DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date OCT 20 1995

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

Subject Premarket Approval of Summit Technology, Inc.
SVS Apex (formerly OmniMed) Excimer Laser System/Workstation for Photorefractive Keratectomy (PRK) - ACTION

To The Director, CDRH
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 Emma Knight, M.D., Quynh Hoang, Morris Waxler, Ph.D., Bruce Drum, Ph.D., Mark Stern, M.D., CDRH, HFZ-460, **Date prepared:**_____, 594-2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

DRAFT

Food and Drug Administration

[Docket No.]

Summit Technology, Inc.; Premarket Approval of Svs Apex (Formerly the Omnimed) Excimer Laser System

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its approval of the application by Summit Technology, Inc., Waltham, MA, for premarket approval, under the Federal Food, Drug, and Cosmetic Act (the act), of the SVS Apex (formerly the OmniMed) Excimer Laser System. After addressing the concerns of the Ophthalmic Devices Panel, FDA's Center for Devices and Radiological Health (CDRH) notified the applicant, by letter on October 20, 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 Drive, rm. 1-23, Rockville, MD 20857.

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FOR FURTHER INFORMATION CONTACT:

Debra Y. Lewis, O.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 October 12, 1993, Summit Technology, Inc., Waltham, MA 02154, submitted to CDRH an application for premarket approval of the SVS Apex (formerly the OmniMed) Excimer Laser System. The excimer laser in the Systems delivers pulses at 193 nm wavelength. The excimer laser is indicated for a 6.0 mm ablation zone photorefractive keratectomy (PRK) in subjects with 1.5 to 7.0 diopters of myopia and astigmatism ≤ 1.5 diopters.

On October 20, 1994, the Ophthalmic Devices Panel, an FDA advisory committee, reviewed and recommended conditional approval of the application. The concerns of the panel have been adequately addressed by Summit Technology, Inc. in subsequent submissions to FDA.

On October 20, 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 section 520(h), 90 Stat. 554-555, 571 ((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:_____.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

OCT 20

Ms. Kimberley Doney
c/o Ms. Maureen O'Connell
Regulatory, Clinical, and Quality Affairs
Summit Technology, Inc.
21 Hickory Drive
Waltham, MA 02154

RE: P930034
SVS Apex (formerly OmniMed) Excimer Laser System for Photorefractive Keratectomy (PRK)
Filed: October 12, 1993
Amended: November 4, 1993; June 28, and 30, July 5, 8, and 14, August 22, September 1, 9, and 16, October 11, and December 20, 1994; February 10 and 21, April 5 and 13, May 1, 9, and 19, June 6 and 28, September 13, 19, 21, 25, 26, and 28, and October 11 and 20, 1995

Dear Ms. Doney:

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 SVS Apex (formerly OmniMed) Excimer Laser System. This device is indicated for a 6.0 mm ablation zone, myopic photorefractive keratectomy (PRK) in patients who meet all of the following criteria:

1. 1.5 to 7.0 diopters of myopia with astigmatism of ≤ 1.5 diopters;

2. refraction is within ± 1.0 diopter for one year prior to the laser treatment; and,

3. 21 years of age or older.

We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (Enclosure). You may begin commercial distribution of the device upon receipt of this letter, after you submit an amendment to this PMA submission with copies of all approved labeling in final printed form (following the format of the manuals presented to FDA for review, the Physician's Information on PRK should be included in Appendix A of the User's Manual).

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.

These restrictions on the use, labeling, promotion, and advertising of the device are applicable to Summit Technology, as well as device purchasers and users. Summit must notify the purchasers and users of these restrictions.

1. Only practitioners who are experienced in the medical management and surgical treatment of the cornea, and who have been trained in laser refractive surgery including laser system calibration and operation, may use the device as approved in this order.

2. Prospective patients, as soon as they express an interest in myopic PRK and prior to undergoing surgery, must receive from the treatment provider the Patient Information Booklet (as described in amendment dated October 20, 1995 to this PMA).

3. Prospective patients, prior to undergoing surgery, must be informed of the alternatives for correcting their myopia including eyeglasses, contact lenses and other refractive surgeries such as radial keratotomy.

4. All promotion and advertising for this device must include the following information on indications, risks and benefits:

   a. Approval is for the Summit Technology's application for the SVS Apex laser to correct mild to moderate nearsightedness (-1.5 to -7.0 diopters when concomitant astigmatism is no greater than 1.5 diopters) in a procedure called photorefractive keratectomy (PRK) using an excimer laser that emits light at a wavelength of 193nm.

   b. PRK is an elective procedure with the alternatives being eyeglasses, contact lenses or radial keratotomy.

   c. Approval of the application is based on clinical trials of more than 1600 eyes together with safety information through 3 years of follow up.

   d. The studies using the 6mm treatment zone found that of the 341 eyes at 6 months, 95% were corrected to 20/40 or better without spectacles or contact lenses, and 65% to 20/20 or better without spectacles or contact lenses. In 23 out of 340 eyes (6.8%), the best vision that can be achieved with spectacles declined by more than 1 line from preop; none was worse than 20/40.

   e. These clinical trials showed the following transient complications: pain (24-48 hrs), corneal swelling, double vision, feeling something in the eye, shadow images, light sensitivity, tearing and pupil enlargement. These problems lasted up to several weeks.

f. The clinical trials using the 6mm treatment zone showed the following adverse events occurred in at least 1.0% of the patients within 6 months post-treatment: night vision difficulty (1.0%); elevation of intraocular pressure (1.8%); hazy cornea affecting vision (2.3%); overcorrection or became farsighted (5.0%); undercorrection or still nearsighted (5.6%); loss of the best vision that can be achieved with glasses (6.8%); mild halo (9.7%); and, minor glare (10.0%).

g. Long term risks of PRK beyond 3 years have not been studied.

h. The manufacturer is being required to continue following patients in the clinical trials to evaluate the long-term stability of vision and associated risks. The manufacturer will conduct a study to determine the incidence of adverse events less than 1.0% and to evaluate losses in contrast sensitivity.

i. This laser is not indicated to correct high myopia (nearsightedness > -7.0 D), astigmatism, or farsightedness. Also, it is not indicated to correct nearsightedness of less than -7.0 D if the accompanying astigmatism is > 1.5 D. It is not to be used in procedures other than PRK as described in the approved User's Manual.

j. Note that the complete name for this ophthalmic laser is "SVS Apex Excimer Laser for Photorefractive Keratectomy (PRK) for the Correction of Mild to Moderate Myopia (-1.5 D to -7.0 D) with Low Astigmatism (≤1.5 D)". Two acceptable versions of this official name are: PRK laser correction of low myopia and PRK laser correction of low nearsightedness. The word excimer, ultraviolet, or UV may be used instead of PRK. Also, these names do not have to contain the qualifiers mild to moderate (-1.5 D to -7.0 D) or low astigmatism (≤1.5 D) as long as the adjacent text provides this information. Names other than those appearing above require approval in a PMA supplement.

In addition to the postapproval requirements in the Enclosure, the following information must also be submitted to the Agency:

1. interim progress reports, for the contrast sensitivity and low adverse event rate studies, as proposed in your amendments dated September 25 and 26, 1995;

2. in your annual report, the data specified in items 2.a (additional follow-ups on premarket study subjects) and 2.b (unscheduled maintenance visits) of the FDA approvable letter dated September 15, 1995; when reporting each unscheduled maintenance visit, please include the data from the PMMA and Wratten filter calibrations performed in the 6 weeks prior to the visit; and,

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3. reports to FDA CDRH's Office of Compliance at the address below of any instances of device tampering or usage outside of the approved indications, and any excimer systems that were exported under an 801(e) order and are now back in the U.S.

OC/Division of Enforcement (HFZ-331)
Center for Devices and Radiological Health
Food and Drug Administration
2098 Oakgrove Drive
Rockville, Maryland 20850

Please note that long-term data must be reflected in the labeling (via a supplement to the PMA) when the additional follow-ups and/or postapproval studies are completed.

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.

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,

Philip J. Phillips

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

Enclosure

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P930034 SUMMARY OF SAFETY AND EFFECTIVENESS DATA
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P930034 SUMMARY OF SAFETY AND EFFECTIVENESS DATA
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SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Ophthalmic Excimer Laser System

Device Trade Name: SVS Apex (formerly OmniMed) Laser System

Applicant's Name and Address: Summit Technology, Inc.
21 Hickory Drive
Waltham, MA 02154 USA

Date of Panel Recommendation: Conditional Approval on October 20, 1994

Premarket Approval Application (PMA) Number: P930034

Date of Notice of Approval to Applicant: October 20, 1995

II. INDICATIONS FOR USE

A. Indications For Use

The SVS Apex Excimer Laser System (henceforth to be called the Apex) is indicated for a 6 mm ablation zone treatment for Myopic Photorefractive Keratectomy (PRK) treatment, in patients who meet the following criteria:

1. 1.5 to 7.0 diopters of myopia with astigmatism of $\leq$ 1.5 diopters;

2. stable refractive history of $\pm$ 1.0 diopter for one year prior to laser treatment; and,

3. 21 year of age or older.

III. CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

A. Contraindications For Use

Photorefractive Keratectomy treatment should not be performed in patients:

1. with uncontrolled vascular disease or auto-immune diseases because it is well known that these patients have difficulty in corneal healing and are more susceptible to corneal melting;

2. who are pregnant or nursing due to the potential for temporary fluctuation in refraction with pregnancy;

3. with pre-keratoconus symptoms or keratoconus since eyes with this condition may have unstable corneas; or,

4. known to have a previous history of keloid formation because their corneal healing response is less predictable.

B. Warnings

1. Photorefractive Keratectomy treatment should not be performed in patients whose refractive history is unstable since an accurate pretreatment baseline refraction for the calculation of the desired correction cannot be obtained.

2. Photorefractive Keratectomy treatment is not recommended in patients with Herpes Simplex Virus or Herpes Zoster since cases of herpes reactivation have been reported after use of the excimer laser. Further clinical experience is necessary regarding the use of the 193 nanometer excimer laser wavelength in patients with these conditions.

C. Precautions

1. Photorefractive Keratectomy treatment should not be performed in patients who are unable to cooperate during the treatment because of the potential difficulty in aligning the laser beam and keeping the eye steady during the treatment.

2. Prior to initiating epithelium removal, the physician should arm and test the laser to ensure that the laser is ready to deliver laser energy.

3. Based on the available clinical data from Summit Technology's U.S.

multicenter clinical investigation, patients undergoing PRK who have previously undergone radial keratotomy (RK) have been reported to be subject to the following increased risks in comparison to patients undergoing PRK alone:

a. a higher incidence of best corrected visual acuity loss;

b. a higher risk of best corrected visual acuity with glare loss;

c. an incidence of uncorrected visual acuity loss; and,

d. a higher incidence/severity of anterior stromal reticular haze.

Physicians should take these factors into consideration when evaluating the potential risk/benefit ratio on an individual patient basis.

4. The safety and effectiveness of PRK in patients with a history of glaucoma has not been established.

5. The long term safety and effectiveness of PRK has not been established.

IV. DEVICE DESCRIPTION

The SVS Apex Laser System is an ophthalmic laser workstation which may contain an excimer laser and/or a holmium laser. The excimer laser is the subject of this PMA and SSED; hence, it will be described in detail. The holmium laser has received marketing clearance in 510(k) applications K915651 and K926470.

A. The excimer laser system

Summit originally proposed for market two models of excimer lasers: SVS Apex (configuration 1) and SVS Apex (configuration 2). The SVS Apex (configuration 1) has a maximum ablation zone of 5.0 mm, while the SVS Apex (configuration 2) has maximum ablation zone of 6.5 mm. In order to achieve a larger zone without changing the fluence, the SVS Apex (configuration 2) contains a different laser head and iris diaphragm. Clinical data for both models were collected in U.S. studies; the clinical results for both systems are described in the clinical summary section of this document (section IX). Throughout the clinical studies, the SVS Apex lasers were named OmniMed.

The excimer laser system operates based on the principle that radiation at the 193 nm wavelength is highly absorbed by the cornea (Srinivasan et al.[1]). The delivered 193 nm radiation or photon energy disrupts the intramolecular collagen bonds of the corneal tissue (Aron Rosa et al.[2]), with the result being that the irradiated area is vaporized. Furthermore, the disruption is precise so that the depth of an ablated area corresponds with the number of laser pulses and the area of tissue removal corresponds with the diameter of the laser beam (Marshall et al.[3] and Trokel et al.[4]). Another advantage of this wavelength is that there is minimal damage to the surrounding tissue (Marshall et al.[3], Trokel et al.[4], Courant et al.[5], and Puliafito et al.[6]).

The delivery of the laser beam to the eye involves 13 primary subsystems, as described below:

1. Excimer laser subsystem:

Laser wavelength:	193 nanometers
Laser pulse duration:	14 nanoseconds
Repetition rate:	10 Hertz
Fluence (at the eye):	180 mJ/cm2
Ablation zone diameter:	system set at 6.0 mm
Composition of gases:	< 1.0% Fluorine
	< 10.0% Argon
	< 60.0% Neon
	Balance Helium

2. Excimer beam delivery subsystem

   The raw laser beam produced by the excimer laser is shaped by the Excimer Beam Delivery Subsystem into a uniform intensity circular shaped beam of 6.0 mm in diameter. This transformation is accomplished by an array of mirrors and lenses. The approximately square beam exiting the excimer laser head is used to illuminate the iris, which is a set of metal leaves like a camera iris arranged to form a circular aperture.

3. Patient fixation subsystem

   The Patient Fixation Subsystem is designed to assist the physician in: (1) properly positioning the patient's eye in the appropriate vertical plane for laser energy delivery, and (2) providing a target upon which the patient can fixate during the PRK treatment. The physician can position the patient's eye at exactly 180 mm from the laser by aligning the red spots from a class I aiming Helium-Neon (HeNe) laser. For the patient, there is a fixation target consisting of a single green light surrounded by a ring of 6 red lights illuminated light emitting diodes (LED's).

4. Microscope subsystem

The laser system comes equipped with a coaxial Operating Microscope. The excimer laser procedure may be viewed safely through the microscope because the glass used to form the image in the microscope is opaque to the 193 nanometer laser wavelength. The microscope has sufficient transmission loss at 2.1 microns, so it can also be used during the holmium procedure.

5. Interlock and safety subsystem

There are ten electromechanical interlocks on the Apex to prevent unintentional exposure to excimer radiation and high voltage: 2 on the Secondary Containment Device (SCD), 2 on the rear holmium laser optics cover, 1 on the rear cover, 2 on the optical rail, and 2 on the holmium laser fiberoptic. The tenth interlock, a remote (external) interlock, can be used at the physician's discretion.

6. SCD subsystem

The Secondary Containment Device (SCD) is a welded, steel enclosure (0.25" thick) which has a 5 sided front section and a back door (0.25" thick) that is attached to the front section by a vertical hinge on one side. The SCD is patented by Summit. It houses the entire Excimer Laser Subsystem which includes all high voltage components in the Apex and all pressurized gases (except for the external N_2 purge gas cylinder). At no time during the operation or maintenance of the Apex Excimer Laser System should the user open the SCD.

7. Electromagnetic Interference Shield subsystem

This subsystem consists of a set of sheet metal covers to block radiated EMI fields from exiting the laser system. The excimer laser system has been tested for radiated and conducted EMI, and found to meet the radiated and conducted emission standards (1046/1984 General Permit, Limit Class B and VDE 0871/6.78 Limit Class B) for medical devices.

8. Power distribution subsystem

The electrical requirements from the wall plug are 110 V +/- 10%, 60 Hz and 15 Amps.

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9. Control subsystem

The Control Subsystem holds the intelligence of the system. All of the sensors report to it, as do all status indicators from many different components. The Control Subsystem has a user interface at the Keypad or Control Pad for entry of the desired attempted correction to be used for a PRK treatment. All buttons are labeled and the software prompts the user through each step of a PRK treatment. An attached printer provides the physician with a written record of the parameters selected for the PRK treatment (both procedural parameters and patient printouts).

10. Gas handling subsystem

There are two components in the Gas Handling System:

a. External gas component

Dry N_2 is used in conjunction with the laser system to protect the excimer laser optics from damage due to the formation of trace O_3 from the energetic 193 nm photons, and to reduce the attenuation throughout the beam path due to exposure to air. The regulated N_2 gas cylinder is external to the laser system and is supplied by the user in accordance with the specifications outlined in the User's Manual. The N_2 is not for blowing over the patient's cornea during laser energy delivery.

b. Internal gas component

The excimer laser gas system includes a cylinder of compressed gas which is pre-mixed to a precise balance of argon, fluorine, helium and neon to achieve the correct lasing conditions in the laser cavity in order to produce the 193 nanometer laser wavelength. All these pressurized components are contained within the SCD as a general safety precaution.

11. Cooling (temperature controlling) subsystem

The Cooling Subsystem is a self contained unit and the laser system requires no external cooling.

12. Patient chair and physician stool

The patient chair allows for both coarse and fine position control in three axes. The headrest is capable of fine vertical control movements. The physician stool was selected based on the height of the microscope system for physician comfort during the ophthalmic laser procedures.

13. System software

The system software controls the laser operation and provides an interface to the user. The major subsystems controlled or monitored by software are the Gas Handling Subsystem, the Laser Subsystems, the Beam Delivery Subsystems, the Cooling (Temperature Controlling) Subsystem, the Safety and Interlock Subsystem, and the User Interface or Control Panel (Key Pad). The software is executed by an Intel 80188 microprocessor, running at 8 MHz.

The software for PRK allows the delivery of temporally and spatially overlapped micro-adjustable pulses which are required for this treatment.

B. Regulation

The excimer laser is a Class IV laser system and conforms to the regulation outlined in 21 CFR Chapter 1, Subchapter J, 1040.10 (Laser Products) and 1040.11 (a) (Medical Laser Products).

V. ALTERNATE PRACTICES AND PROCEDURES

There are currently three other alternatives for the correction of low to moderate myopia:

Contact Lenses
Radial Keratotomy
Spectacles

Each alternative has its own advantages and disadvantages. A prospective patient should fully discuss with his/her ophthalmologist these alternatives in order to select the correction method that best meets his/her expectation and lifestyle.

VI. MARKETING HISTORY

Since 1987 when the first excimer laser was sold overseas, Summit Technology, Inc. has sold over 250 laser systems to users in approximately 40 countries in North America, South America, Europe, Middle East, and Far East. The Summit Excimer Laser System has not been withdrawn from any country or market for reasons of safety or effectiveness.

VII. ADVERSE EFFECTS OF THE DEVICE ON HEALTH

During the immediate/early postoperative period, reported problems are primarily associated with postoperative re-epithelialization and early postoperative healing. They include: postoperative pain (first 24 to 48 hours), corneal edema, diplopia, foreign body sensations, ghost images, photophobia, and anisocoria. These signs and symptoms are temporary in most patients, usually subsiding within several weeks after surgery.

The adverse reactions and complications reported at the postoperative examinations include: bacterial keratitis, cataract, corneal decompensation, corneal edema (persistent), corneal epithelial defect, corneal haze, corneal scarring, corneal ulceration, elevation of intraocular pressure secondary to steroid use, endophthalmitis, foreign body sensation, glare, halo, hypopyon, induced astigmatism, iritis, intraocular infection, lens opacity, loss of best corrected visual acuity, night vision difficulty, patient discomfort, and epidemic keratoconjunctivitis infiltrates due to adenoviral infection.

A discussion of these adverse events is found in the clinical summary section of this document (section IX).

VIII. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

1. Performance evaluation of the iris

Testing was performed to evaluate the performance characteristics of the Excimer Laser Iris System. An optical comparator and a digital micrometer were used to measure the aperture size in 2 orthogonal axes for all conceivable outer beam diameters or ablation zones. Measurements were collected starting at the smallest outer beam diameter and moving to the largest possible outer beam diameter at the intervals allowable by the excimer laser system. The difference between the predicted outer beam diameter and the actual outer beam diameter measured was quantified at the image plane on the eye.

Conclusions:

The outer beam diameter selected across the range of possible outer beam diameter selections closely matched the actual outer beam diameters measured by the optical comparator and digital micrometer.

2. Pulse width and stability

Testing was performed to measure the pulse width and pulse to pulse stability of the excimer laser. A storage oscilloscope connected with a photodiode was used to collect a series of laser pulses delivered from the laser system.

Conclusions:

The photograph of an individual laser pulse was examined and the half width half maximum measured to be 7 nanoseconds. The pulse width and pulse to pulse stability are well within the designed specifications for the laser.

3. Beam divergence measurements

Testing was conducted to measure the cross-sectional size of the Apex beam in the near and far field. These measurements were used to calculate the beam divergence both in the horizontal and vertical directions.

Conclusions:

The beam divergence was calculated to be:

Horizontal	0.39 Milliradians ± 1.5
Vertical	0.42 Milliradians ± 6.0.

4. Effect of laser electrode voltage on beam homogeneity

Testing was performed to determine the effects of varying the electrode voltage (kilovolts: "kv") on the homogeneity of the Apex beam in the image plane. The Apex system was set to run at an electrode potential of 27 kv and 250 laser pulses were delivered to a piece of polymethylmethacrylate (PMMA). This test was repeated at 32 kv. The 27 and 32 kv settings represent the range of electrode potentials normally encountered during the routine operation of the Apex system. Upon completion of the laser energy delivery, a light section microscope was then used to measure the ablation depth of the laser cuts in the two pieces of PMMA. Four depth measurements were made for each kv setting.

Conclusions:

The Apex system is designed to operate at electrode voltages that will vary from approximately 27 to 32 kilovolts. This change in electrode voltage does not affect the homogeneity of the laser output as demonstrated in the similarity in the flatness of the beams and the resulting laser cuts. Ablations in the range of the electrode voltage operating parameters had similar surface quality and flatness.

5. Beam homogeneity testing

The objective of the study was to measure the energy profile of the Apex beam output homogeneity. A commercially available laser beam profiling system capable of analyzing the beam exiting the Apex system was used to evaluate the homogeneity of the beam. The beam profiling system is capable of providing cross sectional and 3-D plots of the laser output beam.

Conclusions:

A homogeneous, or flat, beam is the optimum beam for this corneal surgical application. In order to produce a homogeneous beam across the entire ablation zone, the system software contains beam falloff polynomials that allow the system to adjust for beam non-uniformity beyond the 5.0 mm optical zone. The flatness of the beam over a beam radius was verified.

6. Power monitor assembly testing

Testing was conducted to evaluate the reliability and linearity of the power monitor calibration. An initial stability test was performed by firing over 5,000 shots. After stability testing, the power monitor board was removed and the diffuser was exposed to 20,000 shots off the high reflector in the laser cavity. The diffuser was then replaced and recalibrated as necessary. Long term testing was also conducted by firing 100,000 shots at 20,000 shot intervals off the high reflector. After each 20,000 shots interval, the diffuser was replaced in the power monitor fixture and its calibration was recorded.

Conclusions:

The power monitor showed stability after an initial break-in period of approximately 20,000 shots. The normal final testing alignment procedure during the manufacturing of the laser system is comparable to the 20,000 shot break-in period after which power monitor calibration remains constant within a normal fluctuation of ± 3.0%.

7. Shutter life cycle testing

Testing was conducted to confirm that the two mechanical shutter mechanisms are capable of performing their required function. These shutters are controlled by the microprocessor and have a pair of

photodiode/detectors that monitor the opened or closed status. The shutter units were cycled through their operating parameters to a total of 50,000 cycles.

Conclusions:

All of the shutter units tested passed the 50,000 cycle test; there were no cycle failures. The shutter mechanism is capable of performing its required functions: (1) remaining closed to prevent the emission of laser light, and (2) opening when instructed by the microprocessor.

8. Gelatin perforation data

A retrospective review of the effect of environmental factors (i.e.. humidity, temperature) on the gelatin filter used in conjunction with the Excimer Laser Beam Profile Test and Alignment Procedure was conducted.

Conclusions:

The effects of temperature and humidity differences that occur with the seasonal changes did not effect the gelatin filter used in conjunction with the Excimer Beam Profile and Alignment Tests.

9. Output energy over the course of a gas fill

Testing was conducted to confirm that the output energy of Apex remains constant over the course of a gas fill. Testing was conducted from the start of a gas fill procedure until another gas fill was required by the system. The test was concluded when the laser would no longer come out of the test mode.

Conclusions:

The study results demonstrated that the mean number of pulses (delivered energy) remained constant over the course of the gas fill ranging from 8.48 to 9.34 pulses (10.1%). The data verified that the feedback loop between the laser system's two power monitors was able to control effectively the high voltage power supply in order to compensate for the normal depletion of the gas fill and therefore keep the output energy constant.

10. Beam homogeneity over the course of a gas fill

Testing was conducted to evaluate the Apex beam homogeneity or beam profile over the course of a gas fill for the laser. The beam was sampled at intervals over the life of the gas fill. At each interval, a PMMA disk was subjected to 200 pulses. When the laser would no longer come out of the test mode this signaled the need for a new gas fill and testing was concluded. The uniformity, which is a measure of the ratio of the maximum and minimum ablation depths of the PMMA (uniformity = maximum ablation depth - minimum ablation depth/maximum ablation depth), was determined for the PMMA samples.

Conclusions:

Over the course of the gas fill the beam homogeneity varied in uniformity by a maximum of 2%. The study results confirm that the Apex beam homogeneity remains constant over the course of a gas fill.

B. Animal/Enucleated Human Eye Studies

1. Calculation of normal bovine thickness

This study was performed to determine the natural thickness of the bovine cornea in vivo as a baseline for future in vitro studies. An ultrasonic pachymeter was used to measure the corneal thickness in a series of bovine eyes within 1 minute post mortem.

Conclusions:

Ablation rate calculations performed using eyes in the range of 581 to 671 microns represent an acceptable model for the extrapolation of this data for future research purposes. The data collected during this testing provided the necessary information to develop an in-vitro model to begin a series of bovine ocular experiments to determine the optimal parameters for excimer laser corneal applications.

2. In-vitro energy density/repetition rate studies

Testing was performed to identify the appropriate energy density range in conjunction with the usage of the excimer laser system for corneal surgical applications. Energy density is defined as: Energy Density at the Image Plane (i.e., at the eye) or the Fluence. Testing was performed on both

freshly enucleated bovine eyes with intact epithelium and a second group of eyes with the epithelium removed and hydration controlled.

Conclusions:

An evaluation of the Scanning Electron Micrographs demonstrated that the 193 nanometer laser wavelength could create smooth surface cuts in corneal tissue as seen in the surface quality of the ablated tissue at a range of fluences around 180 mJ/cm^2. No discernible damage to the tissue surrounding the ablated area could be detected. A smooth surface cut was possible with the 193 nanometer wavelength even at both repetition rates and no deleterious effects were noticed at the upper repetition rate limit (20 Hertz) indicating that a range of repetition rates would be appropriate in the clinical setting. Based on this testing, an intermediate repetition rate of 10 Hertz was chosen as a suitable repetition rate for the excimer laser system.

3. Calculation of the ablation rate in bovine eyes at low energy densities

Testing was conducted to measure the ablation rate of the 193 nanometer wavelength of the Summit Technology excimer laser beam in bovine eyes. The energy density for these studies was varied using a range of energy densities, 124 to 205 mJ/cm^2. The study involved the use of freshly enucleated bovine corneas with the epithelium removed. Laser energy was delivered to produce a large area ablation and the laser cut depth was measured using a light section microscope.

Conclusions:

These initial ablation rate studies reported ablation rates between 0.13 microns per pulse at 137 mJ/cm^2 to 0.24 microns per pulse at 205 mJ/cm^2 which were comparable to ablation rates reported by other researchers.

4. Calculation of the ablation rate in enucleated human cornea

Studies were performed to measure the ablation rate of the 193 nanometer laser wavelength Summit Technology excimer laser beam in human corneal tissue. The study involved the use of enucleated human eyes that were explanted about 20 hours ago and also had the epithelium removed. An ultrasonic pachymeter was used to determine the corneal thickness of the human corneal specimens. Laser energy was delivered until the initial perforation of the cornea was achieved and number of laser pulses required for perforation recorded.

Conclusions:

This study confirmed previously reported information that the ablation rate in human corneal tissue is in the range of 0.20 to 0.25 microns per pulse for the 193 nanometer laser wavelength produced by the excimer laser system.

C. Additional Studies

1. Radiated & Conducted Emissions testing

Retlif Laboratories, an independent testing house, conducted tests to evaluate the radiated and conducted electromagnetic emissions from the excimer laser system. The testing was conducted to determine if the laser conforms to accepted standards for the safety of electrical medical devices. The testing involved the measurement of all electric and magnetic fields and conducted electrical interference produced by the Summit Technology excimer laser system.

Conclusions:

Retlif Testing Laboratories concluded that the Summit Technology excimer laser system fulfills the conditions for the GENERAL PERMIT according to the "High Frequency Equipment Law" of August 9, 1949. The excimer laser system was found to be in compliance with the 1046/1984 General Permit, Limit Class B and VDE 0871/6.78 Limit Class B standards. Therefore, the radiated and conducted emissions levels for the excimer laser system are within the conventional standards for electronic equipment indicating that the operation of the device does not pose a safety risk in terms of radiated and conducted emissions.

2. Technischer Überwachungs Verein (TÜV) Rheinland electrical & radiation safety testing

   TÜV Rheinland, an independent testing house in Germany, granted TÜV approval on its evaluation of the device's electrical and radiation safety.

3. Software validation testing

   The device software controls the gas, laser output, beam delivery, temperature control, safety/interlock, and user interface systems. Summit performed an in-house validation testing of the software by introducing the possible hazardous scenarios that could occur during the operation of the device to evaluate their effects on the software. The scenarios are from the hazard analysis of the device.

IX. SUMMARY OF CLINICAL STUDIES

The data used to support the marketing of the excimer laser came from these studies conducted under IDE application G880210: phase III less-than-6.0 (<6) mm ablation zone; phase III 6 mm ablation zone (phase III at 6); a substudy of 30 Navy subjects (Navy); and, a prospective randomized study (steroid) to assess the effect of topical corneal steroid versus no steroids on refraction and acuity.

In this summary, results from the 6.0 mm ablation zone treatments are described first because they employ the approved treatment. The combined data from all the groups (phase III at 6, Navy, and steroid) that utilized a 6.0 mm zone are presented, as their studies utilized the same standardized enrollment criteria, laser parameters, surgical protocol, and follow-up care. (It should be noted that the steroid study does not establish the safety or effectiveness of steroids after PRK, and FDA believes that further study in this area is needed.) Following the discussion of the 6.0 mm data is the discussion on the phase III <6 data. Specifically, long term results from the first eye cohort (first treated eye of all patients) are discussed since they establish the baseline safety and effectiveness of the excimer laser. Next, a comparison of the major safety and effectiveness variables of < 6.0 mm versus 6.0 mm ablation zones is presented to illustrate the decision to approve the 6.0 mm ablation zone treatment.

Additionally, the results of a study conducted under IDE application G910078, PRK after RK, are also reported here as they are the bases for a specific precaution statement in the labeling.

A. Combined Data: Six Millimeter (6.0 mm) Ablation Zone

1. Study Objectives

The common goal in each subgroup study was to demonstrate the safety and effectiveness of the Summit Technology SVS Apex Excimer Laser System for PRK, using a 6 mm ablation zone, to treat myopia of 1.0 to 7.0 D and to reduce/eliminate the need for contact lenses or eye glasses.

2. Study Design

Combined and presented below are data on 394 eyes from three groups: Navy, phase III at 6, and steroids. The Navy and phase III at 6 groups included 194 eyes and came from two prospective, nonrandomized, uncontrolled, and unmasked clinical studies. The Navy data were collected at one center, while the phase III at 6 data were from 7 centers. The steroid subgroup of 200 eyes came from a prospective, randomized, masked, multicenter (6 centers), and controlled study. Each subgroup study focussed on a particular clinical parameter, as indicated by their names; nevertheless, all three utilized the same standardized enrollment criteria, laser parameters, surgical protocol, and follow-up care. Their data are pooled and presented as the "combined data".

3. Inclusion and Exclusion Criteria

Subjects were at least 21 years of age and were enrolled in the study if they met the following conditions: spectacle intolerance; contact lenses intolerance; desire to decrease or eliminate spectacle or contact lens use; rejected the alternative refractive surgical procedures; and, stable refractive error. Subjects were usually chosen from within the geographic area of the investigator to increase accountability at subsequent visits.

Subjects not meeting the above enrollment criteria were excluded from the study. In addition, anyone with an uncontrolled vascular disease or autoimmune disease which could affect corneal wound healing or could cause corneal melting was excluded from the study. Pregnant women were excluded from the study. Subjects had no previous corneal or intraocular surgery and no existing corneal or ocular pathology which could affect results.

4. Study Plan, Subject Assessments, and Effectiveness Criteria

Data on 394 eyes were collected from three studies to establish safety and effectiveness data on the use of the 6.0 mm ablation zone with the excimer laser configuration 2 units. Subjects in these three studies were treated using identical surgical protocols with a 6.0 mm ablation zone. Planned subject visits included a preoperative evaluation, operative day visit, and postoperative examinations on Day 1, Day 3, Week 1, Month 1, 3, 6, 12, 18 and 24.

Preoperatively, the subjects medical and ocular histories including prior ocular surgery were recorded. Immediate postoperatively, re-epithelialization data were collected. During the study, objective parameters measured included best spectacle corrected visual acuity, best spectacle visual acuity with glare, uncorrected visual acuity, manifest refraction, cycloplegic refraction, pupil size, manual keratometry readings, irregular astigmatism, intraocular pressure, glare, contrast sensitivity, photokeratoscope and slit lamp photographs, and status of the cornea, conjunctiva, anterior chamber, lens, vitreous, retina, and externals. A patient questionnaire was administered to all subjects. All subjects were requested to answer a short questionnaire and a subgroup of subjects answered a long form questionnaire to collect additional data on refractive surgery.

Success of the clinical procedure was defined as an uncorrected visual acuity of 20/40 or better. Failure was defined as having an uncorrected visual acuity worse than 20/40, or having a 20/40 uncorrected visual acuity but loss of more than 1 line of best spectacle corrected visual acuity at a 2-4 mm pupil, or having a 20/40 uncorrected acuity but also have a best spectacle corrected visual acuity of 20/25 or worse at a 2-4 mm pupil. Major visual/ocular complications were also considered as failures. These criteria were chosen by the firm based on a publication by Waring, GO[7].

5. Study Period, Investigational Sites, and Demographic Data

a. Study Period

Protocol	Treatment Dates	Number of eyes
Navy Group		
First eyes	8/24/93 to 10/1/93	30
Second eyes	2/1/94 to 3/22/94	26
Phase III at 6 Group		
First eyes	10/15/93 to 3/7/95	70
Second eyes	3/22/94 to 5/12/95	68
Steroid Study		
First eyes	1/12/94 to 9/20/94	200
COMBINED STUDIES	8/24/93 to 5/12/95	394

A total of 394 eyes in three hundred subjects were treated.

b. Investigational Sites

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

SITE	COMBINED studies
Vision Surgery & Laser Center San Diego, CA	160
Eye Surgery Center of LA New Orleans, LA	19
Hunkeler Eye Clinic Kansas City, MO	26
Massachusetts Eye and Ear Boston, MA	43
Emory University School of Medicine Atlanta, GA	2
St. Mary's Hospital The Eye Clinic of Texas Galveston, TX	2
Carraway Medical Center Norwood Eye Clinic Birmingham, AL	48
Montefiore Hospital Bronx, NY	35
Georgetown University Medical Center Washington, D.C.	27
Sioux Empire Medical Center Sioux Falls, CO	32
TOTAL	394

c. Demographics

	COMBINED STUDIES (N=394)
GENDER	
Female	143 (36.3%)
Male	251 (63.7%)
RACE	
White	36.09 (93.6%)
Afro-American	11 (2.8%)
Other	14 (3.6%)
AGE (YEARS)	
Mean	36.1
Range	21 to 69
SD	9.0
OPERATIVE EYE	
Right	177 (44.9%)
Left	217 (55.1%)

There is no evidence that gender is related to safety or effectiveness outcomes. Age is a statistically significant factor. Younger subjects are more likely to be both "predictable" (chi square test p=<0.001) and have uncorrected visual acuity of 20/40 or better (chi square test p=<0.001). There is no evidence in this data that race is related to safety or effectiveness outcomes, however, the sample sizes are small to detect a difference. In the combined studies, analyses for these factors were based on eyes (rather than subjects) because both first and second eyes were considered in the data analysis and eyes were not necessarily the same for factors such as level of myopia, haze, etc. at baseline or postoperatively.

6. Data Analysis and Results

a. Preoperative Ocular Characteristics

A number of baseline characteristics were measured. They included:

1. Visual Acuity: Best Spectacle Corrected Visual Acuity (BSCVA) and Uncorrected Visual Acuity (UCVA)

	COMBINED STUDIES (N=394)
BSCVA 2-4 MM	
20/20 OR BETTER	384 (97.4%)
20/25 TO 20/40	10 (2.6%)
BSCVA 6.0-8 MM	
20/20 OR BETTER	378 (95.9%)
20/25 to 20/40	16 (4.1%)
WORSE THAN 20/40	0
UCVA	
20/200 OR WORSE	305 (77.2%)
20/100 to 20/160	67 (17.1%)
20/50 to 20/80	21 (5.4%)
20/40 OR BETTER	1 (0.3%)

Best spectacle visual acuity of 20/20 or better has been found to be a statistically significant factor when assessing outcomes. The one subject with an uncorrected visual acuity of 20/40 was treated because it was considered to be in the interest of the subject to treat the fellow (second) eye to decrease anisometropia and eliminate the need for correction in only one eye.

ii. Manifest Refraction Spherical Equivalent (MRSE) and Cycloplegic Refraction Spherical Equivalent (CRSE)

COMBINED STUDIES	(N=394)
MRSE (diopters)	
Mean	-4.37
Range	-1.38 to -9.00
Standard deviation	1.48
CRSE (diopters)	
Mean	-4.28
Range	-1.25 to -8.00
Standard deviation	1.49

The correlation between the manifest refraction and the cycloplegic refraction was reliable as shown by the above data. As would be expected, the higher levels of myopia showed greater variability. Overall this is consistent with clinical expectations.

COMBINED STUDIES	(N=394)
MR cylinder (diopters)	
Mean	-0.45
Range	0 to -2.25
Standard Deviation	0.42
CR cylinder (diopters)	
Mean	-0.46.0
Range	0 to -2.00
Standard Deviation	0.41

The correlation between the manifest and cycloplegic cylinder corrections were reliable and clinically reasonable.

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iii. Contact Lens Wear

A total of 269 (68.3%, 269/394) eyes in the combined studies wore contact lenses prior to the PRK procedure.

iv. Keratometry Readings.

COMBINED STUDIES	(N=394)
Keratometry reading (diopters)	
Mean	44.1
Range	40.00 to 48.75
Standard deviation	1.52
Keratometric astigmatism (diopters)	
Mean	0.7
Range	0 to 3.00
Standard deviation	0.51

v. Intraocular Pressure (IOP)

The mean preoperative IOP was for the combined data was 15.8 mmHg with a range from 7 to 23 mmHg and a standard deviation of 2.7.

b. Operative Characteristics

The operative technique was standardized for all the studies reported here. These laser parameters were also standardized for all the studies: fluence at the eye, repetition rate, ablation rate, and a 6.0 mm ablation zone treatment.

ATTEMPTED CORRECTION	COMBINED STUDY (N=394)
1.50 D -- 2.00 D	22 (5.6%)
2.10 D -- 3.00 D	84 (21.2%)
3.10 D -- 4.00 D	79 (20.1%)
4.10 D -- 5.00 D	81 (20.5%)
5.10 D -- 6.00 D	80 (20.3%)
6.10 D -- 7.00 D	46 (11.8%)
7.10 D -- 8.00 D	2 (0.5%)
Total	394 (100%)
LASER PARAMETERS	
Average total pulses	200 (87 to 350)
Ablation zone diameter (mm)	6.0
Fluence @ eye (mJ/CM^2)	180
Pulse repetition rate (Hz)	10
Pulse width (nsec)	14

Laser delivery time ranged from 9 to 35 seconds for the combined study, and was dependent on the number of pulses required. A study which has predominantly lower levels of attempted correction will appear to have better results. No adverse reactions were noted during the procedure. Four of the 394 treatments in the combined study were interrupted due to ocular drift or loss of fixation. Subjects then refixated and the treatments were fully completed.

c. Postoperative Characteristics and Results

I. Accountability

# EYES ENROLLED	FOLLOW-UP EXAM (months)	# EYES ELIGIBLE FOR FOLLOW-UP	# and (%) EYES FOLLOWED
394	1 M	394	381 (96.7%)
	3 M	394	361 (91.6%)
	6 M	394	341 (86.5%)
	12 M	95	82 (86.3%)

Many of the second eye treatments were not yet eligible for the 12 month follow up at the time of device approval. Accountability is based on eyes that are eligible or due for the particular visit.

ii. Re-epithelization

Of the 394 treated eyes, re-epithelialization was reported as follows:

by 48 hours	37 eyes	9.4%
by 72 hours	344 eyes	87.5%
by 1 week	375 eyes	95.4%
by 3 weeks	376 eyes	95.7%
by 1 month	393 eyes*	100.0%

Of the 18 eyes who had re-epithelialized between 3 weeks and 1 month:

- 9 eyes were not seen after the 3 day visit and before the 1 month, therefore exact time of re-epithelialization was not recorded;

- 1 eye was not seen after the 2 day visit and before the 1 month visit therefore exact time of re-epithelialization was not recorded;

- 6 eyes were not seen after the 1 day visit and before the 1 month visit, therefore exact time of re-epithelialization was not recorded;

- 2 eyes were not seen at any short term postoperative visit therefore exact time of re-epithelialization was not recorded.

* The total of eyes has changed from 394 to 393 because of a non-device related death of one subject after the 1 day visit. This subject was not included in these calculated percentages.

iii. Uncorrected Visual Acuity (UCVA) -- Acuity and change

The UCVA in eyes treated with the 6 mm zone were:

UCVA	Preop	1 M	3 M	6 M	12 M
20/200 OR WORSE	305 (77.2%)	2 (0.5%)	1 (0.3%)	4 (1.2%)	0
20/100 to 20/160	67 (17.1%)	0	1 (0.3%)	1 (0.3%)	0
20/50 to 20/80	21 (5.4%)	36 (9.5%)	20 (5.5%)	12 (3.5%)	1 (1.2%)
20/25 to 20/40	1 (0.3%)	161 (42.2%)	115 (31.9%)	101 (29.6%)	15 (18.3%)
20/20 OR BETTER	0	181 (46.7%)	224 (62.0%)	223 (65.4%)	66 (80.5%)
20/40 OR BETTER	1 (0.3%)	342 (90.0%)	339 (93.9%)	324 (95.0%)	81 (98.8%)
TOTAL	394	380	361	341	82

As noted previously, the one eye with UCVA of 20/40 preoperatively was the second eye of a subject who was experiencing anisometropia. It was believed that the best interest of the subject was served by treatment.

iv. Best Spectacle Corrected Visual Acuity (BSCVA) for a 2-4 mm Pupil

a. Acuity (BSCVA)

In the combined studies, for a 2 - 4 mm pupil, the BSCVA in subjects treated with the 6 mm zone were:

BSCVA	Preop	1 M	3 M	6 M	12 M
20/20 or better	384 (97.4%)	331 (87.1%)	340 (94.2%)	323 (95.0%)	82 (100%)
20/25 to 20/40	10 (2.6%)	45 (11.8%)	19 (5.3%)	17 (5.0%)	0
20/50 to 20/80	-	4 (1.1%)	2 (0.6%)	0	0
20/100 to 20/160	-	0	0	0	0
20/200 or worse	-	0	0	0	0
TOTAL	394	380	340	340	82

One eye at the six month postoperative exam did not have BCVA reported.

b. Change in BSCVA from preoperative

Change in BSCVA from preop	6 M (N=340)	12 M (N = 82)
Decrease 5 lines	1 (0.3%)	0
Decrease 4 lines	0.00	0
Decrease 3 lines	6 (1.8%)	0
Decrease 2 lines	16 (4.7%)	1 (1.2%)
No Change (± 1 line)	295 (86.8%)	81 (98.8%)
Increase of 2/3 lines	22 (6.5%)	0

The overall loss of BSCVA of 2 or more lines is 6.8% (23/340). This would have been a concern, if not for the observation that in the larger < 6.0 mm population, losses in unoperated fellow eyes were at

7.3% for two lines and at 3.7% for greater than two lines. The variability noted in the unoperated eyes signifies the variability of the study, and hence, the 6.8% loss is not considered as a significant event. Further assessment of BSCVA loss in association with absolute acuity levels is necessary.

All of the 23 eyes (6.8%, 23/340) that experienced a decrease in BSCVA at the 6 month postoperative examination were preoperatively 20/20 or better. Their 6 month BSCVA were: 12 eyes (3.5%, 12/340) were 20/20 or better; 7 eyes (2.1%) were 20/25; 3 eyes (0.9%) were 20/32 and 1 eye (0.3%) was 20/40. No eyes were worse than 20/40. Although it is a concern that 23 eyes lost BSCVA, the fact that none is worse than 20/40 is reassuring. Furthermore, of the 4 eyes that were worse than 20/25, haze was a contributing factor in 3 eyes; haze and regression in 1; and astigmatism greater than 1.50 diopters in 3.

When haze is a contributing factor, improvement is likely overtime (with the exception of the subject experiencing regression whose course is unpredictable).

v. BSCVA for a 6 - 8 mm Pupil

a. Acuity (BSCVA)

For the combined studies for a 6 - 8 mm pupil, the BSCVA in subjects treated with the 6 mm zone were:

BSCVA	PREOP	1 M	3 M	6 M	12 M
20/20 or better	378 (95.9%)	317 (83.4%)	336 (93.1%)	323 (95.0%)	82 (100%)
20/25 to 20/40	16 (4.1%)	58 (15.3%)	24 (6.6%)	17 (5.0%)	0
20/50 to 20/80	0	5 (1.3%)	1 (0.3%)	0	0
20/100 to 20/160	0	0	0	0	0
20/200 or worse	0	0	0	0	0
TOTAL	394	380	361	340	82

Only four subjects had BSCVA less than 20/25 at 6 months. One subject had haze and regression, and three subjects had haze and associated astigmatism greater than 1.5 diopters. The results at 6 months are similar to the 2-4 mm pupil size.

b. Change in BSCVA from preoperative

Change in BSCVA from preop	6 M (N=340)	12 M (N = 82)
Decrease 5 lines	2 (0.6%)	0
Decrease 4 lines	0	0
Decrease 3 lines	3 (0.9%)	0
Decrease 2 lines	19 (5.5%)	1 (1.2%)
No change/Increase	316 (92.9%)	81 (98.8%)

Only one subject was 20/40, and three others were less than 20/25 at 6 months. No eyes were worse than 20/40 at 6 months. The results parallel the 2-4 mm pupil size results and in no case was any subject dissimilar in loss between the two pupil sizes beyond clinical expectations.

vi. Stability -- Manifest Refraction Spherical Equivalent (MRSE)

This is a primary effectiveness parameter.

a. Combined Studies MRSE

VISIT (N)	MEAN	SD	RANGE
1M (379)	+0.20	0.83	-2.38 to +6.00
3M (361)	-0.13	0.66	-3.75 to +2.75
6M (341)	-0.12	0.70	-3.63 to +3.38
12M (82)	+0.08	0.60	-1.50 to +1.63

Stability for these 6.0 mm combined studies was superior to that of the < 6.0 mm ablation zones as is noted later in this document. Stability is seen as early as the three month visit with higher levels of myopia taking slightly longer to stabilize as would be expected. Of note in this table is the range at the twelve month visit which is reflected in the mean. This represents the difference seen in the mean.

b. MRSE from Navy and phase III at 6 data

VISIT	N	MEAN	SD	RANGE
1M	185	+0.30	0.86	-1.88 to +6.00
3M	173	-0.06	0.70	-2.25 to +2.75
6M	152	-0.05	0.66	-1.75 to +3.38
12M	82	+0.08	0.60	-1.50 to +1.63

Because the subjects from the steroid study had not reached the one year visit, the above MRSE data came from the Navy and the phase III at 6 groups. The ranges here differ from the previous data due to the exclusion of the steroid subjects; hence, this additional information is presented for examination of stability only.

c. Predictability ± 1 diopter of attempted versus achieved by diopter of correction

Predictability	1.50-3.00 D		3.10-4.00 D		4.10-5.00 D		5.10-6.00 D		6.10 - 7.00 D	
	6 M N=92	12 M N=32	6 M N=67	12 M N=17	6 M N=69	12 M N=17	6 M N=76	12 M N=11	6 M N=37	12 M N=5
Overcorrected	3 (3.3%)	2 (6.3%)	4 (6.0%)	1 (5.9%)	3 (4.3%)	5 (21.4%)	6 (7.9%)	0	1 (2.7%)	0
± 1.00 D	89 (96.7%)	30 (93.7%)	62 (92.5%)	16 (94.1%)	63 (91.4%)	11 (64.7%)	63 (82.9%)	10 (90.9%)	28 (75.7%)	4 (80.0%)
Undercorrected	0	0	1 (1.5%)	0	3 (4.3%)	1 (5.9%)	7 (9.2%)	1 (9.1%)	8 (21.6%)	1 (20.0%)

It is noted that the greater the myopia, the greater the attempted correction and the less predictable the outcome. These 6.0 mm results are much improved over those of the < 6.0 mm ablation zones, and the overall rates of overcorrection are lower. The overcorrections with the 6.0 mm ablations are primarily at lower levels than in < 6.0 mm ablations, and these overcorrections were primarily in younger subjects where the attempted correction was likely to be closer to the full refractive error.

d. Predictability: by incremental outcomes.

Predictability within:	1 M (N=379)	3 M (N=361)	6 M (N=341)	12 M (N=82)
± 0.50 D	175 (46.2%)	233 (64.5%)	208 (61.0%)	42 (51.2%)
± 1.00 D	302 (79.9%)	324 (89.8%)	305 (89.4%)	70 (85.3%)
± 2.00 D	368 (97.1%)	354 (98.1%)	330 (96.8%)	82 (100%)
± 3.00 D	378 (99.7%)	360 (99.7%)	339 (99.4%)	0

These results are better to those seen in studies of < 6.0 mm ablation zones. They show good results for standard outcomes for refractive surgery.

vii. Cycloplegic Refraction

a. Spherical component (CRSE)

CRSE (Diopters)	6 M N=321	12 M N=82
Mean	0.02	0.18
Range	-3.38 to +3.63	-1.38 to +1.63
Standard Deviation	0.78	0.63

The correlation with manifest refraction is reliable and within anticipated clinical expectations. The mean at 6 months is within 0.14 diopters and at 12 months 0.10

diopters. This suggests that manifest refraction is an accurate measure of outcomes.

b. Cylinder component (CR --cylinder)

CR -- cylinder (Diopters)	6 M N=321	12 M N=82
Mean	-0.48	-0.44
Range	-2.00 to 0	0 to -1.50
Standard Deviation	0.47	0.43

There was no evidence of induced astigmatism for the population. Only one subject had significant induced astigmatism by the laser, > 1 diopter, and this was after los of fixation during the procedure.

viii. Irregular Astigmatism

Irregular astigmatism occurred postoperatively in 2/394 (0.5%) eyes in the 6.0 mm combined studies. In each case, the amount of astigmatism was less than 1 diopter. This was reported in one subject at 1 and 3 months, and in one subject at 2 months. Subsequent follow-up visits did not report this complication. Ther were no clinically significant complaints because of this complication.

ix. Keratometry Readings

The mean keratometry reading decreased or remained unchanged after PRK. The mean keratometric cylinder remain unchanged aft PRK. For both parameters the postoperative result was stable throughout the postoperative follow up period.

x. Intraocular Pressure

The intraocular pressure (IOP) was measured using applanation tonometry at all long term postoperative examinations. In some cases intraocular pressure increases after PRK, probably contributed to by the use of topical corticosteroids postoperatively for several months. Only one case of significant increased

intraocular pressure was reported which subsided following discontinuance of steroid use. There were no permanent increases in IOP. The mean intraocular pressure at 6 months postoperative was 15.1 mmHg with a range of 9-21 mmHg and a standard deviation of 2.6. The mean intraocular pressure at 12 months postoperatively was 14.8 mmHg with a range of 8-22 mmHg and a standard deviation of 2.5.

xi. Corneal Haze

Haze at each postoperative visit is shown below.

GRADE	1 MONTH N=377	3 MONTHS N=361	6 MONTHS N=340	12 MONTHS N=82
CLEAR	38 (10.1%)	79 (21.9%)	125 (36.8%)	43 (52.4%)
TRACE	291 (77.2%)	250 (69.3%)	182 (53.4%)	36 (43.9%)
MILD	44 (11.7%)	26 (7.2%)	25 (7.4%)	0
MODERATE	4 (1.1%)	6 (1.7%)	8 (2.4%)	3 (3.7%)
SEVERE	0	0	0	0

All subjects who had haze at 6 or 12 months also had haze of some degree at 3 months. The 3 month exam was the peak haze for the population. This is also true for the phase III < 6 group. In the three subjects who reported moderate haze at one year, all had moderate haze at 6 months.

The observation that haze developed in the first 1-2 months and improved over time was determined with the 5 mm ablation zone data and held true for the 6 mm data. There is a trend that the higher degrees of preoperative myopia or the higher the attempted correction, the longer it takes for haze to resolve though this did not reach statistical significance. Haze may take up to one year (or more) to disappear. When associated with acuity regression there appears to be a more unpredictable course of both resolution of haze and stability. No subjects had severe haze.

xii. Externals

There were no external irregularities in the long term postoperative period which significantly affected the safety of the PRK procedure.

xiii. Conjunctiva

There were no conjunctival irregularities in the long term postoperative period which would significantly affect the safety of the PRK procedure.

xiv. Anterior Chamber Summary

There were no anterior chamber irregularities in the long term postoperative period which would significantly affect the safety of the PRK procedure.

xv. Lens Status Summary

Lens opacities occurred infrequently in the long term postoperative period after PRK. The relationship between the lens opacities and the PRK procedure is unknown. There may also be a relationship between steroid use and lens opacity which has been proven with long term steroid use. One subject at 1 month then at 3 months had a reported lens opacity, though visual acuity was not compromised.

xvi. Vitreal Status Summary

There were no vitreal irregularities in the long term postoperative period attributable to the PRK procedure which would significantly affect the safety of the PRK procedure.

xvii. Retinal Status Summary

There were no retinal irregularities in the long term postoperative period attributable to the PRK procedure which would significantly affect the safety of the PRK procedure.

d. Corneal Topography

Topography data were acquired at three centers using the EyeSys Corne Analysis System at these visits: preoperative, 3, 6, and 12 months. The differential topography power map, derived from subtracting preoperati from each subsequent visit, was used in the analysis of centration, topographic pattern, and extent of the irregularity. All maps were grade by two masked observers, with joint review when necessary to resolve a differences.

1. Optical Zone Decentration from Pupil Center (N=175)

Centration measurements in the combined studies were taken at 3 month exam. There were 175 subjects whose three month dat are sufficient for analysis of centration of the optical zone. Thei data are presented below.

Statistical analyses of the association between centration and oth clinical parameters were done on the 98 eyes whose maps were available at all visits. Statistical results are also presented below

a. Stratified by 0.25 mm increments

DECENTRATION (mm)	N (%)
< 0.25	44 (25.1%)
0.25 - 0.50	76 (43.3%)
0.50 - 0.75	35 (20.0%)
0.75 - 1.00	12 (6.8%)
1.00 - 1.25	8 (4.5%)
Total	175

An evaluation by study centers was performed and one s showed significantly better centration than the other two

b. There was no association between attempted correc decentration. A linear regression performed of the attempted correction against decentration (correlati 0.16; p =0.13). Only 2.5% of the variation in centra could be explained by variation in the attempted cor

c. Mean Centration and UCVA

UCVA	N	MEAN DECENTRATION	SD
20/20 or better	73	0.40	0.26
Worse than 20/20, but at least 20/40	23	0.52	0.25
Worse than 20/40	2	0.92	0.61

The difference between eyes with 20/20 or better ar between 20/20 and 20/40 is significant (p=0.05; t-te ANOVA test also shows an association (p=0.006). above data demonstrate that uncorrected visual acu associated with decentration.

d. Mean Centration and BSCVA

Since 97 out of the 98 subjects had BSCVA 20/20 this parameter could not be evaluated.

e. Predictability -- The correlation between predictabil centration was 0.09 (p=0.40). Less than 1% of the in predictability could be explained by the variation centration.

f. Refractive astigmatism -- The correlation between predictability and centration was 0.10 (p=0.35). T 1% of the variation in astigmatism could be explain variation in centration.

g. Keratometric astigmatism -- The correlation betwe change in keratometric astigmatism and centration (p=0.26)

h. Glare/Halo index and mean centration.

GLARE/HALO	N	MEAN DECENTRATION	SD
0	35	0.35	0.24
1	21	0.42	0.22
2	13	0.53	0.27
3	11	0.43	0.26
4	4	0.39	0.18
5	5	0.66	0.49

There is evidence of an association between increased halo and increased decentration (linear regression p = 0.02). This was not corroborated by ANOVA test (p=0.12); therefore this is viewed as a trend.

I. Subject satisfaction and mean centration

Satisfaction	N	Mean Decentration	SD
0-3	15	0.56	0.34
4	22	0.46	0.26
5	51	0.38	0.25

There is a trend between more satisfaction and better centration (linear regression for trend, p = 0.01). ANOVA for difference in categories, p = 0.08.

j. Haze and centration.

Although the mean centration was higher for those with haze rating of 2 or 3, this was not statistically significant because there were only 3 eyes in this category (linear regression, p = 0.40). ANOVA test also was not significant.

ii. Topographic Pattern Classification and Analyses (N=98)

Topography data at all visits were available for 98 eyes. All qualitative characteristics of the color maps were verified by review of the actual numeric data used to derive the topography maps. Each map is classified into one of the seven topography patterns that can be found in the literature: Homogeneous (H), Smooth toric bowtie with axis (WA), Smooth toric bowtie against axis (AA), Irregularly irregular, Keyhole/semicircular (KH/SC), Central island (CI), and Focal topographic variants (FTV). The topography patterns were tested for relationships with clinical outcomes of UCVA, BCVA, predictability, astigmatism, subjective subject satisfaction, and glare/halo index. For statistical analyses, homogeneous, toric-WA and toric-AA were combined into a larger regular group, and keyhole/semicircular, irregular, and FTV were combined into the irregular group.

It is observed that the older subjects and those with higher attempted corrections tend to have a more irregular pattern at one year. Topography patterns do not significantly affect clinical outcomes except that the pooled irregular group tend to be somewhat overcorrected. Topographic irregularity appears to improve over time.

a. Topographic Pattern by Visit

Topography Classification	3 Months		6 Months		12 Months	
	N	%	N	%	N	%
Homogeneous	11	11.2%	17	17.3%	21	21.4%
Toric-with-axis	19	19.4%	20	20.4%	27	27.6%
Toric-against-axis	14	14.3%	9	9.2%	10	10.2%
Irregularly Irregular	6	6.1%	7	7.1%	7	7.1%
Keyhole/Semicircular	36	36.7%	32	32.7%	24	24.5%
Focal topographic variant	12	12.2%	13	13.2%	9	9.2%
Central Island	0	0	0	0	0	0

No central islands were seen with the 6 mm ablation zone sizes.

b. Topography and Age

The mean age for this cohort was 35.8 years. There were no differences in mean age between the regular and irregular groups at each postoperative visit using t-tests. There was a statistically significant difference in the proportion in each of the three age categories (20-29, 30-39, and 40+) at 6 months only, using a chi-square test with two degrees of freedom (p=0.016). There was a tendency for the irregular group to be somewhat older at all three visits.

c. Topography and attempted correction

At all postoperative visits, the mean attempted correction is higher in the irregular group. This is statistically significant only at 3 months (p=0.017). Higher attempted corrections are associated with greater chance of irregular topography pattern.

d. Topography and UCVA

There was no statistically significant difference in mean visual acuities between the two combined groups using a t-test. There was no statistically significant difference of the average mean UCVA stratified to all topography groups.

e. Topography and BSCVA

There was no association between average mean BSCVA stratified to all topography groups.

f. Topography and predictability

The combined irregular group tends to be overcorrected. This is the opposite of the expected outcome if the keyhole group behaved like the central island groups which have been published.

g. Topography and astigmatism, glare/halo, subject satisfaction, corneal haze

There was no statistically significant difference for these factors in association with topography.

h. Change in topography with time

There is a tendency for a shift towards the regular group between the 3 and 12 month visits. There are no statistically significant differences between visits although the 3 and 12 month show non-significant differences (the proportion of the irregular group declines over time). Most of the shift is in the homogeneous and toric-with-axis groups with a decline in the keyhole/semicircular and the FTV groups.

iii. Analysis of the Extent of Corneal Irregularity

The Potential Corneal Acuity (PCA) program measures the extent of corneal irregularity by ascribing a best fit ellipse to the video-captured image of the reflected rings of the topography unit. Point by point differences between the ring and the ellipse are measured in microns are weighted by the area as well as the Stiles-Crawford effect, creating a color map depicting corneal surface irregularity. The point values are also integrated over the entire measured area to yield a quantitative PCA value, which is numerically expressed in the form of predicted Snellen visual acuity. The quantitative descriptor attempts to predict the best corrected visual acuity theoretically supported by the cornea given an entrance pupil of 3 mm, using the rings inside a 3 mm diameter.

A PCA value was determined for 98 eyes at the 3 month, 6 month and 12 month follow up. At each time point, quantitative PCA was determined for the entire subject population as well as subjects stratified to qualitative topography pattern.

a. PCA and Age

Age was not found to be significantly associated with PCA value (i.e., age does not influence the corneal irregularity postoperatively). Using linear regression, 3 month

correlation = 0.08, p =0.44; 6 month correlation - 0.15, p = 0.13; 1 year correlation = 0.18, p =0.08.

b. PCA versus Attempted Correction

PCA	3 MONTHS			6 MONTHS			12 MONTHS		
	N	MEAN CORRECTION (D)	SD	N	MEAN CORRECTION (D)	SD	N	MEAN CORRECTION (D)	SD
10,12	18	3.18	1.26	23	3 44	1.33	21	3.47	1.50
16	33	3.32	1.10	35	3 83	1.39	34	4.04	1.41
20	29	4.60	1.37	27	4 40	1.49	24	4.01	1.40
25-50	16	4.93	1.37	13	4.31	1.33	17	4.26	1.36

There is a statistically significant association of higher correction with higher PCA (i.e., more distortion) at 3 months (linear regression correlation = 0.48; p =0.0001; this explains the 23% of variation in corneal distortion value). This association becomes weaker at 6 months (correlation = 0.19, p = 0.06, explaining 3.8% of variation), and becomes nonexistent at 12 months (correlation = 0.14, p = 0.18, explaining 1.9% of variation). The conclusion from this association is that the greater the attempted corrections, the more the corneal distortion that occurs early after PRK and then resolves with time. This is likely a result of greater and lengthier wound healing effects associated with the greater correction.

c. PCA and Clinical Outcomes

PCA was not found to be associated with UCVA or BSCVA.

PCA and predictability are associated at 3 months (linear regression correlation - 0.37, p = 0.004), but not at 6 or 12 months. The significance of this finding is unclear. PCA was not associated with a change in refractive or keratometric astigmatism. Although it is expected that a higher PCA value (more distortion) would be associated with more astigmatism, since induced astigmatism was minimal overall, it is difficult to show any relationship by statistical analysis.

PCA is related to the glare/halo index at 3 months (linear regression correlation = 0.23, p = 0.04; suggesting that the corneal irregularity as measured by PCA accounts for 5% of the variation in reported glare/halo), but not at 6 or 12 months. PCA was related to corneal haze at all 3 time points (3 months correlation = 0.19, p = 0.08; 6 months correlation = 0.40, p = 0.0002; 12 months correlation = 0.28, p = 0.008). Again, the significance is somewhat difficult to evaluate since most subjects have low haze. However, it is consistent that those subjects with more haze (i.e., more wound healing effects) would have greater distortion PCA values. Subject satisfaction is associated with PCA at 12 months only (correlation = 0.25, p = 0.02). The significance of this is unclear since subjects with higher PCA values had marginally higher satisfaction (opposite that which would be expected.) This may suggest that either the "satisfaction questionnaire" is not a valid measure, or the PCA scale is not very good at measuring corneal irregularity.

d. PCA and Topographic Patterns at One Year

Topography Classification	3 month N	3 month PCA	6 month N	6 month PCA	12 month N	12 month PCA
All	98	20/18	98	20/17	98	20/17
Homogeneous	11	20/18	17	20/18	21	20/18
Toric with axis	19	20/18	20	20/16	27	20/16
Toric against axis	14	20/16	9	20/16	10	20/16
Irregularly irregular	6	20/16	7	20/16	7	20/20
Keyhole/semicircle	36	20/18	32	20/18	24	20/18
Focal topographic/variant	12	20/18	13	20/15	9	20/21
Central Island	0	-	0	-	0	-

e. PCA and Pooled Topographic Patterns at One Year

	3 MONTH		6 MONTH		12 MONTH	
PCA	REGULAR	IRREGULAR	REGULAR	IRREGULAR	REGULAR	IRREGULAR
10,12	10 (22.7)	8 (14.8)	13 (28.3)	10 (19.2)	12 (27.3)	9 (16.7)
16	17 (38.6)	16 (29.6)	14 (30.4)	21 (40.4)	16 (36.4)	18 (33.3)
20	8 (18.2)	22 (40.7)	12 (26.1)	15 (28.8)	9 (20.5)	17 (31.5)
25-50	9 (20.5)	8 (14.8)	7 (15.2)	6 (11.5)	7 (15.9)	10 (18.5)
LogMar Mean	-0.065	-0.044	-0.079	-0.069	-0.083	-0.027
SD	0.124	0.114	0.122	0.127	0.118	0.139

There was a statistically significant association of topography pattern and PCA at 12 months only, with the pooled irregular group showing a higher mean PCA value ($p=0.03$, t-test). There was no association at the 3 and 6 month follow up visits using t-test, nor association at any time point with chi-square tests.

e. Contrast Sensitivity

Contrast sensitivity testing was conducted on 6.0 mm eyes using the VectorVision CSV-1000, with undilated pupils to represent daytime vision and dilated pupils to simulate night vision. Data were obtained and analyzed separately for the Navy study, the Steroid study and the Phase III at 6 study. Testing was conducted preoperatively and at the postoperative times indicated below for the three studies: 6, 12 and 18 months for Navy first eyes and 6 and 12 months for second eyes; 6 months for both steroid treated and control eyes; 6 and 12 months for Phase III first eyes and 6 months for second eyes.

Averages were calculated at each spatial frequency for contrast sensitivity and log contrast sensitivity The preoperative log mean contrast sensitivity served as the baseline for postoperative comparisons. The weighted log mean changes for the combined studies are ≤0.1 log unit for all spatial frequencies, and for both undilated and dilated pupils. These changes are not considered to be clinically or functionally significant at the photopic illumination level tested, but these results cannot be assumed to hold at lower illumination levels.

The contrast sensitivity results are biased by atypical positive contrast sensitivity changes in the Navy study. This improvement of contrast sensitivity following PRK surgery is not fully understood, but it is consistent with the frequent overcorrections and substantial postoperative improvement of BSCVA in the same subjects. The resulting bias is not sufficient to alter the general conclusion.

B. Phase III <6 DATA

The data from the phase III < 6 study, performed with the ExciMed or Apex (configuration 1) units under IDE G880210, are of interest because they served as the foundation on which FDA based its approval of the 6.0 mm zone and contributed to our understanding of the long term (up to 3 years) effects of the Summit excimer laser. Per the approved protocol, Summit had to all subjects for two years, but the applicant has provided 3 years of data in some cases.

1. Study Objectives

The goal for the phase III < 6 group was the same as that for the combined 6.0 mm group.

2. Study Design

The Phase III <6 study was a prospective, nonrandomized, uncontrolled, unmasked, 10 centers clinical study.

3. Inclusion and Exclusion Criteria

The criteria are the same as those for the combined 6.0 mm group.

4. Study Plan, Subject Assessments, and Effectiveness Criteria

The phase III <6 study included 701 first eyes with myopia ≤ 6.0 D and 398 fellow eyes with myopia ≤ 7.0 D. Treatment of the fellow eye was allowed after minimum wait of 6 months following the first eye treatment. Of the 701 first eyes, 229 had a 4.5 mm zone and 472 had a 5.0 mm zone. Of the 398 fellow eyes, 57 had a 4.5 mm ablation zone and 339 had a 5.0 mm zone. Toward the end of the phase III < 6 study, upgrading to the Apex (configuration 2) began; hence, 2 fellow eyes were treated with a 6.0 mm zone.

Subjects were evaluated at the same intervals and for the same clinical parameters as specified for the 6.0 mm group.

Additional subgroup studies, as required by the 1992 FDA draft guidance document, were performed within the 701 first eyes cohort for detailed assessment of certain safety parameters. The substudies included: corneal topography, contrast sensitivity, corneal thickness, endothelial cell count, and visual field tests. Each substudy involved a minimum of 100 eyes, with data collected preoperatively, and at 6, 12, and 24 months postoperatively. For each substudy, a centralized reading center and the same equipment were used.

Two surveys performed preoperatively and at 1 year were given to 110 subjects of the 701 first eyes group. The survey was based on a report by Bourque et al.[8].

Data are reported for the first eye treatments. All fellow eye data were submitted to the application for all of the required parameters. Since the fellow eye data do not differ significantly from first eye treatments, they are not presented in this summary though they did provide further supplemental data for assurance of safety.

5. Study Period, Investigational Sites, and Demographic Data

a. Study Period

Protocol	Treatment Dates	Number of eyes
Phase III at <6 first eyes	6/17/91 to 3/27/92	701
Phase III at <6 fellow eyes	12/16/91 to 1/28/94	398
	TOTAL EYES	1099

A total of 701 subjects in Phase III were treated with a <6.0 mm zone.

b. Investigational Sites

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

SITE	Phase III at <6 first eyes	Phase III at <6 fellow eyes
Vision Surgery & Laser Center San Diego, CA	89	50
Eye Surgery Center of LA New Orleans, LA	104	51
Hunkeler Eye Clinic Kansas City, MO	136	88
Massachusetts Eye and Ear Boston, MA	39	23
Emory University School of Medicine Atlanta, GA	50	26
Galusha Eye Associates Tulsa, OK	54	24
St. Mary's Hospital The Eye Clinic of Texas Galveston, TX	68	32

SITE	Phase III at <6 first eyes	Phase III at <6 fellow eyes
Carraway Medical Center Norwood Eye Clinic Birmingham, AL	58	36
Barnes University Hospital Department of Ophthalmology St. Louis, MO	36	27
Union Medical Campus Colorado Springs, CO	67	41
TOTAL	701	398

c. Demographics

Please refer to the section comparing the results of the 5.0 and 6.0 mm ablation zones.

6. Data Analysis and Results

Only results from the first eye treatments are included in the following summaries as they are used to evaluate the safety and effectiveness of the laser PRK. This is done so as to simplify all analyses given that some subjects have both eyes treated and would therefore be contributing twice to the data.

a. Preoperative Ocular Characteristics

Please refer to the section comparing the results of the 5.0 and 6.0 mm ablation zones.

b. Operative Characteristics

The operative technique was standardized for everyone in phase III. Except for the ablation zone, these laser parameters were also standardized.

Attempted correction	Phase III <6 first eyes	Phase III <6 second eyes
1.50 D -- 1.90 D	23 (3.3%)	16 (4.0%)
2.00 D -- 2.90 D	118 (16.8%)	70 (17.6%)
3.00 D -- 3.90 D	178 (25.4%)	101 (25.3%)
4.00 D -- 4.90 D	167 (23.8%)	87 (21.9%)
5.00 D -- 5.90 D	140 (20.0%)	67 (16.8%)
6.00 D -- 6.90 D	75 (10.7%)	48 (12.1%)
7.00 D -- 7.90 D		9 (2.3%)
8.00 D -- 8.90 D		-
9.00 D -- 9.90 D		-
10.0 D		-
Total	701 (100%)	398 (100%)
Laser parameters		
total pulses	70 to 248	79 to 283
ablation zone diameter (mm)	4.5 and 5.0	5.0 and 6.0

No adverse reactions were noted during the procedure. In Phase III <6, one complication was reported (0.1%) which involved the ablation zone overlapping the epithelium by 0.25 mm; most likely due to the area of epithelium removal being slightly smaller than the ablation zone. During the surgical procedure, 17 subjects experienced interruptions due to loss of fixation. In each case, the procedure was stopped, the subject refixated and the procedure was completed without incident. Interruptions occurred in 6 subjects during their fellow eye treatment.

c. Postoperative Characteristics and Results

1. Subject Accountability

Study	# EYES ENROLLED	FOLLOW-UP EXAM (months)	# EYES ELIGIBLE FOR FOLLOW-UP	# and (%) OF EYES FOLLOWED
Phase III <6	701	1 M	701	691 (98.6%)
		2 M*	701*	664 (94.7%)*
		3 M	701	664 (94.7%)
		4 M*	701*	647 (92.3%)*
		6 M	701	669 (95.4%)
		9 M*	701*	529 (75.5%)*
		12 M	701	600 (85.6%)
		18 M*	701*	525 (74.9%)*
		24 M	701	612 (87.3%)

* Optional visits per Phase III <6 protocol and/or FDA guidelines.

A loss to follow-up analysis was performed on the Phase III <6 cohort to determine if there was a common reason for the loss. Subjects were considered as lost if they relocated to another geographical area, deferred additional examinations, couldn't be contacted/located, became seriously or terminally ill due to other health conditions not related to PRK, or died due to other causes not related to PRK. There were 54 who met the above criteria. Of those, 30 relocated, 20 either refused to come back or could not be located, 3 were bedridden, and 1 died. A majority of subjects who were lost to follow-up had good uncorrected acuity and manifest refractions at their last available follow-up visit; hence, surgical outcome is not expected to be the primary cause for subject discontinuation. Most were male. A significant number of these subjects had follow up to the six month time period.

ii. Re-epithelialization

Within the first postoperative week, re-epithelialization was uneventful without any incidence of recurrent erosion. In the Phase III <6 study, 644 (92%, 644/701) eyes re-epithelialized by 72 hours, and all eyes by 192 hours postoperatively.

iii. Uncorrected Visual Acuity (UCVA)

UCVA	Preop	1 M	3 M	6 M	12 M	24 M	36 M
20/20 or better	0	195 (28.2%)	365 (54.8%)	413 (61.6%)	401 (66.7%)	407 (66.4%)	359 (65.4%)
20/25 to 20/40	1 (0.1%)	272 (39.3%)	218 (32.8%)	203 (30.3%)	146 (24.3%)	157 (25.7%)	138 (25.1%)
20/50 to 20/80	28 (4.0%)	175 (25.3%)	61 (9.2%)	39 (5.8%)	36 (6.1%)	30 (4.9%)	38 (6.9%)
20/100 to 20/160	105 (14.9%)	35 (5.1%)	17 (2.7%)	9 (1.5%)	11 (1.9%)	8 (1.4%)	8 (1.5%)
20/200 or worse	567 (81.0%)	14 (2.1%)	3 (0.5%)	5 (0.8%)	6 (1.0%)	10 (1.6%)	6 (1.1%)
20/40 or better	1 (0.1%)	(67.6%)	(87.8%)	(92.1%)	(91.2%)	(92.2%)	497 (90.5%)
20/20 or better	0 (0)	195 (28.2%)	365 (54.8%)	413 (61.6%)	401 (66.7%)	407 (66.4%)	359 (65.4%)
TOTAL	701	691	664	669	600	612	548

From a statistical standpoint, visual acuity stabilizes at 6 months and remains stable to 24 months. Levels worse than 20/40 do not increase at any time point in follow-up. The mean number of lines of uncorrected visual acuity changed between 12 and 24 months postoperatively is -0.06. On average, there is less than one-tenth of a line of uncorrected visual acuity change in the myopic direction from 1 to 2 years postoperatively.

In addition, if we examine the uncorrected visual acuity changes during the interval of 12 to 24 months postoperatively using two

lines of acuity as a definition for change, 82.6% of subjects had no change in uncorrected visual acuity during this time period and equal proportions gained or lost two lines.

A multivariate analysis of stability to detect factors associated with changes in uncorrected visual acuity between 12 and 24 months postoperatively shows that preoperative MRSE ≥ 3.0 D is a statistically significant factor.

iv. BSCVA for a 2-4 mm Pupil

a. Acuity

BSCVA (2-4 mm)	Preop	1 M	3 M	6 M	12 M	24 M	36 M
20/20 or better	660 (94.3%)	562 (82.1%)	623 (93.8%)	643 (96.4%)	576 (96.0%)	588(96.1%)	533 (97.1%)
20/25 to 20/40	40 (5.7%)	120 (17.6%)	41 (6.2%)	22 (3.4%)	23 (3.8%)	21 (3.4%)	14 (2.6%)
20/50 to 20/80	0	2 (0.3%)	0	1 (0.2%)	1 (0.2%)	2 (0.3%)	2 (0.4%)
20/100 to 20/160	0	0	0	0	0	0	0
20/200 or worse	0	0	0	0	0	1 (0.2%)	0
TOTAL	700	691	664	669	600	612	549

b. Changes in acuity from preoperative

Change in BSCVA from preop (2-4 mm)	6 M (N=665)	12 M (N=599)	24 M (N=611)	36 M (N=548)
Decrease 12 lines	-	-	1 (0.2%)	0
Decrease 6 lines	-	1 (0.2%)	2 (0.3%)	0
Decrease 5 lines	1 (0.2%)	-	1 (0.2%)	1 (0.2%)
Decrease 4 lines	1 (0.2%)	1 (0.2%)	-	4 (0.7%)
Decrease 3 lines	2 (0.3%)	3 (0.5%)	6 (1.0%)	3 (0.5%)
Decrease 2 lines	16 (2.4%)	12 (2.0%)	32 (5.2%)	13 (2.4%)
No change	291 (85.3%)	473 (78.8%)	455 (74.4%)	421 (76.9%)
Increase 2 lines	84 (12.6%)	80 (13.4%)	77 (12.6%)	73 (13.3%)

Increase 3 lines	23 (3.5%)	26 (4.3%)	36 (5.9%)	30 (5.5%)
Increase 4 lines	1 (0.2%)	2 (0.4%)	-	3 (0.5%)
Increase 5 lines	-	1 (0.2%)	1 (0.2%)	0

Loss of BSCVA occurred in 6.9% (42/611) eyes at two years when measured with a 2-4 mm pupil. At the "decrease 2 lines" level, there is a greater loss at the two year (5.2%). This would have been a concern, if not for the observation that in this population, losses in unoperated fellow eyes were at 7.3% for two lines and at 3.7% for greater than two lines. The variability noted in the unoperated eyes signifies the variability of the study, and hence, the 5.2% loss is not considered as a significant event. Furthermore, when associated with absolute acuity, levels of loss worse than 20/25 remain constant from one year (1.3%) to two year (1.7%).

v. BSCVA for a 6 - 8 mm Pupil

a. Acuity

BSCVA (6-8 mm)	PREOP	1 M	3 M	6 M	12 M	24 M	36 M
20/20 or better	650 (92.8%)	559 (80.9%)	609 (91.6%)	644 (96.6%)	570 (95.0%)	569 (93.2%)	516 (94.3%)
20/25 to 20/40	49 (7.0%)	127 (18.4%)	55 (8.4%)	21 (3.2%)	29 (4.8%)	37 (6.1%)	29 (5.3%)
20/50 to 20/80	2 (0.2%)	5 (0.7%)	0	1 (0.2%)	1 (0.2%)	3 (0.5%)	2 (0.4%)
20/100 to 20/160	0	0	0	0	0	0	0
20/200 or worse	0	0	0	0	0	1 (0.2%)	0
TOTAL	701	691	664	669	600	612	547

b. Change in acuity

Change in BSCVA from preop (6-8 mm)	6 M (N=666)	12 M (N=600)	24 M (N=610)	36 M (N=547)
Decrease 11 lines	-	-	1 (0.2%)	-
Decrease 7 lines	-	1 (0.2%)	1 (0.2%)	1 (0.2%)
Decrease 6 lines	-	-	1 (0.2%)	-
Decrease 5 lines	1 (0.2%)	-	1 (0.2%)	-
Decrease 4 lines	1 (0.2%)	4 (0.7%)	2 (0.3%)	3 (0.5%)
Decrease 3 lines	1 (0.2%)	3 (0.5%)	10 (1.6%)	8 (1.5%)
Decrease 2 lines	21 (3.2%)	18 (3.0%)	41 (6.7%)	27 (4.9%)
No change	538 (80.5%)	457 (76.1%)	429 (70.3%)	404 (73.8%)
Increase 2 lines	79 (11.9%)	84 (14.0%)	86 (14.1%)	71 (23.0%)
Increase 3 lines	22 (3.3%)	27 (4.5%)	32 (5.2%)	26 (4.5%)
Increase 4 lines	1 (0.2%)	4 (0.7%)	5 (0.8%)	7 (1.3%)
Increase 5 lines	2 (0.3%)	2 (0.3%)	1 (0.2%)	-

Loss of BSCVA occurred in 9.3% (57/610) eyes at two years when measured with 6-8 mm pupil. The greater loss at the "decrease 2 line" level is also noted. This is consistent with that seen at a 2-4 mm pupil. There are no unexpected differences that would not be predicted by the smaller pupil size.

vi. Manifest Refraction -- MR

a. Predictability -- Spherical Equivalent -- MRSE

MRSE	PREOP	1 M	3 M	6 M	12 M	24 M	36 M
± 0.50 D	0	137 (19.9%)	256 (38.2%)	345 (51.4%)	351 (58.5%)	364 (59.4%)	319 (58.1%)
± 1.00 D	0	234 (34.0%)	413 (61.9%)	512 (76.4%)	466 (77.7%)	485 (79.1%)	437 (79.6%)
± 2.00 D	39 (5.6%)	467 (67.8%)	604 (90.7%)	623 (93.1%)	563 (93.9%)	579 (94.5%)	518 (94.4%)

b. Stability-- based on mean MR

	Preop N=701	6 M N=669	12 M N=600	18 M N=525	24 M N=612	36 M N=545
MRSE (diopters)						
Mean	-4.21	0.35	+0.06	+0.02	-0.08	-0.14
Range	-1.25 to -7.50	-5.75 to +4.37	-4.37 to +3.75	-3.75 to +4.00	-7.00 to +4.37	-5.25 to +4.75
Standard Deviation	1.32	1.03	1.02	0.86	1.04	0.98
MR Cylinder (Diopters)						
Mean	0.44	-0.42	-0.43	-0.40	-0.42	-0.40
Range	1 to 1.75	0 to -3.00	0 to -2.50	0 to -1.75	0 to -2.00	0 to -2.25
Standard Deviation	0.38	0.48	0.46	0.45	0.45	0.44

To further establish stability of refraction, a one-way ANOVA analysis was performed with a significance level of 0.05 and a 95% confidence interval. The mean manifest refraction spherical equivalent was compared at each time period. The change from month 1 to month 3 is statistically significant; the change from month 3 to month 6 is significant; and, the change between consecutive exams from month 6 to month 36 is not significant. Therefore, manifest refraction reaches stability at 6 months based upon the statistical significant changes seen.

c. Change in astigmatism, magnitude and direction

The analysis of astigmatic changes was done by the applicant in accordance with the method described by Waring, GO [7].

The results on the 598 eyes whose manifest refraction are available preoperatively and at 12 months are as follows: mean change in net astigmatism is -0.01 D with a standard

deviation of 0.48; mean change in vectoral astigmatism is 0.45 D with a standard deviation of 0.36; and 73.7% of subjects had less than 10 degrees of shift in the axis of astigmatism.

The results on the 612 eyes whose manifest refraction are available preoperatively and at 24 months are as follows: the mean change in net astigmatism is -0.03 D with a standard deviation of 0.49; the mean change in vectoral astigmatism is 0.46 D with a standard deviation of 0.35; and 74.0% of subjects had less than 10 degrees of shift in the axis of astigmatism.

The majority of subjects did not experience a change is astigmatism.

d. Predictability of the treatment is based on the difference between the attempted and achieved diopter corrections.

Predictability	Attempted Diopters of Correction									
	1.50-2.90 D		3.00-3.90 D		4.00-4.90 D		5.00-5.90 D		6.00 D	
	12 M	24 M	12 M	24 M	12 M	24 M	12 M	24 M	12 M	24 M
Overcorrected	18 (15.7%)	11 (9.9%)	24 (16.1%)	22 (14.3%)	26 (17.8%)	23 (14.8%)	16 (13.0%)	11 (8.8%)	12 (18.5%)	8 (11.9%)
± 1.00 D	93 (80.8%)	98 (88.3%)	122 (81.9%)	124 (80.5%)	111 (76.0%)	116 (74.9%)	87 (70.7%)	94 (75.2%)	42 (64.6%)	44 (65.7%)
Undercorrected	4 (3.5%)	2 (1.8%)	3 (2.0%)	8 (5.2%)	9 (6.2%)	16 (10.3%)	20 (16.3%)	20 (16.0%)	11 (16.9%)	15 (22.4%)

It is noted that the larger the attempted correction the less predictable the outcome. In the 12 to 24 month postoperative time interval, 89.9% of eyes are stable within ±1 diopter (MRSE) with 3.2% shifting in the hyperopic direction and 6.8% in the myopic direction.

A multivariate analysis of stability to detect factors associated with changes in MRSE between 12 and 24 months postoperatively shows that preoperative MRSE≥ 5.0 D is a statistically significant factor.

vii. Cycloplegic Refraction

	Preop N=701	6 M N=669	12 M N=600	18 M N=525	24 M N=612
Mean CRSE (Diopters)	-4.08	+0.63	+0.23	+0.21	+0.13
Mean CR cylinder (Diopters	-0.42	-0.42	-0.41	-0.41	-0.68

The change in the mean CRSE between each postoperative visit shows stability of refraction. It has a good correlation with MRSE as well.

viii. Irregular Astigmatism

Irregular astigmatism occurred postoperatively in less than 3% of the subject population, with the highest incidence at the one month postoperative examination. The incidence decreased over time and was less than preoperative (0.4%) at the one year (0.2%) and 0.5% at two years postoperative.

ix. Keratometry Readings

At the 2 years visit, the keratometric image was graded as distorted in 12 (2.0%) cases. In 598 (98.0%) cases, it was normal. This information was not reported in 2 cases. The mean keratometry reading decreased after PRK, representing the flattening after the procedure. The keratometric cylinder after PRK and was essentially stable throughout the postoperative period.

x. Intraocular Pressure

The intraocular pressure was measured using applanation tonometry at all long term postoperative examinations. In some cases intraocular pressure increases after PRK, probably due to the topical corticosteroids which are used post procedure for several months. The mean intraocular pressure increased from 15.1 mmHg

preoperatively to a high of 16.5 mmHg at 2 months postoperatively. By the six month examination, the mean pressure dropped below preoperative at 14.7 mmHg and henceforth remained at that level. IOP was controlled with medication and or discontinuance of steroids.

xi. Corneal Haze Summary

For each visit, listed below are the anterior stromal reticular haze levels noted during the slit lamp examination.

	Clear (%)	Trace(%)	Mild (%)	Moderate (%)	Marked (%)
Preop (n=701)	99.4	0.6	0.0	0.0	0.0
1 Mo (n=691)	16.6	59.5	21.4	2.2	0.3
2 Mos (n=664)	17.6	60.4	20.0	1.7	0.3
3 Mos (n=664)	25.6	59.1	12.2	2.6	0.5
4 Mos (n=647)	31.1	54.8	9.9	4.2	0.0
6 Mos (n=669)	45.8	41.3	9.3	3.6	0.0
9 Mos (n=529)	50.5	35.5	10.2	3.6	0.2
12 Mos(n=600)	62.1	27.2	6.7	4.0	0.0
18 Mos(n=525)	73.1	21.0	4.6	1.1	0.2
24 Mos(n=612)	72.2	22.5	3.3	1.5	0.5

Anterior stromal reticular haze occurs after PRK during the first 1-3 months then decreases at each postoperative examination. By the 24 month examination, 94.7% of the eyes have Clear or Trace haze with only 0.5% having Marked haze. Interestingly, haze in low myopia peaks at 3 months and then subsides. For higher myopic levels, 6 D or greater, haze has a second peak at 6 months. As in other studies, haze in this study is directly related to the amount of attempted correction.

xii. Externals Summary

Externals' conditions were categorized as present or absent.

Condition	Preop	1 yr	2 yr
Ectropion	0.0%	0.0%	0.0%
Entropion	0.0%	0.0%	0.0%
Blepharitis	0.3%	0.0%	0.2%
Dry Eye	0.0%	0.2%	0.8%
Trichiasis	0.0%	0.0%	0.0%
Ptosis	0.3%	0.3%	0.2%
Other	1.0%	0.2%	0.3%

The rates of external irregularities in the long term postoperative period are small. Their association with PRK is difficult to ascertain.

xiii. Conjunctiva

The conjunctiva was categorized as normal or abnormal.

Examination	Normal	Abnormal
Preoperative	99.0%	1.0%
1 Year	100.0%	0.0%
2 Years	100.0%	0.0%

xiv. Anterior Chamber Summary

The anterior chamber depth was graded as deep, normal or shallow.

Depth	Preop	1 yr	2 yr
Deep	16.0%	30.8%	36.3%
Normal	83.9%	69.2%	63.7%
Shallow	0.1%	0.0%	0.0%

The anterior chamber was evaluated for these conditions at all the visits: cells, flare, hyphema, iritis, particulate matter & debris, and other irregularity. "Other irregularity" was noted in 0.1 % of eyes at preoperative, wasn't reported postoperative.

xv. Lens Status Summary

The percentages below represent the number of lens opacities that were reported.

Examination	No	Yes	
Preop	94.8%	5.2%	
1 Year	98.5%	1.5%	(4 out of 9 were present preoperative)
2 Year	97.4%	2.6%	(5 out of 16 were present preoperative)

Lens opacities occurred infrequently in the long term postoperative period after PRK. The relationship between the lens opacities and the PRK procedure is unknown.

xvi. Vitreal Status Summary

The following conditions were graded as present or absent.

Condition	Preop	1 yr	2 yr
Cells	0.0%	0.0%	0.0%
Floaters	0.1%	0.2%	0.0%
Hemorrhage	0.0%	0.0%	0.0%
Other	0.1%	0.2%	0.3%

The rates of vitreal irregularities in the long term postoperative period are small. Their association with PRK is difficult to ascertain.

xvii. Retinal Status Summary

The following conditions were graded as present or absent.

Condition	Preop	1 yr	2 yr
Cystoid Macular Edema	0.0%	0.0%	0.2%
Diabetic Retinopathy	0.0%	0.0%	0.0%
Macular Degeneration	0.0%	0.0%	0.2%
Retinal Detachment	0.0%	0.2%	0.0%
Retinal Hemorrhage	0.0%	0.0%	0.0%
Other	2.0%	0.8%	0.3%

The rates of retinal irregularities in the long term postoperative period are small. Their association with PRK is difficult to ascertain.

xviii. Substudies

These substudies were conducted with the Phase III <6 eyes: A Scans, Corneal Sensitivity, Corneal Thickness, Corneal Topography, Endothelial Cell Count, In-depth Subject Survey, Near Best Corrected Visual Acuity, and Visual Fields. The Contrast Sensitivity study was conducted on the entire population, rather than a subgroup.

a. A Scans

A-scan measurements were performed using the Ophthasonic A-scan 3 ultrasound system to evaluate the effect of PRK on eyeball axial length. Measurements were obtained preoperatively and at 12 and 24 months postoperatively.

No difference in eyeball axial length as a result of PRK was noticed. The mean axial length was 24.9 mm with a standard deviation of 0.9 for the preoperative visit (n=150). The mean axial length and standard deviation at the 12 M were identical to the preoperative values (n=133). At the 24 month postoperative visit (n=126), the mean axial length was 24.8 mm with a standard deviation of 0.9. No statistically significant difference was noted between the preoperative and postoperative results.

b. Contrast Sensitivity

Contrast sensitivity testing was conducted on all Phase III eyes using the VectorVision CSV-1000, with undilated pupils to represent daytime vision and dilated pupils to simulate night vision. Testing with undilated pupils was conducted preoperatively and at 1, 3, 6, 12, 18 and 24 months postoperatively. Testing with dilated pupils was conducted preoperatively and at 6, 12, 18 and 24 months postoperatively.

Averages were calculated at each spatial frequency for contrast sensitivity and log contrast sensitivity The preoperative log mean contrast sensitivity +/- 1 standard deviation served as the baseline to which all postoperative

results were compared. The log mean was used for quantitative data comparison and graphical display.

At the 1, 3, 6, 12, 18 and 24 month postoperative visits, the undilated log mean contrast sensitivities were decreased relative to the preoperative baselines for all spatial frequencies, but by amounts less than one standard deviation. These changes are not considered to be clinically or functionally significant at the photopic illumination level tested, but this conclusion cannot be assumed to hold at lower illumination levels.

At the 6, 12, 18 and 24 month postoperative visits, the dilated log mean contrast sensitivities were decreased relative to the preoperative baselines for all spatial frequencies, but by amounts less than one standard deviation. These changes are not considered to be clinically or functionally significant at the photopic illumination level tested, but this conclusion cannot be assumed to hold at lower illumination levels.

c. Corneal Sensitivity

The Corneal Sensitivity subgroup study was conducted on all subjects at a single clinical site. Corneal sensitivity measurements were performed using the Cochet-Bonnet esthesiometer. Testing was performed both centrally and peripherally, preoperatively and at the 1, 3, 6, 12, 18 and 24 month visits

The mean central sensitivity showed a slight decrease from preoperative at the 1, 3, 6 and 12 month exams. This decrease was not statistically significant by the 6 month postoperative visit. A slight increase was noted at the 18 month and 24 month exams. At the 24 month postoperative examination, 31 of the 32 eyes (96.9%) had returned to preoperative levels or better.

Mean peripheral sensitivity decreased slightly from preoperative at the 1 and 3 month exams, and returned to the preoperative level at the 6 month postoperative visit. It increased slightly from preoperative at the 18 month and 24

month exams. At the 24 month postoperative examination, 30 of the 32 eyes (93.8%) had returned to preoperative levels or better.

d. Corneal Thickness

Pachymetry readings were taken to evaluate the effect of PRK on corneal thickness.

The decrease in mean central corneal thickness that occurred in this subgroup population was anticipated since corneal tissue is ablated from the central cornea during PRK. The difference in central and peripheral corneal measurements at all visits was consistent with the cornea being thicker in the periphery than in the center.

e. Corneal Topography

An analysis of corneal topography after PRK was completed in a subgroup of subjects at the 3, 12 and 24 months visits to evaluate: centration of the optical zone, conformational change in corneal topography, qualitative topographic patterns, quantitative cross-sectional analysis of the optical zone, and the capability of the computed topography system by comparing the power change measured with the topography system against the change in manifest refractive power.

With respect to centration, ablation zones centers were located within 0.50 mm of the pupillary center in 67.2% of eyes as determined by corneal topographic analysis at 2 years postoperative. In addition 97.9% of eyes had ablation zone centers within 1.0 mm of the pupillary center. Statistical correlations to determine the significance of displacement of the ablation center showed that decentrations are not statistically significant relative to: uncorrected visual acuity, best corrected visual acuity, predictability, refractive astigmatism, achieved refractive correction, glare, halo, optical zone size. Decentrations were statistically significant relative to: change in keratometric astigmatism, attempted refractive correction, subject satisfaction. In addition, there was a statistically

significant correlation between ablation zone size and subject satisfaction.

The mean distance from the ablation center to the pupil center is 0.46 mm, with a median of 0.42 mm, and a range of 0 to 1.44 mm with a standard deviation of 0.26. The mean distance from the ablation center to the corneal apex is 0.51 mm, with a median of 0.45 mm, a range of 0.07 to 1.74 mm with a standard deviation of 0.28. On average, the difference between the distance from the ablation center to the pupil center is 0.05 mm less than the distance between the ablation center and the corneal apex.

Almost all the eyes (93.4%) enrolled in the PRK clinical study had prolate corneas preoperatively. Corneas not considered to be prolate preoperatively were classified as "mixed" (6.6%). After having PRK, the majority of corneas were oblate (98.4%) with 1.6% considered mixed.

Qualitative changes in corneal topography produced by the PRK procedure were determined by review of the normalized scale difference map. Descriptive statistics were generated for the seven topography patterns that can be found in the literature: Homogeneous (H), Smooth toric bowtie with axis (WA), Smooth toric bowtie against axis (AA), Irregularly irregular, Keyhole/semicircular (KH/SC), Central island (CI), and Focal topographic variants (FTV).

The table below shows the mean uncorrected visual acuity for each topography pattern classification at the one year follow up visit. The homogeneous group showed the best mean uncorrected acuity postoperative. The mean uncorrected visual acuity was approximately 2 Snellen lines worse in the irregularly irregular group ($p<0.05$, Kruskal-Wallis test, Wilcoxon Rank Sums).

Pattern	Mean	UCVA Range
H	20/21	20/12.5-20/80
Toric-WA	20/22	20/12-20/63
Toric-AA	20/34	20/16-20/50
Irregular	20/32	20/12-20/400
KH/SC	20/28	20/12-20/63
FTV	20/23	20/12-20/50
CI	none	none

The general optical conformational changes induced by PRK were confirmed. There is a continuous "blend zone" across the optical zone as the untreated cornea is approached.

f. Endothelial Cell Count

In this 5 centers study, endothelial cell density, the coefficient of variation of cell area (polymegathism) and the percentage of hexagonal cells (pleomorphism) were analyzed in 142 eyes at preoperative, 3, 12, and 24 months. Each eye was photographed both centrally and peripherally at each visit.

Specular microscopy was done using a Keeler-Konan Specular microscope mounted with a 35mm camera back. The masked negative sheets were sent to the Ophthalmic Research Facility of the Yerkes Regional Primate Research Center, in Emory University, Atlanta, GA, for digitization and data processing.

No significant changes in central (central ≡ over the pupil within the ablation zone area) endothelial cell density losses or changes in pleomorphism (percent of hexagonality) was observed.

There was a significant improvement in the coefficient of variation of cell size (polymegathism) in the central cornea. Throughout this subgroup analysis, at every postoperative examination of every group analyzed, there was an improvement in the mean central and peripheral coefficient of variation of cell size.

In those subjects who had worn contact lenses prior to PRK, in contrast to the total study population, the change in central corneal coefficient of variation in cell size at both 3 months (p=0.0027) and 2 years (p=0.0012) postoperatively was statistically significant. This improvement in the coefficient of variation of cell size after PRK is attributed to the discontinuation of contact lens wear after the PRK procedure.

g. In-depth Subject Survey

A standardized in-depth psychometric subject survey was administered at the 4 participating centers during the preoperative, 1 and 2 years visits. The survey was based on the one reported by Bourque L. et al[8]. An independent team of observers at the Johns Hopkins University Wilmer Eye Institute conducted the analysis of the data.

The subgroup population reported postoperatively that they had less worry or concern about eyesight (p<.01), they had less limitations due to eyesight problems (p<.001), they wore glasses and contact lenses less (p<.001). No statistically significant differences were found in the scores of preoperative and postoperative measures of health and psychological status.

About 44% chose as their most important reason for PRK the elimination of dependency on glasses or contact lenses. Cosmetically motivated as looks or appearance without glasses was felt to be only of average importance . The predictors of satisfaction with PRK based on postoperative status showed the strongest predictor was the variable indicating the subject had no need for corrective lenses postoperatively (p=.0001). The satisfaction level with PRK was significantly higher (p<.05) with younger age groups (<35 and 35-44) than with the older age group (45+). Age was also associated with needing corrective lenses postoperatively (p<.05), with a larger proportion of older subjects needing corrective lenses after PRK. The survey did not separate the need for corrective lenses due to presbyopia.

h. Near Best Spectacle Corrected Visual Acuity

Of the 135 eyes tested at one year postoperative, 132 (97.8%) eyes had a near best spectacle corrected visual acuity of 14/21 (J2) or better. All 132 eyes had no change (i.e., within ± 1 line) or an increase in near best corrected visual acuity from preoperative.

All 135 eyes reported had a near best spectacle corrected visual acuity of 14/35 (J6) or better. A two-tailed Wilcoxon Rank Sum Test was performed because the data are not normally distributed, using Statistical Program Social Sciences 6.0 (SPSS, Inc., Chicago, IL). There was no statistically significant difference between the preoperative and one year postoperative data for all eyes in this subgroup ($p=0.39$).

Of the 126 tested at 2 years postoperative, 119 eyes (94.4%) had a near best spectacle corrected visual acuity of 14/21 (J2) or better, which was not statistically significant ($p=0.13$). Furthermore, 120 (95.2%) out of the 126 eyes tested had no change in near best spectacle corrected visual acuity from preoperative.

I. Visual Fields

The visual field testing protocol was the full-field 81-point screening test of the Humphrey Field Analyzer, using the threshold-related test strategy. The objective of the test was to monitor for changes in visual sensitivity and in the number of points missed from preoperative to 12 and 24 months postoperative to detect any effects of PRK on peripheral vision. The data were also stratified for analysis with regard to: Attempted Correction (<-4 D vs. ≥-4 D); Pupil Size (<4.5 mm vs. ≥ 4.5 mm); and Ablation Zone Size (4.5 mm vs. 5.0 mm).

Visual field test results were available for analysis on 75 eyes from the preoperative and 12 month postoperative exams, and on 45 eyes from the 24 month postoperative exam.

No clinically or statistically significant changes were observed centrally or peripherally between the preoperative and the 12 or 24 month postoperative numbers of points missed.

Mean sensitivity decreased from preoperative to postoperative by ≤0.1 log unit in both the central and peripheral field and for both the 12 month and 24 month follow-up visits. None of these changes were clinically significant. Also, none of these changes were significantly affected by attempted correction, pupil size or ablation size.

No clinically significant abnormalities or changes in the visual fields of individual subjects were attributable to the PRK procedure.

There were no statistically significant correlations between haze and the total number of central or peripheral points missed.

j. Subject Survey

All Phase III <6 subjects were asked to complete standardized preoperative and postoperative surveys which address subject satisfaction and complaints. A total of 698 surveys were completed at preoperative, 585 at 12 months, and 603 at 24 months. On a scale of 0 to 5, 5 represents "very satisfied".

The percent of subjects giving a satisfaction rating of 5 was 50.1% (293/585) at 12 months and 53.8% (324/603) at 24 months, as compared to 22.8% (159/698) preoperatively. Quality of vision was rated better than preoperative by 88.7% of subjects at 12 months and 89.3% at 24 months (2.7% the same, 3.5% worse and 4.5% no response). The percent of subjects who stated that they would have PRK again was 85.8% at 12 months and 86.8% at 24 months.

With respect to subjects' reliance on corrective eyewear, 87.0% at 12 months and 87.3% at 24 months stated that they could recognize a friend across the street without corrective eyewear, as compared to 7.4% preoperatively.

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The percent of subjects who reported wearing eyeglas
dropped from 89.8% preoperatively to 20.3% at 1 ye
18.6% at 24 months. Similarly, the percent of subject
reported wearing contact lenses dropped from 62.8%
preoperatively to 20.7% at 12 months and 15.1% at 2
months (31.6% at 12 months and 41.5% at 24 month
those responding yes wore corrective lens in both eye
One percent of subjects picked "cosmetic purposes" a
single most important reason why they wanted PRK.
four top reasons for undergoing surgery were:
independence of glasses and contact lenses (43.2%),
comfort/convenience without glasses or contact lens
(23.5%), sports/activities (11.7%), and to improve vi
(8.9%).

The following self reported problems dropped after P

	Preop	1 yr	2 yr
Burning eyes	25.6%	3.4%	3.3%
Tears	10.3%	1.5%	1.8%
Dry eyes	33.7%	10.4%	12.6%
Headaches	15.3%	2.4%	3.0%
Infection	9.3%	0.7%	1.3%
Redness	24.5%	3.1%	2.3%
Pain	11.3%	4.1%	2.8%
Feeling something is in eye	21.3%	5.6%	4.6%
Light sensitivity	21.3%	8.4%	10.9%.

xix. Retreatments

In the phase III <6 study, there were 70 eyes (10.0%, 70/701
underwent to total of 83 additional treatments after PRK. N
the 70 eyes had 2 additional treatments, and two had 3 addit
treatments post PRK. The additional treatments were: astig
keratotomy (AK); mechanical epithelial debridement to treat
induced hyperopia or myopic regression; radial keratotomy (
stromal micropuncture to treat recurrent erosion symptoms,
automated lamellar keratectomy (ALK) to treat induced hyp
retinal laser coagulation for lattice and atrophic holes (untrea
fellow eye had retinal detachment); excimer laser polishing t
decentration, and PRK for residual myopia. Clinical data on
AK, debridement, RK, and stromal puncture retreated subje

included in the overall analyses above, and are not censored from the cohort (the rest are censored).

Retreatments, stratified by the number of months post PRK:

Months Post-op	AK	Mech. Debrid.	RK	Stromal punc.	ALK	Ret. Coag.	Polish	PRK	TOTAL
6 - 12	13	7	0	0	0	1	1	6	29
>12 - 18	6	15	2	1	0	0	1	10	35
>18 - 24	4	3	1	0	1	0	0	3	12
>24	3	1	2	0	0	0	1	1	7
TOTAL	26	26	5	1	1	1	3	20	83

Of the two eyes that had 3 additional treatments, one was -5.00 sph, -0.75x178 cyl preoperative, +0.75 sph prior to two epithelial debridement procedures and one laser polishing procedure, and -0.50 sph at one month after all the retreatments. The other eye was -5.25 sph, -1.75X9 cyl preoperative, 0 sph, -2.75x8 cyl at month 12 prior to the first astigmatic keratotomy retreatment, -0.75 sph,-1.25x20 cyl at month 13 prior to the second astigmatic keratotomy, and "unknown" at month 29 when another PRK treatment was given.

Astigmatic keratotomy procedures were performed to treat cylinder levels of -0.5 to -2.70 D. Outcomes from the 26 attempts were: reduced astigmatism by 0.25 to 2.00 D in 17 eyes, increased astigmatism of at most 0.5 D in two eyes, unchanged in 6 eyes, and not yet reported for one eye. It is not known what factor prior to the retreatment contributed to the outcomes.

Except for two cases of myopic regression, the rest (24 eyes) of the mechanical debridement group were done to treat hyperopia of +0.25 to +3.00 D spherical equivalent. Outcomes from the 24 "hyperopic" debridements included: reduced hyperopia by 0.5 to

3.0 D in seventeen eyes, increased hyperopia of at most +0.75 D in four eyes, unchanged in one eye, and not yet reported for two eyes. It is not known what factor prior to the retreatment contributed to the outcomes.

The 20 eyes that received an additional PRK procedure were either undercorrected (18 eyes were still myopic but at a lower level than preoperative) or more myopic (2) than preoperative. After the second PRK procedure or reablation, 9 eyes became less myopic than before the reablation, 6 became eyes more myopic, 3 were overcorrected or hyperopic, and 2 were not yet reported. It is not known what factor prior to the retreatment contributed to the outcomes.

C. Comparison of the Combined Data (6.0 mm) Against the Phase III <6 Data (4.5-5.0 mm)

1. Objectives

The purpose of this section is to present a comparison of the primary safety and effectiveness variables and other necessary information collected from the combined 6.0 mm studies and the Phase III <6 first eye study. Most of these data have been presented in previous sections. However, this comparison serves as the rationale for approving only the 6.0 mm ablation zone size.

2. Design

Side by side comparison of these two data sets.

3. Inclusion and Exclusion Criteria

These were previously presented for each study, therefore only differences between the two are presented here:

The 6 mm ablation zone allowed myopia up to 7.0 D; the Phase III <6 first eyes allowed myopia up to 6.0 D. All other parameters were identical.

4. Study Plan, Subject Assessments, and Effectiveness Criteria

The study plan, subject assessment, and effectiveness criteria for each study are presented in the earlier sections and are not repeated here. The following discussion pertains to the statistical validity of the comparison of the 6.0 mm and < 6.0 mm data at 6 months.

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From a statistical standpoint, the sample size required to show equivalence based upon a 95% confidence interval, an alpha of 0.05, a beta of 0.80, and a delta of 0.10, is 251 samples. The ability to detect a 5% difference is possible with 122 samples. The sample size in the 6.0 mm study is 340, and therefore is a statistically significant sample size sufficient to detect a difference in safety and effectiveness outcomes.

From the results of the < 6.0 mm data, it is observed that stability with the Summit laser for the low myopia indication is reached by 6 months postoperative. It is also noted that most complications with the Summit excimer laser occur early and then resolve. One factor which has been considered is corneal haze. Interestingly, haze in low myopia peaks at 3 months and then subsides. For higher myopic levels, 6 D or greater, haze has a second peak at 6 months. As in other studies, haze in this study is directly related to the amount of attempted correction. Therefore, 6 months should be adequate to assess any differences in safety and effectiveness outcomes.

In the assessment of when stability is reached, the available one year data from two (Navy and Phase III at 6) of the three combined 6.0 mm studies were also compared against those in the < 6.0 mm study. In addition, data from two prospective, randomized English studies[9,10] comparing 5.0 and 6.0 mm treatments were also reviewed to determine if the results elsewhere differ from those obtained in the U.S. All of the reviewed data supported the assessment of stability at 6 months.

one year age difference seen in this table does not significantly affect comparison of outcomes. Operative eye does not affect outcomes.

Demographics reveal no obstacles to comparison of data from these two populations.

6. Data Analysis and Results

a. Preoperative Ocular Characteristics

1. BSCVA and UCVA

PREOPERATIVE VISUAL ACUITY DATA	<6 MM (N=701)	6 MM (N=394)
BSCVA 2-4 MM		
20/20 OR BETTER	660 (94.3%)	384 (97.4%)
20/25 TO 20/40	40 (5.7%)	10 (2.6%)
BSCVA 6-8 MM		
20/20 OR BETTER	650 (92.8%)	378 (95.9%)
20/25 to 20/40	49 (7.0%)	16 (4.1%)
WORSE THAN 20/40	2 (0.2%)	0
UCVA		
20/200 OR WORSE	568 (81.2%)	305 (77.2%)
20/100 to 20/160	105 (14.9%)	67 (17.1%)
20/50 to 20/80	27 (3.8%)	21 (5.4%)
20/40 OR BETTER	1 (0.1%)	1 (0.3%)

There is a higher level of BSCVA better than 20/20 in the 6 mm data, which is statistically significant ($p<0.05$). This factor is relevant because it has been shown to be associated with a higher chance of loss of BSCVA. The clinical relevance of this statistic probably lies in the variability of acuity at these fine levels of acuity. One subject did not have BSCVA at 6-8 mm pupil preoperatively.

When comparing these two populations for loss of BSCVA, differences in percentages of this baseline characteristic must considered.

ii. Manifest Refraction Spherical Equivalent

a. Comparison of Attempted Correction

ATTEMPTED CORRECTION	<6 MM (N=701)	6 MM (N=394)
Mean Attempted Correction	4.07 D	4.23 D
Range	1.50 - 6.00 D	1.50 -- 7.80

Attempted correction is related to outcomes of predictability (+/- 1 diopter). The 6.0 mm group is sl more myopic than the < 6.0 mm group and would be concern if its mean attempted correction was less tha 6.0 mm group. However, since this is not the case, a differences between the two groups can be assumed t real and not due to differences in baseline attempted correction. Therefore, the two populations are accep for comparison. Attempted correction for the 6 mm population (as in the <6 mm data population) is asso with predictability though not uncorrected acuity. Tl attempted correction is sufficiently close to compare populations and the overall trend is the same betwee two populations.

b. Preoperative Refractive Data

	<6 MM (N=701)	6 MM (N=394)
MANIFEST REFRACTION (MRSE)		
MEAN	-4.21	-4.37
RANGE	-1.25 to -7.50	-1.38 to -9.00
STANDARD DEVIATION	1.32	1.48
MANIFEST REFRACTION (CYLINDER)		
MEAN	0.44	0.45
RANGE	0 to 1.75	0 to -2.25
STANDARD DEVIATION	0.38	0.42

Again this supports the comparison between the two populations. There is no clinically relevant difference in mean MRSE.

b. Operative Characteristics

With the exception of the ablation zone size all other operative techniques were standardized. The breakdown of attempted corrections, laser time and pulses was presented previously.

c. Postoperative Characteristics and Results

Significant factors are presented. Previous sections contain the detailed characteristics for the studies unrelated to the comparison.

I. Visual Acuity Data -- 6 Month data

a. Acuity

	<6 MM (N=669)	6 MM (N=340)
BSCVA 2-4 MM		
20/20 OR BETTER	643 (96.4%)	324 (95.3%)
20/25 to 20/40	22 (3.4%)	17 (5.0%)
WORSE THAN 20/40	1 (0.2%)	0
BSCVA 6-8 MM		
20/20 OR BETTER	644 (96.6%)	324 (95.3%)
20/25 to 20/40	21 (3.2%)	17 (5.0%)
WORSE THAN 20/40	1 (0.2%)	0
UCVA		
20/200 OR WORSE	5 (0.8%)	4 (1.2%)
20/100 to 20/160	9 (1.5%)	1 (0.3%)
20/50 to 20/80	39 (5.8%)	12 (3.5%)
20/25 to 20/40	203 (30.3%)	101 (29.6%)
20/20 OR BETTER	413 (61.6%)	223 (65.3%)
20/40 OR BETTER	616 (91.9%)	324 (95.0%)

For the 6 mm ablation zone, the percent of subjects whose preoperative BSCVA was 20/20 or better but became wor than 20/25 postoperative is 1.2% (4/340). Of these four, 3 eyes were 20/32 and 1 eye was 20/40. All four had greate than 4 D of attempted correction, three had associated astigmatism (pre and post-op, greater than 1.5 diopters), and three had associated haze of mild degree. The subject who was 20/40 had moderate haze and experienced regression, but received no steroids postoperatively.

For the 5 mm ablation zone, the percent of subjects whose preoperative BSCVA was 20/20 or better but became wor than 20/25 postoperative is 0.9% (6/665). Of these six, 1

eye was 20/80, 1 eye was 20/32 and 4 eyes were 20/25. The one eye at 20/80 had cystoid macular edema which wa later determined to be unrelated to the PRK procedure because the untreated fellow eye was also observed to hav the condition at the 18 months exam. The eye with 20/32 had a 6 D correction and experienced regression.

b. Change in BSCVA

CHANGE IN BSCVA FROM PREOP	6 MONTHS	
	<6 MM (N=665)	6 MM (N=340)
DECREASE 5 LINES	1 (0.2%)	1 (0.3%)
DECREASE 4 LINES	1 (0.2%)	0
DECREASE 3 LINES	2 (0.3%)	6 (1.8%)
DECREASE 2 LINES	16 (2.4%)	16 (4.7%)
NO CHANGE(± 1 LINE)	645 (96.9%)	317 (93.2%)

For the 6 mm data, the overall loss of BSCVA is 6.8%. Although this level is statistically significantly higher than that observed at 6 months in the < 6.0 mm group, it is not statistically significant from the 5% loss criterion proposed by the Ophthalmic Devices Panel. Furthermore, the unoperated eyes have these rates of loss: 7.3% at 2 lines loss and 3.7% at greater than two lines. If the variability seen in the unoperated eye and the absolute acuity outcom (only 4 eyes worse than 20/25 and no eyes worse than 20/40) are factored into the evaluation, then a 6.8% loss is acceptable

Additionally, a comparison to the < 6.0 mm data must include an adjustment of baseline for BSCVA between the two populations since this is a significant factor affecting loss. The adjusted differences seen here are within the 95% CI for the two populations and therefore are not significant. The absolute levels of BSCVA do not represent significant differences between the two ablation zone sizes.

c. Visual acuity data -- 12 month comparison

	<6 MM (N=600)	6 MM (N=82)
BSCVA 2-4 MM		
20/20 OR BETTER	576 (96.0%)	82 (100%)
20/25 to 20/40	21 (3.5%)	0
WORSE THAN 20/40	1 (0.2%)	0
BSCVA 6-8 MM		
20/20 OR BETTER	570 (95.0%)	82 (100%)
20/25 to 20/40	29 (4.8%)	0
WORSE THAN 20/40	1 (0.2%)	0
UCVA		
20/200 OR WORSE	6 (1.0%)	0
20/100 to 20/160	11 (1.9%)	0
20/50 to 20/80	36 (6.1%)	1 (1.2%)
20/25 to 20/40	146 (24.3%)	15 (18.3%)
20/20 OR BETTER	401 (66.7%)	66 (80.5%)
20/40 OR BETTER	547 (91.0%)	81 (98.8%)

Best corrected visual acuity was 20/20 or better in all subjects in the 6.0 mm group. Uncorrected visual acuity was 20/20 or better in 80.5% in the 6.0 mm zone data compared to 66.7% in the < 6.0 mm zone data. This difference in the percentage of subjects reaching 20/20 is statistically significant using a chi-square comparison of proportions. For the 20/40 or better group, there is no

statistical significance between 98.8% and 91.0%. However, any statistical inferences are drawn with caution since all 6.0 mm subjects have not yet reached the one year examination.

d. Change In Best Spectacle Corrected Visual Acuity -- 12 month data

CHANGE IN BSCVA FROM PREOP	12 MONTHS	
	<6 MM (N=599)	6 MM (N=82)
DECREASE 6 LINES	1 (0.2%)	0
DECREASE 4 LINES	1 (0.2%)	0
DECREASE 3 LINES	3 (0.5%)	0
DECREASE 2 LINES	12 (2.0%)	1 (1.2%)
NO CHANGE (± LINE)	582 (97.1%)	81 (98.8%)

The one subject in the 6 mm ablation zone group who lost best corrected acuity went from 20/10 to 20/16. The overall loss of BCVA for this population is 1.2% (1 subject). Of the 17 eyes in the < 6.0 group, eight were 20/20 or better, 6 were 20/25, 2 were 20/32, and 1 was 20/80. The 20/80 was the cystoid macular edema eye mentioned previously.

ii. Predictability -- Uncorrected Visual Acuity Versus Attempted Correction -- 6 month data

6 mm ablation zone UCVA (N = 341)	DIOPTERS				
	1.00-3.00 N=92	3.10-4.00 N=67	4.10-5.00 N=69	5.10-6.00 N=76	6.10-7.00 N=37
20/20 OR BETTER	80 (86.9%)	43 (64.2%)	47 (68.2%0	36 (47.4%)	17 (46.0%)
20/25 TO 20/40	11 (12.0%)	22 (32.8%)	17 (24.6%)	36 (47.4%)	15 (40.5%)
20/50 TO 20/80	1 (1.1%)	2 (3.0%)	5 (7.2%)	1 (1.3%)	3 (8.1%)
20/100 TO 20/160	0	0	0	1 (1.3%)	0
20/200 OR WORSE	0	0	0	2 (2.6%)	2 (5.4%)
20/40 OR BETTER	91 (98.0%)	65 (97.0%)	64 (92.8%)	72 (94.7%)	32 (86.%)

<6 mm ablation zone UCVA (N = 635)	DIOPTERS				
	1.00-3.00 N=98	3.10-4.00 N=167	4.10-5.00 N=163	5.10-6.00 N=138	>6.00 N=69
20/20 OR BETTER	98 (100%)	114 (68.2%)	95 (58.3%)	77 (55.7%)	29 (42.0%)
20/25 TO 20/40	0 (0%)	39 (23.4%)	51 (31.3%)	50 (36.2%)	30 (43.5%)
20/50 TO 20/80	0	12 (7.2%)	13 (8.3%)	7 (5.1%)	6 (8.7%)
20/100 TO 20/160	0	2 (1.2%)	3 (1.8%)	2 (1.5%)	2 (2.9%)
20/200 OR WORSE	0	0	1 (0.6%)	2 (1.5%)	2 (2.9%)
20/40 OR BETTER	98 (100.0%)	153 (91.6%)	146 (89.6%)	127 (91.9%)	59 (85.5%)

Regarding UCVA, the percent of subjects reaching 20/40 or better and 20/20 or better uncorrected visual acuity is similar both ablation zone groups. Higher levels of attempted correction tend to do better with larger ablation zone size, usually due to less haze and quicker stabilization of results which may not be well reflected in these data tables. See MRSE tables for stability.

iii. Stability -- Manifest Refraction Spherical Equivalent; by follow up visit

ALL DATA	N		<6mm Ablation Zone			6mm Ablation Zone		
VISIT	<6 MM	6 MM	MEAN	SD	RANGE	MEAN	SD	RANGE
1M	690	381	+1.58	1.16	-2.00 to +5.25	+0.20	0.83	-2.38 to +6.00
2M	664	-	+0.97	1.08	-3.25 to +5.87	NA	NA	NA
3M	664	361	+0.75	1.02	-3.25 to +4.87	-0.13	0.66	-3.75 to +2.75
6M	669	341	+0.35	1.03	-5.75 to +4.37	-0.12	0.70	-3.63 to +3.38
12M	599	82	+0.06	1.02	-4.37 to +3.75	+0.08	0.60	-1.50 to +1.63

These 6 mm data represent a significant improvement in stability at an earlier time point and over time when compared to the < 6.0 mm ablation zone data. Measurement of refraction occurs at 0.25 diopter increments and the visit to visit variability is 0.50 diopters (estimate is based on unoperated PRK fellow eyes). The difference between 6 months and 12 months in the 6.0 mm group of +0.20 diopters is not likely a hyperopic shift given its magnitude.

iv. Complications

COMPLICATION	<6 mm N = 669	6 mm N =340
CATARACT		
1M TRACE	1 (0.2%)	1 (0.3%)
2M TRACE	1 (0.2%)	-
3M TRACE	1 (0.2%)	1 (0.3%)
4M TRACE	1 (0.2%)	-
CORNEAL EDEMA		
1M TRACE	4 (0.6%)	0
EPITHELIAL DEFECT		

1M MILD	1 (0.2%)	0
3M TRACE	1 (0.2%)	0
CORNEAL SCARRING		
1M TRACE	4 (0.6%)	0
2M TRACE	1 (0.2%)	0
4M TRACE	3 (0.5%)	0
6M TRACE	4 (0.6%)	0
MILD	1 (0.2%)	0
12 M TRACE	2 (0.3%)	0
MILD	1 (0.2%)	0
MODERATE	1 (0.2%)	0
CORNEAL ULCER/PERFORATION MILD	1 (0.2%)	0
FOREIGN BODY SENSATION	<6 mm N = 669	6 mm N= 340
1M TRACE	3 (0.4%)	4 (1.1%)
MILD	1 (0.2%)	1 (0.3%)
MODERATE	1 (0.1%)	0
2M TRACE	2 (0.3%)	0
3M TRACE	3 (0.5%)	1 (0.3%)
6M TRACE	1 (0.2%)	1 (0.3%)
12 M TRACE	1 (0.2%)	0

GLARE	<6 mm N = 669	6 mm N = 340
1M TRACE	52 (7.5%)	26 (6.8%)
MILD	30 (4.3%)	5 (1.3%)
MODERATE	12 (1.7%)	2 (0.5%)
SEVERE	3 (0.4%)	0
2M TRACE	62 (9.3%)	NA
MILD	21 (3.2%)	NA
MODERATE	10 (1.5%)	NA
SEVERE	0	NA
3M TRACE	56 (8.4%)	16 (4.4%)
MILD	18 (2.7%)	4 (1.1%)
MODERATE	3 (0.5%)	2 (0.6%)
SEVERE	1 (0.2%)	0
4M TRACE	45 (7.0%)	NA
MILD	37 (5.7%)	NA
MODERATE	4 (0.6%)	NA
SEVERE	0	NA
6M TRACE	59 (8.8%)	27 (7.9%)
MILD	23 (3.4%)	3 (0.9%)
MODERATE	5 (0.8%)	3 (0.9%)
SEVERE	0	0
12M TRACE	37 (6.2%)	2 (2.4%)
MILD	16 (2.7%)	0
MODERATE	6 (1.0%)	0
SEVERE	4 (0.7%)	0

HALO		<6 mm N = 669	6 mm N = 340
1M	TRACE	48 (7.0%)	14 (3.7%)
	MILD	35 (5.1%)	7 (1.8%)
	MODERATE	11 (1.6%)	1 (0.3%)
	SEVERE	5 (0.7%)	0
2M	TRACE	59 (8.9%)	NA
	MILD	17 (2.6%)	NA
	MODERATE	8 (1.2%)	NA
	SEVERE	0	NA
3M	TRACE	56 (8.4%)	13 (3.6%)
	MILD	29 (4.4%)	5 (1.4%)
	MODERATE	12 (1.8%)	1 (0.3%)
	SEVERE	0	1 (0.3%)
4M	TRACE	50 (7.7%)	NA
	MILD	26 (4.0%)	NA
	MODERATE	9 (1.4%)	NA
6M	TRACE	73 (10.9%)	29 (8.5%)
	MILD	26 (3.9%)	3 (0.9%)
	MODERATE	6 (0.9%)	1 (0.3%)
	SEVERE	0	1 (0.3%)
12M	TRACE	44 (7.3%)	2 (2.4%)
	MILD	11 (1.8%)	0
	MODERATE	10 (1.7%)	0
	SEVERE	1 (0.2%)	0

INDUCED ASTIGMATISM	<6 mm N = 669	6 mm N = 340
1M TRACE	6 (0.9%)	5 (1.3%)
MILD	1 (0.2%)	3 (0.8%)
MODERATE	1 (0.2%)	0
2M TRACE	9 (1.4%)	NA
MILD	1 (0.2%)	NA
3M TRACE	10 (1.5%)	3 (0.8%)
MILD	1 (0.2%)	0
4M TRACE	10 (1.6%)	NA
MILD	1 (0.2%)	NA
6M TRACE	5 (0.8%)	0
MODERATE	1 (0.2%)	0
12M TRACE	2 (0.3%)	0
Subject DISCOMFORT		
1M TRACE	0	2 (0.5%)
2M TRACE	2 (0.3%)	NA
3M TRACE	1 (0.2%)	2 (0.6%)
MILD	1 (0.2%)	0
4M TRACE	2 (0.3%)	1 (0.3%)
SEVERE	1 (0.2%)	NA
6M TRACE	1 (0.2%)	0
12M MODERATE	1 (0.2%)	0

Diffuse Nebulae and Hudson Stahli Lines were observed in the <6 mm zone data, but not in the 6 mm zone data. These complications were not observed in either group for up to the 6 month exam: corneal decompensation, ulcer or perforation, endophthalmitis, hypopyon, or iritis. These complications were not observed in either group for up to the 1 year exam: corneal decompensation, endophthalmitis, hypopyon, or iritis. All complications are listed above.

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The rate of occurrence and the severity of glare symptoms are statistically and clinically lower with the 6 mm zone data. The rate and severity of occurrence of the halo symptoms is also statistically lower with the 6 mm zone data. Note in the 6 mm zone data, halo in the mild or greater range is associated with astigmatism (especially, at levels greater than 1.00 diopters) which was present preoperatively. Overall symptoms are decreased in the 6 mm data and no complication is increased or shows any trend of increase over the <6 mm zone size data. This further supports approval of the 6 mm ablation zone size at this time. The significance of a reduction of symptoms of glare and halo with the 6 mm zone size should not be overlooked, nevertheless, they are not gone completely. Each prospective patient should be warned of their occurrence in the early postoperative period, and especially if occupation or hobbies could be affected.

v. Corneal Haze

a. In addition to the above complications corneal haze was specifically assessed in two measures, grossly and on slit lamp examination. The comparison results for one year are:

GROSS HAZE	<6 mm N =669	6 mm N = 82
Trace	11 (1.8%)	0
Moderate	2 (0.3%)	0
SLIT LAMP HAZE		
Trace	163 (27.2%)	36 (43.9%)
Mild	40 (6.7%)	0
Moderate	24 (4.0%)	3 (3.7%)

The same subjects with gross haze had moderate slit lamp haze as would be expected. The positive correlation to slit lamp haze represents the more severe the haze the more likely it is to be seen grossly. The overall severity of haze is less with 6 mm ablation zone sizes. It should be noted that by definition, a haze score of trace is not clinically significant, that is, it is seen on slit lamp but does not interfere with vision or refraction.

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b. Corneal Haze at each postoperative time period is shown for the 6 mm ablation zone size.

	1 MONTH N=377	3 MONTHS N=361	6 MONTHS N=340	12 MONTHS N=82
CLEAR	38 (10.1%)	79 (21.9%)	125 (36.8%)	43 (52.4%)
TRACE	291 (77.2%)	250 (69.3%)	182 (53.4%)	36 (43.9%)
MILD	44 (11.7%)	26 (7.2%)	25 (7.4%)	0
MODERATE	4 (1.1%)	6 (1.7%)	8 (2.4%)	3 (3.7%)
SEVERE	0	0	0	0

Every subject who had haze at 6 or 12 months also had haze of some degree at an earlier time period. The 3 month exam was the peak haze for the population. In the three subjects reporting moderate haze at one year, all had moderate haze at 6 months. That haze develops in the first 1-2 months and improves over time was determined for the <6 mm data and holds true for this 6 mm data. Haze may take up to one to two years (or more) to disappear.

8. Conclusion

The differences in predictability and stability (e.g. for $\pm$ 1.0 diopter the difference is 17.3%) between the 6.0 mm and < 6.0 mm groups are of greater magnitude than the theoretical 5% difference mentioned in the sample size discussion; hence, the comparisons of the two groups are valid. Stability with the 6 mm is reached at an earlier time point, and maintains on subsequent examinations. In addition, statistically significant reduction in the glare and halo symptoms with the 6.0 mm zone supports the approval of the 6.0 mm zone over the < 6.0 mm.

D. PRK After RK Study

1. Objectives

The goal of the investigation, conducted under IDE G910078 was to evaluate the safety and effectiveness of PRK in subjects with previous ocular surgery.

2. Design

A prospective, nonrandomized, uncontrolled, unmasked, multicenter clinical study was carried out.

3. Inclusion and Exclusion Criteria

Subjects were at least 21 years of age and were enrolled in the study if they met the following conditions: less than 8 diopters of myopia; spectacle intolerance; contact lenses intolerance; desired to decrease or eliminate spectacle or contact lens use; rejected the alternative refractive surgical procedures; and, had previously undergone ocular surgery.

Subjects not meeting the above enrollment criteria were excluded from the study. In addition, subjects who were previously treated with an excimer laser were excluded from this study.

4. Study Plan, Subject Assessments, and Effectiveness Criteria

Subjects were treated using identical surgical protocols, and were evaluated at the same intervals and for the same clinical parameters as specified for the 6.0 mm group.

5. Study Period, Investigational Sites, and Demographic Data

a. Study Period

A total of 197 eyes were treated in 197 subjects between 2/25/92 and 12/13/94. Clinical data are available for 197 eyes at pre-op, 166 of the 191 eligible eyes at one year, and 120 of the 162 eligible eyes at two years.

b. Investigational Sites

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

SITE	No. Eyes
Vision Surgery & Laser Center San Diego, CA	47
Eye Surgery Center of LA New Orleans, LA	17
Hunkeler Eye Clinic Kansas City, MO	73
Emory University School of Medicine Atlanta, GA	7
Burlington, VT	5
Jules Stein Eye Institute Los Angeles, CA	12
Montefiore Hospital Bronx, NY	10
Houston Eye Associates Houston, TX	18
Sioux Empire Medical Center Sioux Falls, CO	8
TOTAL	197

c. Demographics

	N=197
GENDER	
Female	108 (54.8%)
Male	89 (45.2%)
RACE	
White	188 (95.5%)
Afro-American	2 (1.0%)
Other	7 (3.5%)
AGE (YEARS)	
Mean	40.0 years
Range	24 to 66 years
SD	8.0
OPERATIVE EYE	
Right	95 (48.2%)
Left	102 (51.8%)

There is no evidence that gender is related to safety or effectiveness outcomes. Age is a statistically significant factor. Younger subjects are more likely to be both "predictable" (chi square test p=<0.001) and have uncorrected visual acuity of 20/40 or better (chi square test p=<0.001). There is no evidence in these data that race is related to safety or effectiveness outcomes, however, the sample sizes are too small to detect a difference.

d. Previous Ocular Surgeries

Radial Keratotomy (RK)	161 eyes (81.8%)
Astigmatic Keratotomy (AK)	11 eyes (5.6%)
Cataract surgery	5 eyes (2.5%)
AK and RK	19 eyes (9.6%)
Myopic Keratomileusis (MKM), AK and RK	1 eye (0.5%)

A majority of the subjects had undergone previous RK surgery.

6. Data Analysis and Results

a. Preoperative Ocular Characteristics

A number of baseline characteristics were measured. They included:

I. Visual Acuity (BSCVA and UCVA) [Not reported in one eye]

	No. Eyes (N=196)
BSCVA 2-4 MM	
20/20 OR BETTER	174 (88.8%)
20/25 TO 20/40	22 (11.2%)
BSCVA 6-8 MM	
20/20 OR BETTER	169 (86.2%)
20/25 to 20/40	27 (13.8%)
WORSE THAN 20/40	0
BSCVA WITH GLARE	
20/20 OR BETTER	169 (86.2%)
20/25 to 20/40	25 (12.8%)
WORSE THAN 20/40	2 (1.0%)
UCVA	
20/200 OR WORSE	105 (53.6%)
20/100 to 20/160	39 (19.9%)
20/50 to 20/80	41 (20.9%)
20/40 OR BETTER	11 (5.6%)

ii. Manifest Refraction Spherical Equivalent (MRSE) and Cycloplegic Refraction Spherical Equivalent (CRSE)

	(N=197)
MRSE (diopters)	
Mean	-3.64
Range	-1.00 to -11.00
Standard deviation	1.75
CRSE (diopters)	
Mean	-3.52
Range	-0.75 to -11.00
Standard deviation	1.77

The correlation between the manifest refraction and the cycloplegic refraction was reliable as shown by the above data. As would be expected, the higher levels of myopia showed greater variability. Overall this is consistent with clinical expectations.

	(N=197)
MR cylinder (diopters)	
Mean	-0.67
Range	0 to -3.00
Standard Deviation	0.49

iii. Contact Lens Wear

A total of 47 (23.9%) eyes in the study wore contact lenses prior to the PRK procedure.

iv. Irregular Astigmatism

Five eyes (2.5%) had irregular astigmatism present preoperatively.

b. Operative Characteristics

The operative technique was standardized for the study reported here. These laser parameters were also standardized: fluence at the eye, repetition rate, ablation rate. A 5.0 mm ablation zone was used in 194 procedures; three procedures were treated with a 6.0 mm ablation zone. No treatments were interrupted.

ATTEMPTED CORRECTION	(N=197)
1.00 D -- 2.00 D	59 (30.0%)
2.10 D -- 3.00 D	58 (29.4%)
3.10 D -- 4.00 D	31 (15.7%)
4.10 D -- 5.00 D	21 (10.7%)
5.10 D -- 6.00 D	27 (13.7%)
6.10 D -- 7.50 D	1 (0.5%)
Total	197 (100%)
LASER PARAMETERS	
Average total pulses	148 (72 to 297)
Ablation zone diameter (mm)	5.0 (6.0 in 3 pts.)
Fluence @ eye (mJ/cm^2)	180
Pulse repetition rate (Hz)	10
Pulse width (nsec)	14

c. Postoperative Characteristics and Results

I. Accountability

# EYES ENROLLED	FOLLOW-UP EXAM (months)	# EYES ELIGIBLE FOR FOLLOW-UP	# and (%) EYES FOLLOWED
197	12 M	191	166 (87.0%)
	24 M	162	120 (74.1%)

ii. Re-epithelization

Of the 197 treated eyes, re-epithelialization was reported as follows:

by 72 hours	177 eyes	89.9%
by 96 hours	192 eyes	97.5%
by 1 week	196 eyes	99.6%
by 4 weeks*	197 eyes	100 %

* One subject not re-epithelialized at the 3 day follow up exam and did not return for a 1 week visit. This subject was re-epithelialized by the 1 month exam.

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iii. Uncorrected Visual Acuity (UCVA) -- Acuity and change

a. Acuity

UCVA	Preop	12 M	24 M
20/200 OR WORSE	105 (53.6%)	10 (6.0%)	6 (5.0%)
20/100 to 20/160	39 (19.9%)	8 (4.8%)	9 (7.5%)
20/50 to 20/80	41 (20.1%)	26 (15.7%)	13 (10.8%)
20/25 to 20/40	11 (5.6%)	60 (36.1%)	42 (35.0%)
20/20 OR BETTER	0	62 (37.3%)	50 (41.7%)
20/40 OR BETTER	11 (5.6%)	122 (73.5%)	92 (76.7%)
TOTAL	196	166	120

The percentage for 20/40 or better in this group is lower than that seen with otherwise normal eyes treated with PRK.

b. Change in Uncorrected Visual Acuity

CHANGE FROM PREOP IN UCVA	12 Month N = 165	24 Month N = 119
Increase of > 2 lines	140 (84.4%)	98 (82.4%)
Increase of 2 lines	5 (3.0%)	1 (0.8%)
NO Change (+/-1 line)	11 (6.7%)	11 (9.2%)
Decrease of 2 lines	3 (1.9%)	5 (4.2%)
Decrease of > 2 lines	6 (3.6%)	4 (3.4%)

At one year 9 eyes (5.5%) had a decrease in UCVA. At two years 9 eyes (7.6%) had a decrease in UCVA. In previously normal eyes treated with PRK, no eyes lost UCVA. See also loss of BSCVA for safety concerns.

iv. BSCVA at a 2-4 mm pupil

I. Acuity

In the study, for a 2 - 4 mm pupil, the BSCVA in subjects were:

BSCVA	Preop	12 M	24 M
20/20 or better	174 (88.8%)	126 (76.0%)	86 (71.7%)
20/25 to 20/40	22 (1.8%)	29 (17.5%)	26 (21.7%)
20/50 to 20/80	-	8 (4.8%)	7 (5.8%)
20/100 to 20/160	-	1 (0.6%)	1 (0.8%)
20/200 or worse	-	2 (1.2%)	0
TOTAL	196	166	120

Preoperative best corrected visual acuity was not available on one eye.

b. Change in BSCVA from preop

Change in BSCVA from preop	12 M (N=165)	24 M (N = 119)
Decrease >2 lines	17 (10.3%)	18 (15.1%)
Decrease 2 lines	28 (17.0%)	17 (14.3%)
No change	111 (67.3%)	82 (69.0%)
Increase 2 lines	8 (4.8%)	1 (0.8%)
Increase 4 lines	1 (0.6%)	1 (0.8%)

At the one year visit, 127 (72.2%) eyes had no change or experienced an increase in BSCVA, and 45 (27.3%) had a decrease in BSCVA in which 11 were worse than 20/40. At the two years exam, 84 (70.6%) eyes had no change or experienced an increase in BSCVA, and 35 (29.4%) had a decrease in BSCVA in which 8 were worse than 20/40.

v. Stability and Predictability

a. MRSE at each follow up visit

VISIT	N	MEAN	SD	RANGE
1M	189	+1.50	1.49	-5.88 to +7.00
2M	174	+0.75	1.12	-2.75 to +3.88
3M	176	+0.23	1.23	-5.38 to +3.25
4M	158	-0.16	1.38	-4.75 to +3.00
6M	176	-0.50	1.56	-6.63 to +3.88
9M	136	-0.73	1.64	-7.00 to +3.38
12M	166	-0.70	1.59	-6.50 to +2.50
18M	145	-0.70	1.60	-6.25 to +2.88
24M	120	-0.76	1.67	-7.75 to +3.25

Stability over time by MRSE is similar to that seen with data from the phase III <6 study. The above data do not raise any questions regarding stability in this population.

b. Predictability -- MRSE at 1 and 2 years

	1 year (N=166)	2 years (N=120)
± 1 diopter	104 (62.7%)	80 (66.7%)
± 2 diopters	140 (84.3%)	99 (82.5%)

These percentages are lower than those seen in otherwise normal eyes undergoing PRK.

vi. Irregular Astigmatism

Five eyes (3.0%) reported irregular astigmatism cases at the 1 year postoperative exam. Five eyes (4.2%) reported irregular astigmatism cases at the 2 year postoperative exam. Only one subject had irregular astigmatism reported preoperatively.

vii. Keratometry Readings

The mean preoperative keratometry reading was 41.4 D, range of 34.5 to 53.0 D, and the standard deviation was 2.2D. The mean preoperative keratometric astigmatism was 0.9D with a standard deviation of 0.74 D.

The mean postoperative keratometry reading at one year was 39.6 D with a range of 31.5 to 48.0 D and a standard deviation of 2.3. The mean keratometric astigmatism at one year was 1.0 D. The one year readings are representative of the readings taken at other exams. The change in mean keratometry from the preoperative value indicate a flattening of the cornea.

viii. Intraocular Pressure

The mean preoperative IOP was 14.8 mmHg, with a range from 8.0 to 22.0 mmHg and a standard deviation of 2.8. The mean postoperative IOP at one year was 14.5 with a range of 8 to 22 and a standard deviation of 2.8. The one year readings are representative of the readings taken at other exams.

ix. Complications

Glare and halo had the highest rates of reporting, as follows:

Glare grade	**6 months** (n = 175)	**1 year** (n = 166)	**2 year** (n = 120)
Trace	7 (4.0%)	4 (2.4%)	6 (5.0%)
Mild	4 (2.3%)	8 (4.8%)	7 (5.8%)
Moderate	2 (1.1%)	4 (2.4%)	5 (4.2%)
Marked	1 (0.6%)	1 (0.7%)	2 (1.7%)

Halo grade	**6 months** (n = 175)	**1 year** (n = 166)	**2 year** (n = 120)
Trace	10 (5.7%)	7 (4.2%)	6 (5.0%)
Mild	6 (3.4%)	6 (3.6%)	5 (4.2%)
Moderate	1 (0.6%)	4 (2.4%)	5 (4.2%)
Marked	1 (0.6%)	1 (0.6%)	2 (1.7%)

Other reported complications whose rate was greater than 1.0 % at a long term postoperative visit included: trace cataract at 18M (3 eyes, 2.1%), moderate epithelial defects at 9M (2, 1.5%) and at 12 M (3, 1.8%), trace foreign body sensation at 6 M (2, 1.1%), and corneal scarring of grade trace (6M: 2, 1.1%; 9M: 3, 2.2%; 12M: 2, 1.2%), grade mild (9M: 2, 1.5%; 12M: 4, 2.4%; 18M: 4, 2.8%), and grade moderate (6M: 2, 1.1%; 24M: 2, 1.7%). .

These complications were not observed: bacterial keratitis, corneal decompensation, edema, ulcer or perforation, endophthalmitis, hypopyon, hyphema, or iritis.

x. Corneal Haze

In addition to the above complications corneal haze was specifically assessed in two measures, grossly and on slit lamp examination.

GROSS HAZE	12 months	24 months
Trace	4 (2.4%)	0
SLIT LAMP HAZE		
Trace	56 (33.7%)	41 (34.2%)
Mild	20 (12.0%)	5 (4.2%)
Moderate	14 (8.4%)	13 (10.8%)
Severe	3 (1.8%)	1 (0.8%)

The incidence and severity of haze at one and two years postoperatively raise safety concerns.

7. Conclusions

The loss of UCVA and BSCVA of 2 or more lines combined with the fact that 6.6% of subjects were worse than 20/40 raise serious concerns regarding the safety of PRK after RK. The incidences of scarring and haze postoperative raise similar safety concerns. The overall benefit of PRK after RK must be carefully considered on an individual basis before treatment.

E. Device Failures

The following represents a summary of device failures reported to date on a worldwide basis for the Summit excimer laser equipment. No permanent injury has been reported from any of these failures.

1. Failure of the laser to come out of the test mode occurred twice.

2. System shutter failure occurred in three instances. Twice it was replaced and did not recur. The other required an engineering service visit.

3. Iris diaphragm failure during a photorefractive procedure in two instances. The iris system was replaced. The failure could not be replicated by the applicant.

4. One system operated in the service mode rather than customer mode. A correction was made to the software of the laser system to eliminate future occurrence.

5. During in vitro research, the laser was missing pulses that the software counted but in actuality the pulses were not being delivered. The High Voltage Power Cable was not fully seated in the High Voltage Power Supply which was corrected. The problem did not recur.

X. CONCLUSIONS DRAWN FROM THE CLINICAL STUDIES

The results of the various studies reported above indicated that the 6mm treatment zone produced fewer adverse events with equivalent correction of myopia, improved predictability, and earlier stability than smaller treatment zones.

A. Safety

The studies showed the following transient complications: pain (24-48 hrs), corneal swelling, double vision, feeling something in the eye, shadow images, light sensitivity, tearing and pupil enlargement. These problems lasted up to several weeks.

With a 6 mm zone, the following adverse events occurred in at least 1.0% of the subjects within 6 months post-treatment: night vision difficulty (1.0%); elevation of intraocular pressure (1.8%); hazy cornea affecting vision (2.3%); overcorrection (induction of farsightedness) (5.0%); undercorrection (still nearsighted) (5.6%); loss of the best vision that can be achieved with glasses (6.8%); mild halo (9.7%); and, minor glare (10.0%).

One complication, haze, developed within the first few months after surgery and then improved over time. The time course of haze development and resolution was first observed with the <6 mm ablation zone data and confirmed for the 6 mm data. Interestingly, haze in low myopia peaked at 3 months and then subsided. For higher myopic levels, 6 D or greater, haze had a second peak at 6 months. In some cases, the haze took a year or more to disappear. The apparent relation between the time needed for haze resolution and the degree of preoperative myopia or attempted correction did not reach statistical significance.

The above studies were designed to detect low rate adverse events over limited periods of follow-up. Long term risks of PRK beyond 3 years have not been studied, but will be investigated in post approval studies.

B. Effectiveness

The studies using the 6mm treatment zone found that of the 341 eyes at 6 months, 95% were corrected to 20/40 or better without spectacles or contact lenses, and 65% to 20/20 or better without spectacles or contact lenses. In 23 out of 340 eyes, the best vision that can be achieved with spectacles declined by more than 1 line from preoperative; however, none was worse than 20/40.

Age is a statistically significant factor in that younger patients are more likely to be both "predictable" and have uncorrected visual acuity of 20/40 or better.

XI. Panel Recommendations

On October 20, 1994, the Ophthalmic Devices Panel reviewed and discussed the following data: 701 first eyes (229 had the 4.5 mm ablation zone and 472 had 5.0 mm); 398 second eyes (57 had the 4.5 mm ablation zone, 339 had 5.0 mm, and 2 had 6.0 mm); and, 30 eyes in the Navy study (all had the 6.0 mm zone). The Panel voted 13 to 1 to conditionally approve the Summit excimer laser, using a <6 mm ablation zone, for the treatment of myopia between 1.50 and 6.00 D with less than 1.5 D of astigmatism. The conditions of approval were as follows:

1. Provide all labeling (manuals) for the Panel to review as homework.

2. BSCVA on monocular vision should show that,
   - no more than 5% of population lose 2 lines or more
   - for those starting with 20/20 or better,
     * no more than 1% below 20/25
     * no more than 0.2% below 20/40
   - bring at least 500 back for this evaluation
   - exclude non-procedural related cases and document these cases

3. For those with at least 20/20 BSCVA preoperative, at least 75% in 500 eyes should have uncorrected monocular acuity of at least 20/25 with cycloplegic refraction of -1 to +0.50 at the 1 year follow-up.

4. Perform additional specular microscopy on the 150 who had it done preoperative to evaluate for central and peripheral cell density changes. Data should be stratified in 1 D increments of attempted correction. Document progressive loss by compare the 1 year to the latest data.

5. Document any deviation from preoperative baseline of halo, glare, and acuity.

6. Perform post market surveillance, and provide data for about 500 eyes of the PMA cohort at years 3 and 4. Depending on year 4 data, it may be necessary to provide periodic data up to year 10.

7. Present a training program, for purchasers and users, that is acceptable to the agency.

8. Provide data to show that the lasers at different centers perform the same, and that the lasers operate properly without the continuing presence of the Summit servicing staff.

9. Provide a patient booklet which contains details of the risk and benefit of the procedure.

In addition, the Panel pointed out that the limited data provided for a 6 mm ablation zone suggested that the larger ablation zone may provide better outcomes; however, the presented data were too limited to be conclusive.

Summit provided re-analyzed data, post-panel, to show that all the conditions posed by the Panel can be met by the laser with the data presented at the panel meeting. In addition, Summit submitted IDE progress report data on 394 eyes which FDA believed to show that the 6.0 mm ablation zone can provide equal or better outcomes with lower complication rates than the < 6.0 mm zone. A summary of the 6 mm data with comparison against the <6.0 mm was provided to the panel members, who were unconflicted as of August 1995 and were present at the October 1994 meeting, for their assessment of the data. In a vote of 5 to 1, the panel member concurred with FDA.

The Panel also reviewed the Patient Information Booklet and Physician Information. Their suggestions were incorporated into the final draft labeling for the device.

XII. FDA Decision

On October 20, 1995, FDA issued an approval order for the Summit SVS Apex Laser System. The device is indicated for a 6.0 mm ablation zone, myopic photorefractive keratectomy (PRK) in patients who meet all of the following criteria:

1. 1.5 to 7.0 diopters of myopia with astigmatism of ≤ 1.5 diopters;

2. refraction is within ± 1.0 diopter for one year prior to the laser treatment; and,

3. 21 years of age or older.

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).

Copies of the Patient Information Booklet for Photorefractive Keratectomy (Attachment B) and Physician Information (Attachment C) are attached.

BIBLIOGRAPHIES

1. Srinivasan R and Wayne-Banton V. Self-developing photoetching of poly(ethylene terephthalate) films by far-ultraviolet excimer laser radiation. Applied Physics Let 1982; 41:576-78.

2. Aron Rosa DS, Boerner CF, Gross M, et al. Wound healing following excimer laser radial keratotomy. Journal of Cataract and Refractive Surgery 1988; 14:173-79.

3. Marshall J, Trokel SL, Rothery S, and Krueger RR. Photoablative reprofiling of the cornea using an excimer laser: photorefractive keratectomy. Lasers in Ophthalmology 1986; 1:21-48.

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5. Trokel SL, Srinivasan R, and Braren B. Excimer laser surgery of the cornea. American Journal of Ophthalmology 1983; 96(6):710-15.

6. Puliafito CA, Wong K, and Steinert RF. Quantitative and ultrastructural studies of excimer laser ablation of the cornea at 193 and 248 nanometers. Lasers in Surgery and Medicine 1987; 7:155-59.

7. Waring, GO. Standardized Data Collection and Reporting for Refractive Surgery. Journal of Refractive and Corneal Surgery 1992, March/April Suppl. 8:1-42.

8. Bourque L., et al. Psychosocial characteristics of candidates for the Prospective Evaluation of Radial Keratotomy (PERK) study. *Archives of Ophthalmology,* 102: 1187-1192, 1984.

9. Corbett M.C., Verma S., O'Brart D.P.S., Oliver K. M., Heacock G., and Marshall J. The effect of ablation profile on wound healing and visual performance one year after excimer laser PRK. (1995) (Unpublished at the time of PMA approval)

10. O'Brart D.P.S., Corbett M.C., Verma S., Heacock G., Oliver K.M., Lohmann C.P., Kerr Muir M.G., and Marshall J. An investigation of the effects of ablation diameter, depth, and edge contour on the outcome of excimer laser photorefractive keratectomy (PRK). (1995) (Unpublished at the time of PMA approval)

Attachment A

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

OCT 20 1995

Ms. Kimberley Doney
c/o Ms. Maureen O'Connell
Regulatory, Clinical, and Quality Affairs
Summit Technology, Inc.
21 Hickory Drive
Waltham, MA 02154

RE: P930034
SVS Apex (formerly OmniMed) Excimer Laser System for Photorefractive Keratectomy (PRK)
Filed: October 12, 1993
Amended: November 4, 1993; June 28, and 30, July 5, 8, and 14, August 22, September 1, 9, and 16, October 11, and December 20, 1994; February 10 and 21, April 5 and 13, May 1, 9, and 19, June 6 and 28, September 13, 19, 21, 25, 26, and 28, and October 11 and 20, 1995

Dear Ms. Doney:

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 SVS Apex (formerly OmniMed) Excimer Laser System. This device is indicated for a 6.0 mm ablation zone, myopic photorefractive keratectomy (PRK) in patients who meet all of the following criteria:

1. 1.5 to 7.0 diopters of myopia with astigmatism of ≤ 1.5 diopters;

2. refraction is within ± 1.0 diopter for one year prior to the laser treatment; and,

3. 21 years of age or older.

We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (Enclosure). You may begin commercial distribution of the device upon receipt of this letter, after you submit an amendment to this PMA submission with copies of all approved labeling in final printed form (following the format of the manuals presented to FDA for review, the Physician's Information on PRK should be included in Appendix A of the User's Manual).

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.

These restrictions on the use, labeling, promotion, and advertising of the device are applicable to Summit Technology, as well as device purchasers and users. Summit must notify the purchasers and users of these restrictions.

1. Only practitioners who are experienced in the medical management and surgical treatment of the cornea, and who have been trained in laser refractive surgery including laser system calibration and operation, may use the device as approved in this order.

2. Prospective patients, as soon as they express an interest in myopic PRK and prior to undergoing surgery, must receive from the treatment provider the Patient Information Booklet (as described in amendment dated October 20, 1995 to this PMA).

3. Prospective patients, prior to undergoing surgery, must be informed of the alternatives for correcting their myopia including eyeglasses, contact lenses and other refractive surgeries such as radial keratotomy.

4. All promotion and advertising for this device must include the following information on indications, risks and benefits:

    a. Approval is for the Summit Technology's application for the SVS Apex laser to correct mild to moderate nearsightedness (-1.5 to -7.0 diopters when concomitant astigmatism is no greater than 1.5 diopters) in a procedure called photorefractive keratectomy (PRK) using an excimer laser that emits light at a wavelength of 193nm.

    b. PRK is an elective procedure with the alternatives being eyeglasses, contact lenses or radial keratotomy.

    c. Approval of the application is based on clinical trials of more than 1600 eyes together with safety information through 3 years of follow up.

    d. The studies using the 6mm treatment zone found that of the 341 eyes at 6 months, 95% were corrected to 20/40 or better without spectacles or contact lenses, and 65% to 20/20 or better without spectacles or contact lenses. In 23 out of 340 eyes (6.8%), the best vision that can be achieved with spectacles declined by more than 1 line from preop; none was worse than 20/40.

    e. These clinical trials showed the following transient complications: pain (24-48 hrs), corneal swelling, double vision, feeling something in the eye, shadow images, light sensitivity, tearing and pupil enlargement. These problems lasted up to several weeks.

f. The clinical trials using the 6mm treatment zone showed the following adverse events occurred in at least 1.0% of the patients within 6 months post-treatment: night vision difficulty (1.0%); elevation of intraocular pressure (1.8%); hazy cornea affecting vision (2.3%); overcorrection or became farsighted (5.0%); undercorrection or still nearsighted (5.6%); loss of the best vision that can be achieved with glasses (6.8%); mild halo (9.7%); and, minor glare (10.0%).

g. Long term risks of PRK beyond 3 years have not been studied.

h. The manufacturer is being required to continue following patients in the clinical trials to evaluate the long-term stability of vision and associated risks. The manufacturer will conduct a study to determine the incidence of adverse events less than 1.0% and to evaluate losses in contrast sensitivity.

i. This laser is not indicated to correct high myopia (nearsightedness > -7.0 D), astigmatism, or farsightedness. Also, it is not indicated to correct nearsightedness of less than -7.0 D if the accompanying astigmatism is > 1.5 D. It is not to be used in procedures other than PRK as described in the approved User's Manual.

j. Note that the complete name for this ophthalmic laser is "SVS Apex Excimer Laser for Photorefractive Keratectomy (PRK) for the Correction of Mild to Moderate Myopia (-1.5 D to -7.0 D) with Low Astigmatism (≤1.5 D)". Two acceptable versions of this official name are: PRK laser correction of low myopia and PRK laser correction of low nearsightedness. The word excimer, ultraviolet, or UV may be used instead of PRK. Also, these names do not have to contain the qualifiers mild to moderate (-1.5 D to -7.0 D) or low astigmatism (≤1.5 D) as long as the adjacent text provides this information. Names other than those appearing above require approval in a PMA supplement.

In addition to the postapproval requirements in the Enclosure, the following information must also be submitted to the Agency:

1. interim progress reports, for the contrast sensitivity and low adverse event rate studies, as proposed in your amendments dated September 25 and 26, 1995;

2. in your annual report, the data specified in items 2.a (additional follow-ups on premarket study subjects) and 2.b (unscheduled maintenance visits) of the FDA approvable letter dated September 15, 1995; when reporting each unscheduled maintenance visit, please include the data from the PMMA and Wratten filter calibrations performed in the 6 weeks prior to the visit; and,

3. reports to FDA CDRH's Office of Compliance at the address below of any instances of device tampering or usage outside of the approved indications, and any excimer systems that were exported under an 801(e) order and are now back in the U.S.

OC/Division of Enforcement (HFZ-331)
Center for Devices and Radiological Health
Food and Drug Administration
2098 Oakgrove Drive
Rockville, Maryland 20850

Please note that long-term data must be reflected in the labeling (via a supplement to the PMA) when the additional follow-ups and/or postapproval studies are completed.

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.

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,

Philip J. Phillips

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

Enclosure

Issued:5-2-95

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.

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

(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.

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

Attachment B

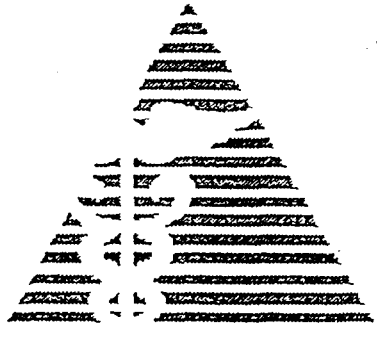
PATIENT INFORMATION

PHOTOREFRACTIVE KERATECTOMY (PRK) FOR CORRECTION OF MYOPIA

Mild to Moderate (-1.5 TO -7.0 D)

With Low Astigmatism (≤1.5 D)

Please speak with you doctor regarding PRK Laser Correction of Myopia (Nearsightedness). Use of any machine for a medical treatment requires discussion with a qualified doctor. It is important that you read this booklet and then carefully discuss its contents with your doctor.



Summit Technology, Inc.
21 Hickory Drive
Waltham, Massachusetts 02154
Phone 617 890 1234
Fax 617 890 0313

IMPORTANT INFORMATION

- PRK is a permanent operation to the cornea; it cannot be reversed.

- Alternatives to PRK include glasses, contact lenses and RK.

- PRK is not a laser version of radial keratotomy (RK); they are completely different from one another.

- Some occupations, such as pilots, do not accept applicants who have had any refractive surgery.

- Refractive error must be stable (within +/-1.0 D) for at least one year before the surgery.

- The following risks of PRK surgery should be noted:

    - transient complications: pain (24-48 hours), corneal swelling, double vision, feeling something in the eye, shadow images, light sensitivity, tearing and pupil enlargement. These problems may last up to several weeks.

    - adverse events: night vision difficulty (1.0%); elevation of intraocular pressure (1.8%); cloudy cornea affecting vision (2.3%); overcorrection or became farsighted (5.0%); undercorrection or still nearsighted (5.6%); loss of best vision that can be achieved with glasses (6.8%); mild halo (9.7%); and, minor glare (10.0%).

- The following benefits of PRK surgery should be noted:

    - Nearsightedness may be reduced so that the amount of time during the day contact lens or eyeglasses are used is reduced or eliminated.

    - PRK may be an alternative to eyeglasses in some patients who are intolerant of contact lenses.

    - Another alternative to correct nearsightedness.

Patients considering PRK surgery should:

- Discuss fully with one or more ophthalmic surgeons the complications of PRK surgery, the risks and the time required for healing, and have a complete eye examination before making a final decision.

- Read both the Patient Information Booklet and the Informed Consent Document (ICD) provided by your doctor carefully before signing the ICD.

TABLE OF CONTENTS: What You Need To Know Preoperatively

You are entitled to be informed about the treatment proposed, including the risks of the treatment and alternatives to it. Please read this booklet and then discuss the content with your doctor so that all of your questions are answered to your satisfaction. Your doctor has been alerted that Informed Consent is the law! Please read the informed consent.

INTRODUCTION

The following information is being provided to persons who are thinking about having Photorefractive Keratectomy (PRK) laser surgery for the correction of mild to moderate (-1.5 to -7.0 D) nearsightedness (myopia). The treatment is for myopia with low astigmatism ($\leq$1.5 D). The options for correction of myopia now include eyeglasses, contact lenses, the refractive surgical procedure known as radial keratotomy (RK), and PRK using the Summit Excimer Laser System. PRK is a completely different technique than RK.

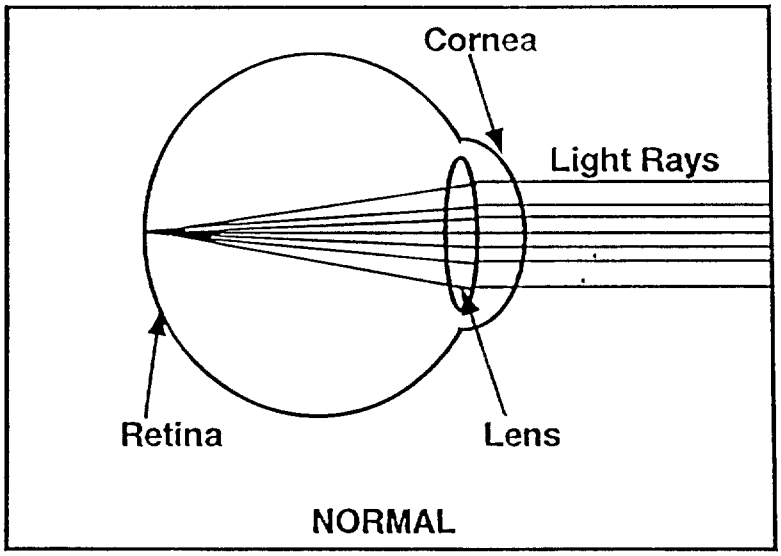
Please note that it may be necessary to have both eyes treated with PRK to achieve a satisfactory result. There are cases where it is appropriate to have PRK on only one eye. This educational information is provided to help you make an informed decision about PRK as a method of changing your cornea to correct your nearsightedness. Please read this material completely and discuss any questions with your doctor in order to decide if PRK is right for you. Only a qualified eye doctor can determine whether or not you are suitable for PRK. You should know that a small percentage of patients treated with the excimer laser have permanent adverse visual effects.

The goal of PRK is to reduce your need for eyeglasses or contact lenses by flattening the cornea through PRK laser surgery.

HOW THE EYE FUNCTIONS

Your eye focuses light to form images or "pictures", very much like a video camera. Your eye changes these images into electrical signals, which are then sent back to your brain. If your eye is out of focus, what you see will be blurred.

The cornea at the front of the eye bends (or refracts) the light rays onto your retina. This clear tissue is responsible for two-thirds of the focusing power of your eye. The lens within your eye finishes the job of focusing the light onto your retina.



FOCUSING WITH YOUR EYE

The eye focuses light by bending (or refracting) all light rays to meet at a single point. If the focusing process works perfectly, a sharp image of the object you are looking at will be focused exactly on the retina and you will see a clear image (emmetropia). However, if the light focuses either in front of or behind the retina, the image on the retina (and the image you see) will be blurred, and you are said to have a refractive error. There are three main types of refractive error, called nearsightedness (myopia), farsightedness (hyperopia) and astigmatism.

Enclosed pictures emphasize the role of the cornea in determining the focusing power of the eye. They show that the more sharply the cornea is curved, the more the light rays are bent. If the cornea is too flat, the image focuses behind the retina and the eye is farsighted. If the cornea is curved too much, the image focuses in front of the retina and the eye is nearsighted.

Since the cornea in a nearsighted eye is curved too much, it should be possible to correct nearsightedness simply by making the cornea flatter.

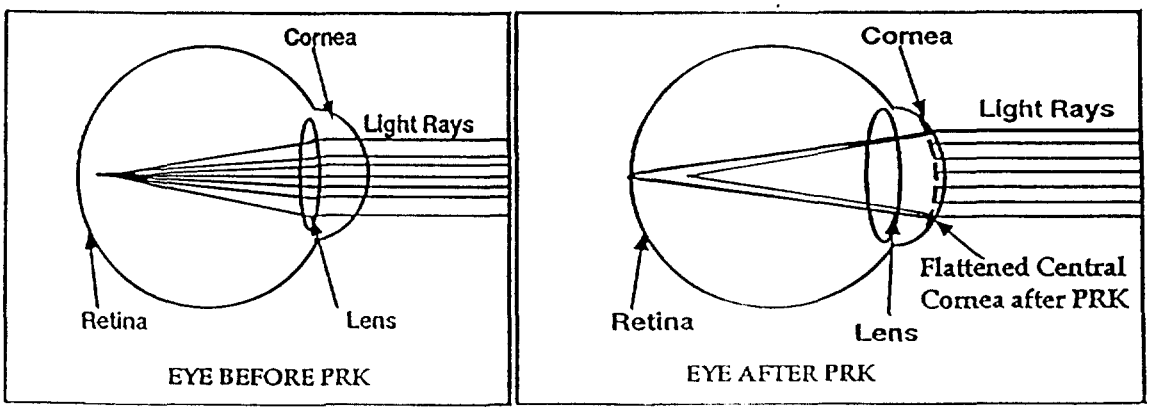
CHECKING YOUR FOCUS

When your doctor checks your vision, he or she considers where the eye focuses light relative to your retina. When your doctor corrects your vision, he or she properly focuses light on the retina. Good focus depends on the overall shape and size of your eyeball, the shape of your cornea, and the power of the natural lens. When your eye cannot focus properly, it is said to have a refractive error. Refractive errors are not diseases, but normal variations or conditions. The three main types of refractive error are myopia (nearsightedness), hyperopia (farsightedness) and astigmatism.

THE NEARSIGHTED EYE (MYOPIA)

The excimer laser has only been approved for the refractive treatment of mild to moderate myopia (nearsightedness). Myopia is the most common refractive condition and affects one in four people in North America. Myopic individuals are nearsighted: they see near objects clearly, but distant objects are blurry. Myopia occurs when light rays entering the eye are focused in front of your retina instead of directly on it. Nearsightedness can be corrected by eyeglasses, contact lenses, or refractive surgery. The first two options, eyeglasses and contact lenses, can be adjusted through new lenses if your vision changes.

Changes due to refractive surgery are permanent and cannot be undone or easily modified if your vision or focus changes or if the initial surgery is not successful (which occurs in a small percentage of cases). The tendency to develop myopia runs in families. Myopia (nearsightedness) usually starts in childhood and typically stabilizes in the late teens or early adulthood.



WHAT IS PHOTOREFRACTIVE KERATECTOMY (PRK)?

PRK is a surgical treatment for nearsightedness in which an excimer laser flattens the front surface of the cornea by removing small amounts of tissue.

WHAT IS AN EXCIMER LASER?

A laser is an instrument that can produce and control a powerful beam of light. Laser light can be directed and controlled more precisely than normal light, and it can be delivered in extremely brief, intense pulses.

The excimer laser produces a beam of ultraviolet light in pulses that last only a few billionths of a second. Each pulse removes a microscopic amount of tissue by evaporating it, producing very little heat and usually leaves underlying tissue almost the same.

HOW IS PRK PERFORMED?

A specially-trained eye doctor uses the beam from the computerized laser to remove small amounts of corneal tissue, precisely reshaping the cornea.

PRK has been studied for six years before approval in the U.S. It uses a computerized laser to correct myopia (nearsightedness). The excimer laser is well-suited for corneal reshaping, because the removal of just tiny amounts of tissue can produce the results you need to correct your nearsightedness.

Prior to PRK, some drops are placed on the eye to numb it. Use of the laser beam lasts about 15-40 seconds. The laser removes a small portion of the surface tissue to reshape the cornea. This treatment is performed on one eye at a time. The second eye can be treated if all goes well and vision stabilizes without complications or adverse reactions. PRK of the second eye can be done 3 months after the first eye.

After this treatment, most people report that they no longer need to wear glasses or contact lenses. In the clinical trials, 66% of people could see 20/20 or better after their vision was corrected with the laser treatment, and greater than 90% of people could see 20/40 or better, reporting that they were able to function normally and even drive without glasses or contact lenses. The remaining people experienced an improvement in vision without glasses or contact lenses but may still need to wear glasses or contact lenses for some tasks. PRK does not eliminate the need for reading glasses. In some patients, reading glasses may be required after treatment even if they were not worn before treatment. Keep in mind that your vision may take months to clear up and stabilize.

WHAT YOU NEED TO KNOW PREOPERATIVELY

If you are interested in having PRK you will need to have a pre-treatment examination to determine if your eye condition is right for the treatment.

Your pre-treatment examination will involve a complete medical and eye history, in which both eyes will be examined by a vision and eyeglass check, a microscopic examination, a glaucoma test, and possibly the computerized mapping of your cornea.

Prior to coming to the surgery please talk with your doctor your normal schedule for taking any prescribed medications. Also, talk with your doctor about the advisability of eating or drinking immediately prior to the surgery. You should arrange for someone to drive you home after the surgery; and to your next doctor's appointment. You should not drive until the doctor gives you permission to do so.

THE DAY OF SURGERY

Just prior to the surgery you will be given some drops in your eyes. You will be escorted into the room that contains the laser system. You will see a large machine with an arm sticking out that has the microscope attached to it. Also you may see a computer screen, a surgeon's chair and the reclining patient chair. You will be asked to sit in the patient chair. You will be laying face up toward the microscope and the ceiling. Your eye will be numbed with more drops.

Overall the surgery will take approximately 10-20 minutes, however the use of the laser beam lasts only 15-40 seconds. The surgeon will place an instrument between your eyelids to hold them open during the treatment. Try to keep both eyes open without squeezing since this will allow you to relax more. The surgeon will ask you to look up through the bottom of the microscope. You will see colored lights in the center of the microscope tube. The fixation light is very important in keeping your eye positioned properly during the laser surgery. The surgeon will instruct you how and when to look at these colored lights. The surgeon will then take you through a practice session with the laser to familiarize you with the sights and sounds of the treatment so that you will be prepared for what to expect during the actual treatment. Remember you and your surgeon are a team, cooperate with your surgeon to get the best possible result.

After the training session, the treatment will begin with the surgeon using a surgical instrument to remove the outermost layer of the cornea called the epithelium. Only after the surgeon has repositioned your head in the chair, refocused the microscope and asked you to fixate on the colored lights will the laser treatment be performed.

After your treatment, your doctor may place some drops or ointment into your eye. Your eye may then be patched for protection and comfort. The treatment itself is painless because of the numbing drops. When these eye drops wear off, your eye will likely hurt for one to two days. The doctor may recommend medicine to make you more comfortable during the immediate post-treatment period.

FIRST DAYS AFTER THE TREATMENT

The patch is usually removed the next day. You may be sensitive to light and glare and have the feeling that something is in your eye for the first few weeks while the outer layer of your cornea grows back completely. Sunglasses may be worn to make you more comfortable during this time. Initially your eye may be overcorrected making you hyperopic (farsighted) and objects up close may be blurry. This is part of the normal healing process after PRK and it may take up to six months for your vision to stabilize. All eyes get some degree of haze or cloudiness in the cornea following treatment which may or may not interfere with vision. The haziness tends to decrease over time and should eventually disappear completely.

ARE YOU A GOOD CANDIDATE FOR PRK?

Read this page then check with your doctor.

Be sure to ask your doctor any questions that occur to you.

Anyone who is considering PRK should:

- Be 21 years of age or older;
- Have healthy eyes which are free from retinal problems, corneal scars, and any eye disease;
- Have mild to moderate myopia (nearsightedness) within the range of treatment: -1.5 to -7.0 Diopters of correction with low astigmatism of (≤1.5 Diopters);
- Discuss with your doctor's office how you will pay for the treatment and follow-up care since laser correction is not covered by most health insurance policies;
- Be fully informed about the risks and benefits of PRK as compare to other available treatments for myopia.

Speak to your doctor about your reasons for choosing PRK and if you would make a good candidate.

The most common risks associated with PRK include glare, halo, and haze.

Please see page 14 for a detailed list and definitions of all known risks associated with PRK.
It is important to thoroughly discuss all possible risks with your eye doctor.

Indications and Use of the Excimer Laser to Perform Photorefractive Keratectomy (PRK)

Device and Treatment

The PRK treatment has been designed to correct myopia (nearsightedness) by changing the shape of the cornea. This involves the removal of very small amounts of corneal tissue (a few microns at a time).

Indications for Use

The Excimer Laser System is intended for use:

- In PRK treatments for the correction of mild to moderate myopia (nearsightedness) of between -1.5 and -7.0 diopters with </= 1.5 diopters of astigmatism.
- In patients with manifest refractions of within +/- 1.0 D for one year prior to the laser treatment.
- In patients who are 21 years of age or older.
- In patients who have been clearly informed of all alternatives for the correction of their myopia including glasses, contact lenses and other refractive surgeries including radial keratotomy.

Contraindications for Use

- The PRK treatment should not be performed in patients with uncontrolled vascular disease or auto-immune diseases, because it is well known that these patients have difficulty in corneal healing and are more susceptible to corneal melting.
- The PRK treatment should not be performed in women who are pregnant or nursing due to the potential for temporary fluctuation in vision (refraction) with pregnancy.
- The PRK treatment should not be performed in patients with signs of keratoconus since eyes with this condition may have unstable corneas.
- The PRK treatment should not be performed in patients known to have a previous history of keloid formation because their corneal healing response is less predictable.

Warnings

- The PRK treatment should not be performed in patients whose refractive history is unstable since an accurate pre-treatment baseline refraction for the calculation of the desired correction can not be obtained.
- The PRK treatment is not recommended in individuals with Herpes Simplex Virus or Herpes Zoster since cases of herpes reactivation have been reported after use of the excimer laser. Further clinical experience is necessary regarding the use of the 193 nanometer excimer laser wavelength in patients with these conditions.

Precautions

- The PRK treatment should not be performed in patients who are unable to cooperate during the treatment because of the potential difficulty in aligning the laser beam and keeping their eye steady during the treatment.
- Based on available clinical data from Summit Technology's U.S. multicenter clinical investigation patients undergoing Photorefractive Keratectomy who have previously undergone radial keratotomy have been reported to be subject to the following increased risks in comparison to patients undergoing Photorefractive Keratectomy alone:
  - A higher incidence of best spectacle corrected visual acuity loss
  - A higher incidence of best spectacle corrected visual acuity with glare loss
  - An incidence of uncorrected visual acuity loss
  - A higher incidence / severity of anterior stromal reticular haze.

  Physicians should take these factors into consideration when evaluating the potential risk/benefit ratio on an individual patient basis.
- The safety and effectiveness of PRK in patients with a history of glaucoma has not been established.
- The long term safety and effectiveness of PRK has not been established.

Benefit / Risk Analysis

The information from the clinical investigation of the Summit Technology Excimer Laser System provides reasonable assurance of safety and effectiveness. Following is an summary of the known benefits and risks.

Benefits

The PRK clinical treatment, performed with the Summit Technology Excimer Laser System, is effective in reducing myopia of -1.5 to -7.0 diopters when astigmatism is </= 1.5 D. PRK allows:

a. The potential to reduce the patient's overall myopia while also reducing the percentage of time during the day contact lenses or glasses are required or eliminating the need in most patients
b. An alternative to spectacles for some patients intolerant of contact lenses.
c. Some patients who are reluctant to wear spectacles, for occupational and life-style issues, a new option to reduce or correct their myopia.

The PRK clinical treatment performed with the Summit Technology Excimer Laser System, is an alternative means of correcting myopia with a reasonable assurance of safety and effectiveness.

This sheet is not intended to be a substitute for a thorough discussion with your doctor about whether this treatment is right for you.

Please read this sheet carefully and then talk to your doctor.

Indications and Use of the Excimer Laser to Perform Photorefractive Keratectomy (PRK)

Risks:
The following adverse events and complications were reported in conjunction with Summit Technology's PRK Clinical Investigations.

- Immediate/Early Post-treatment Complications
  The following complications have been reported in the first month after PRK. They are associated with the normal post-treatment healing process and include: post-treatment pain (first 24 to 48 hours), corneal swelling, double vision, feeling something is in the eye, shadow images, light sensitivity, tearing and pupil enlargement. These symptoms are temporary and occur in many patients during the early post-treatment period.

- Long Term Post-treatment Adverse Events
  The following is a list of the adverse events reported during Summit Technology's PRK U.S. clinical trials that occurred in more than 1.0% of patients: Anterior Stromal Reticular Haze, Glare, Halo, Loss of Best Spectacle Corrected Visual Acuity, Improper Correction, Induced Astigmatism, IOP Elevation, and Night Vision Difficulties.

- Anterior Stromal Reticular Haze: Loss of perfect clarity of the cornea, usually not affecting vision.

- Corneal Scarring: Cloudiness or haze of the cornea, usually severe enough to affect vision.

- Glare: Glare, especially from bright lights may be seen particularly in the early months after treatment.

- Halo: Halo or hazy rings surrounding bright lights may be seen particularly at night after treatment.

- Loss of Best Spectacle Corrected Acuity: A decrease in best corrected visual acuity with glasses.

- Improper Correction: It is possible that the treatment could result in undercorrection, where some degrees of myopia (nearsightedness) may occur requiring the use of glasses or contact lenses. Improper correction may also result in overcorrection (or hyperopia) which may or may not require the use of glasses or contact lenses. It is possible that Improper Correction may increase dependence on reading glasses or require the use of reading glasses at an earlier age.

- Induced Regular/Irregular Astigmatism: A change in astigmatism that may then distort vision and may or may not require patients to continue to wear glasses or contact lenses.

- IOP Elevation: An increase in the intraocular (inner eye) pressure due to usage of post-treatment medications may occur which is usually resolved by drug therapy or discontinuation of post-treatment medication.

- Lens Opacity/Cataract: Opacity or cloudiness of the lens that may prevent a clear image from forming on the retina may occur. Cataracts may be caused by the use of post-treatment medication.

- Night Vision Difficulties: Tasks that are performed without difficulty during the day are performed with visual difficulty in low light or night time conditions.

The following adverse events occurred long term post-treatment in the PRK clinical investigations in less than 1% of patients: blurred vision, corneal epithelial defect, corneal scarring, corneal ulceration/infection, dryness of the eye, feeling something is in the eye, shadow images, corneal deposits, inflammation of the iris, irregular astigmatism, itching, double vision, patient discomfort, light sensitivity, drooping of the eyelid, reading difficulty and corneal inflammation.

This sheet is not intended to be a substitute for a thorough discussion with your doctor about whether this treatment is right for you.

Please read this sheet carefully and then talk to your doctor.

Please read the Informed Consent Document before signing it.

QUESTIONS TO ASK YOUR DOCTOR

- What are the other options for correction myopia?
- Will I have to limit my activities after the treatment ? If yes, for how long ?
- What are the benefits of PRK for my level of vision ?
- If PRK does not correct my vision, could my vision be worse than before ? Could my vision gradually decline ?
- Will I be able to wear contact lenses if I still need them after PRK?
- How is PRK likely to affect my need to use glasses or contact lenses when I get old?
- Will my cornea heal differently if I injure it after having PRK?
- If I have both my eyes done, what vision problems will I experience between the treatment of my first eye and second eye?
- What vision problems will I experience if I have PRK only in one eye?

PATIENT ASSISTANCE INFORMATION

Primary Eye Doctor

Name: _____

Address: _____

_____

Telephone No: _____

Treatment Doctor

Name: _____

Address: _____

_____

Telephone No: _____

Treatment Location

Name: _____

Address: _____

_____

Telephone No: _____

Laser Manufacturer

Summit Technology, Inc.
21 Hickory Drive
Waltham, Massachusetts 02154 USA
Phone: 617-890-1234
Fax: 617-890-0313

Attachment C

SUMMIT TECHNOLOGY, INC.

Apex EXCIMER LASER SYSTEM
PHYSICIAN INFORMATION

PHOTOREFRACTIVE KERATECTOMY

For Mild to Moderate Myopia of -1.5 D to -7.0 D; with Low Astigmatism ≤ 1.5D

CAUTION: RESTRICTED DEVICE: U.S. Federal law restricts this device to sale, distribution, and use by or on the order of a practitioner. U.S. Federal law restricts the use of this device to practitioners who have been trained in laser refractive surgery including laser system calibration and operation. U.S. Federal law restricts the use of this device to practitioners trained in the medical management and surgical treatment of the cornea. This device is not for use in mobile clinics.

Be certain that all patients are advised of the risks inherent in the use of this medical device and in the outcomes of Photorefractive Keratectomy before applying it to their person!

All patients must have the opportunity to read and understand the Patient Information Brochure.

All patients must have the opportunity to read, understand and sign an Informed Consent Document for this treatment.

Improper use of this device may result in physical harm to a patient! If in doubt about the correct way to operate this medical device, seek help! Pay attention to all warnings, cautions and contraindications in the following physician information document and in the Laser System User's Manual.

A. BACKGROUND:

Summit Technology's Apex Excimer Laser System has been designed to perform Photorefractive Keratectomy (PRK) clinical treatments. This physician information document has been developed based on Summit Technology's multicenter clinical studies conducted within the United States to provide you, the physician, with recommendations concerning the use of the Apex Laser System for the Photorefractive Keratectomy technique. Please refer to the Apex Laser System User's Manual for additional information regarding the operation of the Apex Laser System.

The Summit Technology education program should be completed by physicians **prior** to performing their first Photorefractive Keratectomy clinical treatments. The physician and staff should read the Apex User's Manual and the Photorefractive Keratectomy Physician Information document thoroughly in preparation for the first clinical treatments. In addition, Summit Technology strongly recommends that physicians consult peer review journal publications regarding this refractive surgical technique.

Note: The Apex Excimer Laser System is not intended to correct high myopia (nearsightedness > -7.0 D), astigmatism, or farsightedness. Also it is not intended to correct nearsightedness of less than -7.0D if the accompanying astigmatism is > 1.5 D. It is not to be used in procedures other than PRK as described in the approved User's Manual.

B. INDICATIONS FOR USE:

The Apex Excimer Laser System is intended for use:

1. In Photorefractive Keratectomy treatments for the correction of mild to moderate myopia (nearsightedness) of between -1.5 to -7.0 diopters in patients with low astigmatism (≤ 1.5 diopters).

2. In patients with a manifest refraction within +/- 1 diopter for one year prior to the laser treatment.

3. In patients who are 21 years of age or older.

C. CONTRAINDICATIONS FOR USE:

1. The Photorefractive Keratectomy treatment should **not** be performed in patients with uncontrolled vascular disease or auto-immune diseases because it is well known that these patients have difficulty in corneal healing and are more susceptible to corneal melting.

2. The Photorefractive Keratectomy treatment should **not** be performed in women who are pregnant or nursing due to the potential for temporary fluctuation in refraction with pregnancy.

3. The Photorefractive Keratectomy treatment should **not** be performed in patients with signs of keratoconus since eyes with this condition may have unstable corneas.

4. The Photorefractive Keratectomy treatment should **not** be performed in patients known to have a previous history of keloid formation because their corneal healing response is less predictable.

D. WARNINGS:

The Photorefractive Keratectomy treatment should **not** be performed in patients whose refractive history is unstable since an accurate pretreatment baseline refraction for the calculation of the desired correction can **not** be obtained.

The Photorefractive Keratectomy treatment is **not** recommended in individuals with Herpes Simplex Virus or Herpes Zoster since cases of herpes reactivation have been reported after use of the excimer laser. Further clinical experience is necessary regarding the use of the 193 nanometer excimer laser wavelength in patients with these conditions.

E. PRECAUTIONS:

1. The Photorefractive Keratectomy treatment should **not** be performed in patients who are **unable** to cooperate during the treatment because of the potential difficulty in aligning the laser beam and keeping their eye steady during the treatment.

2. Prior to initiating epithelium removal the physician should arm and test the OmniMed Laser to ensure that the laser is ready to deliver laser energy.

3. Based on available clinical data from Summit Technology's U.S. multicenter clinical investigation patients undergoing Photorefractive Keratectomy who have previously undergone radial keratotomy have been reported to be subject to the following increased risks in comparison to patients undergoing Photorefractive Keratectomy alone;

   a. A higher incidence of best spectacle corrected visual acuity loss

   b. A higher incidence of best spectacle corrected visual acuity with glare loss

   c. An incidence of uncorrected visual acuity loss

d. A higher incidence/severity of anterior stromal reticular haze.

See the clinical experience section in this physician information document. Physicians should take these factors into consideration when evaluating the potential risk/benefit ratio on an individual patient basis.

4. The safety and efficacy of Photorefractive Keratectomy in patients with a history of glaucoma has not been established.

5. The long term safety and effectiveness of Photorefractive Keratectomy has not been established.

F. ADVERSE EVENTS:

The following adverse events and complications were reported in conjunction with Summit Technology's Photorefractive Keratectomy Clinical Investigations.

Immediate/Early Post Treatment Complications

The following complications have been reported prior to the one month exam. They are primarily associated with post treatment re-epithelialization and early post treatment healing and include: post treatment pain (first 24 to 48 hours), corneal edema, monocular diplopia, foreign body sensations, ghost images, photophobia, tearing and anisocoria. These symptoms are temporary and occur in many patients during the early post treatment period.

Long Term Post Treatment Adverse Events

Provided below is a description of the incidence of the adverse events reported during Summit Technology's multicenter clinical investigation utilizing a 6.0 mm treatment zone. The adverse events are reported by rate of incidence.

Adverse events at 6 months after treatment are reported below.

Adverse Event	6 Month Exam Incidence
Anterior Stromal Reticular Haze	63.0% Total 53.4% Trace 7.3% Mild 2.3% Moderate 0.0% Marked
Halo	10.0% Total 8.5% Trace 0.9% Mild 0.3% Moderate 0.3% Marked

Glare	10.0% Total 8.2% Trace 0.9% Mild 0.9% Moderate 0.0% Marked
Loss of Best Spectacle Corrected Vision	6.8% lost 2 or more lines (5.6% had a BCVA of 20/25 or better @ 6 month exam)
IOP elevation	1.8% (>5 mmHg increase from preop)

Adverse events at 1 year after treatment are reported below.

Adverse Event	1 Year Exam Incidence
Anterior Stromal Reticular Haze	43.9% Total 43.9% Trace 0.0% Mild 0.0% Moderate 0.0% Marked
Halo	2.4% Total 2.4% Trace 0.0% Mild 0.0% Moderate 0.03% Marked
Glare	2.4% Total 0.0% Trace 0.09% Mild 0.0% Moderate 0.0% Marked
Loss of Best Spectacle Corrected Vision	1.2% lost 2 or more lines (100% had a BCVA of 20/20 or better @ the 1 Year exam)

Adverse Events Reported at a Rate of Less than 1.0%

The following adverse events occurred at any exam in the PRK clinical investigations at a rate of less than 1%: blurred vision, cataract, corneal epithelial defect, corneal scarring, corneal ulceration/infection, diffuse nebulae, dryness, foreign body sensations, ghost images, guttata, iritis, irregular astigmatism, itching,

lens opacity, microcysts, monocular diplopia, patient discomfort, photophobia, ptosis, reading difficulty and superficial punctate keratitis.

One patient had a non-procedure related case of cystoid macular edema and a macular hole. One patient had macular degeneration and peripheral choroidal scar changes secondary to myopia.

The following historical information from Summit Technology's earlier multicenter Phase III Clinical Investigation using a 4.5mm and 5.0mm treatment zone is being provided only as background information.

The adverse events are reported by rate of incidence. Adverse events at one year and three years after treatment are reported below.

Adverse Event	1 Year Exam Incidence
Anterior Stromal Reticular Haze	37.9% Total 27.2% Trace 6.7% Mild 4.0% Moderate 0.0% Marked
Halo	11.0% Total 7.3% Trace 1.8% Mild 1.7% Moderate 0.2% Marked
Glare	10.6% Total 6.2% Trace 2.7% Mild 1.0% Moderate 0.7% Marked
Loss of Best Spectacle Corrected Vision	2.9% lost 2 or more lines (2.4% had a BCVA of 20/25 or better @ 1 year exam)
Induced Astigmatism	1.7% > 1 Diopter
IOP elevation	1.5% (>5 mmHg increase from preop)

Adverse Event	3 Year Exam Incidence
Anterior Stromal Reticular Haze	20.0% Total 16.2% Trace 2.2% Mild 1.1% Moderate 0.5% Marked

Glare	8.3% Total 3.8% Trace 2.4% Mild 1.6% Moderate 0.5% Marked
Halo	7.5% Total 4.2% Trace 1.6% Mild 1.3% Moderate 0.4% Marked
Loss of Best Spectacle Corrected Vision	3.8% lost 2 or more lines (2.6% had a BCVA of 20/25 or better @ 3 year exam)
IOP elevation	3.1% (>5 mmHg increase from preop)
Lens Opacity/Cataract	1.8%
Night Vision Difficulty	1.3% Total 0.7% Trace 0.2% Mild 0.4% Moderate 0.0% Marked
Induced Astigmatism	1.1% > 1 Diopter

G. CLINICAL EXPERIENCE:

The following reports the clinical experience with Summit Technology's multicenter Clinical Investigation which involved the treatment of 394 eyes in 300 patients with a 6.0mm treatment zone.

Re-epithelialization: Occurred in 95.4% of eyes within 72 hours; 100% of eyes within 1 week

6 Months:

•Uncorrected visual acuity: 20/20 or better	66.0%
•Uncorrected visual acuity: 20/40 or better	95.0%
•Predictability: % of eyes within +/- 0.5 D	64.8%
•Predictability: % of eyes within +/- 1.0 D	89.4%
•Success*	91.8%

1 Year:

•Uncorrected visual acuity: 20/20 or better	80.5%
•Uncorrected visual acuity: 20/40 or better	98.8%
•Predictability: % of eyes within +/- 0.5 D	51.2%
•Predictability: % of eyes within +/- 1.0 D	86.6%
•Success*	97.6%

*For this clinical investigation success was defined as an uncorrected visual acuity of 20/40 or better. Any patients who met this criteria but had a loss of best spectacle corrected visual acuity of more than 1 line and a best spectacle corrected visual acuity of 20/25 or worse were considered failures. Also any patients with major visual/ocular complications were considered failures.

The following additional information from Summit Technology's PRK after Radial Keratotomy clinical investigation is provided. This clinical investigation included a PRK treatment on 200 eyes in 200 patients in which 97.5% had a previous radial keratotomy and 2.5% of eyes had previous cataract surgery. Within this population, the following clinical data was reported

	1 Year	2 Years
•Loss of best spectacle corrected visual acuity	27.3%	29.4%
•Loss of uncorrected visual acuity	5.5%	7.6%
•Uncorrected visual acuity: 20/40 or better	73.5%	76.7%
•Corneal haze or scarring greater than mild	10.2%	11.6%

The following historical information from Summit Technology's earlier multicenter Phase III Clinical Investigation using a 4.5mm and 5.0mm treatment zone is being provided only as background information.

The following reports the clinical experience with Summit Technology's Phase III Photorefractive Keratectomy Clinical Investigation which involved the treatment of 701 eyes in 701 patients with a 4.5 mm and 5.0 mm treatment zone.

Re-epithelialization: Occurred in 90.8% of eyes within 72 hours; 100% of eyes within 1 week

1 year outcome:	
•Uncorrected visual acuity: 20/40 or better	91.0%
•Predictability: % of eyes within +/- 1.0 D	76.0%
•Success*	90.2%

3 year outcome:	
•Uncorrected visual acuity: 20/40 or better	90.5%
•Predictability: % of eyes within +/- 1.0 D	80.9%
•Success*	89.6%

*For this clinical investigation success was defined as an uncorrected visual acuity of 20/40 or better. Any patients who met this criteria but had a loss of best spectacle corrected visual acuity of more than 1 line and a best spectacle corrected visual acuity of 20/25 or worse were considered failures. Also any patients with major visual/ocular complications were considered failures.

Post Treatment Protocol

All eyes treated in Summit Technology's clinical investigation were patched for the first night after treatment. Antibiotic ointment was instilled up to four times per day until re-epithelialization was complete. After re-epithelialization

fluorometholone alcohol 0.1% was instilled four times per day for one month, then tapered and discontinued by the end of the third month.

H. BENEFIT/RISK ANALYSIS:

The information from the clinical investigation of Summit Technology's Excimer Laser System provides reasonable assurance of safety and efficacy. Following is an assessment of benefits and risks:

Benefit Analysis:

1. The PRK clinical treatment, performed with the Summit Technology Excimer Laser System, is effective in reducing myopia of -1.5 to -7.0 diopters when astigmatism is ≤ 1.5 diopters. PRK allows:

   a. The potential to reduce the patient's overall myopia while also reducing the percentage of the time during the day contact lenses or glasses are required or eliminating the need in most patients.

   b. An alternative to spectacles for some patients intolerant of contact lenses.

   c. Some patients who are reluctant to wear spectacles, for reasons such as occupational and lifestyle issues, a new option to reduce or correct their myopia.

2. The Photorefractive Keratectomy clinical treatment, performed with the Summit Technology Excimer Laser System, is an alternative means of correcting myopia with a reasonable assurance of safety and effectiveness.

Risk Analysis:

1. The risks reported to date in conjunction with Photorefractive Keratectomy, performed with the Summit Technology laser system, include:
   a. Anterior stromal reticular haze
   b. Lens opacity/cataract potentially due to post treatment medications
   c Corneal scarring
   d. Glare
   e. Halo
   f. Improper correction (undercorrection/overcorrection)
   g. Induced astigmatism
   h. IOP increase due to post treatment medications
   i. Loss of best spectacle corrected visual acuity
   j. Night vision difficulties

Summary:
In conclusion, taking into consideration the incidence of these risks compared to the benefits outlined above, Photorefractive Keratectomy performed with Summit Technology's Excimer Laser System represents a clinically acceptable alternative for the correction of mild to moderate myopia.

I. INFORMATION FOR USE:

1. Ancillary Equipment:

The following items will be needed when performing Photorefractive Keratectomy treatments with the Summit Technology OmniMed Excimer Laser System:

a. Sterile eye speculum
b. Gauze pads and tape
c. Carboxypropyl Methylcellulose 1.0%
d. Agent to constrict the pupil
e. Small ophthalmic sponges
f. Topical anesthetic
g. Slit Lamp available near the OmniMed Laser System
h. Materials to perform Photorefractive Keratectomy Excimer Laser Beam Profile and Alignment Test
i. Patient Bed or Chair capable of performing fine movements (comparable to the chair supplied by Summit Technology)
j. Standard instrument for mechanical epithelium removal
k. A 7.0mm Optical Zone marker.

2. OmniMed Laser System Parameters:

Ablation Rate:	System set at 0.25 microns/pulse.
Treatment Zone Diameter:	System set at 6.0mm
Diopters of Intended Correction:	Input by System User at 0.1D intervals, -1.5 to -7.0 Diopters Intended Correction based upon spherical equivalent of the Manifest Refraction (at the corneal plane)
Pulse Energy Density:	System set at 180 mJ/cm^2
Repetition Rate:	System set at 10 Hz

3. Directions: Photorefractive Keratectomy Clinical Treatment

PRETREATMENT TECHNIQUE

Laser Preparation:

a. Turn on the OmniMed Laser System and allow the system to warm up. Refer to the OmniMed Laser System User's Manual for start up and operating instructions regarding your laser system.

b. If it is the first treatment of the day, the Beam Profile and Alignment Test (refer to Chapter 5, Section 5.3 of the Laser System User's Manual) should be performed in accordance with Summit Technology's Photorefractive Keratectomy Beam Profile and Alignment Test Instructions.

If your test results meet the criteria specified in the Beam Profile and Alignment Test Instructions, proceed with the Photorefractive Keratectomy clinical treatment. If your test results do **not** meet the test criteria; (1) contact Summit's Customer Service Department immediately or your Summit Service Representative and (2) do **not** use the laser on patients because of the potential for improper results.

c. Apply topical anesthetic to the operative eye.

d. Constrict the patient's pupil.

e. Place the patient on the patient bed/chair with the operative eye centered under the OmniMed Laser System delivery system.

f. Topical anesthetic, may be given to the eye **not** to be treated to relax the reflexes.

g. Patch the patient's eye **not** scheduled for treatment. A patch may also be placed on the side of the head next to the treated eye to collect excess fluid from the eye undergoing the laser treatment.

h. Place the speculum in the eye to be treated. Reapply anesthetic drops to the eye to be treated until epithelial removal has been initiated, to ensure adequate anesthesia. Additional drops may be applied after laser energy delivery has been completed.

Patient Training:

Patient Training allows the patient to become familiar with fixating their eye, and with the light, noise and smell produced by the laser system during laser energy delivery. The patient should be made aware that there is no pain associated with the laser beam striking the cornea.

Ask the patient to keep their eye to be treated focused on the green fixation target inside the red fixation ring in the laser downtube. The patient should be aligned so that the diverging helium neon aiming beams appear at 3 and 9 o'clock equally spaced from the center of the pupil. On the anterior surface of the cornea, the helium neon beams should appear as one spot centered over the pupil.

NOTE: The HeNe aiming beams mark the image plane of the excimer beam. The desired vertical area of effect is located where the two HeNe beams appear as one spot. In order to assure that the patient is not exposed to hazardous levels of laser energy, the HeNe beams should not be fired at the patient continuously for longer than 6 1/2 minutes.

It is recommended that two to three training sessions be conducted with each patient.

NOTE: Do **not** lean on the operating microscope or the Excimer Laser System during laser energy delivery.

Training Session A:

a. Choose Patient Training A.
b. Apply Methylcellulose to the eye and ensure that the entire cornea is covered. This layer of liquid will inhibit laser ablation of the patient's cornea.
c. Arm and fire the laser. Closely observe the patient's ability to fixate during laser delivery.
d. If the sound of the ablation changes, stop lasing as you may be ablating epithelium.
e. Repeat this treatment 2 to 3 times, as necessary, until the patient fixates adequately during laser delivery and is comfortable with what will happen during the actual laser treatment.

NOTE: If the patient can **not** fixate after two to three training sessions the physician may reschedule the clinical treatment.

Training Session B:

a. Choose Patient Training B.
b. Using a small ophthalmic sponge, remove **all** remaining Methylcellulose from the entire eye (and around the speculum).

The final patient training exercise should be performed on dry epithelium. Delivering laser energy to the dry epithelium will produce a circular ablation on the patient's epithelium. This final training session allows the physician to double check that the patient is fixating properly. This final training session also familiarizes the patient with the noise, smell and feel of the laser ablating corneal tissue vs. Methylcellulose.

NOTE: Any remaining Methylcellulose will inhibit laser ablation of the epithelium. Carefully remove all traces of these liquids until the epithelium is dry.

c. Check to make sure that the HeNe beams are aligned and then arm and fire the laser. Closely observe the ability of the patient to fixate during laser delivery. This is the most critical training session since this will most closely mimic the actual treatment. The patient should fixate directly on the fixation target inside the laser downtube and ensure that the target is at its brightest.

NOTE: During Patient Training on dry epithelium no more than 25 pulses should be delivered.

PHOTOREFRACTIVE KERATECTOMY TECHNIQUE:

a. Select the Photorefractive Keratectomy Treatment on the laser system keypad.

b. Enter the desired diopter correction into your OmniMed Laser System. Review the entered attempted correction presented on the display and press ENTER to confirm. Arm and test the laser **BEFORE** beginning epithelium removal to ensure that the laser will come out of the test mode allowing delivery of laser energy.

If the laser remains armed for more than 10 minutes without firing, the system will automatically disarm and you will need to clear the error message, then rearm and retest the system.

c. Reposition the patient's eye under the laser. Mark the intended ablation zone using a 7.0mm optical zone marker.

d. Reposition the patient's eye under the laser. Epithelium removal should occur with the patient under the laser to minimize the time period between epithelium removal and laser ablation. The goal is to remove the epithelium approximately 1 mm beyond the intended ablation zone, (ring indicated by optical zone marker). Epithelium removal should be completed with external illumination on high.

NOTE: Do **not** use alcohol, cocaine or any other substances to remove the epithelium. Application of these substances may influence the ablation rate of the excimer laser energy and could lead to a poor treatment result.

e. Mechanically remove the epithelium in the center of the cornea using a standard instrument, designed for epithelium removal. Take great care not to damage Bowman's layer. The area of epithelium removed should be slightly larger than the area to be treated. Remove the epithelium in a circumferential manner, starting at the outer diameter and moving towards the center. Clean Bowman's layer very carefully to remove all debris with a small ophthalmic sponge or other dry sponge.

NOTE: Epithelium removal for all PRK treatments (except reablations) should be performed mechanically.

f. Once the epithelium has been removed, apply 1 drop of Methylcellulose to a small ophthalmic sponge and clean Bowman's layer thoroughly. Continue cleaning Bowman's layer with a small ophthalmic sponge soaked in anesthetic. The Methylcellulose is used to smooth out any surface irregularities commonly present in Bowman's layer. The cleaning should continue until **all** Methylcellulose has been removed.

NOTE: It is important that **all** epithelium is removed prior to performing the Photorefractive Keratectomy treatment. Histology has shown that small particles of epithelium may remain even when they can **not** be seen through the operating microscope.

NOTE: **No** additional drops should be placed on Bowman's layer once the cleaning procedure has been completed. Application of liquids at this time will adversely impact the desired clinical result.

g. Ask the patient to continue fixating on the green fixation light in the red fixation ring located in the laser downtube. The patient should be aligned so that the diverging HeNe's appear at 3 and 9 o'clock equally spaced on the iris from the center of the pupil. On the anterior surface of the cornea, the HeNe beams should appear as one spot centered over the pupil. Alignment of the eye with the HeNe beams may be facilitated by reducing external illumination

NOTE: During laser energy delivery, the physician should concentrate on the position of the HeNe beams on the iris. The physician should **not** be distracted by watching the laser energy impacting the cornea.

h. Press the foot pedal until the laser stops firing. The total number of laser pulses for the desired refractive correction should be delivered in one continuous application, unless the patient's eye moves during the treatment.

i. The physician should observe the treatment through the operating microscope. While the laser is firing, the physician should closely observe the fixation of the patient's eye. If the patient's eye moves during the treatment, firing of the laser should be stopped. The patient should be instructed to re-fixate and the treatment resumed. The laser system will keep track of how many pulses have been delivered and how many are remaining.

NOTE: As stated previously, during laser energy delivery, the physician should concentrate on the position of the HeNe's on the iris. The physician should **not** be distracted by watching the laser energy impacting the cornea.

NOTE: Do **not** lean on the operating microscope or the Excimer Laser System during laser delivery.

POST TREATMENT TECHNIQUE:

a. The patient should be moved to the slit lamp to allow the physician to examine the treated eye after the laser treatment. If the edges of remaining epithelium surrounding the laser ablation have been folded back or are overlapping they should be smoothed back into their original position to facilitate re-epithelialization.

b. Remove the eye speculum.

c. All eyes treated in Summit Technology's clinical investigation were patched for the first night after treatment.

d. Most patients will experience post treatment pain for the first 24-48 hours after the PRK treatment. Post treatment pain medication may be prescribed at the physician's discretion.

e. In reference to post treatment medications during both the immediate post treatment period and for the first several months

after the treatment, the physician should refer to the steroid protocols in the Clinical Experience section of this physician information document and the existing peer review literature to determine the appropriate course of action.

J. REABLATION TECHNIQUE:

1. Background:
A small percentage of PRK patients will experience scarring (the presence of subepithelial haze to a degree that interferes with vision) and/or undercorrection. This may be treated by subjecting the eye to a retreatment. During this treatment, the eye to be retreated is exposed a second time to excimer laser treatment in order to remove scar tissue and/or correct residual myopia.

2. DIRECTIONS: Photorefractive Keratectomy Reablation Technique:

a. Indications for Use
The Summit Technology Excimer Laser System Reablation Technique is indicated for performing the Photorefractive Keratectomy treatment to remove scar tissue and/or to correct residual myopia.

b. Contraindications for Use
The Summit Technology Excimer Laser System should **not** be used to remove scar tissue (haze) that does not interfere with vision, or to perform a reablation treatment to correct a refractive undercorrection of less than 1.0 diopter.

c. Warnings and Precautions

1. The interval between the first Photorefractive Keratectomy treatment and a reablation treatment performed on the same eye should be **no** less than 6 months, to allow the eye's refraction to stabilize before reablation.

2. Patients should have an undercorrection refractive error of greater than or equal to -1.0 diopter in the eye scheduled for a reablation treatment (attempted corrections below this level have not been evaluated).

3. Patients undergoing a reablation treatment for an undercorrection refractive error of greater than or equal to -1.0 diopter should have had a stable refraction in the eye to be retreated for at least 3 months. This is necessary to

ensure that the attempted correction for the reablation treatment accurately reflects the level of necessary correction.

d. Potential Adverse Events:
Potential adverse effects and complications for the reablation treatment are similar to those for the Photorefractive Keratectomy treatment described above, and may be reviewed under "Adverse Events" in Section F.

e. Directions for Use: Reablation Clinical Procedure:

PREOPERATIVE TECHNIQUE:
The "Laser Preparation" procedure for the reablation treatment is exactly the same as for the Photorefractive Keratectomy treatment described previously.

NOTE: Because the laser is being used to remove the epithelium, the "Patient Training" procedure outlined in the Photorefractive Keratectomy information document should be **omitted** during retreatment techniques.

REABLATION TECHNIQUE:
The technique used in the reablation treatment is similar to the Photorefractive Keratectomy treatment described above. However, the exception is that in a reablation treatment, the epithelium should be removed from the eye to be retreated with the Excimer Laser System, and not mechanically removed with a blade.

a. To begin the removal of epithelium, select a phototherapeutic keratectomy treatment, enter a 6.5mm treatment zone and set the laser for 400 pulses. Arm and Test the laser.

NOTE: The laser should be used to remove the epithelium only during reablations. Epithelium removal for all initial PRK's should be performed mechanically.

b. Adjust the placement of the patient until the HeNe aiming beams merge on the anterior surface of the cornea centered over the pupil.

c. Instruct the patient to fixate on the green fixation light inside the red fixation ring in the laser system downtube. The eye to be treated should be aligned so that the diverging

HeNe aiming beams appear at 3 and 9 o'clock equally spaced from the center of the pupil.

NOTE: In a darkened operating room, the area of treatment will be apparent by a fluorescent circular area on the surface of the cornea when laser delivery begins. The fluorescence is bluish when epithelium is being ablated, but the blue color disappears when the laser beam reaches stroma or scar tissue.

d. Begin laser delivery by stepping on the laser system footswitch.

e. Stop the treatment when the dark spots at the periphery of the treatment area form a confluent dark ring around a central bluish area of remaining epithelium.

f. A standard Photorefractive Keratectomy treatment may then be performed. The amount of correction for a retreatment is calculated by increasing the manifest refraction spherical equivalent by 1 diopter. The additional diopter is necessary to account for the remaining epithelium left in the center of the optical zone.

Example: In a retreatment, an attempted correction of -2.5 diopters would require an entry of -3.5 diopters into the laser.

g. Upon completion of the Photorefractive Keratectomy treatment, do not remove the speculum. Have the patient move to the slit lamp. Inspect the ablated area for residual scar tissue or haze. If scar tissue or haze is still present, an additional 10 to 20 laser pulses, using a phototherapeutic keratectomy treatment and the same treatment zone used in the reablation PRK, may be delivered.

POST TREATMENT TECHNIQUE:

After treatment, follow the Post Treatment Technique detailed previously