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SUMMARY MINUTES

of the

OPHTHALMIC DEVICES

PANEL MEETING

January 12, 1999

9200 Corporate Blvd.
Rockville, Maryland

OPHTHALMIC DEVICES PANEL

January 12, 1999

James P. McCulley, M.D., Chair
Sara M. Thornton, Executive Secretary

Voting Members
Mark A. Bullimore, MCOptom, Ph.D.
Eve J. Higginbotham, M.D.
Janice M. Jurkus, O.D.
Marian S. Macsai, M.D.
Jose S. Pulido, M.D.
Joel Sugar, M.D.

Consultants
Karen Bandeen-Roche, Ph.D.
Michael R. Grimmett, M.D.
Alice Y. Matoba, M.D.
Woodford S. Van Meter, M.D.
Ming X. Wang, M.D., Ph.D.

Consumer Representative
Renee A. Middleton, Ph.D.

Industry Representative
Marcia S. Yaross, Ph.D.

CALL TO ORDER/INTRODUCTORY REMARKS

Dr. James P. McCulley, Panel chair, called the Ophthalmic Devices Panel meeting to order at 8:09 a.m.. Ms. Sara Thornton, executive secretary, advised the Panel that the meeting tentatively scheduled for March 11–12, 1999 had been canceled; the status of the May 3–4, 1999 meeting will be known in early March. At Ms. Thornton's request, Panel members and consultants introduced themselves.

OPEN PUBLIC HEARING

Dr. McCulley requested that those who wished to address the Panel during the Open Public Hearing session come forward. There being no one present who wished to address the Panel, the Open Public Hearing was closed.

OPEN COMMITTEE DISCUSSION

Ms. Thornton read the conflict of interest statement. She stated that FDA had taken into consideration matters unrelated to the business before the Panel involving Drs. Jurkus, McCulley, and Wang. She noted that temporary voting status had been granted to Drs. Bandeen-Roche, Grimmett, Matoba, Van Meter, and Wang.

Branch Updates

James F. Saviola, O.D., Chief, Vitreoretinal and Extraocular Devices Branch, reported that the branch had completed review of the Wesley-Jensen Precision UV (Vasurfilcon A) soft contact lens and had modified the device's labeling to include an additional indication statement and a modified UV lens note and warning. This lens is marketed for both daily and extended wear. K982988 was found substantially equivalent and cleared for marketing on January 6, 1999. PMA supplement 940013/S006 was approved on January 7, 1999.

Morris Waxler, Ph.D., Chief, Diagnostic and Surgical Devices Branch, reported that on December 17, 1998, FDA had approved PMA P970053 for the Nidek EC-5000 Excimer Laser System for PRK treatment for the reduction or elimination of mild to moderate myopia. He also noted that FDA has approved a number of sponsor-investigator clinical trials to investigate important variables in the PRK and LASIK treatment of myopia and hyperopia. As a result of the information gained from these trials, many recent applications from sponsor-investigators are redundant and have been disapproved. Additional sponsor-investigator trials for excimer lasers will be approved only if the proposed study has a unique, scientifically sound investigational plan.

Donna R. Lochner, Chief, Intraocular and Corneal Implants Branch, reported that PMA P990091/S14 for the Toric Intraocular Lens, manufactured by STAAR Surgical Co., which was reviewed by the Panel in July 1998, was approved on November 4, 1998. She advised the Panel that the Division of Ophthalmic Devices would soon be releasing a guidance document entitled Accountability Analysis for Clinical Studies for Ophthalmic Devices. In addition, the Branch will shortly release the next draft of the intraocular lens guidance document. Both of these documents will be mailed to Panel members as soon as they are released and Panel members are invited to comment on them. Ms. Lochner also noted that, due to the significant health risk posed by natural rubbers to individuals who are sensitized to natural latex proteins, FDA now requires all medical devices and packaging that contain natural rubber to note this in the product labeling.

PMA P980031: KeraVision Intacts™ Intrastromal Corneal Ring Segments

Ms. Lochner read into the record the names and roles of the members of the review team for PMA P980031. Ms. Ashley Boulware, review team leader, described the structural characteristics of the Intacts™ Intrastromal Corneal Ring Segments (ICRS). The device consists of two semi-circular ring segments that are implanted in the cornea to reshape the corneal curvature, thereby correcting for myopia. The degree of corneal flattening achieved is directly related to the thickness of the implant. Three thicknesses were studied for this PMA: 0.25, 0.30, and 0.35 mm.

The proposed indication for the device is the reduction or elimination of myopia of -1.00 to -3.00D at the spectacle plane in patients at least 21 years old who have documented stability of refraction and preoperative myopic error of -1.00 to -3.50D with no more than 1D of astigmatism. Ms. Boulware noted that FDA is currently considering the appropriate classification of the hand-held surgical instruments, designed by KeraVision, which are used to implant the ring segments.

Sponsor Presentation

Mr. Thomas Loarie, Chairman and CEO of KeraVision, Inc., introduced the speakers for the sponsor's presentation. Ms. Darlene Crockett-Billig, KeraVision's vice president for regulatory affairs and clinical research, described the device, its regulatory history, the design of

the clinical studies conducted for the PMA, the study population, the participating investigators and sites, and the role and membership of the data safety and monitoring board. A total of 454 eyes were evaluated for safety; 410 were evaluated for efficacy at Month 12.

Dr. David Schanzlin, director of keratorefractive surgery, University of California at San Diego, and chief investigator for KeraVision's clinical trials, stated that he has served as a consultant to KeraVision for 12 years and has recently acquired a small equity interest in the company. He described the device's design features and mode of operation and the surgical techniques used in implantation. He noted that the device preserves the central optical zone and is designed to be removed. Most surgeons can complete the implantation procedure in 10 to 15 minutes.

Dr. Schanzlin reviewed the efficacy data for the PMA cohort. Variables assessed were uncorrected visual acuity, predictability of refractive effect, and stability of refractive effect. All of the data presented exceeded the endpoints specified in both the two clinical protocols and the FDA guidance document for refractive surgery lasers, Dr. Schanzlin said. He then discussed the study results within the recommended prescribing range (RPR) for each device thickness. Results for each thickness exceeded the criteria in both the protocol and the FDA refractive laser guidance document, he said.

Dr. Michael Lemp, president of University Ophthalmic Consultants of Washington and chairman of KeraVision's data safety and monitoring board, stated that he has been a consultant

to KeraVision for 5 years and has no ownership interest in the company. He presented the safety assessment data for the PMA cohort. All safety endpoints specified in both the protocol and the FDA guidance document were met or exceeded at Month 12, he said. He summarized the intraoperative clinical findings, adverse events, and clinically significant complications. The overall adverse event rate was 0.7%. Seven percent of subjects reported having "always" or "severe" visual symptoms, a rate similar to those reported for other approved refractive technologies.

Dr. Lemp then reviewed the data concerning the reversibility and adjustability of the device. The ICRS can be removed, if desired, in a brief outpatient procedure. The sponsor's claim of reversibility is based on preservation of the subject's BSCVA and the ability of the subject to return to within 1.00D of preoperative refraction. Adjustability involves an exchange procedure to remove implants of one thickness and replace them with another thickness. Thirty-four removals and 12 exchange procedures were performed in the PMA cohort.

Dr. Lemp made the following points in conclusion:

- All safety and efficacy endpoints were met or exceeded.
- The device is well tolerated in the cornea.
- No patient had a clinically significant loss of BSCVA. Excellent visual acuities were achieved and no clinically significant harm occurred to any subject.
- The performance of the ICRS is predictable and the refractive effect is stable.

A recess took place from 9:37 to 9:58 a.m.

Clinical Review

Dr. Malvina Eydelman, FDA, presented the clinical review of the PMA. She drew the Panel's attention to the following:

- A decrease in peripheral endothelial cell density of 10% or more occurred in 13 eyes. Stratification by implant thickness revealed a greater loss of peripheral cell density for the 0.35 mm ring segments, which was statistically significant. Additionally, a statistically significant decrease occurred in endothelial cell density between Preop and Month 6 as well as Preop and Month 12 in the 0.35 mm implant group.
- Statistically significant increases occurred in frequency of a range of visual symptoms (except fluctuating distance vision) at Month 12 compared with preoperative values. Rates of double images, fluctuating near vision, and fluctuating distance vision were significantly higher for the 0.35 mm ring segments.
- Of subject eyes with a reduction in central corneal sensation of 20 mm or more, 13 of 24 examined at Month 6 and 6 of 13 examined at Month 12 occurred at a single clinical site, suggesting a relationship to surgical technique.
- The predictability of refractive effect at Month 12 is significantly lower for the 0.35 mm ring segments.
- Although the recommended prescribing range for all three thicknesses of implant is -1.00D to -3.00D, the proposed indication for the device refers to patients with

preoperative myopic error ranging from -1.00D to -3.50D.

- Although refractive stability is expected to occur at 6 months, most of the 34 implant removals occurred after Month 6. The 0.35 mm ring segments accounted for 56% of removals.
- The sponsor's reversibility claim is based on data for 22 eyes at 3 months postremoval. No longer-term data are currently available.
- Eleven of the 12 exchange procedures involved an exchange for 0.40 or 0.45 mm ring segments, no data for which are included in the current PMA. Three of the 12 subjects later underwent removals due to continuing undercorrection.
- The sponsor's enhanced visual performance claim is based on three categories. A change of less than two lines in postoperative BSCVA as compared with preoperative BSCVA occurred in 80 eyes.

Dr. Eydelman presented the FDA's questions for the Panel, which related to endothelial cell density; visual symptoms; corneal sensation loss; appropriateness of the requested indication; overall safety and effectiveness of the three implant thicknesses; and the sponsor's claims of reversibility, adjustability, and enhanced visual performance.

Primary Panel Reviews

Drs. Sugar, Van Meter, and Grimmett presented their reviews of the PMA. Dr. Sugar said, in summary, that:

- Stability appears to be achieved at between 1 and 3 months.
- 13.9% of subjects lost one or more lines of BSCVA while 19.5% gained one or more at 12 months. Since examiners and subjects were not masked as to treatment, the phenomenon of enhanced visual performance may not be real.
- The increased likelihood of induced cylinder with increased ring thickness should be mentioned in the package inserts.
- Although mean endothelial cell loss is not clinically significant, the subjects with 10% loss are a concern. Follow-up endothelial analyses on these subjects would be worthwhile.
- Labeling for both physicians and patients should specifically note that the frequency of visual symptoms increased with ring thickness.
- The procedure appears to be reversible.
- Data on exchanges are insufficient to support the claim for adjustability of refractive effect.

Dr. Van Meter said, in summary, that

- The data show a significant improvement in postoperative UCVA compared with preoperative values for all three implant thicknesses.

- Predictability at 12 months was better for the 0.25-mm segments than for the 0.30 and 0.35-mm thicknesses.
- Stability was no worse postoperatively than preoperatively.
- Because the hyperacuity effect is not predictable in individual patients, labeling should not make this claim.
- The data indicate very minimal risk of BSCVA loss.
- Labeling should indicate the possibility of induced cylinder with the 0.35-mm ring thickness.
- Follow-up data should be collected on endothelial cell loss in subjects who received 0.35-mm implants.
- Labeling should note that partial loss of corneal sensation, which may be temporary, is possible, although its clinical significance is not known.
- The data presented support the claim of reversibility.

Dr. Grimmett said, in summary, that

- The rate of BSCVA loss was acceptably low.
- Longer term follow-up of endothelial cell loss is warranted in subjects who received 0.35 mm implants.
- Labeling should acknowledge the potential for altered corneal sensation in some patients.
- Labeling should refer to the number of subjects who experienced "moderate" as well as "severe" visual symptoms and to the numbers who experienced such symptoms "often" as

well as "always."

- The data on postremoval refraction stability are limited to 3 months, which may not be long enough to establish long-term stability.
- The definitions of clinically significant gain and loss of visual acuity should be consistent. Only changes of " 2 lines should be considered significant.
- The data submitted do not support a claim for adjustability.
- The 0.35 mm ring segment requires different labeling to note significantly higher rates of endothelial cell loss, induced cylinder, frequency and magnitude of visual symptoms, and removal and significantly lower rates of UCVA, stability of MRSE, and predictability compared with the 0.25 and 0.30 mm implants.

Panel Discussion

Sponsor representatives made the following statements in response to Panel questions:

- When performing an exchange procedure, it is not necessary to redissect the channel.
- Observations by the sponsor over several years have not shown that the depth of the implant affects efficacy. There is a safety concern that the surgeon performing the surgery would be trained in how to implant at a depth of greater than 50 percent of the cornea.
- Preoperative best contact-lens-corrected vision was not measured.
- Deviation from plano and induced cylinder have a statistically significant association with

visual symptoms. There is no association with pupil size.

- The implants do not interfere with gonioscopy or with examination of the retina.
- According to anecdotal reports, subjects who underwent removals went on to have PRK or LASIK with good visual outcomes and no complications. However, these data are not included in the PMA.
- The Phase 2 protocol defined removals and exchange procedures as adverse events. The Phase 3 protocol defined these as additional procedures but not as adverse events.
- Data analysis indicates that a lower surgeon threshold for offering removal to patients. accounts for the higher removal rates at two centers.
- Optical pressure is raised to approximately 80 mm Hg during the implant procedure.
- Surgeons would be required to take the sponsor's training course before using the device.
- The mean change in BSCVA preoperatively and postoperatively in both protocols was 0.13 lines. However, 19.5% of subjects had an increase in BSCVA of five or more letters or one or more lines, a statistically significant improvement.
- Surgically induced astigmatism was primarily orthogonal and "with the rule."
- Subjects who had the implants removed were included in the safety analysis at Month 12 but not in the efficacy analysis. The percentage of subjects reporting visual symptoms was based on those who had an implant at Month 12; therefore, the 20 subjects who had removals before Month 12 were not included in that analysis.

- There is no evidence that changes in altitude cause fluctuations in vision in implant recipients.
- Changes in refraction were no different in men than in women or in premenopausal women than postmenopausal women.

A recess took place from 12:25 p.m. to 1:38 p.m. The Panel then turned its attention to the FDA questions, responding to them as follows:

1. **Endothelial Cell Density.** A postmarketing study of endothelial cell density should be performed to provide a total of 2 years of follow-up data on the currently enrolled subjects with 0.35 mm implants, with a control group comprising subjects from the 0.25 and 0.30 mm implant groups.
2. **Visual Symptoms.** Discussion of Questions 2 and 5 was combined. (See Question 5 below.)
3. **Corneal Sensation Losses.** Labeling should state that some patients may experience a decrease in corneal sensation that may be temporary and the clinical significance of which is unknown.
4. **Indication.** It was agreed that the data submitted support the proposed indication for correction of myopia ranging from -1.00 to -3.00D in patients with myopic error ranging from -1.00 to -3.50D. Labeling should note that because the average correction achieved with the 0.25 mm ring segments is -1.48D, patients with myopia of -1.00D risk overcorrection of 0.50D or more.
5. **Safety and Effectiveness Outcomes.** Differential labeling was recommended for the 0.35 mm

ring segments. The labeling should clearly summarize, in both text and tabular format, the clinical study outcomes for recipients of the 0.35 mm implants in the following areas: endothelial cell density, induced cylinder greater than 1.00D, implant removal, frequency and magnitude of visual symptoms, uncorrected visual acuity, stability of MRSE, and predictability. Additionally, labeling should

- report frequency of visual symptoms data for both "often" and "always" categories and severity data for both "moderate" and "severe" categories,
- quantify the frequency and magnitude of pain experienced by study subjects,
- make clear the degree of refractive error that each ring size is intended to correct, and
- explicitly note that in addition to the subjects reporting visual symptoms, a 4.7% rate of device removal occurred .

6. **Reversibility.** Labeling and marketing materials for the device should state only that the implantation procedure is reversible in most, but not all, circumstances. It should be made clear that the claim of reversibility is based on evaluation of a small number of patients for 3 months. There are no data on reversibility if removal occurs more than 10 months after implantation. It is not known whether endothelial cell loss is reversible (or whether such loss is clinically significant). There are no data to support any statement regarding patients' suitability for or success with other types of refractive surgery following removal of the ICRS.
7. **Adjustability.** The current data on exchange procedures are insufficient to support a claim

for adjustability of refractive effect. Due to the low predictability of the exchange procedure, the Panel declined to recommend a minimum number of eyes on which follow-up data would be necessary to support a claim of adjustability.

8. **Enhanced Visual Performance.** The current data are insufficient to support a claim of enhanced visual performance.

The Panel made the following additional comments:

- FDA should work with the sponsor to develop guidelines concerning the permitted length of application of continuous suction. It was generally agreed that 5 minutes is too long but that there are no data to support an ideal upper limit.
- Labeling should note that although the definition of preoperative refractive stability in the clinical study was a manifest refraction change of 1.00D or less for at least 6 months before the preoperative examination, in current practice refractive stability is defined as no greater than 0.5D change over the preceding year.
- The following revisions to the patient booklet were recommended.
  - Insert a statement that the safety and effectiveness of the ICRS has not been established in individuals with diabetes and other medical conditions.
  - Specifically identify alternative treatments, as is done in the physician booklet.
  - Insert a statement advising patients to discuss with their doctors whether they have any history of elevated optical pressure or any suspicion of glaucoma.

OPEN PUBLIC HEARING

Dr. McCulley requested that those who wished to address the Panel during the Open Public Hearing session come forward. There being no one present who wished to address the Panel, the Open Public Hearing was closed.

SPONSOR'S CLOSING COMMENTS

Dr. Lemp, on behalf of the sponsor, thanked the Panel and the Agency for their careful evaluation of the PMA. He made the following comments in response to issues raised by the Panel:

- Suction: Mean vacuum time was 1.4 minutes, and suction need not be continuous.
- Reversibility: 89% (24 of 27) of subjects met the criteria of return to within 0.50D of preoperative MRSE, 0.50D of preoperative cylinder, and one line of visual acuity. 100% of subjects returned to within 0.75D of preoperative MRSE, 0.75D of preoperative cylinder, and one line of visual acuity.
- Endothelial cell density: The proportion of patients with greater than 10% cell loss at Month 6 was 12% for the treated eye and 9% for the untreated fellow eye. At Month 12, 14% of patients had greater than 10% cell loss in the treated eye. No fellow-eye data are available beyond Month 6 because fellow eyes were eligible for implantation after 6 months. Due to

low reproducibility in tests of endothelial cell density, it is not clear what can be learned from further longitudinal studies of peripheral endothelial cells.

FDA CLOSING COMMENTS

FDA had no closing comments.

OPEN COMMITTEE DISCUSSION (continued)

Ms. Thornton read the voting options for the record. A motion was moved and seconded to consider PMA P980031 approvable with conditions, the conditions being acceptance of the Panel's recommendations for changes in labeling, revisions to the patient booklet, and implementation of a postmarket study of endothelial cell density. The motion was approved unanimously (11–0). Each voting Panel member stated his or her reasons for voting for approval with conditions.

Dr. McCulley and Ms. Thornton thanked the Panel members, the sponsor, and the FDA for their contributions. The meeting was adjourned at 3:35 p.m.

I certify that I attended the Ophthalmic Devices Panel meeting on June 5, 1998, and that this summary accurately reflects what transpired.

Sara M. Thornton
Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

James P. McCulley, M.D.
Chair

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