

SUMMARY MINUTES

OF THE

108th MEETING OF THE

OPHTHALMIC DEVICES PANEL

OPEN SESSION

March 5, 2004
Hilton Washington DC North/Gaithersburg
Gaithersburg, MD

Ophthalmic Devices Panel Meeting

March 5, 2004

Attendees

Chair

Jayne S. Weiss, M.D.
Kresge Eye Institute
Wayne State University

Executive Secretary

Sara M. Thornton
Food and Drug Administration

Voting Members

Arthur Bradley, Ph.D.
Indiana University

Michael R. Grimmert, M.D.
Bascom Palmer Eye Institute
University of Miami School of Medicine

Allen C. Ho, M.D.
Wills Eye Hospital
Thomas Jefferson School of Medicine

William D. Mathers, M.D.
Casey Eye Institute
Oregon Health Sciences University

Timothy T. McMahon, O.D., F.A.A.O.
University of Illinois at Chicago School
of Medicine

Consultants

Neil M. Bressler, M.D.
Wilmer Eye Institute
The Johns Hopkins University School of
Medicine

Jeremiah Brown, Jr., M.D.
Walter Reed Army Institute of Research
Laboratory

Alexander J. Brucker, M.D.
Scheie Eye Institute
University of Pennsylvania School of
Medicine

Frederick L. Ferris III, M.D.
National Eye Institute
National Institutes of Health

Leo J. Maguire, M.D.
Mayo Medical School

Janine A. Smith, M.D.
National Eye Institute

Walter J. Stark, M.D.
Wilmer Eye Institute
The Johns Hopkins University School of
Medicine

Industry Representative

Ronald E. McCarley
Ophtec USA, Inc.

FDA Participants

Joseph Blustein, M.D., M.P.H.
Don Calogero, M.S.
Malvina B. Eydelman, M.D.
Gene N. Hilmantel, O.D., M.S.
A. Ralph Rosenthal, M.D.
Karen Warburton, M.S.

CALL TO ORDER

Panel Chair Jayne S. Weiss, M.D., called the meeting to order at 9:04 a.m. **Panel Executive Secretary Sara M. Thornton** noted that the meeting's purpose is to discuss general issues relating to the use of intraocular lenses (IOLs) for the correction of presbyopia after clear lens extraction (CLE). She welcomed the participants and introduced the two new consultant members of the panel, Neil M. Bressler, M.D., and Jeremiah Brown, Jr., M.D. She asked panel members to introduce themselves and noted that the consumer representative, Glenda V. Such, M.Ed., would not be in attendance.

Ms. Thornton read the conflict of interest statement. Full waivers had been granted to Alexander J. Brucker, M.D. for his interest in firms in matters that could be affected by the panel's recommendations. The Agency took into consideration other matters concerning Dr. Brucker, Michael R. Grimmatt, M.D., Dr. Bressler, Allen C. Ho, M.D., Frederick L. Ferris III, M.D., and Dr. Weiss for their interests in firms at issue but in matters not related to the day's agenda; they could participate fully in the panel's deliberations.

BRANCH UPDATE

Karen F. Warburton, M.S., presented an update from the Vitreoretinal and Extraocular Devices Branch (VEDB) on recent medical device reports that have identified a connection between ophthalmic sponges and diffuse lamellar keratitis (DLK). Tests from a sample of ophthalmic sponges from one lot associated with a number of DLK cases have shown significantly higher levels of bacterial endotoxins when compared to another lot of sponges. Endotoxin-contaminated ophthalmic sponges have not been previously

identified as a possible cause of DLK; however, reports in the literature have suggested that endotoxins from sterilizer water reservoirs may have caused DLK outbreaks.

The FDA does not require that ophthalmic sponges or other devices used in LASIK surgery be free from endotoxins or pyrogens, and they are not are typically labeled as such (although they may in fact be pyrogen- or endotoxin-free). The VEDB is working with other Center offices to apprise the ophthalmic community of these developments, specifically through letters to professional organizations and letters to editors of appropriate journals.

FDA TEAM PRESENTATION

Malvina B. Eydelman, M.D., began the FDA team presentation on CLE for the correction of presbyopia, an intraocular surgical procedure where a noncataractous lens is removed and replaced with a multifocal intraocular lens (MIOL) to allow for both near and distance vision. The sole purpose of this procedure is for refractive correction.

Dr. Eydelman underscored several points about CLE to panel members:

?? CLE is not currently approved in the United States for any indication.

?? CLE has been performed as an “off label” procedure for several years, mainly in eyes with high refractive errors.

?? There are currently no standards or guidances available for CLE with IOL implantation.

Dr. Eydelman presented information on MIOLs, noting that only one MIOL is approved for use in the United States but several others are under investigation. Only two

IOLs are approved for improving near visual acuity in patients with presbyopia. Because an estimated 1.5 billion people worldwide live with presbyopia, devices that are approved to correct presbyopia will have a major impact on the public's health.

Designing a clinical trial to establish the efficacy and safety of devices to correct presbyopia offers numerous challenges, Dr. Eydelman said. The trial should be as easy and straightforward as practically possible for all parties involved, while also recognizing the impact on public health. To assist in the process of designing the clinical trial, Dr. Eydelman asked the panel to consider the following issues: control population; inclusion and exclusion criteria; acceptable adverse event rates; sample size; study duration; variables investigated; efficacy endpoints; and quality of life assessment.

Joseph N. Blustein, M.D., M.P.H., continued the presentation with a literature review on CLE for presbyopia, CLE with monofocal IOLs, CLE for hyperopia, CLE for high myopia, and retinal detachment risks. With very few articles specifically addressing CLE for presbyopia, the literature review was expanded to include CLE for other refractive corrections. Two articles reported on CLE for presbyopia, (Dick, et al. *J Refract Surg* 2002; Packer, et al. *J Cataract Refract Surg* 2002) evaluated the Array Multifocal IOL. Both studies only reported 6 month follow-up results.

The expanded literature review included articles on CLE with monofocal IOLs for ametropia, hyperopia, and myopia. Most of these studies were for short duration and small numbers. There were a considerable number of short term complications including one study reporting a greater than 50% posterior capsule opacification requiring YAG capsulotomy. Dr. Blustein noted that while several studies looking at CLE for high myopia reported efficacy, these studies were limited because of their short follow-up

times and the exclusion of patients lost to follow-up. However, one study of CLE for high myopia (Colin, et al. *Ophthalmology* 1999) did report a follow-up period of 7 years. This study had shown a retinal detachment rate of 2 % at 4 years and 8.1 % at 7 years. This study also showed an increase in posterior capsular opacification from 37% at 4 years to 61% after 7 years. Despite the efficacy of CLE for high myopia, the potential complications still outweigh the benefits (O'Brien, et al.).

A literature review looking at long-term retinal detachment (RD) rates after cataract extraction (CE), provided the following additional information. About 40% of all RDs occur post-CE. The increased risk of RD after CE persists over time, even at 10 years after CE. Younger age at the time of CE, torn posterior capsule at the time of CE, later posterior capsule opacification requiring YAG capsulotomy and male gender are associated with an increase risk of RD.

Dr. Eydelman presented on the recommended measure to be performed for multifocal IOLs under study, including endothelial cell loss, contrast sensitivity and functional performance. She finished the presentation by going over the eight questions the FDA is asking panel members to consider, given the information from the literature review. (See list of questions below.)

OPEN PUBLIC HEARING SESSION

Dr. Weiss opened the next session by noting that the FDA encourages the open public hearing speakers to advise the panel of any financial relationship they may have with any sponsor, its products and, if known, its direct competitors.

Adrian Glasser, Ph.D., associate professor at the College of Optometry at the University of Houston, reported that he appeared at the meeting as a consultant to industry as well as a scientist. He presented information on accommodation restoration concepts related to pseudophakic accommodation measurement and accommodative IOLs after CLE. Dr. Glasser's presentation also included a list of questions about the FDA's management of clinical trials for accommodative IOLs, subjective testing of accommodation, measurement of accommodation, and comparison of performance with a standard IOL.

Panel member **Arthur Bradley, Ph.D.**, asked Dr. Glasser whether pharmacologically induced accommodation could substitute for voluntary accommodation. Dr. Glasser said that he would not suggest it as a substitute or the sole means to identify whether an accommodative IOL would produce an accommodative change, but as one more tool to assess the accommodative ability of an IOL.

Stephen Lane, M.D., clinical professor of ophthalmology at the University of Minnesota, noted that he appeared at the panel meeting as a consultant. He stated that the Agency could proceed along two pathways: allowing market forces to work through the practice of medicine; or proceeding with formal clinical trials. Ultimately, he asserted, a formal refractive lens exchange clinical study is the most advisable, featuring controls and addressing the outcomes important to patients.

Dr. Lane agreed with many of the trial design considerations mentioned in Dr. Eydelman's presentation, for example, including measurement parameters; risk factor assessments (endothelial cell loss and RD).. He asked the panel to consider a number of proposals, including minimizing the study size and duration by employing exclusion

criteria derived from RD surveys; applying study subjects' own preoperative data to provide the best method of control; using minimum preoperative endothelial cell counts as an exclusion criteria based on the FDA phakic IOL requirement; and employing appropriate quality of life assessments through surveys. He noted that unless reasonable and practical considerations are used to design the trial, this increasingly popular procedure will be performed outside the scope of the best interests of everyone.

Panel members had a number of questions for Dr. Lane about RD rates in younger populations after cataract surgery, and the concern that there is little information on this population. Dr. Lane suggested that younger subjects and subjects with higher myopia be eliminated from any study. But, he added that there is an entire presbyopic patient population that would ultimately want this procedure for strictly presbyopic reasons.

Ms. Thornton read into the record a letter to the Agency from **Randall J. Olson, M.D., chair, Department of Ophthalmology and Visual Sciences and director of the John A. Moran Eye Center at the University of Utah Health Sciences Center.** Dr. Olson's letter commented on the use of IOLs to correct presbyopia after CLE. He believes that, even given the issue surrounding RD in high myopes, a study of clear lensectomy "does not seem warranted, in that our cataract database is already so large and so inclusive." As well, a study of patients with truly clear lens would be difficult, he wrote, because so few of these patients have truly clear lenses.

PANEL DELIBERATIONS

Dr. Weiss began the discussion of the eight questions on which the FDA needs panel feedback and advice.

1. A) Do you recommend a control population for studies of clear lens extraction (CLE) in the correction of presbyopia, or do you believe the study subject's own preoperative data is sufficient for comparison?

B) If you recommend a control population, which one of the following controls do you believe to be appropriate?

?? Historical control of subjects that have undergone CLE for correction of presbyopia

?? Historical control of subjects that have undergone CLE for correction of composite of all refractive indications

?? Historical control of postcataract extraction subjects

?? Historical control of subjects with no previous ocular surgery

?? Active control of subjects with no previous ocular surgery

?? Other

Most panel members agreed that some type of control population is necessary for a study of CLE for presbyopia.

A majority of panel members recommended that the study include historical controls to measure safety and active controls to measure efficacy. A number of panel members felt that the study would still have to stratify patients by such risk factors as refractive error, age, endothelial count, and axial length. Some panel members expressed concern that, while ideal, active randomized controls may be too burdensome for sponsors. However, Dr. Bressler argued that randomization

could ultimately be easier for patients and sponsors with a large enough sample size followed for three years.

2. Should the clinical study inclusion/exclusion criteria limit subject enrollment based on the criteria listed below? If yes, please discuss the appropriate ranges of each limiting criteria for inclusion in the study.

- A) Refractive error/axial length (hyperopia, emmetropia, myopia)**
- B) Patient's age**
- C) Degree of accommodative loss (based on what measurement?)**
- D) Preoperative endothelial cell count**
- E) Any other factors (e.g., best-corrected visual acuity [BCVA])**

Panel members recommended a refractive range from +6 to +8 to -10 to -14 diopters. Dr. Bressler recommended and others supported using the refractive range of what 95% of the refractive errors are in the US population. Eyes with pathologic conditions associated with high myopia or extreme hyperopia (nanophthalmos) should be excluded. Most panel members were in favor of including emmetropes. Since this is for presbyopia, panel members supported a minimum age of between 40 and 45.

Discussion as to what degree of accommodative loss and/or near vision with or without correction was felt to be necessary, but should be determined by the product. There was no consensus on which measurement to use.

Members agreed that the study should have a minimum age-dependent endothelial cell count as an inclusion criterion. Additional inclusion/exclusion criteria proposals included corneal astigmatism, axial lengths, corneal curvature, and a minimum level of preoperative visual acuity for distance.

3. A) What should be the primary safety endpoint for the study?

?? **Retinal detachment rates**

?? **Endothelial cell loss**

?? **Any others**

B) What should be the acceptable adverse event rate associated with this safety endpoint?

A majority of panel members suggested that the primary safety endpoint be the incidence of RD with 0.3% as an acceptable rate with a pre-PMA sample size of 321 followed for 3 years after CLE. The panel came to a consensus at 1,500 endothelial cell density at age 75, for the Agency to use to calculate inclusion criteria.

Panel member Jeremiah Brown, Jr., M.D., and others suggested that the sponsor stratify the population by nonmyopes and myopes. However, Gene N. Hilmantel, O.D., M.S., FDA participant, cautioned that the smaller the acceptable rate of RD for the trial, the larger the required sample size. A number of panel members noted that the CLE procedure is so safe now that it would take an enormous number of subjects to produce calculable risk.

4. A) In order to adequately determine the rates of the adverse events/complications of concern, what do you feel is the appropriate sample size and the appropriate follow-up period for a CLE study prior to the submission of the PMA?

B) Do you believe a postmarket study is indicated? If so, what is the appropriate type of study, sample size and length of follow-up for such a study?

A majority of panel members agreed that the premarket study should include 321 patients followed from preoperative status to 3 years, and that a postmarket study should be conducted for 5 years.

The panel discussed a postmarket study over 5 years with approximately 2,000 eyes or whatever sample size is needed to detect a .05 percent RD rate. Some members believed that this sample size may be too onerous for industry, but others argued that because the market size will be so large a large postmarket study is required.

5. Acceptable adverse event rates for the posterior chamber (PC) IOLs at one year following cataract extraction are listed in the FDA Grid for PC IOLs.

A) Are these rates applicable for correction of presbyopia in noncataractous eyes via CLE at one year postoperative?

B) Should the acceptable adverse event rates be adjusted for the study duration recommended? If yes, how should these rates be adjusted?

C) Do additional adverse events need to be collected? If so, what should be their acceptable rates be?

A majority of panel members agreed that the study should include a cumulative adverse event rate, including that for loss of best-corrected visual acuity, ruptured capsules, vitreous loss, and any others relevant events on the list of refractive surgical guidance.

Dr. Weiss suggested that FDA grids should be created that are similar to those for refractive surgical patients with a cumulative total of acceptable complication rates.

- 6. FDA believes that all multifocal IOLs' safety profile will have to be established in a cataractous population, prior to initiation of a clinical trial in a non-cataractous population. MIOLs' performance in a cataractous population will, therefore, be known for all tests and substudies outlines in ANSI draft standard for MIOLs.**

Which substudies do you recommend for inclusion in the clear lens extraction protocol for evaluation of performance in this non-cataractous population?

A) Functional performance

B) Contrast sensitivity

C) Defocus curves

- D) Fundus visualization**
- E) Endothelial cell evaluation**
- F) Others**

A majority of panel members agreed that the premarket substudies for CLE should include driving simulation , near vision functional performance, i.e., reading speed, vision surveys on functionality in low contrast conditions, contrast sensitivity, and endothelial cell evaluation. New IOLs should be evaluated for fundus visualization and fundus photos.

- 7. The only current performance efficacy endpoint for aphakic posterior chamber IOLs (FDA Grid) is postoperative BCVA of 20/40 or better in 92.5 percent of the subjects.**

A) Is this applicable to non-cataractous eyes undergoing CLE for the correction of presbyopia?

B) Are the predictability (75 percent of eyes with MRSE ± 1.00 D, 50 percent with MRSE ± 0.5 D) and UCVA (85 percent with 20/40 or better) outcomes outlined in the FDA’s Draft Guidance for Refractive Implants applicable?

C) Do we need to establish a performance efficacy endpoint for UCVA at near in this population of subjects undergoing surgery for correction of presbyopia? If yes, what do you recommend?

D) What additional performance efficacy endpoints, if any, need to be set?

A majority of panel members agreed that criteria should be set for combined near and distance uncorrected visual acuity.

Most panel members agreed that Question 7A was not applicable, but they were interested in doing this for safety (distance BCVA), not efficacy.

Panel members suggested the following efficacy criteria; distance UCVA of 90 - 95 percent in the range of 20/25 to 20/30. Panel members also suggested the following efficacy endpoints: low contrast reading tests, and better driving function tests.

8. How do you recommend we evaluate patient's quality of life issues?

A majority of panel members suggested that an appropriate questionnaire be administered to evaluate all patients to include questions related to night vision, night driving, and reading. The questions need to be directed toward refractive surgery as opposed to diseased eye, and more toward the younger patient, as well.

SECOND OPEN PUBLIC HEARING SESSION

Ronald E. McCarley, president and CEO of Ophtec USA, Inc., and panel industry representative, noted that most of the CLE performed have been accomplished with monofocal IOLs. He asked why the panel and the Agency would expect this pattern to change, considering the prospective problems in multifocal IOLs. Dr. Eydelman responded that the panel's discussion covered only multifocal and accommodating IOLs.

ADJOURNMENT

Dr. Eydelman and Ms. Thornton thanked the panel members and participants. Dr. Weiss adjourned the meeting at 3:52 p.m.

I certify that I attended this meeting of the Ophthalmic Devices Advisory Panel Meeting on March 5, 2004, and that these minutes accurately reflect what transpired.

Sara M. Thornton
Executive Secretary

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

Jayne S. Weiss, M.D
Chair

Summary prepared by
Susan C. Sanderson
5932 Lee Highway
Arlington, Virginia 22207
(703) 237-3696
astrobuddy@mindpring.com