

SUMMARY MINUTES

OF THE

OPHTHALMIC DEVICES PANEL MEETING

OPEN SESSION

February 5 and 6, 2004

**Gaithersburg Marriott
Gaithersburg, MD**

OPHTHALMIC DEVICES PANEL ROSTER

Attendees

February 5, 2004

Chair

Jayne S. Weiss, M.D.

Voting Members

Arthur Bradley, Ph.D.

Anne L. Coleman, M.D., Ph.D.

Michael R. Grimmatt, M.D.

William D. Mathers, M.D.*

Timothy T. McMahon, O.D.

Panel Consultants

Karen Bandeen-Roche, Ph.D.

Richard Casey, M.D.

Andrew J. Huang, M.D.

Marian S. Macsai-Kaplan, M.D.*

Oliver D. Schein, M.D.*

Janine A. Smith, M.D.

Woodford S. Van Meter, M.D.

Consumer Representative

Glenda V. Such, M.Ed.

Industry Representative

Andrew K. Balo

FDA Participants

Sara M. Thornton

Panel Executive Secretary

A. Ralph Rosenthal, M.D.

Director, Division of Ophthalmic Devices

Everette T. Beers, Ph.D.

Chief, Diagnostic and Surgical Devices
Branch

James F. Saviola, O.D.

Chief, Vitreoretinal & Extraocular Devices
Branch

Donna R. Lochner

Chief, Intraocular & Corneal Implants
Branch

Jeffrey Toy, Ph.D.

Toxicologist, Intraocular and Corneal
Implants Branch

Team Leader, PMA P030028

Bernard P. Lepri, O.D., M.S., M.Ed.

Optometrist, Vitreoretinal and Extraocular
Devices Branch

Clinical Reviewer, PMA P030028

Gerry W. Gray, Ph.D.

Statistician, Office of Surveillance and
Biometrics

* Primary Reviewer for PMA P030028

CALL TO ORDER

Panel Chair Jayne Weiss, M.D., called the meeting to order at 9:01 a.m. and noted that a quorum was present. **Panel Executive Secretary Sara Thornton** welcomed participants and announced the appointment of William D. Mathers, M.D., as a voting member. She noted that Andrew Balo was acting industry representative for the meeting on February 5, 2004, and asked the panel members to introduce themselves.

Executive Secretary Thornton then read the conflict of interest statement. Full waivers had been granted to Michael R. Grimmatt, M.D., Oliver D. Schein, M.D., and Woodford S. Van Meter, M.D., for their interests in firms that could be affected by the panel's recommendations. She noted for the record that the Agency had taken into consideration other matters involving Drs. Grimmatt and Schein and Arthur Bradley, Ph.D., Anne L. Coleman, M.D., Ph.D., Andrew J. Huang, M.D., Marian S. Macsai-Kaplan, M.D., and Jayne S. Weiss, M.D., all of whom reported past or current interests involving firms at issue but in matters not related to the day's agenda. They may participate fully. She read the appointment to temporary voting status, which granted voting status to panel consultants Karen Bandeen-Roche, Ph.D., Richard Casey, M.D., Andrew J. Huang, M.D., Marian S. Macsai-Kaplan, M.D., Oliver D. Schein, M.D., Janine A. Smith, M.D., and Woodford S. Van Meter, M.D., for the duration of the meeting.

OPEN PUBLIC HEARING

Executive Secretary Thornton read a letter into the record from **Peter D. Van Patten, M.D., Duluth Clinic Virginia, Virginia, MN**, who received Artisan lens implants after experiencing increasing problems with contact lenses. His sight improved significantly after receiving the implants. He now wears glasses only for night driving. He experiences minimal night glare. The Artisan lens is an important investigational surgical option for his patients. The lens is safe and effective when implanted by a skilled surgeon.

Leslie Woodlock, patient advocate, Surgical Eyes Foundation, noted that she became involved with the organization after failed LASIK surgery in 2000. She asked the panel to address numerous issues as it reviewed the PMA, including diameter selection, endothelial cell loss, anterior chamber depth (ACD), risks involving later cataract surgery, risk for unwanted halos and glare, and proper informed consent procedures.

Glenn Hagele, Executive Director, Council for Refractive Surgery Quality

Assurance (CRSQA), noted that the phakic intraocular lens (PIOL) has been available outside the United States for the better part of a decade. The panel should consider including in the physician and patient labeling that it is difficult to determine the probability of induced night vision problems when the scotopic pupil is larger than the size of the full optical correction of the device is not easily determined. Patient labeling should include a representation of these effects, including difficulty driving at night and reading in low-light environments, and it should include a statement indicating that training and practical experience of the surgeon may be an important factor in the probability of a desirable outcome. In addition, the patient labeling should indicate the type and frequency of probable surgery-related long-term care; for example, patients will require periodic evaluation of intraocular pressure (IOP) after PIOL implantation. No clear consensus exists on the long-term effects of PIOL on endothelial cells. The functional life of a PIOL may be as much as 40 years; during this time, the need for regular evaluation of endothelial cell loss is clear, but who will pay for those costs? PIOL implantation is an elective, arguably cosmetic procedure. If patients are properly informed of the immediate and long-term issues relating to the sponsor's PIOL, those who elect to have lens implants will have reasonable expectations and will be able to make the decision that best meets their needs.

Morris John, Ophthalmologist, Louisville KY, implanted the first five Artisan lenses in the United States and has implanted more than 200 lenses to date. The Artisan lens has a short but steep learning curve for surgeons. The lens needs adequate ACD in order to be successfully implanted. Many of his patients do not have glare or have had glare all their lives and experience the lens as an improvement. Other problems are surgeon related. Many surgeons prefer this lens to other PIOLs. With this lens, patients see well and experience minimal side effects.

OPEN COMMITTEE SESSION

Division Updates

A. Ralph Rosenthal, M.D., stated that the Agency strongly recommends that all companies schedule a pre-PMA meeting with the Agency to discuss accountability, stability, and safety and efficacy, even if the company has previously submitted numerous PMAs. Doing so will help ensure a better submission and one that will be less likely to result in a "non-filable" decision or a major deficiency letter.

Donna R. Lochner, Former Chief, Intraocular and Corneal Implants Branch, stated that the Morcher GmbH endocapsular tension ring (P010059), which was reviewed at the January 2002 panel meeting, was approved October 23, 2003. The device is indicated for the stabilization of the crystalline lens capsule in the presence of weak or partially absent zonules in adult patients undergoing cataract extraction with IOL implantation.

The Eyeonics (formerly C&C Vision) CrystaLens™ Accommodating Intraocular Lens (P030002), which was reviewed at the May 2003 panel meeting, was approved November 14, 2003. The device is intended for primary implantation in the capsular bag of the eye for the visual correction of aphakia in adult patients in whom a cataractous lens has been removed. It is intended to provide near, intermediate, and distance vision without spectacles. The lens provides approximately 1.00 diopter (D) of monocular accommodation.

Everette T. Beers, Ph.D., Chief, Diagnostic and Surgical Devices Branch, stated that three PMAs have been approved since the last panel meeting. The Wavelight Allegretto Laser Myopia + Astigmatism device (P020050) was approved for LASIK correction of myopia of up to -12.00 D with or without astigmatism of up to -6.00 D. The Wavelight Allegretto Laser Hyperopia + Astigmatism device (P030008) was approved for LASIK correction of hyperopia up to +6.00D sphere with up to +5.00 D cylinder, with manifest refractive spherical equivalent (MRSE) up to + 6.00 D. The B&L Zyoptix device (P990027/S6) was approved for wavefront-guided LASIK correction of myopia of up to -7.00 D with up to -3.00 D of astigmatism and MRSE up to -7.50 D.

Approximately 36 510(k)s were cleared in 2003.

SPONSOR PRESENTATION

Rick McCarley, President, Ophtec, thanked the FDA review team and introduced the sponsor presenters and consultants.

Vance Thompson, M.D., Sioux Falls, SD, presented information on the design features and history of the lens and described his experience with it. He implanted his first lens in 1998 and since then has implanted the lens in 95 eyes. All of his patients are pleased with the outcome. The Artisan lens has some unique safety features that explain its positive results.

The device is a single-piece, elliptical, polymethylmethacrylate (PMMA) lens with a slight anterior vault. It is designed for implantation into the anterior chamber of the phakic eye. It

is fixated to the mid-periphery of the iris by incorporation of the iris into a cap in the haptics, a process called *enclavation*. Proper fixation requires about 1 mm of iris tissue. An advantage of the lens is its ease of attachment and detachment. It can be repositioned during surgery or easily removed, if necessary. It is available in two sizes, 6 mm and 5 mm, each with a different diopter range. Because the lens attaches to a relatively immobile part of the iris, the pupil can be dilated.

Dr. Thompson then summarized the development of the Artisan PIOL. The current design has been in use since 1991 around the world. It is the most commonly implanted lens in the world today. It is frequently used as a secondary implant, particularly during penetrating keratoplasty (PK). It offers stable fixation over time with normal pupillary function and no iris atrophy. To date, more than 100,000 myopic, hyperopic, and toric lenses have been implanted worldwide by 5,000 physicians.

A European multicenter study of 518 eyes implanted from 1991 to 1999 found low amount of endothelial cell loss and good stabilization over time. Mean endothelial cell density change was -4.8 percent at 6 months and -2.4 percent from 6 months to 1 year; the change was -0.7 percent from Year 2 to Year 3. Best corrected distance visual acuity (BSCVA) was =20/40 for 93.9 percent of participants, and uncorrected visual acuity (UCVA) was =20/40 in 76.8 percent of participants. A total of 57.1 percent of study participants were within 0.50 D of the target, and 76.8 percent were within 1.00 D of the target. The results demonstrate refractive stability and good predictability. The risk-benefit ratio is favorable, and the study demonstrated safety and efficacy. No reports in the literature indicate long-term safety concerns with the lens design.

Doyle Stulting, M.D., Ph.D., Emory University, Atlanta, GA, presented findings from the U.S. clinical investigation. Dr. Stulting was one of the medical monitors of the clinical study and is a paid consultant to the sponsor. The clinical study was an open label, non-comparative study in patients with 4.60 to 22.0 D of myopia. The lenses were provided in 1.00 D power increments; the 5 mm lens is available in -5.00 to -20.00 D, and the 6 mm lens is available in -5.00 to -15.00 D. Patients had eight postoperative visits.

Patients were age 21 to 50 with stable manifest refraction and ACD = 3.2 mm and refractive cylinder = 2.00 D. Endothelial cell density was = 2,000 cells/mm², and pupil size was = 4.5 mm. No study participants had an ocular disease or abnormality that would affect safety. Protocol waivers were requested and granted by FDA until November 2000, when the protocol

was changed to include patients with preexisting clinically insignificant and stable peripheral lens opacities, astigmatism of ≤ 2.50 D, ACD < 3.2 mm, age > 50 , pupil size $>$ optic size, preoperative BSCVA $< 20/40$, and inability to completely correct refractive error. Results were obtained for all eyes and participants.

Outcome measures included uncorrected distance visual acuity (UCVA), best spectacle-corrected distance visual acuity (BSCVA), manifest and cycloplegic refraction, contrast sensitivity, intraocular pressure, pupil shape, endothelial cell density, and slit lamp exam. Cataract formation was not identified as a significant risk because of the device's 6-year history of implantation internationally and anterior placement of the IOL. The approved protocol required only clinical grading of cataracts rather than standardized grading. As the available technologies and knowledge advanced, the sponsor changed investigational procedures consistent with FDA, ANSI and ISO discussion in developing guidelines. The study enrolled 684 participants between October 1997 and July 2003: 662 participants were in the primary study, 478 of whom were bilaterally implanted. Twenty-two patients were implanted for compassionate use. Participants were divided into several groups for the purposes of analysis. The safety analysis is based on results in both eyes, but the efficacy analysis is based on results in first eyes.

The data are from 386 eyes followed for 3 years. The study was originally designed and powered as a 2-year study; some participants therefore did not return for the 3-year follow-up visit. 8 percent were lost to follow-up. Mean patient age was 39.6 years; many study participants were high myopes who were at high risk for undesirable outcomes.

The safety analysis found that 100 percent of study participants had BSCVA $\leq 20/40$ at 2 or 3 years after surgery. At 3 years, 49 percent had gained BSCVA. Losses were due to measurement variability. The results demonstrate improvement after surgery, which other lenses do not provide. Any induction of astigmatism was due to the surgery, not device failure. Early postoperative findings included flare; corneal edema; iris pigment precipitates; increased IOP; and mild, asymptomatic ovalization of pupil. The effects decreased with time. Eighteen of 1,140 eyes experienced acute elevation in IOP, most of which occurred 1 day postoperatively; all resolved by 20 days. IOP increases were attributed to retained viscoelastic or steroid response.

The adverse events of greatest concern are secondary surgical interventions that are lens related, medically necessary (not prophylactic), not treatable with common technologies that would be available after approval, and not preventable. Twenty-seven of 41 adverse events fell

outside these criteria. Most secondary surgical interventions occurred during early surgical experience, and a disproportionate number (12 of 31, or 38.7 percent) occurred at one site. Most secondary surgical interventions (22/31) were due to improper lens fixation. Fifty percent of events occurred among the first 10 participants implanted. Ten lenses required reattachment, two lenses were exchanged, and two were explanted. Twenty preventative repositionings took place. Half of the secondary surgical procedures were due to trauma. Retinal detachment occurred in six eyes, all of which had preoperative MRSE between -11.50 and -18.60 D. Those results are not inconsistent with the literature.

Three of 1,179 eyes (0.25 percent) required cataract extraction; the incidence of cataracts in the study population is not unexpected. Only two eyes lost more than 2 lines of BSCVA; one was due to retinal detachment and subsequent macular hole, and one was due to posterior capsular haze following cataract extraction and PCIOL implantation. The sponsor recommends extensive physician training to reduce secondary procedures.

Two additional adverse events occurred after PMA submission: one consisted of IOL removal, cataract extraction, and PCIOL implantation in an eye that underwent repair of retinal detachment, and the other consisted of IOL reattachment following IOL dislocation due to boxing.

The original protocol did not provide good statistical power to rule out significant changes in endothelial cell density, but the data presented are consistent with the guidance provided to industry by the FDA. A review of raw data indicated that the quality of images could be improved. A recount was done at 12 sites, and one reading center was used to ensure consistency. The best quality image read per eye per visit was used. A total of 353 eyes (representing 215 participants) and a consistent cohort of 57 participants were analyzed. Endothelial cell density was measured at 6 months, 1 year, 2 years, and 3 years. At 3 years, the mean percentage change from baseline was -4.76 percent ± 7.8 percent for all recounted eyes, which is an equivalent yearly rate of -1.59 percent; for the consistent cohort, the mean percentage change from baseline was -3.80 percent ± 9.8 percent, which is an equivalent yearly rate of -1.27 percent. In both groups, the change between consecutive periods was not statistically significant. One site had a statistically significantly larger loss at 3 years; results from that site may not be poolable, and removing that site from the analysis improves the endothelial cell loss data. In addition, based on measurement variability alone, a cell loss

measurement of 10 percent or more would be expected in 13 percent of eyes when no real change in endothelial cell density had occurred. The results are not significantly different from the guidance. Average cell loss over time was 1.72 percent per year. Hexagonality and coefficient of variation data support the conclusion that the lens does not stress the endothelium, and no consistent statistically significant associations were found with various demographic and physiologic variables. The Artisan lens has an excellent safety profile.

UCVA was measured in first eyes at 3 years, and the results were excellent. Seven of 87 eyes did not achieve UCVA, primarily because of residual astigmatism or residual myopia. Only 1.00 D lens power increments were available in the study and that the study included participants with more than 2.50 D of astigmatism without astigmatic correction. UCVA is expected to increase after approval, because 0.50 D power increments are available and astigmatic corrective procedures are likely to be performed. Manifest refraction data show that 94.7 percent of study participants were within 1.00 D of the target refraction and that the mean spherical equivalent remained stable over time.

Patient satisfaction was high; less than 10 percent of participants gave “unfavorable” ratings to quality of vision, satisfaction with surgery, and willingness to recommend the procedure. Most patients had no change in glare, halos, and starbursts. However, the proportion of patients who did not experience halos before surgery but experienced halos postoperatively was 65 percent, a statistically significant difference. Nighttime visual symptoms were not significantly correlated with lens optic size being larger than mesopic pupil size, lens power, or refractive cylinder (except for halos). Symptoms will likely diminish postapproval due to the availability of 0.50 D lens power increments and additional surgery for residual astigmatism.

A substudy at one site found no decrease in contrast sensitivity under different conditions. Statistically significant differences, where present, usually show better contrast sensitivity postoperatively than preoperatively.

Finally, Dr. Stulting presented the sponsor’s labeling and training proposals and asked the panel to recommend approval of the PMA.

Panel Questions for Sponsor

Panel members raised issues concerning outcomes when pupil size was larger than optic size; whether any study participants were on Alphagan at night; whether data from other sources

were available that could be useful; the number of and rationale for protocol deviations; the role of magnification in the improved visual acuity reported; appropriateness of the procedure for people who are in sports careers or were otherwise prone to head trauma; appropriateness of the procedure for relatively young patients; the small number of minority patients in the study; how the sponsor ensured that patients with glaucoma were excluded from the study; the adequacy of the sponsor's training program for preventing adverse events; safety and efficacy in low-myope patients; and possible hindrance of activities among patients experiencing nighttime visual symptoms.

Panel members were concerned about methodology of the sponsor's endothelial cell count data, particularly comparability of the 12 sites that contributed data to those sites that did not contribute data. They expressed concern about additional endothelial cell loss in study participants who required second surgeries and requested endothelial cell count data on patients in the subgroup the sponsor designated as Group E, which includes all eyes not included in the subgroups designated as Groups A and B (i.e., all first and second eyes) as well as compassionate use eyes in eyes with replacement lenses.

FDA PRESENTATION

Jeffrey Toy, Ph.D., Toxicologist, Intraocular and Corneal Implants Branch, and Team Leader, PMA P030028, listed the review team members and introduced the FDA speakers.

Bernard P. Lepri, O.D., M.S., M.Ed., Optometrist, Vitreoretinal and Extraocular Devices Branch, and Clinical Reviewer, PMA P030028, summarized the risks and benefits of the Artisan lens. Operative risks may include improper enclavation, which can lead to surgical repositionings; wound leakage; infection; induced cataract; and corneal damage due to surgical trauma. Postoperative risks include elevated IOP, inflammatory responses, the potential for pigmentary glaucoma as a result of iris irritation, critical losses of corneal endothelial cells and function, retinal detachment, and dislodgement of the IOL itself with concomitant optical side effects such as glare and halo. Benefits include correction of high refractive errors without the optical limitations imposed by spectacles or the complications of long-term wear contact lens. Reversibility and expanded options for treatment of high refractive errors benefit both the practitioner and the patient.

In the sponsor's clinical study, UCVA of 20/20 or better was achieved by more than 30 percent of the total treated population at 1, 2, and 3 years. UCVA of 20/40 or better was achieved by proportions ranging from 84 to 87 percent over the 3-year period of the study. At least 79 percent of study participants had 20/20 BSCVA or better and 100 percent had 20/40 or better in the overall treated population. In the consistent cohort, mean differences in refraction between visits ranged from -0.02 D to -0.05 D over the 3-year period. Of the 49 lens opacities reported, 4 were visually significant: 3 required extraction, and 1 eye lost 2 lines of BSCVA. After 30 years the endothelial cell count may drop to $1,272$ cells/mm². The inclusion criteria specify $=2,000$ cells/mm² as the lower limit for preoperative endothelial cell count, but that may not be sufficient for younger patients. The two lens sizes directly relate to pupil sizes in mesopic conditions and associated glare and halos.

Gerry W. Gray, Ph.D., Statistician, Office of Surveillance and Biometrics, reviewed the sponsor's endothelial cell count data. Endothelial cell counts and measurements were taken at baseline; 6 months; and years 1, 2, and 3. A total of 353 available eyes from reliable machines were recounted in one reading center. That was a total of 1,144 observation eyes by visit. . No control group was available.

It is important to have reasonable assurance that endothelial cell density is preserved. The point for concern is $1,000$ to $1,200$ cells/mm². The ANSI and ISO standards documents suggest that one calculate a sample size for this kind of study using a 2.0 upper 90 percent confidence interval. The FDA draft guidance sets an acceptable loss rate with an upper confidence limit of 90 percent at 1.5 percent per year. The estimates reflect steady-state long-term loss.

Annual rates of endothelial cell loss are highest in the first 3 years, then low thereafter. The data do not indicate any perioperative period with increased endothelial cell loss. Much variability exists in individual rates of loss. The calculations assume a linear loss rate, but it is not clear that is the case. The data conflict with expected outcomes in all guidance documents. The percentage change from baseline is not equivalent to the steady-state long-term rate. The estimate depends somewhat on whether the baseline count is included in the regression.

Extrapolation is always a questionable exercise. If one starts with a baseline endothelial cell density of $2,700$ cells/mm², at the estimated loss rates, it would take 12 to 17 years to reach $2,000$ cells/mm². How individual patients fare is perhaps more important than average cell loss through time. It is difficult to answer with any confidence what proportion of patients will show

cell loss greater than some critical amount or what proportion will have cell densities of less than 1,500 or 800 cells/mm² at a given time point.

Dr. Lepri reviewed the panel questions and presented data tables.

Panel Questions for FDA Personnel

The panel's questions focused on Dr. Gray's extrapolation methodology and findings, which he clarified to their satisfaction.

COMMITTEE DELIBERATIONS

The sponsor provided clarification in response to various panel questions concerning pupil size, explantation, and bias in selection of endothelial cell recount patients.

Panel Review

Dr. Mathers provided the first primary panel review. He raised several safety concerns, primarily related to endothelial cell loss over time and changes in endothelial cell density resulting from lens insertion. For the entire group of participants in the sponsor's study, the endothelial cell loss rate was 1.58 percent per year in the first 3 years; however, the normal loss rate is 0.6 percent over 3 years—2.5 percent at 10 years after cataract surgery. Patients who received the lens at age 20 would reach the point of risk for corneal failure and cataract in 30 years. Although the lens has not been removed from any markets for safety concerns, it would take more than 15 years to achieve a sufficiently low endothelial cell density to create corneal edema. The rate of cataract development in the study group is already higher than average, and postoperative inflammation in the form of cell and flare was persistent in 1.3 percent of subjects at 6 months. The accuracy of the implant appears to be excellent considering the difficulties in determining chamber depth and refractive error in high myopes. MRSE was quite good, and most participants gained at least 1 line of BSCVA. Halos can be expected in night when the pupil is largest and light passes outside the limits of the lens. Responding to the FDA questions for the panel, Dr. Mathers stated that the lens is not safe for the current intended population. Patients should be required to have a preoperative endothelial cell count of more than 2,400 cells/mm² and should be at least 35 years old, regardless of cell count. The restriction would delay onset of the mean risk point to age 75. As an alternative or additional method to reduce risk, the lens

should be limited to patients most in need who had refraction of ≤ -9.00 D; to those with ACD > 3.2 mm. Lens diameter should be limited to the size of the dark-adapted pupil to reduce halos.

Dr. Schein in his primary panel review raised concerns over how the sponsor reported data. The sponsor should not have excluded any patients from the safety analysis, and the safety data and adverse events should have been reported by person rather than by eye, because so many participants were bilaterally implanted. The sponsor was able to report on less than half of the potential 3-year data.

The sponsor also created an arbitrary division between *complications* and *adverse events*; for example, lens opacity, but not cataract extraction, was defined as a complication. Medical and surgical complications with potential to cause harm should be distinguished from trivial events. The lens and the surgical procedure are inextricably linked. Lens opacities were reported in about 5 percent of eyes, but no standardized grading system was used. What proportion of patients receiving the lens will need cataract surgery within 10 years? Comparisons with outcomes for anterior chamber intraocular lenses (ACIOLs) are inappropriate for this device. Patients reported several visual side effects; 16 to 30 percent had symptoms not noted preoperatively. Further analysis is needed to ascertain whether certain subgroups had intolerable adverse event rates.

Finally, with regard to endothelial cell count, the sponsor's data have limitations. Although little evidence indicates systematic bias, the evaluation of means is not helpful, given that about 25 percent of patients lost 10 percent or more cells. How were discontinued participants or those with secondary procedures handled? The reanalyzed endothelial cell count data appear to represent only about 15 percent of images. Canadian and European data are not reassuring.

On the basis of what has been reported to date and the incompleteness of the data, the safety of the device is a concern. Additional analyses on the complete cohort would help alleviate the concern. Should the lens be approved, postmarket surveillance is warranted. Dr. Schein also listed several labeling suggestions, which he had submitted previously.

Dr. Macsai in her primary panel review reiterated many of the concerns of the other panel reviewers and pointed out that the lack of standardization and aspects of the protocol design of the PMA limit the ability to evaluate safety and efficacy of the lens. The sponsor's safety criteria are inadequate. PIOLs should not be compared with ACIOLs because the device is

not being used to treat patients with cataracts who have had vision loss. Use of the FDA grid for ACIOLs to determine acceptable levels of safety is therefore inappropriate. PIOLs must be held to a much higher standard than the FDA grid. In addition, the summary of key safety and efficacy variables was not submitted in a stratified manner for patients from Group E. The lack of this data is a significant deficiency. Consumers must have this information.

Twenty-six eyes had preoperative lens opacities that were not measured in any standardized manner; this oversight invalidates the comparison of the preoperative incidence of lens opacities with the postoperative incidence. In addition, 41 eyes were enrolled with corneal abnormalities. The definition of corneal abnormality is not clear. Without the information it is not possible to tell if the endothelial cell count data may be skewed from including these 41 eyes.

The adverse event rate was 3.9 percent, which is significantly higher than the 1 percent suggested as an approvable level for this PMA. The sponsor cannot arbitrarily decide what an adverse event is—anything that happens that is bad is an adverse event. It is unclear what the real number of adverse events is. It is significant that 23.8 percent of patients with pupils greater than 5.5 mm under mesopic conditions reported halos. These are high numbers and are *induced* problems. Sixty-seven patients experienced spikes of more than 30 mm of Hg, and gonioscopy was not performed in any of those patients preoperatively or postoperatively. The role of pigment dispersion, flare, some level of chronic inflammation, and possible acceleration of cataract formation or glaucoma from an IOL that is stabilized by enclavation of the iris has not been ruled out.

Finally, the endothelial cell data submitted by the sponsor were difficult to analyze. Only 12 sites that used the Konan microscope had endothelial cell images that could be evaluated. Loss of endothelial cells was higher between Years 2 and 3. The data demonstrate an increase in cell loss over time. Eyes with ACD of 3.0 to 3.2 mm had higher rates of cell loss, indicating that ACD plays a role. The data show that the endothelial cell count has not stabilized. The estimated endothelial cell loss rate of 1.58 to 3.05 percent is too high for a young person.

FDA QUESTIONS FOR PANEL

- 1. Do the endothelial cell data presented above in the overall analysis, stratified by anterior chamber depth and the extrapolations over time, provide reasonable assurance of safety of the Artisan myopia lens?**

The panel concurred that the data provided in the overall analysis do not demonstrate reasonable safety.

2. Do the other data presented in the PMA provide reasonable assurance of safety?

Many panel members felt that the data presented in the PMA do not provide reasonable assurance of safety. Lens opacity, retinal detachment, increased IOP, and the need for revision surgery were of concern. The adverse event rates do not take into account the time under observation. Chronic inflammation and other issues may lead to accelerated cataract formation. The sponsor should provide adverse event rates by patient and by eye, along with a timeline. Adverse events that could cause harm or loss of vision should be separated from those that do not have major clinical significance. Data should also be stratified by lens power and should be provided for Groups C–E or all groups together without the separate groupings. The panel was also concerned about cataract formation and retinal detachment, noting that the absence of a control group makes the assessment of cataract formation extremely difficult. The sponsor did not provide adequate data on minority patients. One of the issues with high myopes is that they are at increased risk for glaucoma and there could be a lot of undiagnosed glaucoma that may or may not have gotten worse by the placement of this lens; however, there is no data for this. Also gonioscopy was not performed to determine the status of subjects on medication for increased intraocular pressure. The sponsor needs to address the panel’s safety concerns, whether with new data or reanalysis of existing data. Additional follow-up data on the patients enrolled in the clinical study are needed; data for only 60 percent of patients’ data are available now. A postmarket study may be appropriate.

Panel members noted that this device is trying to address a real need and may be suitable for a narrow range of patients who have few alternatives. However, they were concerned about the device’s impact on long-term endothelial cell loss and the inadequacy of the sponsor’s data for answering questions on the subject. Extrapolated data are not sufficient to determine safety. Agency staff commented that the sponsor had provided data for 300 eyes and had therefore met the Agency’s requirements for adequately powering the study’s safety analysis. Overall, a majority of the panel felt they needed more premarket data to decide whether the device is reasonably safe.

3. The proposed statement of indications reads: “The reduction or elimination of myopia in adults with myopia ranging from greater than –5 to less than –20 D with less than 2D of astigmatism at the spectacle plane; Patients with documented stability of refraction for the prior 6 months, as demonstrated by a spherical equivalent change of less than or equal to 0.50D.” Does the panel recommend any modifications to the proposed statement of indications with respect to: (a) minimum anterior chamber depth of <3.2 mm were excluded in the study); (b) maximum pupil size (the 2 models of Artisan are intended for patients with pupil sizes up to 5.0 mm and up to 6.0 mm); and (c) minimum preoperative endothelial cell

density? The outcomes of ECC changes reported in number 1 above could be used to determine acceptable minimum endothelial cell densities.

Panel members concurred that ACD should be “greater than 3.2 mm.” They also generally agreed that the pupil size should not be larger than the optic, although some panel members stated that the data did not support that conclusion. The panel asked the Agency to use a 2 percent annual cell loss rate to calculate the minimum endothelial cell density for patients at any given age who are contemplating receiving the Artisan lens. The sponsor’s data alone were insufficient to determine minimum preoperative endothelial cell density.

4. Do the panel members have any additional labeling recommendations?

Panel members suggested including the following changes to the labeling:

- ?? Include the table of preoperative and postoperative visual symptoms of glare, starbursts, and halos, by mesopic pupil size
- ?? Possibly include a statement that patients should have explored other options for refractive correction before proceeding to having the surgery
- ?? Dr. Coleman had numerous edits to the labeling involving the language concerning use of the lens in patients with glaucoma, risks involving IOP, and glossary terms; she submitted her recommendations in writing to the panel executive secretary.
- ?? The labeling should state that the effects of loss of endothelial cell density are unknown.
- ?? Long-term effects on corneal function, lens opacities, and corneal edema have not been established.
- ?? The sponsor should not claim that the lens improves contrast sensitivity and add lines of vision, because those effects are artifacts of magnification. The product should clearly state that when switching from spectacle correction to this IOL, magnification will result in myopic eyes, with potential improvements in visual acuity.
- ?? Both physician and patient labeling should include a clear, understandable statement describing the panel’s concerns about the future risks of this product.
- ?? The adverse event rates as written imply that the data are based on the full cohort, which is not accurate. The term “nonadverse event” should not be used in the patient labeling.
- ?? The data should list how many people required additional refractive procedures.
- ?? Complications should include cataract and lens opacity.
- ?? Endothelial cell data should be presented in terms of thresholds.
- ?? The reference to the FDA grid for ACIOLs should be deleted.
- ?? Risk of dislocation due to trauma should be listed under precautions.
- ?? Precautions should include risk of starbursts and halos in low-light conditions.
- ?? The patient brochure uses terminology patients are not likely to understand and should be revised accordingly.
- ?? The glossary is inadequate.

Some panel members felt that the lens should not be approved for use in patients under age 18 because they were not in the study population. Most panel members declined to specify a

minimum age, but they were comfortable with the Agency determining appropriate age/endothelial cell density parameters for patients considering the lens. The panel members also concurred that the minimum refractive error should be 9.00 D. The sponsor should conduct a postmarket study on a new cohort of patients for 2 to 3 years to determine rates of serious adverse events.

OPEN PUBLIC HEARING

Morris Johns, ophthalmologist, Louisville, KY, spoke in favor of approving the lens. Patients outside the 20/40 range benefit the most from the surgery. Refractive surgeons do not have many options. A prudent doctor would do endothelial cell counts every year. It is wise for the panel to suggest that ACD be greater than 3.2 mm because specifying the minimum ACD will reduce some complications. Retinal detachment and cataract are not of great concern. The panel is making a mistake by limiting the minimum refractive error to 9.00 D—the device works well for patients with thin corneas who are not candidates for LASIK.

Sponsor Closing Comments

Dr. Stulting said that he appreciated the panel's concerns. An effective training program can be constructed so that the average ophthalmologist can do the procedure. The technology is available everywhere but the United States. If endothelial cell loss were an issue, it would have appeared after 100,000 implants.

VOTE

Ms. Thornton read the voting options. The panel vote ended in a tie, with 6 voting for and 6 voting against recommending approvable with conditions. Panel Chair Weiss cast the tie breaking vote in the affirmative for approval with the following conditions:

1. Patient ACD should be >3.2 mm.
2. The device is approved for a dioptric range of -9.00 D to -20.00 D.
3. The Agency should determine the age as well as the minimal cell count from which they will work backward as well as whether it will be quartile versus two percent cell loss in order to determine the cell count allowable for implantation of the lens at a given age.

4. A 2- or 3-year postmarket study should evaluate the incidence of retinal detachments, lens explants, and cataract formation with a sample size calculated by the Agency followed for two to three years.
5. Existing data should be reanalyzed for pigment dispersion and increased IOP with respect to the minority cohort subset.
6. The sponsor should revise the labeling as follows:
 - ?? State that trauma is a risk factor for IOL dislocation.
 - ?? Provide an accurate definition of “adverse event” for consumers.
 - ?? Properly stratify data by lens power (± 0.50 D or 1.00 D).
 - ?? State that 38 percent of participants achieved 50 percent reduction in endothelial cell density in 25 years.
 - ?? State that when pupil size is greater than the optic size, visual aberrations may result.
 - ?? The table summarizing data on preoperative and postoperative glare, starburst, and halo should be included.
 - ?? In the physician’s draft directions for use
 1. Item 5h. Replace “medically uncontrollable glaucoma” with “glaucoma”
 2. Item 7. Revise to state “Elevated intraocular pressure has been reported occasionally in patients who have received lens implants. The intraocular pressure of patients should be monitored postoperatively.”
 3. Under Summary of Other Complications – Delete “No incidence of pupillary block” because there was an incidence of presumed pupillary block. Delete “persistent raised IOP” and mention that slightly less than 1% of the patients need medication for intraocular pressure control.
 4. Include a statement that the patient’s risk of glaucoma in the future is unknown.
 5. Include a statement that the effect on the drainage angle is unknown because they didn’t do gonioscopy pre and postoperatively.
 - ?? In the patient labeling
 1. Under No.10, Warnings substitute “glaucoma” for “medically uncontrollable glaucoma”.
 2. Under Precautions replace “secondary glaucoma” with “elevated eye pressures” and change the second sentence to “Intraocular pressures of patients should be monitored postoperatively.
 3. To the index add the terms glaucoma, intraocular pressure or eye pressure.
 - ?? Delete statements referring to “improved” visual acuity and “improved” contrast sensitivity. In the patient information booklet it should be stated that the patient’s visual acuity at distance will be “improved” rather than using the word “clear
 - ?? If the lens is approved, delete the statement that safety and efficacy have not been established
 - ?? State that long-term risk to corneal endothelial cells has not been established and that the short term cell count decreases.
 - ?? A suggestion that physicians could perform a contact lens refraction to improve the accuracy of IOL power prediction for higher myopes.

- ?? Adverse events should be provided on a per eye and per patient basis. Risk for future lens opacities, retinal detachment and cataract formation should be mentioned.
- ?? The contrast sensitivity information should state that spectacle use in the re-op testing versus iris plan IOL testing does not indicate improved contrast sensitivity following the procedure.
- ?? Describe what it means to have corneal edema and cataract surgery.
- ?? State that the future risk for the development of lens opacities is unknown.
- ?? The patient brochure should clarify the difference between complications and adverse events.
- ?? Labeling should provide a list of mean cell loss rate and a chart showing percentage of patients losing certain increments such as 10 percent of cells, 20 percent of cells at various time intervals.
- ?? The reference to the FDA grid for ACIOLs should be deleted.
- ?? The labeling should state that the lower age range in the study was 21, not 18.
- ?? Precautions should include risk of starbursts and halos in low-light conditions.
- ?? The sponsor should rework the glossary so that the terms are accurate and comprehensible to the lay person.
- ?? Improved clarification of study size, duration, and complication rates should be added.

7. The Agency should recalculate the cumulative clinically significant adverse event and adverse reaction rate.

8. Data for safety and efficacy of Group E should be analyzed and reviewed by the Agency.

POLL

Panel members recommending the device to be approvable with conditions, felt that the device offered reasonable assurance of safety and efficacy and was a needed alternative for high myopes. With appropriate restrictions and precautions, patients can be protected from endothelial decompensation.

Panel members recommending against approvable with conditions, believed that the device is not safe or effective enough to warrant approval for a procedure that is essentially cosmetic. They were concerned about the inability to determine risk of complications on a per patient basis and the questions around endothelial cell loss. The sponsor's follow-up data were inadequate.

ADJOURNMENT

Dr. Weiss thanked the participants and adjourned the meeting at 5:46 p.m.

OPHTHALMIC DEVICES PANEL ROSTER

Attendees

February 6, 2004

Chair

Jayne S. Weiss, M.D.

Voting Members

Arthur Bradley, Ph.D.

Anne L. Coleman, M.D., Ph.D.

Michael R. Grimmatt, M.D.

William D. Mathers, M.D.

Timothy T. McMahon, O.D.*

Panel Consultants

Karen Bandeen-Roche, Ph.D.

Richard Casey, M.D.

Andrew J. Huang, M.D.*

Marian S. Macsai-Kaplan, M.D.

Oliver D. Schein, M.D.

Janine A. Smith, M.D.

Woodford S. Van Meter, M.D.

Consumer Representative

Glenda V. Such, M.Ed.

Industry Representative

Ronald E. McCarley

FDA Participants

Sara M. Thornton

Panel Executive Secretary

A. Ralph Rosenthal, M.D.

Director, Division of Ophthalmic Devices

Everette T. Beers, Ph.D.

Chief, Diagnostic and Surgical Devices
Branch

James F. Saviola, O.D.

Chief, Vitreoretinal & Extraocular Devices
Branch

Donna R. Lochner

Chief, Intraocular & Corneal Implants
Branch

Jan Callaway

Microbiologist

Diagnostic and Surgical Devices Branch
Team Leader, PMA 010018/S5

Sheryl L. Berman, M.D.

Medical Officer

Division of Ophthalmic & Ear, Nose and
Throat Devices

Clinical Reviewer, PMA P010018/S5

* Primary Reviewer for PMA P010018/S005

CALL TO ORDER

Panel Chair Jayne S. Weiss, M.D., called the meeting to order at 9:37 a.m. and noted that a quorum was present. **Ms. Thornton** read the Agency's statement on transparency and financial disclosure.

OPEN PUBLIC HEARING

Glenn Hagele, Executive Director, Council for Refractive Surgery Quality Assurance (CRSQA), thanked the sponsor for seeking approval for monovision treatment with conductive keratoplasty (CK). Patients are seeking options for alleviating the need for reading glasses. CK monovision is not a cure; accommodation will not be restored, and the procedure has no effect on crystalline lens. The labeling should reflect that presbyopia remains. The learning curve described by the sponsor is for the best surgeons in world, but not every surgeon is of the same caliber. Patients need to be informed of the practical experience of a prospective surgeon. Successful outcomes depend on surgeon experience. Determining the dominant eye is also an important factor in success, but there is no universal technique in ophthalmology for doing so; the labeling should recommend an appropriate technique.

H.L. "Rick" Milne, M.D., The Eye Center, Columbia, SC, stated that he has performed more than 800 CK procedures and wants to see CK approved for presbyopic patients. More than 80 percent of the procedures he performs are for off-label use. He has had CK to correct his own vision. Presbyopia is disabling in many situations. CK is safe and stable. The panel should recommend approval.

Barbara Jo Morley, clinical trial participant, Overland Park, KS, stated that she has had the CK monovision procedure and is pleased with the results. The procedure itself took 5 minutes and was painless; she could read immediately afterward. She had the surgery 18 months ago and has thrown away her reading glasses.

Charlene Myers, clinical trial participant, Overland Park, KS, had the procedure 3 years ago. She would recommend the procedure to anyone.

Executive Secretary Thornton then read the conflict of interest statement. Full waivers had been granted for Michael R. Grimmatt, M.D., Oliver D. Schein, M.D., and Woodford S. Van Meter, M.D., for their interests in firms that could potentially be affected by the panel's recommendations. She noted that the Agency took into consideration certain matters involving

Anne L. Coleman, M.D., Ph.D., Arthur Bradley, Ph.D., Michael R. Grimm, M.D., Andrew J. Huang, M.D., Marian S. Macsai-Kaplan, M.D., Oliver D. Schein, M.D., and Jayne S. Weiss, M.D., who reported past or current interests in firms at issue but in matters not related to day's agenda. The Agency had determined that they could participate fully.

SPONSOR PRESENTATION

Jon K. Hayashida, O.D., Vice President, Clinical Affairs, Refractec, introduced the sponsor speakers and consultants and provided background on the ViewPoint CK system. CK was approved by FDA in April 2002 for temporary treatment of hyperopia of +0.75 D to +3.00 D. More than 25,000 cases have been performed, and CK's safety profile is excellent. The current PMA is for use of the system for temporary induction of myopia of -1.00 D to -2.00 D to improve near vision in the nondominant eye of presbyopic hyperopes and presbyopic emmetropes with a successful preoperative trial of monovision or history of monovision wear. Improvement in near vision is provided by creating monovision through corneal steepening. The nondominant eye is targeted for a myopic endpoint to provide near vision, and the dominant eye provides distance vision.

Mark A. Bullimore, M.C.Optom., Ph.D., consultant to Refractec, provided information on the history of monovision use. The literature indicates that monovision is an effective modality for managing presbyopia. Patient selection and screening are keys to monovision success. Monovision may be achieved with contacts, IOLs, and refractive techniques. Monovision's limitations include decreased contrast sensitivity, reduced stereopsis, glare and night vision difficulties, and binocular vision abnormalities. The clinical challenge is to achieve good near visual acuity while retaining comfortable binocular vision. Factors contributing to successful monovision include prescreening, a contact lens monovision trial, maintaining binocularity by limiting add power (adds greater than 1.50 to 2.00 D inhibit binocular summation), and patient education.

Marguerite B. McDonald, M.D., Clinical Investigator, noted that monovision treatment with CK uses the same procedure and device previously approved for hyperopia. RF energy is safe and effective for hyperopia treatment. The nomogram and treatment effect are the same as for the approved PMA, but the refractive target is -1.00 to -2.00 D. CK delivers RF energy intrastromally in the mid-periphery of the cornea using a probe tip of 450 μm x 90 μm .

The stroma heats due to the electrical resistance of the corneal tissue, resulting in shrinkage of collagen. A cylindrical, homogeneous, thermal profile is created to approximately 80 percent of the depth of the peripheral cornea, resulting in steepening of the cornea. A nomogram provides the template for treatment.

The clinical trial involved 150 consecutive participants at 5 clinical sites, four of which had participated in the hyperopia trial. Patients were required to be at least 40 years old, to have a preoperative add of +1.00 to +2.00 D, and to be successful contact lens wearers or complete a monovision trial. Preoperative cycloplegic refraction spherical equivalent (CRSE) consisted of hyperopia up to +2.00 D and emmetropia of plano ± 0.50 D.

The treatment goal was to improve near vision by targeting a myopic endpoint in the participant's nondominant eye. Distance vision was provided by the patient's dominant eye. The dominant eye of hyperopes could be treated with CK under the study protocol; the dominant eye of emmetropes was not treated. Target correction was determined by subjective refraction with add determination and addition of plus lenses until best clarity was achieved at 14 inches. Patients were allowed to select a near correction to meet individual preferences. The refractive target was limited to -2.00 D to ensure clinically acceptable anisometropia.

Safety parameters included preservation of BSCVA, induced cylinder, contrast sensitivity, patient symptoms, and complications and adverse events. Effectiveness parameters included stability, predictability, improvement in UCVA-near (UCVA-n), and patient satisfaction and spectacle use. Results were reported for 150 participants and 150 eyes. At 12 months, data were available for 96 percent of participants; 10 patients were lost to follow-up.

All protocol safety targets were met. No more than 1 percent of eyes lost more than 2 lines of BSCVA. Although 34 eyes lost 1 line at 1 month, all eyes were 20/20 or better at 3 months. The proportion of eyes experiencing a gain of 1 line increased and then surpassed the number of eyes with a decrease of 1 line.

To determine the clinical effects of induced cylinder, the study compared eyes with less than 1.00 D and >1.00 D of change; no statistically significant difference was found between the groups. Induced cylinder meets the safety limit in the protocol at more than 2.00 D. The frequency and magnitude of induced cylinder decrease over time. No compromise in either BSCVA or UCVA-n in eyes with clinically significant induced cylinder was found.

A subgroup of 83 eyes had contrast testing with and without glare. No change in contrast sensitivity was found in the following categories: monocular mesopic with and without glare; binocular photopic with near eye uncorrected; and binocular mesopic with near eye uncorrected, with and without glare.

Patient symptoms were rated as significantly worse by a small percentage of participants. The data suggest that symptoms resolve over time; many are typical monovision symptoms. At 12 months, 85 to 95 percent of patients graded their visual symptoms as none or mild. The most common symptoms were blurred vision and variation of vision in dim light. The symptoms and frequency are consistent with published studies of monovision.

A small number of complications were reported. No serious, unanticipated, or sight-threatening adverse events were reported. One participant experienced decrease in BSCVA of more than 2 lines. One case of iritis at 1 week was reported, which resolved. Adverse events were reported in less than 5 percent of eyes, and any single adverse event was reported in less than 1 percent of eyes. The study meets the criteria for adverse events.

Daniel S. Durrie, M.D., consultant to Refractec, presented the effectiveness data. The stability and predictability cohort excluded 3 eyes with protocol deviations. The UCVA-n cohort excluded 14 eyes corrected for distances greater than 14 inches and 3 eyes with protocol deviations. The results met all protocol targets for establishing refractive stability; however, the confidence intervals did not include 0. The stability outcomes are consistent with the results reported in the approved hyperopia PMA. The stability labeling for temporary correction will unchanged from the approved PMA.

The results meet or exceed protocol guidance requirements for predictability of MRSE. Patients outside the target range had undercorrection. In addition, a decrease in predictability occurred for eyes treated with 32 spots. The 32-spot pattern was less effective for both hyperopes and emmetropes. Even so, a high proportion achieved J3 or better for UCVA-n. Using generalized estimating equation (GEE) modeling, the sponsor determined that neither age or baseline status—only spot pattern—was a predictor of low refractive accuracy or the proportion of eyes that reached J3 or better. The 32-spot pattern was not as effective or predictable, but even so, 70 percent of eyes receiving 32 spots were J3 or better. At 6 months, 78 percent of all eyes and 82 percent of eyes receiving 8, 16, or 24 spots had monocular UCVA-n of J3 or better; 84 percent of all eyes and 90 percent of eyes receiving 8, 16, or 24 spots had binocular UCVA-n of

J3 or better. Eighty-one percent of all participants (and 86 percent of eyes receiving 8, 16, or 24 spots) had combined binocular UCVA distance vision of 20/20 and near vision of J3 or better at 6 months.

Two questionnaires were used in the PMA clinical study. The initial questionnaire was not adequately specific in defining near vision tasks because it provided only three categories of use. The second questionnaire was based on recall and provided a more refined list of functional activities performed at near. The second questionnaire found that most patients were able to see items such as street signs, bookshelves, computer screens, menus, and sewing without glasses; however, about one-third of patients needed some correction for fine print. At 12 months, 84 percent of patients were very satisfied or satisfied, 12 percent were neutral, and 4 percent were dissatisfied or very dissatisfied.

The data demonstrate an excellent safety and effectiveness profile.

Panel Questions for Sponsor

Panel members raised questions concerning the stability and functional duration of the procedure; possible complications; whether the procedure was suitable for people with previous refractive surgery; the rate of undercorrection and the outcomes of retreatment; the need for spectacles over time for different patient subgroups; the lack of objective testing for stereopsis; the usefulness of the 32-spot procedure; the role of age in patient outcomes; the rate of protocol deviations; the validity of the patient questionnaires; determination of which eye is dominant; and impact of the procedure on future cataract surgery. Sponsor representative answered the panel's questions.

FDA PRESENTATION

Jan Callaway, Microbiologist, Diagnostic and Surgical Devices Branch, and Team Leader, PMA 010018/S5, listed the team members.

Sheryl L. Berman, M.D., Medical Officer, Division of Ophthalmic & Ear, Nose and Throat Devices, and Clinical Reviewer, PMA P010018/S5, listed several issues that warrant panel discussion. She reviewed the indication for use and the regulatory history of CK. This is the first time a monovision indication has been requested for an ophthalmic surgical device. The

sponsor has updated the original labeling with 24-month study data and is willing to do so with this supplement.

Only four eyes were treated with the 8-spot pattern. For the PMA cohort, given the small magnitude of correction, accuracy of MRSE is less than ideal. At 6 months, 24 percent of study participants were undercorrected by more than 1.00 D, and 16 percent were undercorrected at 12 months. A significant proportion of undercorrection can be attributed to the 32-spot treatment pattern: 59 percent of 32-spot eyes were undercorrected by more than 1.00 D at 6 months. In a recent submission, the sponsor reanalyzed the data to exclude 32-spot eyes. The reanalysis reduces the proportion of undercorrected eyes to 8 percent at 6 months.

Target endpoints for accuracy were met or approximated by the overall cohort. However, GEE modeling found that the 32-spot pattern was associated with less accuracy. Age was confounded by the spot pattern—older patients needed more spots. A reduction in accuracy was observed with the 32-spot group. Excluding the 32-spot eyes from the analysis improved accuracy. Because 32-spot procedures can be done off label, the sponsor wishes to provide information in the physician and patient labeling. The reanalyzed data also indicate modest improvement in UCVA.

Despite limited efficacy, the procedure “still provides adequate levels of J3 or better” according to the sponsor. Efficacy is significantly lower for hyperopes than for emmetropes, who experienced lower J3 near outcome.

A large proportion of patients remain unable to read without glasses: 40 percent at 6 months and 55 percent at 12 months. Eliminating patients who had the 32-spot procedures does not change the proportion by much. The second questionnaire the sponsor used has several methodological problems, including a small number of respondents, no definition of fine print, and recall bias. Again, excluding the 32-spot treatment cohort did not change the results to a clinically significant degree. The sponsor performed comparative analyses of the clinical impact of induced cylinder that demonstrated no clinically significant compromise in near uncorrected acuity.

Reduced stereopsis is a known effect of monovision correction, but the sponsor claims unchanged depth perception from baseline. However, this is based on a comparison to preoperative depth perception with monovision contact lens wear, rather than distance spectacles. Although the sponsor concluded that 90 percent of patients retained the initial

correction at 1 year, the calculation was made by comparing 6-month outcome with 12-month outcome and labeling any eye retaining correction within 0.50 D as retaining the initial effect. Finally, patients reported many subjective symptoms postoperatively that they did not report preoperatively, including gritty feeling, light sensitivity, dryness, glare, halos, blurred vision, double vision, and fluctuation in vision.

In response to a panel question concerning the dropoff rate of the treatment effect at various time points, Dr. Berman stated that the Agency felt that the accuracy of correction was less than ideal and had asked the sponsor to provide information about how much correction can be anticipated at 1 year. That information will be included in the labeling.

Panel Review

Dr. Huang noted that CK has been approved for hyperopic indications and is being used off label for astigmatism and monovision. Safety and efficacy for monovision remain unclear. The safety profile for presbyopia is similar to that of the hyperopic study, but the sponsor's study lacked information regarding future options for undercorrection. At 1 month, 34 percent of study participants had loss of 1 line of BSCVA for distance. It is unclear how that affected their depth perception and quality of life.

The study had a significant number of protocol deviations. At one site, 16 patients received additional intraoperative spots to decrease the CK-induced astigmatism. Ten patients were excluded in the original analysis but included in Amendment 6.

The study met the Agency's guidance targets for clinical efficacy for myopic refractive lasers. However, no guidance has been established for UCVA-n. The sponsor's criterion was 75 percent of patients achieving J3 or better; Dr. Huang would propose, in addition, that 50 percent of patients achieve J1 or better. Dr. Huang presented several data tables illustrating the poorer outcomes for patients receiving 32 spots.

CK for monovision meets the safety criteria, but efficacy is less clear. The procedure provides temporary but irreversible monovision. Forty percent of study participants resumed using full-time reading aids by 6 months (55 percent by 12 months). In addition, 32-spot treatment failed to meet FDA guidance and the sponsor's goals. Cost versus benefit is not clear: A pair of nonprescription reading glasses costs about \$15, but CK costs \$1,500 and is not permanent. The proposed indication should say "induction of monovision, via spherical

hyperopic treatment up to 2.25 D (using 24 spots) in the nondominant eye. The labeling should include warnings about 8-spot treatment because little data are available.

Dr. McMahon provided the clinical review. Accountability was excellent for all time periods. Although enrollment was skewed toward one site, the sponsor's GEE modeling found that the results were not biased by this skewing. Participants were almost exclusively white (96 percent) and mostly female (61 percent). Protocol deviations were small in number and minor.

Regarding safety, the sponsor's target was no more than 5 percent of cohort with ≥ 2.00 D induced cylinder; the data show that no induced cylinder was >1.75 D. Mean cylinder at baseline was 0.32 D, increasing to 0.63 D at 6 months and decreasing to 0.55 D at 12 months.

Collectively, this does not appear to be a worrisome amount of induced cylinder. Among study participants with >1.00 D of induced cylinder, 12 percent and 14 percent lost 1 line of BSCVA at 6 and 12 months, respectively. The sponsor has agreed that these outcomes should be included in the patient and physician labeling. No eyes had worse than 20/40 BSCVA at any visit, and few eyes had a loss of more than 2 lines of BSCVA at any visit, at far or near test distances. IOP was 25 mm Hg or lower at all visits. Corneal haze was present in 2 percent of study participants at 1 month and 1 percent at 6 months, and it had resolved in all participants by 9 months. Adverse events were uncommon, and complications were minor. CK for the inducement of a near correction therefore appears to be reasonably safe; however, 2-year follow-up data on induced cylinder and its effect on BSCVA seem warranted.

The sponsor followed FDA guidance for accuracy of refractive surgery lasers for the treatment of myopia; the target is 75 percent of patients within $+1.00$ D and 50 percent within $+0.50$. Dr. McMahon presented several tables illustrating that the outcomes were within these accuracy parameters for most patients. However, few eyes were treated with 8 spots, and the sponsor acknowledges that the number is too small to analyze. It raises the question of whether the application of 8 spots should be removed from the treatment for near indication. The intended treatment range encompassed 2.00 D, and the targets encompassed 1.00 D; it is not clear that this is a reasonable target range for this or other procedures seeking relatively small correction ranges. CK for near is not very effective with the 32-spot treatment, and the near vision procedure is more effective for emmetropic eyes than for hyperopic eyes. At no visit interval did hyperopic eyes meet the ± 0.50 D target criteria.

With regard to patient satisfaction, the frequency of a change in symptoms (for the worse) appears to persist and, in some cases, increase over time. The quality of vision in terms of “improvement” seems impressive, and 79 to 84 percent of participants reported being satisfied or very satisfied over the 12 month follow-up period. This finding trends with the percentage of patients who see J3 or better.

The sponsor is correct that hyperopes and, to a lesser, extent presbyopes, will appreciate virtually any improvement in their uncorrected vision; this situation is partially responsible for the impressive satisfaction results in the face of a modest treatment effect. The number of study participants using spectacles or contact lenses for reading tasks is high. People generally do not perform near tasks at their threshold near acuity comfortably or for long periods of time. They need one or two steps larger than threshold to view near targets comfortably.

In conclusion, CK for near appears to be reasonably safe. Longer follow-up concerning loss of BSCVA from induced cylinder and symptoms seems warranted. CK for near is modestly effective at best. The 32-spot treatment is not effective and should be excluded from approval. The treatment has not been shown to be effective for less than 1.00 D of intended effect (8 spots) and for more than 2.25 D of intended effect (32 spots). Due to the limited effectiveness range, CK for near should be approved for corrections between 1.00 D and 2.25 D of intended effect, eliminating many hyperopes from the procedure. No data support the efficacy of retreatments or intraoperative placement of additional spots. For future CK applications, FDA should consider dropping the ± 1.00 D target for accuracy in procedures seeking less than 4.00 to 5.00 D of treatment effect, and increase the ± 0.50 D target to 70 percent for intended treatments of less than 4.00 to 5.00 D.

FDA QUESTIONS FOR PANEL

1. Is the length of follow-up sufficient to demonstrate reasonable assurance of safety and efficacy for the requested indication?

Panel members concurred that CK monovision is safe, although effectiveness is less clear. Two-year data, when available, will help clarify the matter. Postmarketing surveillance for at least 1 year should be required. Because the sponsor argues equivalence with a previous PMA, the Agency should conduct an equivalence analysis.

2. Is the magnitude of induced cylinder and axis shift, and the associated effect on UCVA, clinically acceptable for the requested indication?

The panel concurred that the magnitude of induced cylinder and axis shift was clinically acceptable.

3. Is the rate of undercorrection >1.0 D clinically acceptable? Are there subgroups of the PMA cohort for which this outcome is not acceptable?

A majority of the panel felt that the undercorrection rate was not acceptable, particularly for patients undergoing a 32-spot procedure. Insufficient data were provided for patients undergoing 8-spot procedures to make a determination. The other two spot sizes are clinically acceptable.

4. Are the reduced accuracy to target refraction and poorer near-UCVA outcomes (monocular and binocular) reasonable to justify the risk of elective surgery with “temporary” results, and is the near UCVA correction achieved clinically useful in the following groups? If not, how do you suggest the indication and/or labeling be modified...

~~EE~~ for eyes treated with the 32-spot pattern?

~~EE~~ for subjects >55 years of age?

~~EE~~ for hyperopic patients?

~~EE~~ for any other subgroups or attempted magnitude of refractive correction?

The panel concurred that the reduced accuracy and outcomes are not reasonable to justify the risk of elective surgery with temporary results. The procedure is not clinically useful with the 32-spot pattern; more data are needed on the 8-spot pattern. The study was not powered to determine an age effect. The 32-spot pattern, age, and refraction all interact, so the sponsor should use statistics to further analyze the data. The goal is to reduce spectacle dependence, not to achieve a particular refractive outcome. It would be useful to know how the effects deteriorate over time for each spot pattern.

5. Do the spectacle dependence rates for near activities support approval for the requested indication in a presbyopic population?

The panel had mixed views; some members indicated that the data were insufficient to answer the question, whereas others felt that the spectacle dependence rates support approval as long as patients undergo an informed consent process and the labeling is appropriate. They expressed concerns about the quality of the questionnaires used.

6. Do the safety and efficacy data support approval for the requested indication? If not, what indication does the data support?

The panel concurred that the data support approval for the requested indication for all but the 32-spot pattern. More data are needed on the safety and efficacy of the 8-spot pattern. However, because physicians will use CK off label, data on the efficacy of the 32-spot pattern should be

included in the labeling. CK has limited efficacy for hyperopes. It is a safe and effective procedure for intended near corrections of 1.00 to 2.25 D of intended effect.

7. Do you have additional labeling recommendations, explanatory text or data? Are there data tables that should be added to the labeling for physicians and/or patients?

Dr. McMahon recommended incorporating the following patient labeling recommendations from pages 11 and 12 of his clinical review:

- ?? The term “Blended Vision” is used as a euphemism for monovision, seemingly in an attempt to trademark a commonly understood refractive environment; this language will confuse prospective patients and should be removed.
- ?? Page 11, first bullet: The word “keloids” should be added in parentheses after “scars.”
- ?? Page 11, sixth bullet: Nystagmus should be added as a contraindication.
- ?? Page 12: Move the last two paragraphs of “first days” to after the first paragraph of “the weeks.”
- ?? Page 14, bullet item that ends in “retreatment”: The bullet item should be removed because the effectiveness and safety of retreatments were not determined in the clinical trial.
- ?? Pages 13–14: The section does not mention the need for a monovision trial, but it should be included here.
- ?? Page 23, table 8: Add a “worse row.”
- ?? Page 24: Omit the first bullet under “questions to ask your doctor” if nystagmus is contraindicated.
- ?? Add a table defining the frequency-induced cylinder and the effect it had on near and distance vision in the trial.
- ?? Add a cautionary statement after Table 1 (p. 8) indicating that equivalent outcomes in non-Caucasians have not been determined.

Dr. McMahon recommended incorporating the following physician labeling recommendations from pages 12 of his clinical review:

- ?? Remove nystagmus from warnings and place it in contraindications.
- ?? In the section that discusses how long contact lenses should be removed prior to having the procedure, add that a stable refraction should be determined if at any preoperative visit corneal topography is abnormal.
- ?? Add “The effectiveness of this procedure/device has not been determined for patients with less than 20/25 BSCVA preoperatively.”

Panel members had the following additional recommendations for the patient labeling:

- ?? State that patients should talk to their doctor to determine whether their cornea is too thin for the procedure. This should be in the physician labeling, too.
- ?? State that patients with history of glaucoma or elevated IOP, or steroid-response IOP elevation should not have the procedure.
- ?? State that effects on stereovision are not known.
- ?? State that duration of the procedure beyond 2 years is not known.

- ?? It is important to not give the impression that the procedure is reversible; the labeling should clarify the distinction between temporary and reversible.
- ?? Instructions about leaving out contact lenses should be wordsmithed to emphasize, without sounding condescending, the importance of removing contacts.
- ?? Include some warning about how to interpret tables 11 and 12; the information should say that they are based on nonvalidated, nonstandard questionnaires.

Panel members had the following additional recommendations for the physician labeling:

- ?? Add data tables on retreatment if possible and on the 10 excluded patients who had additional spots to reduce induced astigmatism. Physicians need to know that 32-spot procedures may induce astigmatism and require additional treatment.
- ?? Stress the importance of centration.
- ?? Add keratoconus and other ectatic conditions and incisional keratotomy to the contraindications.
- ?? Add data on patients with prior refractive surgery.
- ?? State that with incisional keratotomy, the shrinking cornea may put stress on wounds that are not fully healed.
- ?? State that effects of other procedures after CK are not known.
- ?? State that effects on stereovision are not known.
- ?? State that the procedure has not been studied in pseudophakic patients or in patients with transplants.
- ?? The language describing the consistent cohort should be clarified so as not to mislead.
- ?? State that outcomes of IOL power formulae are unknown after this procedure.
- ?? The results on the proportion of participants who use spectacles to view the computer screen should be removed because too many variables are involved for the information to be meaningful.

OPEN PUBLIC HEARING

No comments were made.

VOTE

Executive Secretary Thornton read the voting options. The panel voted unanimously to approve CK monovision with the following conditions:

1. Change the indications statement to include an intended range of hyperopic refractive correction of +1.00 to +2.25 D of effect.
2. Strengthen the labeling by adding the following information:
 - ?? Insert a graph showing the regression of the treatment effect over time for all eyes, emmetropic eyes only, and hyperopic eyes only.
 - ?? Insert data on the induction of astigmatism and its effect on clinical outcomes.
 - ?? State that no data are available on retreatments.

- ?? Provide information on the efficacy of the spot patterns and efficacy with the intended correction.
- ?? State that no data are available on eyes with prior ophthalmic surgery such as refractive surgery.
- ?? Include a warning that monovision may affect depth perception.
- ?? Include in the precautions patients with a history of glaucoma or steroid-responsive IOP elevation or an IOP >21mm Hg.
- ?? Include prior radial keratotomy as a contraindication.
- ?? Clarify the difference between “temporary” and “non-reversible” effect.
- ?? Note that data on spectacle dependence are from nonvalidated questionnaires.
- ?? Include a data table on excluded eyes.
- ?? Emphasize the importance of proper centration.
- ?? Emphasize that the procedure is temporary and show mean manifest refraction loss data.
- ?? State that the effects of changing corneal curvature have unknown effects on lens power formulae in cataract surgery.
- ?? Delete the reference to patient functioning with computers because it has not been studied sufficiently.
- ?? Reword the instructions on removing contacts to eliminate the condescending tone.
- ?? Include 24-month data in the labeling when it becomes available and establish substantial equivalency to the prior PMA.
- ?? Incorporate the patient labeling recommendations from Dr. McMahon’s clinical review:
 - ?? The term “Blended Vision” is used as a euphemism for monovision, seemingly in an attempt to trademark a commonly understood refractive environment; this language will confuse prospective patients and should be removed.
 - ?? Page 11, first bullet: The word “keloids” should be added in parentheses after “scars.”
 - ?? Page 11, sixth bullet: Nystagmus should be added as a contraindication
 - ?? Page 12: Move the last two paragraphs of “first days” to after the first paragraph of “the weeks.”
 - ?? Page 14, bullet item that ends in “retreatment”: The bullet item should be removed because the effectiveness and safety of retreatments were not determined in the clinical trial.
 - ?? Pages 13-14: The section does not mention the need for a monovision trial, but it should be included here.
 - ?? Page 23, table 8: Add a “worse row.”
 - ?? Page 24: Omit the first bullet under “questions to ask your doctor” if nystagmus is contraindicated.
 - ?? Add a table defining the frequency-induced cylinder and the effect it had on near and distance vision in the trial.
 - ?? Add a cautionary statement after Table 1 (p. 8) indicating that equivalent outcomes in non-Caucasians have not been determined.
- ?? Incorporate the physician labeling recommendations from Dr. McMahon’s clinical review:
 - ?? Remove nystagmus from warnings and place in contraindications.

- ?? In the section concerning how long contact lenses should be removed prior to having the procedure, add that a stable refraction should be determined if at any preoperative visit corneal topography is abnormal.
- ?? Add “The effectiveness of this procedure/device has not been determined for patients with less than 20/25 BSCVA preoperatively.”

The panel left it to the Agency to wordsmith the labeling changes.

POLL

Panel members indicated that the sponsor had demonstrated safety and efficacy of the procedure, and the conditions of approval will further improve CK safety.

ADJOURNMENT

Dr. Weiss thanked the participants and adjourned the meeting at 3:09 p.m. Ms. Thornton noted that the next panel meeting is scheduled for March 5 and will consist of a general issues discussion on the use of IOLs with clear lens extraction.

I certify that I attended the meeting of the Ophthalmic Devices Panel on February 5 and 6, 2004, and that this summary accurately reflects what transpired.

Sara Thornton
Panel Executive Secretary

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

Jayne S. Weiss, M.D.
Panel Chair

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