

# TRANSCRIPT OF PROCEEDINGS

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

OPHTHALMIC DEVICES PANEL

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Pages 1 thru 225

Gaithersburg, Maryland  
November 8, 2000

MILLER REPORTING COMPANY, INC.

735 8th Street, S.E.  
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

OPHTHALMIC DEVICES PANEL

Wednesday, November 8, 2000

8:30 a.m.

Holiday Inn

Walker/Whetstone Rooms

Gaithersburg, Maryland

MILLER REPORTING COMPANY, INC.

735 8th Street, S.E.

Washington, D.C. 20003-2802

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## PARTICIPANTS

Joel Sugar, M.D., Chairman  
Sara M. Thornton, Executive Secretary

## Members:

Arthur Bradley, Ph.D.  
Michael R. Grimmett, M.D.  
Janice M. Jurkus, O.D.  
Alice Y. Matoba, M.D.  
Jose S. Pulido, M.D.  
Jayne S. Weiss, M.D.

## Consultants:

Karen Bandeen-Roche, Ph.D.  
Mark A. Bullimore, MCOptom, Ph.D.  
Anne L. Coleman, M.D., Ph.D.  
Eve J. Higginbotham, M.D.  
Clifford A. Scott, O.D., M.P.H.

Diane K. Newman, Consumer Representative  
Marcia S. Yaross, Ph.D., Industry Representative

## FDA Staff:

A. Ralph Rosenthal, M.D.  
Daniel G. Schultz, M.D.  
Jan C. Callaway  
James F. Saviola, O.D.  
Donna R. Lochner  
Bernard P. Lepri, O.D., M.S. M.Ed.  
Gene Hilmantel, O.D., M.S.  
Don Calogero, M.S.

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**Introductory Remarks**

1 DR. SUGAR: We will call the 100th meeting of the  
2 FDA Ophthalmic Devices Panel to order in a moment, and I now  
3 turn the microphone over to Sally Thornton for introductory  
4 remarks.  
5

6  
7 MS. THORNTON: Good morning, and welcome to the  
8 100th meeting of the Ophthalmic Devices Panel, a very  
9 special occasion for us all. I hope you had a chance to  
10 study our poster here, on the screen, as I am sure you will  
11 recognize some names and perhaps also recall some of those  
12 one hundred meetings.

13 A quick bit of information, as I was going through  
14 the records I noticed that in 1986 the panel had already met  
15 fifty times. So, that gives you some idea of the interest  
16 in developing ophthalmic devices for the medical community  
17 that continues to this day.

18 Before we proceed to today's agenda, I have a few  
19 short announcements to make. I would like to remind  
20 everyone to sign in on the attendance sheets in the  
21 registration area, just outside the meeting room. All the  
22 handouts for today's meeting are available there, at that  
23 registration table. Messages for the panel members and FDA  
24 participants, information or special needs should be  
25 directed through Miss Ann Marie Williams in the registration

1 area. The phone number for calls to the meeting area is  
2 301-948-8900. In consideration of the panel, the sponsor  
3 and the agency, we ask that those of you with cell phones  
4 and pagers either turn them off or put them on vibration  
5 mode while in this room. Lastly, will all meeting  
6 participants please speak clearly into the microphone, and  
7 in the beginning of the meeting we would like you to give  
8 your name clearly so the transcriber and the public will  
9 have an accurate recording of your comments and know who you  
10 are.

11 At this time, I would like to extend a special  
12 welcome and introduce to the public the panel and the FDA  
13 staff, our new panel chair, Dr. Joel Sugar, and new voting  
14 members, Drs. Arthur Bradley, Michael Grimmatt and Jayne  
15 Weiss. The voting member terms of Drs. Mark Bullimore, Eve  
16 Higginbotham and James McCulley have been completed. Their  
17 commitment to bringing the best thinking to our  
18 deliberations will be missed, however, we are happy to  
19 report that they will remain on as consultants to the panel.  
20 So, you may see them at future meetings.

21 To continue, will the remaining panel members  
22 please introduce themselves, beginning with Dr. Yaross, and  
23 Dr. Grimmatt and Dr. Bradley identify yourselves even though  
24 I have mentioned your name. Go ahead, Marcia.

25 DR. YAROSS: Marcia Yaross, Director of Regulatory

1 Affairs at Allergan in Irvine, California and industry  
2 representative to the panel.

3 MS. NEWMAN: Diane Newman, nurse practitioner,  
4 Philadelphia, and I am on loan from another panel.

5 MS. THORNTON: As consumer rep.

6 MS. NEWMAN: I am a consumer rep.

7 DR. SCOTT: Cliff Scott, Chairman of the  
8 Department of Public Health, New England College of  
9 Optometry.

10 DR. BRADLEY: Arthur Bradley, Associate Professor  
11 of Optometry and Visual Sciences, Indiana University.

12 DR. HIGGINBOTHAM: Even Higginbotham, University  
13 of Maryland School of Medicine, Baltimore.

14 DR. JURKUS: Dr. January Jurkus, Professor of  
15 Optometry, Illinois College of Optometry.

16 DR. SUGAR: Joel Sugar, Professor of  
17 Ophthalmology, University of Illinois, Chicago.

18 DR. PULIDO: Jose Pulido, Professor and Head,  
19 Department of Ophthalmology, University of Illinois,  
20 Chicago.

21 DR. MATOBA: Alice Matoba, Associate Professor,  
22 Baylor College of Medicine, Department of Ophthalmology.

23 DR. GRIMMETT: Michael Grimmett, Assistant  
24 Professor, University of Miami School of Medicine, Medical  
25 Director at the Bascom Palmer Eye Institute of the Palm

1 Beaches.

2 DR. WEISS: Jayne Weiss, Professor of  
3 Ophthalmology and Pathology, Kresge Eye Institute, Wayne  
4 State University, Detroit.

5 DR. COLEMAN: Anne Coleman, Associate Professor of  
6 Ophthalmology, Jules Stein Eye Institute UCLA.

7 DR. BULLIMORE: Mark Bullimore, Associate  
8 Professor Optometry and Physiological Optics, the Ohio State  
9 University.

10 DR. BANDEEN-ROCHE: Karen Bandeen-Roche, Associate  
11 Professor of Biostatistics, Johns Hopkins University,  
12 consultant to the panel.

13 DR. ROSENTHAL: Ralph Rosenthal, Director,  
14 Division of Ophthalmic and ENT Devices.

15 MS. THORNTON: Thank you. I would like to now  
16 read the conflict of interest statement into the record.  
17 The following announcement addresses conflict of interest  
18 issues associated with this meeting, and is made part of the  
19 record to preclude even the appearance of an impropriety.

20 To determine if any conflict existed, the agency  
21 reviewed the submitted agenda for this meeting and all  
22 financial interests reported by the committee participants.  
23 The conflict of interest statutes prohibit special  
24 government employees from participating in matters that  
25 could affect their or their employers' financial interests.

1 However, the agency has determined that participation of  
2 certain members and consultants, the need for whose services  
3 outweigh the potential conflict of interest involved, is in  
4 the best interest of the government. Therefore, waivers  
5 have been granted for Drs. Arthur Bradley, Anne Coleman, Eve  
6 Higginbotham and Jose Pulido for their interests in firms  
7 that could potentially be affected by the panel's  
8 recommendations. Copies of these waivers may be obtained  
9 from the agency's Freedom of Information Office, Room 12A-15  
10 of the Parklawn Building.

11 We would like to note for the record that the  
12 agency took into consideration matters regarding Drs.  
13 Bradley, Higginbotham, Janice Jurkus and Clifford Scott who  
14 reported interest in firms at issue but in matters that are  
15 not related to today's agenda. The agency has determined,  
16 therefore, that they may participate fully in all  
17 discussions. In the event that the discussions involve any  
18 other products or firms not already on the agenda for which  
19 an FDA participant has a financial interest, the participant  
20 should excuse him or herself from such involvement and the  
21 exclusion will be noted for the record.

22 With respect to all other participants, we ask in  
23 the interest of fairness that all persons making statements  
24 or presentations disclose any current or previous financial  
25 involvement with any firm whose products they may wish to

1 comment upon.

2 I would like now to read the appointment to  
3 temporary voting status for today's meeting. Pursuant to  
4 the authority granted under the Medical Devices Advisory  
5 Committee charter, dated October 27, 1990, and as amended,  
6 August 18, 1999, I appoint the following individuals as  
7 voting members of the Ophthalmic Devices Panel for this  
8 meeting on November 8, 2000: Dr. Karen Bandeen-Roche, Dr.  
9 Mark Bullimore, Dr. Anne Coleman, Dr. Eve Higginbotham and  
10 Dr. Clifford Scott. For the record, these individuals are  
11 special government employees and consultants to this panel  
12 or other panels under the Medical Devices Advisory  
13 Committee. They have undergone the customary conflict of  
14 interest review, and have reviewed the material to be  
15 considered at this meeting. Signed, David W. Feigal, Jr.,  
16 M.D., Director, Center for Devices of Radiological Health,  
17 October 31, 2000. Thank you, Dr. Sugar.

18 DR. SUGAR: Thank you. We now move into the open  
19 public hearing. To the best of my knowledge, no one has  
20 applied to the agency to participate in the open public  
21 hearing. Is there anyone in the audience who had intended  
22 to do so? If not, the open public hearing is now closed.

23 We now move on to the open committee discussions  
24 and we begin with the FDA presentation, with a special  
25 presentation by Daniel Schultz. Dr. Schultz?

**FDA Presentation**

1  
2 DR. SCHULTZ: Thank you, Mr. Chairman, committee.  
3 It is a pleasure to be here with you. My name is Dan  
4 Schultz. I am the Deputy Director for Clinical and Review  
5 Policy and, as part of my new assignment, I am privileged to  
6 have the opportunity to work with the ophthalmology group  
7 and the panel. It is a pleasure to be here, talking to you  
8 this morning.

9 Clearly, today is a momentous day, the 100th  
10 meeting of this panel, and I would just like to say a few  
11 words. I guess under normal circumstances I would begin  
12 with an acknowledgement of my new commander in chief but,  
13 given the fact that I don't know who that is going to be I  
14 think I will dispense with that and move directly to an  
15 acknowledgement of the dedication, the hard work and all the  
16 accomplishments that have been made by this panel over the  
17 last twenty-five years.

18 One of the buzz words that we have in Washington  
19 these days is leveraging, and I am not sure exactly what  
20 that means but one of the things that I take it to mean is  
21 that we are given assignments and not given the resources in  
22 order to be able to carry those assignments out. So, we are  
23 supposed to look to the outside and figure out ways to  
24 bribe, cajole or otherwise encourage people outside the  
25 agency to help us. It seems to be that the advisory panel

1 system is a shining light of our ability to be able to do  
2 that. And, we have been able to leverage the best and the  
3 brightest from the academic and scientific communities for  
4 the last twenty-five years.

5 This panel is an excellent example of that.  
6 Through your hard work and dedication you have looked at  
7 such things as classifying all of the devices used in the  
8 eye prior to 1976 into a logical and meaningful  
9 classification system. You have looked at contact lenses.  
10 You have looked at IOLs. You have looked at lasers. You  
11 have looked at a wide variety of products that have  
12 benefited the public health of the people of the United  
13 States, and we thank you.

14 Specifically, there are also two people, or  
15 actually three people that I would like to recognize today,  
16 who are going off the panel, unfortunately, as Sally  
17 mentioned. But we don't let anybody leave permanently. We  
18 put you in another status and that way we are allowed to  
19 call you back whenever we want to. So.

20 I would like to read a letter. This is addressed  
21 to Dr. Bullimore and it is signed Jane Henney, M.D.,  
22 Commissioner of Food and Drugs: I would like to express my  
23 deepest appreciation for your efforts and guidance during  
24 your term as a member of the Ophthalmic Devices Panel of the  
25 Medical Devices Advisory Committee.

1           The success of this committee's work reinforces  
2 our conviction that responsible regulation of consumer  
3 products depends greatly on the participation and advice of  
4 a non-governmental health community. In recognition of your  
5 distinguished service to the Food and Drug Administration, I  
6 am pleased to present you with the enclosed certificate.

7           [Applause]

8           And Dr. Higginbotham, similarly: Dear Dr.  
9 Higginbotham, I would like to express my deepest  
10 appreciation for your efforts and guidance during your term  
11 as a member of the Ophthalmic Devices Panel of the Medical  
12 Devices Advisory Committee. Again, the success of this  
13 committee's work reinforces our conviction that responsible  
14 regulation of consumer products depends greatly on the  
15 participation and advice of the non-governmental health  
16 community.

17           In recognition of your distinguished service to  
18 the Food and Drug Administration, I am pleased to present  
19 you with the enclosed certificate.

20           [Applause]

21           Finally, I would like to recognize the efforts and  
22 achievements of Dr. James P. McCulley, the former chair of  
23 this committee. I think people have described being a chair  
24 of an advisory committee as something similar to herding  
25 cats and, in my experience, that is sort of appropriate.

1 So, Dr. McCulley, I guess, began as a voting member in 1996  
2 and assume the role of chair in 1998. It says here that he  
3 started his service with the 90th panel meeting. So, that  
4 is about ten panel meetings and that is an extraordinary  
5 achievement. So, why don't you all join me in recognizing  
6 Dr. McCulley, and we will be sending him his plaque.

7 [Applause]

8 Finally in closing, once again I would just like  
9 to provide my sincere thanks to you as representing both the  
10 office, the Center of Devices and the agency and, most  
11 importantly, the American public for your continued work in  
12 protecting and promoting the public health. I thank you.

13 [Applause]

14 DR. SUGAR: Thank you, Dr. Schultz. I would also  
15 like to personally thank Mark, Eve and Jim. I am sure the  
16 ten meetings for Jim felt like a hundred meetings.

17 I would like to now move on to the Division  
18 update, which is by Ralph Rosenthal.

19 **Division Update**

20 DR. ROSENTHAL: Thank you, Dr. Sugar. I have two  
21 personnel issues that I would like to call to your  
22 attention. The first has to do with departure from the  
23 Division of Ophthalmic and ENT Devices. During the past few  
24 months, Morris Waxler has retired from government service  
25 and is currently working in the private sector, and Claudine

1 Krawczyk has moved to Connecticut, I think to have another  
2 baby. Is that true?

3 MS. THORNTON: I don't think that was the reason.

4 [Laughter]

5 DR. ROSENTHAL: Anyway, her husband moved jobs and  
6 we are going to miss her desperately, as we are going to  
7 miss Morris desperately.

8 But, on the other side, we have hired three new  
9 individuals and I would like to introduce them to you today  
10 and hope that, if they are here, they will stand up and  
11 identify themselves. The first is Gene Hilmantel. Dr.  
12 Hilmantel is an optometrist who has his B.S. in physics at  
13 the City College of New York and his optometry degree from  
14 Indiana University, and his master's degree at the  
15 University of Texas at San Antonio. He has done clinical  
16 optometry and, more recently, has been a statistician on an  
17 ophthalmic research team at the University of Texas at San  
18 Antonio, and we are delighted that he has agreed to join us  
19 in VEDB to work on both statistical and clinical issues.

20 Dexiu Shi is a vision scientist and physicist.  
21 She has her bachelor's and master's in optical and precision  
22 engineering in China, a master's in biomedical engineering  
23 and applied optics from Duke, and a Ph.D. in biomedical  
24 engineering and visual sciences from Duke. She has enormous  
25 experience in electrophysiology, psychophysics laser optics,



1 serving as Acting Branch Chief of the Diagnostic and  
2 Surgical Devices Branch. He was unable to be here today so  
3 I am giving the branch updates for him.

4           Since the last update, in May, 2000, CDRH approved  
5 one original PMA, PMA number P990078 for the Sunrise  
6 Hyperion LTK for the temporary reduction of hyperopia  
7 between +0.75 and +2.5 diopters.

8           The following panel track PMA supplements also  
9 were approved: P970053, supplement 2, for the Nidek EC-5000  
10 for the LASIK correction of myopia from -1 to -14 diopters  
11 MRSE plus astigmatism equal to or less than 4 diopters;  
12 P970043, supplement 7, for the Summit Autonomous LaserVision  
13 excimer laser for LASIK correction of hyperopia with and  
14 without astigmatism and mixed astigmatism with up to +6  
15 diopter sphere and up to -6 diopter cylinder; and P930016,  
16 supplement 10, for the VISX Star excimer laser for PRK  
17 correction of hyperopia between +0.5 and +5.0 diopter sphere  
18 with astigmatism from 0.5 to +4 diopters.

19           During the last year DSDB cleared several  
20 technologically different 510(k)'s: the Intralase 600C laser  
21 keratome, a femtosecond Nd:YAG; the Dodick laser  
22 phakoemulsification system, another Nd:YAG; the VisiJet  
23 Hydrokeratome, using the waterjet principle; and two  
24 ophthalmic aberrometers, using wavefront analysis  
25 technology, the VISX WaveScan Wavefront Analysis System and

1 the Autonomous CustomCornea Measuring Device. Thank you.

2 DR. SUGAR: Thank you. Next, James Saviola for  
3 the Vitreoretinal and Extraocular Devices Branch -- in  
4 uniform!

5 [Laughter]

6 DR. SAVIOLA: Good morning. It is Wednesday so it  
7 is our uniform day.

8 I would like to update the panel on a couple of  
9 510(k)'s and also a couple of PMA items. the ChromaGen  
10 contact lens, K994320, which are tinted prescription contact  
11 lenses intended as optical aid for people with red-green  
12 color deficiencies -- that application was cleared on  
13 October 20 of this year. These lenses are designed to  
14 improve discrimination of specific colors that look the same  
15 to people with red and green color deficiencies.

16 Contrary to what you may read on some web sites,  
17 we did not address the indication for dyslexia, only for  
18 red-green deficiencies. These lenses are not intended for  
19 people who are totally color-blind, and this is a limited  
20 marketing clearance and does not address yellow-blue  
21 deficiencies or total color-blindness.

22 Although ChromaGen lenses are the first lenses to  
23 be cleared by FDA for commercial marketing in the States,  
24 this idea is far from new. The use of colored filters as an  
25 optical aid for color deficiency has been reported in the

1 scientific literature since the 1850s. A red-tinted hard  
2 contact lens, known as the X-Chrom lens, which is a pre-  
3 amendment device, has been used for decades, and the FDA  
4 recently cleared filtered spectacle lenses for the same  
5 intended use.

6 In the contact lens care product area, Opti-Free  
7 EXPRESS Multi-Purpose Disinfecting Solution, manufactured by  
8 Alcon Laboratories, has recently received two marketing  
9 clearances to modify their directions for use to eliminate  
10 the rubbing step during the cleaning step of soft contact  
11 lens care.

12 The first application, K001214, was found  
13 substantially equivalent in July for lenses replaced 30 days  
14 or less. The 30-day limitation was removed by K002589 that  
15 was found substantially equivalent on October 23. Soft  
16 contact lenses prescribed on any replacement schedule now  
17 have the modified directions for us in that more recent  
18 labeling.

19 The steps include a rinse, followed by a six-hour  
20 soak, followed by a final rinse. Language does appear in  
21 the labeling to advise users that additional products or  
22 procedures, such as rubbing their lenses, may be recommended  
23 by their eye care provider.

24 The last item deal with perfluoropropane gas,  
25 C3F8, used as a tamponade within the eye to place pressure

1 on a detached retina. That PMA is held by Scott Medical  
2 Products, although Alcon does the marketing of the device.

3 Supplement 3 to P900066 was approved back in  
4 March. In that application the company requested a change  
5 in manufacturing site, an alternate synthesis route for  
6 perfluoropropane, and the changing release specification for  
7 the gas.

8 A second supplement, supplement 4, was reviewed as  
9 a special PMA supplement - changes being effected. That was  
10 approved on September 5. In that application the company  
11 requested approval for a change to the toxicity test  
12 protocol to increase the number of samples to be tested from  
13 each production lot of perfluoropropane from one sample per  
14 lot to three samples per lot.

15 I want to provide this update on the retinal gas  
16 in case there were some questions regarding availability of  
17 that product. There is a single manufacturer and we are  
18 extremely sensitive to potential supply products that may  
19 develop in resultant shortages of the device.

20 That is all I have today regarding the  
21 applications.

22 DR. SUGAR: Thank you. Are there any questions  
23 from the panel on any of these presentations? If not, Donna  
24 Lochner will talk about the Intraocular and Corneal implants  
25 Branch.

1 MS. LOCHNER: First, I would like the panel to  
2 know that FDA approved P990013 Staar Surgical Company's  
3 Collamer UV-Absorbing Posterior Chamber IOL on April 2,  
4 2000. This IOL was not brought before the panel because FDA  
5 determined that no new issues of safety or effectiveness  
6 were raised in this PMA. All PMAs that have been brought  
7 before the panel from ICIB have received a final action by  
8 the agency.

9 Next, I am very pleased to announce that Ashley  
10 Boulware has been named FDA Engineer of the Year for the  
11 year 2001. This is an important honor for a highly  
12 competitive award. I am sure that those of you that have  
13 worked with Ashley are aware of the high caliber of her work  
14 and will be pleased to know of this award. Her engineering  
15 expertise, particularly in the areas of biomaterial and  
16 optical, is greatly valued by the division and we are  
17 grateful that she is receiving this award as an  
18 acknowledgement of her knowledge and ability. Thank you.

19 DR. SUGAR: Thank you. Go ahead, Ralph.

20 DR. ROSENTHAL: I have one more comment which I  
21 neglected to make prior to the branch update, and that is  
22 that for the past several weeks, and possible for the future  
23 several weeks, Jim Saviola has agreed to be the branch chief  
24 not only for VEDB of which he is the permanent branch chief,  
25 but as the acting branch chief for ENTB, which doesn't come

1 to this panel but you should know that he now has two branch  
2 chief jobs. Thank you, Jim.

3 DR. SUGAR: Thank you. We now move on to PMA  
4 P000026, and begin with the sponsor's presentation. The  
5 sponsors have one hour to give their presentation, and they  
6 can introduce themselves as they come to the podium.

7 **PMA P000026**

8 MR. ZIEMBA: Thank you, Dr. Sugar; thank you,  
9 Sally. I am Steve Ziemba. I am vice president of clinical  
10 research and regulatory affairs for Staar Surgical Company,  
11 in Monrovia, California.

12 Today I would like to introduce the people that  
13 will be making our formal presentations for Staar Surgical  
14 Company. First of all, it is going to be Dr. Stephen  
15 Bylsma, from Santa Maria, California. Dr. Bylsma is an  
16 assistant clinical instructor of ophthalmology at the  
17 University of California, Los Angeles. He is also the  
18 medical monitor for the subject PMA.

19 Also, Dr. Donald Sanders, who is the director of  
20 the Center for Clinical Research in Chicago, Illinois and  
21 also a regulatory and clinical consultant to Staar Surgical  
22 Company. Then, finally, I am very pleased to announce that  
23 we will have with us today Dr. Andre Mermoud who is an  
24 associate professor of ophthalmology from the Hospital Jules  
25 Gonin in University of Lausanne in Switzerland. Dr. Mermoud

1 is one of the most experienced physicians in the world, with  
2 the AquaFlow Collagen Glaucoma Drainage device, having done  
3 over two thousand of those procedures in Switzerland.

4 With that, if Dr. Bylsma is ready, I will  
5 introduce him and we will begin our clinical presentation.

6 **Clinical Presentation**

7 DR. Bylsma: Thank you and good morning. I am  
8 Steve Bylsma. By way of disclosure, I am a paid consultant  
9 to Staar Surgical. As we get the lap-top up and running, we  
10 will begin the presentation.

11 [Slides]

12 Glaucoma is a disease where the treatment choices  
13 have evolved, and are evolving, and in the day of  
14 increasingly potent medicines it is unfortunate that some  
15 eyes continue to lose visual field despite maximal tolerated  
16 medications. For those eyes that do lose vision on maximal  
17 tolerated medications, trabeculectomy is the standard of  
18 care for lowering IOP, and it lowers IOP very well but it is  
19 associated with certain risks.

20 The risks of trabeculectomy really can be divided  
21 into two basic areas. Overfiltration in the early period  
22 that can produce hypotony is a real concern from  
23 trabeculectomy, and that is why meticulous closure and  
24 suturing the flap tightly are so important. Then, after  
25 that early period of potential overfiltration we get into

1 the later period of underfiltration or fibrosis and, of  
2 course, this is where antimetabolites have become very  
3 popular, maneuvers such as suture lysis or releasable  
4 sutures, needling of the bleb -- those things have been very  
5 important.

6 The solutions that the AquaFlow Collagen implant  
7 provide really are addressing that early overfiltration and  
8 avoiding it, and avoiding the underfiltration and late  
9 fibrosis. In the early period, overfiltration is avoided by  
10 use of a surgery that is not a penetrating surgery but,  
11 rather, the non-penetrating deep sclerectomy. You will also  
12 see the initials today of deep sclerectomy with collagen  
13 implant. Essentially, the non-penetrating deep sclerectomy  
14 is the surgery that is used at the time of the AquaFlow  
15 implant and, because it does not have a full thickness  
16 opening into the eye, resistance is maintained at a higher  
17 level than with standard trabeculectomy.

18 After that collagen implant is in place, of  
19 course, the collagen implant resorbs slowly, and we will  
20 look at some information about that today, and it does so  
21 without antimetabolites and there is very minimal  
22 inflammation which means less scarring, which means less  
23 fibrosis. So, by avoiding underfiltration, avoiding  
24 overfiltration, this AquaFlow implant has some real  
25 benefits.

1           There is one other issue which is a late Yag  
2 goniotomy, which can be performed to lower the IOP in those  
3 eyes that have a failing bleb.

4           If we look at a schematic of the procedure, the  
5 deep sclerectomy is achieved by first retracting a  
6 superficial flap, and then this deep sclerectomy region is  
7 removed and excised, exposing the Schlemm's canal and  
8 removing the outer wall, and the surgery then proceeds up to  
9 Descemet's membrane. So aqueous humor can exit from the  
10 anterior chamber both through Descemet's membrane and  
11 through Schlemm's canal.

12           Now, to help promote the fluid egress through the  
13 trabecular meshwork, the inner wall of Schlemm's canal is  
14 also removed as a separate step with these forces. This  
15 greatly increases the flow of fluid. It is important, of  
16 course, to have that flow in order for the implant to work.

17           A pre-placed 10-0 nylon suture is used, followed  
18 by placement of the collagen implant, and the idea is that  
19 this is placed as far anteriorly as possible, over this  
20 region of Descemet's membrane and over the remaining  
21 trabecular meshwork, to act as a space maintainer and to  
22 save this site to help prevent fibrosis in this site so that  
23 the surgery will have a long-lasting effect.

24           The superficial flap is then pulled back. The  
25 AquaFlow implant is then resorbed over the following months,

1 and we will look at a little bit of data about that.

2 Now, this is a standard textbook histology slide  
3 from Dr. Hoyt's text. Let's just review a little bit about  
4 the anatomy to tell where we are. Of course, cornea goes up  
5 here, to the upper right, and iris down here. So, this is  
6 the angle. The scleral sulcus is here, and this is the  
7 scleral spur. Schlemm's canal is this region in here.

8 So, the idea with the surgery is to dissect down  
9 right through Schlemm's canal and actually open up Schlemm's  
10 canal so that the outer wall is on the roof, an excised  
11 portion, and the inner wall, with its closely associated  
12 juxtacornicular trabeculecar meshwork remains on the floor  
13 of that dissection initially. The dissection is carried  
14 anteriorly onto Descemet's membrane, and then that deep  
15 sclerectomy portion is excised.

16 We go down with forceps next and remove this inner  
17 wall complex and juxtacornicular meshwork, and some  
18 histology has been done.

19 These were scanning EMS taken from patients in the  
20 U.S. study, and this is Dr. Hoyt's. It is very clear that  
21 these are trabecular tissue. When we do light microscopy,  
22 we see trabecular beams and trabecular cells, and it is  
23 clear that this is the meshwork with trabecular cells and  
24 collagen beams.

25 So, if we take a look at the video, we can review

1 a couple of aspects about this surgery. The surgical  
2 technique is performed. You see here that the superficial  
3 flap has already been retracted and is held back by a  
4 suture. Now the deep sclerectomy region is being outlined,  
5 and the dissection will start posteriorly, and tunnels  
6 anteriorly at a depth of about 90 percent. There is an  
7 emissary vessel that is seen here. The trabecular meshwork  
8 will be right in this region, under the deep sclerectomy  
9 and, in fact, you can just start to see a potential space  
10 starting to open, and as that opens up a very clean,  
11 potential space just opens right up.

12 You see that same view here, once again showing  
13 that as the dissection is brought forward there is an  
14 opening, and as that proceeds you will start to see egress  
15 of aqueous humor coming from that dissection area. Of  
16 course, as it is wiped with a sponge here you can see fluid  
17 just starting.

18 That dissection now needs to carry up onto  
19 Descemet's membrane so that we can have as much fluid flow  
20 as possible. Of course, if the implant is placed without  
21 fluid leaving the anterior chamber, the implant would do no  
22 good. We have to have fluid having a way to get out of the  
23 anterior chamber and exiting the anterior chamber in order  
24 for the implant to work.

25 So, here we are approaching further into

1 Descemet's membrane. Now this deep sclerectomy portion is  
2 excised, and you will see here a clear window of Descemet's  
3 membrane that extends anteriorly, and here is the trabecular  
4 meshwork. This blue arrow shows the remaining meshwork.  
5 These are the forceps that are used to remove the remaining  
6 inner wall of Schlemm's canal and juxtacornicular meshwork.  
7 This comes out reproducibly every time. You will see this  
8 is very stiff, like a wire, right there, in that view. That  
9 is very typical, and verifies that it is the right tissue.  
10 Then, the flow really picks up after that.

11           So, now we have good flow, and now the AquaFlow  
12 implant is placed. First a 10-0 nylon suture to hold the  
13 implant in place, and here is the collagen AquaFlow implant  
14 that is placed as far anteriorly as possible to help save a  
15 space. Should a late Yag goniotomy be needed, then that  
16 space is available and is maintained by the implant. Even  
17 after the implant resorbs a late goniotomy can be performed.  
18 The superficial flap is then retracted, and then the  
19 conjunctival closure.

20           Notice how quiet, how normal and undisturbed the  
21 anterior chamber is. It is very typical for these  
22 procedures since it is non-penetrating surgery. Seidel  
23 negative closure is critical, and that is the AquaFlow  
24 implant technique.

25           So, what happens to the device? Dr. Andre

1 Mermoud's group has done some fantastic work with ultrasound  
2 biomicroscopy, and we are fortunate to have Dr. Andre  
3 Mermoud here with us today to address issues that might come  
4 up. This is some of his work and what he did -- this is a  
5 one-week view -- the cornea, the iris, and here is the  
6 implant with its very typical girdled appearance where the  
7 10-0 nylon suture holds this down.

8           What they did, they measured the height and the  
9 length of this device over time. Here is just a view at 18  
10 months, verifying that it is completely gone. But the data  
11 that they found was that when measuring height or measuring  
12 length the device was completely resorbed between six and  
13 nine months.

14           The typical postop course that these patients  
15 experienced is that they tend to have large, diffuse, quiet  
16 blebs. They tend not to be thin blebs. They are very  
17 normal looking conjunctiva with diffuse, quiet conjunctiva  
18 overlying the area. They recover vision very quickly and  
19 generally have no, or very few, medicines. Essentially,  
20 these patients recover within the first one to two weeks  
21 very typically.

22           One of the issues is that if there is a late  
23 failure of the bleb, and this can be very late, there is a  
24 procedure, a Yag goniotomy, which is used as just a standard  
25 Yag like we use for capsulotomy. This procedure is similar

1 to ALT in that we aim the Yag laser through a gonioscope at  
2 the area internally of the dissection and, because that is  
3 so thin, a very low energy and controlled opening can be  
4 performed with the Yag laser, using energy between five and  
5 eight millijoules, and usually three to eight shots. And,  
6 it opens up and we don't see a big gush of fluid by any  
7 means, but IOP really can drop for these eyes that do come  
8 to a more fibrotic state.

9 I think of this as very comparable to modulation  
10 after trabeculectomy, such as suture lysis or needling of  
11 the bleb but, of course, this goniopuncture can be done  
12 much, much later and it is unique to the AquaFlow. When the  
13 non-penetrating deep sclerectomy is performed without the  
14 implant this goniopuncture is much less successful and, once  
15 again, Dr. Andre Mermoud has some data that he can present  
16 if you would like more information about that.

17 If we look at Dr. Mermoud's results that were out  
18 at two years, following the collagen implant, of course,  
19 those eyes that came to goniotomy had a pressure around 22.5  
20 and dropped down to the mid-teens, and that pressure was  
21 sustained over time, at least two years.

22 If we look at the AquaFlow study that is in  
23 discussion here, these are the eyes that came to goniotomy  
24 and this is their preoperative IOP before the deep  
25 sclerectomy with collagen implant; after surgery their pre-

1 goniotomy IOP and a lowering of IOP that, once again, was  
2 maintained over time.

3 This is a typical appearance of an eye, and these  
4 eyes looked very similar whether it is at two to four weeks,  
5 two months, six months, and some patients are out beyond two  
6 years now with the same type of appearance. It is not an  
7 ischemic bleb. It is not thin. It is very normal  
8 vascularization, but you can see some of the area underneath  
9 where the dissection was performed.

10 So, in conclusion, the AquaFlow advantages really  
11 avoid that early overfiltration because of the use of the  
12 non-penetrating deep sclerectomy, and avoid the late  
13 fibrosis by use of the collagen AquaFlow implant. These  
14 patients have good IOP control, with a quick return to  
15 baseline vision, without antimetabolites generally, no  
16 hypotony, and this unique Yag goniotomy can save surgery  
17 that might otherwise fail. In essence, this is good IOP  
18 control without frequent postop modulation.

19 Dr. Donald Sanders will present some of the data.

20 **AquaFlow Study Presentation**

21 DR. SANDERS: Thank you, Steve. What I would like  
22 to do is present to you some of the data from the AquaFlow  
23 study. I am a research and regulatory consultant to Staar  
24 Surgical.

25 [Slide]

1           The indication that the sponsor is asking for is  
2 the use of the AquaFlow device for the reduction of IOP in  
3 patients with open-angle glaucoma, uncontrolled on maximum  
4 tolerated medical therapy.

5           [Slide]

6           The current study design that was utilized was  
7 simply an observational study of the results after deep  
8 sclerectomy with a collagen implant. We also provided  
9 information in the PMA regarding a comparison with non-  
10 randomized historical trabeculectomy data. One of the  
11 reviewers questioned why we did not do a randomized  
12 prospective study, and as a matter of fact, the original  
13 design requested by the sponsor was, indeed, a randomized  
14 prospective comparison of deep sclerectomy with collagen  
15 implant compared to a trabeculectomy with antimetabolites.  
16 However, this study design was rejected by the FDA in our  
17 discussions with them because antimetabolites are not  
18 currently labeled for use with trabeculectomy, and the  
19 agency did not want to do a study where an off-label use of  
20 a drug was used in a device study. So, this was rejected.

21           [Slide]

22           We did think about doing the alternative design of  
23 deep sclerectomy with collagen implant compared to  
24 trabeculectomy without antimetabolites, however, this design  
25 was rejected by our glaucoma consultants as being not the

1 current standard of care and they felt it would be  
2 difficult, if not impossible, to enrol the trabeculectomy  
3 arm of the studies. So, that is when we agreed with the  
4 agency to do a simple observation study.

5 [Slide]

6 One other question that has come up is how we came  
7 to bring this to panel with in excess of 100 cases at one  
8 year postop. This was in conjunction with a meeting with  
9 the FDA where it was decided between the agency and the  
10 sponsor to submit the data with greater than 100 cases at  
11 one year postop.

12 [Slide]

13 The rationale for that was that since the AquaFlow  
14 device resorbed before one year postop there were really no  
15 late safety concerns for the device itself. As a matter of  
16 fact, this is supported by both of the panel reviewers and  
17 the FDA reviewer because really no safety concerns have been  
18 brought up with regard to the AquaFlow device itself. Once  
19 late safety becomes a non-issue, then we really only needed  
20 to have a sufficient number of cases to document efficacy at  
21 one year postop once the device was resorbed within  
22 acceptable statistical standards, and that was determined to  
23 be 100 cases. In fact, we submitted with approximately 40  
24 percent more than what was determined to be acceptable at  
25 one year.

1 [Slide]

2 With regard to our investigational sites, the nine  
3 sites are listed here.

4 [Slide]

5 Accountability at all time points, using the FDA's  
6 definition of accountability, was at least 92 percent, and  
7 at 12 months we had 97 percent accountability.

8 [Slide]

9 The demographics included 194 eyes that were  
10 treated, with open-angle glaucoma. The mean age of the  
11 patients was 67 years, and 79 percent of the patients were  
12 Caucasian and 59 percent were female.

13 [Slide]

14 With regard to preexisting conditions, the most  
15 prominent preexisting condition was the presence of some  
16 cataract in almost 80 percent of the cases, which is not  
17 unusual in this patient population.

18 [Slide]

19 With regard to previous procedures, argon laser  
20 trabeculoplasty was the most common, with 22 percent of the  
21 cases, and none of these cases had previous filtering  
22 surgery. In response to one of the questions from one of  
23 the panel reviewers, Dr. Higginbotham was quite correct,  
24 approximately 92 percent of the patients had a fornix-base  
25 flap as a peritomy, and you were correct in your assumption.

1 [Slide]

2 With regard to safety outcomes, these were the  
3 adverse events that were described in the IDE that was  
4 approved by the agency, and the only adverse event that was  
5 defined in the protocol was one sudden loss of vision which  
6 was a central retinal occlusion in a patient that had  
7 discontinued aspirin therapy right before surgery. There  
8 were no secondary surgical interventions to remove the  
9 AquaFlow device.

10 [Slide]

11 With regard to surgical complications, there were  
12 only two surgical complications reported, vitreous  
13 hemorrhage secondary to a perforation with an anesthesia  
14 needle, which required no treatment and the patient did  
15 quite well both visually and had control of the intraocular  
16 pressure; and a microperforation of Descemet's membrane with  
17 iris to the sclerectomy site. It was felt that both of  
18 these were related to the deep sclerectomy procedure and not  
19 to the AquaFlow device per se.

20 [Slide]

21 The secondary surgical procedures that were  
22 performed included three additional filtering surgeries  
23 which were considered surgical failures of the procedure  
24 and, of note, cataract extraction was performed in 8.2  
25 percent of the cases, which is not unexpected given that

1 almost 80 percent of the patients had cataract at the time  
2 of enrolment.

3 [Slide]

4 With regard to the postoperative complications,  
5 they are listed here, both the percentages that were seen at  
6 any time period and the percentages that were seen at  
7 greater than or equal to one week after treatment.

8 [Slide]

9 In general, with regard to postoperative  
10 complications, the overwhelming majority of the  
11 complications were reported at less than one week after the  
12 deep sclerectomy with collagen implant, and it was felt to  
13 be due to the normal postoperative course and, indeed, the  
14 normal healing process. The only complications reported at  
15 the six-month visit or later were one case of mild hyphema  
16 that resolved in six days; one iris prolapse due to trauma;  
17 and the cataract progression of preexisting cataracts.

18 [Slide]

19 With regard to best corrected acuity, best  
20 corrected acuity 20/40 or better increased modestly from the  
21 preop to 6 months and 12 months, probably related to the  
22 cataract extractions that were done that improved the  
23 vision.

24 [Slide]

25 If we specifically look at the cases that lost

1 greater than two lines of vision, the overwhelming reason  
2 for losing two lines of vision was cataract progression, and  
3 three cases of worsening macular degeneration, and these  
4 other problems occurred -- loss of vision occurred in one  
5 patient each.

6 [Slide]

7 With regard to effectiveness outcomes, here we can  
8 see the mean intraocular pressure with the 95 percent  
9 confidence interval by visit and the pressure, as you can  
10 see, dropped, and the pressure drop was maintained over the  
11 12-month period and the difference between the prop and the  
12 12-month was high statistically significant to a p value of  
13 less than 0.0001.

14 [Slide]

15 With regard to the mean number of glaucoma meds,  
16 it was 2.3 preoperatively and was 0.36 at 12 months  
17 postoperatively and, again, the drop in number of glaucoma  
18 meds was highly significant.

19 [Slide]

20 We looked at success criteria, and what we did is  
21 we reviewed the trabeculectomy literature and used the most  
22 commonly found success criteria that were given in the peer-  
23 reviewed trabeculectomy literature. These were the most  
24 common criteria for complete success, IOP less than or equal  
25 to 21 mmHg on no medications, and IOP less than or equal to

1 20 mmHg and no medications. And, using this criteria, we  
2 had a success rate in the low 70 percentage.

3 [Slide]

4 If we look at overall success, these were the  
5 three most common criteria for overall success. The first  
6 two are essentially the same as the previous ones, except it  
7 included patients that had medications so that you had an  
8 opportunity to have a success in the presence of some  
9 glaucoma medication. You can see that the percentages,  
10 regardless of which of the overall success criteria you  
11 used, is in the high 80s, low 90s at 12 months.

12 [Slide]

13 Failure rates were really the inverse of the  
14 overall success rates, and you can see that they were  
15 approximately in the 10-12 percent range.

16 [Slide]

17 So, with regard to safety, we felt that the  
18 incidence of adverse events, surgical complications and  
19 postoperative complications were quite low, and the majority  
20 of the complications seen were seen less than one week  
21 postoperatively due to the normal postoperative course.

22 [Slide]

23 With regard to effectiveness, the deep sclerectomy  
24 with collagen implant with the AquaFlow device produces a  
25 statistically significant reduction in IOP. The deep

1 sclerectomy with collagen implant with the AquaFlow device  
2 produces a statistically significant decrease in glaucoma  
3 medicines prescribed.

4 [Slide]

5 We are making no claims whatsoever with regard to  
6 the relative safety and efficacy of the AquaFlow device and  
7 standard trabeculectomy, but we did think it would be  
8 worthwhile to show you some of the comparisons between the  
9 results in the trabeculectomy peer-reviewed literature and  
10 our study, just for informational purposes.

11 Remember that the AquaFlow device was performed  
12 with no antimetabolite therapy, and it was compared to the  
13 trabeculectomy peer-reviewed literature both with  
14 antimetabolite therapy and without antimetabolite therapy.

15 [Slide]

16 The comparators, those studies we looked at, were  
17 chosen based on similarity to the PMA cohort. A majority of  
18 the cases had to be open-angle glaucoma. They had to be  
19 initial filtering surgeries in a majority of cases in these  
20 studies, and one to two years success outcomes had to be  
21 provided in the study.

22 [Slide]

23 Using the criteria for complete success at 12  
24 months, IOP less than or equal to 20 mmHg and no glaucoma  
25 meds is shown here. This is cases both with and without

1 antimetabolites. Although I am not sure it is very well  
2 seen, we followed the suggestion of Dr. Coleman who was kind  
3 enough to calculate the 95 percent confidence intervals for  
4 our values, we have 95 percent confidence intervals on here,  
5 which are these little black lines here. While our outcome  
6 using this criteria was 72 percent, you can see that the  
7 outcome is in the upper mid-range of what one sees with all  
8 the trabeculectomy literature both with and without  
9 antimetabolites using this success criteria.

10 [Slide]

11 If we use the overall success criteria of less  
12 than or equal to 21 mmHg with or without glaucoma meds, we  
13 are at 90.1 percent, and here are the studies that have been  
14 reported without antimetabolites and, again, we are pretty  
15 much in the mid-range of what one sees with trabeculectomy.

16 [Slide]

17 Here is the series of cases that were reported  
18 using this overall success criteria with antimetabolites  
19 and, again, we are at the upper level of the range of what  
20 one sees with trabeculectomy.

21 [Slide]

22 With regard to additional filtering surgery, we  
23 had a 1.5 percent rate, which I think compares quite  
24 favorably with the published rates in the trabeculectomy  
25 articles in patients with no antimetabolites, where it is

1 definitely at the low end of the range.

2 [Slide]

3 Here is the same graph comparing the literature  
4 rates of trabeculectomy with antimetabolites. Again, we are  
5 pretty much at the low end of the range in terms of patients  
6 requiring additional filtering surgery.

7 [Slide]

8 Some of the questions that have been asked, such  
9 as does the AquaFlow device enhance the outcome of deep  
10 sclerectomy alone, were not addressed in the current PMA.  
11 However, thanks to Dr. Mermoud and his colleagues and some  
12 of the other investigators in Europe, we do have some data  
13 on these points and we thought we would share some of this  
14 information with you.

15 [Slide]

16 There is an article from Dr. Mermoud's group by  
17 Sanchez et al. It was a prospective study with matched  
18 controls. It had 168 eyes; 86 patients had deep sclerectomy  
19 with collagen implant and 82 patients had deep sclerectomy  
20 alone.

21 [Slide]

22 If we look at the Kaplan-Meier curves for  
23 cumulative complete success, there was a highly significant  
24 difference between deep sclerectomy alone and deep  
25 sclerectomy with collagen implant, in favor of the deep

1 sclerectomy with collagen implant having a better outcome.  
2 So, in this particular case it did demonstrate efficacy.

3 [Slide]

4 Here was the cumulative overall success, and you  
5 can see that basically within the first 12 months you really  
6 don't see much of a difference, but the deep sclerectomy  
7 with collagen implant continues to maintain its efficacy  
8 while the deep sclerectomy alone produces more failures.

9 [Slide]

10 With regard to number of glaucoma meds required in  
11 this study, you can see that there was very little  
12 difference preoperatively between the two groups. However,  
13 there was a highly significant difference with regard to the  
14 number of glaucoma medications required in the deep  
15 sclerectomy group versus the deep sclerectomy with collagen  
16 implant group, with significantly less postoperative  
17 medications than the group with deep sclerectomy alone.

18 [Slide]

19 The study also found a significant difference in  
20 blood fibrosis between the two groups, with less than one-  
21 fifth the number of cases having blood fibrosis in the deep  
22 sclerectomy with collagen implant compared to the deep  
23 sclerectomy alone group.

24 [Slide]

25 The authors' conclusions from that study were that

1 the collagen implant allowed better long-term complete and  
2 overall success; lower postoperative need for glaucoma  
3 medication; and a lower risk for blood fibrosis.

4 [Slide]

5 Another study by another group, Dr. Demailly et  
6 al., was a retrospective study of 203 eyes, 128 who received  
7 the deep sclerectomy with collagen implant and 55 with the  
8 deep sclerectomy alone.

9 [Slide]

10 In this particular study the overall success rate  
11 at 12 months was 94 percent with the deep sclerectomy with  
12 collagen implant. It was 74 percent with the deep  
13 sclerectomy alone. Again, it was a statistically  
14 significant difference.

15 [Slide]

16 Demailly, in that same paper, also reported a  
17 prospective series of only 31 eyes, 17 in the deep  
18 sclerectomy with collagen implant group and 14 in the deep  
19 sclerectomy without collagen implant group, and in this  
20 particular study he did not find that the deep sclerectomy  
21 with collagen implant improved the results.

22 [Slide]

23 However, the authors' own conclusions were this:  
24 The results of our prospective study are not convincing.  
25 The number of eyes treated in the two groups is low. This

1 prospective study should be repeated with a greater number  
2 of eyes and only one surgeon. So, apparently there was some  
3 potential bias with the fact that with these 31 eyes there  
4 were two surgeons involved in doing the treatment.

5 Now, the sponsor is aware of another study that  
6 has been done by Dr. Mermoud. If the panel wishes to  
7 discuss it with him, he is here to provide any information  
8 that you need.

9 [Slide]

10 Our conclusion, based on these studies, is that  
11 deep sclerectomy with collagen implant demonstrated  
12 significantly better success rates than deep sclerectomy  
13 alone in two large series, both series having between 150  
14 and 200-plus cases.

15 [Slide]

16 Another question that has come up is are there  
17 studies documenting the long-term efficacy of the AquaFlow  
18 device? Now, the AquaFlow device is actually resorbed and  
19 gone at nine months, and that is the reason why we have an  
20 endpoint at 12 months. But there are studies that have  
21 shown the long-term effect.

22 [Slide]

23 We have seen this graph before, which was the  
24 Sanchez et al. paper, and it shows that the cumulative  
25 overall success is maintained in the deep sclerectomy with

1 collagen implant group up to two years.

2 [Slide]

3 Another study, done by Dr. Mermoud and his group,  
4 was a matched control group study with trabeculectomy, with  
5 44 patients in each group, in the deep sclerectomy and the  
6 trabeculectomy group.

7 [Slide]

8 As you can see, this is the mean IOP with time.  
9 It was very similar pre-treatment and, again, the IOP  
10 appears to be maintained through 24 months post-treatment.

11 [Slide]

12 If we look at the cumulative complete success  
13 rate, you can see that numerically the deep sclerectomy with  
14 collagen implant was actually higher than the trabeculectomy  
15 but, in any case, the effect is maintained with the deep  
16 sclerectomy with collagen implant up to 24 months.

17 [Slide]

18 The overall success rate in this group was  
19 virtually identical between deep sclerectomy with collagen  
20 implant and trabeculectomy out through 24 months.

21 [Slide]

22 With regard to number of glaucoma meds required to  
23 obtain this very similar result between these two, there was  
24 significantly less, almost half of the amount of  
25 postoperative glaucoma meds required in the deep sclerectomy

1 with collagen implant group than in the trabeculectomy  
2 group. So, there were significantly less meds required  
3 using the collagen implant.

4 [Slide]

5 In another study, by Karlen et al., 100  
6 consecutive patients with basically open-angle glaucoma were  
7 treated. The mean follow-up was 18 months, with follow-up  
8 up to 3 to 4 years.

9 [Slide]

10 Here is the IOP with time, and you can see that up  
11 to 36 months we have a maintenance of the lowered IOP.

12 [Slide]

13 Another study, and this again is from Dr.  
14 Mermoud's group. This is a prospective, non-randomized  
15 study, 105 eyes of 105 patients. They were operated on in  
16 late 1994 through early 1996. These were, again, open-angle  
17 glaucoma patients.

18 [Slide]

19 The mean follow was 43 months, with follow-up up  
20 to 5 years. I believe Dr. Mermoud has follow-up up to 6.5  
21 years in some of these cases.

22 [Slide]

23 The mean IOP was 29.6 preoperatively and was  
24 virtually identical at 3 months postoperatively and 48  
25 months postoperatively, showing a good enhanced long-term

1 effect.

2 [Slide]

3 If we look at the IOP less than or equal to 21  
4 mmHg at 60 months postoperatively, the complete success rate  
5 was 63 percent and the overall success rate was 95 percent,  
6 which is very comparable to what we found at one year -- as  
7 a matter of fact, it is a little higher than what we found  
8 at one year in our study.

9 [Slide]

10 With regard to glaucoma meds, at 60 months there  
11 still is this maintenance of a large drop in the amount of  
12 glaucoma meds required preop to postop.

13 [Slide]

14 In conclusion, the deep sclerectomy with collagen  
15 implant literature shows efficacy sustained out through as  
16 long as 60 months. There were in none of these studies any  
17 new late-term complications that have been noted with the  
18 procedure.

19 [Slide]

20 Now, as I said, we are not making any claims with  
21 regard to superiority of this procedure with trabeculectomy,  
22 but it is interesting that there have been some studies that  
23 directly compared the two.

24 [Slide]

25 Again, we are looking at Dr. Mermoud's study of 44

1 cases with deep sclerectomy with collagen implant and 44  
2 matched controls with trabeculectomy.

3 [Slide]

4 If we look at the best corrected acuity, there was  
5 a statistically significant difference in best corrected  
6 acuity in the early postoperative period. The higher on  
7 this graph, the better the visual acuity so that the  
8 trabeculectomy cases dropped initially and then stabilized  
9 out, and the deep sclerectomy cases did not have as dramatic  
10 a drop and, indeed, there was a statistically significant  
11 difference through one month postoperatively, and then,  
12 again, they were very similar after that point, probably  
13 related to less hypotony in the early postoperative period  
14 in the deep sclerectomy group.

15 [Slide]

16 With regard to complications observed, there was a  
17 highly significant difference in the rate of hyphema, much  
18 less in the deep sclerectomy group. There was no flat  
19 chambers in the deep sclerectomy group versus 18 percent in  
20 the trabeculectomy group, and a difference in the anterior  
21 chamber inflammation -- this lack of anterior chamber  
22 inflammation was also shown in a laser flare cell meter  
23 study which was reported in the PMA application.

24 [Slide]

25 There was also only one-quarter the incidence of

1 choroidal detachment when compared to the trabeculectomy  
2 group and, again statistically significant.

3 [Slide]

4 The rate of cataract formation, both surgically  
5 related -- and surgically related was defined as the  
6 cataract accelerating within the first month of surgery. It  
7 didn't occur at all in the deep sclerectomy group; it  
8 occurred in 14 percent of the trabeculectomy group. In  
9 terms of the total cataract formation, it is almost two-  
10 thirds less in the deep sclerectomy with collagen implant  
11 than the trabeculectomy group, again statistically  
12 significant.

13 [Slide]

14 So, our conclusion is that the comparison studies  
15 report significantly lower complications with the deep  
16 sclerectomy with collagen implant than the trabeculectomy,  
17 with similar control of IOP.

18 [Slide]

19 So, we believe that significant international  
20 experience supports the safety and efficacy outcomes  
21 reported in the AquaFlow PMA study.

22 [Slide]

23 Again, we are asking for the following indication,  
24 for the reduction of IOP in patients with open-angle  
25 glaucoma uncontrolled on maximum tolerated medical therapy.

1 Thank you very much.

2 DR. SUGAR: Does that end the sponsor's  
3 presentation?

4 DR. SANDERS: Yes.

5 DR. SUGAR: Thank you. The sponsor can come to  
6 the table and, for issues of clarification, the panel may  
7 now question the sponsor. Go ahead, Jose. For at least the  
8 first couple of rounds, identify yourself when you speak  
9 into the microphone.

10 DR. PULIDO: Jose Pulido. Just a few questions  
11 for clarification. This study took place over what period  
12 of time? What were the years involved?

13 DR. BYLSMA: From 1997 and November 1999.

14 DR. PULIDO: Were the medicines used to lower  
15 ocular pressure the same at the start and at the end of the  
16 study? In other words, I couldn't find that in the study.  
17 Were certain medications the only ones allowed to be used  
18 before and after?

19 DR. SANDERS: They were essentially allowed by  
20 groups -- you know, beta blockers, and so on. Basically,  
21 based on the success rate, 70 percent of the patients  
22 required no medications. So, there were the failures, which  
23 was approximately 10 percent, and then there was an  
24 additional 20 percent that required some medication. But,  
25 we didn't break them out by the exact non-generic grouping.

1 DR. PULIDO: Well, for instance, if there was a  
2 prostaglandin derivative that might have been used  
3 postoperatively that wasn't used preoperatively, that might  
4 have had a significant effect on pressure.

5 DR. BYLSMA: Yes, that is correct. The protocol  
6 did not proscribe the stepped medication regimen for  
7 postoperative use of medicines. That is correct.

8 DR. PULIDO: That is, I think, a little bit of a  
9 problem because you are comparing apples to oranges pre- and  
10 postoperatively if you didn't say you have to use this one,  
11 this one, this one and that one.

12 DR. BYLSMA: That is correct. The protocol that  
13 was used was used as defined and brought by the sponsor and  
14 the FDA, and for eyes that came to medicine postoperatively  
15 each investigator used what they thought was best for that  
16 individual.

17 DR. SANDERS: I think it is fair to say, however,  
18 that the time frame for when a patient was enrolled till  
19 they completed the one-year visit was 12 months. So, I  
20 don't think the investigators chose less efficacious  
21 medications preoperatively and more efficacious  
22 postoperatively. There would be no need to do that. And,  
23 we can certainly go back and get that data for you.

24 DR. PULIDO: Okay. And, there were 2.2  
25 medications preoperatively on average. The other two or

1 three medicines were not tolerated? Is that why it was an  
2 average of only 2.2?

3 DR. BYLSMA: That is correct. There was a range  
4 of medicines that were seen.

5 DR. SANDERS: I mean, there were patients who  
6 simply couldn't tolerate any. So, the range was from 0-5  
7 preoperatively. You know, maximum tolerated medication  
8 included the non-compliers also.

9 DR. PULIDO: All right. One last question, you  
10 really rely a lot on the Sanchez study to show that the deep  
11 sclerectomy with the collagen implant is better than deep  
12 sclerectomy alone, and you dismiss the Demailly study that  
13 is a prospective study because it is, quote, too small and  
14 because at the end he says, well, I don't know if it is  
15 worthwhile or not because it is a small study. But in the  
16 Sanchez study they allowed them to use antimetabolites. So,  
17 we don't know which ones used antimetabolites and which ones  
18 didn't. So, can you truly say that the Sanchez study is  
19 similar to the study that you did in the United States where  
20 no antimetabolite was used?

21 DR. SANDERS: No, we can't say for sure. It was  
22 simply a different study design.

23 DR. PULIDO: So, I still am in a quandary. How  
24 can you justify that the DSCI and the DS are not the same?

25 DR. SUGAR: Dr. Bandeen-Roche?

1 DR. BANDEEN-ROCHE: Yes, I have a few questions  
2 about your literature review. First, with respect to the  
3 articles that you cited, except for the Demailly et al.  
4 article, isn't it true that Dr. Mermoud did all of the  
5 surgeries with the exception of maybe a couple of dozen by  
6 Dr. Paggioni?

7 DR. SANDERS: I don't know.

8 DR. SUGAR: Do you want to introduce yourself?

9 DR. MERMOUD: Yes, I am Dr. Mermoud, from  
10 Switzerland. Dr. Paggioni was my predecessor and did about  
11 five to ten surgeries. All the other surgeries were done by  
12 myself.

13 DR. BANDEEN-ROCHE: Thank you very much. I would  
14 like to ask a few questions about the Sanchez et al. article  
15 as well. First of all, the Kaplan-Meier curves that you  
16 showed started to diverge noticeably around 12 months.  
17 There were 86 and 82 respectively in the DSCI-DS groups at  
18 baseline, but isn't it so that at 12 months there were only  
19 39 and 46 respectively, and at 18 months there were only 27  
20 and 10 respectively?

21 DR. SANDERS: I don't know.

22 DR. BANDEEN-ROCHE: I believe that is so. I have  
23 the article in front of me.

24 DR. SANDERS: I know there has been further  
25 follow-up in Dr. Mermoud's group. I don't know whether you

1 want to discuss it with him because he is here and has had a  
2 great deal of experience with deep sclerectomy versus deep  
3 sclerectomy alone. So, if you would like more information,  
4 the source is here.

5 DR. BANDEEN-ROCHE: Yes, I wonder if that would be  
6 beyond clarification --

7 DR. SUGAR: I believe so. At least, data that has  
8 not been presented to us is not open for discussion here.

9 DR. BANDEEN-ROCHE: Then, the final question would  
10 be how were the two groups chosen in the Sanchez et al.  
11 study? At least to my reading, they were not randomized.  
12 So, how were those groups defined?

13 DR. MERMOUD: Yes, we have many more patients with  
14 the collagen implant than without collagen implant. So,  
15 what we did, we took all of our patients without collagen  
16 implant and chose a matched group of patients who got the  
17 implant, matching age, sex, race and preoperative  
18 intraocular pressure. So, they were actually two matched  
19 groups.

20 DR. SUGAR: But not randomized?

21 DR. MERMOUD: Not randomized.

22 DR. BANDEEN-ROCHE: And why would a patient have  
23 gotten DS without CI?

24 DR. MERMOUD: Because in the beginning of our  
25 experience in '94, '95 the collagen implant was not

1 available all the time. So, in some period we had it  
2 available and in some period there was no collagen implant.  
3 That is why there were some patients, about 86 patients, who  
4 got collagen implants during our experience.

5 DR. BANDEEN-ROCHE: Thank you.

6 DR. SANDERS: Could I just make a comment related  
7 to that? I mean, in our discussions, the question of doing  
8 a group with and without was not brought up. I was under  
9 the impression that it wasn't the sponsor's obligation to  
10 prove that deep sclerectomy alone is efficacious. I mean,  
11 it might be worthwhile to try and get some clarification.

12 DR. SUGAR: I believe that that is correct but,  
13 Ralph, do you want to comment?

14 DR. ROSENTHAL: You want me to comment now? The  
15 regulatory burden is to determine whether or not the device,  
16 used in conjunction with the surgical procedure which, of  
17 course, we do not regulate, but the device with the surgical  
18 procedure has a reasonable assurance of safety and efficacy.  
19 That is the regulatory burden. The regulatory burden is not  
20 to determine whether or not the implant itself adds clinical  
21 value to the procedure. Therefore, in making the  
22 determination, the sponsors are quite right in submitting  
23 the surgical procedure plus the implant, as a stand-alone  
24 study, and comparing it with whatever they feel is  
25 reasonable to compare it with so that the panel can

1 determine whether or not their clinical trial showed that  
2 the device gave you, the panel, a reasonable assurance of  
3 safety and efficacy.

4 DR. SUGAR: We can pursue this point briefly -- we  
5 are going to discuss it more probably as the day goes along,  
6 but go ahead, Jose.

7 DR. PULIDO: Just a point of clarification then.  
8 I mean, Ralph, you could take that ad absurdum and have a  
9 patient that had deep sclerectomy and gave them peppermint  
10 candy, and peppermint candy plus deep sclerectomy had a good  
11 result.

12 DR. ROSENTHAL: You could, but you would not have  
13 any evidence that the peppermint candy did anything.

14 DR. PULIDO: My point here --

15 DR. ROSENTHAL: No, the company has submitted  
16 information relating to the mechanism by which they feel the  
17 collagen implant acts to facilitate the success of the  
18 surgical procedure.

19 We are not here to tell clinicians which is the  
20 best thing to do. I mean, hopefully, for people who are  
21 interested in this ultimately clinical studies can be done  
22 to come to this conclusion. We are here to evaluate a  
23 clinical study which they did quite correctly and compare it  
24 to what they chose to compare it to quite correctly, and  
25 take their understanding and their theory of how the device

1 works.

2 DR. SUGAR: Thank you. I think that that actually  
3 clarified it and maybe we will curtail further discussion on  
4 that. Eve?

5 DR. HIGGINBOTHAM: I have a couple of questions.  
6 Since Dr. Sanders referred to Dr. Mermoud's clinical series,  
7 if I could ask him a couple of questions just to clarify in  
8 my own mind more about your study. Dr. Mermoud, do you  
9 mind?

10 DR. SUGAR: Eve, you understand that we can't ask  
11 him about data subsequent to what was presented to the FDA?

12 DR. HIGGINBOTHAM: But Dr. Sanders referred to his  
13 study. So, I can certainly direct my question to Dr.  
14 Sanders.

15 DR. SUGAR: Oh, you can direct it to Dr. Mermoud  
16 too. The question is if he has subsequent data acquired,  
17 not presented in the PMA and, therefore, not presented to us  
18 in advance, we can't pursue that.

19 DR. HIGGINBOTHAM: I understand that, Dr. Sugar.  
20 This is peer-reviewed literature and it was presented in the  
21 PMA as part of the document.

22 DR. ROSENTHAL: Let me make a clarification, if I  
23 may. The company and Dr. Mermoud can't give you all the  
24 data tables --

25 DR. HIGGINBOTHAM: I am not asking for that.

1 DR. ROSENTHAL: Which you are not asking for. A  
2 general issue, a general impression, a general discussion  
3 about what is researched I think is quite legitimate.

4 DR. HIGGINBOTHAM: Thank you, Dr. Rosenthal. May  
5 I proceed?

6 DR. SUGAR: Please.

7 DR. HIGGINBOTHAM: Thank you. Dr. Mermoud, can  
8 you generally give me an idea of the demographic  
9 characteristics of your patients, presented in the peer-  
10 reviewed literature that Dr. Sanders referred to in his  
11 presentation, specifically related to race as well as  
12 previous filtration surgery or conjunctival surgery?

13 DR. MERMOUD: Yes, our patients were, on average,  
14 between 70 and 75 years old, depending on the studies.  
15 There was usually an equal number of females and males, and  
16 they were mainly Caucasian. In Switzerland we don't have  
17 many Black, Asian or Hispanic patients. So, I would say  
18 they were 98 percent, globally speaking, Caucasian patients.  
19 They were taking an average of 2.2 medications before  
20 surgery. In all studies it was about the same number, which  
21 corresponds actually to the number of the U.S. study.

22 As you said before, some didn't take any drops so  
23 it went from 0 medication to 5 medications per patient  
24 before surgery. Patients had long-term medications before  
25 surgery, for a great majority of them. Not many had

1 previous surgery. Less than 10 percent of the cases had  
2 previous glaucoma surgery or other type of ocular surgery.

3 DR. HIGGINBOTHAM: Thank you, Dr. Mermoud. That  
4 was my only question for Dr. Mermoud. I would like to ask a  
5 question now to the sponsor. Forgive me if this is buried  
6 in the document but I know that one of the inclusion  
7 criteria included those patients who had had local retinal  
8 cryotherapy in two quadrants. Could you give me a  
9 percentage of the number of patients in the cohort who had  
10 had previous cryotherapy.

11 DR. SANDERS: Zero percent.

12 DR. HIGGINBOTHAM: Thank you. So, all patients  
13 had no previous conjunctival surgery in your study?

14 DR. SANDERS: Correct.

15 DR. HIGGINBOTHAM: Thank you very much. That is  
16 the end of my questions.

17 DR. SUGAR: Alice Matoba?

18 DR. MATOBA: You had made a statement that because  
19 the collagen implant resorbs over six to nine months, and  
20 you do not have a penetrating wound into the eye, there are  
21 no late complications to be concerned about. My question  
22 is, in those patients who undergo a goniotomy  
23 postoperatively, have you not now produced a macroscopic  
24 opening into the eye and converted it into a situation that  
25 is akin to trabeculectomy and, therefore, you couldn't say

1 in your label that perhaps there are no late complications  
2 to be concerned about.

3           The second part is that in your present study only  
4 a small percentage of patients underwent a goniotomy but I  
5 notice that in Dr. Mermoud's study 44 out of 100 patients  
6 underwent a goniotomy. So, that is a large number of  
7 patients who required that procedure.

8           DR. SANDERS: Yes, it is true that those patients  
9 that have the goniotomy have a through and through filtering  
10 procedure but in our study, for instance, what that means is  
11 that approximately 85 percent of the patients who have the  
12 AquaFlow device do not, and it is only 15 percent that have  
13 a through and through procedure, which I think is definite  
14 benefit. Also, those patients that do have the Yag  
15 goniotomy are certainly no worse off than a patient who had  
16 a trabeculectomy. So, the long-term outcome would in those  
17 10 percent would be expected to be no worse than a  
18 trabeculectomy. Indeed, in those cases we did follow we  
19 observed no complications and I don't believe Dr. Mermoud  
20 has either after goniotomy.

21           DR. MATOBA: Well, I think it is right that they  
22 are no worse off than patients who have had a  
23 trabeculectomy, but then I am not sure it is fair to make a  
24 statement that there is no concern about literature  
25 complications because of the lack of an opening into the

1 eye.

2 Also, could you tell us why there is such a big  
3 discrepancy, 15 percent versus 40 percent, of patients  
4 requiring a goniopuncture, and which might be the more  
5 accurate estimate of what you might expect when it becomes  
6 more widely used?

7 DR. MERMOUD: Yes, we had actually a lot of even  
8 normal pressure glaucoma patients with pressure around 18 to  
9 20 preoperatively, and the aim was for the pressure to come  
10 down to less than 12. That is why when the pressure of our  
11 patients is more than 15 we ordinarily perform the  
12 goniopuncture. That is why our latest results are actually  
13 even more than 50 percent of patients having undergone a  
14 goniopuncture. It also explains why our mean pressure is  
15 much lower than the mean pressure of the U.S. study. Our  
16 mean pressure at 5 years is 11.8 mmHg compared to about 15,  
17 16 in the U.S. study.

18 DR. SUGAR: I think Dr. Scott is next, and then  
19 Coleman, Weiss and Newman.

20 DR. SCOTT: In the protocol for the U.S. study the  
21 postoperative medication regimen was left to the discretion  
22 of the surgeon. It seems very difficult, to me, to  
23 determine the number of medications given postoperatively,  
24 reported at the end of the study, to have any real impact  
25 because of the lack of a control whereby patients would be

1 taken off all medications in a stepped fashion, put on  
2 medications to control intraocular pressure to whatever  
3 acceptable level, either by intraocular pressure or field  
4 changes.

5 But taking the other side of the issue, you  
6 actually may be under-reporting the efficacy of the  
7 procedure itself because it may be patients who are kept on  
8 medications that really weren't required to keep it to a  
9 level that was reported. Also, if you compare it against  
10 the postoperative medications in trabeculectomy, I don't  
11 know how you can compare them. It is not a controlled  
12 comparison.

13 DR. SUGAR: Thank you. Dr. Coleman?

14 DR. COLEMAN: Yes, one of my questions is that in  
15 the study that you did, in the United States, how many  
16 unsuccessful deep sclerectomies were done in individuals  
17 that didn't get the collagen implant and actually had to be  
18 converted?

19 DR. BYLSMA: Yes, there were five procedures that  
20 had undergone essentially uneventful trabeculectomy  
21 procedures and there were no complications related to the  
22 conversion, and there was adequate control of pressure in  
23 all cases.

24 DR. COLEMAN: So, that is five overall?

25 DR. BYLSMA: Five overall.

1 DR. COLEMAN: One of the questions I have is since  
2 you are not penetrating the anterior chamber, why are you  
3 seeing flat chambers and hyphema and hypotony in the first  
4 week postoperatively with this procedure?

5 DR. BYLSMA: Generally, those were not seen. The  
6 frequency was relatively low. When the deep sclerectomy is  
7 done, there will be reflux of blood through Schlemm's canal  
8 because, of course, venous pressure is higher than  
9 atmospheric at that point so that we do see some reflux  
10 coming out at Schlemm's canal, and because the inner wall is  
11 stripped to get more flow there is a potential for some  
12 back-flow. There can also be some iris vessels that could  
13 leak. I don't have a reason why these hyphemas develop. I  
14 didn't see them generally at the time of surgery. I think  
15 that there were flat chambers associated with Seidel  
16 positive situations because of the fornix-base flap and  
17 inadequate closure, and I think that those have a close  
18 relationship.

19 DR. COLEMAN: Okay, and then, what is your theory  
20 for why the collagen implant decreases the risk for a blood  
21 fibrosis?

22 DR. BYLSMA: Well, we know the device is  
23 maintained for six to nine months and then dissolves.  
24 During the early healing phase, when much scarring may  
25 occur, this device acts as a space maintainer and, as such,

1 it helps to prevent fibrosis. Then, when it dissolves most  
2 of the incentive to fibrose is gone at that later stage.

3 DR. SANDERS: Excuse me, in answer to the question  
4 about flat chambers, there was only one that occurred in the  
5 first week, with an incidence of 0.05 percent.

6 DR. COLEMAN: Well, the question comes up because  
7 a lot of times when you use other drainage devices you do  
8 see capsules develop around space maintainers potentially.  
9 So, the question is why you aren't seen that around this  
10 collagen implant.

11 DR. BYLSMA: Well, this is a dissolvable device  
12 and it is a very inert material.

13 DR. SUGAR: Dr. Weiss?

14 DR. WEISS: This is a follow-up to the one flat  
15 chamber that you saw. Was any histopathology done on any of  
16 the patients who died during the course of the study to see  
17 if there were any microperfs that might not be evident at  
18 the time of surgery?

19 DR. BYLSMA: No.

20 DR. WEISS: Okay, and two questions that related  
21 to Dr. Mermoud's study. You showed the longer-term follow-  
22 up in his patient population. Do you have any idea of how  
23 many patients were seen at 12 months and at 24 months, in  
24 terms of was the number that was seen at 24 months still  
25 enough to determine that the success rate was still quite

1 high?

2 DR. MERMOUD: Yes, this was the first study which  
3 was published four years ago. Of course, there are less  
4 patients at two years than at one year, about half of the  
5 patients. Now we have reanalyzed those same patients with 5  
6 years follow-up. So, the mean follow-up was 42 months, if I  
7 remember the number, fm 3 to 6 years follow-up, with a mean  
8 of roughly 3.5 years follow.

9 DR. WEISS: So, with the advantage of more time  
10 following these patients, did you have approximately now, in  
11 retrospect, as many patients at 12 months as at 24 months,  
12 or did you have a great drop-off?

13 DR. MERMOUD: No, no. The drop-off is always at  
14 the end of the follow-up period. I would say now, after 5  
15 years, less than half of the patients are in the statistic.  
16 But, in the first four years they were almost all in. As I  
17 told you, the patients were 75 years old, on average,  
18 preoperatively. That means that after 5 years their average  
19 age is 80 and more than 20 percent of the patients died in  
20 the meantime.

21 DR. SUGAR: I think Diane Newman is next.

22 MS. NEWMAN: In the U.S. your criteria was 25 to  
23 85 years of age. So, no one over 85, you are recommending,  
24 should have it?

25 DR. SANDERS: I think for the purposes of the

1 study we chose an upper level limit, but there is no a  
2 priori reason why an older patient -- if they could undergo  
3 a trabeculectomy, there is no reason why they shouldn't.

4 MS. NEWMAN: But the European work is the 70s.

5 DR. SANDERS: Well, the average is 75. Dr.  
6 Mermoud, did you have any patients over -- what was the  
7 upper limit?

8 MS. NEWMAN: Your upper limit was 85.

9 DR. MERMOUD: Yes, our oldest I think was 92 and  
10 the youngest was a newborn.

11 MS. NEWMAN: I just was wondering because, you  
12 know, this is a disease of the aged and 85 isn't really that  
13 old.

14 The other thing is you are saying that the device  
15 dissolves. I don't know a lot about eyes, why is this  
16 success still going on at 60 months?

17 DR. BYLSMA: What typically causes failure of  
18 glaucoma surgery is fibrosis. In that early period we worry  
19 about the pressure being too low. In the late period we  
20 worry about the fluid, once it is out, not being able to get  
21 back into the venous system. Because this device dissolves,  
22 it prevents fibrosis in the early period but by 6 months  
23 most of the incentive for the surgical site to scar down is  
24 gone. So, it prevents fibrosis in the early period by  
25 maintaining a space and that space is maintained then

1 through the long run because it was there initially, which  
2 is the time when it would normally scar close if the device  
3 wasn't there.

4 MS. NEWMAN: Well, is there a chance then that  
5 this could be done again on the same patient? An additional  
6 procedure because you are doing them in younger people?

7 DR. BYLSMA: There is that chance.

8 MS. NEWMAN: Is there any experience with that?

9 DR. MERMOUD: We went back to the same site in  
10 failing cases, and usually what I found is that we get a  
11 fibrosis at the level of the superficial scleral flap.  
12 Interestingly, when you dissect that flap again, inside the  
13 deep spectrum is always opened and as soon as we open the  
14 flap actually the fluid is coming out and the pressure is  
15 again controlled. So, it is possible to reoperate those  
16 patients to reopen the scleral flap. Usually inside it is  
17 intact, and we can reuse a new collagen implant.

18 DR. SUGAR: Eve, you can ask any questions you  
19 want.

20 [Laughter]

21 DR. HIGGINBOTHAM: Thank you. I am glad that last  
22 question was asked because that was the question I actually  
23 wanted to pursue and, to continue that discussion, since as  
24 we know episcleral scarring is the most common cause of  
25 filtration surgery and this device dissolves by nine months,

1 how are you addressing the fibrosis which occurs between the  
2 scleral flap and the conjunctiva which oftentimes can become  
3 closely adherent so that they are almost one space? And,  
4 since you are saying that the early overfiltration is taken  
5 care of by the deep sclerectomy and this device acts as a  
6 space maintainer up to nine months, and this is the early  
7 period, is considering twelve months late then, considering  
8 that that is the length of your cohort follow-up? Is twelve  
9 months considered late in your mind? So, those are two  
10 questions.

11 One last question for Dr. Mermoud, since he came  
12 so far, were you the only surgeon in your peer-reviewed  
13 publication that Dr. Sanders referred to in his presentation  
14 and that is in the document? Three questions. Thank you.

15 DR. MERMOUD: So, maybe I will start with the last  
16 one. I was the only surgeon in the peer-reviewed paper,  
17 except, as we said before, there were a few cases, about  
18 five or ten patients who were operated by Dr. Paggioni, who  
19 was my mentor and a very good surgeon.

20 The second question was about the fibrosis. I  
21 think it is important to understand that with this procedure  
22 there is something new compared to trabeculectomy. In  
23 trabeculectomy we are mainly creating a subconjunctival  
24 bleb. In deep sclerectomy we are actually putting a second  
25 mechanism, that is, with the collagen implant we are

1 creating an intrascleral bleb. So, we still get a  
2 subconjunctival bleb, like in trabeculectomy, however, this  
3 bleb is much more shallow and diffused. Then, we get a  
4 second inside the sclera, and that is the one we are aiming  
5 for since it won't give late postoperatively complications  
6 such as late hypotony.

7           These are two different blebs and the scarring  
8 effect is also different. In terms of the subconjunctival  
9 bleb, we have the same problem as for trabeculectomy. For  
10 the intrascleral bleb, I think that is the point where the  
11 collagen implant is useful. That collagen implant will keep  
12 a space open for nine months, and after nine months usually  
13 all the scarring mechanism is asleep, if I can say that, and  
14 we don't see anymore scarring inside this space. But under  
15 the conjunctiva there may still be scarring effects.

16           Now, to also answer the question, it is possible  
17 in difficult cases to use mitomycin with this operation, as  
18 for trabeculectomy, and we did some studies using mitomycin  
19 and it definitely increases the results of difficult cases,  
20 such as secondary open-angle glaucoma.

21           DR. HIGGINBOTHAM: Can I ask a follow-up question?

22           DR. SUGAR: Go ahead, like I said, anything you  
23 want.

24           DR. HIGGINBOTHAM: Thank you very much. You are  
25 generous. Since most of the fibrosis really doesn't occur

1 underneath the scleral bleb -- I mean, it has been my  
2 experience in going back and reoperating on these patients,  
3 there isn't a lot of scarring underneath the flap, I mean,  
4 what is the advantage of having this implant in if most of  
5 the activity is not in the area where you are targeting, and  
6 it dissolves after nine months?

7 DR. MERMOUD: I had the same question as you when  
8 I started to use the implant. I said, why should we use an  
9 implant? I mean, it is expensive and it may not be really  
10 useful. That is why we did those studies. Now, after five  
11 years, the latest results show that difference between  
12 patients having an implant or no implant. The difference  
13 which was already significant after two years is even more  
14 significant after four years, the success rates being 65  
15 percent with the implant -- complete success, without  
16 therapy, compared to 20 percent without the implant. It is  
17 a big difference. So, the implant does something good.

18 My thinking is that when you put an implant, it is  
19 much easier to do a goniopuncture and the goniopuncture is  
20 more successful. The mean pressure with the goniopuncture  
21 is, in our series, 22 mmHg and comes down to 10-11 if the  
22 implant was used and only down to 16 when there was no  
23 implant. So, the implant actually helps to do a  
24 goniopuncture later and may save some surgeries.

25 DR. HIGGINBOTHAM: The twelve month issue, is that

1 late?

2 DR. BYLSMA: Clearly, twelve months is not late  
3 when we are talking about glaucoma.

4 DR. SANDERS: I don't think we are saying it is  
5 late. I think that the issue, when we discussed it with the  
6 FDA, was that the device is no longer there. So, since the  
7 evaluation is on the device and not the procedure, the  
8 determination was made that that was going to be the  
9 endpoint.

10 DR. SUGAR: Just a housekeeping issue, Dr.  
11 Mermoud, could you just state for the record your financial  
12 involvement with the device or the company?

13 DR. MERMOUD: Yes, I was a consultant for Staar  
14 Surgical between 1995 and 1997, and then I was not a  
15 consultant anymore but I am still supported for some  
16 research on the device, mainly on animal studies we did with  
17 rabbits.

18 DR. SUGAR: And they supported your travel here?

19 DR. MERMOUD: And they supported my travel.

20 DR. SUGAR: Thank you.

21 DR. ROSENTHAL: Could I just clarify something Dr.  
22 Sanders said? I think the agreement with the agency was  
23 that at a year the device would be gone and, therefore,  
24 there would not be any complications related to the device,  
25 and the efficacy at that point could be evaluated but the

1 long-term efficacy, obviously, could not be evaluated.

2 DR. SANDERS: I just wanted to briefly say that in  
3 the approval letter for the IDE the one-year time point was  
4 established. I mean, what we agreed to in conjunction with  
5 the agency was that we would do a two-year study but that we  
6 would come to panel when we had a significant amount of one-  
7 year data. It specifically stated in the letter that the  
8 rationale was simply that we documented that the device was  
9 gone three months before.

10 DR. SUGAR: Thank you. Dr. Grimmett?

11 DR. GRIMMETT: Two questions. First, regarding  
12 sterilization of the device since Dr. Coleman raised the  
13 issue in her primary review. Just for my own information,  
14 if there were such a thing as a transmissible spongiform  
15 encephalopathy or prion disease in pigs, if that existed  
16 would your rendering procedure lyophilization gamma  
17 irradiation take out the infectious agent of prion disease,  
18 if that were to exist?

19 MR. ZIEMBA: The simple answer is yes. We did do  
20 some testing on that, both for prions and viral agents,  
21 especially for spongiform encephalitis and found that, yes,  
22 a spiked sample with those items were destroyed during the  
23 processing of it.

24 DR. GRIMMETT: Great! Thank you. To my  
25 knowledge, there hasn't been yet a report of transmissible

1 spongiform encephalopathy in pigs.

2 DR. ROSENTHAL: Yes.

3 DR. GRIMMETT: There has? I know it can be  
4 reproduced experimentally but there has?

5 DR. ROSENTHAL: Oh, not naturally, but it does  
6 transfer species. Yes, it can transmit into pigs.

7 DR. GRIMMETT: Question number two, just for my  
8 own information. Since I am a cornea specialist, my  
9 knowledge of glaucoma literature in the past may be rusty.  
10 Dr. Sanders mentioned deep sclerectomy alone in the Sanchez  
11 study and, if my memory serves me correctly, didn't Tom  
12 Zimmermann do studies such as that back in the last '70s,  
13 early '80s, and did they generally fail, or why didn't you  
14 present any of that information? And if he did do that, was  
15 it a different procedure than you are doing now?

16 MR. ZIEMBA: Actually, Zimmermann did present that  
17 as well as Eduardo Arenas, from Bogota, and Prof. Kraznov,  
18 from Moscow. It didn't seem to add to the equation to point  
19 out that those had shown already the deep sclerectomy by  
20 itself has been abandoned because it wasn't terribly  
21 efficacious.

22 DR. GRIMMETT: Was it the same procedure in effect  
23 as what was described --

24 MR. ZIEMBA: Yes, it is, except for the fact that  
25 he didn't remove the juxtacornicular membrane. That was

1 actually an innovation developed during this trial.

2 DR. MERMOUD: If I could just answer the question  
3 because it is not the same procedure actually. What they  
4 did, Zimmermann, Arenas and Kraznov, in Russia, was just to  
5 open Schlemm's canal. They didn't actually do a deep  
6 sclerectomy. So, I think there is a difference because by  
7 creating a deep sclerectomy you are promoting an  
8 intrascleral bleb, which you don't do if you just open  
9 Schlemm's canal and remove the inner wall. Plus, in the  
10 deep sclerectomy, which was done in Switzerland or in  
11 America, the dissection was anterior, meaning, opening of  
12 Schlemm's canal, removing of the cornea behind the anterior  
13 trabeculum, plus removing the cornea behind the Descemet  
14 membrane. Whereas, in the Zimmermann study it was just  
15 opening of Schlemm's canal. So, there was no aqueous  
16 percolation through the anterior trabeculum or through the  
17 Descemet's membrane. It is a major difference between the  
18 two techniques. And the results were, indeed, less good in  
19 the Arenas and Zimmermann studies. In the long-term follow-  
20 up the results were not so good.

21 DR. SUGAR: I guess we have a couple of questions  
22 and then we will take a break and then we will have the FDA  
23 presentation. Go ahead, Jose.

24 DR. PULIDO: In terms of the learning curve, could  
25 you review your data as to the successes subsequently and

1 initially, because obviously this is a significant problem  
2 once you have scarred conjunctivas as Eve has talked about.  
3 You decrease chances of a second procedure from working.  
4 So, is the learning curve steep overall or not?

5 DR. BYLSMA: The learning curve is moderately  
6 steep. The difficulty of the procedure from the learning  
7 standpoint is recognizing the few landmarks that are useful  
8 and generally within three cases it is -- I felt to be well  
9 up on the learning curve before I started my first case in  
10 the study because we had training sessions to go through the  
11 learning curve even before starting this study. So, the  
12 learning curve really came in the training sessions and  
13 then, yes, there is a recognition that the trabecular  
14 meshwork may be variable. In some patients it may be more  
15 posterior; in others it may be more anterior. But  
16 recognizing what the depth is, is really the key. So, I  
17 think that the learning curve is something that is easily  
18 overcome.

19 DR. SANDERS: I think also one has to bear in mind  
20 that during the learning curve, if you have to get some  
21 aqueous percolation in the learning curve the problem would  
22 be more that you perforate, in which case you now have a  
23 standard trabeculectomy. So, the downside is a standard  
24 trabeculectomy.

25 DR. SUGAR: Go ahead, Dr. Jurkus?

1 DR. JURKUS: As a non-surgeon, I would like a  
2 little bit more information about the procedure. When you  
3 put the implant in, I understand that it is held with a  
4 nylon suture. Is that suture then removed?

5 DR. BYLSMA: No, there is no removal of that  
6 suture.

7 DR. JURKUS: Does the suture then have any  
8 relationship to the fibrosis that might occur?

9 DR. BYLSMA: That is not known; it is presumed  
10 not.

11 DR. SANDERS: It is 10-0 nylon, very small and it  
12 absorbs.

13 DR. SUGAR: I take it that that ends the questions  
14 we have for the sponsor. We will have additional comments  
15 from the sponsor after the FDA's presentation.

16 DR. ROSENTHAL: May I just comment?

17 DR. SUGAR: Go ahead.

18 DR. ROSENTHAL: I don't think absorbs. I think it  
19 probably stays there a very long time but it doesn't set up  
20 an inflammatory reaction.

21 DR. SANDERS: Yes, my apologies.

22 DR. SUGAR: We will take a break until 10:40, and  
23 please try to be back on time.

24 [Brief recess]

25 DR. SUGAR: We now move on to the FDA presentation

1 of PMA P000026, which will be introduced by Donna Lochner.

2 **FDA Presentation**

3 MS. LOCHNER: Thank you. I was asked to make a  
4 few introductory comments about the use of control  
5 populations in medical device clinical studies. First, it  
6 should be understood that there is no regulatory or  
7 statutory requirement for sponsors to conduct controlled  
8 clinical studies of medical devices. Rather, a sponsor is  
9 required to provide valid scientific evidence that their  
10 device is safe and effective.

11 When clinical data are needed in order to support  
12 safety and effectiveness, the use of controlled studies is  
13 the conventional but not only way of providing information  
14 to justify that the device is reasonably safe and effective.

15 Specifically, the regulations Section 860.7 state  
16 valid scientific evidence is evidence from well-controlled  
17 investigations, partially controlled studies, studies and  
18 objective trials without matched controls, well-documented  
19 case histories conducted by qualified experts and reports of  
20 significant human experience with a marketed device, from  
21 which it can fairly and responsibly be concluded by  
22 qualified experts that there is reasonable assurance of the  
23 safety and effective of a device under its conditions of  
24 use.

25 However, as I said, it is conventional for

1 clinical studies to include a control arm. One type of  
2 control population is the historical control population  
3 which was used for the PMA you will be reviewing today. For  
4 devices reviewed by this panel, the IOL historical control  
5 or grid is a good example of a historical control  
6 population.

7           There can be shortcomings whenever control data  
8 are not prospectively randomized with the investigational  
9 device. But it is important to keep in mind that a  
10 historical control or any control population, for that  
11 matter, is not considered by FDA to be an absolute  
12 performance standard but, rather, provides a means of  
13 understanding the significance of the outcomes for the  
14 investigational device.

15           The issue of the control population can become  
16 complicated when the comparative factor is not another  
17 medical device but a drug, a biologic or surgical procedure.  
18 As I am sure you are aware, the device you will be  
19 discussing today is the first implant to be reviewed by the  
20 panel for the indications requested by the sponsor. The  
21 sponsor has compared their device to outcomes for  
22 trabeculectomy from the literature. Unlike a 510(k)  
23 application, the sponsor is not required to demonstrate  
24 substantial equivalence to another device.

25           That concludes my remarks about control

1 populations. At this time, I would like to thank the review  
2 team for this PMA: Don Calogero, the team leader and  
3 engineering reviewer; Bernard Lepri, clinical; Jake  
4 Romanell, microbiology; Susanna Jones, toxicology; and Chang  
5 Lao, statistical. Thank you.

6 MR. CALOGERO: PMA P000026 has been submitted for  
7 the Staar AquaFlow Collagen Glaucoma Drainage device. The  
8 device is cylindrically shaped, 4 mm long by 0.5 mm wide,  
9 and made from cross-linked collagen.

10 The AquaFlow device is designed to be placed in  
11 the subcleral space following non-penetrating deep  
12 sclerectomy to facilitate aqueous outflow and reduce IOP in  
13 patients with open-angle glaucoma uncontrolled on maximal  
14 tolerated medical therapy.

15 The primary panel reviewers for this PMA are Drs.  
16 Higginbotham and Coleman. The sponsor has been advised of  
17 the questions and concerns raised by the primary panel  
18 reviewers and FDA's clinical, Dr. Bernard Lepri. Following  
19 the sponsor's presentation, Dr. Lepri will summarize his  
20 clinical review. Thank you.

21 DR. LEPRI: Good morning. My comments this  
22 morning will be brief, and I wish to present to you some  
23 summary information that will, hopefully, assist you in  
24 addressing the questions for which FDA seeks your expert  
25 advice.

1           At this time, before I begin, I would like to  
2 thank the sponsor for presenting a very concise and clear  
3 PMA to review, including all their data tables and  
4 narratives, and I appreciate their cooperation in that  
5 matter.

6           [Slide]

7           The sponsor has presented the clinical data for  
8 PMA P000026, AquaFlow Collagen Glaucoma Drainage device.  
9 The AquaFlow is indicated for the reduction of IOP in  
10 patients with primary open-angle glaucoma that is  
11 uncontrolled on maximum medication.

12          [Slide]

13          The AquaFlow device facilitates the non-  
14 penetrating sclerectomy by maintaining the subscleral space  
15 created by the surgical procedure itself. The AquaFlow  
16 device is utilized in the second-line therapy of the  
17 treatment of primary open-angle glaucoma via non-penetrating  
18 anterior sclerectomy.

19          Numerous studies, published and unpublished,  
20 regarding the effectiveness of anterior sclerectomy, both  
21 with and without the AquaFlow device, have been presented by  
22 the sponsor in their PMA and some in their presentation  
23 today.

24          [Slide]

25          The sponsor conducted a non-randomized, clinical

1 trial using the results reported for trabeculectomy in the  
2 ophthalmic literature for comparison. These studies  
3 reported outcomes for trabeculectomy performed both with and  
4 without the use of antimetabolites.

5 [Slide]

6 The objective of the U.S. clinical trial conducted  
7 by the sponsor was to determine the safety and effectiveness  
8 of the AquaFlow when used in a non-penetrating sclerectomy  
9 procedure as a second-line therapy for primary open-angle  
10 glaucoma and not deep sclerectomy per se.

11 [Slide]

12 The sponsor has presented the bulk of their data  
13 regarding safety and effectiveness for those subjects whose  
14 eyes have reached the one-year postoperative interval. They  
15 had 138 of 194 eyes present at the 12-month postoperative  
16 interval and this accounted for 97.2 percent of the  
17 available cohort at that time period.

18 [Slide]

19 There were no device-related adverse events  
20 reported in this investigation .

21 [Slide]

22 Those complications that did occur were in the  
23 immediate postoperative period and related to the anterior  
24 sclerectomy, and were of a nature that would occur without  
25 the presence of the AquaFlow. After the one-week

1 postoperative interval the complications rates were very,  
2 very low, further supporting the sponsor's premise that it  
3 is the procedure and not the device that contributes to the  
4 early complications.

5 [Slide]

6 Ultrasound biomicroscopy photographs verify the  
7 absorption of the AquaFlow between six and nine months  
8 postop and presence of a subscleral space which purports to  
9 facilitate the outflow of aqueous from the surgically  
10 unroofed Schlemm's canal

11 [Slide]

12 This subscleral space is in actuality the primary  
13 method of assessing the effectiveness of this device.  
14 Ultrasound biomicroscopy is not practical to perform in the  
15 office at all postoperative visits. Therefore, the sponsor  
16 resorted to secondary endpoints to evaluate primary open-  
17 angle glaucoma. By use of conventional clinical means, they  
18 utilized endpoints such as IOP, optic nerve head changes,  
19 nerve fiber layer changes, and reduction in glaucoma  
20 medication, to mention a few, and these were analyzed in the  
21 PMA. Definitions of success used in the trabeculectomy  
22 literature were used for comparative analysis.

23 [Slide]

24 Considering the overall success rates, I tried to  
25 synopsise some of their results. The A and the NA at the

1 bottom of the chart refer to antimetabolites and no  
2 antimetabolites, and I included the ranges of results  
3 reported in the trabeculectomy literature.

4 For overall success, defined as IOP less than or  
5 equal to 21 mmHg with or without meds, we can see that the  
6 AquaFlow had a success rate at that point of 12 months of  
7 90.1 percent and the trabeculectomy literature, using the  
8 antimetabolites, showed a range of success between 74-91  
9 percent. Without antimetabolites that range was 73 percent  
10 to 100 percent.

11 When success was defined as an IOP of less than or  
12 equal to 20 mmHg with or without meds, the AquaFlow also had  
13 a success rate of 88.6 percent, and the range with  
14 antimetabolites was 92-94 and without antimetabolites it was  
15 68-73 percent.

16 When IOP success was defined as less than or equal  
17 to 20 mmHg, with a 20 percent decrease in medication, and  
18 medications less than or equal to 1, the success rate for  
19 AquaFlow was reported as 87.9 percent, and in the  
20 literature, both with and without antimetabolites -- it was  
21 not separated -- the range was 46 percent to 92 percent.

22 [Slide]

23 Additionally, the sponsor presented data regarding  
24 the decrease in the use of medication after sclerectomy with  
25 the use of the AquaFlow, clinically significant changes in

1 IOP from preoperative levels, etc. I am not going to review  
2 the whole chart here, but it is here for your perusal for  
3 those of you who do not recall it from the PMA.

4 One thing that I think is important to note, that  
5 has been noted by both the sponsor and primary reviewers, is  
6 that a postoperative IOP lowering medication regimen was not  
7 standardized, and that this may have effects upon the  
8 reported success rates, especially for those eyes showing  
9 decreases of 1-5 mm from preoperative levels.

10 [Slide]

11 This graph portrays the change in IOP from preop  
12 to 12 months. Five percent had no change; 89.9 percent had  
13 a decrease in IOP of greater than or equal to 1 mmHg; 60.9  
14 percent had a decrease of greater than 5 mmHg; and 21.7  
15 percent had a decrease of greater than 10 mmHg.

16 [Slide]

17 When analyzing the change in the mean number of  
18 glaucoma meds from the preoperative level to the one year  
19 postop interval, the mean number of glaucoma meds used  
20 decreased from 2.31 at preop to 0.362 at 1 year postop, and  
21 this change was determined to be statistically significant  
22 at the 0.0001 level.

23 [Slide]

24 These highlights of the PMA being presented to  
25 you, I would now like to seek your advice on the following

1 questions. Question number one, the sponsor has proposed  
2 the following indication statement: The AquaFlow device is  
3 indicated for the reduction of intraocular pressure in  
4 patients with open-angle glaucoma uncontrolled on maximum  
5 tolerated medical therapy. This question now has two parts,  
6 does the indication as stated adequately describe the  
7 intended action in the population for treatment?

8 Question number two, does the panel have any  
9 additional labeling recommendations?

10 Finally, do the data presented for the AquaFlow  
11 device support reasonable assurance of safety and  
12 effectiveness for the indication as stated? Thank you.

13 DR. SUGAR: Does the panel have questions for Dr.  
14 Lepri? If not, I would like to move on to the primary  
15 review presentations. I am sorry, the sponsor can respond  
16 to FDA's review if they wish.

17 DR. SANDERS: We have no comment.

18 DR. SUGAR: The primary reviewers are Dr. Eve  
19 Higginbotham and Anne Coleman, and Dr. Higginbotham will  
20 begin.

21 **Primary Panel Reviews**

22 DR. HIGGINBOTHAM: Mr Chairman, I have a  
23 technological challenge momentarily. We just need to switch  
24 to the projector --

25 DR. SUGAR: It still holds, anything you want.

1 [Laughter]

2 DR. HIGGINBOTHAM: Can I tell my husband that?

3 DR. SUGAR: I would rather you didn't!

4 [Laughter]

5 DR. HIGGINBOTHAM: I apologize for the pause, and  
6 I want to acknowledge my pleasure that finally I get a  
7 glaucoma PMA after four years of being on this panel so I  
8 can say more than just intraocular pressure during the  
9 meeting. And, I appreciate Dr. Lepri's review and the  
10 sponsor's presentation of their information as well.

11 [Slide]

12 I just have a few comments I would like to make  
13 and, because it is my last meeting, I decided to do a power-  
14 point presentation. Certainly, as has been noted in our  
15 discussion, this device is fabricated from collagen and it  
16 appears to be biocompatible.

17 I just wanted to make note of some  
18 characteristics. Certainly, there is no indication of cell  
19 lysis after exposing the material to cultured fibroblasts.  
20 The sterilization leaves no toxic residue, which is  
21 important, and the shelf life extends up to 18 months.

22 [Slide]

23 So, it does appear that this material is safe but  
24 does not, by itself, impart any anti-inflammatory effects on  
25 its own accord, based on at least the information that was

1 supplied. Essentially, this is a space maintainer up to  
2 nine months because it dissolves by then.

3 [Slide]

4 As you have heard, certainly this was a nine-  
5 center, prospective trial, and there were 194 eyes of 130  
6 patients. Some of these patients did have both eyes  
7 included in the study but the sponsor was kind enough to  
8 also supply primary eye analyses.

9 Demographically, I would like to note because  
10 unlike intraocular lenses, unlike refractive surgery, when  
11 it comes to glaucoma surgery there is a significant amount  
12 of variation that can occur in terms of outcomes based on  
13 the demographics of the population. So, I didn't want to  
14 under-highlight that but actually emphasize the fact that it  
15 is important to point out that most of these patients were  
16 Caucasians and most of these patients were older. In fact,  
17 49.2 percent of these patients were over 70 years of age.  
18 Lastly, most of these patients had POAG but, more  
19 importantly, it was the older Caucasian population that is  
20 important to point out because this is a pristine population  
21 that can, in ordinary circumstances, do quite well with  
22 simple trabeculectomy with 90 percent success rate. We have  
23 noted that in the studies from the United Kingdom.

24 [Slide]

25 So, none of the eyes actually had undergone

1 previous filtration surgery. So, that is going to influence  
2 the efficacy results, a very important issue. And, we  
3 learned just today that none of the eyes actually had the  
4 transconjunctival retinal cryoplexy that would be considered  
5 a higher risk category because that would be a conjunctival  
6 procedure that could actually enhance the postoperative  
7 inflammatory cascade of events in particular patients.

8 In the PMA it was not actually noted, and it is  
9 noted in the labeling either, specifically if this was a  
10 fornix-based flap versus a limbal-based conjunctival  
11 peritomy. It wasn't specified. We heard that most of these  
12 were fornix-based. Why is that important? Because it is  
13 going to influence complications. I would think, at the  
14 very least, that should be specifically noted in the  
15 labeling.

16 Stepped regimen for adding back medications -- I  
17 think we have all actually alluded to this so I am not going  
18 to spend any time on it. Certainly, that is going to  
19 influence efficacy. In fact, if you look at the PMA, there  
20 is at least one center that seemed to have on average higher  
21 pressures, and a lot of that has to do with the choices that  
22 that particular practitioner made regarding whether or not a  
23 particular patient needed meds.

24 [Slide]

25 The percentage of the original cohort certainly

1 diminishes over time. I actually chose to look at the  
2 actual numbers of the original cohort that continued to be  
3 followed up over time as opposed to the available patients  
4 that would be ordinarily ready for that particular time  
5 point. That would, I think, artificially increase or  
6 enhance the levels of patients that would be reportable in  
7 the PMA.

8           So, certainly, as you can see there are just a few  
9 patients available for 24 months. Admittedly, that wasn't  
10 required for this PMA, but as a glaucoma specialist and  
11 recognizing this as a long-term disease, it is important to  
12 note that in this American cohort we really don't have much  
13 information past 12 months. Even if you look at the 12  
14 months, it really is only about a little more than two-  
15 thirds of the patients that actually were available for  
16 follow-up or had the follow-up.

17           [Slide]

18           So, given the primarily Caucasian population and  
19 the absence of previous filtration surgery, certainly, as I  
20 noted, a high success rate would be ordinarily expected.  
21 So, does the device impart any enhanced level of success?  
22 At the very least, in my opinion, longer follow-up is needed  
23 to help us with this since we only have the 12 months  
24 available with any sizeable numbers and, certainly as we all  
25 have heard earlier, most of these patients have their device

1 dissolved by 9 months.

2 [Slide]

3 Complications noted are largely related to the  
4 performance of the surgical procedure and not the device. I  
5 just wanted to clearly state that. You would expect central  
6 retinal artery occlusion and branch vein occlusion to occur  
7 in an elderly population with glaucoma.

8 I just also wanted to note that we don't really  
9 know what these blebs look like long term because that would  
10 be important as it relates to long-term complications.  
11 Certainly, we would expect, if there was any local reaction  
12 to the implant, conjunctiva hyperemia to be noted, but that  
13 was not actually reported. So, I don't know if the  
14 investigators, for instance, were asked to actually  
15 characterize the blebs over time. That would be an  
16 important thing to recognize.

17 [Slide]

18 So in summary, the AquaFlow Collagen Glaucoma  
19 Drainage device is safe. The question is does this device  
20 add to the effectiveness of filtration surgery. It is  
21 unclear in my opinion and, in my opinion, longer follow-up  
22 is needed.

23 Finally, Mr. Chairman, it is my understanding that  
24 the sponsor sent to the FDA a copy of an article from Aqua  
25 Surgery News. That article included an interview with me

1 regarding the topic of non-penetrating trabeculectomies and  
2 my personal experience performing such procedures as a  
3 resident with Dr. Tom Zimmermann more than a decade ago. It  
4 was actually longer but I won't admit it --

5 [Laughter]

6 The topic of that article was not collagen  
7 drainage device. I just wanted to clearly state that. The  
8 sponsor did not present complete information. They did not  
9 mention other interviews and podium presentations where I  
10 did affirm a potential place for non-penetrating  
11 trabeculectomies. I did not allude to a collagen device in  
12 the surgical armamentarium of clinicians.

13 I will restate my comments that I noted at the  
14 Glaucoma Subspecialty Day at the American Academy of  
15 Ophthalmology meeting in 1999, where I moderated a session  
16 during which another non-penetrating trabeculectomy  
17 procedure was presented, and I did state that non-  
18 penetrating trabeculectomies may be potentially a good  
19 option for patients with early glaucoma, as you note here.  
20 This presentation was also covered by Ocular Surgery News in  
21 a subsequent article, and is available by CD from the  
22 Academy. That subsequent article, or any additional  
23 information, was not shared with the FDA. Therefore, to  
24 provide a more balanced perspective, I thought it important  
25 to add this information to the public record. Thank you.

1 DR. SUGAR: Thank you. Any clarifications for  
2 Eve? Go ahead, Jose.

3 DR. PULIDO: Eve, a question for you. Go back to  
4 your previous slide.

5 DR. HIGGINBOTHAM: I am trying. Well, I can still  
6 respond to your question. Oh, here we go.

7 [Slide]

8 DR. PULIDO: Does this device add to the  
9 effectiveness of filtration surgery? I don't know whether  
10 that is the correct question. The correct question should  
11 be does this deep sclerectomy -- is there evidence that a  
12 deep sclerectomy with a collagen implant lowers the  
13 intraocular pressure.

14 DR. HIGGINBOTHAM: Based on the information that  
15 was provided, certainly it appears that it lowers the  
16 intraocular pressure. What I don't know is what happens  
17 once it is dissolved, which is at 9 months. So, that is  
18 why I would be interested in knowing what happens to more of  
19 these patients after even 12 months, or at least get more  
20 information on these patients at 12 months. But this,  
21 again, is a group of patients who would do well with just  
22 about anything, or even without antimetabolites because they  
23 are old and they are Caucasian.

24 DR. SUGAR: Dr. Coleman?

25 DR. COLEMAN: I am glad I didn't have to wait four

1 years for a glaucoma PMA like Eve. Dr. Bullimore has  
2 requested that I be brief, so I am going to --

3 [Laughter]

4 -- actually concentrate on those things in my  
5 review that I feel still need to be addressed. One of the  
6 things that I wanted to encourage sponsors and also the FDA  
7 is to require Kaplan-Meier lifetable analyses when you are  
8 looking at positive outcomes or success rates because it  
9 does take into account loss to follow up and also deaths.  
10 As I pointed out in my review, in this study there were five  
11 subjects that were lost to follow up but there were also  
12 five deaths. So, that is a little under ten percent, but it  
13 is important to keep that in mind when you are looking at  
14 these rates and comparisons.

15 In terms of the questions for the panel, one of  
16 the issues that I have and I still am a little bit confused  
17 is that I think that an adverse event needs to be well  
18 defined. I think a lot of times, as surgeons, we define  
19 complications and we don't say that they are adverse events,  
20 but when I read the definition of what an adverse event is,  
21 that also is a postoperative complication. So, it is "an  
22 undesirable and unintended, although not necessarily  
23 unexpected, result of therapy or other intervention (such as  
24 a headache following spinal tap or intestinal bleeding  
25 associated with aspirin therapy)." So, one of the questions

1 I have is that although there were no specific device-  
2 related adverse events, there were adverse events related  
3 with the device plus the procedure. And, without the  
4 procedure you can't place the device. Therefore, I think  
5 that those adverse events are part of the device plus the  
6 procedure, which is part of the labeling issues that I felt  
7 were indicated.

8 In addition, another issue was the indication for  
9 the device. In the indication statement they said that it  
10 was indicated for the reduction of intraocular pressure in  
11 patients with open-angle glaucoma uncontrolled on maximum  
12 tolerated medical therapy. It is important to realize that  
13 in the study they really only were looking at primary open-  
14 angle glaucoma. They did have some other types, however,  
15 they didn't include uveitic or neovascular, pseudophakic,  
16 aphakic or congenital glaucomas -- all things that are going  
17 to be different than a primary open-angle glaucoma. So, I  
18 would recommend that that be included in the labeling  
19 because that is what the study did, to consider that.

20 Once again, as I said, I mentioned about the  
21 adverse events, how you look at it and whether it is device  
22 related or the device plus procedure. The gamma radiation  
23 was discussed in terms of that that does eliminate viral  
24 particles, by the sponsor.

25 So, in conclusion, I felt that the device plus the

1 procedure was safe, and I also felt that it was as effective  
2 as trabeculectomy. So I recommend, pending considerations,  
3 that it be approved.

4 DR. SUGAR: Thank you. Any questions for Dr.  
5 Coleman? Dr. Pulido?

6 DR. PULIDO: I was castigated by Sally for not  
7 talking into the microphone, so I will try to shape up.

8 On page 594, they do a logistic analysis of risk  
9 factors for the device not working, the odds ratios. Could  
10 you help me interpret what these mean, the odds ratios here?

11 DR. COLEMAN: I will let Karen do it.

12 [Laughter]

13 DR. BANDEEN-ROCHE: So, for instance, age group 2,  
14 and remind me what the outcome here is.

15 DR. PULIDO: Success rate.

16 DR. BANDEEN-ROCHE: So, a 1 would be a success.  
17 We are estimating the probability of success rather than a  
18 failure. If that is the case, then age group 2, their odds  
19 of success exceed those of age group 1 by a factor of 3.766,  
20 adjusting for the other factors in this model.

21 DR. PULIDO: For African Americans?

22 DR. BANDEEN-ROCHE: It is lower. It means that  
23 the success rate would be lower by a factor of about a  
24 quarter of the odds. So, 0.25 --

25 DR. PULIDO: So, 76 percent less?

1 DR. BANDEEN-ROCHE: Yes.

2 DR. PULIDO: And in older patients it is more  
3 efficacious by a factor of 300?

4 DR. BANDEEN-ROCHE: Well, 300 percent, yes, but  
5 the odds increase by a factor of 3.7.

6 DR. SUGAR: Did that answer your question, Jose?

7 DR. PULIDO: Yes, it did.

8 DR. SUGAR: Dr. Higginbotham?

9 DR. HIGGINBOTHAM: Karen, to what extent would the  
10 numbers of patients within those various categories  
11 influence the odds ratio in terms of, you know, how  
12 important it is or how valid it is?

13 DR. BANDEEN-ROCHE: Well, certainly what the  
14 number by itself would influence would be the precision with  
15 which we could estimate the odds ratio. So, for instance,  
16 for Black the standard error is, you know, 0.7877. You can  
17 see that that would lead to a confidence interval that sort  
18 of barely overlapped the null but, indeed, there is  
19 relatively low power to estimate that odds ratio in the  
20 study.

21 In terms of the bias introduced, just the number  
22 per se doesn't estimate any bias but the sampling method for  
23 the population -- you know, for instance, which African  
24 Americans were included -- could very much influence the  
25 bias.

1 I actually had a question about the sampling of  
2 the care providers and I apologize for not asking this  
3 earlier. If you want me to wait, I certainly will.

4 DR. SUGAR: I think it is fine, Don, if you can  
5 respond to her question. I hope that the FDA doesn't mind.

6 DR. BANDEEN-ROCHE: I do apologize for not asking  
7 this at the right time. I was just wondering how the  
8 providers were selected for the study. You know, in what  
9 sense are they representative of any population of providers  
10 who would be using this device.

11 DR. SANDERS: Well, they run the gamut from  
12 glaucoma specialists to private practitioners who have a  
13 large number of glaucoma practices. So, I would think that  
14 they would be fairly representative. They are certainly not  
15 overweighted, for instance, with glaucoma specialists. We  
16 have people who are largely cataract surgeons, and so on.  
17 So, I believe they would probably be fairly representative  
18 in that respect.

19 DR. BANDEEN-ROCHE: But I don't think they were  
20 chosen randomly --

21 DR. SANDERS: No, no.

22 DR. BANDEEN-ROCHE: So, how were they chosen?

23 DR. SANDERS: Well, it had to do with the people  
24 who were aware of the device and expressed an interest in  
25 getting involved with the study, and also our evaluation of

1 their ability to collect good quality data which, in my  
2 experience, is usually the case whether it is a refractive  
3 procedure or a glaucoma procedure.

4 DR. BANDEEN-ROCHE: And it is true that Dr. Bylsma  
5 did surgeries on more than a third of the eyes, right?

6 DR. SANDERS: Yes, that is correct.

7 DR. BANDEEN-ROCHE: I have one more follow-up  
8 question but I am not sure that it is actually for you. It  
9 is about the poolability analyses. It is somewhat related.  
10 May I go ahead, Mr. Chairman?

11 DR. SUGAR: Please.

12 DR. BANDEEN-ROCHE: So, I am looking at the GEE  
13 analyses, Appendix 3, page 530. This was a poolability  
14 analysis having to do across providers with respect to the  
15 outcome of decrease in pressure, in IOP. So, at the bottom  
16 of the page there is a table with sites listed. I take it  
17 that site 1 is Dr. Bylsma.

18 DR. SANDERS: I have to check. That is correct.

19 DR. BANDEEN-ROCHE: Certainly that looks like the  
20 best outcome. There was an analysis done for whether the  
21 mean decrease varied across sites, and the finding was that  
22 it did not. Was an analysis done that had site 1 as the  
23 reference? The reason I am asking this is because that  
24 would be an analysis that had much higher power than the one  
25 that was done here.

1 DR. SANDERS: I am afraid that it wasn't.

2 DR. BANDEEN-ROCHE: All right. I think that is  
3 all. Thank you.

4 DR. SUGAR: Other questions for the primary  
5 reviewers? We have probably an hour in which we can maybe  
6 even come to closure on this. We can take longer but if we  
7 can finish it before lunch it would be nice.

8 We have three questions in front of us. I would  
9 first like to ask for any general statements from any of the  
10 panel members or any questions. Go ahead, Arthur.

11 DR. BRADLEY: This is just a general question for  
12 the surgeons, I guess. I just wondered, listening to the  
13 discussion, whether there would be any reason for a surgeon  
14 to choose a traditional trabeculectomy versus this deep  
15 sclerectomy collagen implant. Is there some subpopulation  
16 of eyes for which one procedure would be preferable over  
17 another? Because it seems to me that we are doing a  
18 comparison and this new method is being compared to the sort  
19 of standard, and I just wondered if there would be some  
20 reason in some eyes where this new method would be  
21 preferable.

22 DR. SUGAR: Dr. Higginbotham?

23 DR. HIGGINBOTHAM: Well, first of all, assuming  
24 that the surgeon is well adept in terms of performing the  
25 procedure, because it is technically challenging I believe

1 generally, then one might choose this procedure in those  
2 instances where the patient has excellent vision centrally,  
3 20/30, 20/40 or better than that. So, you would not want to  
4 actually increase the rate of complications unnecessarily by  
5 actually penetrating by the trabeculectomy. But, again,  
6 there is the strong possibility that if it is your first or  
7 second procedure you could microperforate.

8 DR. SUGAR: Dr. Coleman, do you want to comment?

9 DR. COLEMAN: Yes, I actually find them comparable  
10 when you are looking at the different rates, and stuff. So,  
11 as Dr. Higginbotham said, it might be if you are looking at  
12 visual acuity, but just looking at the information that the  
13 sponsors presented today and the PMA, the visual acuity  
14 seems to be a little bit better in the first one to two  
15 months compared to the standard trabeculectomy. But you  
16 still see complications with this procedure, just like you  
17 do with trabeculectomies. So, I think it is probably going  
18 to end up being surgeon's preference because, as I  
19 understand, they are not proving that this procedure is  
20 better than trabeculectomy or has less complications than  
21 trabeculectomy. So, then it would definitely be up to the  
22 individual clinician.

23 DR. SUGAR: Other issues? Go ahead, Mark.

24 DR. BULLIMORE: My gut reaction, based on --

25 DR. SUGAR: Make it brief, Sally said!