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SUMMARY OF SAFETY AND EFFECTIVENESS DATA

AUG 3 0 1999

I. GENERAL INFORMATION

Device Generic Name: ICRS® (Intrastromal Corneal Ring Segments)

Device Trade Name: KeraVision Intacs™

Applicant's Name and Address: KeraVision, Inc.
48630 Milmont Drive
Fremont, CA 94538-7353

Premarket Approval Application (PMA) Number: P980031

Dates of Panel Recommendation: January 12, 1999

Dates of Good Manufacturing Practice Inspection: November 24, 1998 (KeraVision), October 7, 1998 (Ocularvision), and March 1, 1999 (Quality Sterilization Services)

Date of Notice of Approval to Applicant: AP[illegible]9

II. INDICATIONS FOR USE

The KeraVision Intacs™, herein called the Intacs™, are intended for the reduction or elimination of mild myopia (-1.00 to -3.00 diopters spherical equivalent at the spectacle plane) in patients:

- who are 21 years of age or older;
- with documented stability of refraction as demonstrated by a change of less than or equal to 0.50 D for at least 12 months prior to the preoperative examination; and
- where the astigmatic component is + 1.00 diopter or less.

III. CONTRAINDICATIONS

Intacs™ are contraindicated:

- in patients with collagen vascular, autoimmune or immunodeficiency diseases;
- in pregnant or nursing women;
- in the presence of ocular conditions, such as keratoconus, recurrent corneal erosion syndrome or corneal dystrophy, that may predispose the patient to future complications; or

- in patients who are taking one or more of the following medications: isotretinoin (Accutane[1]); amiodarone (Cordarone[2]); sumitriptan (Imitrex[3]).

IV. WARNINGS AND PRECAUTIONS

The following warnings and precautions can be found in the Intacs™ labeling (Attachment 1).

Warnings

Use of the Vacuum Centering Guide subjects the eye to increased intraocular pressure. **Continuous application of vacuum should be limited to 3 minutes or less and to no more than 750 mBar.** If it is necessary to reapply the Vacuum Centering Guide, it is recommended that the eye be perfused for 5 minutes before reestablishing suction.

Intacs™ are not recommended in patients with systemic diseases likely to affect wound healing, such as insulin-dependent diabetes or severe atopic disease.

Intacs™ are not recommended in patients with a history of ophthalmic *Herpes simplex* or *Herpes zoster*.

Intacs™ are intended for single use only; do not reuse or resterilize.

Precautions

Patients who receive the 0.35 mm Intacs™ may experience a reduced outcome as compared to patients who receive the 0.25 mm or 0.30 mm Intacs™. Additionally, there may be an increased removal rate for 0.35 mm patients due to dissatisfaction with their outcomes.

Patients with myopia of -1.00 diopter (D) are more likely to be overcorrected.

The long-term effect of Intacs™ on endothelial cell density has not been established.

A temporary decrease in central corneal sensation has been noted in some patients. No clinical consequences were demonstrated within the context of the U.S. clinical trials.

Some patients with large dilated pupil diameters (≥ 7.0 mm) are predisposed to low light visual symptoms postoperatively and should be appropriately advised.

Under mesopic conditions, patients may experience some loss in contrast sensitivity at low spatial frequencies (1.5 cycles per degree).

The safety and effectiveness of alternate refractive procedures following the removal of Intacs™ have not been established.

The safety and effectiveness of Intacs™ have not been established:

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[1] Accutane® is a registered trademark of Roche Pharmaceuticals.
[2] Cordarone®is a registered trademark of Wyeth-Ayerst Laboratories.
[3] Imitrex® is a registered trademark of Glaxo-Wellcome, Inc.

- in patients with progressive myopia or astigmatism, nuclear sclerosis or other crystalline lens opacity, corneal abnormality, or previous corneal surgery or trauma;
- for patients under 21 years of age;
- for corneas that are steeper than 46 D or flatter than 40 D;
- for corneas with a central thickness less than 480 microns or peripheral thickness less than 570 microns;
- in patients with greater than -3.50 D of myopia or with astigmatism greater than +1.00 D; or
- in long-term use.

V. DEVICE DESCRIPTION

Intacs™

The Intacs™ are designed to reshape the anterior surface of the cornea for the reduction or elimination of mild myopia (-1.00 to -3.00 D). The device consists of two arc-shaped segments made of polymethylmethacrylate (PMMA) (Figure 1). The Intacs™ are surgically inserted through a radial incision and are placed at two-thirds depth in the peripheral corneal stroma. The Intacs™ correct myopia by raising the peripheral cornea and indirectly flattening the central cornea.

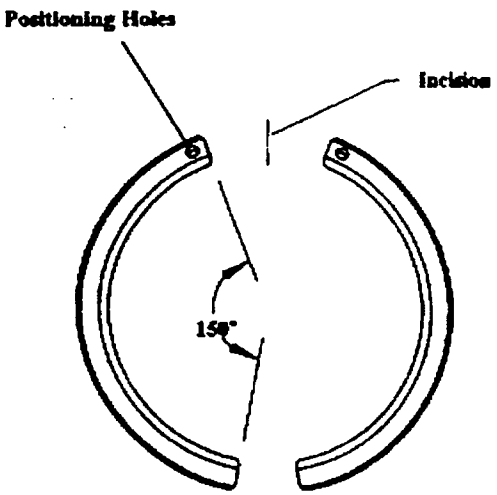

Figure 1 KeraVision Intacs™

The Intacs™ have a fixed outer diameter of 8.10 mm, a width of 0.8 mm and are available in three thicknesses: 0.25 mm, 0.30 mm, and 0.35 mm. The amount of correction achieved is directly related to the thickness of the segments; the thicker Intacts™ are used for higher amounts of correction. The predicted nominal correction and recommended prescribing range for each Intacs™ thickness are based on data from the U.S. clinical trial (Table 1). The Intacs™ have been designed to be removed or replaced.

Table 1

Intacs™ Thickness	Predicted Nominal Correction	Recommended Prescribing Range
0.25 mm	-1.30 D	-1.00 to -1.625 D
0.30 mm	-2.00 D	-1.75 to -2.25 D
0.35 mm	-2.70 D	-2.375 to -3.00 D

Surgical Instruments

KeraVision has developed a set of surgical instruments to be used in the Intacs™ procedure. They include: corneal thickness gauges, glides, incision and placement marker, pocketing hook, pocketing lever, ring forceps, stromal spreader, vacuum centering guide with vacuum system and clockwise and counterclockwise dissectors. These instruments have been evaluated through the premarket notification (510(k)) process.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

Conventional procedures used in the treatment of mild myopia include spectacles, contact lenses, radial keratotomy (RK), photorefractive keratectomy (PRK), and laser in situ keratomileusis (LASIK).

VII. MARKETING HISTORY

The Intacs™ have been marketed in the European Communities and other countries recognizing the CE mark since December 2, 1996. The Intacs™ have also been marketed in Canada since June 11, 1998. The Intacs™ have not been withdrawn from marketing for any reason related to the safety or effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

A total of 452 subjects were enrolled in the U.S. Phase II and Phase III clinical trials to determine the safety of Intacs™. In the 452 initial surgical attempts, 447 implants were successfully placed. Of the five subjects who did not have successful initial surgeries, two subjects had the Intacs™ successfully implanted in the contralateral eye (for a total of 449 implants). A total of 454 surgical attempts (see Figure 2 in section X. Summary of Clinical Studies) were considered in the safety evaluation described below. Subjects with a successful initial surgery who later had the Intacs™ implanted in the fellow eye had comparable rates of adverse events and complications.

The study protocols defined adverse events as those observations that if left untreated or undetected, were considered to be serious and potentially sight-threatening or could have permanent sequelae associated with them. Similarly, the protocol defined complications as those findings that had the potential to be clinically significant but were likely to clear without permanent sequelae and not result in injury to the eye.

Adverse Events

Five adverse events occurred in five subjects in the U.S. clinical trial, resulting in an overall incidence rate of 1.1% (Table 2). All five subjects recovered without clinically meaningful sequelae.

Table 2 - Adverse Events

Description of event	Incidence (N = 454)	
	n	%
Infectious keratitis - both segments removed	1	0.2%
Shallow placement of temporal segment - one segment removed	1	0.2%
Loss of 2 lines of BSCVA at two consecutive exams[1]	1	0.2%
Anterior chamber perforation during initial procedure - Intacs™ not placed	1	0.2%
Anterior chamber perforation during exchange procedure - Intacs™ not replaced	1	0.2%

[1] BSCVA was regained later

Ocular Complications

Intacs™ were not successfully placed for four subjects due to intraoperative complications: corneal surface perforation (3), and chemosis (1). All of these intraoperative complications were considered to be related to the surgical procedure, not the device.

Table 3 provides a summary of the complications that occurred at Month 6 and at Month 12. A total of 64 subjects at Month 6 and 45 subjects at Month 12 experienced ocular complications.

Table 3 - Complications[1]

Description of complication		Month 6		Month 12	
		n/N	%	n/N	%
Reduction of central corneal sensation ≥ 20 mm[2]		24/259	9.3	13/237	5.5
Increase in cylinder	>1D to 2D	19/437	4.3	15/410	3.7
	>2 D	1/437	0.2	0/410	0.0
Neovascularization:	Pannus	2/438	0.5	6/410	1.5
	Deep	5/438	1.1	5/410	1.2
Loss of ≥ 10 letters or ≥ 2 lines BSCVA[3]		7/436	1.6	4/410	1.0
Persistent Epithelial Defect		2/435	0.5	1/410	0.2
Iritis/Uveitis		2/438	0.5	1/410	0.2
Intraocular pressure (IOP) increase of > 10 mmHg		0/432	0.0	0/406	0.0
Noninfectious infiltrate (no loss of BSCVA)		2/438	0.5	0/410	0.0

[1] Clinical findings occurring between exams were included with the subsequent exam.
[2] This test was performed on a subgroup of subjects.
[3] The study protocol defined BSCVA loss as an adverse event only if present at 2 or more consecutive exams.

Secondary Surgical Interventions

A total of 17/449 (3.8%) Intacs™ subjects had a surgical intervention performed during the twelve month reporting period. The surgical interventions included: Intacs™ repositioning (5), punctal plug occlusion (5), cyst/plug removal (3), filament removal (2), foreign body/iron rust ring removal (1), and wound revision (1). Of the 17 interventions performed, only 3 were considered to be clinically meaningful (3/449, 0.7%). Two subjects had a new tunnel dissected to improve the position of the Intacs™ and one subject had a "relaxing incision" to reduce his induced cylinder.

Other Ocular Findings

Deposits were observed in the intrastromal tunnel and/or in the incision area at the Month 12 exam in 213/312 (68%) subjects enrolled in Phase III of the U.S. clinical trial. At the Month 12 postoperative exam, 115/312 (36.9%) had a grade of "Trace," 87/312 (27.9%) had a grade of "+1," 10/312 (3.2%) had a grade of "+2," and 1/312 (0.3%) had a grade of "+3." The specific origin and etiology of the deposits were not conclusively established. The prevalence and level of deposits remained stable from the Month 6 to the Month 12 postoperative exams. In all cases, the deposits were confined to the intrastromal tunnel with no visual consequence.

Patient Reported Visual Symptoms

Among the 39 Intacs™ removals during the reporting period, 19/39 (49%) were due to dissatisfaction with visual symptoms. Among subjects with Intacs™ in place at Month 12, the following visual symptoms were reported.

Table 4 provides a summary of the visual symptoms reported by subjects who completed the Month 12 exam with a frequency of "Always" and a magnitude of "Severe." All subjects who reported these visual symptoms had a BSCVA of 20/20 or better. No subject who reported these visual symptoms lost 10 or more letters or 2 or more lines of BSCVA.

Table 4 - Visual Symptoms at Month 12 (All thicknesses)

	Response of "Always" and "Severe"	
Visual Symptoms	**n/N**	**%**
Difficulty with night vision	15/314	4.8
Blurry vision	9/314	2.9
Diplopia	5/314	1.6
Glare	4/313	1.3
Halos	4/312	1.3
Fluctuating Distance Vision	3/313	1.0
Fluctuating Near Vision	1/313	0.3
Photophobia	1/314	0.3

Visual symptoms that were reported for the initially implanted eye at the Month 12 exam with a frequency of "Often" or "Always" are as follows:

Table 5 - Frequency of Visual Symptoms at Month 12 by Intacs™ Thickness

Visual Symptoms	0.25 mm (N = 109)				0.30 mm (N = 110)				0.35 mm (N = 110)			
	Often		Always		Often		Always		Often		Always	
	n	%	n	%	n	%	n	%	n	%	n	%
Difficulty with night vision	9	8.3	9	8.3	7	6.4	8	7.3	7	6.4	17	15.5
Blurry Vision	5	4.6	8	7.3	5	4.5	6	5.5	7	6.4	9	8.2
Diplopia	2	1.8	2	1.8	3	2.7	3	2.7	3	2.7	9	8.2
Glare	8	7.3	2	1.8	9	8.2	3	2.7	5	4.5	5	4.5
Halos	6	5.5	4	3.7	11	10.0	4	3.6	8[1]	7.3	6[1]	5.5
Fluctuating distance vision	1	0.9	0	0.0	1	0.9	1	0.9	3	2.7	5	4.5
Fluctuating near vision	1	0.9	1	0.9	2	1.8	0	0.0	4	3.6	4	3.6
Photophobia	5	4.6	5	4.6	3	2.7	2	1.8	7	6.4	1	0.9

[1] N = 109

Visual symptoms were reported with a magnitude of "Moderate" or "Severe" as follows:

Table 6 - Magnitude of Visual Symptoms at Month 12 by Intacs™ Thickness

Visual Symptoms	0.25 mm				0.30 mm				0.35 mm			
	Moderate		Severe		Moderate		Severe		Moderate		Severe	
	(N = 131)				(N = 130)				(N = 131)			
	n	%	n	%	n	%	n	%	n	%	n	%
Difficulty with night vision	19	14.5	3	2.3	20	15.4	2	1.5	19	14.5	12	9.2
Halos	14	10.7	2	1.5	20[1]	15.5	6[1]	4.7	20[3]	15.4	5[3]	3.8
Glare	19	14.5	1	0.8	18[1]	14.0	3[1]	2.3	17	13.0	5	3.8
Photophobia	19	14.5	1	0.8	14	10.8	0	0.0	16	12.2	1	0.8
Diplopia	7	5.3	1	0.8	6	4.6	3	2.3	16	12.2	4	3.1
Fluctuating distance vision	5	3.8	0	0.0	12[1]	9.3	0[1]	0.0	15	11.5	4	3.8
	(N = 106)				(N = 102)				(N = 105)			
Blurry Vision	13	12.3	3	2.8	9[2]	8.7	2[2]	1.9	18	17.1	5	4.8
Fluctuating near vision	6	5.7	0	0.0	5	4.9	0	0.0	8	7.6	1	1.0

[1] N = 129; [2] N = 103; [3] N = 130

IX. SUMMARY OF PRECLINICAL STUDIES

Laboratory Studies

The applicant has performed testing in accordance with ANSI/AAMI/ISO 10993-1, "Biological Evaluation of Medical Devices," to establish the safety of the materials, processes and packaging components used in the manufacturing of the Intacs™. The results of these tests demonstrate that the Intacs™ are nontoxic at the cellular, systemic, local and immunological levels.

Microbiological evaluations, including Limulus Amebocyte Lysate (LAL) and presterilization bioburden testing, were performed in accordance with the United States Pharmacopoeia (USP XXIII). The results of these tests were acceptable.

Intacs™ were exposed to accelerated aging conditions to confirm that the packaging would continue to provide a sterile barrier 36 months after the date of manufacture. This testing was performed in accordance with ISO 11607:1997, "Packaging for Terminally Sterilized Medical Devices." The results of this testing demonstrated that the package assembly seal strength and barrier properties are not adversely affected by normal manufacturing, handling, and storage conditions for a time period equivalent to 36 months. The applicant is currently performing real-time aging to confirm the results of the accelerated aging.

Transit (or shipping) tests were conducted to determine if routine distribution and shipping activities would adversely affect the Intacs™ and the packaging assembly. The transit tests were designed to simulate normal and expected transport conditions and were performed in accordance with ASTM D4169, "Performance Testing of Shipping Containers"; ASTM D642, "Test Methods for Compressive Resistance"; ASTM D999, "Test Methods for Loose Load Vibration"; ASTM D4728, "Test Methods for Random Vibrations"; and ASTM D5276, "Test Methods for Package Drop." The results of this testing demonstrated that the product and packaging were sufficient to withstand normal handling and transport conditions.

Validation studies were performed to demonstrate that the sterilization process would adequately sterilize the Intacs™ within the package assembly. Sterilization was performed using 100% ethylene oxide (EO) gas. The validation studies were performed in accordance with ANSI/AAMI/ISO 11135:1994, "Medical Devices - Validation and Routine Control of Ethylene Oxide Sterilization." The validation results demonstrated that the EO sterilization process is acceptable for sterilizing the Intacs™ and does not adversely affect the functionality of the product and package assembly.

Additional validation studies were performed to demonstrate that the Intacs™ could be successfully resterilized by KeraVision. The purpose of the validation studies was to verify that a second sterilization cycle would not adversely affect or compromise biocompatibility, package integrity, visual and dimensional attributes, or product functionality. These studies demonstrated that the Intacs™ could be resterilized by KeraVision without adversely affecting the product or packaging.

An aeration process was validated for removing EO residuals from the packaged Intacs™ product. The validation study was performed in accordance with ISO 10993-7:1995, "Ethylene Oxide Sterilization Residuals" and the FDA-proposed residue limit for EO on intraocular lenses (Published in Federal Register 43, June 23, 1978). Based on the results of the validation study, the applicant concluded that the Intacs™ and package assembly would not be adversely affected by the aeration process and that the process was capable of removing EO residuals from the Intacs™ to acceptable limits.

Intacs™ were exposed to simulated aging conditions to determine whether exposure to UV radiation or hydrolysis would adversely affect the product's material strength or dimensional stability. Test results after simulated long-term exposure to UV radiation and hydrolysis demonstrated that the product was not adversely affected by these conditions; no material changes were observed.

Animal Studies

The rabbit model was used to provide information on the safety of the Intacs™ material implanted in the cornea. Rabbits were selected as a safety model because rabbit eyes have been

widely used for ophthalmic research, and the rabbit's response to a foreign body has been historically used to approximate the human response from a safety perspective.

The study results demonstrated that the Intacs™ could be implanted safely into a rabbit cornea. The rabbit eyes were clinically quiet and safely tolerated the Intacs™ implant. The device did not appear to initiate vessel formation or stromal scarring as determined by slit lamp examinations. No inherent reactivity or physiological abnormalities were observed between the Intacs™ material and the rabbit cornea.

From a histological standpoint, the rabbit eyes appear to have safely tolerated the Intacs™ implant. The cellular response was quite focal and was comparable to the response typically observed with intraocular lens implants. The histopathology indicated that the cells present were primarily associated with a mild, chronic inflammation and healing injury response. Evidence of cellular necrosis was not observed in any of the histological sections evaluated.

X. SUMMARY OF CLINICAL STUDIES

Objective and Study Design

The objective of the clinical studies was to assess the safety and effectiveness of the KeraVision Intacs™ for the reduction or elimination of myopia from -1.00 to -3.00 D. Two prospective, non-randomized, unmasked, multicenter U.S. clinical trials were conducted. The Phase II trial evaluated the results from 90 subjects enrolled at 6 investigational sites. The Phase III trial evaluated the results from 362 subjects enrolled at 10 investigational sites. The study protocols for Phase.II and Phase III were very similar; the few differences were not substantial. Statistical analyses confirmed that the data could be pooled for the evaluation of safety and effectiveness parameters. For all subjects, the fellow eye served as a control during the first 6 months postoperatively, however, the fellow eye was eligible for Intacs™ placement six months after the initial eye procedure.

Three thicknesses of Intacs™ were evaluated: 0.25 mm, 0.30 mm, and 0.35 mm. The number of subjects implanted was approximately equal for the three groups: 148, 150, and 151, respectively.

Subject accountability for the 452 subjects enrolled (449 subjects successfully implanted - see Figure 2 below) was excellent, with complete follow-up data available for 410/420 (97.6%) of eligible subjects at the Month 12 exam. Thirty-nine subjects were unavailable for analysis at the Month 12 exam. Of these, 29 subjects were ineligible for the Month 12 exam due to: removal (21), exchange (4) and Month 12 exam performed outside the analysis cutoff date (4). Five subjects were lost to follow-up and 5 subjects missed their Month 12 exams.

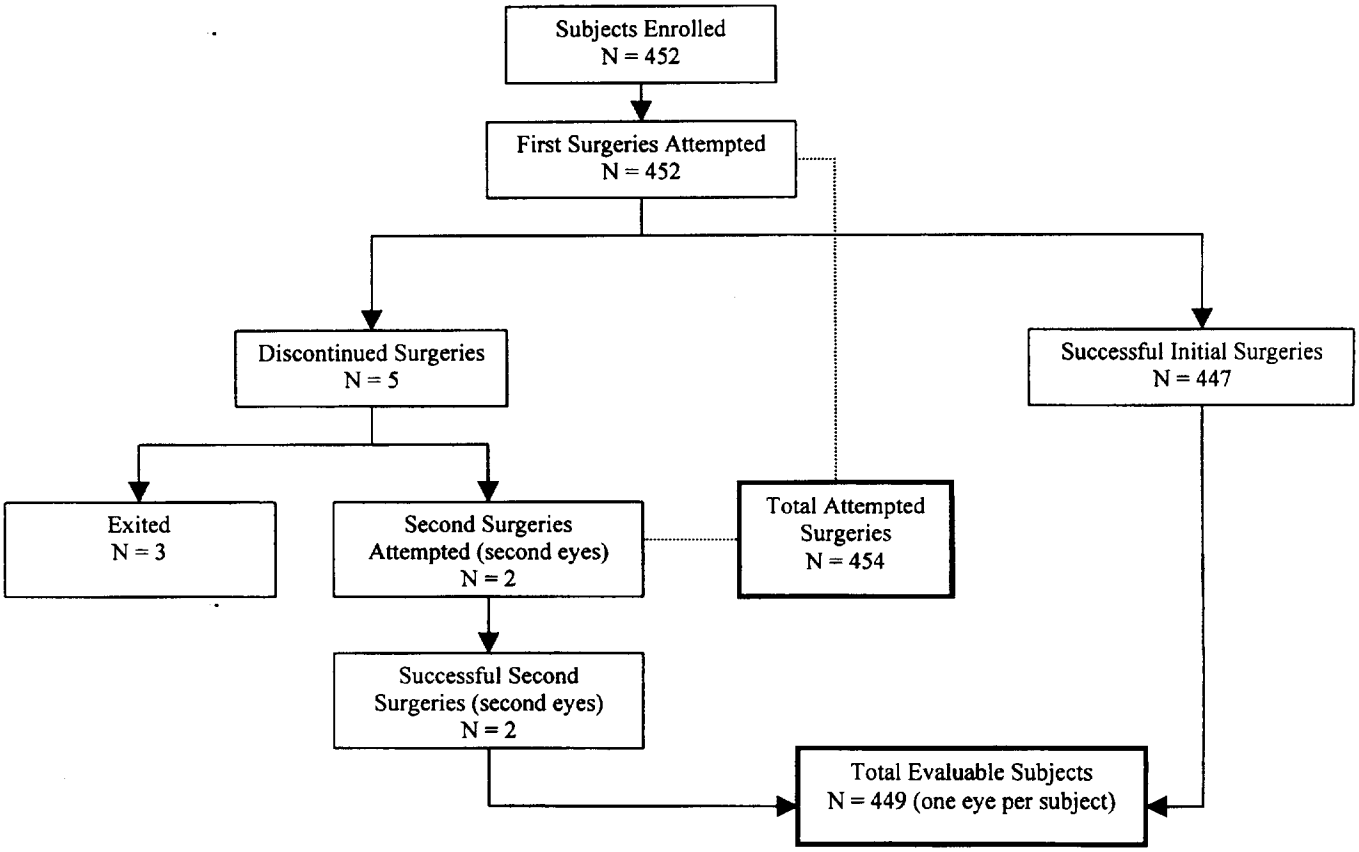

FIGURE 2 - SUBJECT DISPOSITION AT MONTH 12 EXAM

Data were collected from study subjects preoperatively; at 1, 3, 7 and 14 days postoperatively; and at 1, 2, 3, 6, 9, 12, 18 and 24 months postoperatively. The subjects' medical and ocular histories were recorded. Objective measurements included: uncorrected visual acuity (UCVA); BSCVA; near visual acuity (VA); manifest refraction; cycloplegic refraction; corneal topography; glare testing; keratometry; tonometry; pachometry; ophthalmoscopy; contrast sensitivity; limbal diameter measurement; axial length; assessment of anterior chamber, vitreous, retina and crystalline lens; and assessment of ocular complications or adverse events. The subjects were asked whether they experienced any visual or ocular symptoms both preoperatively and postoperatively. The subjects' satisfaction with their vision was assessed both preoperatively and at designated postoperative intervals. Additional evaluations were performed for the following subgroups: specular microscopy, automated visual fields, central corneal sensation, A-scan and slit lamp photography.

Patient Population and Demographic Data

The patient population for these studies included subjects with -1.00 to -3.50 D of myopia spherical equivalent at the spectacle plane with +1.00 D or less of astigmatism, who were at least 21 years of age; who had a stable manifest refraction as documented by a 1.00 D change or less within the previous six months; and who had a BSCVA of 20/20 or better in both eyes. Subjects who exhibited any of the following conditions were excluded: significant corneal abnormalities; prekeratoconus or keratoconus; corneas steeper than 46 D or flatter than 40 D; active ocular disease likely to affect wound healing; history of glaucoma; irregular astigmatism; herpetic eye disease; central corneal thickness less than 480 microns or peripheral thickness less than 570

microns; evidence of retinal vascular disease and/or history of hypercoagulability; abnormal tear status; use of systemic medications likely to affect wound healing; subjects who were immunocompromised, pregnant or had insulin-dependent diabetes or connective tissue disease; history of acute or chronic disease or illness or prior ophthalmic surgery.

Demographics and preoperative parameters are presented in Tables 7 and 8 for the 449 subjects who were successfully implanted with the Intacs™. Subjects who underwent the procedure ranged in age from 21 to 65 years, with a mean age of 39.4 years. The data were determined to be poolable across studies and sites after statistical analyses demonstrated that there were no differential visual refractive outcomes based on sex, ethnicity, age, implanted eye, or contact lens use.

Table 7 - Demographics (N = 449)

		n	%
Gender			
	Female	228	51
	Male	221	49
Race			
	Caucasian	373	83
	Hispanic	32	7
	Black	22	5
	Asian	12	3
	Other	10	2

Table 8 - Preoperative Parameters

Manifest Refraction (D)	**Mean ± SD[1] (D)**	**Range (D)**
Spherical Equivalent	-2.24 ± 0.69	-0.75, -4.125
Sphere	-2.40 ± 0.71	-1.00, -4.50
Cylinder	0.31 ± 0.30	0, 1.00
UCVA	**n/N[2]**	**%**
20/125 or worse	194/448	43
20/50 to 20/100	196/448	44
20/25 to 20/40	55/448	12
≤ 20/20	3/448	1

[1] SD = standard deviation
[2] UCVA not reported preoperatively for one subject.

Data Analysis and Results

The following table presents a summary of the key safety and efficacy results for all initially implanted eyes that were evaluated through the Month 24 exam. The primary clinical outcome assessment was performed at the Month 12 postoperative exam.

Table 9 - Summary of Key Safety and Efficacy Variables

	Month 3		Month 6		Month 12		Month 24	
Variables	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
UCVA 20/16 or better	218/442	49%	212/438	48%	**216/410**	**53%**	32/51	63%
UCVA 20/20 or better	316/442	71%	303/438	69%	**303/410**	**74%**	41/51	80%
UCVA 20/25 or better	379/442	86%	374/438	85%	**356/410**	**87%**	44/51	86%
UCVA 20/40 or better	427/442	97%	421/438	96%	**396/410**	**97%**	49/51	96%
MRSE ± 0.50 D	298/442	67%	295/437	68%	**284/410**	**69%**	34/51	67%
MRSE ± 1.00 D	406/442	92%	397/437	91%	**377/410**	**92%**	47/51	92%
MRSE Stability ±0.50 D[1]	310/437	71%	363/435	83%	**356/392**	**91%**	39/47	83%
MRSE Stability ±1.00 D[1]	395/437	90%	421/435	97%	**386/392**	**98%**	46/47	98%
Loss of ≥10 letters or ≥2 lines BSCVA	13/442	3%	7/436	2%	**4/410**	**1%**	0/51	0%
BSCVA worse than 20/40	0/442	0%	0/436	0%	**0/410**	**0%**	0/51	0%
Increased cylinder >2.00 D	0/442	0%	1/437	0.2%	**0/410**	**0%**	0/51	0%

[1]Stability was assessed as the change in MRSE from the previous scheduled exam.
MRSE = Manifest Refraction Spherical Equivalent

Stability of refractive effect is defined as the proportion of subjects with a change in MRSE of 1.00 D or less between two refractions taken three months apart. Table 10 demonstrates that stability was first achieved between Month 3 and Month 6. All (100%) subjects with the 0.25 mm Intacs™ achieved stability during this time period; 95.2% of the 0.30 mm and 95.2% of the 0.35 mm groups achieved stability in this time period.

Table 10 - Stability of Refractive Effect

Change in MRSE	Month 1 to Month 3		Month 3 to Month 6		Month 6 to Month 9		Month 9 to Month 12		Month 12 to Month 18		Month 18 to Month 24	
	N = 437		N = 435		N = 409		N = 392		N = 68		N = 47	
	n	%	n	%	n	%	n	%	n	%	n	%
Within ± 0.50 D	310	71	363	83	336	82	356	91	63	93	39	83
Within ± 1.00 D	395	90	421	97	398	97	386	98	68	100	46	98
Mean Difference ± SD	0.21 ± 0.64		0.04 ± 0.44		-0.00 ± 0.44		-0.01 ± 0.36		-0.03 ± 0.33		-0.05 ± 0.45	
95% CI*	0.15 to 0.27		0.00 to 0.09		-0.05 to 0.04		-0.04 to 0.03		-0.11 to 0.05		-0.18 to 0.08	

*CI = confidence interval

A summary of the performance for key safety and efficacy variables by Intacs™ thickness is provided in Table 11. Overall, the 0.25 mm and 0.30 mm Intacs™ had better outcomes than the 0.35 mm Intacs™. Statistically significant differences ($p \leq 0.05$) were seen among thicknesses for the proportion of subjects that had an UCVA of 20/20 or better ($p<0.001$), 20/40 or better ($p = 0.028$), a manifest refraction outcome within 0.50 D of predicted ($p = 0.004$) and within 1.00 D of predicted ($p = 0.005$), the proportion of eyes with an induced cylinder greater than or equal to 1.00 D ($p = 0.018$), and the rate of removals ($p = 0.004$).

Table 11 - Performance by Intacs™ Thickness

	Total		0.25 mm		0.30 mm		0.35 mm	
Variables	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
UCVA 20/20 or better	303/410	73.9	113/135	83.7	107/138	77.5	83/137	60.6
UCVA 20/40 or better	396/410	96.6	134/135	99.3	134/138	97.1	128/137	93.4
MRSE ± 0.50 D	284/410	69.3	94/135	69.6	108/138	78.3	82/137	59.9
MRSE ± 1.00 D	377/410	92.0	129/135	95.6	131/138	94.9	117/137	85.4
MRSE Stability ±1.00 D[1]	421/435	96.8	144/144	100	138/145	95.2	139/146	95.2
Loss of ≥10 letters or ≥2 lines BSCVA	4/410	1.0	2/135	1.5	1/138	0.7	1/137	0.7
BSCVA worse than 20/40	0/410	0.0	0/135	0.0	0/138	0.0	0/137	0.0
Induced Cylinder ≥1.00 D	30/410	7.3	4/135	3.0	10/138	7.3	16/137	11.7
Induced Cylinder >2.00 D	0/410	0	0/135	0.0	0/138	0.0	0/137	0.0
Removals[2]	34/449	7.6	5/148	3.4	9/150	6.0	20/151	13.3

[1] Stability was assessed as the change in MRSE from the Month 3 to Month 6 exam.
[2] Removal data are cumulative and extend beyond the Month 12 exam.

As described in "Device Description" above, the Intacs™ are associated with a recommended prescribing range. Table 12 provides a summary of the Intacs™ performance at Month 12, stratified by thickness, for subjects with preoperative refractive errors within the recommended prescribing range.

Table 12 - Performance Based on Recommended Prescribing Range

	Intacs Thickness (Preoperative CRSE)							
	0.25 mm (-1.00 to -1.625 D)		0.30 mm (-1.75 to -2.25 D)		0.35 mm (-2.375 to -3.00 D)		Total	
	N = 112		N = 110		N = 95		N = 317	
Variables	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
UCVA 20/16 or Better	71	63.4	59	53.6	47	49.5	177	55.8
UCVA 20/20 or Better	94	83.9	90	81.8	63	66.3	247	77.9
UCVA 20/40 or Better	111	99.1	109	99.1	91	95.8	311	98.1
CRSE ± 0.50 D	80[1]	72.1	85	77.3	59	62.1	224[2]	70.9
CRSE ± 1.00 D	104[1]	93.7	103	93.6	79	83.2	286[2]	90.5
MRSE ± 0.50 D	82	73.2	86	78.2	57	60.0	225	71.0
MRSE ± 1.00 D	107	95.5	103	93.6	81	85.3	291	91.8

CRSE = Cycloplegic refraction spherical equivalent; [1] N = 111; [2] N = 316

Clinical Substudies

Endothelial cell counts were collected preoperatively and at Month 12 postoperatively using noncontact specular microscopy. Table 13 provides the endothelial cell density percent change from the preoperative baseline. The change in endothelial cell density from the preoperative exam was statistically significant ($p<0.001$) among Intacs™ thicknesses for the 10:00 peripheral region at the Month 12 exam. The greatest decrease, 4.7%, was seen for the 0.35 mm Intacs™; the 0.30 mm Intacs™ actually had a slight increase in cell density, 0.2% for the same region.

Table 13 - Endothelial Cell Density -Percent Change at Month 12 from Preoperative

Region		0.25 mm	0.30 mm	0.35 mm	Total
Central	n	42	36	32	110
	Mean ± SD	+0.9% ± 4.5%	+0.7% ± 5.4%	-1.0% ± 3.4%	-0.4% ± 4.6%
6:00 Peripheral	n	40	38	35	113
	Mean ± SD	-2.7% ± 5.5%	-0.9% ± 6.1%	-1.8% ± 5.4%	-1.8 ± 5.7%
10:00 Peripheral	n	44	33	34	111
	Mean ± SD	-1.4% ± 5.2%	+0.2% ± 5.1%	-4.7% ± 4.2%	-1.9% ± 5.2%

*Data collected as Phase III subgroup test.

Because preoperative contact lens wear can influence endothelial cell density, the applicant also analyzed these data by preoperative method of visual correction (Table 14). In the first six months, subjects who wore contact lenses preoperatively had an increase in cell density centrally and very slight losses peripherally. Subjects who did not wear contact lenses preoperatively had slightly larger decreases in cell density between the preoperative and Month 6 measurements. Both groups had small losses in all but one region between Months 6 and 12. These findings are consistent with literature reports that subjects who wear contact lenses preoperatively may have smaller losses or even gains in cell density in the time period immediately following surgery.

Table 14 - Endothelial Cell Density by Method of Preoperative Visual Correction

Subjects Using Contact Lenses Preoperatively			
Region	n	**Preop to Month 6 exam** Mean change ± SD	**Month 6 to Month 12 exam** Mean change ± SD
Central	63	+1.1% ± 5.9%	-1.3% ± 4.9%
6:00 Peripheral	68	-0.13% ± 7.4%	-1.5% ± 7.3%
10:00 Peripheral	64	-0.20% ± 6.7%	-1.6% ± 4.8%
Subjects Using Glasses Only Preoperatively			
Region	n	**Preop to Month 6 exam** Mean change ± SD	**Month 6 to Month 12 exam** Mean change ± SD
Central	47	-1.1% ± 3.9%	+0.2% ± 3.8%
6:00 Peripheral	45	-1.0% ± 6.1%	-1.4% ± 5.4%
10:00 Peripheral	47	-2.1% ± 6.0%	-0.4% ± 4.5%

Contrast sensitivity testing using a F.A.C.T.™ (Functional Acuity Contrast Test) chart was performed under mesopic conditions, with and without a glare source for subjects in the Phase III trial. The mean change in contrast sensitivity at Month 6 and Month 12 relative to preoperative levels was less than 0.1 log unit for all spatial frequencies and independent of the presence of glare. However, the proportion of implanted eyes with a functional decrease (defined as a two-patch decrease on the F.A.C.T. chart, where a patch corresponds to a set level of contrast) at Month 6 was greater than that of the non-operated fellow eyes at 1.5 cycles per degree (cpd) (7.9% versus 3.5%, respectively; $p = 0.013$) and at 6 cpd (15% versus 9.2%, respectively; not statistically significant) without glare. With glare, no statistically significant differences were found between eyes at any spatial frequency.

Patient satisfaction surveys were administered preoperatively and at Month 12 postoperatively in the Phase III trial. The results are summarized in Table 15.

Table 15 - Subject Satisfaction at Month 12

	N = 288	
Response	**n**	**%**
Strongly satisfied	192	67
Somewhat satisfied	66	23
Neutral	9	3
Somewhat dissatisfied	12	4
Strongly dissatisfied	9	3
Not reported	44	--

Removals and Exchanges

Intacs™ have been removed from 34 primary eyes and 5 contralateral eyes. Reasons for Intacs™ removals included: 19 for subject dissatisfaction with visual symptoms (glare, halos, difficulty with night vision, etc.), 15 for subject dissatisfaction with correction achieved (undercorrection, overcorrection or induced astigmatism), 1 for infection, and 4 for other reasons (non-monovision correction, FAA restrictions, deferred exchange due to a posterior perforation during the exchange procedure).

Analyses of the removals indicate that the refractions returned to preoperative levels by three months following removal, in most instances. The BSCVA was 20/20 or better in all cases. The central cornea remained clear in all eyes. Slit lamp findings were limited to stromal haze and deposits within the peripheral tunnels. A small percentage of subjects reported more frequent and/or more severe visual symptoms three months following removal than was documented preoperatively.

Table 16 provides a summary of the refractive status of the 29 subjects with three months postremoval data available.

Table 16 - Refractive and Visual Acuity Change from Preoperative to Month 3 Postremoval Exam

Variables	n/N	%	95% CI
MRSE ± 0.50 D	25/29	86%	68%, 96%
MRSE ± 1.00 D	29/29	100%	88%, 100%
MRSE Stability ±1.00 D[1]	20/20	100%	83%, 100%
Loss of ≥5 Letters or ≥1 Line BSCVA	2/29	7%	1%, 23%
Loss of ≥10 Letters or ≥2 Lines BSCVA	0/29	0%	0%, 12%
Cylinder ±0.50 D	27/29	93%	77%, 99%
Cylinder ±1.00 D	29/29	100%	88%, 100%

[1] Stability was assessed as the change in MRSE from Month 1 to Month 3 postremoval. Only patients with results within the specified time window for both exams were included in the analysis.

Visual symptoms were also assessed at the Month 3 postremoval exam. Table 17 summarizes visual symptoms reported at a frequency greater than the preoperative exam. Table 18 provides a similar summary for the reported magnitude of visual symptoms.

Table 17 - Assessment of Frequency of Visual Symptoms

N = 19[1]			
Visual Symptom	**n**	**%**	**95% CI**
Blurry Vision	8	42%	20%, 67%
Photophobia	5	26%	9%, 51%
Glare	2	11%	1%, 33%
Difficulty with Night Vision	2	11%	1%, 33%
Diplopia	2	11%	1%, 33%
Halos	0	0%	0%, 18%
Fluctuating Near Vision	0	0%	0%, 18%
Fluctuating Distance Vision	0	0%	0%, 18%

[1] Data collected for Phase III patients only.

Table 18 - Assessment of Magnitude of Visual Symptoms

N = 9[1]			
Visual Symptom	**n**	**%**	**95% CI**
Fluctuating Vision	1[2]	12%	0%, 53%
Halos	1	11%	0%, 48%
Difficulty with Night Vision	1	11%	0%, 48%
Diplopia	1	11%	0%, 48%
Glare	0	0%	0%, 34%
Photophobia	0	0%	0%, 34%

[1] Preoperative magnitude collected for Phase II patients only.
[2] N = 8; one subject did not answer the question preoperatively.

Table 19 provides a summary of those visual symptoms reported as "Severe" at the Month 3 postremoval exam.

Table 19 - Magnitude of Visual Symptoms
Proportion "Severe" at the Month 3 Postremoval Exam

N = 22			
Visual Symptom	**n**	**%**	**95% CI**
Blurry Vision	1[1]	8%	0%, 38%
Difficulty with Night Vision[2]	1	5%	0%, 23%
Diplopia[2]	1	5%	0%, 23%
Fluctuating Distance Vision	1	5%	0%, 23%
Glare	0	0%	0%, 15%
Halos	0	0%	0%, 15%
Photophobia	0	0%	0%, 15%
Fluctuating Near Vision	0[1]	0%	0%, 26%

[1]N =12; data collected for Phase III patients only.
[2]The same patient reported both severe difficulty with night vision and diplopia.

Intacs™ were exchanged for 12 patients in an attempt to improve their refractive outcome. Sufficient data are not currently available to determine the efficacy of exchanging Intacs.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

The preclinical testing indicates that:

a. the Intacs™ material should be well-tolerated within the human eye;

b. the manufacturing processes should result in a product that consistently meets performance specifications; and

c. the Intacs™ can be safely and successfully sterilized and aerated up to two times by KeraVision.

The clinical trials indicate that:

a. the safety and effectiveness endpoints established in the clinical protocols were met;

b. the rates of adverse events and complications associated with the Intacs™ are acceptably low; and

c. if Intacs™ are removed, the patient's refraction will return to preoperative levels in most instances, but a chance exists that visual symptoms may be more frequent or more severe than experienced preoperatively.

Therefore, it is reasonable to conclude that the benefits of use of the Intacs™ for the reduction or elimination of myopia of -1.00 D to -3.00 D at the spectacle plane in patients with preoperative myopic error ranging from -1.00 to -3.50 D spherical equivalent where the astigmatic component is +1.00 D or less outweigh the risk of adverse events and complications when used as indicated in accordance with the directions for use.

XII. PANEL RECOMMENDATION AND CDRH DECISION

At an advisory meeting held on January 12, 1999, the Ophthalmic Devices Panel recommended that KeraVision's PMA for the Intacs™ be approved subject to submission to and approval by, the Center for Devices and Radiological Health (CDRH) of the following:

- a proposal for a postapproval study to provide additional, two-year postoperative data on endothelial cell counts in subjects who received 0.35 mm Intacs™;
- a modification of the proposed claim that the Intacs™ procedure is reversible;
- revised labeling that omits proposed adjustability and enhanced visual performance claims, since there were inadequate data to support these claims; and
- a number of modifications to the physician and patient labeling.

CDRH concurred with the Panel's recommendation of January 12, 1999 and issued a letter to KeraVision on February 10, 1999, advising that its PMA was approvable subject to the submission of an amendment with changes as recommended by the Panel and required by FDA.

In amendments dated February 26 and March 12, 1999, KeraVision submitted the required information. Specifically, the applicant agreed to continue measurement of endothelial cell densities for all subjects enrolled in this substudy according to the Phase III protocol. The applicant stated that two-year data would be collected for over 100 subjects, with 30 or more subjects with each Intacs™ thickness. Additionally, the applicant planned to continue follow-up of these subjects for a total of 5 years to provide further long-term information. The applicant also provided labeling with modifications as requested by the Panel and CDRH.

This information was reviewed by CDRH and found to comply with the Panel's recommendations and FDA's requests. The applicant's manufacturing facilities were inspected on November 24, 1998 (KeraVision), October 7, 1998 (contract manufacturer), and March 1, 1999 (contract sterilizer) and found to be in compliance with the device Good Manufacturing Practice regulations. FDA issued an approval order on April 9, 1999.

Attachments: Physician Booklet
Patient Booklet