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**TRANSCRIPT OF PROCEEDINGS**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**FOOD AND DRUG ADMINISTRATION**

**GASTROENTEROLOGY AND UROLOGY DEVICES PANEL**

**—OF THE**

**MEDICAL DEVICES ADVISORY COMMITTEE**

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Pages 1 thru 237

Rockville, Maryland  
October 29, 1998

**MILLER REPORTING COMPANY, INC.**

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DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

GASTROENTEROLOGY AND UROLOGY DEVICES PANEL  
OF THE  
MEDICAL DEVICES ADVISORY COMMITTEE

Thursday, October 29, 1998

8:40 a.m.

Main Conference Room  
Office of Device Evaluation  
9200 Corporate Boulevard  
Rockville, Maryland

MILLER REPORTING COMPANY, INC.  
507 C Street, N.E.  
Washington, D.C. 20002  
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Mary Cornelius, Executive Secretary

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1 DR. HAWES: My name is Rob Hawes. I am a  
2 Professor of Medicine in the Division of Gastroenterology in  
3 the Digestive Disease Center at the Medical University of  
4 South Carolina in Charleston. I am a voting member.

5 DR. DONATUCCI: Craig Donatucci. I am a  
6 urologist, Duke University Medical Center, and I am a voting  
7 member.

8 DR. WHITE: Barbara White, Professor of Medicine,  
9 University of Maryland. I am a rheumatologist.

10 DR. STEINBACH: Joseph Steinbach, engineer,  
11 University of California at San Diego. My office is at the  
12 VA Medical Center in Gastroenterology. I am a voting  
13 member.

14 DR. JANOSKY: Janine Janosky, University of  
15 Pittsburgh, Department of Family Medicine and Clinical  
16 Epidemiology, Division of Biostatistics. I am a  
17 biostatistician. I am a voting member of the Dental  
18 Products Panel and a consultant to this panel.

19 DR. BOULWARE: Dennis Boulware, Professor of  
20 Medicine, Rheumatologist, University of Alabama at  
21 Birmingham, and a consultant.

22 DR. HORTIN: I am Glen Hortin. I am Acting Chief  
23 of Clinical Chemistry in the Clinical Pathology Department  
24 at NIH. I am a consultant and temporary voting member.

25 DR. CLAUW: I am Dan Clauw, Department of

1 Medicine, Division of Rheumatology at Georgetown University,  
2 and I am a consultant.

3 MS. CORNELIUS: Mary Cornelius, Urology and  
4 Lithotripsy Devices Branch, and Executive Secretary for this  
5 panel.

6 DR. KALLOO: Tony Kalloo. I am a  
7 gastroenterologist. I am an Associate Professor of Medicine  
8 at Johns Hopkins University, and Director of  
9 Gastrointestinal Endoscopy, and I am a voting member.

10 Next, Dr. DonaBee Tillman will give a presentation  
11 on the FDA Year 2000 Initiative.

12 Dr. Tillman.

13 **FDA Year 2000 Initiative**

14 DR. TILLMAN: Thank you. Today, I want to just  
15 briefly spend five or 10 minutes telling the panel a little  
16 bit about FDA's Year 2000 Initiative.

17 [Slide.]

18 For those of you who haven't heard about this so  
19 for, I think you would probably have to have been maybe  
20 sleeping under rock, but the Year 2000 problem is the  
21 failure of certain computer systems to properly process or  
22 recognize dates that represent the year using only two  
23 digits instead of four digits, and the example given on the  
24 viewgraph there is that 00 could be interpreted as either  
25 2000 or 1900.

1 [Slide.]

2 What we want you to know is medical devices are  
3 subject to Year 2000 problems, and this includes medical  
4 devices that are based on microprocessors or use PCs,  
5 medical devices that are really just software applications  
6 that do different kinds of data analysis, devices that  
7 interface to databases or recordkeeping systems, and then  
8 devices that you might not even realize have a computer chip  
9 in them, and these are devices that contain embedded  
10 microprocessors, and we have seen more and more devices use  
11 microprocessors nowadays, things in your operating rooms  
12 like light sources and EKG machines and ventilators, and  
13 just about every piece of complex electromedical equipment  
14 actually has a microprocessor in it and conceivably could be  
15 subject to problems when the Year 2000 rolls around.

16 [Slide.]

17 So, what is FDA and CDRH doing to address the Year  
18 2000 problem? We have sent out several letters to  
19 manufacturers reminding them that this is a problem, that  
20 they need to do something about it.

21 We have developed some guidance documents telling  
22 manufacturers what they can do. We have established a  
23 database of product information that is available on our web  
24 site. We have done monitoring and assessment of what people  
25 are doing, and we have also done some educational

1 activities.

2 [Slide.]

3 I am going to go into just a brief little more  
4 detail on each of those items.

5 What we have done internally is we have sat around  
6 and thought about all the devices that we review and which  
7 are the ones that we think use date functions and could  
8 conceivably have a Year 2000 problem, and contacted those  
9 manufacturers.

10 We sent a letter back in June of last year to all  
11 manufacturers of devices that we thought used software, and  
12 we advised them of the problem. We told them that they  
13 could go and fix the problem, they wouldn't have to resubmit  
14 an application to us, and we told them that if they had  
15 products out in the field that they wanted to repair or  
16 update, that that would not be considered a recall.

17 [Slide.]

18 We have been participating in a Biomedical  
19 Equipment Working Group, which is governmentwide and is  
20 chaired by our department, and we are basically  
21 consolidating information that we get from all different  
22 agencies and working with public and private health care  
23 organizations.

24 [Slide.]

25 We established a web site in the spring of this

1 year, and I am going to tell just in a little more detail  
2 about that in the next couple of slides, and we have also  
3 published some guidance on what we expect.

4 [Slide.]

5 Our web site includes this biomedical equipment  
6 database, and the idea here is that companies that have  
7 products that are Year 2000 compliant or aren't Year 2000  
8 compliant dial into our web site and publish information  
9 about which of their products are Year 2000 compliant and  
10 which aren't.

11 The manufacturers enter the data directly by  
12 themselves and submission of data is voluntary. What they  
13 do is they basically certify that their products are Year  
14 2000 compliant, so if you have got a product and you are  
15 concerned that it might not be, you can get into this  
16 database, you can look it up by manufacturer, and you can  
17 see whether those products are Year 2000 compliant or not.

18 It is continuously updated and it is searchable,  
19 and you can download information off of it.

20 [Slide.]

21 The address of FDA's web site is [www.fda.gov](http://www.fda.gov), and  
22 once you get onto that FDA home page, you can select, there  
23 is a Year 2000 item, and that will take you to the database  
24 if you are interested in looking at it.

25 [Slide.]

1           In addition to the database, we have sent several  
2 more letters to manufacturers. They are listed up there.  
3 The one I want to note is the most recent one, September  
4 21st.

5           One of the concerns that has arisen lately is that  
6 the biggest problem with the Year 2000 may not be that the  
7 devices are going to fail, but it may be that there might be  
8 a shortage of devices, because so much of the manufacturing  
9 process now is automated and computer controlled, and there  
10 is the concern that when the Year 2000 rolls around, this  
11 equipment may not function appropriately, and so we want to  
12 make sure that manufacturers understand that they need to  
13 look at their manufacturing processes, as well, and this  
14 includes drug manufacturers, device manufacturers, foods,  
15 any kind of FDA-regulated industry.

16           In the future, we are also planning to provide  
17 additional letters to manufacturers and to health care  
18 facilities and directly to consumers.

19           [Slide.]

20           As I mentioned before, the product database that  
21 is on the web site lists which products are affected by Year  
22 2000, in other words, which are noncompliant, and the  
23 manufacturer certifies the status of their compliance.

24           The other thing that is on the web page is there  
25 is a link directly to the web site of a manufacturer, so if

1 you look up a company, company X, and they say that they are  
2 Year 2000 compliant except for these two particular  
3 products, then, they often provide a link to their own web  
4 site where there is additional information about what the  
5 implications are of the Year 2000 issues.

6 [Slide.]

7 One of the things that has been a little  
8 controversial is what the definition of the Year 2000  
9 compliance is, and basically, it means that the system can  
10 appropriately handle dates, and the thing that we want to  
11 emphasize is that noncompliant does not mean a risk to  
12 public health. Devices that aren't necessarily Year 2000  
13 compliant can still be safely used as long as the way in  
14 which they are noncompliant is fully understood and taken  
15 into account.

16 So, we don't want to be getting people concerned  
17 that this is going to be a huge public health hazard, but we  
18 think it is important that people are aware of these issues.

19 [Slide.]

20 In terms of the product database we have set up,  
21 one of the problems we have had is that many companies have  
22 not yet reported their information. Some of it is just due  
23 to the fact that they haven't gotten around to it, in other  
24 cases, they are still in the process of assessing their  
25 product lines.

1           Most of the noncompliant products that we have  
2 seen use obvious date displays, in other words, if you have  
3 got an ECG device that prints out a record and it prints the  
4 date, those kinds of obvious problems with dates are the  
5 things that we are seeing most frequently, and they are not  
6 terribly clinically significant.

7           We have seen a limited number of products that  
8 have significant operational problems that could really  
9 impact on how they function, and there is a lot of different  
10 solutions going around that manufacturers are working to  
11 address the problems.

12           [Slide.]

13           We can recall devices that present a significant  
14 risk to public health if they have a Year 2000 problem, and  
15 we are keeping an eye out on those products. We are  
16 monitoring reports of Year 2K problems that we see on web  
17 sites and on list servers in different news groups, so we  
18 are keeping an eye on what is going out there, and where we  
19 find that there is a significant risk to patients, we go out  
20 and investigate, and we will take action where necessary.

21           [Slide.]

22           Our future activities are we are working with the  
23 Department of Veterans Affairs. They also have a database,  
24 and we are trying to establish a more specific database that  
25 gets down to looking at actual model numbers and things of

1 devices, so we are trying to consolidate their database with  
2 ours.

3 We want to continue our outreach and  
4 communications with the industry and with the clinical  
5 community as yourselves, and we want to take prompt action  
6 on any products that we think are not Year 2K compliant and  
7 present a public health hazard, so are keeping close watch  
8 on this.

9 In our inspections where we go out and look at  
10 manufacturing facilities, we are increasing our emphasis on  
11 looking at Year 2K problems, as well.

12 [Slide.]

13 What do we want you to do? We would like you to  
14 provide advice to us on any experience that you have had in  
15 terms of products that you think might be problematical in  
16 terms of Year 2K problems.

17 If you have got ideas about which kind of devices  
18 that you think that use dates could present a risk to  
19 patients if they are not addressed, we would like to hear  
20 from you about that, and any suggestions that you have about  
21 what we can do to reduce risks from the Year 2K problem, we  
22 would love to hear about it.

23 At the end of my talk, I am going to put up a  
24 slide, and I think it is in your handout or it was mailed to  
25 you, that has the address of the contact person who you can

1 send this information to.

2 [Slide.]

3 Some of the things that you can do back at your  
4 own health care facilities, you know, your health care  
5 facilities should be inventorying and assessing their own  
6 devices. They should be going through and looking at them  
7 and making sure that they understand which ones could be  
8 Year 2K compliant and which ones might not be, and it is  
9 important to obtain information on the device status from  
10 the manufacturers, calling up the manufacturers and say, you  
11 know, what have you done to assure Year 2K compliance.

12 Testing is possible with some kinds of devices.  
13 You need to watch out for devices that are interconnected or  
14 sit on a computer network, because computer networks could  
15 conceivably have problems when the Year 2000 rolls around,  
16 and you need to plan and develop work-arounds and  
17 contingency plans, so that if devices or things that are  
18 critical for your health care facility stop functioning on  
19 January 1, 2000, that you have got a way to still continue  
20 to deliver health care as needed.

21 [Slide.]

22 So, if you have any comments or concerns or any  
23 information you think you can share with us, Tom Shope, in  
24 our Office of Science and Technology, is the contact person  
25 for the Year 2000, and you can phone him or you could E-mail

1 him. The other person you can communicate with if you don't  
2 get this name or phone number is Mary Cornelius, your panel  
3 executive secretary, and she can make sure that your  
4 comments are sent to Tom Shope.

5 Does anybody have any questions or comments?

6 Thank you for your attention.

7 DR. KALLOO: Thank you, Dr. Tillman.

8 I will now turn the meeting over to Mary who will  
9 read the Executive Secretary's statement.

10 **Executive Secretary's Statement**

11 MS. CORNELIUS: Good morning. Before I begin, I  
12 would like to read a statement concerning appointments to  
13 temporary voting status.

14 Pursuant to the authority granted under the  
15 Medical Devices Advisory Committee Charter, dated October  
16 27, 1990, as amended April 20, 1995, Drs. Lawrence Agodoa,  
17 Dennis Boulware, Daniel Clauw, Glen Hortin, Janine Janosky,  
18 Anthony Kalloo, Matthew Liang, and Barbara White have been  
19 appointed voting members by Dr. Bruce Burlington, Director  
20 of the Center for Devices and Radiological Health, for this  
21 meeting on October 29, 1998, of the Gastroenterology and  
22 Urology Devices Panel.

23 The following announcement addresses conflict of  
24 interest issues associated with this meeting and is part of  
25 the record to preclude even the appearance of impropriety.

1           The Conflict of Interest Statutes prohibit special  
2 government employees from participating in matters that  
3 could affect their or their employers' financial interests.  
4 To determine if any conflict existed, the Agency reviewed  
5 the submitted agenda and all financial interests reported by  
6 the committee participants. The Agency has no conflicts to  
7 report.

8           In the event that the discussions involve any  
9 other products or firms not already on the agenda for which  
10 the FDA participant has a financial interest, the  
11 participants should exclude themselves from such involvement  
12 and their exclusion will be noted for the record.

13           With respect to all other participants, we ask in  
14 the interest of fairness that all persons making statements  
15 or presentations disclose any current or previous financial  
16 involvement with any firm whose products they may wish to  
17 comment upon.

18           Dr. Kalloo will ask all persons making statements  
19 either during the open public meeting or during the open  
20 committee discussion portions of the meeting to state their  
21 name, professional affiliation, and disclose whether they  
22 have any financial interest in any medical device company.

23           Finally, I would like to inform you that the  
24 tentative panel meeting dates scheduled for 1999 are January  
25 28 and 29, April 22 and 23, July 29 and 30, and November 18

1 and 19.

2 I would also like to remind everyone, panel  
3 members and visitors, if they have not signed in, they need  
4 to sign in on the sheets outside the room.

5 DR. JETER: Mary, excuse me. Could you do those  
6 dates again?

7 MS. CORNELIUS: Yes. They are January 28 and 29,  
8 April 22 and 23, July 29 and 30, and November 18 and 19.

9 **Open Public Hearing**

10 DR. KALLOO: We will now proceed with the Open  
11 Public Hearing section of this meeting.

12 I would ask at this time that all persons  
13 addressing the panel come forward to the microphone and  
14 speak clearly, as the transcriptionist is dependent on this  
15 means of providing an accurate transcription of the  
16 proceedings of the meeting.

17 Before making your presentation to the panel,  
18 state your name and affiliation, and the nature of your  
19 financial interests in that company. Let me remind you that  
20 the definition of financial interests in the sponsor company  
21 may include: compensation for time and services of clinical  
22 investigators, their assistants and staff in conducting the  
23 study, and in appearing at the panel meeting on behalf of  
24 the applicant; direct stake in the product under review,  
25 that is, inventor of the product, patent holder, owner of

1 shares of stock, et cetera; owner or part owner of a  
2 company.

3 No statement is necessary from employees of that  
4 company.

5 I would ask that all persons addressing the Panel  
6 come forward to the microphone and speak clearly, just to  
7 emphasize that.

8 The first speaker listed on the agenda is Norine  
9 M. Walker. If Ms. Walker could come up to the microphone.

10 MS. WALKER: Good morning, ladies and gentlemen.  
11 My name is Norine Walker. I am a patient advocate. I am  
12 not affiliated with Cypress Bioscience in any way. I have  
13 not been paid to be here. I am here of my own accord.

14 I appreciate the opportunity to present my  
15 perspectives and opinion about furthering the research for  
16 the Prosorba column. I am a resident of Alexandria,  
17 Virginia, I am a local person. I work in the City of  
18 Alexandria.

19 I feel as if it is important for decision-makers  
20 to understand the position associated with research which  
21 some people with rheumatoid arthritis as well as others  
22 associated with treatment and care of people with arthritis  
23 have. I am a volunteer with the Arthritis Foundation, the  
24 only non-profit health agency devoted to finding the cause  
25 of, and the cure for, arthritis.

1 I come in contact with other people that have one  
2 or many of the over 100 types of arthritis on a daily basis.  
3 Through my volunteer work, I also interact with general  
4 physicians, specialists, such as rheumatologists, physical  
5 therapists, and other caregivers.

6 As a volunteer, I am devoted to ensuring that the  
7 mission of the Arthritis Foundation is carried out. That  
8 mission includes supporting research to find the cause of,  
9 the cure for, and one day in the future, hopefully, the  
10 prevention of arthritis, as well as improving the quality of  
11 life for those people that have arthritis.

12 In 1985, over 35 million people have had  
13 arthritis. That number increased to 37.9 million by 1990,  
14 and to 40 million by 1995. Statistics indicate that that  
15 will increase to 59.4 million by the year 2020, facts I am  
16 sure you are familiar with.

17 It is the most prevalent chronic health problem  
18 and the nation's leading cause of disability among Americans  
19 over 15 years of age. It also costs the U.S. economy \$65  
20 billion, an impact equal to a moderate recession. It  
21 crosses all lines of diversity and something has to be done  
22 about it.

23 I am one of the lucky ones. I am celebrating this  
24 year 1998 having been diagnosed with rheumatoid arthritis 20  
25 years ago next month. Yes, I celebrate, although I am

1 considered to have moderate disease, better than the severe  
2 level that I have had in the past over the last 20 years.

3           Because of research advances, I have been able to  
4 be a success in many aspects of my life. Research into  
5 medicines has helped to retard the disability that I was  
6 told I would experience within five years of my diagnosis.

7           I have been on many types of medicines with side  
8 effects that are disturbing. One of the most difficult  
9 decisions of my life was deciding whether to be treated with  
10 a drug that would cause me to determine, as a young woman of  
11 childbearing age, which many patients with rheumatoid  
12 arthritis have, whether I was going to have children.

13           Believe me, that decision was a no-win situation.  
14 These decisions affect your physical well being, but also  
15 psychological and psychosocial decisions. They also impact  
16 other family members and relationships.

17           Research and development of assistive devices and  
18 physical therapy has allowed me to function almost fully in  
19 most categories of mobility and range of motion.

20 Remembering when I was first diagnosed in my freshman year  
21 at the University of Maryland how painful and literally  
22 impossible it was for me to raise my hands above my head to  
23 brush my hair or the pain associated with simply brushing my  
24 teeth.

25           Research into techniques for betterment of quality

1 of life also have been important for me. These include  
2 medicines for short-term, long-term, and possibly forever  
3 treatments.

4           But I have also seen those not as fortunate in  
5 their battle with rheumatoid arthritis, and I am here on  
6 their behalf, as well. Some medicines that I have responded  
7 to well, others have not, and they have not been able to  
8 find the balance in their lives to make it tolerable to the  
9 level that I have. People with RA are faced with different  
10 treatment philosophies and lots of potential side effects,  
11 some of which are more difficult to tolerate than the  
12 chronic pain.

13           Management of RA includes medicines, as well as  
14 other treatments. A team approach to medical treatment has  
15 been very successful in my case and new devices to  
16 aggressively control the disease until the cause and further  
17 cure can be found are very important.

18           The bright side can be seen as new medicines and  
19 devices, such as the ProSORBA column, allow for these new  
20 advances to be further researched specifically for people  
21 that cannot successfully be treated by the current treatment  
22 programs available. The initial studies seem promising. It  
23 appears that the devices might be helpful in my friends that  
24 have severe RA.

25           One of the most interesting aspects of this

1 disease is that as a chronic disease, for many of us, it has  
2 its ebbs and tides. For instance, since I was diagnosed 20  
3 years ago, I have gone from being in severe pain, unable to  
4 walk or care for myself, to periods of total independence.  
5 Then something hits me and I require hospital admittance,  
6 perhaps from a side effect influenced by the low  
7 immunosuppressive qualities of the disease or the drugs  
8 themselves.

9           Then, I get back up for a period of time to set  
10 the world on fire. The uncertainty is very scary. It is  
11 not fair that we have to deal with this, we need more  
12 research. The research should be expanded to a larger pool  
13 of patients. The combinations of medicines that people with  
14 rheumatoid arthritis are often taking as part of their  
15 treatment should also be considered.

16           There should also be considerations of caregivers  
17 from professionals to families, appropriate use of any and  
18 all medicines, education about RA, appropriate amounts of  
19 rest and exercise, and learning how to self-manage the  
20 disease from the patient side.

21           I look forward to future positive performance of  
22 the ProSORBA column for those people with RA, and hope that  
23 this will alleviate the painful existence that many of us  
24 have to struggle with on a day-to-day basis.

25           Thank you for the opportunity to present my

1 position.

2 DR. KALLOO: Thank you, Ms. Walker.

3 Next is Ms. Lisa Caswell.

4 MS. CASWELL: My name is Lisa Caswell. I am a  
5 patient presenter. Thank you for allowing me to speak at  
6 this panel.

7 I would like to tell you how I came here from my  
8 home city of Seattle. At my insistent request, Cypress  
9 Bioscience agreed to pay my trip expenses so I could speak  
10 today. I am not in any way connected with the company. I  
11 do not own stock. I am a patient with limited resources who  
12 considered it important for me to share my experience.

13 There currently exists no government or industry  
14 scholarship for patients who have been involved with a  
15 treatment under review, most of whom are likely economically  
16 compromised, the patients that is, to allow for them to come  
17 and speak regarding efficacy. Perhaps this could be  
18 suggested at the next budget meeting? That is a joke.

19 I am part of the 1 percent of the population with  
20 rheumatoid arthritis. I am currently working on a research  
21 project at the University of Washington, and decided to  
22 research some of the social costs of RA. RA is a costly  
23 disease in dollars.

24 I was diagnosed about eight years ago, in the  
25 usual age range of between 30 and 50 years old, right in the

1 middle of what should have been my peak earning years.  
2 Experts have reported that those afflicted with RA suffer an  
3 average lifetime earnings loss of 50 percent.

4           For me, that actually translated into an income 70  
5 percent lower at my current job than at my previous position  
6 as Operations Director for a restaurant chain, from which I  
7 was let go because I could no longer keep up with the  
8 demands of the job due to the disease.

9           Productivity loss due to symmetrical polyarthrititis  
10 has been estimated at \$20 billion annually in the United  
11 States alone. I visit physicians more frequently than the  
12 average person. RA accounts for 9 million physician visits  
13 annually, with yearly direct health care costs exceeding \$5  
14 billion. I will likely die prematurely, as RA patients  
15 mortality is double the expected rate, often due to  
16 complications from medications rather than the disease  
17 itself.

18           After being diagnosed, as previously stated, I  
19 lost my job along with my health care benefits. I quickly  
20 ran through my reserves, as my physician had elected to  
21 treat my aggressive disease aggressively, necessitating my  
22 spending over \$600 a month in medication alone.

23           I began a downward spiral into excruciating pain,  
24 depression, and incapacitation. I resolved to remember  
25 these early experiences because, as is true with most of

1 life, they might become funny later. Like the time the  
2 woman from the welfare office remarked, "You know, honey, I  
3 don't recall ever giving benefits to someone who drives a  
4 Mercedes." The car was sold soon after to pay for my health  
5 care.

6 In addition to receiving welfare for a short time,  
7 I was awarded food stamps. I made my partner at the time,  
8 now my husband, procure the groceries while I hid in the  
9 car. I had him get only necessary items, no fun foods.  
10 During the first year I was diagnosed, I lost 30 pounds due  
11 to nausea from the medications. I had a real close  
12 relationship with my carpet.

13 Up until now, RA patients had few clear treatment  
14 choices. Available medications, which sometimes provided  
15 temporary relief, had associated side effects so frightening  
16 it made me question my judgment to elect to use them.

17 Throughout my disease, I have taken several  
18 medications, including gold shots, methotrexate, high doses  
19 of prednisone, chloroquin, hydroxychloroquin, Cyclosporine,  
20 and diclofenac. Please allow me to review some of these  
21 medications side effects.

22 Methotrexate, a standard in the treatment of RA,  
23 is used for chemotherapy and as a medical form of abortion.  
24 It can cause lymphomas, kidney and liver damage, and blood  
25 disease. For me, methotrexate caused painful mouth ulcers,

1 hair loss, and unrelenting nausea.

2           Prednisone can cause atherosclerosis,  
3 osteonecrosis (that means bone death), weight gain,  
4 cataracts, and unstable blood sugars. It also can cause  
5 osteoporosis. Two years ago, after a bone density scan, my  
6 physician told me I have the hips of a 100-year-old woman.

7           Chloroquin can cause irreversible eye damage.  
8 After taking chloroquin for only three months, I had to be  
9 switched to the somewhat less toxic, somewhat less effective  
10 hydroxychloroquin because I had corneal deposits.

11           Cyclosporine is used for organ transplant patients  
12 to cripple their immune systems. I was only allowed on it  
13 for a short time, for fear of toxicity. Diclofenac, the  
14 non-steroidal anti-inflammatory I have been taking since  
15 diagnosis, is probably the most benign of the drugs I have  
16 taken. It can only cause lethal gastrointestinal bleeding  
17 with no warning. While these descriptions sound scary, the  
18 alternative was a somewhat quicker demise due to the RA.

19           Having RA was quite unpleasant. After being  
20 diagnosed, my "day" quickly shrank to 3 to 4 hours, with the  
21 rest of the time spent agonizing in bed or balled up  
22 nauseous on the aforementioned carpet.

23           I changed from a dynamic, energetic, independent  
24 woman to a helpless and indeed hopeless person. Tasks  
25 everyone takes for granted were impossible. I could not

1 open jars or cans, use door keys, or even dress or bathe  
2 independently.

3 I cut off my long hair because I could not dry it  
4 or brush it. When I left the house, I used a cane when my  
5 hands weren't too sore, and even occasionally employed a  
6 wheelchair. I have endured several surgeries to my hands,  
7 including joint replacement and tendon repositioning, in an  
8 effort to maintain use after the curling, crippling effects  
9 of the RA set in.

10 Then came the ProSORBA column. The huge plus  
11 about starting treatments was the requirement that I stop  
12 taking most of my toxic medications. In fact, to me the  
13 most positive feature of this treatment is the low side  
14 effect profile.

15 I wasn't adding something toxic to my system, I  
16 was washing something out. What a concept. I felt better  
17 just hearing about it. The physical relief I got after the  
18 treatments was miraculous, but more amazing to me is that I  
19 have been maintained since treatment on lower doses of other  
20 medications.

21 Prior to beginning treatments, increased  
22 prednisone doses had caused my weight to increase and I  
23 became moon-faced. Since the ProSORBA column treatments, I  
24 have returned to my normal weight and facial features, and  
25 have maintained a significantly lower dosage of prednisone.

1 I have been asked about unpleasant side effects,  
2 such as soreness at the needle site or difficulty with the  
3 lengthy treatment session times. When one has RA and  
4 endures daily excruciating pain, perception of pain changes.  
5 A poke with a needle does not register as painful. And,  
6 regarding treatment session length, I would gladly spend  
7 most of the rest of my life receiving weekly sessions to  
8 enjoy the benefits I received.

9 Allow me to describe my life now. My nightly  
10 sleep requirement has gone from 20 hours to 9. The hallways  
11 in my house seem to have gotten shorter. The sun seems to  
12 shine a bit brighter. The incredible weight on my shoulders  
13 I used to walk around with is gone.

14 I have found much of my lost energy. I can dress  
15 and bathe independently, and I am starting to let my hair  
16 grow again. I have two jobs and am finishing my  
17 dissertation towards a Ph.D. in Clinical Psychology.  
18 Choosing my area of specialization was easy. I hope to work  
19 in rehabilitation psychology helping those confronted with  
20 the devastation to their lives that chronic illness causes.

21 I hope you will choose to approve this treatment  
22 for RA. For me, it was too late to save me from some of the  
23 destructive changes to my joints. It was not too late to  
24 give me some of my life back. My husband recognizes a smile  
25 lately he thought he had seen the last of. For newly

1 diagnosed persons, starting this treatment earlier might  
2 prevent some of the negative life changes.

3 Thank you.

4 DR. KALLOO: Thank you, Ms. Caswell.

5 Next is Merrill Meyer.

6 MS. MEYER: Good morning. My name is Merrill  
7 Meyer. I am here as a patient and the recipient of the  
8 Prosorba column.

9 I would like to thank the FDA for allowing me the  
10 opportunity to present my experience and views during this  
11 public hearing portion of the advisory committee meeting  
12 regarding the procedure using the Prosorba column developed  
13 by Cypress Bioscience, Inc.

14 I am here on my own accord to speak to you about  
15 the procedure. I do not own any stock or have any financial  
16 interests or holdings in Cypress Bioscience. However, they  
17 are covering my travel-related expenses to appear before  
18 this advisory committee today.

19 I was diagnosed with sero-positive rheumatoid  
20 arthritis in 1972. Since the initial diagnosis, the disease  
21 has been virulent and non-relenting, and I was told, at the  
22 age of 22, that I could expect to be in a wheelchair and  
23 physically nonfunctional in five years.

24 I chose to be aggressive in my pursuit to control  
25 the disease activity and began following the pyramid of

1 medications. I began with aspirin, progressing to the  
2 quinine drugs, then combining NSAIDS, and later adding  
3 steroids and Solganol to the regime.

4 As these protocols failed, we eliminated the  
5 Solganol and added methotrexate orally and eventually IM, in  
6 addition to NSAIDS, steroids, and the Plaquinel. As the  
7 methotrexate began to fail, we added Imuran and then  
8 Thiotepea was added to the treatment. Eventually, my body  
9 and the immune system was blasted with nitrogen mustard IV.  
10 As I am sure you are aware, the body pays a high price for  
11 the long-term use of these drugs.

12 I made the choice and the decision to take these  
13 drugs because it was important for me to have a life of  
14 quality and not quantity or length of time, and these drugs  
15 have given me the opportunity to continue functioning in the  
16 world, but I am now living with osteoporosis, I have Type 2  
17 diabetes, and I have just recently have been diagnosis with  
18 sinus tachycardia.

19 Despite my aggressiveness with the medications,  
20 over an 18-year period, it became apparent that I was going  
21 to have go through reconstructive surgery. I have had six  
22 surgeries in the last eight years. I have replaced all the  
23 metatarsals of the left foot, I have had bone fusions of the  
24 cuneiform of the navicular foot which had three stress  
25 fractures on its own prior to the bone fusion because of the

1 arthritis.

2 I have had a total knee joint replacement just 10  
3 weeks ago. I have had the synovectomy and realignment of  
4 the tendons of both my left and right hands, and in two  
5 weeks I will have a tendon transfer of the left hand and the  
6 fingers and the wrists, so I will be able to regain the use  
7 of my hand.

8 Additionally, I have had to go through liver  
9 biopsy, and I opted for sterilization after I was informed  
10 on the severity of the drugs that I was or possibly could  
11 take in the future.

12 In 1996, I was hospitalized with a major  
13 exacerbation that eventually led to my body's inability to  
14 take any more medications. I was taken off all of my  
15 medications except for the dexamethasone, and my health and  
16 quality of life continued to deteriorate rapidly along with  
17 my inability to take care of my family and myself.

18 Additionally, I was forced to give up a successful  
19 career, one of three in the last 15 years. I could not  
20 perform basic life tasks such as brushing my teeth, combing  
21 my hair, basic body hygiene, driving my car -- which is an  
22 automatic by the way -- and getting in and out of bed and  
23 dressing myself. The simple tasks became impossible.

24 As I stated, as the rheumatoid arthritis became  
25 more virulent, it forced me to give up the pursuit of three

1 very successful careers, the first that I started right  
2 after college, working in an Outward Bound type, therapeutic  
3 recreation program; then, one in management and fund-raising  
4 when I could no longer climb mountains and kayak rivers.

5           The third I had to recently give up, and that is  
6 working as a stained glass artist, and I can no longer  
7 provide the materials for the art galleries at this time,  
8 and I am going to have to make the decision how I am going  
9 to use my hands to preserve them for the future.

10           As my physical ability to work has deteriorated,  
11 it was determined by the Social Security Administration in  
12 December of 1996 that I was 100 percent disabled.

13           It was at this point I was given the opportunity  
14 to become involved with the Cypress Bioscience research  
15 protocol for the Prosorba column. Three main points  
16 attracted me and my doctor to the procedure. One, the  
17 procedure would be cleansing the blood and not adding any  
18 chemicals to my body; two, the treatment was short term (12  
19 weeks); and, three, it was safe with minimal adverse side  
20 effects expected.

21           I applied for the study and I was accepted and  
22 began the procedure in February of 1996. The only side  
23 effect that I experienced in the 12 weeks I was in the  
24 double-blind study was a buzz from the drop of calcium, and  
25 that was my high each week. This was countered by taking

1 Benadryl and Tums, so I not only was high, I was nodding off  
2 in the chair from the Benadryl.

3           The first six weeks of the treatment, I had flares  
4 and I continued in flares. My joints were still swollen,  
5 and when I left, I was in more of a flare and my joints were  
6 more painful, but as the procedure continued, that began to  
7 decrease.

8           As each week went by, my energy level began to  
9 increase and by the sixth week, there was a drop in the  
10 joint swelling. By the twelfth week, the quality of my life  
11 was greatly improved, I was able to physically take care of  
12 myself, there was no flaring, the joints were no longer  
13 swollen, I was walking without a cane, and prior to that I  
14 was also walking with a walker and/or in a wheelchair.

15           There was no devastating fatigue, and the pain  
16 level was gone. I was able to care for myself, I was able  
17 to run errands, I was able to drive a car now, I was able to  
18 go back and exercise, exercise in a swimming pool, and  
19 occasionally meet with friends for an outing.

20           When I started the procedure my CRP was 3.4. At  
21 the end of the procedure my CRP had dropped to 0.1.  
22 Fantastic, I thought, for 12 weeks. My initial joint count  
23 was 101 swollen joints. At my last appointment, October  
24 22nd, 1998, my swollen joint count was 9.

25           I elected not to go back onto any of the previous

1 medications. Sixteen weeks after completion of the double-  
2 blind study, I chose to go on the open label. I experienced  
3 the same basic response as I had in the double-blind study,  
4 same time frames, same physical response.

5 I believe that ProSORBA has given my body the  
6 ability to fight the disease with minimal medication. I  
7 presently take 1.5 mg of dexamethasone for the rheumatoid  
8 arthritis.

9 The ProSORBA is not toxic to the body for me, it  
10 is short-term use and has minimal side effects. It has  
11 restored my life to be a wife, to participate in retail  
12 therapy. For those of you who don't understand that, that  
13 is known as shopping the sales.

14 I dress myself, I drive a truck, I take care of my  
15 personal hygiene. I can once again take care of my dogs,  
16 participate in community activity services, but most  
17 important, my husband and I now have a relationship outside  
18 of the house.

19 I hope you approve the ProSORBA column and  
20 procedure and give to others a choice of treatment that is  
21 not toxic to the body and will attack the disease activity,  
22 thus giving them the opportunity to actively and fully  
23 participate in all that life has to offer.

24 Once again I would like to thank you for this  
25 opportunity and your time to relate to you my support for

1 the ProSORBA column as a dynamic and minimally invasive  
2 treatment for rheumatoid arthritis.

3 DR. KALLOO: Thank you, Ms. Meyer.

4 If there is anyone else wishing to address the  
5 panel, please raise your hand and you may have an  
6 opportunity to speak.

7 Then, I would like to ask the two members of the  
8 panel who have recently joined, if they would, please, Dr.  
9 Bennett and Dr. Foote, please state your specialty, position  
10 title, institution, and status on the panel, whether you are  
11 a voting member or consultant.

12 Dr. Bennett?

13 DR. BENNETT: Yes, I am Alan Bennett. I am a  
14 urologist. I am the Industry Representative to the panel,  
15 and I am the Vice President of Medical Affairs at C.R. Bard.  
16 I am not a voting member.

17 DR. FOOTE: My name is Jenelle Foote. I am a  
18 urologist in private practice with a clinical affiliation at  
19 Emory University, from Atlanta, Georgia, and I am a  
20 consultant member to the board.

21 DR. KALLOO: Since there are no other requests, we  
22 will now proceed to the open committee discussion of the  
23 Cypress Bioscience, Inc., ProSORBA column pre-market  
24 approval supplement for an extracorporeal immunoadsorption  
25 device intended for the treatment of rheumatoid arthritis.

1 The number is P850020/S11.

2 I would like to remind public observers at this  
3 meeting that while this portion of the meeting is open to  
4 public observation, public attendees may not participate  
5 except at the specific request of the panel.

6 I would like to remind the panel that they may ask  
7 for clarification of any of the points included in the  
8 sponsor's presentation, but discussion should not go beyond  
9 clarification.

10 The first speaker is Dr. Debby Jo Blank, President  
11 and Chief Operating Officer of Cypress Bioscience, Inc.

12 **OPEN COMMITTEE DISCUSSION**

13 **Cypress Bioscience Prosorba Column**

14 **for Treatment of Rheumatoid Arthritis**

15 **Sponsor Presentation: Cypress Bioscience, Inc.**

16 **Overview**

17 DR. BLANK: Good morning. I will just wait a  
18 minute while we are getting our slides organized.

19 DR. KALLOO: If you could, please, as you come up,  
20 mention your financial interests, et cetera.

21 DR. BLANK: Well, since I am the president of the  
22 company, I obviously have substantial financial interests.

23 [Slide.]

24 I would like to start off by thanking the FDA.  
25 Actually, our team wanted me to make a particular comment to

1 recognize -- actually, I think we can leave the lights on,  
2 we can turn them down if we need them for particular slides  
3 -- my team wanted me to comment on the particularly  
4 collaborative approach that has been taken throughout the  
5 entire process, and thank the FDA in particular.

6 I also want to thank our advisers who we have  
7 really leaned on and appreciate very much their incredible  
8 help, and I want to thank my colleagues who have been really  
9 working hard and who have made today possible.

10 I am going to kick off our meeting starting with a  
11 very brief talk, and I would just like to mention who our  
12 other speakers are going to be.

13 Dr. Mike Gendreau is our VP of R&D. Dr. David  
14 Felson, who many of you know, is a rheumatologist from  
15 Boston University and he will describe his involvement with  
16 this study during his talk.

17 Dr. Dan Furst was our lead investigator of the  
18 Phase III or pivotal trial that you are going to hear about,  
19 and Dr. Jerry Nepom is an immunologist, also from Seattle,  
20 who is going to talk.

21 [Slide.]

22 Just to give you a little lay of the land of what  
23 you are going to hear, Dr. Gendreau will talk about the two  
24 pilot studies, Dr Felson will talk about the Phase III  
25 study. Then, Mike will take over and talk about the

1 continuation phase of the pivotal trial, as well as the  
2 safety results.

3 Jerry Nepom will then talk about our science  
4 program, and then Dan Furst will give you his perspective on  
5 the product. Finally, I will come back with a short  
6 summary.

7 [Slide.]

8 Let's talk about what our objective is for the  
9 day: to extend the existing ProSORBA column labeling for  
10 use in the treatment of severe rheumatoid arthritis.

11 [Slide.]

12 The reason that this is our objective is that this  
13 is a supplemental PMA. We have had approval for a much  
14 smaller autoimmune disease idiopathic thrombocytopenic  
15 purpura since 1987.

16 Since the product has been approved, approximately  
17 10,000 patients have been treated in the United States.  
18 Cypress Bioscience has been the manufacturer and marketer of  
19 this product since January of 1996.

20 Prior to Cypress, two other companies were  
21 involved - the Baxter Corporation and the Imray Corporation.

22 [Slide.]

23 Now, I want to just describe very briefly the  
24 product and the procedure. The product contains 200 mg of  
25 Protein A, which we manufacture by fermentation in our

1 manufacturing facility in Seattle.

2           It is covalently bound to a silicon matrix. The  
3 patient is hooked up to any apheresis equipment on the  
4 market via an IV. Then, the cellular component is separated  
5 from the plasma in that apheresis equipment, and the plasma  
6 is run through the column. Then, the reconstituted blood is  
7 returned back to the patient. In this pivotal RA trial, it  
8 was a two-hour procedure done on an outpatient basis.

9           As you can see from this slide, the column is  
10 known to bind immunoglobulins, the column is known to bind  
11 immunoglobulins and immune complexes, however, Dr. Nepom  
12 will talk later in much greater detail about our thoughts on  
13 the mechanism.

14           [Slide.]

15           Historically, we started this pivotal trial based  
16 on the promising results of two smaller studies, the first  
17 by Craig Wiesenhutter in Idaho, and the second sponsored by  
18 the company. Both of these small trials led us to conclude  
19 that it was worth the investment in a pivotal trial, which  
20 we began in early 1996.

21           We finished the trial according to our DSMB's  
22 recommendations, and you will hear more about that, in  
23 January of 1998. We submitted the supplemental PMA to FDA  
24 just recently, this summer, and because of the potential  
25 importance of this therapy, an accelerated review by the

1 Agency created this opportunity for us to be here just three  
2 months after the completion of our submission, which has put  
3 a stress on all of us to move this quickly.

4 [Slide.]

5 Let's briefly review the disease which most of you  
6 are very familiar with. Conservatively, there are just over  
7 2 million patients in the United States with the disease,  
8 who have very significant morbidity and mortality associated  
9 with having the disease, and many of them become  
10 unresponsive or intolerant to their therapies.

11 This is a bad disease to have, as you have heard  
12 so eloquently by the patients who first talked - high rates  
13 of disability, severe limitations in activities of daily  
14 living, high direct health care and indirect health care  
15 costs especially in severe patients, and a total estimated  
16 cost again on the conservative side for RA alone of \$9  
17 billion to the U.S. health care system.

18 I am now going to hand the podium over to Mike  
19 Gendreau.

20 **Prosorba Column in Rheumatoid Arthritis**

21 **Efficacy Results of Pilot Studies**

22 DR. GENDREAU: Good morning. I am Mike Gendreau,  
23 an employee of the company. I serve as the Vice President  
24 of Research and Development, and am the Chief Medical  
25 Officer for the company. I became involved in the company

1 with the intention of trying to bring this product forward  
2 as a rheumatoid arthritis treatment.

3 [Slide.]

4 It is my pleasure to present this morning, in  
5 which I, along with Dr. David Felson, will present the  
6 efficacy results from the pivotal trial, and also I will  
7 present some limited data on our pilot studies.

8 [Slide.]

9 By way of introduction, the ProSORBA column, as  
10 you know, is a medical device and as the patients explained  
11 this morning, perhaps more eloquently than I, it is quite  
12 different from most of the alternatives we have available  
13 for rheumatoid arthritis.

14 The treatment is a procedure. This distinction  
15 carries along a unique set of challenges and opportunities,  
16 and we have the opportunity to remove patients from their  
17 current drug regimes at least for a period of time.

18 I will present some pilot results. Dr. Felson  
19 will then present the primary efficacy results, as he was  
20 very involved with the design and the conduct of the study,  
21 as he will explain. Then, finally, I will come back and  
22 talk about the safety.

23 [Slide.]

24 The pilot trial was an open label design. This  
25 was conducted after the publication by Dr. Wiesenhutter,

1 which indicated that there was potential to use the ProSORBA  
2 column to treat rheumatoid arthritis patients. Seeing this  
3 publication, the company elected to conduct its own open  
4 label trial.

5           Fifteen patients were recruited, and this was  
6 designed as a wash-out trial, where the patients were  
7 removed from all their existing rheumatoid arthritis  
8 specific medications. They underwent a treatment regime  
9 where once a week, for 12 weeks, they were treated with  
10 ProSORBA column.

11           At the end of 12 weeks of treatment, they were  
12 stopped, there were no longer treatments going on, and the  
13 Paulus criteria, which was a forerunner to the ACR  
14 definition of improvement, that we will be discussing for  
15 the rest of the day, was used to assess the patients'  
16 improvement compared to their baseline status at week 16 or  
17 four weeks after the completion of all their treatments.

18           On the next slide, I would like to discuss the  
19 patients who were enrolled.

20           [Slide.]

21           The patients who entered this trial were of the  
22 profile perhaps similar to the patients who have presented  
23 this morning. They had active disease as evidenced by the  
24 tender and swollen joint counts. They tended to have fairly  
25 long-standing disease, that is, that had time to run through

1 a number of different treatments, as we can see by the  
2 number of previous DMARD failures.

3 In general, they were looking for something  
4 different. That is why they would volunteer to enter an  
5 experimental trial, as such, and on the next slide we will  
6 see what the results were.

7 [Slide.]

8 We were very encouraged by this. This was open  
9 label. It was really the first study that the company did  
10 where we had efficacy results, and as shown in the table on  
11 the left, 60 percent of the patients enrolled were improved  
12 by the Paulus criteria at the fourth month of the study,  
13 which was one month after treatments were completed, and the  
14 response actually peaked at month 5, where 66 percent of the  
15 patients reported objective improvement by the Paulus  
16 criteria.

17 On the right panel, we have the change in tender  
18 and swollen joint count, and we can see that both tender and  
19 swollen joint count in the population treated also improved  
20 over time with a 60 percent decrease on average for the  
21 treated patient population by treatment month 5.

22 [Slide.]

23 So, safety was also of intense interest to us, as  
24 this was the really first data the company generated in the  
25 rheumatoid arthritis population. We were gratified to find

1 that all 15 patients were evaluable. We had no withdrawals  
2 secondary to complications.

3 Fourteen of the 15 patients enrolled completed all  
4 12 treatments. The fifteenth patient completed 10 out of 12  
5 treatments, had an intercurrent illness, and elected not to  
6 receive his last two treatments, but he also received  
7 benefit from his treatment protocol.

8 The successful outcome of this trial led to the  
9 development of the pivotal trial we will be discussing the  
10 rest of the day, which we designed in consultation with FDA,  
11 and the next slide compares the pilot study we just  
12 described to the pivotal trial which we will be describing  
13 next.

14 [Slide.]

15 The pivotal trial, as you have already heard, it  
16 was designed as a randomized, Sham controlled, double-blind  
17 trial. As you are probably aware, controlling device trials  
18 is a little bit more challenging than the typical  
19 pharmaceutical trial. We went to a lot of effort to assure  
20 that this double-blinding scheme would be effective.

21 We used the ACR criteria as the assessment for  
22 primary outcome. We moved point in time to assess outcome  
23 to month 5 or two months after the completion of all  
24 treatments while the patient is off medication.

25 We used 12 clinical sites around the country to

1 enroll patients, and it was designed to be a multiple  
2 interim analysis trial where after approximately every 50  
3 patients, we would assess response.

4 With that, I would like to turn the podium over to  
5 Dr. Felson, who will describe the initial efficacy studies.

6 **Efficacy Results of Core Studies**

7 DR. FELSON: Good morning. I am Dr. David Felson.  
8 I am an academic rheumatologist at Boston University and a  
9 clinical epidemiologist, and I am here in large part because  
10 Cypress funded our site to design and analyze this trial. I  
11 am also being paid as a consultant here today. I don't have  
12 any stock in the company.

13 [Slide.]

14 The pivotal trial was designed with the following  
15 organization. We were charged with study design and  
16 analysis at Boston University. We did this with interim  
17 analyses, and therefore there was a Data Safety Monitoring  
18 Board, chaired by Dr. Hal Paulus at UCLA, and other members  
19 of that DSMB included Dick Pollison at Harvard, both of  
20 those two are rheumatologists. Bob Glynn, in the Department  
21 of Preventive Medicine at Harvard, who is a biostatistician,  
22 and Jeane Hester, who is an apheresis expert.

23 The monitoring and data management of the trial  
24 were performed by BRI-Quintiles, which has now been renamed  
25 MTC, and a lot of the analysis subsequent to the trial's

1 ending that is presented today has been performed by another  
2 company called Statistical Resources.

3 [Slide.]

4 We anticipated that this treatment would be  
5 designed for and targeted to patients with especially severe  
6 and long-standing disease, and therefore we designed  
7 criteria which would recruit such patients.

8 They had to meet ACR definition of rheumatoid  
9 arthritis functional class II or III. Patients, in order to  
10 get into the trial, had to have at least 20 tender joints  
11 and 10 swollen joints. Those levels, those thresholds are  
12 substantially higher than most other trials in rheumatoid  
13 arthritis.

14 They had to have failed either methotrexate, which  
15 is the standard DMARD, or at least two other DMARDS. They  
16 may be on a stable dose of low-dose corticosteroid about  
17 less or equal to 10 mg of prednisone equivalent, and they  
18 cannot use or could not have used concomitant DMARDS.

19 [Slide.]

20 The design of the trial is shown here. Patient on  
21 DMARDS were washed out for one to three months. The  
22 duration of the wash-out depended on what DMARD they were  
23 on, since it takes a little shorter time to wash out  
24 methotrexate, those were washed out for a month, and the  
25 DMARDS would take longer to wash out were washed out for

1 longer.

2           After the wash-out, patients were randomized to  
3           Prosorba column treatment or Sham apheresis, and treated  
4           weekly for 12 weeks. Then, they were followed to a primary  
5           endpoint at weeks 19 to 20 after randomization, which is  
6           week 7 to 8 after the treatments were ended. Now, those are  
7           an average of week 19 to 20 scores.

8           Then, subjects at that point were rolled into  
9           follow-up phases that will be described later.

10           [Slide.]

11           The primary endpoint for this trial, the measure  
12           of efficacy is the ACR definition of improvement, which on  
13           many of these slides is entitled the ACR Criteria. Those  
14           are synonymous.

15           For a patient to improve using the ACR definition  
16           of improvement, they have to have at least 20 percent  
17           improvement in their tender joint count, at least 20 percent  
18           improvement in their swollen joint count, and at least 20  
19           percent improvement in at least three of the following five:  
20           patient pain assessment, patient global assessment of  
21           disease activity, physician global assessment of disease  
22           activity, patient assessment of physical function, and in  
23           this trial, the Health Assessment Questionnaire, a widely  
24           used survey of physical function was used, and an acute  
25           phrase reactant, in this particular trial, C-reactive

1 protein.

2 This is currently the most widely used definition  
3 of improvement in response in rheumatoid arthritis trials.

4 [Slide.]

5 As Dr. Gendreau already mentioned, there was  
6 considerable attention to making sure the Sham treatment  
7 really worked as a Sham. There is a curtain here, behind  
8 which an unblinded operator would determine whether the  
9 patient received the Sham treatment or the ProSORBA column  
10 treatment.

11 This whole method was developed and tested prior  
12 to the trial in volunteer subjects and monitored during the  
13 trial, and it required additional staff, so there was an  
14 unblinded operator and then there were blinded nurses and  
15 physicians.

16 [Slide.]

17 If you look more closely inside the curtain, what  
18 you see is stopcocks below and above the ProSORBA column.  
19 In a patient who would receive ProSORBA, the plasma would be  
20 routed right through the ProSORBA column up and out.

21 In a patient randomized to Sham, the stopcocks  
22 would be turned, and the plasma would be routed around the  
23 ProSORBA column up and out. The extracorporeal volume and  
24 transit times for the ProSORBA and Sham treatments were  
25 matched.

1 [Slide.]

2 We projected a 35 percent response rate in  
3 Prosorba, and a 15 percent Sham response rate, and using 90  
4 percent power estimates, suggested that the maximal sample  
5 size needed would be 268, but that based on simulations of  
6 different groups of patients with these response rates, that  
7 the likely mean sample size would be roughly 120 using  
8 interim analysis.

9 We planned interim analysis at every 50 patient  
10 completions using the triangular test of Whitehead, which I  
11 will describe now.

12 [Slide.]

13 Now, this is the DSMB's test of whether to stop  
14 the trial or not. On the vertical axis is a test statistic,  
15 and in this binomial, yes/no trial for individual patients,  
16 this would be a chi-square number. The horizontal axis is  
17 the amount of information that the trial had produced at  
18 that point, and that corresponds closely to the number of  
19 patients who have completed.

20 There are three areas on this curve. One is a  
21 success result above this triangle or Christmas tree, at  
22 which time the trial would be recommended to be stopped  
23 because the treatment worked.

24 The bottom is failure when the treatment is not  
25 sufficiently better than the placebo, so that the trial

1 would be characterized as a failure, and it would also be  
2 recommended to be stopped for failure.

3 In the middle of this Christmas tree -- and I will  
4 characterize it as a Christmas tree and tell you why in a  
5 minute -- is the situation in which the trial results are  
6 indeterminate, and the DSMB is urged to continue the trial.

7 What is shown here is three different potential  
8 illustrative interim analyses. Let me just comment on the  
9 difference here between tri-1 and Christmas tree. The test  
10 is called the triangle test, but, in fact, it only works as  
11 a triangle when there is statistical analysis after every  
12 single patient, which is not the case here. We are doing  
13 looks only after every 50 patients.

14 In that case, it really boils down to a Christmas  
15 tree, and, in fact, it should really be called the Christmas  
16 tree test. So, what you look for is the borders of the  
17 Christmas tree, and the first interim analysis, the result  
18 falls right in the middle of the Christmas tree, and the  
19 DSMB would be urged to continue the trial.

20 The second X here is one in which the X falls on  
21 the Christmas tree at the border, and the DSMB would be  
22 urged to stop the trial for failure. The third X is here,  
23 and the DSMB would be urged in this case to stop the trial  
24 for success.

25 [Slide.]

1           There were 91 patients randomized in the trial, 48  
2 to the Prosorba arm, and 43 to the Sham arm. The number is  
3 slightly different because at two sites, the randomization  
4 ratio was not 1 to 1, it was a little bit higher than that.

5           In many ways, the patients in this trial were  
6 typical of patients with rheumatoid arthritis and in  
7 rheumatoid arthritis trials. They were mostly women, and  
8 the mean age was in the 50s. A very high percent had  
9 positive rheumatoid factor.

10           What is unique about the patients in this trial is  
11 how very long they had disease before entering this trial,  
12 and how many treatments they had failed prior to getting  
13 into it.

14           The mean disease duration in this trial was 15.5  
15 years before entry. Having done meta-analyses in RA trials,  
16 I can tell you that the mean duration of disease in RA  
17 trials which don't restrict entry to early disease is about  
18 10 years. This is longer than any trial I have ever seen.

19           The mean number of DMARD regimens failed here is  
20 5.46, which is higher than any I have ever seen. This is a  
21 unique group of patients which has had very long-standing  
22 disease, which has been refractory to many treatments. A  
23 large percent are also in functional class III, which  
24 suggests they are more functionally impaired.

25           [Slide.]

1 Another characterization of these patients that  
2 would be accurate is they have active and severe disease.  
3 The mean tender joint counts at baseline were 36.6, and the  
4 mean swollen joint count is 24.1, and those tend to be  
5 higher numbers than we see in almost all other rheumatoid  
6 arthritis trials.

7 Patients had active disease as characterized by  
8 patient and physician assessments of disease, pain, and  
9 their health assessment questionnaires were uniformly higher  
10 than is seen in RA cohorts. Generally speaking, the number  
11 is about 1 to 1.5, higher scores denote more physical  
12 disability. These were a very disabled group.

13 [Slide.]

14 This is what happened to those 91 patients who  
15 were randomized to either ProSORBA or Sham; 34 of them  
16 completed through week 19-20. Among the 48 randomized to  
17 ProSORBA, 34 completed through week 19-20, 14 withdrew. Of  
18 those 14, 4 withdrew due to adverse events, 2 due to lack of  
19 blood access, and 8 due to lack of efficacy or lost to  
20 follow-up.

21 Of the 43 who were randomized to Sham, 30  
22 completed, 13 withdrew, 5 due to adverse events, 2 due to  
23 lack of blood access, and 6 to lack of efficacy or lost to  
24 follow-up.

25 [Slide.]

1           These are the data that DSMB saw during their two  
2 meetings. The first one, at the first meeting, the results  
3 had actually already reached the border of the Christmas  
4 tree, and suggested stopping the trial. Because of the  
5 small amount of data that was presented at that time, and  
6 the limited number of patients who had been accrued and  
7 finished, the DSMB at that recommended continuing the trial,  
8 and not stopping it.

9           These are the data presented to the DSMB at the  
10 second interim analysis, and at that time the DSMB stopped  
11 the trial for efficacy.

12           DR. KALLOO: The second point, is it within the  
13 triangle?

14           DR. FELSON: It is at the border of the triangle.  
15 The triangle is not really the issue here, it's the  
16 Christmas tree that is the issue. It really should be  
17 called the Christmas tree test. The triangle is the test  
18 for an evaluation of analysis after every single patient,  
19 but, yes, the answer is that it went at the border of the  
20 Christmas tree or slightly beyond it.

21           [Slide.]

22           These are the data that were presented to the DSMB  
23 using an intent-to-treat approach. The response rate among  
24 those randomized to Prosorba, of the 48, were 16 responders,  
25 a rate of 33.3 percent. The response rate in the Sham group

1 was 4 out of 43, or 9.3 percent.

2 Adjusting for the interim analyses, that yields a  
3 p value of 0.006.

4 [Slide.]

5 Now, the company, in doing quality control work at  
6 a later point, realized that one of the patients who was  
7 randomized for ProSORBA actually was treated with Sham, and  
8 that that patient was a responder, and they reported this to  
9 the FDA.

10 The analysis on the left is the intent-to-treat  
11 analysis I just showed you, with the p value I just showed  
12 you. After that patient was discovered, it was agreed that  
13 the analysis had changed to as-treated analysis, in which  
14 that particular patient was switched to the Sham arm, and  
15 continued to be characterized as a responder. That analysis  
16 is shown here, an as-treated analysis, in which the rate in  
17 ProSORBA drops to 32 percent, and the rate in Sham increased  
18 to 11.4 percent, a result adjusted with interim analyses is  
19 still significant.

20 In addition, there is a likely protocol violator  
21 in the ProSORBA group that is being now treated in this  
22 modified as treated analysis as a non-responder because of  
23 likely protocol violations. That drops the response rate to  
24 29.8 percent, the p value remains significant between the  
25 ProSORBA and the Sham treated groups.

1 [Slide.]

2 This is the time frame of ACR response in the  
3 ProSORBA treated group and the Sham treated group, and you  
4 will notice the rates that were presented, about 30 percent  
5 in the ACR and about 11 percent in the Sham group. By the  
6 way, all of the analyses of efficacy that will be presented  
7 from hereon in are the righthand -- go back a slide for a  
8 minute. Thanks.

9 So what is going to happen from hereon in is that  
10 we will focus on the analysis depicted on the right, the  
11 modified as treated analysis for all presentations from this  
12 point.

13 [Slide.]

14 These are the modified as treated analyses, and  
15 you can see the time frame of response.

16 [Slide.]

17 Important individual outcome measures in the ACR  
18 definition of improvement are tender and swollen joint  
19 count, and what is shown here is the response rates in  
20 swollen and tender joint counts.

21 This is the mean Sham baseline tender joint count.  
22 It falls modestly during Sham treatment. The ProSORBA  
23 treatment group falls substantially more, and the difference  
24 between these two is significant.

25 Swollen joint count starts off high in both

1 groups, falls very mildly in the Sham group to 20 to 22, and  
2 falls a bit more in the Prosorba group, to 18 roughly, and  
3 that difference is also significant.

4 [Slide.]

5 We also performed analyses looking at those  
6 subjects who had completed through week 19 to 20 of the  
7 trial, and 14 of 34 Prosorba treated patients who completed  
8 were responders, a rate of 41.2 percent; 16 percent of the  
9 Sham treated completers responded, and that difference is  
10 also significant.

11 [Slide.]

12 Now, this is a unique situation because the DSMB  
13 stopped the trial in the middle, leaving a bunch of patients  
14 in the middle of the trial, and therefore we are left with a  
15 bunch of additional patients, and I want to tell you how  
16 those were dealt with.

17 What I have been talking about up until now has  
18 been the core data set of those patients who were presented  
19 to the DSMB and who had completed the trial at the time of  
20 the second interim analysis.

21 There is also 8 additional patients who actually  
22 completed treatment, had completed treatment at the time the  
23 DSMB met, and they remained blinded and were followed to the  
24 efficacy endpoint.

25 Then, there is an additional 10 patients who were

1 in the midst of treatment at the time the DSMB stopped the  
2 trial. The DSMB said, look, this stuff work, it is  
3 unethical to continue to treatment patients with Sham, you  
4 have to unblind them, and they are included in the total  
5 data set and characterized as "rollover" patients, who will  
6 be described.

7           Then, there is a continuation data set which  
8 discusses and focuses on retreatment, which will be  
9 described by Dr. Gendreau.

10           [Slide.]

11           The extended data set, which includes those  
12 patients who had already been treated, in addition to the  
13 core data set, shows responses of 28.9 percent in the  
14 Prosorba treated patient, and about 11 percent or 10.6  
15 percent in the Sham treated patients, a difference that is  
16 significant, and a completer analysis focusing on the  
17 extended data set shows roughly similar numbers to the  
18 completer analysis in the core data set.

19           [Slide.]

20           So, just to summarize, the efficacy analyses that  
21 we have presented to you relating to the pivotal trial, they  
22 show statistical significance on primary endpoints in all  
23 analyses, and with all of these overlapping data sets and  
24 various data sets. I know you will remember now that we  
25 have intent-to-treat and modified as treated. We have core

1 data sets and extended data sets, and I realize that is a  
2 bit confusing, but suffice as to say that it frankly doesn't  
3 matter how you define these data sets, the results seem to  
4 be significant irrespectively.

5           Prosorba response rates range from 29.8 percent to  
6 45.9 percent, and Sham response rates, from 9.3 to 16.1  
7 percent.

8           [Slide.]

9           I am going to turn the microphone now back over to  
10 Mike Gendreau, who is going to discuss retreatment and  
11 continuation.

12           DR. KALLOO: We have questions.

13           DR. AGODOA: Is your stopping group based solely  
14 on intent-to-treat or as treated, in other words, had you  
15 presented the data to the DSMB as treated, where would that  
16 fall?

17           DR. FELSON: It would still be beyond the boundary  
18 of the Christmas tree.

19           DR. LIANG: You showed us that slide of the  
20 stopcocks, and having screwed up many stopcocks, is there  
21 another way to know whether, in fact, the fluid went to the  
22 Prosorba column independent of what the unblinded technician  
23 was doing?

24           DR. FELSON: Let me defer that question to Dr.  
25 Gendreau.

1 DR. LIANG: You get the gist of my question.

2 DR. GENDREAU: There is a real easy answer to  
3 that. When the unblinded operator is setting up the  
4 stopcock, there is a transfer bag that matches the external  
5 volume that the column would otherwise take, so they can see  
6 plasma flowing either through to the column or to the  
7 transfer bag, so it is readily apparent to the operator  
8 whether or not they have got the stopcock set.

9 DR. LIANG: Going the right way.

10 DR. GENDREAU: Yes.

11 DR. LIANG: But there was that one patient -- I  
12 forgot which way it went -- that was randomized to Sham and  
13 got the ProSORBA.

14 DR. GENDREAU: That was because every week when  
15 they set the stopcock, they have an envelope they open which  
16 tells them which way to set it, and they used the wrong set  
17 of envelopes. So, they thought they did the right thing,  
18 but they were doing it wrong every week.

19 DR. LIANG: Could I have another question?

20 DR. KALLOO: Yes.

21 DR. LIANG: I think this is really an exciting  
22 design, and I guess maybe the second time it has been used  
23 in RA. The first time, as I remember, it was used for  
24 evaluation of wrist splints, but as I get it, David, that  
25 this was a stop rule based on the Christmas tree, so what

1 was the DSMB's function? I think this an a priori  
2 definition of stopping.

3 DR. FELSON: DSMB is an advisory committee just  
4 like this one, Matt. I mean the DSMB initially was  
5 presented in their first meeting with data that, frankly,  
6 suggested they ought to stop the trial, because it had  
7 already reached that level at the first meeting, but they  
8 decided, with us, we were the unblinded group, that there  
9 wasn't enough data yet, that the numbers of patients were  
10 still small.

11 DR. LIANG: So, it was sort of an a priori stop  
12 role with a little judgment.

13 DR. FELSON: Right.

14 DR. LIANG: Can I just ask you just in terms of  
15 structure, were the members of the DSMB paid?

16 DR. FELSON: Yes, they were paid.

17 DR. LIANG: So, there was an incentive in the  
18 opposite way to really continue the DSMB.

19 [Laughter.]

20 DR. LIANG: I was just checking.

21 DR. GENDREAU: I should ask Dr. Paulus to address  
22 that since he was the Chair.

23 DR. LIANG: No, no, I am not accusing any of those  
24 people. I was just interested in how you set that up.

25 AUDIENCE: We weren't paid enough. Matt, the

1 answer was we weren't paid enough.

2 DR. GENDREAU: Very small company. We don't pay  
3 that much.

4 One other thing, can we tell if the stopcocks are  
5 set wrong. There was also a secondary quality assurance  
6 that the columns were ultimately packaged up and all  
7 returned to Cypress after the fact, and we have all those  
8 columns in storage, and anytime a question arose, we can  
9 take the column out and we can tell if plasma has been  
10 through the column or not. So, there is a secondary check  
11 in place, as well.

12 DR. HORTIN: Was there any measure of patients  
13 whose disease process became worse with the treatment?  
14 Basically, you only show benefits of treatment. Was there  
15 any measure to see whether the disease process was worsened  
16 by treatment in a subset of patients that you might actually  
17 cause harm rather than benefit in some? For example, your  
18 criteria of whether they had a 20 percent improvement, was  
19 there any measure of whether some people got 20 percent  
20 worse?

21 DR. FELSON: I am not exactly sure how to answer  
22 that. Let me answer it in two ways. One is that we, I  
23 think, need in rheumatoid arthritis to develop ways of  
24 measuring and defining worsening. We don't usually follow  
25 it or think about it in any trials. It is an excellent sort

1 of question to be asked. So, I am not sure I know how to  
2 answer it in this particular trial.

3           There is a particular issue in this trial that Dr.  
4 Gendreau will discuss, which is a post-arthritic flare  
5 issue, a posttreatment flare of mild joint pain that  
6 occurred in some subjects that I think Dr. Gendreau will  
7 comment on that relates a little bit to your question.

8           I can't tell you that we looked specifically for,  
9 you know, number of patients who worsened dramatically or  
10 worsened really substantially, and I am not sure exactly how  
11 we would define that entity.

12           DR. JANOSKY: Can I follow up that question? You  
13 presented a slide -- it looks like No. 28, I don't know if  
14 that would be important to get back up there -- it addresses  
15 that question, and it also raises another issue. I wanted  
16 to touch on it before we move off this point.

17           I think that was at 28. Yes. The last column  
18 here, can you please tell me what those subjects are again?  
19 These are subjects that are being dropped out due to lack of  
20 efficacy?

21           DR. GENDREAU: These are patients who voluntarily  
22 decided to stop their continuation in the protocol. The  
23 patient always has a right to, for whatever reason, decide  
24 they don't want to come back. Some of these decided early  
25 on, there were a few cases I am aware of where after two or

1 three treatments, they didn't feel better, and they said I  
2 don't want to do this anymore. There are a few patients in  
3 this category who moved away. We are treating them over a  
4 three-month period, and if they couldn't come back to that  
5 same location every week for three months, they couldn't  
6 participate in the trial. So, we had a few move, and all  
7 those would be in that category of lost to follow-up.

8 DR. JANOSKY: Right. That is why I am somewhat  
9 confused because those are two different reasons for not  
10 continuing the trial. One is I don't feel like I am getting  
11 better, and the other is I moved away, so I can't attend the  
12 treatment.

13 DR. GENDREAU: It is sometimes hard to separate  
14 those, because, in fairness, maybe they decided to move away  
15 or they decided not to come back because they weren't  
16 feeling better. We didn't really try and sort out why they  
17 left, we just said, okay, they left, it wasn't due to an  
18 adverse event. That is about the extent of it.

19 DR. JANOSKY: But your analyses is not counting  
20 those as non-completers in terms of non-responders. A fair  
21 number of those are non-responders.

22 DR. GENDREAU: They are all treated as non-  
23 responders.

24 DR. JANOSKY: I don't want to spend too much time  
25 with this point, but your numbers do not take these into

1 account from the continuing --

2 DR. GENDREAU: The intent-to-treat analysis, the  
3 patient had to be in the study at weeks 19 and 20 to be  
4 considered a responder, so if they withdrew and left before  
5 week 19, they are considered a non-responder.

6 DR. JANOSKY: Right, that's my point, yes, that's  
7 my point.

8 DR. GENDREAU: And that is the analysis.

9 DR. JANOSKY: Maybe you will present it a little  
10 later, do you do an analysis where you actually consider  
11 these worst-case scenarios, these last two, which you are  
12 saying they didn't complete, and they weren't responders?

13 DR. GENDREAU: That is exactly how they are  
14 treated in our intent-to-treat analysis.

15 DR. JANOSKY: Not in the presentation that you  
16 went through.

17 DR. FELSON: Let me be clear about how the  
18 protocol was designed, because there are certain things you  
19 have to streamline to get this down to 20 minutes, and the  
20 protocol is pretty complicated. It actually isn't that  
21 complicated. In order to be defined as a responder, you had  
22 to not only meet efficacy criteria at week 19-20, but make  
23 it to week 19-20. If you dropped out doing great, moving  
24 away before week 19-20, you were characterized as a failure.

25 DR. JANOSKY: And that is not the issue I am

1 concerned with. The issue is I don't feel that I am getting  
2 the changes that I hope to get, so I am dropping out, and  
3 you are lumping those with your I moved away, and those are  
4 actually due to efficacy, so that are actually your non-  
5 responders.

6 DR. GENDREAU: We consider all of those non-  
7 responders. If they move away with a great response, they  
8 are still a non-responder.

9 DR. JANOSKY: Right. I will pick up on that a  
10 little later.

11 **Efficacy Results of Continuation Phase**

12 **Safety Results**

13 [Slide.]

14 DR. GENDREAU: My task at the moment is to discuss  
15 the continuation phase. You will remember this morning from  
16 this chart, patients went through an initial follow-up  
17 period to week 24, so 12 weeks after the treatments, at the  
18 end of their reaching week 24, they either moved into a  
19 long-term follow-up group if they had an ACR response, and  
20 we continued to follow them for up to another year to look  
21 at how they did, if they were non-responders, they had the  
22 option of voluntary enrollment in the continuation phase  
23 where they were given the opportunity to be re-treated  
24 again, 12 more times, on an open label basis.

25 [Slide.]

1           So, the continuation phase then was designed  
2 partly as an incentive for patients to be able to complete  
3 24 weeks of follow-up, so we could get as much information  
4 as we could. Patients and physicians remained blinded to  
5 what they received in the double-blind phase, so they had to  
6 make the decision to re-enroll and go through this again  
7 without knowing whether they received the column the first  
8 time. They were not provided that information.

9           The patient had to be a non-responder by ACR  
10 criteria at the time they entered the continuation phase,  
11 and from a safety perspective, they had to meet the original  
12 enrollment criteria in the double-blind trial.

13           [Slide.]

14           We were very encouraged by the rate of re-  
15 enrollment in the trial. As shown in this slide, among  
16 patients who were responders in the double-blind phase of  
17 the trial, who were eligible for treatment, there were 17 of  
18 those at the time this analysis was done, and 16 of those 17  
19 patients elected to be re-treated again. The only patient  
20 who declined retreatment had already entered another  
21 experimental protocol which precluded his participation in  
22 this study.

23           Among patients who did not receive benefit or did  
24 not meet ACR response criteria in the initial round of  
25 treatments, two-thirds of those also elected to go through

1 this all again and be re-treated 12 more times. We think  
2 that is a comment on the tolerability of the treatment.

3 I would like to now, in the next slide, show the  
4 results of those treatments.

5 [Slide.]

6 This data shows fewer patients than the previous  
7 slide because many of these patients are still being  
8 followed and are getting out to their endpoints now, but at  
9 the time this data was put together there were 9 initial  
10 Prosorba responders who had responded to the column, been  
11 followed, and then had ultimately lost their response and  
12 became eligible to be treated again, and then re-enrolled.

13 Of the 9 who went through that cycle, 6 of 9 had  
14 another ACR response to the second run of treatments for a  
15 two-thirds response rate among retreatments.

16 Among 6 patients who turned out to have been  
17 treated with Prosorba initially, who opted to be re-treated,  
18 zero out of 6 of those patients responded with a second run  
19 of treatments.

20 We had 1 patient who was in the Sham arm, who was  
21 a responder, who lost that response, was re-treated again,  
22 responded a second time, so she was very consistent.

23 Among 14 Sham non-responder patients, of patients  
24 who had not previously been exposed the Prosorba column,  
25 when they were treated for their actually first time now, 6

1 out of 14 achieved a response, and you can see this 42  
2 percent response rate is very familiar from the double-blind  
3 phase where we keep seeing a response rate in this 40  
4 percent range when a patient is first treated with the  
5 Prosorba column.

6 [Slide.]

7 So, in summary, then, to just emphasize what I  
8 have just said, the patients who had treated with the  
9 Prosorba column in continuation, who had been Sham, so this  
10 is their first exposure, responded with a frequency similar  
11 to what we expected from the double-blind phase of the  
12 trial.

13 Patients who responded to the column the first  
14 time, seemed likely to respond the second time, and patients  
15 who do not respond the first time, seemed likely to not  
16 respond the second time, so suggesting a mechanistic basis  
17 for that response that Dr. Nepom will be discussing a bit  
18 later when we talk about some of the mechanism of action  
19 studies.

20 [Slide.]

21 With that, that is what we have for this morning's  
22 presentation on efficacy, and I will turn to safety in a  
23 minute.

24 DR. WHITE: Could you tell me something about the  
25 duration between the first and second sets of treatments?

1 DR. GENDREAU: The requirement was the patients,  
2 if they had been ACR responders, have now lost their  
3 response. As we have some data we can show later, the  
4 average duration of response for patients who responded from  
5 the first round of treatments, was out to about study week  
6 40, so on average, a patient would become eligible to be re-  
7 treated after about study week 40.

8 If a patient was a non-responder, they were  
9 eligible immediately after week 24, if they met the safety  
10 criteria for entry and if they met all the other entry  
11 criteria, so it was very variable depending on the patient.

12 DR. WHITE: But, in general, non-responders would  
13 have had a shorter duration, responders would have had a  
14 longer duration.

15 DR. GENDREAU: That is correct.

16 DR. WHITE: How did you define, just if you would  
17 tell me, loss of response? Did they have to go back to  
18 their baseline or did they just have to dip below the ACR20?

19 DR. GENDREAU: They had to dip below ACR20  
20 criteria relative to baseline.

21 [Slide.]

22 I would like to provide a little bit of  
23 perspective on safety. As this is a product that has been  
24 marketed for over 10 years, we have quite a big of  
25 experience with the safety profile of the column. We really

1 in some ways know quite what to expect. The difference here  
2 is we are now dealing with a different population.

3 Historically, the column has been used in ITP,  
4 which in general is a more severe group of patients. It has  
5 been used as an acute intervention in patients who are very  
6 sick and usually bleeding.

7 We have collected 10 years of data on that, and I  
8 would like to put that in perspective. First, the column  
9 itself and the apheresis procedure that you need to perform  
10 to use the column, both have a very good safety record over  
11 the last 10 years, and we will present a little bit of data  
12 on that

13 The pivotal trial differed a little bit in  
14 methodology about how we collected safety information. We  
15 collected a lot of safety information, so the absolute  
16 numbers of adverse events look a little bit different  
17 perhaps than the historical numbers I will show you, and we  
18 will do that comparison, but we think the profile is very  
19 similar to what we are used to seeing.

20 Finally, there were a few adverse events that were  
21 of concern in the trial that we will present and discuss  
22 some of the steps we think should be taken to prevent those  
23 from being major issues.

24 [Slide.]

25 First, to talk a little bit about the apheresis

1 procedure itself, the ProSORBA column is a very tiny part of  
2 the universe with respect to apheresis. The most common use  
3 for apheresis is plasma collection, blood component  
4 collection from normal volunteers. The estimate is there  
5 were approximately 8 million of those collections done last  
6 year.

7           A therapeutic apheresis where the device is being  
8 used to treat a disease as opposed to collect blood  
9 components is a much smaller part of the total. It is about  
10 90,000 procedures a year, and last year there were 3,000  
11 ProSORBA column treatments done out of that 90,000. So, you  
12 can see we are a very small fraction of a small fraction of  
13 the usage, but this tells you there is a tremendous amount  
14 of experience with apheresis in the community. There are  
15 many, many centers that have the equipment and the expertise  
16 and familiarity with performing it, and we are looking to  
17 fit into this small sliver right here.

18           [Slide.]

19           Now, on exposure history, on this slide, the  
20 ProSORBA column over the last decade has been used in  
21 approximately 10,000 patients in commercial usage, and there  
22 has been another approximately 500 patients that have been  
23 studied in various prospective trials, pilot trials, in this  
24 pivotal trial, where considerably more safety data was  
25 collected than you get from an ad-hoc safety reporting

1 system from commercial sales, but there is a considerable  
2 exposure history that we do have experience with.

3 The next slide summarizes our complaint history  
4 from the last 10 years from the commercial sales of the  
5 product.

6 [Slide.]

7 There have been 215 complaints reported to the  
8 company in the last 10 years, which reported 649 side  
9 effects that were deemed worthy of reporting. 363 of those  
10 side effects, shown here, were deemed as serious, which  
11 represents a rate of about 8/10ths of 1 percent of  
12 treatments involved a serious adverse event in this very  
13 generally sick population I have described of ITP patients  
14 and autoimmune disease patients with serious disease, and  
15 there have been 3 related deaths reported to the company  
16 over the last 10 years in some way associated with this  
17 treatment or the underlying disease the patient had at the  
18 time they were undergoing therapy.

19 [Slide.]

20 This slide indicates the relative frequency of the  
21 adverse events that have been reported historically, and as  
22 we can see, the most common adverse event due to the product  
23 is hypotension. This is not unexpected as this is an  
24 extracorporeal device. The apheresis cell separator is also  
25 an extracorporeal device, so we have a significant volume of

1 blood and plasma that is outside the patient's body for a  
2 period of time, and that can lead to volume shifts in  
3 hypotensive events. It occurs slightly over 1 percent of  
4 the time in our historical experience. The other adverse  
5 events listed on this chart all occur in decreasing  
6 frequency in our experience.

7 [Slide.]

8 So, now I would like to transition to the pivotal  
9 trial and show how our safety results compare to our  
10 historical experience.

11 There is three general observations I would like  
12 to make at the start of this, and we will discuss in more  
13 detail. The first is that we used a very comprehensive  
14 recording methodology. This was the first time the ProSORBA  
15 column had been studied in a double-blind trial where we  
16 thought we could differentiate column effects from treatment  
17 effects, and so we were very interested in capturing as much  
18 information as we could to try and see what the column was  
19 doing versus what the procedure itself was doing.

20 The second is that, as I will show in a minute,  
21 there was no statistical difference seen in any adverse  
22 event category between Sham and ProSORBA treatments.

23 The third is that the great majority of adverse  
24 events were transient and manageable and not of major  
25 concern to patients, and I will describe why we think that

1 is the case in a minute.

2 [Slide.]

3 First, on the methodology used in the pivotal  
4 trial, it was a form that was three pages long, it was a  
5 check box based form. We developed this in the planning  
6 stages of the trial thinking this would give us  
7 comprehensive recording.

8 The patient had inputted every visit either for  
9 treatment or for follow-up to record as many check boxes as  
10 they thought was appropriate for the entire last week since  
11 they were seen list.

12 The coordinator also had the opportunity to enter  
13 data on this form if they saw anything in the lab results or  
14 the reports that were going on that they thought might be an  
15 adverse effect due to the treatments.

16 Finally, the apheresis staff who saw the patient  
17 when they went in for the procedure, also had an opportunity  
18 to input after every treatment on what they thought might be  
19 adverse effects, such as hypotension occurring with  
20 treatments.

21 As a result, there were a lot of effects recorded.  
22 The relatedness that we will discuss in the next chart was  
23 based on physician judgment, so the patient ranked mild,  
24 moderate, severe, and the physician judged whether they  
25 thought it was related or unrelated.

1           If there were a serious adverse event, which was  
2 deemed worse than a severe event, that required recording on  
3 a different form, so then the physician got involved in  
4 making a serious adverse event report on a separate form  
5 from the general, three-page form.

6           [Slide.]

7           This shows the overview of the total number of  
8 adverse events reported in the trial. There were 2,920  
9 reports, which came from 109 patients in 1,961 visits.  
10 Slightly over half of them were felt to be unrelated, 54  
11 percent were unrelated to the procedure or the column, 5  
12 percent were classed as severe, and 1.4 percent were classed  
13 as serious, and that is where they were reported on a  
14 separate form.

15           I should say the most commonly reported serious  
16 event was fatigue. So, patients were reporting if they felt  
17 tired, so there was some interpretation needed to interpret  
18 a lot of these adverse events.

19           Now, I would like to show the distribution between  
20 the Sham and Prosorba arms.

21           [Slide.]

22           This chart on the y axis is the percent of  
23 patients reporting at least once during the trial that  
24 particular adverse event. It is sorted by decreasing order  
25 of prevalence. The Prosorba arm is shown in blue, and the

1 Sham arm is shown in orange.

2 As you see, almost 90 percent of the ProSORBA  
3 patients reported joint pain at least once during the trial.  
4 When I first looked at this, I thought, gee, this is high,  
5 and then I thought about it more, and you take these very  
6 severe RA patients, take them off their medications, at some  
7 point in time they are going to complain about their joints,  
8 so it is probably surprising this isn't 100 percent  
9 actually.

10 Then, as we follow over time, we can see fatigue  
11 and joint swelling are very common. Hypotension was common,  
12 and that really is no surprise. When we look at our  
13 historical database, that is the most common adverse event  
14 expected with the use of this treatment. Followed by  
15 nausea, which was common, and then we go down the list, and  
16 these are decreasing frequency of adverse events reported.

17 The take-home message here was that there was no  
18 difference in any category, so we didn't view this as having  
19 a column bias, that this was an underlying function of the  
20 procedure and the reporting methodology.

21 [Slide.]

22 I would like to talk about the fact that most of  
23 the adverse events were transient and manageable, and we  
24 have three reasons we believe that. Briefly, I will talk  
25 about the pivotal trial dropout rate, the continuation phase

1 participation, and the adverse event rate recorded in the  
2 continuation phase where some of these same patients had the  
3 opportunity to go through the procedure a second time.

4 [Slide.]

5 As you have already seen, the dropout rates due to  
6 adverse events were relatively low, 4 patients out of 48 in  
7 the ProSORBA arm withdrew due to an adverse event. That is  
8 less than 10 percent, and we are told that is well under the  
9 average experience with rheumatoid arthritis trials with  
10 other medications, so it doesn't look like patients are  
11 withdrawing from the trial due to adverse events serious  
12 enough to cause them to terminate participation at a high  
13 rate.

14 [Slide.]

15 This shows the discontinuations that are on the  
16 previous table. There were 4 ProSORBA patients and 5 Sham  
17 patients who did discontinue. We looked at this and the  
18 only pattern that emerges from this is that there were two  
19 withdrawals in the Sham arm that are due to central line  
20 complications. Some patients had a central line placed to  
21 get easier access for vascular access, and that did have a  
22 number of problems associated with it that I will describe  
23 in more detail in a minute, but other than the central line  
24 complications, there is really no pattern here, and it  
25 really reflects the severity of the underlying medical

1 condition of many of these patients.

2 [Slide.]

3 Remember that the participation in the  
4 continuation phase was very high, 16 out of 17 initial  
5 responders re-enrolled, and two-thirds of the non-responders  
6 re-enrolled, so although we are getting a lot of adverse  
7 event reports, this was voluntary. These patients said I am  
8 happy to do this again, I will go through it again, so while  
9 the adverse events may be a nuisance, from the patient's  
10 risk-benefit standpoint, as I think we heard from some of  
11 the patients this morning, they considered this well worth  
12 the opportunity that it might provide them some clinical  
13 benefit.

14 [Slide.]

15 Finally, the adverse event rate in the  
16 continuation phase. Remember, this is really the same group  
17 of patients going through the treatment a second time, and  
18 we have compared the adverse event rate in just the ProSORBA  
19 treated patients in the core phase to ProSORBA treated  
20 patients in the continuation phase, and you can see in most  
21 cases the rates drop, so this suggests that as the patients  
22 get more comfortable with this treatment, and/or perhaps as  
23 their physicians get more comfortable with this treatment,  
24 the rate of reporting adverse events and the rate of real  
25 adverse events being experienced, such as hypotension, drops

1 quite dramatically, and we think this is typical of what has  
2 been seen with other new therapies over time as patients and  
3 physicians know more what to expect, get more comfortable  
4 with it, they tolerate it better, and they have fewer  
5 reporting and they generally have fewer adverse events.

6 [Slide.]

7 Now, I would like to turn and talk about some of  
8 the adverse events that I would like to talk about in a  
9 little more detail.

10 Hypotension, first. Hypotension from our  
11 historical database was the most common expected adverse  
12 event, so we certainly were prepared to see this. It  
13 occurred in about 6.6 percent of treatments provided, and 40  
14 percent of patients reported it at least once during their  
15 treatment period.

16 However, the hypotension we see with this is  
17 generally mild, interventions were uncommon. There was not  
18 a single case of a vasopressor being required for systolic  
19 pressure. Typically what apheresis units do when they see  
20 hypotension is they pause the treatment, they don't stop it,  
21 they pause it, so they stop the flow back to the patient  
22 temporarily. They give a bolus of normal saline to increase  
23 fluid volume of the patient. They might put them in  
24 trendelenburg, and then within a few minutes, the pressure  
25 usually rebounds, and they will continue the treatment.

1           So, that is typically what happens in 22 percent  
2 of these hypotensive episodes where they are gave them  
3 saline. That is usually the extent of the intervention  
4 required.

5           There were no discontinuations due to hypotension  
6 in the trial. There were no serious adverse event reports  
7 due to hypotension. There was one event reported as severe,  
8 which we have more data on.

9           [Slide.]

10           This shows the systolic pressure curve for all  
11 patients treated in the double-blind phase of the trial. It  
12 is hard to read the axes here. The bottom axis is time of  
13 treatment, so this is the pressure at baseline, 30 minutes,  
14 60 minutes, out to three hours, so during the entire  
15 treatment process.

16           In the y axis is systolic blood pressure. The  
17 solid line is the ProSORBA patients, the dotted line, the  
18 Sham patients. The boxes are the 25th to 75th percentile of  
19 pressure, and what look like error bars are actually the  
20 full range. This is the highest and lowest pressures ever  
21 recorded in any patient at that point in time.

22           So, as you can see, there is a slight decrease in  
23 pressure from zero to 15 minutes, and this is as we start  
24 building extracorporeal volume as the blood is being removed  
25 from the patient, hasn't begun to be returned yet.

1           It actually reaches a minimum at 60 minutes as the  
2 patient is now recumbent, they are relaxed, they are  
3 probably taking benadryl. They have got extracorporeal  
4 volume. And then it slowly drifts back up and by the end of  
5 the treatment, it is back to baseline, and the actual range  
6 of systolic pressure is noted, is smaller than the range at  
7 baseline, so the patients stabilize back out quite nicely.

8           [Slide.]

9           This is the diastolic pressure. It shows the same  
10 pattern. We see a slight drop at 15 minutes. The maximal  
11 drop is at 60 minutes, and it returns to baseline by the end  
12 of the treatments.

13          [Slide.]

14          We want to explore a little bit further the  
15 incidents of individual, clinically significant hypotensive  
16 episodes. As I mentioned, there was 1 severe adverse event  
17 reported for hypotension. When we really looked at the  
18 actual blood pressure recordings from the apheresis, we  
19 discovered there were 5 events that we thought would qualify  
20 as significant systolic decreases pressure decreases where  
21 the systolic pressure was below 80 millimeters of mercury at  
22 some point in time. That occurred in 5 different patients,  
23 4 were ProSORBA, 1 was Sham.

24          Sixty minutes into the treatment was the point at  
25 which the patient achieved minimum pressure on average, and

1 the average drop among patients at that point time is 25  
2 millimeters systolic, and 30 in the Sham. We did have 1  
3 patient who went down 60, and the biggest drop in the trial  
4 was a patient who dropped 93 points, which was going from a  
5 pressure of 164 to 70.

6 That patient, despite that large drop, was treated  
7 with IV fluids and completed the treatment, and was fine.  
8 Again, no patient withdrawal secondary to hypotension.

9 [Slide.]

10 The next adverse event we would like to describe  
11 is anemia. Anemia for purposes of definition is being  
12 described here as a hemoglobin less than 9 grams per  
13 deciliter. Rheumatoid arthritis patients have an anemia of  
14 chronic illness. Some rheumatologists have told me this is  
15 not a terribly low value, but this a threshold we set that  
16 if a patient had a value below this, we would not treat them  
17 and we would consider them having clinical anemia.

18 Thirteen patients met this definition at some  
19 point during the trial, which was 14 percent of treated  
20 patients. I turns out that 5 of these 13 came from  
21 scientific site 10, where we were drawing an additional 340  
22 milliliters of blood during the first 12 weeks for  
23 mechanistic work, so we understand part of the basis for  
24 that, so these 5 patients were scientific patients who were  
25 donating extra blood.

1           There were 8 cases at other sites of anemia, 4  
2 from ProSORBA, 4 from Sham. There is no difference in the  
3 rate or the amount of drop of hemoglobin between arms, so  
4 this seems to be a function again of the procedure.

5           Interventions for anemia were uncommon. Only 1  
6 patient in the trial received a transfusion for anemia.  
7 Erythropoietin was used electively in 5 patients during the  
8 double-blind trial, 4 of them were for these patients in the  
9 scientific arm, and there was 1 other site where a patient  
10 received a course of erythropoietin, and it was used  
11 electively in 2 patients during the continuation/re-  
12 treatment phase of the trial

13           During continuation, there was only 1 additional  
14 case of anemia where hemoglobin was below 9, and again there  
15 were no withdrawals in trial secondary to anemia. So,  
16 although there is a drop, it was manageable, and did not  
17 cause patients to exit the trial.

18           [Slide.]

19           This shows the change in hemoglobin over time.  
20 The solid curve is the ProSORBA treated group. The dotted  
21 line is the Sham treated group. You can see they start out  
22 at the baseline value, it drops with a minimum at treatment  
23 week 9, again the axis is hard to read, but the minimum  
24 point here is treatment week 9. Both arms begin to recover  
25 and rise through the end of treatments and through the end

1 of follow-up period as the patient compensates for the  
2 initial decrease in hemoglobin.

3           There is no statistical difference between these  
4 two curves.

5           [Slide.]

6           Now, in the continuation phase, the pattern was a  
7 big different. The patients started at slightly lower  
8 baseline levels of hemoglobin/hematocrit, but we did not see  
9 a significant change from baseline to the end to treatments  
10 at week 13 or to the end of follow-up at week 24, suggesting  
11 that these patients begin compensating earlier during the  
12 initial round of treatments, and also in the continuation we  
13 weren't drawing as much blood.

14           We only withdrew one-third as much blood for  
15 testing in continuation, so perhaps the combination of the  
16 patients not being drawn so much and having adapted some,  
17 the anemia did not seem to be a problem in continuation.

18           [Slide.]

19           I would like to turn to something that was of  
20 concern, and that was the placement of central lines in this  
21 population. Peripheral venous access was always the  
22 preferred requirement for patients to undergo ProSORBA  
23 treatments. Typically, the way this procedure is  
24 administered is an IV is placed in each arm, so one draws  
25 blood out, the other returns to the patients, so it requires

1 two needlesticks weekly.

2           There was a provision in the trial, it was  
3 originally written that if a patient did not have adequate  
4 peripheral venous access, and both the patient and physician  
5 wished, we would permit a central line to be placed for this  
6 treatment to be provided.

7           There were 4 patients in the trial who had to  
8 leave because of inadequate peripheral access, who did not  
9 have central lines, but in the pivotal trial, 9 central  
10 lines were ultimately placed, and among those 9 lines, we  
11 had unfortunately 5 serious adverse events recorded due to  
12 those central lines.

13           Once we saw that pattern, in July of 1997, we  
14 changed the protocol to require adequate peripheral venous  
15 access to enter the trial, no longer permitted a central  
16 line placement for this treatment, and we think we will  
17 continue to strongly recommend that central lines not be  
18 used in this population.

19           [Slide.]

20           This details the complications due to central  
21 lines. These are the 5 patients that did have  
22 complications. Three were Sham, 2 were Prosurba. It was a  
23 combination of central line thrombosis and infection at the  
24 site, probably due to inadequate home care during the  
25 ambulatory phase while the patients were in between

1 treatments.

2           The first patient on this list, 658, never even  
3 got a treatment, because his catheter was thrombosed by the  
4 time he came for his first treatment.

5           [Slide.]

6           The next subject is perhaps of slightly less  
7 medical importance, but it is an important patient  
8 management issue. We heard a comment this morning by both  
9 Dr. Felson and by one of the patients, that they did have  
10 flares with their treatments.

11           This is a syndrome that we have characterized as  
12 an acute worsening of their joint pain and swelling,  
13 occurring within a few hours of the treatment typically, and  
14 lasting for up to several days.

15           It had been noted in the pilot trial, it had been  
16 reported in the literature, so we think this is something  
17 characteristic of rheumatoid arthritis patients undergoing  
18 this treatment. It is common in both arms, which was a new  
19 observation from the double-blind trial, and it was managed  
20 in the pivotal trial successfully with pain medications  
21 including narcotics, and Dr. Furst, who is speaking later  
22 about some of his experience, will provide a little bit more  
23 insight on what he thinks about management of these flares.

24           I think it is important that we let patients know  
25 what to expect. They do generally decrease over time,

1 although different patients are quite variable.

2 [Slide.]

3 The final thing I would like to talk about is  
4 infections recorded in the trial. We had no reason going  
5 into the pivotal trial to think that the ProSORBA column was  
6 immunosuppressive in any way. We had no scientific data or  
7 no experience to suggest that, so we didn't really expect an  
8 increase in infections, but it is of great interest in this  
9 population who might be immunocompromised otherwise, so we  
10 did a careful study of infection rates, and this chart has  
11 categorized potential infectious causes. Some of these  
12 patients maybe allergic rhinitis, for example, but we have  
13 included everything for the sake of completeness.

14 The dark blue bar is the ProSORBA treated group,  
15 the orange bar again is the Sham treated group, and have an  
16 adjusted bar in here, the lighter blue, which is the  
17 ProSORBA patients adjusted for the fact that there are 20  
18 percent more ProSORBA observations than Sham arm. The  
19 patients stayed in the trial an average longer, so we had  
20 more observation time on those patients.

21 Actually, with or without the adjustment, there is  
22 no statistical difference in any of these categories, so  
23 there did not seem to be an increase in incidence of any  
24 infection category between the two arms, and when we looked  
25 at the upper respiratory tract, the group which is the most

1 frequent group with the highest number of events, when we  
2 consider the rate in the general population, over 50 patient  
3 years of observation, this rate of reported upper  
4 respiratory tract infection is within what you would expect  
5 for the normal population.

6 [Slide.]

7 We had 5 medically important or medically  
8 significant infections, which we have defined as requiring  
9 hospitalization and/or intravenous antibiotic usage. Two of  
10 them, both in the Sham arm, were directly related to central  
11 line complications or central line infections.

12 There was 1 case in the ProSORBA arm of a patient  
13 who had a septic arthritis of an artificial joint, and I  
14 will describe this in a moment. We had a case of cellulitis  
15 in the Sham arm, and a fever of unknown origin, urinary  
16 tract infection, in the ProSORBA arm. The next slide  
17 provides some detail on these.

18 [Slide.]

19 The first two patients on this chart are the two I  
20 previously alluded to, that had central line infections.  
21 They were both treated with IV antibiotics and recovered  
22 from that infection. This first patient went on to have  
23 another infection seven months later, but unrelated to the  
24 first infection.

25 This patient in the middle here went through all

1 her treatment successfully, and during follow-up was noted  
2 to have a skin ulcer. She was an amyloidosis patient with a  
3 very complex medical history. She was admitted for  
4 debridement of her ulcer, and in the hospital developed a  
5 series of infections including a gallbladder removal,  
6 ultimately went into total body failure eight months later.

7           There is a patient on the ProSORBA arm who went  
8 for elective joint replacement after all his treatments were  
9 over, he was feeling better from his therapy, decided to get  
10 one of the joints taken care of, and post-surgery from his  
11 joint replacement, the joint itself became infected, and  
12 that was a complication requiring IV antibiotics.

13           These four are all deemed as unrelated to their  
14 treatment course. There is one patient here that is  
15 potentially related to her ProSORBA experience. The patient  
16 presented at week 6 of treatment with a fever of unknown  
17 origin, potential urinary tract infection, was seen in the  
18 emergency room, given oral antibiotics, came back the next  
19 day intolerant of the oral antibiotics and with a rash,  
20 which was diagnosed as a herpetic rash.

21           She was then admitted for IV antibiotics, and was  
22 treated successfully in the hospital and discharged.

23           [Slide.]

24           The really serious things that can happen on a  
25 trial like this, we had no deaths on the ProSORBA arm, two

1 unrelated deaths occurred in the Sham arm generally about a  
2 year later due to complications of what looked like their  
3 underlying medical conditions. No malignancies were  
4 reported in either arm during the trial.

5 [Slide.]

6 Finally, our summary of what we think about the  
7 adverse events and some of our recommendations to make this  
8 product even safer in routine usage.

9 We think that anemia is manageable. It is routine  
10 practice when performing apheresis to check  
11 hemoglobin/hematocrit prior to performing the procedure to  
12 set up the processing variables properly on the machine.

13 We would recommend continuing that practice and  
14 withholding treatments if the hemoglobin is found to be  
15 below 9 grams per deciliter.

16 Hypotension is something the apheresis units are  
17 actually quite good at managing already. We think it is  
18 worth monitoring the patient for at least 30 minutes after  
19 the end of the procedure to make sure their pressures have  
20 stabilized.

21 Central lines. We have proposed a  
22 precaution/warning statement in our draft product labeling,  
23 warning against using central lines in this population due  
24 to the adverse event experience in this trial.

25 Finally, the patient flares, which is really more

1 of a patient management issue, we think can be managed with  
2 pain medications, in setting the patient expectations, that  
3 this is something that can happen with this treatment, and  
4 we think with the knowledge of its potential and proper  
5 management, it can be easily handled.

6 With that, I would like the podium over to Dr.  
7 Nepom. I will take some questions first.

8 DR. STEINBACH: I would like to ask a question.  
9 Cypress does not manufacture apheresis equipment?

10 DR. GENDREAU: That is correct.

11 DR. STEINBACH: Do you set specifications on that  
12 equipment?

13 DR. GENDREAU: We do not set specifications on  
14 that equipment. This trial was all conducted on Cospectra,  
15 which is the most common therapeutic apheresis equipment out  
16 there. We have designed procedures and instructions for use  
17 of the commercially available equipment that we consider  
18 appropriate, which is two manufacturers.

19 DR. LIANG: For your ITP indication, do you have  
20 any language about central lines?

21 DR. GENDREAU: We do not. This experience with  
22 central lines in rheumatoid arthritis patients was really  
23 unexpected. As we can talk perhaps more in the afternoon,  
24 in the surgical populations, in the hematology populations,  
25 they use central lines quite commonly for this sort of

1 treatment without problems, with very low incidence rates of  
2 infections.

3 DR. LIANG: On one of the vignettes, I can't find  
4 it now, but I read it at home, that one of the patients had  
5 anticardiolipin antibody or antiphospholipid antibody, and  
6 would you like to comment on that, where that may be a  
7 contraindication?

8 DR. GENDREAU: It is already a contraindication in  
9 the product labeling that if they coagulopathy, you know,  
10 anticardiolipins, that is a contraindication to the  
11 treatment. This patient did turn out to have a lupus  
12 anticoagulant, but it was unknown at the time she enrolled  
13 in the trial. It was an incidental discovery.

14 DR. LIANG: You don't recommend that people check  
15 that actively?

16 DR. GENDREAU: We have discussed that, and the  
17 advice from our advisers is they don't want us dictating how  
18 the physicians practice medicine, but it is a known  
19 contraindication.

20 DR. FOOTE: As a surgeon, I was also very much  
21 surprised about your high incidence of central line  
22 complications, and I was wondering what kind of protocol was  
23 used for the central lines, what type of central lines was  
24 used, was there anything that was standardized in regards to  
25 how these central lines were placed, the type of them, and

1 how they were maintained during the course of treatment.

2 DR. GENDREAU: I don't have anything specific on  
3 that. We had a home health care protocol that was developed  
4 that described flushing and use of heparin that was provided  
5 to sites who placed central lines.

6 They typically hired a home health care nurse to  
7 assist the patient with the management. I think in all nine  
8 cases that was the case. Dr. Frust, who just jumped up  
9 here, had a patient with a central line, as well, and I  
10 think he wants to say what his experience was.

11 DR. FURST: Dan Furst. I was one of the  
12 investigators. I think one of the problems is that these  
13 folks have difficulty with their hands, and if they don't  
14 have a spouse who is pretty good at the home care, they may  
15 run into trouble. That certainly seemed to be the problem  
16 with the patients that I was aware of with the central line.

17 DR. FOOTE: So, you know, again when I look at  
18 these incidents of central line complications, I am  
19 wondering if maybe the problem was not with the use of  
20 central lines in these patients per se as the problem in  
21 regards to care, and that perhaps, you know, if this could  
22 be looked at in patients in whom adequate care was given,  
23 then, perhaps central lines may not necessarily be  
24 contraindicated.

25 DR. BLANK: I would just like to make one comment,

1 and any rheumatologist is welcome to augment what I am about  
2 to say. I have done a lot of reading about the  
3 complications of rheumatoid arthritis, and infection seems  
4 to be one of the clear epidemiological sequelae of having  
5 the disease, so I have thought that it is possible that the  
6 central line placement in such patients has particular  
7 risks, and in addition, we spoke to some of the physicians  
8 involved versus hematology/oncology people and surgeons who  
9 are very used to managing central lines. These physicians  
10 aren't as used to the management of central lines, so I  
11 think there were both issues involved, multifactorial, could  
12 be underlying disease, as well as a new group of patients  
13 not normally receiving central lines.

14 DR. LIANG: A number of these patients have  
15 arthroplasties and hardware. Can you tell us anything about  
16 that patients that were enrolled in the study in terms of  
17 whether they had those and whether you used prophylactic  
18 antibiotic before you do this?

19 DR. GENDREAU: Among the central line patients?

20 DR. LIANG: Or any actually.

21 DR. GENDREAU: I don't think we have that easily  
22 available. Perhaps we can get you an answer this afternoon.

23 DR. WHITE: Could you give clarification on the  
24 medically significant infections your slide 72, the first  
25 two patients. It said that they had central line

1 infections, and these were judged to be not related to the  
2 procedure.

3 DR. GENDREAU: Correct.

4 DR. WHITE: It would be my impression that if a  
5 patient had a central line placed to enter this protocol,  
6 and they had a central infection, that that medically  
7 significant infection would be related, not unrelated.

8 DR. GENDREAU: I agree. The relatedness here is  
9 as the physician scored it. We have made no attempt to  
10 change how it was recorded by the investigator. I think  
11 what they were saying here was not related to the  
12 therapeutic treatment. They were relating it to the central  
13 line placement, not to the Prosorba treatments.

14 DR. WHITE: But the point I would like to take is  
15 that, you know, I understand that you take what you are  
16 given by the investigators, but my judgment would be that if  
17 a line was placed for the protocol purposes, and they got an  
18 infection, it was related to the protocol.

19 DR. FURST: Let me try to clarify how the  
20 investigators were looking at it, as one of the  
21 investigators. It was fairly clear to us that the procedure  
22 itself was associated with the problems. The question that  
23 was asked was, was the problem related to the gidget, to the  
24 Prosorba column.

25 So, was it to the procedure apheresis or the

1 column, and I think the answer was in this case, that the  
2 thought might have been it was due to the procedure, not the  
3 column per se, and therefore not related. It has nothing to  
4 do with the question you are asking, which is if you have to  
5 set up them up to do it, is the problem sort of inherent.

6 DR. DONATUCCI: As a urologist, I am unfamiliar  
7 with the procedure of apheresis. Do patients require  
8 sedation for this? Did any of the patients get sedation?

9 DR. GENDREAU: The practice is usually routine  
10 premedication in most apheresis units of Tylenol and  
11 benadryl. It is not required, and usually the antihistamine  
12 is onboard just to deal with any of the mild side effects of  
13 complement activation that might occur with extracorporeal  
14 blood contact.

15 DR. DONATUCCI: My second question has to do with  
16 in one of the slides, I think it was slide 49 at least in  
17 our handout, you have historical data from your ITP patients  
18 who used the ProSORBA column, and I note that the fourth  
19 most common adverse effect was arthralgia occurring in 0.14  
20 percent of patients. Is that typical for the apheresis  
21 population in general also?

22 DR. GENDREAU: That is an excellent question. Dr.  
23 Hester, do you want to address that? Dr. Hester is one of  
24 our consultants who is a hematologist and apheresis  
25 provider. We did also note the frequency of arthralgia in

1 our database, and I will let her address that, the apheresis  
2 itself.

3 DR. HESTER: I am Dr. Jeane Hester. I am a  
4 Professor of Medicine and hematologist and oncologist at the  
5 University of Texas, MD Anderson Cancer Center, retired. I  
6 am now an independent consultant. I was not part of this  
7 trial, but I used in our apheresis unit the column for the  
8 treatment of ITP and the chemotherapy-induced mitomycin  
9 hemolytic uremic syndrome.

10 Arthralgias in normal donor procedures, which  
11 would be platelet collection, plasma collection, stem cell  
12 collection for transplant. are not associated with  
13 arthralgia, but all of the other symptoms listed on the  
14 slide would be complaints and complications that we see from  
15 a variety of the 15 to 20 different applications of  
16 apheresis.

17 DR. DONATUCCI: I guess as a follow-up question,  
18 then, the patient populations I don't again, as a urologist,  
19 deal much with ITP, but I assume that is also at least in  
20 part a rheumatologically mediated process.

21 So, is it apheresis in patients with rheumatologic  
22 disease that predisposes to arthralgia? Obviously, with RA,  
23 the disease is arthralgia, so they are obviously at much  
24 higher risk I would suppose, but I guess that is what I am  
25 trying to understand. Is it the process in these patients?

1 DR. HESTER: We have done therapeutic procedures  
2 for a variety of diseases, Goodpasture's syndrome, Guillain-  
3 Barre, hyperviscosity, the myeloma hyperproteinemias,  
4 disseminated intravascular coagulopathy, acute respiratory  
5 distress syndrome, lots of different pathologies with  
6 abnormal molecules, and arthralgia, to my recollection over  
7 several thousand therapeutic apheresis, is not a common or  
8 expected complication or complaint from the procedure  
9 itself, and normal donors, who are on the same machine, that  
10 are simply donating normal blood component products, do not  
11 have complaints of arthralgias.

12 As you saw, there was a million platelet donations  
13 last year in the field from normal donors, and that would  
14 not be a complaint I would expect from the normal donor.

15 DR. WHITE: I noted that our information packet  
16 said there were 17 adverse events leading to  
17 hospitalizations. I wondered if you could give a breakdown  
18 of these, some description of who got them, and some  
19 comparison to what might be expected.

20 I am particularly concerned because putting a sick  
21 rheumatoid in the hospital in general is not a good thing.

22 DR. GENDREAU: I agree. We have a slide on that.  
23 Let me see if we can find it.

24 [Slide.]

25 This is the adverse events that required

1 hospitalization. When we looked at this, you will see quite  
2 a few of these are elective joint replacements. There are a  
3 number of them related to the central line complications  
4 that were already discussed. These are the infections we  
5 have just discussed a minute ago, elective surgeries.

6           There were not a lot of pattern to it other than  
7 what I have already described in terms of the five cases of  
8 serious infections in the joint replacements. I think the  
9 overall conclusion we had looking at this is these were very  
10 medically ill patients in general, and among these 109  
11 patients, a variety of things happened to them over the six  
12 months that we saw them.

13           DR. KALLOO: Although I am tempted to take a  
14 break, I think we will await until the end of all the  
15 presentations by Cypress.

16           DR. GENDREAU: Dr. Nepom will now discuss our  
17 ongoing research program.

18                           **Mechanism of Action Studies**

19           DR. NEPOM: Thank you, Mike. I am Jerry Nepom. I  
20 am a Professor of Immunology at the University of Washington  
21 and Director of the Virginia Mason Research Center, which is  
22 a private, non-profit academic research institute in  
23 Seattle.

24           I have some financial interactions with Cypress.  
25 They sponsor a collaborative research agreement protocol in

1 my laboratory to support the studies that I am going to  
2 describe, and I think I am probably listed as principal  
3 investigator on that study. I am also paid a consulting fee  
4 by Cypress, and as a member of the founding external  
5 scientific advisory board for Cypress. I also hold some  
6 stock option.

7 [Slide.]

8 So, my presentation is going to be a discussion of  
9 some of our ideas about mechanism of action for the  
10 therapeutic efficacy that you have seen. I thought I would  
11 preface my remarks by just acknowledging that those of us  
12 that are interested in the immunology of arthritis, I have  
13 to be a little humble about understanding mechanism. Many  
14 of the most commonly used drugs, hydroxychloroquine and  
15 methotrexate, for instance, we still actively debate  
16 possible mechanisms of action.

17 [Slide.]

18 But at first glance, the ProSORBA column seemed a  
19 simpler case, because the ProSORBA column contains protein A  
20 as its active ingredient, as its known active ingredient,  
21 and protein A is known to bind immunoglobulin, so the  
22 starting point for our studies was to try and understand  
23 whether this antibody-binding activity of protein A had  
24 something to do with the therapeutic efficacy.

25 The ProSORBA column, of course, is constructed as

1 a blood filtering device, and so the column is often  
2 referred to as a filter for serum immunoglobulins, but we  
3 immediately recognized that this raised some important  
4 issues.

5 All of us think of rheumatoid arthritis as  
6 predominantly a cellular mediated autoimmune disease with T  
7 cells and monocytes and synoviocytes all interacting, and it  
8 is not a priori clear what immunoglobulin removal might do.

9 We also recognize that the column is small  
10 relative to the human body, and that the immunoglobulin and  
11 binding capacity of the protein A on the column rapidly  
12 saturates during the apheresis procedure.

13 So, our goal was to try and understand this and to  
14 systematically study the effect of the column and to try and  
15 identify immunologic effects correlating with clinical  
16 response.

17 [Slide.]

18 To do this, we designed a formal scientific  
19 subprotocol, which was run as a component of the pivotal  
20 trial that you have been hearing about. Trial patients  
21 enrolled at Virginia Mason Medical Center and at UCSD were  
22 enrolled in the scientific subprotocol, and samples from  
23 these patients were distributed to the four participating  
24 laboratories, and I am representing were done in all four  
25 labs today.

1           My laboratory concentrated on immunoregulation  
2 studies and the T cell biology. Dr. Eric Sasso at the  
3 University of Washington studied protein A itself and the  
4 immunochemistry of protein A.

5           Dr Silverman at UCSD studied B-cell biology and  
6 effects, and Specialty Laboratories in Santa Monica did our  
7 clinical laboratory studies.

8           [Slide.]

9           Our goal was to use this as a hypothesis-  
10 generating study, to try and understand something about  
11 plausible hypotheses to explain mechanism of action.

12           Now, because this was run as part of the pivotal  
13 trial, all investigators in the scientific component were  
14 also completely blinded throughout the study, both to the  
15 Sham versus ProSORBA column treatment and to the  
16 responder/non-responder status of the patients.

17           [Slide.]

18           Now, I will briefly just summarize a lot of  
19 negative data. We studied some of the general and gross  
20 immunologic parameters of cellular and humoral immune  
21 function, things like serum immunoglobulins, IgG, IgM,  
22 Rheumatoid Factor, Immune Complexes using four different  
23 assays, things like that. B-cell quantitation and B-cell  
24 activation with cell surface markers, gross measures of  
25 global T-cell function, such as MLC cultures, mixed

1 lymphocyte cultures, and mitogen responses, as well as  
2 markers such as CD3, CD4, CD8.

3           There was no evidence for immune perturbations at  
4 this kind of macro level.

5           [Slide.]

6           This is just one illustration of this kind of  
7 data. This shows you values for the 91 evaluated patients  
8 at week 1 and week 12 of a therapeutic program, showing some  
9 decrement in the IgM rheumatoid factors in the serum, very  
10 little change in the overall IgM or IgG, although the trends  
11 are down, but the main point of this slide is that the same  
12 thing happened in the Sham arm, and none of these mean  
13 values which are illustrated here are significantly  
14 different from any other because of the very wide range of  
15 variability seen in individual patients.

16           [Slide.]

17           That lack of overall effect on patients' serum  
18 immunoglobulin is probably explained by very simple  
19 observation. This is from in-vitro binding studies  
20 performed under idealized binding conditions to evaluate  
21 what the column capacity is.

22           These are the amount of immunoglobulin that can  
23 bind a gram of the ProSORBA, which is the protein A bound to  
24 a silicon matrix. Each column has 123 mg of ProSORBA. So,  
25 at most, there is about a gram of immunoglobulin removed,

1 which represents somewhere between 1 and 2 percent of the  
2 circulating immunoglobulin in an individual.

3 DR. KALLOO: Question. How much IgG would you  
4 lose by removing 500 ml of blood?

5 DR. NEPOM: Anybody faster than I am with math  
6 that want to come up with the number back there?

7 Okay. Ten percent is the number from our  
8 hematologist.

9 DR. KALLOO: Ten percent?

10 DR. NEPOM: Ten percent of circulating IgG.

11 DR. KALLOO: How many milligrams would that be?

12 DR. NEPOM: In milligrams?

13 DR. BOULWARE: If you assume 1.5 grams per  
14 deciliter, and you remove 5 deciliters, that is going to  
15 come out to about 9 grams.

16 DR. NEPOM: I knew there was somebody better with  
17 math. This is by any measure a relatively insignificant  
18 amount of immunoglobulin removed by the column. Thank you  
19 for the quick calculation.

20 [Slide.]

21 Now, since this issue of what is being removed  
22 from the patient plasma by the column did not seem to be  
23 giving us very attractive possibilities here, we also  
24 analyzed the issue of what is being returned from the column  
25 to the patient, what is present in the effluent flow-through

1 plasma that is being returned to the patient.

2 We considered this issue in terms of four  
3 possibilities, the possibility that the procedure or the  
4 column is activating complement and that the complement, the  
5 products are in this flow-through. We considered the  
6 possibility that since protein A is made from Staphylococcal  
7 aureus, that there might be contaminating enterotoxins or  
8 endotoxins on the column that could be eluted or leached  
9 into the patient.

10 We considered the possibility that protein A  
11 itself was being shed from the column, and we considered the  
12 possibility that the immune complexes present in outpatients  
13 were being remodeled on the complex being returned in a  
14 different form.

15 I will briefly walk you through some of the  
16 highlights of that.

17 [Slide.]

18 There was indeed complement activation occurring  
19 during the apheresis procedure. This occurred through the  
20 apheresis procedure itself in all patients undergoing both  
21 Sham and ProSORBA therapy, was detected as increased C3a and  
22 C5a levels. However, there was no complement consumption as  
23 C3 and C4 levels were unchanged.

24 [Slide.]

25 As far as enterotoxins go, the major

1 staphylococcal enterotoxins are Staph enterotoxin A, B, E,  
2 and TSST-1, the one that you will know as the shock  
3 syndrome.

4 We developed a very sensitive bioassay for these  
5 enterotoxins using human T-cell clones with defined T-cell  
6 receptors that react with each of these enterotoxins, and  
7 analyzed the post-column effluent, the plasma coming off the  
8 column for the presence of these enterotoxins, and in no  
9 case did we detect bioactivity.

10 We also looked directly in the patients'  
11 peripheral T-cell compartment to ask whether there was  
12 evidence of exposure to these enterotoxins in a biologically  
13 significant way. We looked at individual V-beta or, in  
14 other words, T-cell receptor components that would reflect  
15 prior exposure to these, and in no case did we find evidence  
16 for this kind of enterotoxin exposure.

17 [Slide.]

18 What we did find was that protein A itself is  
19 being actively shed from the column throughout the  
20 procedure. This represents two-hour time of a patient on  
21 apheresis apparatus. As soon as plasma starts transiting  
22 the column, there is an immediate leaching or shedding of  
23 protein A, bioactive protein A in the column effluent,  
24 continues for the two-hour procedure.

25 When plasma in the patient is measured, you can

1 actually detect this protein A circulating in the patient  
2 over the course of the two-hour procedure. By the time the  
3 patient is removed from the apheresis machine, there is  
4 approximately 20 to 30 ng/mL of circulating protein A in the  
5 patient at that time.

6 [Slide.]

7 Now, I would like to make a couple comments about  
8 that. 20 ng/mL is a relatively small number. Given the  
9 serum immunoglobulin and the known binding of immunoglobulin  
10 to protein A, there is roughly a 10,000 to 1 ratio of  
11 immunoglobulin to protein A, so this circulating protein A  
12 is very likely complexed with immunoglobulin, not  
13 functioning as free protein A, and therefore both for that  
14 reason and because the quantity is in the ng/mL range, we  
15 don't consider Fc blockade or functions like that as likely  
16 mechanistic possibilities, but we are very interested in the  
17 idea that the type of immune complex that is formed by the  
18 10,000 to 1 ratio of immunoglobulin to 20 ng/mL of protein A  
19 might itself be potentially bioactive.

20 Now, that observation, of course, raises more  
21 questions than it raises answers, and because I have  
22 something like a total of five minutes to tell you this  
23 story, I am just going to highlight here our current  
24 mechanistic hypotheses to explain how these remodeled immune  
25 complexes may be bioactive.

1 [Slide.]

2 What is illustrated here is a protein A molecule  
3 complexed to immunoglobulins, serum immunoglobulins in  
4 multiple ways. I am illustrating the known ability of  
5 lymphocytes, B lymphocytes to be down-regulated to receive  
6 inhibitory signals through complexes which cross-link the B-  
7 cell surface, B-cell receptor with the Fc receptor. We  
8 consider that one a very interesting, plausible mechanism of  
9 action.

10 Diagramed over here is my favorite hypothesis,  
11 which is that on the monocyte level, there is a known  
12 interaction between the C3B receptor, called CD46, and  
13 cross-linking of the Fc receptor, again through a very  
14 specialized complex here in the presence of activated  
15 complement, as I have described, that will give negative  
16 regulatory signals in specifically down-regulating IL-12, a  
17 very potent immune cytokine.

18 [Slide.]

19 To conclude, these kinds of studies done in  
20 conjunction with the pivotal trial identified no direct  
21 evidence that the ProSORBA treatment results in any kind of  
22 immunosuppression in a general way.

23 There was no obvious explanation for the mechanism  
24 of the profound clinical effect that you have seen  
25 described, and our efforts currently are shifted toward

1 studying more subtle forms of immunomodulation.

2 DR. KALLOO: Has anyone looked at directly giving  
3 protein A?

4 DR. NEPOM: Well, you know, that is a very  
5 interesting question. You heard earlier that the column  
6 experience now covers about 10,000 patients treated over the  
7 last decade or so with ProSORBA for ITP and other  
8 indications, and based on the data I have just shown you, I  
9 would contend that that is a pretty good clinical experience  
10 of injecting little bits of protein A.

11 There have been some animal studies reported, but  
12 I am not aware of any intentional human trials with  
13 injections of protein A.

14 DR. AGODOA: Do you think the protein A is going  
15 back in there as a complex with the immune complexes from  
16 before or is it going in as free protein A and then  
17 complexing with what is in the patient's serum?

18 DR. NEPOM: Right, that is also a good question  
19 that we are currently trying to study. I should remind you  
20 that this trial that I have just described was run when we  
21 were completely blinded to everything including column and  
22 response, and all that, so our understanding and our  
23 hypotheses were only generated in the last few months after  
24 the fact, and we weren't therefore able to sample the  
25 material at the appropriate times and in the appropriate

1 ways to really answer that question carefully.

2 DR. WHITE: A question slightly different. Since  
3 the arthritis flares occurred, as I remember, both in the  
4 Sham and the ProSORBA treated patients, and are apparently a  
5 lot more than have been seen in other groups of people who  
6 have had this kind of treatment, did you have an opportunity  
7 to look for TNF or IL-1 immediately after the procedure in  
8 any of these patients in any way?

9 DR. NEPOM: We didn't look at serum levels, but we  
10 did look at intracellular cytokines in lymphocytes  
11 circulating in the patients as a general activation marker,  
12 and we found evidence for some activated T-cells, but  
13 nothing that was different in ProSORBA versus Sham.

14 My interpretation of the arthralgias, now that you  
15 ask me, is that it relates to the aflatoxins, the C3a and  
16 C5a, the procedure itself. Remember that both Sham and  
17 ProSORBA arms showed the arthralgias in this patient  
18 population, and I think what we are dealing with circulating  
19 activated complement in the setting of some inflamed or  
20 potentially inflamed joint tissue.

21 DR. WHITE: So, you didn't look at anything in  
22 monocytes, mostly you focused on cytokines and T-cells  
23 rather than in monocytes?

24 DR. NEPOM: Right, that is correct.

25 DR. LIANG: Jerry, what would you think about

1 taking the effluent and then giving it back to the patient  
2 and seeing what happens, especially after the post-arthritis  
3 flare?

4 DR. NEPOM: I would like to ask our Chair, I have  
5 a couple slides I can show on that, or I can save that for  
6 this afternoon, whichever you prefer.

7 DR. KALLOO: Why don't you show it quickly.

8 DR. NEPOM: Okay, if we can call up M36, and then  
9 a couple of slides after that.

10 DR. BOULWARE: Mr. Chairman, while you do that, I  
11 would like to self-correct myself since this is being  
12 recorded, 5 times 1.5 would be 7.5.

13 [Laughter.]

14 DR. BOULWARE: I was thinking 1.8 when I said 1.5.

15 DR. NEPOM: With the Chair's permission I will  
16 take another three or four minutes here to address Dr.  
17 Liang's issue of the activity of the material in the column  
18 effluent itself or what we think might be going on.

19 [Slide.]

20 There are additional clues that point us towards  
21 this immune modulatory concept. You have seen that the  
22 clinical improvement is delayed relative to therapy. It  
23 starts around weeks 8 to 10 to 12, and it builds, it is  
24 cumulative, it is maximal around week 18 or 20 after the  
25 patient is off the column. So, we think that is an argument

1 for immunomodulation, the long-lasting efficacy, and then  
2 the data that you saw from Dr. Gendreau that patients who  
3 responded the first time continued to respond the second  
4 time. Patients who failed to respond the first time do not  
5 respond in the continuation phase the second time.

6 That kind of segregation also would suggest to us  
7 a genetic basis for responder/non-responder phenotypes, and  
8 again suggests a kind of immunoregulation phenotype.

9 [Slide.]

10 In the specific model that I was illustrating for  
11 you, we have B-lymphocytes with their B-cell receptors  
12 surfacing immunoglobulin, and the fc receptors, that we  
13 postulate or hypothesize are activated by this kind of  
14 complex in the effluent.

15 The way we measure that is in my laboratory, we  
16 have created reporter genes that drive beta-galactosidase on  
17 the lac Z gene here with a promoter element that is  
18 sensitive to calcium flux, and one of the known interactions  
19 when these two receptors are co-ligated is to phosphorylate  
20 an intracellular phosphatase called [SHIP], and one of the  
21 things that SHIP does besides inhibit the lymphocyte is it  
22 opens the calcium channel. So, this is our reporter gene  
23 readout for when this event happens.

24 We have transfected this reporter gene into both  
25 mouse cells and human cells to address the question that Dr.

1 Liang suggests. This is the mouse data over here which  
2 shows that indeed this is a plausible mechanism of action on  
3 the mouse cell with intact cross-linking performing the  
4 activation whereas the control fab fragment doesn't.

5 [Slide.]

6 This is the assay we are using for lymphocyte  
7 function, and then a maybe more relevant question for Dr.  
8 White is the monocyte function -- I am sorry. Let me just  
9 say this for one second. A lot of immunologists know of  
10 protein A as a B-cell mitogen. I just put this slide in to  
11 make the point that that is not how this is working. As I  
12 mentioned before, the protein A is complexed by  
13 immunoglobulins. There is no free protein A to bind  
14 directly to the B-cell as is shown here.

15 [Slide.]

16 Now, on the monocyte side, it is more complicated  
17 because the thing that cross-links the Fc receptor and CD46  
18 is actually a C3b, one of the complement components which is  
19 covalently attached in this kind of immune complex to the  
20 immunoglobulins as well as the protein A, and provides this  
21 cross-linking function.

22 The interesting part of this is that the pathway  
23 isn't completely known. We don't know all the  
24 intermediates, but we do know the phenotype is to decrease  
25 the release of IL-12 from monocytes.

1 [Slide.]

2 I will give you two seconds on IL-12, so those of  
3 you who are urologists understand why this is so interesting  
4 to us. Okay. Ten seconds. Immunology 101.

5 The first event that happens in the naive immune  
6 response is that the antigen-presenting cell transmits a  
7 signal to the T-cell receptor. That signal, through these  
8 molecules, triggers a second signal through these molecules,  
9 which back-signals this direction into the antigen-  
10 presenting cell.

11 That second signal -- this is how the immune  
12 system regulates itself -- that second signal then triggers  
13 the release of IL-12. IL-12 is a very potent cytokine when  
14 it acts on T-cells that have their receptor for IL-12, it  
15 activates those T-cells, and they make lots of things  
16 including proinflammatory cytokines.

17 Now, the step that I just showed you, the  
18 inhibition of monocyte function that inhibits at this step  
19 stops this interaction and decreases IL-12 release.

20 [Slide.]

21 This slide shows you the results of our work on  
22 this where we are working through CD-46 when we do  
23 inactivate the monocyte through that CD-46 interaction,  
24 which is shown here, we do decrease the release of bioactive  
25 forms of IL-12 measured here in an ELISA format from primary



1 patients who are refractory to the usual therapies.

2 Third, I want to emphasize the severity of the  
3 patients that we actually saw in this trial and who still  
4 responded and did so despite long duration of disease, which  
5 normally results in less response.

6 Finally, I would like to acquaint you with some of  
7 the patients in our center itself, and my conclusions as to  
8 where this kind of therapy might be useful in our  
9 armamentarium.

10 [Slide.]

11 What this slide shows you is that, in fact, over a  
12 relatively short period of time, six years, patients with  
13 rheumatoid arthritis develop a lot of disability. This  
14 disability is defined as loss of ability to work. So, over  
15 six years or so, 30 to 40 percent of patients with  
16 rheumatoid arthritis become disabled as defined by this sort  
17 of criteria.

18 [Slide.]

19 In fact, in patients with really severe disease,  
20 and this is admittedly an older slide, patients who have a  
21 lot of disease have a mortality that is equivalent to the  
22 mortality of Stage IV Hodgkin's in the early eighties. Now,  
23 obviously, this is a little bit better for Hodgkin's, but  
24 the morality for RA is still very, very severe in that group  
25 of patients.

1 [Slide.]

2 Now, we do have an awful lot of therapies. Here  
3 is a list of some of them that we use, but you will notice  
4 that over about a five-year period, even the so-called best  
5 therapy that we have to date has only continued to be used  
6 by about 60 percent of the patients, meaning that even with  
7 this therapy, 30 or 40 percent of the patients really aren't  
8 getting sufficient relief, so that they are continuing on  
9 that therapy.

10 What is not on this slide are various combinations  
11 of therapies which are also being used as potential  
12 treatment, but even in that group, at least a survey in our  
13 hospital revealed that 20 percent of the patients simply  
14 were not able to stay on the drug. So, there is a niche for  
15 another therapy.

16 [Slide.]

17 Now, our patients or the patients in this pivotal  
18 trial, just to remind you, really were pretty severe. They  
19 had a lot of tender joints and swollen joints, and just to  
20 give you a vague comparison, in many of the other DMARD  
21 trials, you would see numbers in the 25 and 20 range rather  
22 than 36 and 24 range, and these numbers being worst at  
23 higher numbers, would frequently be found in the range of 5  
24 or so instead of 7, so that these are more severe, both by  
25 semi-objective measures and by subjective measures.

1           These patients also had very long duration  
2 disease. Again, in many trials, it is much less than this,  
3 in the range of sometimes less than a year, frequently in  
4 the range of seven or eight years, and they had had disease  
5 having failed numerous DMARD regimens.

6           Again, this, if you look at one of the drugs that  
7 was recently approved, the average prior DMARD regimens in  
8 that particular trial was about one DMARD failed. So, this  
9 is significantly high.

10           Finally, the measure of activities of daily living  
11 or physical disability was very high here. To give you a  
12 feel again, many trials are in the range of 1 to 1.4, and a  
13 difference of 0.1 is clinically meaningful. So, these are  
14 patients who really were pretty bad, and would fit into that  
15 group of severe patients that might benefit from a niche  
16 therapy.

17           [Slide.]

18           To remind you that these patients with class III  
19 disease, that means disease that results in difficulty  
20 functioning despite therapy, responded in about 28 percent  
21 of the cases.

22           [Slide.]

23           To compare them to other patients who had had long  
24 disease, this is a study that is going to be presented at  
25 the meetings next week, which showed that patients who had

1 longer duration disease tended to do worse on whatever  
2 therapy they had. This is DMARD therapy, and the Prosoarba  
3 group, a very small group, mind you, at least did not get  
4 worse. It may be stable, it may be more as duration gets  
5 longer, but at the very least they don't seem to get less  
6 effect over the longer duration disease, so that despite  
7 long duration disease, these patients continue to respond,  
8 we hope.

9 [Slide.]

10 Now, what about those patients who did respond,  
11 how well do they respond? In this group of patients, the  
12 responders in the pivotal trial, you can see that if you  
13 look at swollen joints or tender joints, that the response  
14 is really significant. The response here by 12 weeks of  
15 treatment, ranging about 50 percent for tender and swollen  
16 joints. I think 50 percent response is clinically important  
17 to the patient. If it were a much smaller response, all by  
18 itself, it might be less, but this is real response.

19 [Slide.]

20 Now, what were our patients like in our trial per  
21 se? About 50 percent of them were functional class III, and  
22 they had the duration that you would expect. In fact, this  
23 group of patients had failed more DMARDS than apparently the  
24 mean group of patients, and yet the response rate was about  
25 40 percent, and if you recall, when we looked at the

1 responses in this group of patients, no matter how you did  
2 it, the most conservative way, you still got about a 30  
3 percent response rate, so that the response rate was pretty  
4 good.

5           Duration, 40 weeks or so, although the duration of  
6 response ranged from relatively less to a good deal longer,  
7 and this is a plus because some of the patients seemed to  
8 continue to be responding at this point.

9           Although we had very patients who were redone, at  
10 least one of those two did respond.

11           [Slide.]

12           Now, that is not done without the potential for  
13 side effects, and in our group of patients, we had that one  
14 patient who developed a central line infection that we  
15 thought was due to the procedure, if not to the ProSORBA  
16 column itself.

17           One of the patients developed a petechial rash,  
18 and when we saw the patient about 10 days after it occurred,  
19 she completely cleared. We were never sure whether this was  
20 a rash or a vasculitis, but the fact that it had completely  
21 cleared, and she brought pictures, so we could see what it  
22 was like at its worst, the fact that it completely cleared  
23 within a week made us think that it probably wasn't  
24 vasculitis, it was some sort of a reaction, but not a  
25 vasculitis.

1           One of the patients developed an NSAID associated  
2 Crohn's presentation, which certainly does occur and has  
3 been well documented, and one patient had a complication of  
4 severe rheumatoid arthritis.

5           [Slide.]

6           So, with that kind of experience, in my mind,  
7 where ProSORBA treatment might fit would be that it would be  
8 for the patients with severe RA, and only in a subgroup of  
9 patients, but in that subgroup of patients, it could be  
10 effective with some really durable responses, and although  
11 there is no question that there was some toxicity, the  
12 toxicity that the patients experience, for example, the  
13 flares, really were not of great concern to them.

14           Did I have to treat some of them? Yes, we did,  
15 with some pain medications, but none of them decided to stop  
16 because of that. You know, it just occurred to me that  
17 post-treatment flares actually occur with some of our  
18 DMARDS, some of the ones we use now.

19           We used to get that with gold, for example, and  
20 you occasionally get it with methotrexate, so if it not  
21 absolutely specific for ProSORBA, so that there is an  
22 acceptable toxicity in my view.

23           [Slide.]

24           Is it completely safe for everyone? I really do  
25 believe that patients ought not to participate if they

1 require a central line. I think there is a problem there.

2 On the other hands, this is procedure based rather  
3 than drug based, and it represents, in my mind, an  
4 intervention, not something that we are going to have to do  
5 again and again and again, but something that can be done  
6 occasionally if it needs to be.

7 It is nice to see that, in fact, occasionally, the  
8 patients who do respond will re-respond, and I think there  
9 is a place for some retreatment.

10 Thank you very much.

11 DR. KALLOO: Would you tell me about the response  
12 rates? You gave a mean and a range. Do you have any slides  
13 to show how that scatter was?

14 DR. FURST: You mean the duration of response?

15 DR. KALLOO: Correct.

16 DR. FURST: I don't know if we have a slide, but I  
17 can give you a sort of gut feel. I think the 72-week  
18 response is definitely unusual, but I think you will find  
19 many of the patients will respond in the range of 30, 35  
20 weeks-ish after the completion of treatment, so in the range  
21 of 40 to 50.

22 We might be able to find that distribution, but I  
23 don't have it.

24 DR. KALLOO: At the time of relapse, do their  
25 symptoms go back, what is the relapse like, does it go back

1 to the baseline? Is it worse?

2 DR. FURST: Interestingly, now, remember I was  
3 blinded, so I don't know exactly, but the sense I got was  
4 the first type of response people got was they started to  
5 feel less fatigued, and then the joints got better, and the  
6 same thing happens in reverse. When their response seems to  
7 go away, they first begin to be more fatigued, less  
8 energetic, and then their joints begin to become more  
9 painful.

10 DR. HAWES: Put into context for me a little bit  
11 more over the long term, it is the disease that lasts years  
12 and years, you have tested a group of patients who have been  
13 refractory to virtually everything, and now you are  
14 proposing to offer to patients a treatment that requires  
15 this procedure once a week over a fairly long period of  
16 time, and then they, let's say, have a mean duration of  
17 response of 40 weeks just for purposes of argument.

18 What then happens? They are already refractory to  
19 other medications. Are these patients then going to be  
20 coming back for retreatment every, you know, sort of twice a  
21 year for the rest of their lives, and do we have any data?  
22 It seems to me that it is going to present some problems in  
23 the long term, and yet I have not seen any data at all about  
24 sort of repeated exposures to the column.

25 DR. FURST: That is actually a larger issue. It's

1 a good question, of course. The problem with our treatment  
2 of rheumatoid arthritis is we have nothing that lasts for  
3 really long times as you think about five, 10 year  
4 treatments. So, all of our data, in fact, tends to be what  
5 one would call moderate to short term. So, all of the  
6 disease modifiers we use to date are used in six-month  
7 trials or eight-month trials, and then, over time, you get  
8 some cohort sort of studies that tell you how long they  
9 last. That is where that slide came from.

10 So, I think the first answer is we have nothing  
11 that lasts really long term as we would like it to date.  
12 So, this would be another addition to that group. It is  
13 not, in my view, something where you would want or think or  
14 need to treat repeatedly. Despite the fact that you would  
15 like to do that, we don't have a lot of data to support that  
16 except in responders you can say they may respond one more  
17 time. That does not mean, in my view, it remains that in  
18 patients who are refractory to everything, or a lot of  
19 things, this is something that will give them some response  
20 for an unknown period of time.

21 Is it the answer? No. Is it an answer? I think  
22 it might be.

23 DR. HAWES: What do you do with these patients, do  
24 you then go back to methotrexate and other things? For a  
25 gastroenterologist, put it into context. I mean what do you

1 do?

2 DR. FURST: There is anecdotal experience that  
3 some of these patients now seem to respond better to their  
4 older drugs. When you go back to that, you go back to other  
5 combinations, you look for another experimental therapy,  
6 some patients respond for prolonged periods.

7 The answer is it is not a very perfect answer, but  
8 it is something for them.

9 DR. HAWES: I have one other question. I assume  
10 there is no data, then, at all, about multiple and long-term  
11 exposures to a ProSORBA column. ITP, I assume, is a limited  
12 thing, and so there is nobody that has really had treatments  
13 over once a year for five years, just repeated exposures to  
14 the ProSORBA?

15 DR. FURST: I am not aware of that. That might be  
16 something one could do in the future, I certainly don't  
17 know.

18 DR. GENDREAU: There is a few examples. There are  
19 patients who are being with the ProSORBA column for some  
20 renal diseases and some other conditions. There is one  
21 patient that I am aware of at Stanford who the last time I  
22 checked had been treated 93 times over three years, and they  
23 were treating her monthly. I can't recall her diagnosis,  
24 but they are dealing with an autoimmune disease where they  
25 find it stabilizes her. So, there are a very few patients,

1 but there are probably a handful of patients that have been  
2 treated with column 50 to 100 times. It has used a little  
3 bit in transplant rejection where the treated patients 20,  
4 30, 40 times, and again it has been tolerated.

5 Patients who have reactions to column therapy  
6 usually do it in the first couple. If a patient gets out to  
7 six or to eight or to 10 treatments, they can probably go 50  
8 or 100.

9 DR. KALLOO: Could you give us an idea of the  
10 relative cost compared to conventional treatment?

11 DR. BLANK: Today, a column costs \$1,090 a column,  
12 and it is generally used six times per patient for ITP. We  
13 do anticipate having a substantial price reduction with an  
14 RA indication. The major driver behind that price reduction  
15 that we will be able to offer will be based on economies of  
16 scale in the manufacturing facility, but I just want to  
17 remind everybody that the cost of the column is not the only  
18 cost of the treatment, so we are also undertaking a number  
19 of initiatives to lower the overall cost of the entire  
20 therapy.

21 We are working with the manufacturers of the  
22 apheresis equipment to come out with better software and  
23 better disposable kits. This may sound silly, but the most  
24 important cost of apheresis is nursing time, and if we can  
25 ease the nursing time, that will be a big factor.

1           The other thing that we want you to note is that  
2 in the trial, we had very slow flow rates of 5 to 20 mL per  
3 minute, and this is exceedingly slow. In our Phase IV  
4 trial, we would like to try speeding up the flow. If we can  
5 get the time of the column down as much as an hour, that  
6 would lower the overall cost.

7           Finally, we are exploring all other kinds of  
8 scenarios and options, some of which I can't talk about  
9 today, where we are expecting to be able to get the overall  
10 cost of the treatment down to competitive rates, more  
11 relative to the biologics than to generic DMARDS.

12           DR. WHITE: I would like to ask a follow-up  
13 question again on medically significant infections, if I  
14 could go back just a bit again to the table on page 72. I  
15 found in the detailed data that were presented on  
16 complications related to the device, so that wouldn't be the  
17 ones that weren't judged to be unrelated, that one of the  
18 patients, 0361, in fact, was hospitalized for two episodes  
19 of sepsis, one was thought to be possibly and one was  
20 thought to be probably related to the device.

21           I see but one episode on here. Was the other  
22 infection that required hospitalization not judged to be  
23 medically important?

24           DR. GENDREAU: I have a detailed slide on that  
25 patient, so I am going to ask that we put that up to look

1 at.

2 DR. WHITE: I just want to be certain, it is hard  
3 for me with all the data and all the patients know that, in  
4 fact, I have a clear look of people that had medically  
5 significant infections, whether or not the investigator  
6 judged they were related, because we might argue relatedness  
7 to the whole protocol or not, and that all of them are  
8 presented to us in an easy to follow format.

9 [Slide.]

10 DR. GENDREAU: I think you will see here the  
11 reason there were probably two reports in the database, is  
12 that the patient came for IV treatments, and that would have  
13 been a report, that emergency room visit, and she was  
14 treated and sent home, then she came back, because she was  
15 intolerant of the antibiotic, and then she was hospitalized,  
16 and I believe that would have generated a second entry  
17 though.

18 DR. WHITE: So, it was the same episode.

19 DR. HORTIN: I don't follow exactly how you  
20 decided in terms of your protocol design what the number of  
21 treatments should be or the dosage of treatment. Oftentimes  
22 for therapeutic plasma apheresis procedures, you would  
23 perhaps have an adjustment for body size or intervascular  
24 volume, or some such treatment.

25 How did you arrive at our protocol or know whether

1 12 treatments would be preferable versus one, or 1,240  
2 milliliters of volume requires no adjustment for body size  
3 or other factors?

4 DR. GENDREAU: Those are excellent questions, and  
5 it is one of the dilemmas of having a device that it is a  
6 little harder to study what you call pharmacokinetics than  
7 you would have with a drug.

8 The reason for 12 treatments is based on primarily  
9 experience of Craig Wiesenhutter in his published study and  
10 then our pilot study, where he looked at 15 treatments and  
11 at 12 treatments, and saw no difference, and I believe he  
12 did a limited number of studies where he looked at 3 and 4  
13 treatments and saw less effect, so somewhere closer to the  
14 12 range seemed appropriate, that is what he published and  
15 recommended.

16 The pilot trial that accompanied it was meant to  
17 confirm his experience, so we duplicated that 12-column  
18 schedule and it was successful. In going into the pivotal  
19 trial, that was the data we had to design the pivotal trial  
20 around, so the answer to the question about why 12, it is  
21 historical.

22 In terms of why process 1,250 cc's versus more, it  
23 is a very good question. Some of our apheresis consultants  
24 have suggested we should process more total volume, that two  
25 liters would be appropriate than 1,250 cc's. There is

1 really not hard data to support it either way. The 1,250  
2 cc's was really arrived at processing time.

3 We used the slow flow rate, as Debby Joe  
4 mentioned, and we did not want the procedure to run more  
5 than about two hours just for patient convenience  
6 standpoint, so the 1,250 cc's was the volume we could  
7 routinely complete in a two-hour period comfortably for the  
8 patient.

9 Now, as we explore higher flow rates, that will be  
10 one of the things we may look at is also looking at higher  
11 treatment volumes per treatment.

12 I am reminded also that one of the goals of our  
13 scientific program that Dr. Nepom talked about is we are  
14 looking for surrogate endpoints of effectiveness of the  
15 treatments, and if we do find a good marker, that will  
16 certainly make it simpler to optimize volume treatments and  
17 number of treatments and treatment schedule.

18 We will now have a summary.

19 **Summary**

20 [Slide.]

21 DR. BLANK: I want to tell you a little about the  
22 Phase IV protocol that we have already submitted to FDA for  
23 review, emphasizing that it is very much in preliminary form  
24 and we can change it and add things to it, and also one of  
25 the key success factors for conducting any clinical trial is

1 to have your investigators have input into that protocol, so  
2 let's consider it a draft protocol at this time.

3           So, the goal of this trial will be to develop  
4 safety and efficacy data in a group of patients who are on  
5 methotrexate, but not doing well on that methotrexate, and  
6 that we would be able to study the addition of the Prosurba  
7 column to their methotrexate therapy.

8           We would also be able to incorporate formally some  
9 health economic analyses and to continue our scientific sub-  
10 protocol, and we would be able to get some data on how  
11 combination therapy with the Prosurba column affects the  
12 overall response rate, the duration of response, and the  
13 intensity of response.

14           We have optimism that all of these factors might  
15 improve with methotrexate onboard.

16           Another thing that we are committed to in the  
17 protocol that may not come through if you have read it, is  
18 that it gives us another opportunity for long-term follow-up  
19 that is useful for both the efficacy side and it is useful  
20 for the safety side, and we can incorporate more formal  
21 prospective data on repeat treatment if that is desirable,  
22 and I will just describe briefly the protocol.

23           [Slide.]

24           The idea here is to establish a baseline for  
25 approximately 100 evaluable patients, so we would have to

1 enroll, say, 150 to get 100 evaluable, and that each patient  
2 would be randomized one to one, to either a early treatment  
3 arm or a late treatment arm.

4           The early treatment arm, which is on the bottom,  
5 patients would receive ProSORBA column therapy immediately  
6 and then be followed up. Their control would be the delayed  
7 treatment arm on the top where these patients would continue  
8 along with their current methotrexate therapy for five  
9 additional months, and then receive a late ProSORBA column  
10 therapy and be followed up again.

11           Each of the follow-ups would continue on  
12 methotrexate, so that we essentially have this arm serving  
13 as the control for the early treatment, and this late  
14 treatment arm serving as a cross-over design where they  
15 would serve as their own controls.

16           This trial would not be blinded, however, we would  
17 use a blinded assessor to establish the baseline, as well as  
18 response to therapy as we follow them out in time.

19           I think that is all the comments that I would have  
20 to make today if there are not any questions, I will go on  
21 with my concluding comments.

22           [Slide.]

23           We are aware that in addition to the clinical  
24 program that I have just very briefly outlined, our Phase IV  
25 program, and continuing our scientific research, that this

1 is a very unique product, it is procedure based, and it will  
2 require some specific measures with respect to supporting  
3 the medical community in implementation.

4 A comment that may not be immediately obvious is  
5 that there are two separate groups of physicians that will  
6 require support - rheumatologists, who will be the  
7 prescribers of the therapy, and apheresis physicians, who  
8 will be the providers of therapy, and we have thought this  
9 through in some detail and we are prepared to have materials  
10 that support the flow of information between the  
11 rheumatologist's office and the apheresis site, as well as  
12 training rheumatologists in apheresis-related issues, and  
13 training for the apheresis community in rheumatology-related  
14 issues.

15 We have also developed materials for patients.  
16 Normally, when patients receive drugs, they can ask their  
17 pharmacist about issues. We have developed a patient video  
18 and other patient materials, so that it will make it easy  
19 for them to understand what they are about to have done to  
20 them at these sites for apheresis.

21 We are also concentrating on fine-tuning our  
22 clinical programs and focusing on uses of the ProSORBA  
23 column in combination, and continuing our mechanistic  
24 studies.

25 [Slide.]

1           So, now we would just like to conclude the entire  
2 morning with our thoughts, and if we could, respectfully  
3 submit our point of view about this product.

4           First of all, efficacy. This product works. All  
5 scenarios analyzed achieved statistical significance, and in  
6 some cases, the responses can be quite dramatic and long-  
7 standing. For example, in the responders to the ProSORBA  
8 column, the swollen and tender joint count was reduced  
9 approximately 65 percent.

10           In addition, we think the results exceed  
11 expectations given the severity and stage of disease of the  
12 patients treated.

13           With respect to safety, there are definitely a lot  
14 of issues, however, we think when we look closely at all of  
15 those issues, the only one that surfaces that has real  
16 clinical significance were the sequelae related to central  
17 lines, and that is why we submitted in our draft labeling  
18 that therapy should not be undertaken with central lines.

19           Finally, this group of patients, the severe  
20 rheumatoid arthritis patients, are still in need of  
21 alternatives, despite new therapies recently approved, and  
22 despite emerging therapies that will be approved shortly.

23           [Slide.]

24           So, in conclusion, I just want to give you a feel.  
25 There are a lot of other people here in the room that can

1 help you with your questions after we have had our break.

2 Dr. George Ehrlich and Dr. Richard Panush are both  
3 members of our Rheumatology Advisory Board, and are very  
4 familiar with all of these issues. You have already met Dr.  
5 Hester. Dr. Paulus is here, being quiet as usual. He was  
6 the Chairman of our DSMB, but has remained very involved  
7 with us after the completion of the trial.

8 Dr. Eric Sasso, another of the researchers  
9 involved, is a rheumatologist. Our people that FDA has  
10 gotten to know very well, Francis Smith and Geraldine  
11 Thoren, and lastly, the person who is running the slides is  
12 Mike Thorn, who is a statistical expert and specifically an  
13 expert on the Whitehead technique that you heard about.

14 So, thank you very much.

15 DR. KALLOO: Thank you.

16 DR. STEINBACH: I have one question if it is not  
17 out of order, with the Phase IV trial. That, unfortunately,  
18 is going to be confounded with an expectation bias. One  
19 possibility would be to have the two arms -- one arm would  
20 be methotrexate plus the ProSORBA column, the other arm  
21 would be the ProSORBA column plus a placebo. One  
22 possibility.

23 DR. BLANK: Actually, we have thought of having  
24 the study run as a three-arm study and having a placebo  
25 methotrexate versus a real methotrexate in the two arms,

1 however, all of these issues can easily be incorporated into  
2 the final draft, and we welcome any input that people have.

3 Dr. Paulus, who has been helping us with this,  
4 seems to want to make a comment.

5 DR. PAULUS: Well, I didn't really want to make a  
6 comment. I am Harold Paulus from UCLA. I am a  
7 rheumatologist. I am a consultant to the company. I was  
8 Chairman of the DSMB.

9 One of the questions that we were looking at was  
10 the question of whether one should try to have a Sham  
11 control in this study, and looking at it carefully we felt  
12 that it was not appropriate. Unlike placebo controls in  
13 other treatments, where you expect the placebo control is  
14 not going to have side effects or risk in taking the  
15 placebo, there is considerable side effects and some risks  
16 associated with the pheresis procedure itself, and having  
17 established that in this pivotal trial, I think it is  
18 probably not ethical to do a Sham control.

19 Your question is the opposite of that, is to treat  
20 everybody with ProSORBA and look at people who are withdrawn  
21 from methotrexate and it is compared to people who are  
22 continued on methotrexate, and that is a possible study  
23 design which has, I am not sure what the advantages or  
24 disadvantages of that would be.

25 We often expect to see even people who have an

1 inadequate response to methotrexate often will have a flare  
2 when you withdraw the methotrexate, the disease sometimes  
3 gets worse, and comparing people who are on methotrexate  
4 with an inadequate response, then withdrawn, with people who  
5 are on methotrexate, an adequate response, and continued,  
6 and then adding Proscar to it, maybe the rheumatologists on  
7 your committee can help to figure that one out.

8 DR. KALLOO: Thank you. If there are no other  
9 questions, we will adjourn for lunch and resume at 12:30,  
10 please. Thank you.

11 [Whereupon, at 11:45 a.m., the proceedings were  
12 recessed, to be resumed at 12:30 p.m.]

## 1 AFTERNOON SESSION

2 [12:40 p.m.]

3 DR. KALLOO: Before we begin, I would like to  
4 inform the panel that although we brought up a question of  
5 relative cost of the device, cost in no way should affect  
6 the decisionmaking process. The decisionmaking process is  
7 only concerned with the scientific merits of the  
8 application.

9 We will reconvene with the open committee  
10 discussion with Dr. Provost, who will give the FDA overview  
11 of the study. Again, the panel may ask for clarification of  
12 any points, but should not go beyond clarification of the  
13 specific area.

14 **FDA Presentation**15 **Overview**

16 DR. PROVOST: Thank you. As Dr. Kalloo mentioned,  
17 my name is Miriam Provost. I am a chemical engineer, and I  
18 was the lead reviewer for this PMA supplement.

19 [Slide.]

20 The FDA review team consisted of myself, Dr. Sahar  
21 Dawisha, who provided a clinical review, Dr. Daniel Schultz,  
22 who provided another clinical review, Dr. Lilly Yue, who  
23 provided a statistical review, and Dr. John Langone, who  
24 provided an immunology-toxicology review of the data in the  
25 PMA supplement.

1 [Slide.]

2 As you have already heard, the ProSORBA column was  
3 approved on December 23rd, 1987, for the therapeutic removal  
4 of IgG and IgG-containing circulating immune complexes from  
5 plasma in patients with ITP having platelet counts less than  
6 100,000 cubic millimeters.

7 Since this approval in 1987, there have been no  
8 device changes, only some labeling changes, which included  
9 the addition of a leukocyte filter in the line to remove any  
10 particles, and a labeling change eliminating reference to an  
11 off-line procedure for using the column, and now it is only  
12 recommended for use in an on-line procedure.

13 Since this is an already approved device, there  
14 are no preclinical safety or performance issues to be  
15 considered today. The only issues to be considered in the  
16 PMA supplement are clinical issues.

17 So, at this time I would like to turn the  
18 presentation over to Dr. Dawisha, who will provide a  
19 clinical review of the data in the PMA supplement.

20 **Clinical Considerations**

21 DR. DAWISHA: Thank you and good afternoon. My  
22 name is Sahar Dawisha, and I am a rheumatologist and a  
23 medical officer in the Division of General and Restorative  
24 Devices, which is a different division than this panel is  
25 used to seeing.

1 I wanted to point out that some of the information  
2 that I will be presenting was submitted subsequent to the  
3 PMA and was summarized in my review, which was provided to  
4 you last week.

5 [Slide.]

6 I am going to try to avoid some repetition because  
7 you have already heard a lot of details this morning. The  
8 device description is shown here. The product contains 200  
9 mg of protein A from Staph aureus that is covalently bound  
10 to an inert silica matrix, and the device requires the use  
11 of plasmapheresis.

12 [Slide.]

13 The mechanism of action of the product for the  
14 treatment of RA, or for the treatment of ITP, is currently  
15 unknown, despite commercial availability of the product  
16 since 1987.

17 The sponsor estimates that a single apheresis  
18 removes about 1.7 percent of circulating IgG, which they  
19 acknowledge cannot significantly deplete circulating IgG  
20 levels.

21 The sponsor described a limited investigation of  
22 10 patients at one site in which preliminary mechanism of  
23 action data were shown. The results were already  
24 summarized, but I just want to point out that they noted no  
25 significant decrease in IgM rheumatoid factor, there was

1 evidence of complement activation seen with elevated levels  
2 of C3a and C5a, but no decreases in total complement levels.

3           The total protein A released from the column was  
4 estimated to be 100 to 200 micrograms per treatment, and  
5 there was no evidence of superantigen or superantigen T-cell  
6 activation.

7           You have also heard the sponsor's proposal for  
8 conducting additional mechanism of action studies in their  
9 subsequent post-marketing study, which you will be asked to  
10 comment on in the panel questions.

11           [Slide.]

12           In the PMA, the results of three open label, small  
13 studies, two of which were conducted under an approved IDE,  
14 and one pivotal study, which was also conducted under an  
15 approved FDA IDE, were reported.

16           [Slide.]

17           Study RA1, which was not discussed by the sponsor  
18 this morning, was an open label, feasibility study in 14  
19 patients who underwent 15 treatments in 12 weeks.

20           Only 6 of the 14 patients in this study completed  
21 the study; 3 discontinued due to flare of RA, 1 due to  
22 catheter related embolism, 2 due to difficult blood access,  
23 and 2 due to apheresis symptoms.

24           Only 5 of the 6 patients were evaluable because  
25 they were rheumatoid factor positive as stipulated in the

1 protocol.

2           Of the 5 evaluable patients, no response, defined  
3 by the Paulus criteria, was noted in 3 of the 5.

4           Based on the results of the study, the sponsor  
5 proposed decreasing the number of treatments to once per  
6 week, and requested a second feasibility study, which is  
7 shown on the next slide.

8           [Slide.]

9           This study was discussed in detail by the sponsor.  
10 The study enrolled 15 patients who underwent treatment once  
11 a week for 12 weeks.

12           At 4 weeks after the last treatment, there were 7  
13 of 15 patients who had a greater than 50 percent Paulus  
14 response, 2 of 15 who had a 20 percent Paulus, and 6 non-  
15 responders.

16           At 8 weeks after the last treatment, there were 9  
17 of 15 Paulus 50 percent responders, 1 Paulus 20 percent  
18 responder, and 5 non-responders.

19           Post-treatment arthritis flares, which were  
20 previously discussed, characterized by joint pain, joint  
21 swelling, and fatigue were reported commonly in the patients  
22 within the post-treatment phase up to 72 hours.

23           [Slide.]

24           An independent study of 11 RA patients was also  
25 reported in the PMA. In this study, the treatments were

1 generally once a week and were generally for 12 weeks. The  
2 patients remained on their DMARDS.

3 At 13 weeks after the last treatment, 9 of 11  
4 patients were Paulus 50 percent responders, and at 24 weeks,  
5 4 of 11 patients were 50 percent responders, 2 of 11 were 20  
6 percent responders.

7 In this study, as well, fatigue and pain were  
8 reported after the treatments.

9 [Slide.]

10 The RA3 clinical trial was a prospective,  
11 randomized, Sham controlled clinical trial, which was  
12 conducted under an FDA approved IDE at 12 sites.

13 Patients in both treatment arms underwent standard  
14 apheresis and the Sham patients underwent a bypass loop  
15 around the column.

16 The sponsor already discussed the blinding that  
17 went on, so I am not going to discuss that again.

18 [Slide.]

19 The inclusion criteria are shown on the next  
20 slide. It should be pointed out that in this study, DMARD  
21 failure was defined as worsening of symptoms or flare of  
22 disease, but not necessarily discontinuation of therapy due  
23 to lack of efficacy.

24 Intolerance was defined as side effects  
25 necessitating discontinuation.

1           The patients were not allowed on DMARDS, but were  
2 allowed to maintain stable doses of nonsteroidals and  
3 steroids.

4           [Slide.]

5           The exclusion criteria are shown next.

6           Contraindication in the first criterion was defined as  
7 patients with prior hypersensitivity to immunoadsorption,  
8 patients with inability to anticoagulate, or patients who  
9 were using ACE inhibitors. Patients on ACE inhibitors were  
10 excluded because anaphylaxis has been reported in these  
11 patients with protein at column A use.

12          [Slide.]

13          The treatment schedule was already gone over by  
14 the sponsor. I am going to repeat a few things here.

15          The patient were washed out of their DMARDS prior  
16 to baseline assessments. This was 30 days for methotrexate  
17 and sulfasalazine and 3 months for the other agents.

18          Note that joint counts and patient and physician  
19 global assessments were not performed prior to the DMARD  
20 wash-out to assess the potential of return to baseline.

21          For the purpose of establishing a baseline, 3  
22 assessments within 15 days were averaged, and Sham and  
23 ProSORBA treatments were administered in 12 consecutive  
24 weeks, weekly.

25          Rescue medications such as narcotics,

1 acetaminophen, and tramadol were allowed during the study  
2 for flare of symptoms, but were to be discontinued within 12  
3 hours of an assessment visit.

4 The endpoint of the study for the purpose of  
5 determining effectiveness was 8 weeks after the last  
6 treatment, or the average of weeks 19 and 20.

7 Patients were followed for at least 24 weeks or  
8 six months, which is in accordance with the FDA intercenter  
9 RA guidance document. Although this was not the primary  
10 endpoint, I will show the ACR response at this time later in  
11 my presentation.

12 [Slide.]

13 The primary outcome measure for the study was the  
14 1995 ACR preliminary definition of improvement, which again  
15 involves 20 percent improvement in several parameters.

16 Statistical analyses were based on an intent-to-  
17 treat with patients who dropped out prior to the 19-20 week  
18 time point included in the analysis as non-responders.

19 Patients who initiated DMARD or experimental  
20 therapy during the 20-week period were considered non-  
21 responders, as well as patients who initiated or increased  
22 their doses of steroid or tricyclic antidepressants, and as  
23 well as patients who were withdrawn due to an adverse event  
24 felt related to the treatment.

25 If a patient was a non-responder by week 24, that

1 patient exited the study and was offered the option of open  
2 label treatment in an extension study which the sponsor  
3 called the continuation phase.

4 Patients who met ACR criteria at both weeks 19-20  
5 and at week 24 were followed until they no longer met these  
6 criteria or until 72 weeks, whichever occurred first.

7 [Slide.]

8 A sample size of 268 patients was proposed based  
9 on a proposed ProSORBA response of 35 percent and a 15  
10 percent for Sham, a 20 percent lost to follow-up, a two-  
11 tailed alpha of 0.05, and 90 percent power.

12 [Slide.]

13 The sponsor initially proposed to conduct an  
14 interim analysis after half of the patients had followed up,  
15 up the 20-week time point. They subsequently proposed to  
16 conduct two sequential interim analyses after approximately  
17 50 patients, utilizing the Whitehead Triangle Test,  
18 correcting for the interim analysis with rejection of the  
19 null hypothesis at 0.006.

20 They also proposed the open label extension study  
21 whereby patients who were no longer ACR responders by week  
22 24 or after could be offered open label treatment.

23 Because the basis for determining safety and  
24 effectiveness of the product is based on the data from the  
25 randomized, blinded portion of the study, my presentation

1 will focus on that group.

2 [Slide.]

3 As mentioned earlier, there were two planned  
4 interim analyses which were conducted by an independent Data  
5 Safety Monitoring Board and Boston University, wherein the  
6 effectiveness results, not safety, were reviewed.

7 After the second review of the unblinded results  
8 in January of 1998, the Data Safety Monitoring Board  
9 recommended stopping the trial due to achievement of  
10 effectiveness and because it would be unethical to continue  
11 Sham treatments.

12 The sponsor ceased enrollment at this time, and  
13 there were 109 patients who had been enrolled. The results  
14 reviewed by the DSMB indicated 16 Prosurba responders and 4  
15 Sham responders, and as I will discuss later, and as was  
16 corroborated by the sponsor, of the 16 Prosurba responders,  
17 1 patient, No. 155, actually underwent Sham treatments, and  
18 another patient, 957, potentially used a DMARD, and  
19 therefore these patients would be considered respectively a  
20 Sham responder and a Prosurba non-responder.

21 Therefore, the effectiveness data I will present  
22 shows 14 rather than 16 Prosurba responders, and 5 rather  
23 than 4 Sham responders. This is the modified as treated  
24 analysis referred to by the sponsor.

25 [Slide.]

1           When the sponsor stopped the study, there were  
2 patients in the active treatment arm and in the follow-up  
3 phase of the study, and this slide defines these data sets.

4           The patients who had completed the 20-week follow-  
5 up at the time the study was stopped are called the core  
6 data set. This is an N of 91.

7           The extended data set, N of 99, includes 8  
8 additional patients who had completed the 12 weeks of  
9 treatment, but who were in the post-treatment follow-up  
10 phase, and these patients remained blinded.

11           The core and extended data sets are used for  
12 effectiveness determinations.

13           The total data set, N of 109, includes an  
14 additional 10 patients, called "roll over," who had not yet  
15 completed the 12 week treatments. These 10 patients were  
16 unblinded, and the total data set, which incorporates the  
17 extended data set, is used for safety determinations.

18           The continuation data set, which was shown on that  
19 slide, shows the 40 patients who elected to undergo open  
20 label treatment plus the 10 patients who were the unblinded,  
21 roll over, making an N of 50.

22           [Slide.]

23           This slide shows some of the data handling issues  
24 with the study. Note that noncompliant patients, which was  
25 defined as missing more than 6 of the 12 treatments or

1 missing more than two of consecutive treatments, were  
2 included in the primary effectiveness analysis.

3           Because the sponsor averaged the 3 baseline values  
4 and the two final values at weeks 19 and 20, patients who  
5 had all three baseline measurements missing or both week 19  
6 and 20 measurement missing were classified as having no  
7 improvement in that measure for the purpose of determining  
8 ACR response.

9           During the course of the study, some patients  
10 underwent corticosteroid injections of joints, particularly  
11 the knee. Because this was not specifically addressed in  
12 the protocol, it was determined that joints that had  
13 undergone steroid injection during any time would be  
14 considered tender and swollen for the purpose of determining  
15 ACR responder status.

16           [Slide.]

17           I am going to next briefly discuss protocol  
18 violations which are clinically significant.

19           There were a total of 490 protocol violations  
20 during the study, the majority of which were clinically  
21 insignificant and due to vital signs or visits beyond the  
22 proscribed time or due to incomplete premedication prior to  
23 treatment.

24           [Slide.]

25           For the majority of the 20 patients with protocol

1 violations due to steroid use, steroids were either doubled  
2 for 7 to 10 days or increased from 5 mg/day to 10 mg/day.

3 For the most part, this occurred within 2 months  
4 of study entry and may have been related to discontinuing  
5 the patient's DMARDS prior to entry.

6 Note that the two Prosorba responders, shown here,  
7 underwent steroid dose changes after the 34th week of the  
8 trial, after the effectiveness endpoint at 20 weeks.

9 Because the dose changes were small, occurred for  
10 short durations, and were back to baseline levels well  
11 before the endpoint of the trial, these protocol violations  
12 are included in the effectiveness analyses, although the  
13 protocol stipulated that these patients would be deemed non-  
14 responders.

15 [Slide.]

16 This slide shows the protocol violations due to  
17 NSAID dose changes or initiation.

18 Of the 13 patients with this event, in the  
19 majority, the type of NSAID was changed. Of the 5 Prosorba  
20 responders in this group, in most cases NSAID violation  
21 occurred after week 20 or were very minor dose changes, for  
22 example, the addition of one additional tablet on one day or  
23 the addition of 325 mg of aspirin for cardiovascular  
24 prophylaxis, and are therefore not clinically significant.

25 [Slide.]

1           As mentioned previously, there was one Prosoꝛba  
2 responder, patient 957, who received an unknown dose,  
3 duration, and type of medication "for treatment of  
4 arthritis" in Mexico.

5           Because the sponsor could not verify that this was  
6 not a DMARD or an experimental agent, and because this was  
7 prohibited and was deemed as a non-responder, this patient  
8 will be considered a Prosoꝛba non-responder for the  
9 remainder of my presentation.

10           [Slide.]

11           This slide shows the patient disposition for the  
12 99 patients in the extended data set. Recall that 109  
13 patients were enrolled. The distributions and reasons for  
14 withdrawal are similar for the two groups and differ  
15 slightly from the presentation from the sponsor.

16           For example, patient 1355, who is a Sham, is  
17 classified as an adverse event in this table due to mental  
18 status or confusion, and patient 155, which I mentioned  
19 previously, who was randomized to Prosoꝛba but actually  
20 underwent Sham, is included here as a Sham patient.

21           You can see that the patients discontinued due to  
22 lack of effectiveness is similar, adverse events, and lost  
23 to follow-up, similar.

24           The withdrawal rate of 31 percent for Prosoꝛba and  
25 32 percent for Sham is not statistically significant. The

1 two deaths in the Sham group include one patient with Staph  
2 sepsis due to an infected Hickman catheter, and one patient  
3 with Pseudomonas necrotizing cellulitis.

4 [Slide.]

5 This slide shows the patient demographics for the  
6 core data set, an N of 91.

7 This presentation also differs slightly from the  
8 one shown by the sponsor because patient 155 is classified  
9 as a Sham patient here.

10 There were no statistically significant  
11 differences between the two groups except for mean duration  
12 of RA, which was greater for the Sham patients than for the  
13 Prosorba patients.

14 The majority of patients were female and  
15 Caucasian, which is representative of the general population  
16 of patients with RA.

17 The patients had a long mean duration of RA, 13  
18 for Prosorba and 18 for Sham, had failure or intolerance of  
19 approximately 5 DMARDS, with over 80 percent of the patients  
20 intolerant or failing methotrexate.

21 [Slide.]

22 The mean baseline arthritis activity is shown here  
23 for the core data set. The patients had high levels of  
24 disease activity as shown and as discussed by Dr. Furst.

25 There were no statistically significant differences between

1 the groups with respect to these parameters.

2 Note that morning stiffness and sed rate, two  
3 customary measures of RA activity, were not included in this  
4 trial.

5 [Slide.]

6 The effectiveness results for the core data set  
7 are shown with patient 155 and 957 switched. The difference  
8 in ACR20 response between the two groups, approximately 30  
9 percent of ProSORBA and 11 percent for Sham, is  
10 statistically significant when adjusted for the two interim  
11 analyses and with no covariate adjustments.

12 [Slide.]

13 The effectiveness results for the extended data  
14 group, an N of 89 is shown. Again the difference in ACR  
15 response between the ProSORBA, 29 percent, and Sham treated  
16 patients, 11 percent, is also statistically significant when  
17 adjusted for the two interim analyses with no covariate  
18 adjustments.

19 [Slide.]

20 The percent of patients who are ACR20 responders  
21 at selected times is shown for the core data set, N of 91.  
22 As seen, the greatest difference in response begins after  
23 week 13 and persists until week 24. The response rate at  
24 week 24 is similar to that seen at week 19-20, and is  
25 actually more favorable for ProSORBA.

1 [Slide.]

2 This figure graphically shows the information in  
3 the previous table. The percent of patients in each  
4 treatment group who had ACR response over time.

5 There is a black line that is the Sham response,  
6 and the pink line is the Prosorba response. You can see  
7 that there is a difference over time.

8 I think in the photocopy it looks a lot better,  
9 which the panel has, so that is the important thing.

10 [Slide.]

11 This one you can see a little better. This slide  
12 shows the number of patients who had an ACR20 response  
13 remaining. This point here is the 20 week time point, and  
14 this is the 30 week time point. You can see that even out  
15 to 30 weeks, there were still significant patients who had  
16 ACR response.

17 [Slide.]

18 This table shows the approximate mean and median  
19 point estimate duration of response for the two groups in  
20 the extended data set, which is the N of 99. You can see  
21 the mean duration of response was approximately 37 weeks for  
22 Prosorba and 30 weeks for Sham.

23 The median point estimate duration of response was  
24 32 weeks for Prosorba and 28 for sham.

25 [Slide.]

1           The per patient incidence of the most frequent  
2 adverse events is shown for the group of patients who were  
3 randomized in the study, which is the N of 109.

4           The incidence of at least one adverse event in  
5 each treatment arm was high, which is approximately 98  
6 percent for ProSORBA and 94 percent for Sham. However, the  
7 types of events were generally self-limited.

8           Although the incidence of the most common events  
9 shown here was not statistically significantly different  
10 between the two treatment groups, the incidence was greater  
11 in the ProSORBA treated patients than for Sham with the  
12 exception of dizziness and edema, which were more common in  
13 the Sham patients.

14           In terms of a per event basis, there were  
15 approximately 26 events per treatment, with approximately  
16 2.8 events per patient-treatment per group.

17           [Slide.]

18           The distribution of adverse event severity based  
19 on the investigators' categorization of mild, moderate,  
20 severe, and life threatening is shown.

21           There were a total of 1,561 events in the ProSORBA  
22 patients and 1,359 events in the Sham patients.

23           There were no statistically significant  
24 differences between the groups with respect to these  
25 parameters, and the majority of events were reported as mild

1 or moderate.

2           The two life threatening events reported in the  
3 Prosorba patients occurred in two patients, and were  
4 unrelated to the treatment: one patient with  
5 atherosclerosis experienced a CVA, and one patient with  
6 Crohn's disease experienced a perforated bowel.

7           [Slide.]

8           The majority of patients experienced acute  
9 exacerbation of joint pain during at least one treatment.  
10 This was 77 percent of Sham patients and 88 percent of  
11 Prosorba patients. Those patients experiencing both joint  
12 pain and swelling following treatment are shown for the 109  
13 patients who were randomized here.

14           There were no statistically significant  
15 differences between the groups with respect to this  
16 parameter, and you can see that the incidence was  
17 approximately 30 percent for both groups.

18           [Slide.]

19           With respect to changes in clinical laboratory  
20 parameters, there were no statistically significant  
21 differences between the groups with respect to hemoglobin,  
22 hematocrit, MCV, platelet count, liver function tests, renal  
23 tests, coagulation parameters, or serum complement.

24           There was a mean increase of approximately 8  
25 percent in the platelet count for both groups over time.

1 There was a mean decrease of approximately 11 percent in  
2 both hemoglobin and hematocrit as well as a decrease in MCV  
3 over time for both groups.

4           Although there were no significant difference  
5 between groups with respect to anemia, it is important to  
6 note that there were two patients who underwent transfusion  
7 during the study, and those were both in the Prosorba group,  
8 one patient with anemia which was related to the treatment,  
9 and one patient with a rectal bleed due angiodysplasia,  
10 which was unrelated to the treatment. There were five  
11 patients who underwent erythropoietin treatments due to  
12 treatment related anemia, three in the Prosorba group and  
13 two in the Sham group.

14           [Slide.]

15           The per patient incidence of events reported as  
16 severe occurred in approximately 50 percent of the patients  
17 for both groups, which is quite high.

18           For serious events, which was defined as requiring  
19 hospitalization or occurring at a frequency and/or severity  
20 greater than expected, the incidence was approximately 30  
21 percent of patients in each group, which is also high.

22           There was one Prosorba patient who potentially  
23 experienced a vasculitic rash, characterized by petechiae  
24 and ecchymoses, after the second treatment. The patient  
25 recuperated when the treatments were discontinued in this

1 patient, and it should be noted that nuance of vasculitis in  
2 patients with no prior history has been reported in patients  
3 with ITP and malignancies treated with protein A columns.

4           There were five patients who had sepsis. For the  
5 two ProSORBA patients, one was due to UTI and one was post-  
6 op following hip replacement. For the three Sham patients  
7 with sepsis, in two patients it was due to an infected  
8 central line and in one patient due to Pseudomonas  
9 necrotizing cellulitis.

10           [Slide.]

11           The sponsor is proposing to conduct a Phase IV  
12 marketing study to evaluate the safety and efficacy of the  
13 combination of methotrexate and ProSORBA therapy. They  
14 propose to randomize patients to immediate versus delayed  
15 ProSORBA, which is 20 weeks after methotrexate alone.

16           Patients must be willing to be washed out of  
17 DMARDS, and there is no minimal disease duration or minimal  
18 number of DMARD failure/intolerance.

19           They are currently proposing to enroll patients  
20 with mild disease activity with scores as low as 4 out of 10  
21 on the patient's and physician's global assessment, as well  
22 as only 9 tender and 6 swollen joints.

23           The panel will be asked to comment on what  
24 additional studies are needed in this regard.

25           [Slide.]

1           In summary, the patients in the study had severe,  
2 active, long-standing RA with failure or intolerance of  
3 multiple DMARDS. The study was stopped after only  
4 approximately half of the patients were enrolled due to  
5 achievement of statistical significance.

6           While there is statistically significant  
7 differences in ACR responses, with a 30 percent response in  
8 ProSORBA, and 11 percent response in Sham patients, the  
9 panel will be asked to comment on the clinical significance  
10 of these statistical findings given the small number of  
11 patients studied.

12           Adverse events were reported in the vast majority  
13 of patient and occurred more frequently in ProSORBA  
14 patients, but these events were generally self-limited and  
15 not statistically different between groups.

16           Although the adverse events were not statistically  
17 different between groups, because apheresis is inherent in  
18 ProSORBA treatment, the adverse events will be considered in  
19 totality.

20           Treatments resulted in a decrease in hematocrit,  
21 hemoglobin, and MCV over time, as well as an increase in  
22 platelet count over time, which is of concern in patients  
23 with anemia of chronic disease and RA.

24           Although sepsis is probably more related to the  
25 invasive nature of the procedure rather than to the



1 designed study. The trial duration is half a year with 12  
2 treatments in three months, and 12 follow-up visits in 3  
3 months.

4 The sequential analysis was planned with a  
5 triangular test developed by Professor Whitehead.

6 [Slide.]

7 The primary endpoints is the proportion of  
8 responders, also response rate at week 19 and 20. The  
9 observation is binary, responder or non-responder.

10 The proposal is null hypothesis if the two  
11 response rates are equal, or hypothesis if the two response  
12 rates are different.

13 The sponsor tried to show that Prosorba is better  
14 than the Sham. The notations here,  $P_e$  stands for response  
15 rate for the Prosorba, and  $P_c$  stands for the response rates  
16 for the Sham.

17 The test is a two-sided with proposed power at 90  
18 percent, and the significance level at 0.05. The projected  
19 response rate is 35 percent for the Prosorba, and 15 percent  
20 for the Sham.

21 The interim look after every patients using  
22 triangular test approach.

23 [Slide.]

24 The proposed sample size is a random variable with  
25 a mean of 120 patients, median 101, and maximum 268

1 patients.

2           The trial was stopped after the second interim  
3 look, and ended up with 91 patients in the core study, 99  
4 patients in the extended study, and a total of 109.

5           [Slide.]

6           I will follow the sponsor's notation and talk  
7 about the intent-to-treat as the treated and modified  
8 treated analyses.

9           Let's look at the intent-to-treat first. At the  
10 first interim look, there were 60 patients recruited, 10  
11 responders in the ProSORBA arm, and 1 responder in the Sham  
12 arm.

13           At the second look, there were 91 patients with 15  
14 responders in the ProSORBA arm, and 4 responders in the  
15 Sham.

16           [Slide.]

17           One responder was switched from the ProSORBA to  
18 the Sham due to incorrect treatment, so this is "as treated"  
19 case.

20           In the modified as treated, the number of  
21 responders in the ProSORBA reduced to 14 because of protocol  
22 violation.

23           [Slide.]

24           An available method for testing the equality of  
25 the two response rates, we look at the three, Triangular

1 test, Fisher's Exact test, and Chi-Square test.

2           The Triangular test was adjusted for the  
3 sequential nature of the design, by the baseline asymptotic  
4 theory. The Fisher's Exact test allows for the exact nature  
5 of the observations, but ignores the interim looks. The  
6 Chi-Square test ignores the sequential nature of the design  
7 and is also based on asymptotic theory.

8           From this table we can see no matter what test it  
9 yields, the Triangular test, or Fisher's Exact test, or Chi-  
10 Square test, and no matter what the situation is, the  
11 intent-to-treat or as treated or modified as treated, the p-  
12 value here is always less than 0.05, which means the test of  
13 equality is significant.

14           DR. STEINBACH: Can I interrupt? Does the Chi-  
15 Square test include the Yates correction?

16           DR. YUE: No. The Chi-Square test ignores the  
17 sequential nature of the design.

18           DR. STEINBACH: I learned it as the Yates  
19 correction where you essentially rounded the next integer or  
20 truncated to the next integer. I guess the answer is no.

21           DR. YUE: The answer is no, no.

22           Now, here there are two interim looks. I don't  
23 think that one does.

24           When taking a close look, we can find the p-values  
25 from the Triangular test and the Chi-Square test are

1 similar. The p-values from the Fisher's Exact test are  
2 larger. It increases from 0.01 to 0.04 when we switch from  
3 the intent-to-treat to modified as treated.

4 Question. If the two treatments are different, is  
5 Prosorba better or worse than the Sham? If better, how much  
6 better?

7 [Slide.]

8 Let's see what the data can tell us. The observed  
9 response rate for the Prosorba is as high as 33 percent and  
10 as low as 29 percent. The observed response rate for the  
11 Sham is as high as 12 percent and as low as 9 percent.

12 Even though the Triangular test corrects for the  
13 interim looks, and the conventional method does not, and  
14 adjusts the ratio of the number of responders to the number  
15 of patients in each group, the results from the two tests  
16 are similar.

17 [Slide.]

18 Please note what we are interested in is the  
19 improvement of the Prosorba over the Sham, the difference  
20 between the two response rates, from data we can see the  
21 observed difference in the two response rates, about 24  
22 percent, 20 percent, and 18 percent.

23 The projected response rates for the two  
24 treatments are about 35 percent and 15 percent respectively  
25 with the difference 20 percent. Compared to results here,

1 so the original guess is good. However, the numbers 24, 20,  
2 and 18 percent alone cannot say much about the true  
3 difference. This is because the true difference is a  
4 parameter. The estimator of the parameter is a random  
5 variable.

6 For available data, we have these three point  
7 estimates, but if the trial is repeated under the same  
8 conditions, we may get different numbers here.

9 So, it is important to consider both point  
10 estimates and variation. The proper way to do this is to  
11 look at the confidence intervals. The intent-to-treat case,  
12 with the 95 percent confidence, the true difference of the  
13 two response rates is between 4.3 percent and 44 percent by  
14 exact method, or is between 8 percent and about 40 percent  
15 by asymptotic method.

16 Generally speaking, these confidence intervals are  
17 very wide due to the small sample size and the high  
18 variability, but we can take a look here about the  
19 improvement of the Prosorba over the Sham, for example, how  
20 high or how low the improvement can be.

21 For example, using asymptotic theory, the  
22 improvement can be as low as 3 percent, and as high as about  
23 40 percent.

24 The exact method gives even wider confidence  
25 intervals since this method is too conservative, and the

1 intent is not to reject the null hypothesis. The intervals  
2 are wider than they should be, so please do not put too much  
3 attention to this negative number. It is just to get a  
4 rough idea.

5           You may notice here, recall that the modified as  
6 treated case, the Fisher's Exact test gives a p-value of  
7 0.04, which means the test of equality is significant, but  
8 here, using the exact test, it includes zero, which means  
9 the test of equality is not significant.

10           The reason that the two exact methods are  
11 different in terms of assumptions, Fisher's Exact test is  
12 more reliable, so please do not put too much faith in this  
13 negative number. Anyway, it is close to zero.

14           Question. After the confidence interval here, is  
15 the improvement good enough?

16           [Slide.]

17           With 99 patients, in the modified as treated case,  
18 there were 15 responders in the ProSORBA and 5 in the Sham.  
19 The results are similar to those in the core studies here.

20           The improvement of the ProSORBA over Sham can be  
21 as low as 4 percent and as high as 33 percent. Compared to  
22 the core study with 8, no patients in the extended study,  
23 and why more responders in the ProSORBA.

24           The Fisher's Exact test gives a p-value of 0.02  
25 compared to the 0.04 in the core study.

1 [Slide.]

2 In summary, the design is very good. Question:  
3 Is the improvement of Prosorba over Sham high enough?

4 Thank you.

5 DR. LIANG: I know there are other sequential  
6 designs. Why Whitehead over others?

7 DR. YUE: I cannot say it's over others.

8 DR. LIANG: What are the merits, plus or minus,  
9 versus any other method?

10 DR. YUE: Actually, it controls the significance  
11 level, 0.05. It give more chance to look at early histology  
12 is my impression.

13 DR. JANOSKY: I know that you didn't present the  
14 results here, but do you have access or did you take a look  
15 at what effect prior disease duration might have on the  
16 outcome variable?

17 DR. YUE: No, we didn't consider that. Actually,  
18 they didn't consider, no. Why they consider the response  
19 rate, they didn't do a covariate analysis -- oh, there is  
20 one -- for this one, just a pure chi-square test or  
21 triangular test or Fisher's exact test.

22 DR. JANOSKY: Because the sponsor is making a  
23 point about it being overall 15 year prior disease duration,  
24 but it is statistically different between the Sham and the  
25 Prosorba group, with it favoring the Prosorba group.

1 I did notice in the packet that was provided to  
2 us, someone had done a multivariate analysis. Was that done  
3 by the sponsor, do you know, or by FDA? Does this sound  
4 familiar to you?

5 DR. YUE: No.

6 DR. GENDREAU: We did do a multivariate analysis,  
7 and if we get our projector hooked up, I would be happy to  
8 put that on there.

9 DR. JANOSKY: Okay, please, that is one of the  
10 issues that I wanted to raise.

11 DR. LIANG: This is a question for Dr. Dawisha.

12 Did this post-hoc inclusion of people who had  
13 gotten steroids PO or intra-articular, I mean how was that  
14 made? I mean you presented, those were to be considered  
15 non-responders, and then it was switched, or at least that  
16 was the impression I got.

17 DR. DAWISHA: You are talking about the oral  
18 steroid protocol violation?

19 DR. LIANG: One slide said that if they got  
20 steroids in any form, they were yanked as non-responders.

21 DR. DAWISHA: Right.

22 DR. LIANG: But we saw the analysis with them  
23 included.

24 DR. DAWISHA: Right.

25 DR. LIANG: And was that something that they did

1 or you did, and why?

2 DR. DAWISHA: After the sponsor looked at the data  
3 and looked at who did and who didn't get a steroid dose  
4 change or initiation, we asked the company to tell us based  
5 on treatment group what were the treatment groups for those  
6 patients who had oral steroid protocol violations, and were  
7 they or were they not non-responders, so the data that I  
8 showed is just clarifying what treatment group the patients  
9 were in who had oral steroid violations, and whether they  
10 were or were not a responder based on the ACR criteria.

11 DR. LIANG: But they were included in the final  
12 analysis, the people who got steroids.

13 DR. DAWISHA: Well, if you look at the slide,  
14 there were only two ProSORBA responders, and there were no  
15 Sham responders, and we asked the company to give us some  
16 more information about those two ProSORBA responders, and  
17 they told us that those patients had oral steroid changes  
18 after week 34, which was after the 20-week time point.

19 So, we said that it would be okay to include them  
20 as responders, although the protocol specifically --  
21 actually, the protocol said that if there were steroid dose  
22 changes within 20 weeks, and since this was after the 20  
23 weeks, it would be acceptable to include them as responders.

24 DR. LIANG: How about people who got intra-  
25 articular steroids?

1 DR. DAWISHA: I had mentioned that the protocol  
2 initially didn't specifically address, it didn't  
3 specifically say one way or the other whether they would be  
4 considered non-responders or responders, and again the  
5 company provided information on the number of patients who  
6 got injections.

7 We asked them to provide additional information as  
8 to what the treatment groups were and whether they were and  
9 were not responders. They also consulted with the Data  
10 Safety Monitoring Board and with Boston University, and  
11 concluded that because steroid injections into the joints  
12 are not known to have a systemic effect --

13 DR. LIANG: That's wrong.

14 DR. DAWISHA: Well, this was their conclusion, so  
15 maybe you should ask them.

16 [Sound interference.]

17 DR. FELSON: Early in the trial it became clear  
18 that the problem would arise, and we changed the protocol in  
19 concert with seeking FDA help on this, and Dr. Dawisha  
20 wasn't necessarily involved at that time.

21 It was decided at that time that joints which  
22 received corticosteroid injections would be characterized  
23 from then on in the trial as failure joints, meaning they  
24 couldn't improve.

25 Now, those joint injections occurred primarily

1 during treatment and just after, so even with what you say,  
2 remember that the efficacy point here is week 19-20 only,  
3 there is no last observation brought forward, so if you got  
4 a corticosteroid injection at week 2 or 3, that joint you  
5 got the steroid injection in was then characterized as  
6 unimprovable, it got counted as active every single time  
7 even if it improved, and you were still allowed to be a  
8 responder at week 19-20 based on basically improvement in  
9 your other joints.

10 DR. HORTIN: A question about how the decision was  
11 made in terms of the timing to perform interim analyses.  
12 Your design said that you were going to perform the analyses  
13 at points after 50 and 100 patients, and this was done, in  
14 fact, at 60 and 91. Did people who made those decisions  
15 know about the ongoing results or were they blinded as to  
16 the results?

17 DR. FELSON: Let me comment on that, because the  
18 actually the company can't comment on it. Frankly, they  
19 don't know why. We were having this discussion at lunch,  
20 and I think to this day they are probably in the dark as to  
21 why the DSMB recommended that we re-study these patients at  
22 91, when roughly, 90 patients had accumulated.

23 When we performed the initial DSMB evaluation at  
24 61 patients, as I mentioned to you earlier, based on the 80  
25 percent rule, the trial was already being characterized as

1 one that ought to be stopped on the basis of efficacy.

2           The DSMB at that time decided not to stop the  
3 trial because there weren't a lot of patients in the trial,  
4 and as you saw from the data that was just presented by the  
5 FDA, there was only one Sham responder, and we frankly  
6 anticipated there would likely be more than that.

7           So, we then went back at BU and said let's run a  
8 few simulations and see how likely we are to keep outside  
9 this stopping boundary if we assume there will be  
10 substantially more Sham responders and a continuing rate of  
11 Prosorba responses, roughly what we currently see.

12           We ran a bunch of scenarios including more  
13 conservative ones, frankly, than the one that turned out,  
14 and it turned out that we would be able to be fairly  
15 definitively at about 91 patients, that it would be a robust  
16 analysis that would withstand things like what ultimately  
17 happened, you know, one patient switching back and forth.

18           So, we recommended to the sponsor that we come  
19 back at an additional 30 patients. Let me also suggest --  
20 there were a lot of questions earlier about the DSMB, and I  
21 know you are asking one now, we raised a number at the  
22 break, and they are of great interest, but I think the  
23 bottom line here is not what the DSMB decided or when they  
24 met or what action necessarily that they took, but rather  
25 whether the evidence accumulated on this based on the data

1 provided suggests the stuff works or not.

2 DR. WHITE: I don't know if this is the time to  
3 raise this issue, but I just would like some clarification  
4 from the FDA about actually bringing this to the panel, and  
5 this is having sat on the Arthritis Advisory Panel, it  
6 struck me, a couple things struck me about this.

7 The first is while this is a device, it appears  
8 that it is delivering something that is immunomodulatory, it  
9 is not clear what it is, but even the sponsor said we don't  
10 think we are removing anything, we think we are doing  
11 something.

12 So, that is a little bit different than the way I,  
13 as an initiated device person, views a device. I would view  
14 this more as delivering an agent, modulating something. So,  
15 if that kind of an agent came to the Arthritis Advisory  
16 Panel, there, we usually use two trials rather than one  
17 trial, and that raises my concern about the robustness of  
18 the data, in addition, you know, why is this considered a  
19 device, yes, you have to use a device, but in fact you are  
20 doing something, not just the device like an endoscopic  
21 piece of machinery.

22 We usually require two trials, two independent  
23 trials, and I am concerned about having judgments made about  
24 the efficacy. Why would the FDA -- I mean is it different,  
25 what you require here different than what we might require

1 in the Arthritis Advisory Panel?

2 Here, we have 15, maybe 17 patients who have  
3 responded. We have seen 10 percent of the total responding  
4 patients, they are here in our audience. The statistical  
5 data is kind of marginal. It is there, it is there any way  
6 you look at it, but it's just there. And if you had a  
7 patient goes this way or a patient go that way, it might not  
8 be there.

9 The question is more about a patient going this  
10 way or a patient going that way is raised by the placebo  
11 response rate. It's 11 percent. In most trials in  
12 rheumatoid arthritis, the placebo rate is significantly  
13 higher, perhaps 25, 30 percent, not being unrealistic.

14 Granted, this is a very special group of patients,  
15 and maybe that is why it is low, but since we don't have  
16 experience with such a very special group of patients to be  
17 certain that that placebo rate is very expected, it raises  
18 again the concern the placebo rate is very low, lower than I  
19 might have expected, but maybe I am wrong. It would be nice  
20 to have a bit more experience with such a select group of  
21 patients, to know that that is reasonable, that the placebo  
22 rate is right.

23 So, I am asking the FDA, did you consider these  
24 things, did you really feel these data were robust enough to  
25 bring forth for consideration?

1 DR. SCHULTZ: My name is Dan Schultz. I am the  
2 Chief Medical Officer in the division, and I actually  
3 preceded Dr. Dawisha as the medical officer that was  
4 involved in this investigation.

5 I think the answer to your question is, number  
6 one, yes, we do consider it a device, let me make that very  
7 clear, and I think what you heard was a lot of theories as  
8 to how this may work and what it may be either taking out or  
9 putting back, but I think what we looked at three years ago  
10 or whenever this started, was very clearly a device that was  
11 doing something, and I think that devices certainly do do  
12 things as opposed to just looking and diagnosing, so I think  
13 that from our standpoint, there is no question that this is  
14 a device, and five years from now, 10 years from now, when  
15 all the various scientific studies are completed, we may  
16 reach a different conclusion, but I think at this point we  
17 can be very comfortable in calling this a device and  
18 regulating as a device.

19 In that light, I guess in terms of the  
20 requirements for numbers of studies, traditionally, yes, we  
21 have required at least a single, well-controlled, randomized  
22 study for devices as opposed to drugs, which have  
23 traditionally, and I think that may be changing as well,  
24 required multiple studies.

25 So, yes, the regulations are different, the law is

1 different, the drug law says, I think the word is  
2 substantial evidence of safety and effectiveness. The  
3 device law says reasonable evidence of safety and  
4 effectiveness. You can interpret that any way you want, but  
5 there is a difference in the law, and there has  
6 traditionally been a difference in the exact requirements  
7 for studies.

8           What is not different is the requirement for valid  
9 scientific evidence, and that is why you are here today,  
10 because I think what we want to hear from you is whether you  
11 consider this to be valid scientific evidence, whether it be  
12 one study, two studies, or 10 studies. I think that is the  
13 bottom line, and the question that you raise as to the  
14 robustness of the data, again, is something I think we are  
15 all very interested in hearing your opinions on.

16           Maybe I should stop there. Again, the decision  
17 that we were confronted with in January, when the company  
18 approached us and said, you know, the DSMB had made this  
19 determination and basically said that the data was so  
20 overwhelming at that point that it would be unethical to  
21 continue the trial, we did not feel that that was a decision  
22 that we could question in terms of the validity of that  
23 determination.

24           We were concerned, as you are obviously, about the  
25 numbers. We expressed that concern. The decision as to

1 whether to bring this forward to a panel for review was a  
2 decision that was made both by the company and by us, and we  
3 thought, we obviously believed that there is enough data  
4 here at least to warrant a thorough public discussion.  
5 Again, that is what we are here for, and that is what we  
6 hope to be listening to this afternoon.

7           May I ask another question?

8           DR. SCHULTZ: Sure.

9           DR. WHITE: It has to do with the placebo and the  
10 use of Sham, then, because it is something that I am also  
11 concerned, since it is clear and everybody says we have no  
12 idea how this works.

13           The Sham was to bypass the device. I would  
14 presume that what the sponsor would like us to believe is  
15 the Staph A in the device is what is responsible for the  
16 activity.

17           Was there consideration given in the design to  
18 pass things through the same device just minus the Staph A?  
19 I am concerned, as well about the meaning of what is  
20 actually doing things. We know what happens if you don't  
21 pass it through the device. We don't have any concept of  
22 what in the device is responsible.

23           DR. SCHULTZ: I believe, as a matter of fact, I  
24 think I can say definitively that I know that a lot of  
25 different trial designs were considered by the company. I

1 think probably there is somebody from the company that can  
2 answer that question better than I could, but I think that  
3 the answer to your question essentially is yes, that there  
4 were a lot of different ideas and that given all the  
5 possibilities and all the pluses and minuses of all those  
6 different trial designs, the company, including their  
7 advisers, felt that this was the most reliable in terms of  
8 trying to determine the efficacy of this device, but they  
9 probably have a lot more to say on that, and I would yield  
10 the podium to them unless you have any other questions for  
11 me.

12 DR. GENDREAU: Briefly, we did look at a lot of  
13 different ways we might be able to run a Sham control. It  
14 is not obvious the best way to do it. We did consider a  
15 proserver column without the protein A being coupled to the  
16 column. We looked at the logistics of doing that, and there  
17 were some technical issues with it. We had never  
18 manufactured a column without protein A. The silica matrix  
19 we use as kind of a special compound. It's a unique  
20 material, it is not just sand.

21 It goes through some processing steps where we do  
22 covalent chemistry. We do purifications. There was some  
23 concern about this would now be a new product that has never  
24 been toxicologically tested, it has never been sterilized in  
25 that format, probably a minor concern, but it was enough to

1 say that there is enough issues with that design and there  
2 is no obvious reason that that would be better than a shunt  
3 bypass, which we felt could be absolutely safe and  
4 absolutely reproducible.

5 We chose to go with something we could define  
6 completely.

7 DR. AGODOA: This is also for the FDA. In a  
8 device issue like this, is dose response not required?

9 DR. SCHULTZ: I guess the answer to that question  
10 is that for -- I mean devices is a very broad category of  
11 medical products, and I think that a lot of the devices that  
12 we regulate dose response is not an issue.

13 Obvious, in this particular case, and in cases  
14 like it, I guess what you are referring to is the question  
15 of looking at one treatments, two treatments, five  
16 treatments, 10 treatments, that was brought up before, and  
17 whether or not that would be either an interesting or a  
18 necessary component of the approval of this device, and, in  
19 fact, that is one of the questions that we are asking you  
20 specifically in terms of any kind of post-market study, you  
21 know, should you recommend approval for this device.

22 We obviously consider both the numbers of  
23 treatments and the duration of response and the issue of  
24 retreatments, and all these other questions, I think are  
25 very important questions. I think the sponsor has told you

1 how they came up with the number that they came up with,  
2 which was sort of more on an empirical basis than on I guess  
3 a strict scientific basis.

4 I guess what we felt, and I guess the question to  
5 be considered here today, is whether or not the device, as  
6 studied, is in fact safe and effective, not whether or not  
7 there may be another way that may be more safe and  
8 effective.

9 I think that that is a question, but I think there  
10 are two questions there, whether or not the way the device  
11 was used in this study and on these patients, whether or not  
12 that is, in fact, safe and effective, and then the other  
13 question is are there other ways to do it that may offer  
14 some additional advantages.

15 So, I guess the short answer to your question is  
16 no, in all instances we do not require dosing studies in the  
17 same way that the drugs people do.

18 DR. KALLOO: I have a sense here that the  
19 questions are getting along the lines of issues that the  
20 panel should be addressing, so what I would like to do is to  
21 move along to Dr. Clauw, who is the panel primary reviewer  
22 of this application to make his presentation.

23 **Panel Primary Reviewer**

24 DR. CLAUW: As usual, the FDA reviewers have done  
25 an excellent job of summarizing my findings, so I am really

1 going to try to limit what I say to comments that either  
2 haven't been brought forth already by the FDA or something  
3 that I think might need to be reinforced.

4           They are going to be in four general areas:  
5 First, overall study design; secondly, efficacy; third,  
6 safety; and then fourth, just touch on some of the other  
7 issues that the FDA asked us to address.

8           With respect to overall study design, I come from  
9 sort of the same background as being a rheumatologist as Dr.  
10 White, but the last five or six years I have been entirely  
11 on device panels, and I actually want to applaud the company  
12 for the best designed device study that I have ever seen as  
13 an FDA reviewer.

14           I think the company went to great lengths to make  
15 sure that there was blinding with respect to what was being  
16 used, and that isn't necessarily always the case with  
17 respect to device evaluations, and the other thing that I  
18 think that they went to great lengths to do was to make sure  
19 that a statistically significant improvement was a  
20 clinically meaningful improvement. Again, I would applaud  
21 them for that.

22           There is a couple of comments, though, I would  
23 like to make about the study design that I think are  
24 important. Again, one of them touches a little bit on what  
25 Dr. White just said.

1 I think we need to consider the fact that the Sham  
2 group in this study is not necessarily a placebo group. In  
3 fact, it is possible that the apheresis alone is somehow an  
4 active biological treatment. Now, I agree with Dr. White's  
5 comments that a 10 percent response rate is rather low in an  
6 RA trial, but this isn't an average RA trial.

7 These patients who have had 15 years of disease  
8 activity and have failed five and a half DMARDS are way  
9 different than we do in average RA trials, and especially  
10 during this early wash-out period that was involved where  
11 people were essentially taken off all of their medications,  
12 a 10 percent response rate in the "Sham" arm again may  
13 actually be an active treatment in some regards.

14 There is two reasons that I say this. One is that  
15 I am intrigued by this post-pheresis flare that occurs in  
16 equal frequency in both patients receiving the ProSORBA  
17 column and in patients receiving the Sham treatments.

18 This is a biologically active procedure that  
19 somehow is doing something to these patients. This is not a  
20 placebo response as we classically think of a placebo  
21 response.

22 The other thing that struck me is that if you look  
23 at the length of response amongst some of the Sham  
24 responders, some of these patients stayed well, continued to  
25 meet ACR criteria as responders for 20 weeks or more.

1 Again, something I really wouldn't have expected to see in a  
2 classic placebo response in people who were as severely  
3 affected, who have had disease as long as they have had, and  
4 who have failed as many DMARDS as these patients had failed.

5 So, one of the things we need to consider is that  
6 in some ways, this study set the bar up high for the active  
7 treatment to show superiority over pheresis because, in  
8 fact, part of the active treatment is the pheresis itself.

9 The second point I would like to make, and other  
10 people have made this, but again to reiterate this for non-  
11 rheumatologists, is how sick these patients are, and at  
12 least until recently, where now there is a couple other  
13 drugs that might theoretically be used in the same setting  
14 that Prosrba would be used in clinical practice, how little  
15 we have to offer patients who have failed five and a half  
16 DMARDS and who have had disease for 15 or 16 years.

17 Again, this is a group of patients who is very  
18 difficult to show any kind of clinical response in, and so,  
19 a 30 percent response rate is in many ways a tremendous  
20 response rate and a very high response rate given the  
21 population of patients who were being studied.

22 With respect to efficacy, then, I think that the  
23 sponsor has adequately demonstrated that this is an  
24 effective treatment in severe rheumatoid arthritis. I, like  
25 other clinical investigators, am somewhat troubled and

1 uncomfortable with the rather small numbers of patients  
2 studied, however, I am reassured by several data.

3           One is that the response rate was strikingly  
4 similar in all of the different trials that were done, the  
5 two pilot studies, as well as the early part of the pivotal  
6 trial, and was similar when the non-responders were then  
7 carried out in an open fashion in the end part of the  
8 pivotal trial, the so-called continuation data set. That to  
9 me was very reassuring that what we are seeing here is not  
10 something that is occurring by chance.

11           The other thing that was heartening was that there  
12 seemed to be a parallel improvement in nearly all of the  
13 outcome measures in the Prosorba group, again, not something  
14 that you would have expected if we were just seeing a chance  
15 occurrence of a good outcome in people who were receiving  
16 the treatment because of the fact that the sample size was  
17 too small.

18           With respect to safety, I think the Prosorba  
19 column has likewise been demonstrated to be relatively safe.  
20 I use the term "relatively" because again we need to  
21 recognize what this group of patients otherwise would have  
22 been subjected to had they not received treatment with the  
23 Prosorba column.

24           I don't think there is any way of comparing apples  
25 to apples, but I suspect that the adverse events that were

1 seen in the ProSORBA group were about the same, if not even  
2 less, than the adverse events that would be seen with the  
3 six, seventh, and eighth DMARD in people that have 15 years  
4 of disease activity and this severity of rheumatoid  
5 arthritis.

6           So, is this an absolutely safe product or  
7 absolutely safe device? No. Is it relatively safe given  
8 the other treatment options that we have for this set of  
9 patients? Yes.

10           Now, just two minor points with respect to other  
11 things that the FDA asked us to address. I agree that our  
12 absence of knowledge about the mechanism of action of this  
13 device should not make us reluctant to approve it. There is  
14 virtually no disease modifying drug where we are entirely  
15 comfortable where we know the mechanism of action.

16           However, one of the things I would encourage the  
17 sponsor to consider is that non-immunologic mechanisms might  
18 be operative in effecting the improvement seen in these  
19 patients. There is tendency on behalf of rheumatologists  
20 and on behalf of immunologists to think that the immune  
21 system is the center of the universe, but as someone who  
22 studies rheumatology patients in non-immune manners and  
23 looks at mechanisms of pain and looks at mechanisms of  
24 fatigue, there is a lot of non-immunologic, neuroendocrine,  
25 neurotransmitter changes that could be affected by either

1 apheresis itself or by passing plasma over the ProSORBA  
2 column that could potentially be responsible for the types  
3 of improvements that are being seen in these patients,  
4 especially when I heard a couple of the investigators, as  
5 Dr. Furst explained how the clinical improvement occurred,  
6 that it was really more of a subjective improvement in  
7 fatigue and a subjective improvement in sort of an overall  
8 sense of well being of the patient before they saw any more  
9 objective improvement, and, in fact, if you look at the  
10 data, even at the end of the study, the objective  
11 improvement in things like swollen joints was pretty modest  
12 compared to the subjective improvement in things like  
13 painful joints and global improvements in patient status,  
14 whether it be patient global status or physician global  
15 status.

16           Now, the final thing I have to say, the only  
17 negative thing I have to say about the study or the sponsor,  
18 and that is about the Phase IV study that is being proposed.  
19 They have already indicated that it is open to discussion,  
20 and I think that they need a lot of discussion about how  
21 they do this Phase IV study.

22           I don't like the study at all. I don't think it  
23 is going to do what you are trying to do. There is a number  
24 of problems with the design, not the least of which is if  
25 you use an intent-to-treat analysis and you take a group of

1 people who you define as being unresponsive or minimally  
2 responsive to methotrexate, and then you require that they  
3 stay in the study for five months longer, and if they drop  
4 out of the study, they are counted a non-responder, you are  
5 tremendously biasing the study towards showing a benefit of  
6 the group that receives the Prosorba column.

7           What I would suggest to the sponsor -- and again  
8 this is not something that rheumatologists are very  
9 comfortable with, it is something that is rarely done in  
10 classic drug trials -- is more of an effectiveness design  
11 rather than an efficacy design.

12           An efficacy design again is what we usually use to  
13 evaluate drugs, and that is where the comparison group is  
14 very tightly controlled and you try to only have essentially  
15 one variable that is different in the patients and the non-  
16 patients, and that is the variable that you are trying to  
17 study.

18           What I would propose to the sponsor is a very  
19 simple effectiveness study wherein a group of patients with  
20 moderate to severe rheumatoid arthritis gets randomized  
21 either to receive the Prosorba column or not receive the  
22 Prosorba column, both groups get usual and customary care,  
23 and you look at the efficacy, the safety, the cost, and you  
24 compare these two groups with respect to what really is the  
25 incremental benefit in all regards to adding the Prosorba

1 column.

2 That will approximate how this product is going to  
3 be used in clinical practice, and I really can't think of an  
4 efficacy design, a classic drug design that is going to do  
5 any better than that type of design as far as trying to look  
6 at the issues that you are trying to look at it.

7 So, I will end there. Thank you.

8 DR. KALLOO: Thank you, Dr. Clauw.

9 Any comments or questions from the panel?

10 [No response.]

11 DR. KALLOO: Then, I would like to ask Dr. Provost  
12 to present the questions that the FDA would like the panel  
13 to discuss.

14 DR. JANOSKY: Excuse. I had asked a question of  
15 the sponsor, and are you prepared to answer that question?

16 DR. KALLOO: Could you repeat the question?

17 DR. JANOSKY: Sure. I wanted to find out about  
18 the analysis of covariance looking at prior disease duration  
19 on the primary outcome, and the response was that you had  
20 that information and you were going to get it.

21 DR. GENDREAU: We have just got to turn the  
22 projector on. It will take a second. I am going to ask  
23 Mike Thorn to address it. He is our statistician, and he  
24 did the analysis, and he can explain the outcome.

25 DR. THORN: My name is Mike Thorn and I am the

1 independent consultant who has been working with Cypress  
2 over the duration of this project.

3           The concern that we had was trying to define the  
4 set of variables that would be likely to predict which  
5 patients are responding, and also one of the concerns that  
6 we also noticed was that imbalance in the duration of  
7 disease between the two treatment groups at baseline.

8           So, what we did was to do a regression analysis, a  
9 logistic regression analysis taking the endpoint be either  
10 responders or non-responders by the ACR criteria that was  
11 used and put in each of the baseline variables that were  
12 noted in the demographics, in addition, each of the  
13 individual ACR component criteria.

14           [Slide.]

15           What we found -- and this is actually the set of  
16 variables that we used in the model -- was that the only  
17 thing that was able to predict whether or not a patient was  
18 a responder or not was the treatment that the patient was  
19 assigned to.

20           Physician assessment of disease also turned out to  
21 be close to significant, but no other variable in the model  
22 entered into that including the duration of disease, prior  
23 disease, what you will see is the second to the bottom  
24 variable in that list.

25           So, from that I would conclude that even though we

1 have an apparent imbalance in the duration of disease at  
2 baseline, it did not appear to confound the results that we  
3 noted.

4 DR. JANOSKY: Thank you for showing us those  
5 results, but actually the question is just looking at that  
6 one covariate. Given the number of subjects that you have,  
7 you are losing quite a number of degrees of freedom if you  
8 are putting these all in concomitantly.

9 So, one concern is you don't have enough power to  
10 do this analysis. So, what if you just look at the  
11 imbalance, the prior disease duration as a covariate, do you  
12 have that analysis where you are looking at responders, non-  
13 responders as the outcome group assignment.

14 DR. THORN: With each individual separately.

15 DR. JANOSKY: Right, exactly, with prior disease  
16 duration as the covariate. Am I making myself clear?

17 DR. THORN: Yes.

18 DR. FURST: I don't think we are going to be able  
19 to answer this thing statistically in any way because the  
20 numbers really are small, but if you remember that one slide  
21 that I showed where there was a group of patients treated  
22 with other DMARDS by duration, where the slope was generally  
23 downward, and a few points with the Prosorba patients where  
24 the slope was relatively stable by duration.

25 It seemed to me to indicate that the duration of

1 disease did not affect the percent of patients responding.

2 DR. JANOSKY: But that is also taking into account  
3 the number of previous treatments. Again, you are losing  
4 degrees of freedom by putting that variable in that model.

5 DR. FURST: I am not sure. Did it include  
6 background number of DMARDS?

7 DR. JANOSKY: If you are saying number of prior  
8 DMARDS, prior disease duration.

9 [Slide.]

10 DR. FURST: This one. The red line just refers to  
11 a bunch of studies in DMARD treated patients, not previous  
12 numbers of DMARDS.

13 DR. JANOSKY: Right.

14 DR. FURST: So, that red line just says this is  
15 your control group.

16 DR. JANOSKY: Right, but that is not the question.

17 DR. FURST: Right, but the blue line is the  
18 question, I think.

19 DR. JANOSKY: No, it's not. If you look at what  
20 you had on page 26, and it was a point that you were making,  
21 not you personally, but the sponsor was making numerous  
22 times is that the average prior disease duration was five  
23 years overall, but you do have substantial, probably half a  
24 decade difference between the Sham group and the ProSORBA  
25 group in terms of prior disease duration.

1           So, an analysis that is very straightforward, that  
2 would answer this question, would be to use that as a  
3 covariate looking at the outcome.

4           DR. FELSON: And actually we did that.

5           DR. JANOSKY: Do you have those results?

6           DR. FELSON: I don't have the results. It was  
7 done in the intent-to-treat analysis and presented to the  
8 DSMB at the time because we already had anticipated the  
9 disease duration would be important.

10           It does get at the issue of there being multiple  
11 data sets here with different patients characterized as  
12 improvers in each one. It doesn't matter at all to the p-  
13 value, and the reason it doesn't is because of the blue  
14 curve you see there, forget the red one, which is from a lot  
15 of other studies, it relates to the fact that in this  
16 particular trial, unlike almost every other, the response  
17 rates were actually higher in those with very long disease  
18 duration although they were not really different.

19           So, it went in the opposite direction of almost  
20 every other trial. So, it doesn't really change the results  
21 at all. When you just put disease duration in and  
22 treatment, and look in a logistic or survival curve -- I  
23 think we did in a logistic -- look in a logistic as to  
24 whether treatment remains a significant predictor of  
25 response once adjusting for disease duration doesn't matter.

1 DR. JANOSKY: And you don't have those to show us,  
2 right, but that is your recollection?

3 DR. FELSON: I don't have those to show you. In  
4 fact, they weren't done as a modified -- I can tell you they  
5 weren't done as modified as treated. They were done for the  
6 original DSMB as an intent-to-treat, and they didn't change  
7 the p-value that we saw in the intent-to-treat analysis. I  
8 really couldn't tell you whether they would change this p-  
9 value, but I don't think they would because the trend is  
10 really not in the right direction to have a confounding  
11 effect on the primary result of the trial.

12 DR. JANOSKY: Actually, it's preferential for the  
13 Prosorba. You have less prior disease duration in the  
14 Prosorba.

15 DR. FELSON: I understand that, but what I was  
16 saying is that for that to be a confounder, you would have  
17 to show that with longer disease duration in this particular  
18 trial, there was less response. In fact, in this particular  
19 trial, the effect is ironically different than that, and you  
20 can see that from the blue curve, that in this particular  
21 trial, the longer disease duration actually goes along with  
22 slightly higher response rates.

23 DR. JANOSKY: Right, I see that, but these data  
24 are not actually getting at the question, but that is  
25 sufficient. Thank you.

1 DR. KALLOO: Thank you.

2 Any other questions or comments? Then, Dr.  
3 Provost, if you could look at the questions that the panel  
4 need to address.

5 **Questions for Panel Consideration**

6 DR. PROVOST: Questions concerning safety. The  
7 adverse events observed during the randomized and open label  
8 studies were typical of those seen for patients treated with  
9 apheresis. No statistical differences were noted in the  
10 frequency of adverse events between the Sham and the  
11 ProSORBA arms.

12 However, given that most RA patients are not  
13 usually treated with apheresis, all adverse events must be  
14 considered in assessing risk/benefit, regardless of whether  
15 they occurred with the same frequency in the Sham arm.

16 Therefore, we would like the panel to address the  
17 following:

18 a. Please comment on the frequency and severity  
19 of the adverse events, for example, sepsis, anemia,  
20 hypersensitivity, hypotension, nausea, et cetera.

21 b. A decline in hemoglobin, hematocrit, and MCV  
22 was noted for patients in both the Sham and ProSORBA arms  
23 that was attributed to the apheresis procedure. We would  
24 like the panel to comment on the clinical significance of  
25 this finding, especially considering that many RA patients

1 already suffer from anemia of chronic illness and chronic  
2 fatigue.

3 c. In the randomized study, 5 patients developed  
4 sepsis. We would like the panel to comment on the clinical  
5 significance of this result, especially considering that RA  
6 patients are immunocompromised and may be taking  
7 immunosuppressive agents.

8 d. Finally, we would like to hear your discussion  
9 of any other safety concerns that you may have.

10 The second question concerns the effectiveness.  
11 The sponsor has provided data from a prospective,  
12 multicenter, randomized, Sham-controlled trial of 109  
13 patients with severe, active RA. The data demonstrate a  
14 statistically different response rate of approximately 29  
15 percent for the ProSORBA group as compared to 11 percent for  
16 the Sham group.

17 Are these data adequate to demonstrate the  
18 clinical effectiveness of the therapy for the therapeutic  
19 reduction of the signs and symptoms of rheumatoid arthritis?

20 a. We would like to hear your comments on the  
21 adequacy of the proposed Indication for Use statement that  
22 is, "Indicated for the therapeutic reduction in the signs  
23 and symptoms of rheumatoid arthritis in patients who have  
24 failed disease-modifying anti-rheumatic drugs or DMARDs,  
25 such as methotrexate, sulfasalazine, hydroxychloroquine or

1 gold." Does this indication properly reflect the subset of  
2 RA patients for which this therapy may be appropriate?

3           b. Next, we would like to hear your discussion of  
4 any modifications of the Indication for Use statement that  
5 you believe may more accurately reflect the data provided in  
6 the PMA. For example, you may want to consider the  
7 following issues: disease activity and severity;  
8 indications for this therapy relative to currently available  
9 DMARDS and other therapeutic agents; duration of disease,  
10 that is, greater than X number of years; and duration of  
11 effect, that is, short-term management of signs and  
12 symptoms.

13           The next question concerns labeling. We would  
14 like to hear your comments on the following labeling issues.

15           a. First, what information relating to the risk  
16 of developing or exacerbating anemia should be included in  
17 the labeling?

18           b. Next, in the randomized study, 5 of the 9  
19 patients who received central lines experienced  
20 complications related to their use, including thrombosis,  
21 infection, and sepsis, in one case leading to death.

22           What information should be provided in the  
23 labeling regarding the high potential for severe  
24 complications for any patient with inadequate peripheral  
25 venous access requiring a central line?

1           Finally, are there any issues not adequately  
2 addressed by the data in the PMA supplement that require a  
3 mandated post-market study? For example, duration of  
4 response; retreatment with the ProSORBA column; use of  
5 ProSORBA in combination with other DMARDs, for example,  
6 methotrexate; use of ProSORBA in an expanded treatment  
7 population, for example, early RA or less active disease;  
8 mechanism of action studies, for example, ACR responder/non-  
9 responder analyses, HLA markers, or serological testing; and  
10 a study of post-arthritis flares, which have been described  
11 by the sponsor, as you have heard, as increased pain and  
12 fatigue lasting from 12 to 72 hours after treatment.

13           Thank you.

14           DR. KALLOO: Thank you. For the members on the  
15 panel, these questions are on this, so you may want to use  
16 this to refer as we go along. The plan is that we will take  
17 each question in turn, and I will re-read the question.  
18 Some of these questions have several parts, and I will  
19 attempt to take it part by part, and get a response from  
20 each panelist.

21           At the end, Dr. Clauw has the admirable task of  
22 doing a summary of the comments.

23           We will start with Question No. 1. I will read it  
24 first, and I will ask the first part, and we will go around  
25 to each panelist.

1           The adverse events observed during the randomized  
2 and open label studies were typical of those seen for  
3 patients treated with apheresis. No statistical differences  
4 were noted in the frequency of adverse events between the  
5 Sham and the ProSORBA arms.

6           However, given that most RA patients are not  
7 usually treated with apheresis, all adverse events must be  
8 considered in assessing risk/benefit, regardless of whether  
9 they occurred with the same frequency in the Sham arm.

10           Therefore, please address the following:

11           a. Please comment on the frequency and severity  
12 of the adverse events, for example, sepsis, anemia,  
13 hypersensitivity, hypotension, and nausea.

14           I will start on my right and I will go around. If  
15 there are any comments on the frequency and severity.

16           DR. LIANG: I think the sepsis, without question,  
17 that is of great concern. The patient would not normally  
18 get access without this procedure, so that is the one that  
19 is of most concern to me, I think.

20           DR. AGODOA: My impression is that there is an  
21 awful lot of adverse events in both the treated and the Sham  
22 group in individuals who are already severely compromised in  
23 many ways, and I am concerned particularly, as mentioned  
24 earlier, about the sepsis and the catheter issues that  
25 actually we will be addressing separately later on. So,

1 yes, I am concerned.

2 DR. VERTUNO: I think the issue of sepsis and  
3 anemia need to be discussed separately. The other  
4 incidences have been observed with this kind of therapy for  
5 many years, although their etiology may not be well  
6 understood, they are short lived and self-limited, and their  
7 management is well understood, so save for the infection and  
8 anemia, I am not troubled by the other complications of the  
9 procedure.

10 DR. HAWES: Nothing besides that. I agree with  
11 the last comment.

12 DR. FOOTE: The same here. It appears that aside  
13 from the sepsis and anemia, the other side effects are  
14 fairly nonspecific and may be expected in this type of  
15 population.

16 DR. WHITE: I would say that the anemia probably  
17 can be dealt with as can the others that follow it. I  
18 remained concerned about sepsis. I still don't have a good  
19 sense whether or not the incidents of sepsis during the  
20 period of the procedure was higher than would be expected in  
21 an untreated group of rheumatoid patients.

22 DR. STEINBACH: No comment.

23 DR. JANOSKY: Nothing to add.

24 DR. BOULWARE: Nothing.

25 DR. HORTIN: I have a safety issue that wasn't

1 listed here. It relates to the indications for use. It  
2 wasn't completely clear to me, and we will get that in the  
3 next section, whether this will be indicated specifically  
4 for use without other DMARDS being applied, and I didn't  
5 know whether that posed a significant risk in terms of  
6 worsening the disease of patients by taking them off other  
7 medications. I know this is supposed to be for patients who  
8 basically have been failing other treatments.

9 DR. KALLOO: I think that will be brought up, but  
10 specifically on the frequency and severity of the adverse  
11 events. Do you have any comments? We will get to that  
12 issue.

13 DR. HORTIN: Nothing related to these issues  
14 specifically.

15 DR. KALLOO: Dr. Clauw, do you want to summarize  
16 or do you want to wait until the end of this whole section?

17 DR. CLAUW: I think this one is easy, so I will  
18 summarize this. What I would say in summary is the adverse  
19 events associated with this device are generally self-  
20 limited except for the frequency of sepsis and perhaps  
21 anemia.

22 DR. KALLOO: The second part of the question,  
23 which I think will add, we will go into further details into  
24 some of the issues that were discussed.

25 A decline in hemoglobin, hematocrit, and MCV was

1 noted for patients in both the Sham and ProSORBA arms that  
2 was attributed to the apheresis procedure. Please comment  
3 on the clinical significance of this finding, especially  
4 considering that many RA patients already suffer from anemia  
5 of chronic illness and chronic fatigue.

6 DR. LIANG: It is a little significant to be dealt  
7 with, and as long as we know the possibility, I think these  
8 things can be managed adequately.

9 DR. AGODOA: I agree. I think this can be  
10 adequately dealt with, and I am not so concerned about this.

11 DR. VERTUNO: I was surprised by that, and I think  
12 the etiology of it needs to be investigated further. We  
13 don't want this group of patients to wind up getting  
14 multiply transfused, and I would be very interested in  
15 whether EPL is effective or not.

16 DR. HAWES: I would agree with the earlier two  
17 comments. It seems to not have had any long-term sequelae  
18 and could be dealt with without any problem.

19 DR. FOOTE: I would agree with the previous  
20 comment. I was especially impressed that even though anemia  
21 was appreciated, it was dealt with by blood transfusion in  
22 only one patient who had a blood transfusion, and then just  
23 several of the other patients required EPL, which is not  
24 that invasive a therapy.

25 DR. WHITE: I agree. It is a manageable issue.

1 DR. STEINBACH: No additional comment.

2 DR. JANOSKY: No additional comment.

3 DR. BOULWARE: I guess my only concern would be  
4 the duration of treatment for this. We know the severity of  
5 anemia for 12 weeks or 12 treatments, but if this goes on  
6 further and further, we don't have that, and perhaps some  
7 more explicit warning, I guess, regarding it, but I do think  
8 it can be treated and handled.

9 DR. HORTIN: No additional comment.

10 DR. KALLOO: Dr. Clauw?

11 DR. CLAUW: Again, this is a summary, and not my  
12 independent comment. The anemia associated with this device  
13 is generally mild and can typically be easily managed, but  
14 it would be helpful if the mechanism of this adverse event  
15 were known.

16 DR. KALLOO: The third part of this question.

17 In the randomized study, 5 patients developed  
18 sepsis. Please comment on the clinical significance of this  
19 result, especially considering that RA patients are  
20 immunocompromised and may be taking immunosuppressive  
21 agents.

22 DR. LIANG: It is obviously serious. As one  
23 commenter said earlier, it is likely once it gets out of the  
24 box, that patients are going to be treated with other  
25 medications that should make their immunocompromise even

1 worse, and plus the fact that as we heard, and was seen in  
2 the trial, a lot of these patients are also getting  
3 hardware, which will be another complication or a place that  
4 can be seeded.

5 DR. AGODOA: I think this is probably the most  
6 bothersome for me, this sepsis, that is a high number of  
7 individuals with sepsis, which is potentially lethal and  
8 fatal. Whether this is all due to the patients being  
9 immunocompromised or poor care of the access, because this  
10 group of medical staff may not be used to this kind of  
11 procedure and may not be very careful about this, but then  
12 if this goes public and more and more inexperienced people  
13 are using this therapy, we are going to see more and more  
14 sepsis and perhaps more deaths, so this is one area that I  
15 think needs particular attention.

16 DR. VERTUNO: If this treatment becomes widely  
17 available, the pressure to use central lines for patient  
18 convenience and personnel convenience will be considerable,  
19 and it will be need to be resisted at all costs.

20 DR. HAWES: I would agree with prior comments. It  
21 seems that we can't really subscribe the sepsis to the  
22 Prosorba, which is the subject of the discussion today, but  
23 I think that serious consideration will have to be made with  
24 the way we instruct people on the use of this column, maybe  
25 to the extent of making it an absolute contraindication that

1 people use central lines.

2 I would echo what was said earlier, and that is  
3 that I am always concerned about these kind of results in  
4 basically a desperate population, and the expanded use of a  
5 device and the problems that can occur, and the substantive  
6 issue, if it gets out of control, obviously, it will have  
7 devastating effects. So, I think that again to me, it  
8 doesn't appear to be due to the column itself, but I think  
9 that we are going to have to make serious considerations  
10 about the labeling and how the blood access is obtained.

11 DR. FOOTE: I would agree with the above. It  
12 appears that the access issue is associated with the sepsis,  
13 and not the column itself, and that is where the labeling  
14 should be specific.

15 DR. WHITE: Infection is a major cause of death in  
16 rheumatoid arthritis. Anything that will increase the risk  
17 of infection is very significant.

18 DR. STEINBACH: No additional comment.

19 DR. JANOSKY: Nothing to add.

20 DR. BOULWARE: Nothing further.

21 DR. HORTIN: As already noted, the main problem  
22 appears to be with access, and I think this is a relatively  
23 special population that has had many years of treatment and  
24 many prosthetic procedures.

25 Without having some control data about what the

1 baseline level of sepsis would be, we might be  
2 overexaggerating the problem, that this is going to be a  
3 relatively high risk group to start with, and it may be that  
4 this level of sepsis, I do not know whether this would  
5 represent kind of a typical baseline or not, so it is a  
6 little bit hard for me to evaluate, but I think that it is  
7 probably related mainly to the access issue.

8 DR. KALLOO: Before we get a summary, I would like  
9 to take that a little bit further because the sepsis and  
10 death is a significant problem, and a comment was made about  
11 maybe this should be contraindicated, and I would just like  
12 to get the panel's comments on how strongly they feel if  
13 this should be a contraindication, if I can just get a quick  
14 comment about the use of central access as a  
15 contraindication.

16 DR. LIANG: It is hard to say. You are asking us  
17 to use the evidence, but then that is what you are  
18 presenting us with.

19 DR. KALLOO: Correct, based on the evidence that  
20 you have.

21 DR. LIANG: I guess you might say that in the  
22 limited experience to date, the principal problems have  
23 occurred with a central line. I am not so sure that you can  
24 go so strong and say it is an absolute contraindication, but  
25 you certainly have to warn the provider and the patients

1 about the problems that we have experienced in these earlier  
2 trials.

3 DR. AGODOA: Based on the evidence we have here, I  
4 would say it is a contraindication.

5 DR. VERTUNO: I don't think you can say it's an  
6 absolute contraindication, however.

7 DR. HAWES: Based on the data, I would say yes.

8 DR. FOOTE: I feel strongly that it should not be  
9 a contraindication. I take an example that you may have a  
10 patient that is undergoing treatment and doing well, and  
11 then again, you have someone who has had multiple  
12 operations, they develop a problem with the venous access.  
13 I think it should be a warning, and not a contraindication  
14 because what you are saying is that if that patient in the  
15 middle of treatment develops a problem with access, that the  
16 patient has to stop treatment, and I don't think that would  
17 be fair.

18 DR. WHITE: I think the only data we have are  
19 sparse. There are two patients perhaps that had medically  
20 significant infections with the central line. My feeling is  
21 that is not enough for me to feel comfortable saying it is  
22 an absolute contraindication.

23 DR. STEINBACH: I think in view of the few number  
24 of patients involved, I don't think it is an absolute  
25 contraindication, and certainly it should be a warning.

1 DR. JANOSKY: No to contraindication; yes to a  
2 trailing or a warning.

3 DR. BOULWARE: Yes to a warning; no to a  
4 contraindication.

5 DR. HORTIN: I agree that it should be a warning,  
6 but no contraindication.

7 DR. KALLOO: Dan, do you want to make your  
8 comments and then summarize?

9 DR. CLAUW: I don't have any comments. What I  
10 would summarize is to say that sepsis is a severe adverse  
11 event that is likely associated with the pheresis procedure  
12 rather than the Prosorba device, and this may be accentuated  
13 by using central venous access.

14 Labeling should strongly indicate this caution to  
15 both the patient and the health care provider, and there is  
16 no unanimity amongst the panel about whether there should be  
17 an absolute contraindication to using central venous access.

18 DR. KALLOO: Any other safety concerns in addition  
19 or beyond what we have spoken about?

20 DR. LIANG: None.

21 DR. AGODOA: None other.

22 DR. VERTUNO: None.

23 DR. HAWES: None..

24 DR. FOOTE: None.

25 DR. WHITE: None.

1 DR. STEINBACH: None.

2 DR. JANOSKY: None.

3 DR. BOULWARE: None.

4 DR. HORTIN: The manufacturer mentioned some other  
5 contraindications that were standard ones. I don't recall  
6 seeing those listed or discussed. In the presentation, they  
7 were mentioned, the ACE inhibitor, and others.

8 DR. KALLOO: There was a whole list of  
9 contraindications.

10 DR. HORTIN: And the anticoagulation, so  
11 basically, the existing contraindications that they have  
12 listed.

13 DR. KALLOO: Dr. Clauw, could you summarize?

14 DR. CLAUW: The ProSORBA device should have all of  
15 the same contraindications as for the other indications of  
16 this product.

17 DR. KALLOO: Moving on to Question 2.

18 The second question concerns the effectiveness.  
19 The sponsor has provided data from a prospective,  
20 multicenter, randomized, Sham-controlled trial of 109  
21 patients with severe, active RA. The data demonstrate a  
22 statistically different response rate of approximately 29  
23 percent for the ProSORBA group as compared to 11 percent for  
24 the Sham group.

25 Are these data adequate to demonstrate the

1 clinical effectiveness of the therapy for the therapeutic  
2 reduction of the signs and symptoms of rheumatoid arthritis?

3 a. Please comment on the adequacy of the proposed  
4 Indication for Use statement that is, "Indicated for the  
5 therapeutic reduction in the signs and symptoms of  
6 rheumatoid arthritis in patients who have failed disease-  
7 modifying anti-rheumatic drugs," such as listed here.

8 Does this indication properly reflect the subset  
9 of RA patients for which this therapy may be appropriate?

10 DR. LIANG: This is the bottom line. I think that  
11 the sponsors have demonstrated this is an effective drug, it  
12 has got a small buzz, but in this group of patients, a small  
13 difference can be a big difference in the individual as we  
14 have heard from the patients and also from our own  
15 experience, I think. It is a really artificial situation.  
16 We have stopped someone's DMARDS and they are flaring, but I  
17 think that they have made the case for this indication.

18 DR. AGODOA: I think their presentation is  
19 convincing, the numbers that they have provided, but I am  
20 still concerned about the small number, total number of  
21 patients examined, and the total number in the three studies  
22 that they presented. So, I am lukewarm.

23 DR. VERTUNO: The efficacy is small and  
24 incremental, but appears to be definite.

25 DR. HAWES: I think they have shown efficacy under

1 the conditions of the trial. I think my concern, speaking  
2 as a gastroenterologist and relying on the rheumatology  
3 people in the group, is that it is an extremely artificial  
4 situation. They are asking for us to approve a device for  
5 people that have failed, but likely are going to be  
6 continuing a lot of those things even though they are deemed  
7 as a failure.

8           So, I think that is my only concern, that to  
9 actually follow this indication for use, it seems to me that  
10 we are going to be asking rheumatologists to stop all of the  
11 other DMARDS that they are on and then begin the ProSORBA,  
12 but that is, in fact, probably not going to happen. They  
13 are just going to add the ProSORBA on, and that is my  
14 concern.

15           DR. FOOTE: My reading of this description does  
16 not indicate that the clinician would be required to stop  
17 any additional DMARDS. In fact, I was impressed that in the  
18 Sham group, those patients, 11 percent of those patients  
19 actually a little bit better, which made me think that these  
20 DMARDS may have more significant side effects for a subset  
21 of patients.

22           I think, in summary, I would say I think this is  
23 adequate, and I would agree with use of this statement in  
24 labeling.

25           DR. WHITE: I have a slightly different take on

1 this, and I feel I am put in a quandary, because I think we  
2 have two standards. We have the standard of the Device  
3 group, which is one trial that shows reasonable efficacy.  
4 We have the standards that have been set forth and are  
5 usually used for therapeutic reduction in signs and symptoms  
6 of rheumatoid arthritis, and those standards are different,  
7 at least as applied in the Arthritis Advisory Panel than  
8 what the Device Section has.

9           So, in fact, I feel in a real quandary. If you  
10 say do you have a trial that is reasonable to think showed a  
11 statistical difference, yeah, they probably have it,  
12 although there are some concerns.

13           If you say, would you apply the usual standards  
14 that might come up in the Arthritis Advisory group where we  
15 usually require two trials, I have major concerns about the  
16 robustness of this data, and my view is we ought to take the  
17 higher set of standards given that this is going to be  
18 applied to an enormous number of patients in a much less  
19 controlled setting.

20           DR. STEINBACH: I think it should be pointed out  
21 that the test was done without other DMARDS, and patients  
22 have told us that they would like to be off the other DMARDS  
23 because of side effects, so I don't think that is totally  
24 unrealistic. Probably this is more a product labeling in  
25 the sense that the effectiveness is for no other DMARDS.

1 DR. JANOSKY: I will answer in relation to the  
2 Indication for Use statement as appears on this overhead.  
3 First, a question, though. If you state that the patients  
4 have failed the DMARDS, does that imply that they are RA  
5 function class II or III, or is it possible that they could  
6 be class I and still have failed?

7 DR. KALLOO: I am gastroenterologist.

8 DR. JANOSKY: I don't know the answer to the  
9 question, so I need to pose it to panel.

10 DR. CLAUW: Yes.

11 DR. JANOSKY: It implies that they would be class  
12 II or III?

13 DR. CLAUW: No.

14 DR. JANOSKY: They could be class I?

15 DR. BOULWARE: Yes. There is a trend now for  
16 people to start using DMARDS at a very early disease, so not  
17 necessarily does that mean if somebody failed a DMARD is a  
18 class III.

19 DR. JANOSKY: In light of that response, I would  
20 suggest that the Indication for Use statement also include a  
21 classification of RA functional class II or III, because  
22 those were the patients that were actually studied. That  
23 would be the addition.

24 DR. BOULWARE: I also interpreted your request for  
25 a comment very literally, and based on the evidence that we

1 have here today, and what we really saw were not just  
2 patients with rheumatoid arthritis, but people who had long-  
3 term disease duration, more than what would be expected in  
4 just a general rheumatology population.

5 We also saw people who had failed multiple DMARDS,  
6 well, with the exception of just methotrexate, and we also  
7 saw it where the device was used alone and not in  
8 combination with a disease-modifying drug, and as a  
9 practicing rheumatologist, I think it would be very hard for  
10 me to convince the patient to stop a disease-modifying drug  
11 they are using, which may not be totally effective, but  
12 partially effective in order to switch to this.

13 I am a little uncomfortable and the only data we  
14 have is that of the device alone, and not in combination  
15 with a drug. More than likely my suspicion is it would work  
16 and that 29 percent efficacy may be added on to what we  
17 have, but there is no evidence here that supports that.  
18 That is speculation on my part.

19 DR. HORTIN: I share concerns about what the  
20 effect is going to be in combination. We have no way to  
21 predict what is going to happen in that situation, and I  
22 think this indication should state the disease  
23 classification, either the class II or III.

24 The point Dr. White brought up, I tend to agree  
25 that we don't fully understand the mechanism of action of

1 this device, but our best hypothesis at the moment is that  
2 basically it is a drug delivery device, that is delivering  
3 metered amounts of small amounts of material coming off, and  
4 I think that the standards that should be applied maybe more  
5 appropriately would have been those of a drug delivery  
6 device. As Dr. White mentioned, I would consider that we  
7 don't know for sure, but it may be misclassified somewhat as  
8 a traditional device.

9 DR. KALLOO: Dr. Clauw, I do not envy you.

10 DR. CLAUW: It is not that I have no independent  
11 thought, but it happens to be redundant, so let me try this  
12 as far as a summary.

13 The sponsors have demonstrated a marginal efficacy  
14 of this product in a highly selected cohort of patient with  
15 long-standing, RA refractory to treatment. The labeling  
16 should somehow indicate that only patients with moderate to  
17 severe RA receive treatment with this device.

18 How do people think about that? This is the first  
19 one that I don't feel entirely comfortable that I captured  
20 it.

21 DR. LIANG: Would you repeat the last sentence?

22 DR. CLAUW: Sure. The labeling should somehow  
23 indicate that only patients with moderate to severe RA  
24 receive treatment with this device.

25 Here is my first independent thought in this part

1 of the program. I am not sure that we put class II and III  
2 because I think a lot of practicing rheumatologists don't  
3 necessarily use those classification criteria.

4 Maybe this is better left until the next area  
5 where we are actually going to talk about some of these  
6 issues, but somehow I think there is sentiment amongst many  
7 members of the panel that we have to indicate that this is  
8 used in people with more severe rheumatoid arthritis.

9 DR. KALLOO: I think the next part of the question  
10 will address some of those issues, and I think you have  
11 actually done an excellent summary.

12 The next part is please discuss any modifications  
13 of the Indication for Use statement that you believe may  
14 more accurately reflect the data provided in the PMA. For  
15 example, you may want to consider the following issues:  
16 disease activity and severity; indications for this therapy  
17 relative to currently available DMARDS and other therapeutic  
18 agents; duration of disease, duration of effect.

19 DR. LIANG: I think we need to get the wording  
20 down for this co-therapy that is going to inevitably be  
21 used. I mean this is the real life situation, and I would  
22 be trying to be really explicit about what data is  
23 available, which is in a very sort of special sort of  
24 situation where drugs are withdrawn, and to say that what is  
25 known about its use with other DMARDS is really not known,

1 and just say it like that, because I think it might be more  
2 efficacious, but it also may produce more toxicity, and all  
3 of these things are unstudied.

4 I am not sure that using the functional classes  
5 will help one way or the other. I don't think it is going  
6 to accomplish anything, because what the patient and the  
7 doctor believe is active and severe, is their own judgment.

8 DR. KALLOO: But what do you believe?

9 DR. LIANG: I think if this thing is as safe as we  
10 think outside of the central catheter, I could imagine it  
11 being used as bridge therapy, for instance, in milder  
12 disease with less structural damage as a way to buy time,  
13 especially if you have a prolonged effect.

14 I just think these are sort of untested  
15 applications.

16 DR. KALLOO: Again, the comments, but again we  
17 have to use the data that we have, as well, to make our  
18 decisions.

19 DR. AGODOA: I think the disease activity and  
20 severity, based on the data that we are presented will need  
21 to be emphasized that this is as was summarized previously a  
22 moderate to severe disease.

23 As far as duration, I feel less comfortable about  
24 dealing with that issue because I don't believe that we  
25 necessarily have to take rheumatoids with 15 years of

1 disease to treat with this therapy, and I think anyone with  
2 disease activity that is severe enough should be given the  
3 opportunity for the device if approved.

4           As far as use with DMARDS, as this study actually  
5 showed, and they are recommending not to use it with DMARDS,  
6 I know the practical issue is it is going to be used with  
7 these DMARDS, and the sooner the data is made available  
8 about concomitant use with DMARDS, the safer it is going to  
9 be for everyone, because it is going to be used, we might as  
10 well study it as soon as possible. That is my take on it at  
11 this point.

12           DR. VERTUNO: Nothing to add except the labeling  
13 needs clearly to indicate what we know and what we don't  
14 know.

15           DR. KALLOO: Needs to clearly indicate?

16           DR. VERTUNO: How limited our information is,  
17 e.g., that we don't know how it works with concomitant use  
18 of DMARDS.

19           DR. HAWES: To my view, we have a single study, by  
20 all consensus a very well designed study, but it seems to me  
21 with a little data, that my own feeling is that we ought to  
22 label it in a very strict sense according to the way the  
23 study was done and the population in which the study was  
24 done. So, I would agree that I think there should be some  
25 disease activity and severity labeling on there to go along

1 with classification II and III.

2 I think we have no data about the indications for  
3 this therapy relative to the available DMARDS. I don't  
4 think there is any comparative data available at all. I  
5 think disease duration, to my view, I would agree with what  
6 was said earlier. I don't think we ought to put a  
7 stipulation on the number of years that the people have had  
8 their disease.

9 The duration of effect, I think ought to be  
10 emphasized. This seems to be something that is for a short  
11 term control, and I think it needs to be very, very clearly  
12 stated that we don't know what the long-term effects of  
13 repeated applications of the ProSORBA device is.

14 MR. SEGERSON: Dave Segerson. We would like to  
15 clarify the meaning of that question. Could I ask Dr.  
16 Dawisha to come up here and explain it a little further?

17 DR. DAWISHA: I just wanted to clarify the second  
18 bulleted item. I think when you read this, unfortunately,  
19 it doesn't convey what we really wanted to ask, so if I  
20 could just clarify.

21 When we are asking about the indications for  
22 therapy relative to current available DMARDS, we are not  
23 really asking about the indications for concomitant or  
24 concurrent DMARDS. What we really would like the panel to  
25 address is the indications relative to failure or

1 intolerance to the number of DMARDS. It, unfortunately,  
2 didn't really get reflected here.

3 DR. FOOTE: Could you say that again?

4 DR. DAWISHA: I just wanted to clarify that what  
5 we would like you to comment on is not the indications for  
6 use of the product relative to concurrent DMARD use. What  
7 we would like your input on is the indications for use of  
8 the product relative to the number of DMARDS failed or  
9 intolerant, similar to the next question, greater than X  
10 number of DMARDS failed or intolerant.

11 DR. FOOTE: Can I restate that question and see if  
12 I am understanding correctly? Is it that you want us to  
13 make a comment as to what place this product has in the  
14 armamentarium of treatments for RA?

15 DR. DAWISHA: Based on the data that was  
16 presented, based on the patients that were entered into the  
17 study, and based on the baseline demographics of the  
18 patients in the study, we would like you to comment on the  
19 indications for use with respect to the number of DMARDS  
20 failed or intolerant.

21 DR. KALLOO: That is, should the patients from the  
22 indication be zero DMARDS, one DMARD, or failure of  
23 multiple, is that correct?

24 DR. DAWISHA: Right, and then use the data that  
25 was presented to help you make that decision.

1 DR. KALLOO: Let me just start again, if you could  
2 just comment, if you have any more comments on that.

3 DR. LIANG: If you want to generalize back from  
4 the study, the patients who failed or who were intolerant to  
5 multiple DMARDS, I don't think you can be more explicit.  
6 The average was 5-something, but there were others that were  
7 less or more.

8 DR. AGODOA: That is what the study may show, but  
9 I am still saying that that is not a practical way of  
10 looking at this because rheumatologists who are faced with  
11 difficult to treat patients, are going to do something  
12 different, so I think it is impractical to hold us to that  
13 study result.

14 DR. KALLOO: But based on the data that you have?

15 DR. AGODOA: No comment.

16 DR. VERTUNO: I don't have any problem labeling it  
17 to use of people who have failed treatment with multiple  
18 DMARDS.

19 DR. HAWES: I sort of agree with Matt. I think  
20 multiple is a reasonable way to put it as opposed to  
21 subscribing a specific number.

22 DR. KALLOO: Now we go back to looking at all of  
23 the indications because that is where we left off.

24 DR. FOOTE: I think I would agree with what  
25 everyone else has said, and that we can only comment about a

1 very specific patient population in the labeling, and I  
2 think that as long as you indicate that there are some data  
3 available about a specific subset of patients, however,  
4 there is no data available about other populations of  
5 patients, but yet not contraindicating it for those groups  
6 of patients, I think that is going to be the most honest  
7 labeling.

8           As was mentioned before, clinicians are going to  
9 be using their own clinical judgment. I think our charge,  
10 as a committee that has looked at all this data, should be  
11 to give the clinician a reasonable expectation of what a  
12 specific population will do, but on the other hand, letting  
13 them know that they are going to have to use their own  
14 clinical judgment with patients that fall outside of that  
15 specific group.

16           DR. WHITE: I have particular -- I agree with  
17 that, but I think the issue of disease activity, the first  
18 on there, this is really an active group with very bad  
19 disease, and a group that is so severe that the placebo or  
20 even an active placebo effect is 11 percent, whereas, with  
21 people with milder RA, a higher placebo rate might be  
22 expected, a placebo rate which would nearly identical or  
23 overlapping with the efficacy rate here.

24           So, I really have concerns about whether or not it  
25 might be useful, it may not be useful in people with

1 moderate disease, because there might be no difference from  
2 placebo.

3           So, I think there is very clearly a need for the  
4 labeling, and the DMARDS, in fact, the study design was they  
5 only had to fail methotrexate. We saw no breakdown of the  
6 data on methotrexate failure alone, a single DMARD failure  
7 versus multiple DMARD failures, so I have no idea whether we  
8 should say multiple or if methotrexate alone is adequate. I  
9 haven't seen the data.

10           DR. STEINBACH: I think on point 1, disease  
11 severity is important because there are side effects with  
12 plasmapheresis, and the side effects may outweigh the  
13 benefits in a patient that does not have moderate to severe  
14 activity.

15           I think as far as methotrexate versus multiple,  
16 the indications of the protocol would be the most accurate  
17 label. Duration of disease, probably not an issue.  
18 Duration of effect should be information supplied to the  
19 physician.

20           DR. JANOSKY: I think the answer to these  
21 questions lie in the marriage of the entry criteria with any  
22 subgroup analyses or any type of differential patient  
23 population analyses that were done. My understanding is  
24 that those were not done, subgroup analyses, so, in other  
25 words, patients entering with five failed DMARDS, were they

1 responding differently than patients entering with two?

2           So, since that was not done, I would use the entry  
3 criteria to list the indications for use, because that was a  
4 population on which the subjects were studied. So that,  
5 going back to, was either a failed MTX or two other DMARDS.

6           DR. BOULWARE: I think I agree with her with one  
7 exception, that your third question asked about the X number  
8 of years, and I would just be less specific than that and  
9 say long duration.

10           DR. HORTIN: I have no added comment.

11           DR. WHITE: Could I make one comment that I  
12 forgot, and I will try and make it short, and this has to do  
13 with the duration of effect. Again, I just bring this up to  
14 raise to point out discrepancies between labeling that might  
15 come from devices and might come from the Arthritis Advisory  
16 group.

17           There, the guidelines usually for therapeutic  
18 effectiveness of signs and symptoms, I believe require six  
19 months duration of study, and here the endpoint was short of  
20 the six months, so again, I don't know how you deal with it,  
21 I am just raising it for your information.

22           DR. LIANG: Dr. Clauw.

23           DR. CLAUW: I have one long compound sentence that  
24 we might need to break apart, but I think it perhaps  
25 summarizes all of what we are trying to say.

1           This device should generally be reserved for  
2 persons with long-standing moderate to severe rheumatoid  
3 arthritis that have failed or are intolerant of other  
4 DMARDS. I think the panel agrees that there are no data  
5 available with respect to the indications of this therapy  
6 relative to other DMARDS or with concurrent other DMARDS.

7           DR. KALLOO: Let's move along to Question No. 3.

8           Please comment on the following additional  
9 labeling issues: what information relating to the risk of  
10 developing or exacerbating anemia should be included in the  
11 labeling? I think I will just deal with part b, as well.

12           In the randomized study, 5 of the 9 patients who  
13 received central lines experienced complications related to  
14 their use, including thrombosis, infection, and sepsis, in  
15 one case leading to death.

16           What information should be provided in the  
17 labeling regarding the high potential for severe  
18 complications for any patient with inadequate peripheral  
19 venous access? So, the two questions.

20           DR. LIANG: I don't know if this is a trick  
21 question, include it in the labeling. I mean I think you  
22 have to include these things in the labeling, and basically  
23 report what was found in the studies.

24           DR. CLAUW: Could I re-read the statement that we  
25 came up with before, because I am not sure that we haven't

1 already covered this.

2           The statement that we suggested before is sepsis  
3 is a severe adverse event that is likely associated with the  
4 pheresis procedure rather than the Prosorba device, and this  
5 may be accentuated by using central venous access.

6           Labeling should strongly indicate this caution to  
7 both the patient and the health care provider.

8           DR. KALLOO: Yes, I agree. I think we can move  
9 along to Question No. 4.

10           Are there any issues not adequately addressed by  
11 the data in the PMA supplement that require a mandated post-  
12 market study? For example, duration of response;  
13 retreatment with the Prosorba column; use of Prosorba in  
14 combination with other DMARDS, for example, methotrexate;  
15 use of Prosorba in an expanded treatment population, for  
16 example, early RA or less active disease; mechanism of  
17 action studies, for example, ACR responder/non-responder  
18 analyses, HLA markers, or serological testing; and a study  
19 of post-arthritic flares, which have been described by the  
20 sponsor, as you have heard, as increased pain and fatigue  
21 lasting from 12 to 72 hours after treatment.

22           DR. LIANG: With this menu, I think the biggest  
23 priority for me would be Item (c), and along the lines that  
24 Dr. Clauw mentioned, an effectiveness study.

25           DR. AGODOA: There are two areas that I would like

1 to see addressed. I don't recall whether the labeling  
2 actually specifically states it has to be used in adults  
3 only, because the study was done primarily in adults, so  
4 children were not actually dealt with, this particular  
5 study, and I think that needs to be looked at very shortly  
6 after marketing.

7 A second area is when we look at the demographics,  
8 I think there was only one African-American that was studied  
9 in all three studies, only one African-American, so I think  
10 we had 9 Latinos that were studied, and I think 3 Asians and  
11 the rest Caucasians.

12 When we label this, it is going to be for  
13 everyone, and I think that is a significant deficiency, and  
14 I am certain that I would like to see more ethnic diversity  
15 in the data before I feel comfortable about this.

16 DR. VERTUNO: I would like to see data on item  
17 (c), as well.

18 DR. HAWES: All the questions listed are  
19 interesting, and I would encourage the company to pursue all  
20 of them, but I would regard (b), (c), and (d) as mandatory  
21 areas to study.

22 DR. FOOTE: I agree with the above. No additional  
23 comments.

24 DR. WHITE: I think many of them would be  
25 interesting, but I don't think any of them need to be

1 mandated.

2 DR. STEINBACH: I think items (b) and (c) are the  
3 most important, and (c) must be done in a blinded fashion to  
4 study efficacy.

5 DR. JANOSKY: If I read the question, it says are  
6 there any issues not adequately addressed by the data, I  
7 would conclude that all of these items listed here in my  
8 mind are not adequately addressed by the data.

9 In terms of priority, though, I would say (b),  
10 (c), and (d), somewhat ranking within there, not in that  
11 order, would be the priority, but again, all of those I feel  
12 are not addressed by the data.

13 DR. KALLOO: I think there are two issues not  
14 adequately addressed, and requires a mandated post-market  
15 study.

16 DR. JANOSKY: If there is an indication or a need  
17 or a want, more like it, more than indication for an  
18 expanded label, then definitely require mandated post-market  
19 study.

20 DR. BOULWARE: I would agree. I think (b), (c),  
21 and (d) are going to be the three issues in which the device  
22 will be used the most. It will be considered for  
23 retreatment because as we have seen with other treatments,  
24 they do not last with rheumatoid arthritis. People will be  
25 tempted to use them again or to maintain people under

1 control.

2           There will be concurrent use with other DMARDS,  
3 and we have no idea what that does based on the evidence  
4 shown today, and also we don't know what it would do in  
5 other populations of rheumatoid arthritis, and it may  
6 actually have a better net effect because all of the adverse  
7 effects that we have seen are really related to the delivery  
8 mechanism or the pheresis itself, and that may actually be  
9 less of a problem and be useful in a healthy population that  
10 isn't quite so devastated by decades of the disease.

11           I think item (e) should probably be looked at  
12 again, too, because all of the adverse effects we have seen  
13 here are very serious and related to the catheter problem  
14 and/or the pheresis problem, and if this is truly a drug  
15 delivery device, there may be safer drug delivery devices,  
16 mechanisms, or maybe perhaps just inject SPA if you have to,  
17 a few nanograms, and get rid of all the adverse effect and  
18 prove it to be very effective or effective without the  
19 adverse effect.

20           DR. HORTIN: I think in terms of mandatory  
21 studies, I think that really item (c) should be mandatory  
22 for a couple of reasons. First of all, based on the data  
23 that we have seen in this study, it would suggest that you  
24 would perhaps need to take people off the DMARDS before you  
25 would put them on this treatment, and that might deprive

1 them of some benefit of their medication and pose a slight  
2 risk for them, so it would be useful to know whether you do  
3 not have to discontinue that and have a wash-out period  
4 before using it.

5           The second point is that since it has not been  
6 studied in combination, you don't know whether use of the  
7 combination therapy will have harmful effects or negate the  
8 beneficial effects of either therapy alone, so I think I  
9 would consider that probably a mandatory element in terms of  
10 post-market studies.

11           The other components are all very interesting, but  
12 I think that item is the one that I would single out as the  
13 component that really should have some mandated post-market  
14 study.

15           DR. KALLOO: Dr. Clauw, if you could summarize the  
16 comments, please.

17           DR. CLAUW: Again, I would like everyone to listen  
18 carefully to this because there wasn't unanimity on these  
19 points. There are inadequate data to address any of these  
20 issues at present. There should be a mandated post-  
21 marketing surveillance study that addresses items (b), (c),  
22 and (d). The other questions are interesting, but answers  
23 are not necessarily required or mandated.

24           We would also encourage the sponsor to consider  
25 using alternative designs other than that proposed.

1 DR. KALLOO: Any comments on that summary? I  
2 think that is the last question.

3 We will open this to public discussion, if there  
4 any comments or questions.

5 [No response.]

6 DR. KALLOO: If there are no requests for comments  
7 or questions, then, before entertaining a motion  
8 recommending an action on this PMA, Mary will remind the  
9 panel of our responsibilities in reviewing today's premarket  
10 approval application and of the voting options open to us.

11 MS. CORNELIUS: Before you vote on a  
12 recommendation, please remember that each PMA has to stand  
13 on its own merits. Your recommendation must be supported by  
14 the data in the application or by publicly available  
15 information. You may not consider information from other  
16 PMA's in reaching your decision on this PMA.

17 Your recommendation may be one of the following:

18 You may recommend approval of the PMA.

19 You may recommend that the PMA be found approvable  
20 subject to specific conditions such as resolution of clearly  
21 defined deficiencies cited by you or the FDA staff.

22 Examples could include resolution of questions concerning  
23 some of the data or changes in the draft labeling.

24 You may conclude that post approval requirements  
25 should be imposed as a condition of approval. These

1 conditions may include a continuing evaluation of the device  
2 and submission of periodic reports. If you believe such  
3 recommendations are necessary, then your recommendations  
4 should address the following points: the reason or purpose  
5 for the post approval requirement; the number of patients to  
6 be evaluated; the reports required to be submitted; and the  
7 reports required to be submitted.

8 Or you may recommend that the PMA is not  
9 approvable. Of the 5 reasons that the Act specifies in  
10 Section 515B2(a) through (e), 3 are applicable.

11 1. The data do not provide reasonable assurance  
12 that the device is safe under the conditions of use  
13 prescribed, recommended, or suggested in the labeling. To  
14 clarify the definition of "safe," there is a reasonable  
15 assurance that a device is safe when it can be determined  
16 based on valid scientific evidence that the probable  
17 benefits to health from the use of the device for its  
18 intended uses and conditions of use, when accompanied by  
19 adequate directions and warnings against unsafe use,  
20 outweigh the probable risks.

21 2. The data do not provide reasonable assurance  
22 that the device is effective under the conditions of use  
23 prescribed, recommended, or suggested in the labeling. A  
24 definition of "effectiveness" is as follows: There is a  
25 reasonable assurance that a device is effective when it can

1 be determined, based on valid scientific evidence, that in a  
2 significant portion of the target population the use of the  
3 device for its intended uses and conditions of use, when  
4 accompanied by adequate directions for use and warnings  
5 against unsafe use, will provide clinically significant  
6 results.

7           3. The PMA may be denied approval if, based on a  
8 fair evaluation of all the material facts, the proposed  
9 labeling is false or misleading.

10           If you make a non-approvable recommendation for  
11 any of these stated reasons, we request that you identify  
12 the measures that you believe are necessary or steps that  
13 should be undertaken to place the application in an  
14 approvable form. This may include further research.

15           DR. KALLOO: Before we take a vote, does anyone  
16 wish to address the panel, please raise your hand. Again,  
17 this can include members of Cypress or anyone in the  
18 audience, please raise your hand and approach the  
19 microphone.

20           [No response.]

21           DR. KALLOO: We will now consider the panel's  
22 report and recommendations concerning approval of the  
23 Cypress Bioscience for a new indication for treatment of  
24 rheumatoid arthritis for the ProSORBA Column together with  
25 the reasons or recommendation as required by Section 515

1 part C(2) of the Act.

2           The underlying data supporting a recommendation  
3 consists of information and data set forth in the  
4 application itself, the written summaries prepared by the  
5 FDA staff, the presentations made to the panel, and the  
6 discussions held during the panel meeting, which are set  
7 forth in the transcript.

8           The recommendation of the panel may be approval,  
9 approval with conditions that are to be met by the  
10 applicant, or denial of approval.

11           May I please have a motion?

12           DR. CLAUW: I move that we recommend the PMA as  
13 approvable based on the sponsor agreeing to conduct a post-  
14 marketing study that will address the use of ProSORBA in  
15 combination with other DMARDS and the effect of retreatment  
16 with ProSORBA. If the sponsor requests an indication of the  
17 use of ProSORBA in persons with mild RA, then, a post-  
18 marketing study must also address this issue.

19           DR. KALLOO: Will all those voting members in  
20 favor of approval with the conditions set forth, raise their  
21 hands.

22           Is there someone that seconds?

23           DR. BOULWARE: Second.

24           DR. STEINBACH: Item 2 says approvable with  
25 condition, number of subjects to be evaluated. The number

1 of subjects should be equal to the number in the original  
2 proposed study before the Christmas tree. We were asked for  
3 this number, and I suggest that be the number.

4 DR. KALLOO: Any comments on that addition?

5 DR. LIANG: I think I would like to make that  
6 decision once I see what the study design and hypothesis is  
7 actually. I am not sure that we have a specific design in  
8 mind.

9 DR. KALLOO: So, the numbers should be contingent  
10 on the statistical design. Any other comments?

11 DR. JANOSKY: I have a question about the motion.  
12 Included in that motion is the indication for use statement  
13 presented by the sponsor or the revised or suggested revised  
14 indication for use statement discussed by panel today?

15 DR. KALLOO: We can stipulate that it is the  
16 revised indications are stipulated by the panel today.

17 DR. JANOSKY: So, that motion included the revised  
18 then?

19 DR. CLAUW: Yes.

20 DR. JANOSKY: At that point, I will second the  
21 motion.

22 DR. KALLOO: Will all those voting members in  
23 favor of the approval with these conditions raise your  
24 hands.

25 [Show of hands.]

1 VOICE: Mr. Chairman, call for negatives.

2 DR. KALLOO: Those against the motion, please  
3 raise your hand.

4 [One hand raised.]

5 DR. KALLOO: It appears that the panel has  
6 recommended approval with the following conditions, and if I  
7 can just have you restate them again.

8 MR. SEGERSON: Can you announce the vote, announce  
9 what the vote was?

10 DR. KALLOO: Can I just have a show of hands again  
11 of how many?

12 [Show of hands.]

13 DR. KALLOO: 10 to 1.

14 DR. AGODOA: Mr. Chairman, is the motion  
15 approvable or approval? I thought he said approvable.

16 DR. KALLOO: The motion is approved.

17 DR. AGODOA: The motion was approvable.

18 DR. KALLOO: The motion is approvable.

19 DR. JANOSKY: I understood the motion to be  
20 approvable with conditions.

21 DR. KALLOO: With conditions, and I will ask Dr.  
22 Clauw to restate the conditions. Can you do that right now,  
23 please?

24 DR. CLAUW: The motion was that we recommend that  
25 the PMA be approvable based on our suggested modifications

1 to labeling, as well as the sponsor agreeing to conduct a  
2 post-marketing study that will address the use of Prosorba  
3 in combination with other DMARDS, as well as the effect of  
4 retreatment with Prosorba. If the sponsor requests an  
5 indication of the use of Prosorba in persons with mild RA,  
6 then, a post-marketing study must also address this issue.

7 DR. WHITE: I would like to go on the record that  
8 I think it would be approvable with all those things if a  
9 second study were done.

10 DR. KALLOO: This concludes the report and  
11 recommendations of the panel for a new indication of  
12 treatment of rheumatoid arthritis for the Prosorba Column  
13 Supplement 11 of PMA 850020.

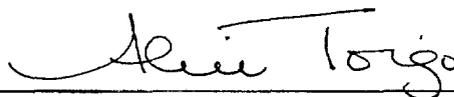
14 I didn't make many comments during this  
15 presentation, but I want to congratulate the company. As a  
16 clinical researcher, I thought this was a really well done  
17 study in a very difficult group of patients.

18 On behalf of the FDA, I would like to thank the  
19 entire panel and very much so, Dr. Clauw, for an outstanding  
20 job summarizing, and this meeting is now adjourned.

21 [Whereupon, at 3:10 p.m., the meeting was  
22 adjourned.]

**C E R T I F I C A T E**

I, **ALICE TOIGO**, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

A handwritten signature in cursive script that reads "Alice Toigo". The signature is written in black ink and is positioned above a horizontal line.

**ALICE TOIGO**