | 2 (2%) |
| 1.01 - 1.99 | 10 (11%) | 14 (10%) | 5 (6%) |
| Total toward myopia | 22 (25%) | 38 (27%) | 14 (17%) |
| | | | |
| Within ±1D | 51 (57%) | 68 (50%) | 56 (69%) |
| | | | |
| Hyperopic 1.01 - 1.99 | 9 (10%) | 14 (10%) | 4 (5%) |
| 2.0 - 2.99 | 2 (2%) | 8 (6%) | 2 (2%) |
| 3.0 - 3.99 | 1 (2%) | 3 (2%) | 2 (2%) |
| 4.0 - 4.99 | 1 (1%) | 1 (1%) | 0 |
| > 5.0 | 3 (3%) | 5 (4%) | 3 (4%) |
| Total toward hyperopia | 16 (18%) | 31 (23%) | 11 (14%) |

Percentages do not add up to 100% due to rounding error.

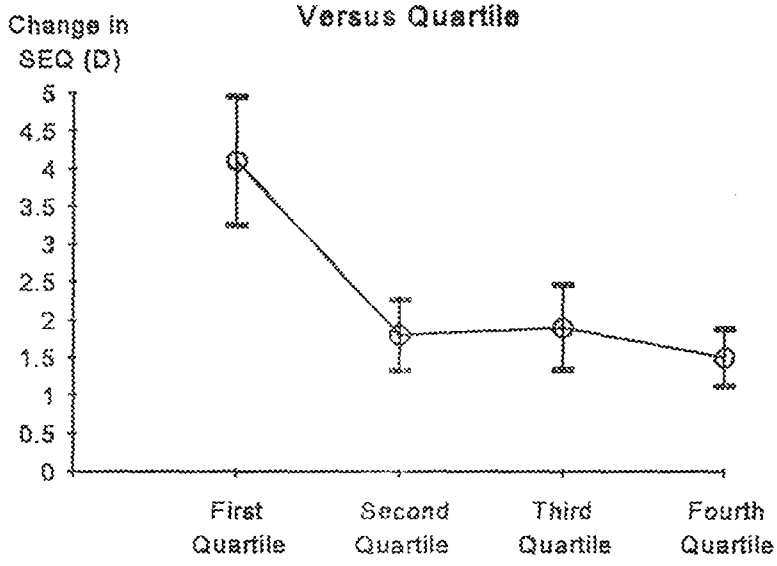
e. Analysis of Hyperopic Shift

The hyperopic shift observed in this study is possibly attributed to the learning curve associated with a new procedure. This can be seen by grouping the subjects into four equal groups based on their dates of treatment. Only those subjects with refractive data available at preop and ≥ 1 year postop were included in this analysis.

| Quartile | Dates of Treatments | No. of subjects |
|---|---|---|
| Q1 | 7/31/89 to 1/23/91 | 28 |
| Q2 | 1/24/91 to 9/23/91 | 28 |
| Q3 | 9/24/91 to 7/18/92 | 28 |
| Q4 | 7/19/92 to 4/20/93 | 27 |

One hundred eleven subject had refractions available for this analysis. In Q1 group, the average refractive change from preop was +4.1 D. In Q4 group, the average refractive change from preop was +1.5 D. The difference in refractive change between Q1 and all the other quartiles was statistically significant (p=0.003). The average change from preop in spherical equivalent is shown in Figure 1.

Figure 1
Change in Spherical Equivalent (SEQ) Versus Quartile




The vertical bars represent ±1 standard error of the mean.

This statistically significant difference could not be explained by gender, age or reason for therapeutic treatment. Although the mean spherical equivalent refractions between the various quartiles are not significantly different from one another at preop nor at postop, multiple regression analysis revealed that the change in spherical equivalent refraction for each quartile from preop was significantly influenced by treatment date ($p=0.001$) and pre-treatment spherical equivalent ($p=0.006$). Subjects treated later in the investigation experienced less hyperopic change in spherical equivalent than those enrolled at an earlier date. It is theorized that those who were treated earlier in the protocol received a more aggressive treatment for their pathologies.

Independent of treatment date, subjects who were myopic pre-treatment experienced a greater hyperopic change in spherical equivalent than those who were hyperopic pre-treatment.

f. Comfort

At pre-treatment and post-treatment visits, subjects were asked to judge the degree to which they experienced pain, tearing, photophobia, conjunctival erythema (physician assessment) and foreign body sensation. The conditions were graded on a scale: none, mild, moderate, or severe.

Overall, the subjects believed that their conditions improved. Seven patients who graded their condition as none or mild at preop had graded their discomfort level as moderate or severe at $\geq$ 1 year postop; however, 4 experienced an improvement in corneal clarity.

The post-op responses of those who at preop experienced moderate or severe pain were as follows.

| CONDITION | | 3 M | 6 M | 1 Yr | ≥ 1 Yr |
|---|---|---|---|---|---|
| | | | | | |
| Pain n = 23 | Improvement | 23 | 13 | 13 | 20 |
| | Same | 0 | 0 | 0 | 0 |
| | Worse | 0 | 0 | 0 | 0 |
| | Not known | 0 | 10 | 10 | 3 |
| | | | | | |
| Tearing n = 19 | Improvement | 19 | 11 | 11 | 16 |
| | Same | 0 | 0 | 0 | 1 |
| | Worse | 0 | 0 | 0 | 0 |
| | Not known | 0 | 8 | 8 | 2 |
| | | | | | |
| Photophobia n = 68 | Improvement | 59 | 34 | 32 | 49 |
| | Same | 9 | 2 | 5 | 8 |
| | Worse | 0 | 1 | 0 | 3 |
| | Not known | 0 | 31 | 31 | 8 |
| | | | | | |
| Conjunctival erythema n = 22 | Improvement | 21 | 15 | 9 | 18 |
| | Same | 1 | 1 | 1 | 1 |
| | Worse | 0 | 0 | 0 | 1 |
| | Not known | 0 | 6 | 12 | 2 |
| | | | | | |
| Foreign body sensation n = 27 | Improvement | 27 | 13 | 17 | 24 |
| | Same | 0 | 0 | 0 | 0 |
| | Worse | 0 | 0 | 0 | 0 |
| | Not known | 0 | 14 | 10 | 3 |

g. Corneal Clarity

The clarity of the superficial epithelium, deep epithelium, and anterior stroma were graded as: none/mild if refraction was not affected, moderate if refraction was affected but still possible, and severe if unable to refract. Clarity may be affected by haze or opacity.

| Corneal Layer | | Preop n = 269 | 3 M n = 240 | 6 M n = 146 | 1 Yr n = 138 | ≥ 1 Yr n = 222 |
|---|---|---|---|---|---|---|
| Superficial epithelium | None/Mild | 158 | 211 | 132 | 121 | 191 |
| | Moderate | 50 | 18 | 7 | 8 | 12 |
| | Severe | 52 | 6 | 2 | 3 | 7 |
| | Not reported | 9 | 5 | 5 | 6 | 12 |
| Deep epithelium | None/Mild | 119 | 199 | 125 | 116 | 184 |
| | Moderate | 78 | 26 | 13 | 13 | 17 |
| | Severe | 66 | 10 | 3 | 3 | 8 |
| | Not reported | 6 | 5 | 5 | 6 | 13 |
| Anterior stroma | None/Mild | 55 | 142 | 92 | 82 | 142 |
| | Moderate | 123 | 76 | 39 | 42 | 51 |
| | Severe | 88 | 18 | 10 | 8 | 13 |
| | Not reported | 3 | 4 | 5 | 6 | 16 |

Overall, the clarity of the cornea improved post PTK as indicated by a significant improvement in mean clinical clarity scores for all three layers of the cornea ($p < 0.0001$).

At ≥ 1 year, 7 eyes received a severe score for all three layers. Four of these eyes were also graded as severe preoperatively. Of the seven patients, 5 demonstrated improvement in at least one or more of the patient comfort symptoms assessed (i.e., pain, tearing, photophobia, conjunctival erythema or foreign body sensation). The remaining two patients showed no improvement post-PTK in either BCVA or comfort symptoms. Both were treated with the excimer system which was thought to be less invasive than the only other therapeutic option of penetrating keratoplasty. One of



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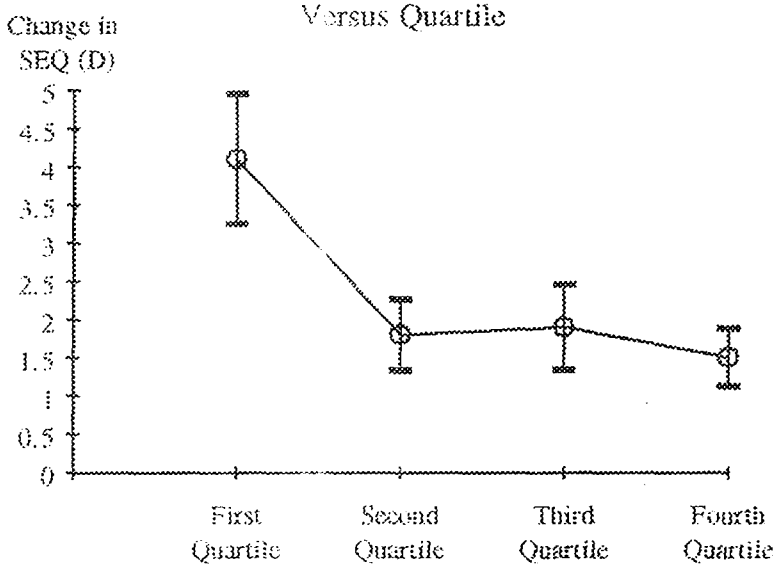
these two patients had a history of Grave's disease with prior orbital decompression and corneal neovascularization. Following PTK this patient experienced a recurrence of the corneal neovascularization with a hypertrophic corneal scar. The second patient who showed no improvement also had a history significant for corneal neovascularization and a dense central scar. Additionally, this patient underwent an unsuccessful PKP procedure prior to treatment. Post-treatment this patient underwent a radiation keratoplasty.

There were 4 patients who worsened from preop.

h. Intraocular Pressure

Figure 2 demonstrates that there is no trend toward increased IOP in the PTK subjects. Some subjects showed transiently elevated IOP, probably due to postop steroid use.

Figure 1
Change in Spherical Equivalent (SEQ) Versus Quartile



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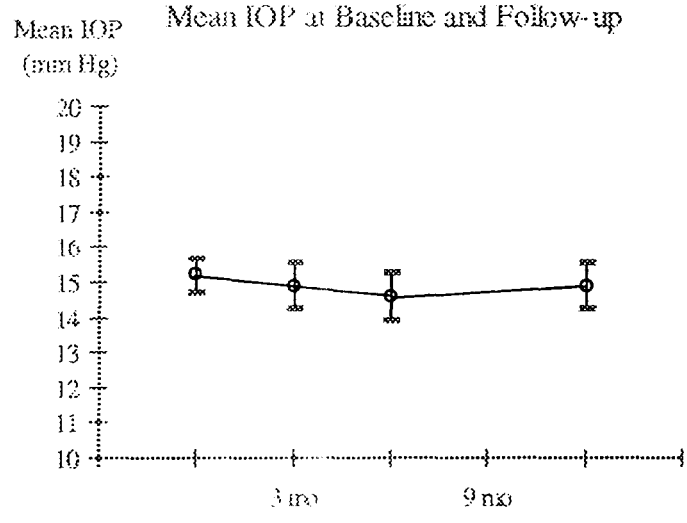
g. Pachymetry

As expected, average pachymetry dropped since a portion of the anterior stroma is ablated. The mean average pachymetry dropped 60 microns between the baseline and one year or later.

Figure 2
Mean IOP at Baseline and Follow-up




h. Complications and Adverse Events

Immediately postop, the most common occurrence 6/269 (2.2%) was a transient increase in IOP, possibly related to the use of postoperative topical corticosteroids. The ocular hypertension resolved in all cases when topical corticosteroid was discontinued. Herpes simplex virus infection occurred in three subjects (1.1%) who received no anti-viral medication and were treated for corneal scarring which was not known to be herpetic (e.g., leukoma). Delayed reepithelialization with secondary corneal ulceration occurred in a diabetic with band keratopathy secondary to neurotrophic keratitis.

The most frequently encountered adverse events and complications in the post-op period were:

| Condition | | Rate (n = 269) |
|---|---|---|
| Delayed Re-epithelialization at > 1 week postop | | 25 (9%) |
| Transient increase in IOP | | 6 (2%) |
| Recurrence/Reactivation of herpes simplex keratitis | | 3 (1%) |
| Non-herpetic late corneal infection/ulcer | | 2 (1%) |
| Recurrent dystrophy | | 3 (1%) |
| Corneal vascularization | | 1 (> 1%) |
| Increased corneal haze at ≥ 1 year | Superficial epithelium | 7/205 (3%) |
| | Deep epithelium | 10/206 (5%) |
| | Anterior Stroma | 8/204 (4%) |
| New anisometropia >3D at ≥ 1 year | | 40/113 (35%) |

3. Additional PTK Treatment

Nine of 269 cases (4%) required retreatment from 3 weeks to 12 months post PTK, largely for insufficient effect at initial treatment. One additional subject was treated after the 1 year visit. There were no further complications or adverse effects in this small group of retreated cases.

4. Additional Surgical Intervention

A total of 13 of 269 cases (4.8%) required PKP within 1 year of PTK and an additional 5 cases (1.9%) had PKP after 1 year follow-up for a total of 18/269 (6.7%) Of these 18 cases, 4 required PKP due to persistent or recurrent epithelial defects or breakdown and the remainder were treated because of insufficient improvement in visual function for the subject's needs.

5. Device Failures

The following represents a summary of device failures reported to date on a worldwide basis for the VISX Excimer Laser System. No permanent injury has been reported from any of these failures.

a. One laser stopped firing during a patient treatment. It was restarted and treatment was completed satisfactorily. Later, it could not be started. Replacement of a defective part (thyratron) by a service technician corrected the problem.

b. Another two laser systems stopped firing during patient treatments. Again treatment was completed satisfactorily. An upgrade of the system software corrected the problem.

c. A fourth laser stopped firing during a patient treatment because of a broken shutter hinge. Treatment was suspended after 90% completion. The shutter hinge material was changed from plastic to stainless steel and all laser systems were retrofitted with the new hinges.

d. A fifth laser had an intermittent failure (block) of the iris motor. The block was cleared and the treatment was completed. The block was caused by a positioning sensor which was re-aligned by a service technician.

## X. CONCLUSIONS DRAWN FROM THE CLINICAL STUDIES

### A. Stratification of Results by Diagnoses

Outcomes stratified by diagnostic categories are presented below in tables.

### B Adverse Events

Although no acute vision-threatening complications presented during this clinical study with the VISX Excimer Laser System, the potential exists for corneal perforation, acute bacterial keratitis, reactivation of herpetic keratitis, endophthalmitis, hypopyon, and corneal decompensation.

VISX EXCIMER LASER SYSTEM: PHOTOTHERAPEUTIC KERATECTOMY
PATIENT ACCOUNTABILITY BY DIAGNOSIS
(COHORT PATIENTS, USING ALL AVAILABLE DATA IN THE SUBMISSION)

| Diagnosis | Scars & Leukomas | Dystrophies | Surface Irregularities without Scar | All Patients Treated |
|---|---|---|---|---|
| TOTAL EVALUABLE | 143 (80%) | 74 (87%) | 5 (83%) | 222 (83%) |
| Evaluated** | 143 [100%] | 74 [100%] | 5 [100%] | 222 [100%] |
| Not Evaluated (missed visit) | 0 [0%] | 0 [0%] | 0 [0%] | 0 [0%] |
| NOT EVALUABLE | 35 (20%) | 11 (13%) | 1 (17%) | 47 (17%) |
| Removed From Study Prior to Visit* | 2 (1%) | 0 (0%) | 0 (0%) | 2 (1%) |
| Retreated Prior to Visit | 7 (4%) | 1 (1%) | 1 (17%) | 9 (3%) |
| Died or Terminally Ill Before Visit | 8 (4%) | 1 (1%) | 0 (0%) | 9 (3%) |
| Lost to Follow-up at or Before Visit | 18 (10%) | 9 (11%) | 0 (0%) | 27 (10%) |
| TOTAL ENROLLED | 178 (100%) | 85 (100%) | 6 (100%) | 269 (100%) |

(%) Percentage based on TOTAL ENROLLED: 178 (Scars & Leukomas), 85 (Dystrophies), 6 (Surface Irregularities without Scar), and 269 (All Patients Treated).

[%] Percentage based on TOTAL EVALUABLE: 143 (Scars & Leukomas), 74 (Dystrophies), 5 (Surface Irregularities without Scar), and 222 (All Patients Treated).

* 1) Herpetic keratitis scar with pre-treatment history of recurrent epithelial breakdown failed to reepithelialize after 16 days. Placed in a clinical study for persistent epithelial defect.
2) Radial keratotomy performed.

** Include PKP cases: 11 (Scars & Leukomas), 2 (Dystrophies), 2 (Surface Irregularities without Scar), and 15 (All Patients Treated).

VISX EXCIMER LASER SYSTEM: PHOTOTHERAPEUTIC KERATECTOMY
EFFICACY AND SAFETY RESULTS AT ≥ 1 YEAR STRATIFIED BY DIAGNOSIS
(COHORT PATIENTS, USING ALL AVAILABLE DATA IN THE SUBMISSION)

| Diagnosis | Scars & Leukomas | Dystrophies | Surface Irregularities without Scar | All Patients Treated |
|---|---|---|---|---|
| | | | | |
| I. VISION: BCVA | | | | |
| Pre-op BCVA 20/40 or Better | 27/178 (15.2%) | 22/85 (25.9%) | 0/6 (0%) | 49/269 (18.2%) |
| Post-op BCVA 20/40 or Better at ≥ 1 Year | 49/133 (36.8%) | 47/70 (67.1%) | 0/2 (0%) | 96/205 (46.8%) |
| Pre-op BCVA 20/25 or Better | 9/178 (5.1%) | 3/85 (3.5%) | 0/6 (0%) | 12/269 (4.5%) |
| Post-op BCVA 20/25 or Better at ≥ 1 Year | 21/133 (15.8%) | 18/70 (25.7%) | 0/2 (0%) | 39/205 (19.0%) |
| Pre-op BCVA 20/20 or Better | 3/178 (1.7%) | 1/85 (1.2%) | 0/6 (0%) | 4/269 (1.5%) |
| Post-op BCVA 20/20 or Better at ≥ 1 Year | 10/133 (7.5%) | 5/70 (7.1%) | 0/2 (0%) | 15/205 (7.3%) |
| Gain of 2 Lines or More BCVA at ≥ 1 Year | 61/133 (45.9%) | 47/70 (67.1%) | 0/2 (0%) | 108/205 (52.7%) |
| Loss of 2 Lines or More BCVA at ≥ 1 Year | 14/133 (10.5%) | 3/70 (4.3%) | 0/2 (0%) | 17/205 (8.3%) |
| | | | | |
| II. CORNEAL CLARITY | | | | |
| Deep Epithelial Opacity Improvement ≥ 2 Categories at ≥ 1 Year | 66/132 (50.0%) | 43/70 (61.4%) | 0/4 (0%) | 109/206 (52.9%) |
| Anterior Stromal Opacity Improvement ≥ 2 Categories at ≥ 1 Year | 76/133 (57.1%) | 39/67 (58.2%) | 1/4 (25.0%) | 116/204 (56.9%) |
| Deep Epithelial Opacity Improvement ≥ 2 Categories & Pre-op Opacity ≥ 1.5 at ≥ 1 Year | 62/76 (81.6%) | 36/41 (87.8%) | 0/1 (0%) | 98/118 (83.1%) |
| Anterior Stromal Opacity Improvement ≥ 2 Categories & Pre-op Opacity ≥ 1.5 at ≥ 1 Year | 71/110 (64.5%) | 36/50 (72.0%) | 1/4 (25.0%) | 108/164 (65.9%) |
| | | | | |

VISX EXCIMER LASER SYSTEM: PHOTOTHERAPEUTIC KERATECTOMY
EFFICACY AND SAFETY RESULTS AT ≥ 1 YEAR STRATIFIED BY DIAGNOSIS
(COHORT PATIENTS, USING ALL AVAILABLE DATA IN THE SUBMISSION)

| Diagnosis | Scars & Leukomas | Dystrophies | Surface Irregularities without Scar | All Patients Treated |
|---|---|---|---|---|
| | | | | |
| III. REFRACTION | | | | |
| Change in Spherical Equivalent >+1 to +3 Diopters at ≥ 1 Year | 19/65 (29.2%) | 10/46 (21.7%) | 0/0 (-%) | 29/111 (26.1%) |
| Change in Spherical Equivalent > 3 Diopters at ≥ 1 Year | 18/65 (27.7%) | 17/46 (37.0%) | 0/0 (-%) | 35/111 (31.5%)* |
| Pre-op Anisometropia > +1 to +3 Diopters | 29/97 (29.9%) | 17/64 (26.6%) | 0/0 (-%) | 46/161 (28.6%) |
| Post-op Anisometropia > +1 to +3 Diopters at ≥ 1 Year | 25/73 (34.2%) | 17/54 (31.5%) | 0/0 (-%) | 42/127 (33.1%) |
| Pre-op Anisometropia > +3 Diopters | 19/97 (19.6%) | 11/64 (17.2%) | 0/0 (-%) | 30/161 (18.6%) |
| Post-op Anisometropia > +3 Diopters at ≥ 1 Year | 26/73 (35.6%) | 24/54 (44.4%) | 0/0 (-%) | 50/127 (39.4%)** |
| | | | | |

*Improved to 23/95 (24.2%) for phase III patients.
**Improved to 33/106 (31.1%) for phase III patients.

VISX EXCIMER LASER SYSTEM: PHOTOTHERAPEUTIC KERATECTOMY
EFFICACY AND SAFETY RESULTS AT ≥ 1 YEAR STRATIFIED BY DIAGNOSIS
(COHORT PATIENTS, USING ALL AVAILABLE DATA IN THE SUBMISSION)

| Diagnosis | Scars & Leukomas | Dystrophies | Surface Irregularities without Scar | All Patients Treated |
|---|---|---|---|---|
| IV. PATIENT COMFORT SYMPTOMS | | | | |
| Pre-op % of Patients with Moderate / Severe Ocular Discomfort | | | | |
| Pain | 15/178 (8.4%) | 12/85 (14.1%) | 0/6 (0%) | 27/269 (10.0%) |
| Photophobia | 52/178 (29.2%) | 24/85 (28.2%) | 1/6 (16.7%) | 77/269 (28.6%) |
| Foreign Body Sensation | 18/177 (10.2%) | 11/85 (12.9%) | 1/6 (16.7%) | 30/268 (11.2%) |
| Tearing | 13/178 (7.3%) | 8/85 (9.4%) | 0/6 (0%) | 21/269 (7.8%) |
| Conjunctival Erythema | 17/178 (9.6%) | 5/85 (5.9%) | 5/6 (83.3%) | 27/269 (10.0%) |
| Post-op % of Patients with Moderate / Severe Ocular Discomfort at ≥ 1 Year for Patients with None / Mild Ocular Discomfort Pre-op | | | | |
| Pain | 1/129 (0.8%) | 1/59 (1.7%) | 1/4 (25.0%) | 3/192 (1.6%) |
| Photophobia | 6/98 (6.1%) | 4/50 (8.0%) | 1/4 (25.0%) | 11/152 (7.2%) |
| Foreign Body Sensation | 3/123 (2.4%) | 1/60 (1.7%) | 1/4 (25.0%) | 5/187 (2.7%) |
| Tearing | 3/127 (2.4%) | 1/64 (1.6%) | 1/4 (25.0%) | 5/195 (2.6%) |
| Conjunctival Erythema | 3/125 (2.4%) | 0/65 (0%) | 0/1 (0%) | 3/191 (1.6%) |
| Post-op % of Patients with Moderate / Severe Ocular Discomfort at ≥ 1 Year for Patients with Moderate / Severe Ocular Discomfort Pre-op | | | | |
| Pain | 0/9 (0%) | 0/11 (0%) | 0/0 (-%) | 0/20 (0%) |
| Photophobia | 12/40 (30.0%) | 2/20 (10.0%) | 0/0 (-%) | 14/60 (23.3%) |
| Foreign Body Sensation | 0/14 (0%) | 0/10 (0%) | 0/0 (-%) | 0/24 (0%) |
| Tearing | 2/11 (18.2%) | 0/6 (0%) | 0/0 (-%) | 2/17 (11.8%) |
| Conjunctival Erythema | 2/12 (16.7%) | 0/5 (0%) | 1/3 (33.3%) | 3/20 (15.0%) |

VISX EXCIMER LASER SYSTEM: PHOTOTHERAPEUTIC KERATECTOMY
EFFICACY AND SAFETY RESULTS AT ≥ 1 YEAR STRATIFIED BY DIAGNOSIS
(COHORT PATIENTS, USING ALL AVAILABLE DATA IN THE SUBMISSION)

| Diagnosis | Scars & Leukomas | Dystrophies | Surface Irregularities without Scar | All Patients Treated |
|---|---|---|---|---|
| | | | | |
| V. OTHERS | | | | |
| (a) Re-epithelialization | | | | |
| Delayed re-epithelialization > 7 Days | 17/ 176 (9.7%) | 7/85 (8.2%) | 1/4 (25.0%) | 25/265 (9.4%)* |
| | | | | |
| (b) Retreatment | | | | |
| Retreated at ≤ 1 Year | 7/178 (3.9%) | 0/85 (0%) | 1/6 (16.7%) | 8/269 (3.0%) |
| Retreated at > 1 Year | 1/178 (0.6%) | 1/85 (1.2%) | 0/6 (0%) | 2/269 (0.7%) |
| | | | | |
| © PKP | | | | |
| PKP at ≤ 1 Year | 9/178 (5.1%) | 2/85 (2.4%) | 2/6 (33.3%) | 13/269 (4.8%) |
| PKP at > 1 Year | 4/178 (2.2%) | 1/85 (1.2%) | 0/6 (0%) | 5/269 (1.9%) |
| | | | | |
| VI. N | | | | |
| Total with Pre-op Data | 178 | 85 | 6 | 269 |
| Total with Post-op Visits at ≥ 1 Year | 143 | 74 | 5 | 222 |
| | | | | |

*Improved to 13/232 (5.6%) for phase III patients.

C. Complications

The most frequently encountered complications in the post-op period were: 32% with hyperopic shift greater than +3.0D, 35% with induced anisometropia greater than 3D at ≥ 1 year, 9% with delayed re-epithelialization at greater than one week postop, 8% lost 2 lines or more of BCVA at ≥ 1 year, 3% with increased corneal haze in the superficial epithelium, 5% with increased corneal haze in the deep epithelium, 4% with increased corneal haze in the anterior stroma, 2.2% with a transient increase in IOP that resolved when topical corticosteroid was discontinued, 1% with recurrence/reactivation of herpes simplex keratitis in three subjects treated for leukoma of unknown etiology who did not received prophylactic anti-viral coverage, 1% with non-herpetic late corneal infection/ulcer, 1% with recurrent dystrophy and finally 1% with corneal neovascularization. Four percent required retreatment from 3 weeks to 12 months post PTK, ostensibly for insufficient beneficial effect from the initial treatment. Failure to meet the patients' visual needs or persistent/recurrent epithelial defects necessitated PKP in 5% of cases after one year and in an additional 2% thereafter. Several device failures resulted in design improvements, but no permanent injury has been reported from any of these failures.

D. Hyperopic Shift

As can be seen by the above summary of refraction, hyperopic shift has been a major safety issue following PTK. Hyperopic shift appears to be a consequence of deep corneal ablation in some cases and an unpredictable occurrence in others. In PTK, the problem of anisometropia greater than 3 D secondary to the hyperopic shift can detract from an otherwise successful, clear corneal excimer laser ablation.

E. Refractive Safety Parameters

Manifest refraction seems to be stable over time with no statistically significant differences seen in the frequency of cases that were within ±1 D between the various time periods. A gain of 2 or more lines of BCVA with spectacles at 1 year or later was documented in 53%, while 8% lost two or more lines. 37% of cases were within ±1 D of emmetropia pre-op, while 28% were at ≥1 year post-treatment.



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F. Overall Success/Failure

At one year or later, a total of 169/222 (76%) benefited either by improvement in vision or improvement in comfort as demonstrated below.

| OUTCOME ASSESSMENT<br>PERCENTAGE IMPROVEMENT IN VISION OR SYMPTOMS | |
|---|---|
| DEFINITIONS OF SUCCESS | PERCENTAGE (169/222) |
| Refractive/Visual Improvement | 49% |
| Improved Comfort Symptoms | 27% |
| Pain | 10% |
| Photophobia | 6% |
| Foreign Body Sensation | 5% |
| Tearing | 3% |
| Conjunctival Erythema | 2% |
| Overall percentage of success | 76% |

The improvement in visual and refractive efficacy parameters resulted from an improvement in corneal clarity.

Of the 53/222 (23.8%) who failed to improve in BCVA or comfort symptoms at later than one year post-treatment, 8/222 (3.6%) improved substantially at 3 months post-treatment, but recurrence of the underlying corneal disease again decreased BCVA. An additional 2/222 (0.9%) were treated to heal an epithelial defect which was done successfully and an additional 2/222 (0.9%) the cornea was smoothed sufficiently to allow contact lens wear, which had not been possible pre-treatment.

| OUTCOME ASSESSMENT<br>PERCENTAGE WITHOUT IMPROVEMENT IN<br>VISION OR SYMPTOMS | |
|---|---|
| Explanation for the Lack of Efficacy | Percentage |
| Recurrence of Corneal Disease Causing: | |
| Decreased vision | 4% |
| Increased Patient Discomfort | 2% |
| Insufficient Removal | 11% |
| PKP Required | 3% |
| Unrelated Ocular Disease | 2% |
| Healed Epithelial Defects | 1% |
| Improved CL Tolerance | 1% |
| Total Without Improvement | 24% (53/222) |

G. Effects of gender or age

To evaluate possible differences in the study outcome variables due to gender, Analyses of Variance (ANOVA) were performed to test the statistical significance of this factor. None of the study outcome variables exhibited any differences between males and females enrolled in the study.

The mean age of the patients was 54.4 +/- 19 years. There is no evidence that age less than 55 or greater than 55 significantly affects vision or comfort. Increasing age is not associated with a greater likelihood of failure.

H. Conclusion

The clinical data provide reasonable assurance that the VISX Excimer Laser System is safe and effective for the treatment of signs and symptoms of corneal dystrophies, corneal scars, opacities, and irregular surfaces.

## XI. PANEL RECOMMENDATIONS

On March 21, 1994, the Ophthalmic Devices Panel unanimously recommended that the premarket approval for the excimer laser be conditionally approved, with the conditions

that one year or more of follow-up data be submitted for review by the Panel and the FDA. The Panel subsequently received and reviewed the requested information. An approval recommendation was received from a majority of the Panel.

## XII. FDA DECISION

On June 8, 1994, FDA issued a major deficiency letter to VISX which requested an update of the clinical data to include one year or more of follow-up results, as well as labeling changes. In amendments received by FDA, VISX submitted the requisite data and revisions to the device's labeling. FDA issued an approval order on September 29, 1995. The sponsor's manufacturing facility was inspected on November 2 and 4, 1994 and was found to be in compliance with the Good Manufacturing Practice regulations.

## XIII. APPROVAL SPECIFICATIONS

Continued approval of the device is contingent upon the submission of postapproval reports to the Food and Drug Administration as described in the conditions of approval enclosed in the approval letter (Attachment A), and the conditions that VISX must also report to the Agency the following information as they become available to VISX:

1. any instances of device tampering (such as the removal of the PRK lockout mechanisms) or device usage outside of the approved indications;

2. any excimer systems that were exported under the 801(e) order, but are now back in use in the U.S.; and,

3. all complications to be included in the annual reporting.

A copy of the Professional Use Information for Phototherapeutic Keratectomy is attached (Attachment B).



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**Bibliography**

1. Srinivasan R, Wynne JJ, and Blum SE, Far-UV photo etching of organic material. *Laser Focus* 19:62, 1983.

2. Trokel SL, Srinivasan R, and Braren B. Excimer Laser Surgery of the Cornea. *Am J Ophthal.* 96 (6):710-15, 1983.

# VISX EXCIMER LASER SYSTEM

## PROFESSIONAL USE INFORMATION

## PHOTOTHERAPEUTIC KERATECTOMY
(PTK)

CAUTION: RESTRICTED DEVICE: U.S. Federal Law restricts this device to sale, distribution, and use by or on the order of a physician. U.S. Federal Law restricts the use of this device to physicians who have been trained in its calibration and operation. U.S. Federal Law restricts the use of this device to physicians with experience in the medical and surgical management and treatment of corneal pathologies.

This document provides information concerning the intended clinical use of the VISX Excimer Laser System. For complete information concerning system components, safety instructions, installation, maintenance, and troubleshooting, refer to the VISX MODEL C Excimer Laser System *Operator's Manual.*

Carefully read all instructions prior to use. Observe all contraindications, warnings, and precautions noted in these instructions. Failure to do so may result in patient and/or user complications.

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| *Revision | Description | Date | ECN # |
|---|---|---|---|
| xa | Draft | 02/16/95 | |
| xb | Draft | 03/02/95 | |
| C | Product Release | 10/11/95 | |
| | | | |

* Sections contained in this manual may be revised individually; thus, the section footer may not reflect the latest revision level. Several sections may also be revised at the same time, and included on one Engineering Change Notice (ECN). If this occurs, the revision level may skip on some sections to the lastest revision letter.

* Revisions to sections identified by individual part numbers, (which may be incorporated into the sections of this manual) are not noted on the revision grid above, and are contained herein for reference only.

This edition of the VISX *Professional Use Information Manual* is Rev C. Rev C incorporates information regarding software version 1.01 (PTK Only).

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# GENERAL WARNINGS

- **RESTRICTED DEVICE:** U.S. Federal Law restricts this device to sale, distribution, and use by or on the order of a physician. U.S. Federal Law restricts the use of this device to physicians who have been trained in its calibration and operation. U.S. Federal Law restricts the use of this device to physicians with experience in medical and surgical management and treatment of corneal pathologies.

- Performance of procedures, use of controls, or any other adjustments other than those specified herein may result in a hazardous condition.

- Never operate the laser in the presence of flammable anesthetics or other volatile substances, such as alcohol.

## GAS HANDLING

High pressure gas cylinders are contained in a protected compartment within the VISX MODEL C Excimer Laser System. Storage of additional cylinders and the replacement of used cylinders must be done in accordance with the Safe Operating Procedures outlined in the *Operator's Manual* (Chapters 2 and 3).

The premix (argon/fluorine) gas mixture used in this laser system is highly toxic. VISX, Incorporated recommends that anyone working with the gas cylinders: 1) be trained in the proper handling of toxic and compressed gases; 2) know the location of the emergency exhaust fan/room purifier switch; 3) have easy access to protective respirators; and 4) be familiar with safety procedures provided by the site's safety officer. Gas discharge into the atmosphere may be evidenced as a sharp penetrating odor, and eye, nose, and throat irritation.

## SKIN AND EYE EXPOSURE

The VISX MODEL C Excimer Laser System contains a Class IV laser with an output at 193 nm, which is potentially hazardous only to the skin and the surface layers of the cornea. This laser radiation will not enter the eye and poses no threat to retinal structures or the crystalline lens. However, the fixed optical system restricts the beam path which is bounded by the operating table or the floor. Reflectivity from objects in operating rooms, including surgical instruments, is extremely low for 193 nm radiation.

Analysis of the Nominal Hazard Zone (personal communication from David H. Sliney[1] to VISX, Inc.), within which the Maximum Personal Exposure may be exceeded shows that the area of potential hazard (Nominal Hazard Zone) for production of a photochemical keratitis is less than 40 cm. It is recommended that direct exposure to the skin or eye by the primary beam be avoided by all health care personnel. While no hazard exists further than 40 cm from the patient, the use of protective eyewear is recommended if the possibility exists that heath care personnel will approach closer than this distance to the eye.

[1] David H. Sliney, Laser Microwave Division, U.S. Army Environmental Hygiene Agency, Aberdeen Proving Ground, MD 21010-5422

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# 1.0 DEVICE DESCRIPTION

The VISX MODEL C Excimer Laser System is designed to create a superficial lamellar keratectomy on exposed corneal tissue. The removal of corneal tissue is done cleanly and precisely using a process known as *Ablative Photodecomposition.* Ablative Photodecomposition occurs when far-ultraviolet radiation reacts with organic molecules, resulting in the photochemical breakdown of the molecular bonds, with virtually no local thermal effect. The source of the far-ultraviolet photons is a high efficiency, gas discharge excimer laser that electronically excites a combination of argon and fluorine, producing an ultraviolet wavelength of 193 nm.

The VISX MODEL C Excimer Laser System combines submicron precision of tissue removal by an excimer laser with a sophisticated computer controlled delivery system. Features and components of this system include:

| | |
|---|---|
| **Excimer Laser** | An argon-fluoride excimer laser module, with an output wavelength of 193 nm. |
| **Gas Management System** | A gas cabinet containing working gas cylinder for laser operation; a gas cleaning system; a gas leak audio alarm with a sensor to detect fluorine (one part-per-million); a gas discharge system, using an activated charcoal filter to absorb fluorine; an emergency safety system using a positive-action solenoid safety valve, which automatically seals the premix cylinder in the event of a power failure; and a second charcoal scrubber to neutralize fluorine in case of a leak. |
| **Laser Beam Delivery System** | A beam shaping and homogenizing optics design to produce a highly uniform, coaxial beam profile; a spatial integrator and beam rotator for temporal integration; an iris diaphragm and rotating slit blades used to shape the beam. |
| **Patient Management System** | An operating microscope with reticle, used to observe a patient procedure, and to assure accurate focus and laser beam alignment; debris removal system designed to evacuate the debris plume that occurs during ablation; a patient operating chair, used to align the patient for treatment; a video camera and monitor, used to monitor and record a patient treatment; an illumination device, used to illuminate the patient's eye for observation and treatment; and a fixation LED, used by the patient to maintain proper alignment during treatment. |
| **Computer Control Station** | An IBM Compatible computer and video monitor; a computer keyboard with trackball for user interface; printer, VisionKey card driver, and system software. |
| **VisionKey Card** | A write-once-read-many (WORM) optical memory card designed to allow accurate and detailed compilation, storage, and printout of essential patient data, and procedural information |

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# 2.0 INDICATIONS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

## 2.1 INDICATIONS

Phototherapeutic Keratectomy (PTK) procedures using the VISX MODEL C Excimer Laser System (here in after called the excimer system) are primarily indicated for subjects with decreased best corrected visual acuity and/or with disabling pain that are the result of superficial corneal epithelial irregularities or stromal scars in the anterior one-third of the cornea. The subjects must have failed alternative treatment options. For safety, the immediate postoperative corneal thickness must not be less than 250 microns. Examples of those conditions that may warrant PTK are:

- Corneal scars and opacity (from trauma or inactive infections)
- Dystrophies (e.g., lattice; Reis-Buckler's)
- Thygeson's superficial keratitis
- Irregular corneal surfaces associated with filamentary keratitis and Salzmann's nodular degeneration
- Residual baud keratopathy after unsuccessful EDTA treatment
- Scars subsequent to previous (not concurrent) pterygium excision

## 2.2 CONTRAINDICATIONS

The Phototherapeutic Keratectomy procedure should not be performed if the post-operative thickness would be less than 250 microns (excluding the epithelium and Bowman's layer), or if a deep scar is present which is not contained in the anterior one-third of the cornea.

## 2.3 WARNINGS

- Hyperopic shift has been a major safety issue following PTK. It is advisable to ablate only to a depth that is necessary to improve vision and/or relieve symptoms, and not to attempt to remove all scar tissue. Aggresive attempts to ablate all visible scar tissue risk hyperopic shift and corneal ectasia. Subjects should be informed concerning the possibility of hyperopia and subsequent possible induced anisometropia.

- Reactivation of herpes simplex keratitis has occurred after PTK. A course of oral acyclovir is recommended if there is a history of herpetic infection.

- If topical steroids are used post-operatively, subjects must be monitored for possible steroid side-effects, such as ocular hypertension and/or glaucoma with subsequent damage to the optic nerve, or development of posterior subcapsular cataract.

- Subjects with systemic disease likely to affect wound healing, such as connective tissue disease, diabetes, severe atopic disease, or an immunocompromised status should be

approached cautiously, as the safety and effectiveness of the VISX Excimer Laser has not been established in patients with these conditions.

## 2.4 PRECAUTIONS

### 2.4.1 THE SAFETY AND EFFECTIVENESS OF THE VISX EXCIMER LASER SYSTEM HAS NOT BEEN ESTABLISHED IN

- Treatment of recurrent corneal erosions.
- Treatment of corneal disease in eyes with recurrent or active ocular disease such as iritis, uveitis, keratitis sicca, and severe blepharitis.
- Treatment of scars and irregularities in patients with keratoconus.
- Patients with corneal neovascularization near the ablation zone.
- Patients who have had previous corneal surgery.
- Pregnant women.
- Patients under 18 years of age.

### 2.4.2 CONSIDERATIONS IN DETERMING APPROPRIATE PATIENTS FOR PTK

Considerations should be given to the following in determining the appropriate patients for PTK:

- The potential induced refractive error would result in significant uncorrectable anisometropia and/or induced astigmatism
- The patient should have the ability to tolerate local or topical anesthesia.
- The patient should have the ability to lie flat without difficulty.

### 2.4.3 DURING THE PTK PROCEDURE

- The output of the laser is potentially hazardous only to the skin and the surface layers of the cornea. This radiation has not been shown to pose a threat to retinal structures or the crystalline lens. Analysis of the Nominal Hazard Zone[2] within which the Maximum Permissible Exposure (MPE) may be exceeded shows that the area of potential hazard (Nominal Hazard Zone) for production of a photochemical keratitis is less than 40 cm. It is recommended that direct exposure to the skin or eye by the primary beam be avoided by all health care personnel. While no hazard exists beyond 40 cm for the patient, the use of protective eyewear is recommended if the possibility exists that the health care personnel will approach closer than this distance.

- While the estimated depth and size of the abnormal pathologic tissue are the necessary starting points for the PTK procedure, the pre-treatment slit-lamp examination can only estimate the depth and size of the abnormal pathologic tissue and not the clinically important issue of tissue ablation rate.

[2] D. Sliney and T. Clapham, *Safety of Medical Excimer Lasers with an Emphasis on Compressed Gases*, (Data on File VISX, Inc.)

examination can only estimate the depth and size of the abnormal pathologic tissue and not the clinically important issue of tissue ablation rate.

- It must be recognized that ablation rates of pathologic corneal tissues can be unpredictable. Only at the time of treatment can the tissue ablation rate be determined that will in turn be the key piece of information upon which the treatment depends.

- The main therapeutic endpoint should always be the production or maintenance of a smooth corneal treatment bed upon which appropriate healing response is dependent. In addition in opacified corneal tissue, a sufficient ablation depth should be reached to provide for the adequate transmission of light.

- In order to achieve a smooth corneal treatment bed, a necessary prerequisite for a predictable healing response upon which optical performance is ultimately dependent, one must compensate for the differential rate of ablation among normal, diseased corneal tissue and within the diseased tissue itself.

- The use of a smoothing agent is to avoid producing an uneven corneal treatment bed that would occur if the differential rate of ablation were not compensated for among normal, diseased corneal tissue and within the diseased tissue itself.

- When using smoothing agents in treating pathologic corneal tissue, the surgical plan should be flexible, responding in real time to the way the corneal tissue is behaving in relation to the tissue ablation rate per laser pulse which cannot be known until the laser treatment is underway.

- The laser treatment should be periodically interrupted for a slit-lamp examination to determine corneal surface smoothness and/or estimate treatment depth since examination through the operating microscope alone may not provide this information.

### 2.4.4 ADVERSE EVENTS

Potential adverse events of the device include: corneal perforation, infection, corneal decompensation, difficulty with re-epithelialization, loss of best and uncorrected visual acuity, induced refractive change, decreased corneal clarity, and worsening of patient comfort symptoms.

Excimer laser energy has the potential to induce micromechanical damage to endothelial cells, induce cataracts, or cause mutations. These effects have not been observed in any clinical use, nor have they been reproducible in various animal and in-vitro test systems.

No acute, vision-threatening complications were noted during clinical studies of the VISX Excimer Laser System. There were no corneal perforations, acute bacterial keratitia, endophthalmitis or hypopyons, or corneal decompensations in clinical trials conducted in 269 patients. Please refer to Section 6.0, *Clinical Results*, regarding the clinical outcome of these 269 patients.

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# 3.0 SURGICAL PLANNING AND PROCEDURES


**After reading this section, please refer to the step-by-step VISX MODEL C Excimer Laser procedure provided in Section 4.0 before proceeding with the surgery.**

## 3.1 INTRODUCTION

PTK creates a superficial lamellar keratectomy whose success will reflect the diagnostic effort the surgeon has placed into understanding the extent and the depth of the corneal pathology. Careful slit lamp biomicroscopy is required which allows the surgeon to estimate the depth of the abnormal corneal tissues that are to be removed with the laser. This may be estimated on the basis of known corneal anatomy (i.e., corneal thickness of roughly 500 µm and corneal epithelium of 50 µm). An increased precision can be obtained by use of an optical pachymeter to measure the corneal thickness and estimate the depth of the scar. The aim of the surgery is to remove stromal tissue that is not optically clear and to create a more optically regular surface. Planning of the surgery must consider that the ablation depth must be restricted so that the final corneal thickness is more than 250 µm (excluding the depth of the epithelium and Bowman's membrane).

Surgical planning must recognize that ablation rates of pathologic corneal tissues are not known. While the estimated depth and size of the abnormal pathologic tissue is the necessary starting point for estimating the PTK parameters, the total amount of surgery can rarely be pre-determined. When using smoothing agents, the end point of PTK is determined by the appearance of the cornea as viewed under the operating microscope of the laser system or as studied in a slit lamp biomicroscope. It is for this reason that a slit-lamp should be available in proximity to the operating laser.

## 3.2 PRE-OPERATIVE (EXAMINATION OF THE PATIENT)

Careful examination of the patient is required to determine the overall corneal thickness and the extent of the corneal pathology. The surgeon should have determined, prior to the surgery, where tissue has to be removed during the procedure. In cases where the pathology is uniform, a surgical plan consisting of a single ablation pattern may suffice. In other patients, there may be extensive and varying superficial changes which require different ablation patterns to be placed at different areas of the cornea to achieve both clarity and a uniform, smooth optical surface. In these complex patients a drawing of the pathology and a treatment plan will aid the surgeon. No treatment should be done beyond the anterior third of the cornea or that would reduce the corneal thickness (excluding the epithelium and Bowman's membrane) to less than 250 µm.

## 3.3 PERI-OPERATIVE

### 3.3.1 SETTING THE WIDTH AND DEPTH OF THE ABLATION

The actual ablation size is intimately related to the extent of the corneal pathology. For relatively uniform pathology (i.e. lattice or granular dystrophy), a 6.0 mm diameter circular ablation at the depth estimated biomicroscopically may be entered

into the machine. For an extremely small scar (i.e., a scar associated with a retained foreign body), the actual dimension of the scar may be programmed for the ablation.

Many corneal scars are markedly irregular and may be lobulated or even multiple. In these patients, multiple ablations of varying diameter and shape may be necessary to treat the diseased areas. Complex and irregular shapes may be treated with the two therapeutic shapes available in the VISX MODEL C Excimer Laser System. These include a circular aperture, which can be adjusted from 2.0 to 6.0 mm diameter in 0.1 mm increments, and a slit aperture, which can be adjusted from a minimum width and length of 0.6 mm to a maximum of 6 mm.

### 3.3.2 ANESTHESIA AND ANALGESIA

Extensive clinical experience has shown that PTK excimer surgery is well tolerated and rarely causes significant pain. For this reason, systemic sedatives and local anesthetics are not required. Topical anesthesia applied just before insertion of the lid speculum will give adequate control of pain during the surgery. For those patients with an unusual degree of anxiety, diazepam (Valium™) may be given pre-operatively.

## 3.4 INTRA-OPERATIVE

### 3.4.1 EPITHELIAL REMOVAL

The epithelium is known to reduce surface irregularity of the cornea by varying its thickness to compensate for underlying stromal irregularities. The thin portion of the epithelium will ablate first, allowing some degree of preferential ablation of stromal high spots.

The decision therefore to ablate through the epithelium or to remove it surgically is based on the surgeon's evaluation of the regularity of the stromal. Advantage may be taken of this by ablating through the epithelium in patients with corneal scarring who have an uneven and irregular stromal interface determined biomicroscopically. When the epithelium is of uniform thickness and the underlying pathology has not produced an uneven stromal surface, then the epithelium may be removed mechanically prior to ablation. This is commonly the situation in patients with corneal dystrophies.

### 3.4.2 METHYLCELLULOSE AND OTHER SMOOTHING AGENTS

Because pathological scars and dystrophic tissue will ablate at different rates from normal corneal stroma, it is often necessary to place methylcellulose or other smoothing agents such as Tears Naturale® (a combination of Methylcellulose and Dextran) on the ablating surface to help create a smooth uniform surface. The smoothing fluid fills the valleys of the stroma which prevents ablations of low points on the corneal surface during the ablation of high points.

### 3.4.3 WHEN TO STOP LASER ABLATION

Observation through the operating microscope is usually sufficient to determine when to stop the procedure. Visible scars and dystrophic areas are seen to fade and

disappear. If there is any uncertainty as to the adequacy of the ablation, a slit lamp evaluation will allow visualization of details of the remaining pathology.


**A small degree of residual pathology is clinically tolerable and therefore, the depth of the ablation should be kept to a minimum**

## 3.5 POST-OPERATIVE

### 3.5.1 PATCHING AND ANTIBIOTICS

Following completion of the excimer laser surgery, antibiotics and a firm patch must be applied to the eye. This requires daily observation to monitor the cornea as the epithelium heals.

### 3.5.2 REFRACTIVE CHANGES AFTER PTK

Hyperopic shift has been a major safety issue following PTK. Ablation depth is believed to be a major cause. It is suggested that in the case of deep corneal scar, the surgeon ablate only to a depth that improves vision and/or relieves symptoms. Patients should be informed concerning the possibility of hyperopia and subsequent possible induced anisometropia.

When tissue is removed from the central corneal area, some degree of flattening of the corneal optical surface will occur which will produce a hyperopic shift. While this may be acceptable if the patient is myopic, usually, it is desirable to minimize this refractive change. This can be done by the use of a large optical zone, and minimizing the depth of the ablation. Finally, ablating the edge of the ablation zone to enlarge its effective diameter will also reduce the hyperopic shift caused by the surgery.

### 3.5.3 HANDLING COMPLICATIONS

Delayed epithelialization of the ablated surface may be anticipated in some patients. It is essential that these patients be monitored on a daily basis with installation of antibiotics and maintenance of a firm patch. The surgeon must remain alert to the possible developments of corneal infiltrates which will require suitable diagnostic and therapeutic measures.

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# 4.0 VISX MODEL C EXCIMER LASER SURGICAL PROCEDURES


**Before proceeding please refer to the laser preparation and shut-down procedures presented in the VISX MODEL C Excimer Laser *Operator's Manual*, Chapter 7, *Operating Instructions.***

**The VISX MODEL C Excimer Laser System contains a Class IV laser with an output at 193 nm which is potentially hazardous only to the skin and the surface layers of the cornea. This laser radiation will not enter the eye and poses no threat to retinal structures or the crystalline lens. However, the fixed optical system restricts the beam path which is bounded by the operating table or the floor. Reflectivity from objects in operating rooms including surgicl instruments is extremely low for 193 nm radiation.**

**Analysis of the Nominal Hazard Zone (personal communication, David Sliney[3] to VISX, Inc.) within which the Maximum Permissible Exposure (MPE) may be exceeded shows that the area of potential hazard (Nominal Hazard Zone) for production of a photochemical keratitis is less than 40 cm. It is recommended that direct exposure to the skin or eye by the primary beam be avoided by all health care personnel. While no hazard exists further than 40 cm from the patient, the use of protective eyewear is recommended if the possibility exists that health care personnel will approach closer than this distance to the eye.**

The *Profcssional Use Information Manual* is to be used in conjunction with the VISX MODEL C Excimer Laser *Operator's Manual.* Refer to the *Operator's Manual* regarding designated sections listed below.

## 4.1 STEP-BY-STEP PROCEDURE

1. Prepare a VisionKey card with patient information and parameters for the PTK procedure as described in the *Operator's Manual*, Chapter 2, *Device Description—Interactive Computer Menus*. This may be done in advance of treatment.

   The desired treatment may be entered either as depth of tissue to be removed, or as the number of pulses.

2. Perform the *fluence, sphere, flat*, and *cylinder* calibration procedures as described in the *Operator's Manual*, Chapter 6, *Calibrations—Daily Calibrations.* If a new gas fill is executed, (resulting in a change of fluence or energy), perform these calibration procedures again.

3. Determine the method of epithelium removal. The epithelium may be removed using either conventional surgical techniques or the laser. If the underlying stroma is *regular*, then the surgeon may remove the epithelium mechanically and proceed with the laser removal of diseased tissue. If, on the other hand, the underlying stroma is *irregular*, the surgeon may wish to ablate through the epithelium to take advantage of its smoothing effect.

[3] David H. Sliney, Laser Microwave Division, U.S. Army Environmental Hygiene Agency, Aberdeen Proving Ground, MD 21010-5422

If *mechanical* epithelium removal is planned, place one to two drops of topical anesthetic, as indicated, in the operated eye at least 30 minutes prior to commencing the surgical procedure.
If *laser* epithelium removal is planned, topical anesthetics may be placed immediately before placement of the lid speculum.


**Ablate a -4.0 D, 6.0 mm lens before every third patient treatment to verify the calibration of the VISX Excimer Laser System. Refer to the *Operator's Manual*, Chapter 6, *Calibrations—Daily Calibrations* for additional information.**

4. Ensure that all attendees obey all safety regulations. Caution all attendees in the laser operating room against touching the laser, patient, or patient chair during the procedure. Movement of personnel in the operating room should be minimized during the procedure.

5. Allow the patient the opportunity to observe the laser calibration process to become familiar with operational noises associated with the laser action. Ask the patient if there are any questions about the treatment.

6. Insert the preprogrammed VisionKey card into the card drive when prompted. Follow the system software prompts. **Verify that the card corresponds with the patient to be treated.** When successfully verified, the system will open the most recently programmed treatment screen. Select the appropriate PTK procedure, (if not already selected), which will open the respective PTK treatment screen on the computer screen.

7. Carefully review the patient parameters, then select the *Treat* command button to calibrate the system using a -4.0 D lens ablation.

8. Lower the patient chair to its lowest position, swing away from the operating position, and raise the chair backrest to a seating position.

9. Center the mechanical position of the chair using the guide marks found on the chair base.

10. Seat the patient and lower the patient chair backrest to a full reclining position, while monitoring patient clearance. Ensure that the patient is comfortable.

11. Position the patient so the lateral canthus is parallel to the marker on the headrest.

12. Place the vacuum pillow under the patient's head with the bottom portion of the "U" supporting the patient's neck.

13. Cover the untreated eye with a shield that protects the eye and occludes vision. A post-operative surgical shield covered with surgical tape is suitable for this purpose. Instruct the patient to keep both eyes opened during the surgical procedure.

14. Monitor patient clearance while rotating the patient chair to the treatment position until it stops. Lock the patient chair in place by pressing the foot pedal in a counterclockwise direction. The chair must be fully rotated and the foot pedal locked for the laser to operate.


**If indicated, continue giving anesthetic drops as prescribed earlier.**

15. Check the surgical parameters entered into the computer against the surgical plan and confirm that all interlocks are cleared. **This is the responsibility of the surgeon.** When ready, select the *Treat* command button.

16. Set the illuminator on a low setting initially and adjust to the desired intensity. The patient's visibility of the blinking red light is facilitated when operating illumination is less intense.


**If the chair is not in the treatment position and securely locked, the laser will not fire. Check the interlock message on the status screen.**

17. Adjust the patient's head and vacuum pillow for comfort, angle, alignment, and stability. Connect the vacuum pillow suction tubing to the suction port located to the left of the patient chair headrest. While keeping the patient properly aligned, conform the pillow shape to the patient's head, creating support under the occiput of the skull. This is more effective than creating lateral support for the head. Holding the pillow support against the occiput, power ON the suction pump switch, located on the patient chair headrest. After several seconds, the pillow will harden and conform to the patient's head. This creates a comfortable, stable platform for the patient. Disconnect the tubing after the pillow has hardened.

18. Position the patient with the microscope set at low zoom magnification. When the cornea is visible in the microscope, focus the image of the cornea and increase the magnification to 16. Instruct the patient to begin fixating on the blinking red light.

19. Focus on the cornea surface and move the patient so the microscope reticle is centered on the surgical area. If the pathology is uniform, the pupil will be centered in the reticle. This will not be true if the pathology is eccentric. For peripheral pathology, the reticle should be centered over the area of pathology to be treated, with the excimer laser beam not encroaching on the visual axis. The patient will not be fixating on the fixation light. (See step 28.) Patient chair alignment is controlled using the joystick on the doctor's panel.

20. Verify the position of the reticle with respect to the corneal pathology or the line-of-sight.

21. Verify all status bars display a **Ready** message at the base of the computer monitor. Any red status bars will prevent operation and must be corrected before continuing.

22. Verify the debris removal nozzle is properly positioned and operative. This fixed position will effectively remove the plume with minimal corneal drying, and protect the laser optics.

23. Verify that the physician and patient chairs are securely locked and all interlock conditions are cleared. Warn all attendees to stand clear of the laser, patient, and patient chair. Accidental bumping of the laser, patient, or patient chair during the surgery can cause decentering of the treatment area.

24. Insert a lid speculum into the eye to hold the eyelid open. Focus the operating microscope and realign the eye. The treatment zone dimension is determined by the surgeon and varies with each specific pathology. Remove overlying epithelium as required. If laser epithelium removal is planned, proceed to step 26.

25. If *mechanical* epithelium removal is planned, remove the epithelium from all areas of the cornea in which treatment is planned. Starting at one edge of the marked ablation site, quickly remove the epithelium. Many light, even strokes at a fixed site may be necessary to start the epithelial removal process. Avoid hard pressure that deforms the cornea. Use rapid, even strokes until the epithelium is completely removed.

26. If *laser* epithelium removal is planned, apply a single anesthetic drop to the operated eye prior to placement of the lid speculum.

27. If, during the epithelial removal process, the surface of the cornea appears too dry, wipe the area with a nonfragmenting sponge that has been soaked with an irrigating solution and then squeezed out.

28. Patient ocular fixation will depend on the location and depth of the planned ablation. Fixation on the blinking red light will be necessary only in the central optical zone to be ablated, and only if the pathology is uniform. If the area of pathology to be treated is eccentric, the patient may not observe the red blinking light, as the area of pathology will be centered in the reticle. If the vision is poor, it may be necessary to hold the eye in position. This may be done with any standard eye fixation device.

29. Position and focus the eye so the surgical area of pathology is centered in the ocular reticle.


1. **There should be no epithelial cells in the treatment zone.**
2. **Position the head so the cornea sits midway between the lids with the speculum in place. This minimizes the potential for tears to touch the corneal surface during surgery.**

**WARNING! Avoid adding fluids to the cornea after epithelium removal has started. Should fluid inadvertantly or inappropriately be added to the cornea after epithelial removal has started, a nonfragmenting sponge may be used to remove the fluid with care taken to only remove the additional fluid and not attempting to dessicate the remaining stroma or epithelium. If the surface appears too dry, wipe the area with a nonfragmenting sponge that has been soaked with an irrigating solution and then squeezed out.**

30. Again, verify that the surgical area of pathology is centered in the ocular reticle. If the ablation is centered over the line of sight, have the patient confirm the red blinking light is straight ahead.


**Keep the patient relaxed by explaining the process as you go along, Use the dimmest light possible to maintain visibility of the surgical area.**

31. Check the focus and alignment on the corneal pathology and reduce the illumination to the lowest level that allows the surgeon to monitor the eye position during surgery. Fully depress the laser footswitch to initiate the procedure. The laser footswitch has two positions. The first position powers ON the aspirator and pumps within the laser. The laser footswitch is only partially depressed in the first position. The second position allows the laser to fire and initiates the procedure. The laser footswitch is fully depressed

in the second position. It is the surgeon's responsibility to continually monitor the position of the patient's eye to assure proper centration of the ablation.


**The surgeon may interrupt the procedure for any reason, at any time, by releasing the laser footswitch. This may be done if the patient should move and the treatment area becomes decentered. The surgeon then realigns the eye and continues the procedure by reapplying the laser footswitch. The procedure will automatically start from where it was interrupted, unless further commands are entered.**

32. The surgeon may wish to repeat laser applications at different sites on the cornea using different parameters. Each procedure must be entered into the VisionKey card separately. A smoothing agent may be used between successive procedures, or may be applied any time by releasing the laser footswitch, which will interrupt the procedure. Operation may be resumed by reapplying the laser footswitch.

33. The surgeon may wish to examine the patient at a slit-lamp either during the course of an exposure, or between successive treatments. This helps the surgeon to determine the extent of remaining pathological tissue and treatment depth.


**The depth of a PTK treatment may be difficult to determine. The use of smoothing agents reduces the effectiveness of the laser and reduces the amount of tissue removed. Furthermore, removal of tissue at different sites contributes to the difficulty in determining the exact amount of tissue removed.**

34. When surgery is complete, remove the speculum and allow the patient to close his/her eye. Power OFF the microscope light and relieve the vacuum in the patient's pillow.

35. Lower the chair to its lowest position, then rotate the patient chair from under the laser, while carefully monitoring patient clearance. Remove the eye shield from the untreated eye.

36. If indicated, place appropriate post-operative medications in the operated eye. Following installation of medication, apply a pressure patch to the eye.

37. Raise the chair back to a sitting position. Assist the patient in putting on any spectacles, and escort to a waiting room.

38. Ensure that the patient is given post-operative instruction. An analgesic may be given to the patient prior to leaving the facility.

39. Review post-operative instructions, confirm the first follow-up appointment, and discharge the patient when stable.

40. Clean the debris removal nozzle with isopropanol wipes and prepare the system for the next patient.

**WARNING! Never operate the laser in the presence of flammable anesthetics or other volatile substances, such as alcohol.**

**WARNING! Never allow the patient to drive immediately following surgery. The combination of analgesic and eye patch can be very dangerous.**

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# 5.0 EMERGENCY STOP

If a system emergency situation arises, press the **Laser Stop** button located on the doctor's panel. This will power OFF the system; however, the gas cleaning and gas detector systems will continue to operate. When the emergency condition no longer exists, turn the **Laser Stop** button in the direction of the arrows; turn the System Power Key first OFF and then ON; then power ON the system using the **System Power** button, which will re-energize the laser.

If the emergency appears to involve the electrical system (visible smoke, fire, etc.), switch OFF the wall mounted electrical disconnect switch.

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# 6.0 CLINICAL RESULTS

## 6.1 INTRODUCTION

VISX sponsored a prospective, nonrandomized, uncontrolled, unmasked multicenter clinical study to determine the safety and efficacy of PTK in improving vision and/or symptoms of pain that were caused by superficial corneal epithelial irregularities or stromal scars. Besides being 18 years or older, inclusion criteria included best corrected visual acuity not better than 20/40, pathology in the anterior one-third of the cornea, and an immediate post-treatment corneal thickness of at least 250 microns. Exclusion criteria included any of the following conditions: immunocompromised, uncontrolled uveitis, severe blepharitis, lagophthalmos, dry eyes, inability to tolerate procedure under local or topical anesthesia, unable to lie flat without difficulty, and inability to comply with postop medical therapy.

## 6.2 ABOUT THE STUDY

VISX conducted the PTK study under an approved investigational device exemption granted by the FDA. The 269 primary eyes, treated from 7/31/89 to 5/18/93 in 17 participating centers, formed the basis for the safety and efficacy determination. The VISX study plan included the examination protocol for the preoperative, peri-operative, intra-operative and immediate, as well as long term, postoperative periods. Success or failure of the clinical procedure was determined by either an improvement in comfort or vision. A breakdown of the pre-treatment options for the 269 patients included 56 (21%) as candidates for penetrating keratoplasty, 89 (33%) as candidates for lamellar keratectomy, and 124 (46%) could be considered as candidates for either surgery. The patients' medical and opthalmic history reveal: 6% diabetes, 35% prior ocular surgery, 48% prior corneal trauma, 12% glaucoma, 13% PKP and other pre-existing surgical conditions.

## 6.3 PATIENT ACCOUNTABILITY

Patient accountability was assessed at each time period for those patients that were eligible to be examined; those that actually were examined; and, those that were not evaluated. From the initial cohort of 269 patients, 240 were examined at three months, 146 at six months, 138 at one year and 222 at ≥ one year. One percent were removed from the study, 3% were retreated, 3% died an 10% were lost to follow-up.

## 6.4 DATA ANALYSIS AND RESULTS

### 6.4.1 PREOPERATIVE CHARACTERISTICS

Preoperative characteristics showed BSCVA (Best Spectacle Corrected Visual Acuity) in the range of 20/40 or better = 18%, 20/50 to 20/100 = 42% and worse than 20/100 = 40%. UCVA (Uncorrected visual acuity) showed 20/40 or better = 2%, 20/50 to 20/100 = 21% and worse than 20/200 = 77%. Patient comfort was evaluated preoperatively using a four-point scale to assess pain, tearing, photophobia, conjunctival erythema and foreign body sensation. Only those patients with moderate or severe symptoms were included in the evaluation of PTK to effectively relieve symptoms. Patients reported the following symptoms as moderate or severe: 8%

tearing, 29% photophobia, 10% erythema, 10% pain, and 11% foreign body sensation.

Preoperative corneal clarity was assessed in the superficial and deep epithelia and anterior stroma. The scores were as follows: none/mild if refraction was not affected; moderate if refraction was affected but not prevented; and, severe if unable to refract. In the 260 eyes reported on superficial epithelium, the scores were: 61% none/mild; 19% moderate; and, 20% severe. For the 263 eyes reported on deep epithelium, the scores were: 45% none/mild; 30% moderate; and 25% severe. For the 266 eyes reported on anterior stroma, the results were: 21% none/mild; 46% moderate; and, 33% severe.

## 6.4.2 POST-OPERATIVE RESULTS

### 6.4.2.1 Re-Epithelialization

In 265 eyes where epithelium removal technique was specified, 56% were performed with the laser and 44% were by mechanical scraping. No mechanical debridement was allowed beyond epithelium removal. Re-epithelialization was complete in 70% by 4 days, 89% by seven days and 97% by 30 days. Four (1%) patients failed to re-epithelialize secondary to a herpetic scar, a neurotrophic keratopathy and two with alkali burns.

### 6.4.2.2 Visual Efficacy

The percent of post-treatment eyes with a BCVA of 20/40 or better with only spectacles showed a statistically significant improvement from pre-op at each visit ($p<0.01$). A gain of 2 or more lines of BCVA with spectacles at one year or later was documented in 53%, while 8% lost two or more lines. A gain of 3 or more lines of BCVA with spectacles was recorded in 41% compared to a loss in 6.8% of eyes. The reasons for decreased BCVA with spectacles at ≥ 1 year included: 1.8% from the PTK procedure causing some corneal surface irregularity; 2.6% from other unrelated pre-existing disease or a recurrence of the underlying corneal pathology; and, 0.7% from pre-existing corneal or other pathology. PKP was requested in 1.1% of eyes before one year post-op due to a lack of visual improvement. Improvement in UCVA with a gain ≥ 2 lines at ≥ one year was seen in 46%, no change ± one line in 40% and a loss ≥ 2 lines in 15% at ≥ one year. About 3 times as many eyes had improvement in UCVA as had a loss in UCVA.

### 6.4.2.3 Refractive Efficacy

Post-operatively, the percentage of eyes that were more myopic than -1.0 D was decreased and was reflected in a proportional increase in the percentage of eyes that are more hyperopic than +1.0 D. The average refractive change was +2.4 D hyperopic at 3 months and +2.3 D at one year or more post-treatment. While only 8% of cases were hyperopic by ≥ 3.0 D pre-treatment, 32% were this hyperopic at one year, one year or later post-treatment. Thirty-seven percent of cases were within 1.0 D of emmetropia pre-treatment and 28% of cases were within this range at one year or later. Nineteen percent (19%) were ≥ 3.0 D myopic pre-treatment while 9% were in this group at one group at one year or later post-treatment. This data

demonstrates a refractive shift toward hyperopia as a consequence of excimer laser corneal ablation. A comparison of Phase III data against the entire study cohort revealed a reduction in the hyperopic shift from 32% to 24% and in anisometropia from 39% to 31%. Manifest refraction was reported to be stable over time with no statistically significant differences seen in the frequency of cases that were within ± 1.0 D between the various time periods.

#### 6.4.2.4 Improvement in Patient Symptoms

Patient comfort was another primary efficacy parameter. At pre-treatment and post-treatment visits, patients were asked to judge the degree to which they experienced pain, tearing, photophobia, conjunctival erythema (physicians assessed) and foreign body sensation. These conditions were graded on a scale: none, mild, moderate, or severe. Overall, the patients believed that their comfort improved. Eleven patients who graded their discomfort as none or mild at pre-op had graded their discomfort level as moderate or severe at ≥ 1 year post-op; however, 4 of them experienced an improvement in corneal clarity. In those patients who experienced moderate or severe discomfort at pre-op, the post-op responses at greater than one year were as follows: 20/20 improvement in pain; 16/17 improvement in tearing with one worse; 49/60 improvement in photophobia with 8 unchanged and 3 worse; 18/20 improvement in conjunctival erythema with one unchanged and one worse; and, 24/27 improvement in foreign body sensation. The missing data in each symptom category do not detract significantly from the improvement in this primary efficacy parameter as experienced by these cases.

#### 6.4.2.5 Improvement in Corneal Clarity

The clarity of the superficial epithelium, deep epithelium, and anterior stroma were graded as: none/mild if refraction was not affected; moderate if refraction was affected but not prevented; and, severe if unable to refract. Overall, the clarity of the cornea improved post PTK as indicated by a highly significant improvement in mean clinical clarity scores for all three layers of the anterior cornea ($p < 0.0001$). The improvement in visual and refractive efficacy parameters are reflected in the remarkable improvement in the corneal clarity. As expected, average pachymetry dropped 0.06mm between the baseline and one year or later since a portion of the anterior stroma was ablated.

#### 6.5.2.6 Stratification of Results by Diagnosis

The sister tables entitled "Patient Accountability by Diagnosis at ≥ 1 Year" and "Efficacy and Safety Results at ≥ 1 Year Stratified by Diagnosis" present the data extracted from the clinical investigation into a more physician-friendly format. The first column of the table entitled "Patient Accountability by Diagnosis at ≥ 1 Year" presents the patients' evaluable status in relation to each data point generated for the diagnostic categories in the next three columns. This provides the reader a reference for accountability by diagnostic category at a glance. The first column of the table entitled "Efficacy and Safety Results at ≥ 1 Year Stratified by



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Diagnosis" presents the main safety and efficacy categories. The four remaining columns represent the three diagnostic categories and finally the total cohort. Under the first column are the main categories which are Vision, Corneal Clarity, Refraction, Patient Comfort Symptoms, and Others including Re-epithelialization, Retreatment and PKP. The value of this presentation is its clinical utility as a reference for outcomes stratified by clinically useful diagnostic categories.

# VISX EXCIMER LASER SYSTEM: PHOTOTHERAPEUTIC KERATECTOMY PATIENT ACCOUNTABILITY BY DIAGNOSIS AT ≥ 1 YEAR (COHORT PATIENTS, USING ALL AVAILABLE DATA IN THE SUBMISSION)

| Diagnosis | Scars & Leukomas | Dystrophies | Surface Irregularities Without Scar | All Patients Treated |
|---|---|---|---|---|
| TOTAL EVALUABLE | 143 (80%) | 74 (87%) | 5 (83%) | 222 (83%) |
| Evaluated ** | 143 (100%) | 74 (100%) | 5 (100%) | 222 (100%) |
| Not Evaluated (missed visit) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| NOT EVALUABLE | 35 (20%) | 11 (13%) | 1 (17%) | 47 (17%) |
| Removed From Study Prior to Visit * | 2 (1%) | 0 (0%) | 0 (0%) | 2 (1%) |
| Retreated Prior to Visit | 7 (4%) | 1 (1%) | 1 (17%) | 9 (3%) |
| Died or Terminally Ill Before Visit | 8 (4%) | 1 (1%) | 0 (0%) | 9 (3%) |
| Lost to Follow-up at or Before Visit | 18 (10%) | 9 (11%) | 0 (0%) | 27 (10%) |
| TOTAL ENROLLED | 178 (100%) | 85 (100%) | 6 (100%) | 269 (100%) |

(%) Percentage based on TOTAL ENROLLED: 178 (Scars & Leukomas), 85 (Dystrophies), 6 (Surface Irregularities without Scar), and 269 (All Patients Treated)
(%) Percentage based on TOTAL EVALUABLE: 143 (Scars & Leukomas), 74 (Dystrophies), 5 (Surface Irregularities without Scar), and 222 (All Patients Treated)
* 1) Herpetic keratitis scar with pre-treatment history of recurrent epithelial breakdown failed to reepithelialize after 16 days. Placed in a clinical study for persistent epethelial defect.
2) Radial keratotomy performed.
** Include PKP cases: 11 (Scars & Leukomas), 2 (Dystrophies), 2 (Surface Irregularities without Scar), and 15 (All Patients Treated)

# VISX EXCIMER LASER SYSTEM: PHOTOTHERAPEUTIC KERATECTOMY EFFICACY AND SAFETY RESULTS AT ≥ 1 YEAR STRATIFIED BY DIAGNOSIS (COHORT PATIENTS, USING ALL AVAILABLE DATA IN THE SUBMISSION)

| Diagnosis | Scars & Leukomas | Dystrophies | Surface Irregularities Without Scar | All Patients Treated |
|---|---|---|---|---|
| I. VISION: BCVA | | | | |
| Pre-op BCVA 20/40 or Better | 27/178 (15.2%) | 22/85 (25.9%) | 0/6 (0%) | 49/269 (18.2%) |
| Post-op BCVA 20/40 or Better at ≥ 1 Year | 49/133 (36.8%) | 47/70 (67.1%) | 0/2 (0%) | 96/205 (46.8%) |
| Pre-op BCVA 20/25 or Better | 9/178 (5.1%) | 3/85 (3.5%) | 0/6 (0%) | 12/269 (4.5%) |
| Post-op BCVA 20/25 or Better at ≥ 1 Year | 21/133 (15.8%) | 18/70 (25.7%) | 0/2 (0%) | 39/205 (19.0%) |
| Pre-op BCVA 20/20 or Better | 3/178 (1.7%) | 1/85 (1.2%) | 0/6 (0%) | 4/269 (1.5%) |
| Post-op BCVA 20/20 or Better at ≥ 1 Year | 10/133 (7.5%) | 5/70 (7.1%) | 0/2 (0%) | 15/205 (7.3%) |
| Gain of 2 Lines or More BCVA at ≥ 1 Year | 61/133 (45.9%) | 47/70 (67.1%) | 0/2 (0%) | 108/205 (52.7%) |
| Loss of 2 Lines or More BCVA at ≥ 1 Year | 14/133 (10.5%) | 3/70 (4.3%) | 0/2 (0%) | 17/205 (8.3%) |
| | | | | |
| II. CORNEAL CLARITY | | | | |
| Deep Epithelial Opacity Improvement ≥ 2 Categories at ≥ 1 Year | 66/132 (50.0%) | 43/70 (61.4%) | 0/4 (0%) | 109/206 (52.9%) |
| Anterior Stromal Opacity Improvement ≥ 2 Categories at ≥ 1 Year | 76/133 (57.1%) | 39/67 (58.2%) | 1/4 (25.0%) | 116/204 (56.9%) |
| Deep Epithelial Opacity Improvement ≥ 2 Categories & Pre-op Opacity ≥ 1.5 at ≥ 1 Year | 62/76 (81.6%) | 36/41 (87.8%) | 0/1 (0%) | 98/118 (83.1%) |
| Anterior Stromal Opacity Improvement ≥ 2 Categories & Pre-op Opacity ≥ 1.5 at ≥ 1 Year | 71/110 (64.5%) | 36/50 (72.0%) | 1/4 (25.0%) | 108/164 (65.9%) |

## VISX EXCIMER LASER SYSTEM: PHOTOTHERAPEUTIC KERATECTOMY EFFICACY AND SAFETY RESULTS AT ≥ 1 YEAR STRATIFIED BY DIAGNOSIS (COHORT PATIENTS, USING ALL AVAILABLE DATA IN THE SUBMISSION)

| Diagnosis | Scars & Leukomas | Dystrophies | Surface Irregularities Without Scar | All Patients Treated |
|---|---|---|---|---|
| | | | | |
| III. REFRACTION | | | | |
| Change in Spherical Equivalent >+1 to +3 Diopters at ≥ 1 Year | 19/65 (29.2%) | 10/46 (21.7%) | 0/0 (-%) | 29/111 (26.1%) |
| Change in Spherical Equivalent > 3 Diopters at ≥ 1 Year | 18/65 (27.7%) | 17/46 (37.0%) | 0/0 (-%) | 35/111 (31.5%) * |
| Pre-op Anisometropia > +1 to +3 Diopters | 29/97 (29.9%) | 17/64 (26.6%) | 0/0 (-%) | 46/161 (28.6%) |
| Post-op Anisometropia > +1 to +3 Diopters at ≥ 1 Year | 25/73 (34.2%) | 17/54 (31.5%) | 0/0 (-%) | 42/127 (33.1%) |
| Pre-op Anisometropia > +3 Diopters | 19/97 (19.6%) | 11/64 (17.2%) | 0/0 (-%) | 30/161 (18.6%) |
| Post-op Anisometropia > +3 Diopters at ≥ 1 Year | 26/73 (35.6%) | 24/54 (44.4%) | 0/0 (-%) | 50/127 (39.4%) ** |

* Improved to 23/95 (24.2%) for phase III patients.
** Improved to 33/106 (31.1%) for phase III patients.

## VISX EXCIMER LASER SYSTEM: PHOTOTHERAPEUTIC KERATECTOMY EFFICACY AND SAFETY RESULTS AT ≥ 1 YEAR STRATIFIED BY DIAGNOSIS (COHORT PATIENTS, USING ALL AVAILABLE DATA IN THE SUBMISSION)

| Diagnosis | Scars & Leukomas | Dystrophies | Surface Irregularities Without Scar | All Patients Treated |
|---|---|---|---|---|
| IV. PATIENT COMFORT SYMPTOMS | | | | |
| Pre-op % of Patients with Moderate / Severe Ocular Discomfort | | | | |
| Pain | 15/178 (8.4%) | 12/85 (14.1%) | 0/6 (0%) | 27/269 (10.0%) |
| Photophobia | 52/178 (29.2%) | 24/85 (28.2%) | 1/6 (16.7%) | 77/269 (28.6%) |
| Foreign Body Sensation | 18/177 (10.2%) | 11/85 (12.9%) | 1/6 (16.7%) | 30/268 (11.2%) |
| Tearing | 13/178 (7.3%) | 8/85 (9.4%) | 0/6 (0%) | 21/269 (7.8%) |
| Conjunctival Erythema | 17/178 (9.6%) | 5/85 (5.9%) | 5/6 (83.3%) | 27/269 (10.0%) |
| Post-op % of Patients with Moderate / Severe Ocular Discomfort at ≥ 1 Year for Patients with None / Mild Ocular Discomfort Pre-op | | | | |
| Pain | 1/129 (0.8%) | 1/59 (1.7%) | 1/4 (25.0%) | 3/192 (1.6%) |
| Photophobia | 6/98 (6.1%) | 4/50 (8.0%) | 1/4 (25.0%) | 11/152 (7.2%) |
| Foreign Body Sensation | 3/123 (2.4%) | 1/60 (1.7%) | 1/4 (25.0%) | 5/187 (2.7%) |
| Tearing | 3/127 (2.4%) | 1/64 (1.6%) | 1/4 (25.0%) | 5/195 (2.6%) |
| Conjunctival Erythema | 3/125 (2.4%) | 0/65 (0%) | 0/1 (0%) | 3/191 (1.6%) |
| Post-op % of Patients with Moderate / Severe Ocular Discomfort at ≥ 1 Year for Patients with Moderate / Severe Ocular Discomfort Pre-op | | | | |
| Pain | 0/9 (0%) | 0/11 (0%) | 0/0 (-%) | 0/20 (0%) |
| Photophobia | 12/40 (30.0%) | 2/20 (10.0%) | 0/0 (-%) | 14/60 (23.3%) |
| Foreign Body Sensation | 0/14 (0%) | 0/10 (0%) | 0/0 (-%) | 0/24 (0%) |
| Tearing | 2/11 (18.2%) | 0/6 (0%) | 0/0 (-%) | 2/17 (11.8%) |
| Conjunctival Erythema | 2/12 (16.7%) | 0/5 (0%) | 1/3 (33.3%) | 3/20 (15.0%) |

VISX EXCIMER LASER SYSTEM: PHOTOTHERAPEUTIC KERATECTOMY
EFFICACY AND SAFETY RESULTS AT >/= 1 YEAR STRATIFIED BY DIAGNOSIS
(COHORT PATIENTS, USING ALL AVAILABLE DATA IN THE SUBMISSION)

| Diagnosis | Scars & Leukomas | Dystrophies | Surface Irregularities Without Scar | All Patients Treated |
|---|---|---|---|---|
| V. OTHERS | | | | |
| (a) Re-epithelialization | | | | |
| Delayed re-epithelialization > 7 Days | 17/176 (9.7%) | 7/85 (8.2%) | 1/4 (25.0%) | 25/265 (9.4%) * |
| | | | | |
| (b) Retreatment | | | | |
| Retreated at ≤ 1 Year | 7/178 (3.9%) | 0/85 (0%) | 1/6 (16.7%) | 8/269 (3.0%) |
| Retreated at > 1 Year | 1/178 (0.6%) | 1/85 (1.2%) | 0/6 (0%) | 2/269 (0.7%) |
| | | | | |
| (c) PKP | | | | |
| PKP at ≤ 1 Year | 9/178 (5.1%) | 2/85 (2.4%) | 2/6 (33.3%) | 13/269 (4.8%) |
| PKP at > 1 Year | 4/178 (2.2%) | 1/85 (1.2%) | 0/6 (0%) | 5/269 (1.9%) |
| | | | | |
| VI. N | | | | |
| Total with Pre-op Data | 178 | 85 | 6 | 269 |
| Total with Post-op Visits at ≤ 1 Year | 143 | 74 | 5 | 222 |

* Improved to 13/232 (5.6%) for phase III patients.

#### 6.4.2.7 Adverse Events

Although no acute vision-threatening complications presented during this clinical study with the VISX Excimer Laser System, the potential exists for corneal perforation, acute bacterial keratitis, reactivation of herpetic keratitis, endophthalmitis, hypopyon, and corneal decompensation.

#### 6.4.2.8 Complications

The most frequently encountered complications in the post-op period were: 32% with hyperopia shift greater than +3.0 D, 31% with induced anisometropia greater than 3.0 D at ≥ 1 year, 9% with delayed re-epithelialization at greater than one week post-op, 8% lost 2 lines or more of BCVA at ≥ 1 year, 3% with increased corneal haze in the superficial epithelium, 5% with increased corneal haze in the deep epithelium, 4% with increased corneal haze in the anterior stroma, 2.2% with a transient increase in IOP that resolved when topical corticosteroid was discontinued, 1% with recurrence/reactivation of herpes simplex keratitis in three patients treated for leukoma of unknown etiology who did not receive prophylactic anti-viral coverage, < 1% with non-herpetic late corneal infection/ulcer, 1% with recurrent dystrophy and finally < 1% with corneal neovascularization. Four percent required retreatment from 3 weeks to 12 months post PTK, ostensibly for insufficient beneficial effect from the initial treatment. Failure to meet the patients' visual needs or persistent/recurrent epithelial defects necessitated PKP in 5% of cases after one year and in an additional 2% thereafter. Several device failures resulted in design improvements, but no permanent injury has been reported from any of these failures.

#### 6.4.2.9 Hyperopic Shift

As can be seen by the above summary of the patients' refraction, hyperopic shift has been a major safety issue following PTK. Hyperopic shift appears to be a consequence of deep corneal ablation in some cases and an unpredictable occurrence in others. In PTK, the problem of anisometropia greater than 3.0 D secondary to the hyperopic shift can detract from an otherwise successful, clear corneal excimer laser ablation.

## 6.5 OVERALL SUCCESS / FAILURE

At one year or later, a total of 169/222 (76%) benefited either by improvement in vision or improvement in comfort as demonstrated in the following table.

The favorable improvement in visual and refractive efficacy parameters resulted directly from the overall improvement in corneal clarity associated with corneal healing that allowed a good return of optical performance. It is also that benevolent healing process, initiated in an ultrastructurally smooth corneal treatment bed and coupled with a high degree of surgical skill using a sophisticated excimer laser device, that afforded these patients a significant improvement in their level of ocular comfort.



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| OUTCOME ASSESSMENT<br>PERCENTAGE IMPROVEMENT IN VISION OR SYMPTOMS | |
|---|---|
| **DEFINITIONS OF SUCCESS** | **PERCENTAGE (169/222)** |
| Refractive/Visual Improvement | 49% |
| Improved Comfort<br>Symptoms: | 27% |
| Pain | 10% |
| Photophobia | 6% |
| Foreign Body Sensation | 5% |
| Tearing | 3% |
| Conjunctival Erythema | 2% |
| **Overall percentage of success** | 76% |

Of the 53/222 (23.8%) who failed to improve with regard to BCVA or comfort symptoms at later than one year post-treatment, 8/222 (3.6%) improved substantially at 3 months post-treatment, but recurrence of the underlying corneal disease again decreased BCVA. An additional 2/222 (0.9%) were treated to heal an epithelial defect which was done successfully and in another 2/222 (0.9%) the cornea was smoothed sufficiently to allow contact lens wear, which had not been possible pre-treatment.

| OUTCOME ASSESSMENT<br>PERCENTAGE WITHOUT IMPROVEMENT IN VISION OR SYMPTOMS | |
|---|---|
| Explanation for the Lack of Efficacy | Percentage (53/222) |
| Recurrence of Corneal Disease Causing:<br>• Decreased Vision<br>• Increased Patient Discomfort | <br>4%<br>2% |
| Insufficient Removal | 11% |
| PKP Required | 3% |
| Unrelated Ocular Disease | 2% |
| Healed Epithelial Defects | 1% |
| Improved CL Tolerance | 1% |
| **Total Without Improvement** | 24% |

The improvement is visual, refractive, and patient comfort parameters are reflected in the substantial improvement in the corneal clarity and corneal surface smoothing following PTK. The PTK treatment equation is governed by efforts to minimize induced anisometropia while trying to achieve an acceptable visual result or improved level of patient comfort. The treating physician must always be mindful that a satisfactory outcome can be achieved without fully ablating all of the corneal pathology. Overly aggressive treatment runs the risk of hyperopic shift with attendant induced anisometropia. Hyperopic shift and other complications can be minimized through proper patient selection, good clinical judgement and conservative laser treatment. Successful outcomes using the excimer laser for PTK is very much dependent on the training, experience, expertise, planning and meticulous attention to detail of the treating physician. Because depth of treatment is such a critical issue, establish a treatment plan pre-operatively, check the patient at the slit-lamp intra-operatively and be intentionally conservative. The patient may always be brought back for retreatment, but no conservative remedy exists following excessive corneal ablation. The results of multiple treatments for



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residual or recurrent pathology have not been assessed. The issue of multiple treatments for some of these recurrent diseases spread out over the patient's lifetime further reinforcing the need to be conservative in treatment.

Although room still exists to help those not improved by phototherapeutic keratectomy, the benefit obtained here for the successful patients has no conservative equivalent. PTK has potential benefit for many patients whose only alternative treatment involves a partial or full-thickness corneal surgical procedure. Initial enthusiasm must, however, be tempered with caution, for this procedure is not without risk.

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