

UNITED STATES OF AMERICA  
FOOD AND DRUG ADMINISTRATION

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ORTHOPEDIC AND REHABILITATION DEVICES PANEL  
of the  
MEDICAL DEVICES ADVISORY COMMITTEE

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WEDNESDAY, JUNE 2, 2004

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**This transcript has not  
been edited and FDA  
makes no representation  
regarding its accuracy**

The above-entitled Meeting was conducted at 10:00 a.m., at the Gaithersburg Marriott, Salons A, B, C, D, 9751 Washingtonian Boulevard, Gaithersburg, Maryland, Dr. Michael J. Yaszemski, Panel Chairperson, presiding.

PANEL MEMBERS PRESENT:

- MICHAEL J. YASZEMSKI, M.D., Ph.D., Chairperson, Mayo Clinic Graduate, School of Medicine
- JANET L. SCUDIERO, M.S., Acting Executive Secretary
- MAUREEN A. FINNEGAN, M.D., Voting Member, University of Texas, Southwestern Medical Center
- JOHN S. KIRKPATRICK, M.D., Voting Member, University of Alabama, School of Medicine
- SANJIV S. NAIDU, M.D., Ph.D., Voting Member, Pennsylvania State College of Medicine
- SALLY L. MAHER, ESQ., Industry Representative, Smith and Nephew Endoscopy
- KLEIA LUCKNER, J.D., M.S.N., Consumer Representative, The Toledo Hospital
- MARCUS P. BESSER, Ph.D., Deputized Voting Member, Thomas Jefferson University
- BRENT A. BLUMENSTEIN, Ph.D., Deputized Voting Member, TriArc Consulting
- FERNANDO G. DIAZ, M.D., Ph.D., Deputized Voting Member, Detroit Medical Center
- CHOLL W. KIM, M.D., Ph.D., Deputized Voting Member, University of California, San Diego

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PANEL MEMBERS PRESENT: (cont.)

JAY D. MABREY, M.D., Deputized Voting Member,  
University of Texas, Health Science Center  
CELIA WITTEN, M.D., Ph.D., FDA Division Director,  
General Restorative & Neurological Devices

SPONSOR PRESENTERS:

SCOTT L. BLUMENTHAL, M.D., Texas Back Institute,  
Plano, Texas  
WILLIAM P. CHRISTIANSON, Vice President of Clinical  
and Regulatory Affairs, DePuy Spine, Inc.  
BRYAN CUNNINGHAM, M.Sc., Director of Spinal Research,  
Orthopedic Biomechanics Laboratory, Union  
Memorial Hospital, Baltimore, Maryland  
GEORGE DEMUTH, M.S., President, Stat-Tech Services,  
LLC, Chapel Hill, North Carolina  
PAUL C. MCAFEE, M.D., Spine and Scoliosis Center,  
St. Joseph's Hospital, Towson, Maryland

FDA PRESENTERS:

SERGIO M. del CASTILLO, B.S., Biomedical Engineer,  
Lead Reviewer  
JIANXIONG "GEORGE" CHU, Ph.D., MAS, Statistician  
JOVE H. GRAHAM, Ph.D., Mechanical Engineer

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P-R-O-C-E-E-D-I-N-G-S

9:58 a.m.

MS. SCUDIERO: Good morning. We're ready to begin this meeting of the Orthopedic and Rehabilitation Devices Panel. I'm Jan Scudiero. I'm the Acting Executive Secretary of this Panel and a reviewer in the Division of General Restorative and Neurological Devices. We have the usual housekeeping matters first. If you haven't already done so, please, sign in at the tables outside the door. The agenda information for this meeting is on the tables. There is also Advisory Committee website information about upcoming meetings, summary meetings and transcripts.

Before I turn the meeting over to Dr. Yaszemski, I'm required to read two statements into the record. The Deputization of Temporary Voting Members statement and the Conflict of Interest statement.

First, the appointment to temporary voting status. Pursuant to the authority granted under the Medical Devices Advisory Committee Charter, dated

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1 October 27, 1990, and amended April 20, 1995, I  
2 appoint the following as voting members of the  
3 Orthopedic and Rehabilitation Devices Panel for the  
4 duration of this meeting on June 2<sup>nd</sup> and 3, 2004:  
5 Marcus P. Besser, Ph.D., June 2<sup>nd</sup> and 3<sup>rd</sup>, Brent A.  
6 Blumenstein, Ph.D. on June 2<sup>nd</sup>, Fernando G. Diaz,  
7 M.D., Ph.D. on June 2<sup>nd</sup>, Choll W. Kim, M.D., Ph.D. on  
8 June 2<sup>nd</sup> and 3<sup>rd</sup>, Jay D. Mabrey, M.D., on June 2<sup>nd</sup> and  
9 3<sup>rd</sup>, and Michael B. Maher, M.D. on June 3<sup>rd</sup>, the  
10 morning session only.

11 For the record, these people are special  
12 Government employees and are consultants to this Panel  
13 or another panel under the Medical Devices Advisory  
14 Committee. They have undergone the customary Conflict  
15 of Interest review and have reviewed the material to  
16 be considered at this meeting. This is signed by  
17 Daniel G. Schultz, M.D., Acting Director, Center for  
18 Devices and Radiological Health on May 28<sup>th</sup>, this  
19 year.

20 The Conflict of Interest statement for  
21 June 2<sup>nd</sup>. The following announcement addresses  
22 Conflict of Interest issues associated with this

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1 meeting and is made a part of the record to preclude  
2 even the appearance of an impropriety. To determine  
3 if any conflict existed, the Agency reviewed the  
4 submitted agenda for this meeting and all financial  
5 interests reported by the Panel participants.

6 The Conflict of Interest statute prohibits  
7 special Government employees from participating in  
8 matters that could affect their or their employer's  
9 financial interest. However, the Agency has  
10 determined that the participation of certain members  
11 and consultants, the need for whose services outweighs  
12 the potential Conflict of Interest involved is in the  
13 best interest of the Government. Therefore, waivers  
14 have been granted for Dr. John Kirkpatrick and Jay  
15 Mabrey for their interest in firms that could be  
16 affected by the Panel's recommendations.

17 Dr. Kirkpatrick's waiver involves a  
18 stockholding in a parent of the sponsor, which is  
19 valued between \$15,000 and \$25,000. Dr. Mabrey's  
20 waiver involves consulting with an unaffected division  
21 of the sponsor's firm on matters unrelated to today's  
22 agenda. Dr. Mabrey receives less than \$10,001 for

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1 this consulting.

2 We would like to note for the record that  
3 the Agency took into consideration certain matters  
4 regarding Drs. Maureen Finnegan, Choll Kim, John  
5 Kirkpatrick and Jay Mabrey. Each of these panelists  
6 recorded current and/or past interest in firms at  
7 issue, but in matters not related to today's agenda.  
8 The Agency has determined therefore that they may  
9 participate fully in today's deliberations.

10 In event that the discussions involve any  
11 other products or firms not already on the agenda for  
12 which an FDA participant has a financial interest, the  
13 participant should excuse himself or herself from such  
14 involvement and the exclusion will be noted in the  
15 record. With respect to all other participants, we  
16 ask in the interest of fairness that all persons  
17 making statements or presentations disclose any  
18 current or previous financial involvement with any  
19 firm whose products they may wish to comment upon.

20 Please, note that Drs. Besser, Blumenstein  
21 and Diaz, Kim and Mabrey are deputized voting members  
22 for today's meeting. The remaining tentatively

1 scheduled meetings for this Panel, this calendar year,  
2 are August 12<sup>th</sup> and 13<sup>th</sup> and December 2<sup>nd</sup> and 3<sup>rd</sup>.  
3 Please, remember these are tentative dates and monitor  
4 the CDRH Panel website for updated Panel meeting  
5 information.

6 I would now like to turn the meeting over  
7 to Dr. Yaszemski.

8 CHAIRPERSON YASZEMSKI: Thanks, Mrs.  
9 Scudiero. Good morning. I'm Dr. Michael Yaszemski.  
10 I'm the Chairperson of the Orthopedic and  
11 Rehabilitation Panel. I'm an orthopedic surgeon and  
12 a chemical engineer. I work at the Mayo Clinic in  
13 Rochester, Minnesota. My area of interest in  
14 orthopedics is spinal surgery and my engineering area  
15 of interest is polymeric biomaterials.

16 At this meeting, the Panel will be making  
17 a recommendation to the Food and Drug Administration  
18 on the approvability of pre-market approval  
19 application for the DePuy Charite Artificial Lumbar  
20 Disc intended for spinal arthroplasty in skeletally  
21 mature patients with degenerative disc disease at one  
22 level from L4 to S1.

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1           Before we begin the meeting, I would like  
2           to ask our distinguished Panel Members, who are  
3           generously giving of their time, to help the FDA in  
4           the matter being discussed today and other FDA staff  
5           seated at this table to introduce themselves.  
6           Members, please, state your name, your area of  
7           expertise, your position and your affiliation. I  
8           would like to start to my right with Dr. Kirkpatrick.  
9           Yes, sir.

10                   DR. KIRKPATRICK:     My name is John  
11           Kirkpatrick. I am an Associate Professor of  
12           Orthopedic Surgery at the University of Alabama,  
13           Birmingham. I also have significant background in  
14           biomechanics and training in bioengineering.

15                   DR. NAIDU: My name is Sanjiv Naidu. I'm  
16           an Associate Professor of Orthopedic Surgery at Penn  
17           State College of Medicine. My area of expertise is in  
18           orthopedic surgery and material science.

19                   DR. KIM: I'm Choll Kim. I'm an Assistant  
20           Professor at the University of California at San  
21           Diego. I'm fellowship trained in spine surgery and  
22           that is my area of expertise.

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1 DR. FINNEGAN: I'm Maureen Finnegan. I'm  
2 an Associate Professor of Orthopedic Surgery at UT  
3 Southwestern and my area of expertise is basic  
4 science, particularly with bone healing.

5 DR. MABREY: I'm Jay Mabrey. I've just  
6 been reassigned to Baylor University Medical Center in  
7 Dallas where I'm the Chief of the Department of  
8 Orthopedics. My expertise is in total joint  
9 replacement, hip and knee, and I also have extensive  
10 experience in analysis of particulate wear debris.

11 DR. DIAZ: My name is Fernando Diaz. I am  
12 a Neurosurgeon, Professor of Neurosurgery at Wayne  
13 State University. One of my areas of interest is  
14 spine surgery and reconstruction of the spine.

15 DR. WITTEN: I'm Dr. Celia Witten. I'm  
16 the FDA representative at the table and the Division  
17 Director of the Reviewing Division for this product.

18 MS. LUCKNER: I'm Kleia Luckner. I'm the  
19 Consumer Rep. I am a hospital Administrator from  
20 Toledo, Ohio.

21 MS. MAHER: My name is Sally Maher. I'm  
22 the group Director of Regulatory and Clinical with

1 Smith and Nephew and I'm here as the Industry  
2 Representative.

3 DR. BESSER: I'm Marcus Besser, Associate  
4 Professor at Thomas Jefferson University. My  
5 background is in biomechanics and bioengineering. My  
6 current interests are in gait and motion analysis and  
7 biomechanics of the hip and the knee.

8 DR. BLUMENSTEIN: My name is Brent  
9 Blumenstein. I'm a Biostatistician working  
10 independently from Seattle.

11 CHAIRPERSON YASZEMSKI: Ms. Scudiero has  
12 already introduced herself. I would like to also note  
13 for the record that the voting members here at the  
14 Panel table constitute a quorum as required by 21 CFR  
15 Part 14. Next, we're going to ask Ms. Barbara  
16 Zimmerman, Chief of the Orthopedic Devices Branch at  
17 FDA to update the Panel on several matters deliberated  
18 on at the last meeting of the Panel in December 2003.  
19 Ms. Zimmerman?

20 MS. ZIMMERMAN: Good morning, everyone.  
21 I'm going to give a brief update today since our last  
22 Panel meeting, which was in December of 2003. Since

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1 that meeting, we have taken action on a few items from  
2 previous Advisory Committee meetings, one of which was  
3 the infused bone graph manufactured by Wyeth. We  
4 approved the PMA on April 30, 2004. This PMA is now  
5 owned by Medtronic Sofamor Danek and this device is  
6 indicated for treating acute and tibial fractures that  
7 have been stabilized with IM nail fixation after  
8 appropriate wound management. Infused bone graph must  
9 be applied within 14 days after the initial fracture.  
10 Perspective patients should be skeletally mature.

11 At that last Panel meeting on December 11,  
12 2003, we discussed the topic that we discussed was the  
13 reclassification of inner body fusion devices, cages  
14 and I just wanted to update everyone and let them know  
15 we are in the process, FDA is in the process of  
16 generating a special controls guidance document and a  
17 Federal Register notice. We continue to work on this  
18 and you can monitor the Federal Register notice  
19 webpage in order to see when we do this. Although, I  
20 don't anticipate it will be in the next month. It  
21 will be much later than that.

22 Other significant approvals or clearances

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1 are the HDE for the OP-1 Putty by Stryker. It was a  
2 humanitarian device exemption which did not require a  
3 Panel meeting. It was a collaborative review between  
4 the Center for Drugs and Biologics and CDRH. This  
5 approval occurred on April 17, 2004 and it is  
6 indicated for use as an alternative to autograft and  
7 compromised patients requiring revision, posterior  
8 lateral lumbar spinal fusion for whom autologic bone  
9 and bone marrow harvest are not feasible or are not  
10 expected to promote fusion.

11 In addition, we have approved a PMA for  
12 the Oxford Meniscal Unicompartmental Knee, Phase III.  
13 This is manufactured by Biomed. No Panel meeting was  
14 necessary to approve this PMA. It was approved on  
15 April 21, 2004 and was indicated for use in patients  
16 who have osteoarthritis or avascular necrosis limited  
17 to the medial compartment of the knee and indicated to  
18 be implanted with bone cement.

19 We have also cleared two human  
20 demineralized bone matrix, DBM, based bone void  
21 fillers. One was the Exactech Resorbable Bone based  
22 which was February 27, 2004, and there was also the

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1 right AlloMatrix Putty, which was cleared March 5,  
2 2004. In addition, we have cleared a PMA cement for  
3 pathological fracture of the vertebral body. This was  
4 submitted by Kyphon for the KyphX Bone Cement and it  
5 was cleared on April 1, 2004.

6 That concludes my update. Thank you.

7 CHAIRPERSON YASZEMSKI: Thanks very much,  
8 Ms. Zimmerman. We are now going to proceed to the  
9 open public hearing portion of today's Panel meeting.  
10 I would like to ask, at this time, that all persons  
11 addressing the Panel speak clearly into the  
12 microphone, the transcription is dependent upon, this  
13 means to provide an accurate recording of the meeting.  
14 Please, also, when you come up identify yourself and  
15 your affiliation and any conflicts that you may have,  
16 so that we can enter them into the record. Ms.  
17 Scudiero is now going to read a statement prepared for  
18 open public hearings.

19 MS. SCUDIERO: Both the FDA and the public  
20 believe in a transparent process for information  
21 gathering and decision making. To ensure such  
22 transparency at open public hearing sessions of

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1 Advisory Committee meetings, FDA believes that it is  
2 important to understand the context of any individuals  
3 presentation. For this reason, FDA encourages the  
4 open public hearing speaker at the beginning of your  
5 oral statement to advise the Panel of any financial  
6 relationship you may have with the sponsor, its  
7 product and if known its direct competitors.

8 For example, this financial information  
9 may include the sponsor's payment of your travel,  
10 lodging or other expenses in connection with your  
11 attendance at the meeting. Likewise, FDA encourages  
12 you, at the beginning of your statement, to advise the  
13 Committee if you do not have such financial  
14 relationships. If you choose not to address this  
15 issue of financial relationships at the beginning of  
16 your statement, it will not preclude you from  
17 speaking.

18 I would like to note for the record that  
19 seven patients and family members of patients with  
20 lumbar spine disease wrote to the FDA requesting  
21 approval of this product, the DePuy Charite Artificial  
22 Lumbar Disc. And I have another short statement. We

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1 received two abstracts of two presentations given at  
2 the Spine Week 2004 meeting currently being held in  
3 Porto, Portugal, May 30<sup>th</sup> through June 5<sup>th</sup>. One  
4 abstract contains information about the complications  
5 related to the Charite device and the other was a case  
6 report of osteolysis associated with the presence of  
7 polyethylene wear debris. Okay.

8 CHAIRPERSON YASZEMSKI: Okay. Thanks, Ms.  
9 Scudiero. And prior to this meeting, we received six  
10 requests to speak at the open public hearing. Three  
11 people will speak in the morning and three people will  
12 speak in the afternoon. We're going to have a second  
13 open public hearing in this afternoon's session. The  
14 morning presenters are going to be Dr. Kurtz, Dr.  
15 Pelosa and Dr. Polly. In the afternoon, we will have  
16 talks from Dr. Hochschuler, Dr. Ben Ooij and Ms.  
17 Adams.

18 And I would like to proceed now if Dr.  
19 Kurtz is here. I ask Dr. Kurtz to come up and give  
20 his presentation. And I'll mention for all the  
21 speakers that we have a lot of time in the meeting for  
22 your presentations and I will put the time in, so that

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1 you have a two minute sum-up when the light up by you  
2 turns yellow, you've got two minutes to go. And Dr.  
3 Kurtz, you are scheduled for 10 minutes.

4 DR. KURTZ: Thank you very much. Good  
5 morning. My name is Steve Kurtz and I'm a principle  
6 engineer and the office director of X-Bone in  
7 Philadelphia. I also have a research faculty  
8 appointment at Drexel University. The work that I'm  
9 going to present today was made possible with  
10 institutional funds provided by Medtronic Sofamor  
11 Danek. Medtronic Sofamor Danek also covered my travel  
12 costs to be here today.

13 I do not have any personal financial  
14 interests in either DePuy or Medtronic. For the past  
15 14 years, I have been performing research on the  
16 clinical performance of Ultra High Molecular Weight  
17 Polyethylene. I have authored a textbook on the  
18 subject of clinical performance of Ultra High  
19 Molecular Weight Polyethylene. I am the director of  
20 a Hip and Knee Implant Retrieval Program at Drexel  
21 University where I am studying the effect of in-vivo  
22 oxidation on the mechanical properties and surface

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1 damage of polyethylene.

2 I would like to thank the FDA for the  
3 opportunity to present before the Panel. I would also  
4 like to thank the Panel Members for their time and  
5 attention this morning. My purpose in speaking here  
6 today is to present the analysis of a retrieved  
7 Charite total disc replacement. This component was  
8 retrieved by Dr. John Pelozo in Dallas, Texas who I  
9 understand is going to be speaking after me. And it  
10 is my understanding from speaking with DePuy that this  
11 event has been reported to the FDA.

12 The analysis I will be presenting today  
13 was performed with the consent of the patient and the  
14 revising physician. This slide shows the polyethylene  
15 component immediately after it was retrieved in the  
16 operating room. The larger image shows the component  
17 after it was thoroughly cleaned and disinfected. I  
18 would like to draw your attention to the transverse  
19 cracks that were observed on the surface of the  
20 polyethylene core, but only on one side, which was  
21 labeled as Side 2.

22 We can deduce that these cracks were

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1 present in the polyethylene core while it was  
2 implanted as they were observed on the surface  
3 immediately after it was removed from the patient, as  
4 is shown on the image at the right. I don't know if  
5 you can see that here, but they are right here. If  
6 you look closely, I have oriented the images  
7 approximately the same so the core is lined up the  
8 same way. You can see also how blood has been drawn  
9 up under the crack and filtered in through the cracks  
10 in the material.

11 I would like to also draw your attention  
12 to damage near the rim. Dr. Pelozo will provide more  
13 details about this case, but in synopsis this device  
14 was implanted at the L5-S1 level in a 49 year-old  
15 female patient in February 2001. These are  
16 radiographs obtained prior to the patient undergoing  
17 posterior fusion on October 2002 after 1.6 years of  
18 implantation. The device was ultimately removed in  
19 January 2004 and Dr. Pelozo can comment about the  
20 reasons surrounding its removal.

21 It was implanted a total of 2.9 years.  
22 The objectives of this retrieval analysis were to

1 answer the following questions as they pertained to  
2 the polyethylene component. Is there evidence of  
3 oxidation and degradation of mechanical properties?  
4 Is there evidence of adhesive abrasive wear? Is there  
5 evidence of damage? What are the stress distributions  
6 in the polyethylene?

7 To accomplish this goal, we used a variety  
8 of methods that are available to us. We used white  
9 light interferometry. We used optical microscopy of  
10 thin sections, FTIR, small punch testing, MicroCT and  
11 we also used finite element modeling. Here are the  
12 images and measures obtained from the white light  
13 interferometry at two distinct areas near the pole on  
14 the polyethylene surface. We looked for evidence of  
15 removal of machining marks which would be indicative  
16 of abrasive or adhesive wear.

17 We found only irregular machining marks as  
18 well as some evidence of multidirectional scratches.  
19 Because of the presence of original machining marks,  
20 we concluded that there was minimal evidence of  
21 adhesive abrasive wear on the surface. Here is a thin  
22 slice from the polyethylene component made with a

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1 Microtome. The central axis of the component is on  
2 the right side. The rim of the component towards the  
3 left. During Microtoming, the section fragmented near  
4 the rim where it is only 3 millimeters thick.

5 This is a cross-sectional view of one of  
6 the transverse cracks that I mentioned previously.  
7 The crack is not parallel to the surface and its  
8 trajectory is such that it angles toward the pole or  
9 the center of the component. This crack trajectory is  
10 not consistent with the lamination. In addition, this  
11 image shows no evidence of a white band or any  
12 consolidation defects.

13 Following the standard protocol, the  
14 oxidation index was measured through the thickness of  
15 the component, as shown here in the top right. The  
16 oxidation as plotted here with the X axis denoting the  
17 distance from the side to surface. We see that there  
18 are low levels of oxidation at the surface. The  
19 oxidation drops down to near undetectable levels near  
20 the center of the component.

21 In addition, using another standard  
22 protocol, we were able to assess the mechanical

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1 properties near the surface of the component where the  
2 oxidation was greatest. Here is a comparison of the  
3 low displacement curb of the Charite polyethylene near  
4 the surface, that's in white, along with the  
5 comparison to a historical control, shown in yellow.  
6 Consistent with low levels of oxidation, we found that  
7 the polyethylene exhibited comparable ductility and  
8 ultimate strength as a historical control.

9 The retrieval analysis also included  
10 MicroCT scanning of the polyethylene core to evaluate  
11 internal crack trajectories. Here is a two  
12 dimensional slice, MicroCT slice, where we can exam/  
13 observe the trajectory, right here, of the transverse  
14 crack, which is consistent with what we saw in the  
15 FTIR sectioning. On this cut view of the three  
16 dimensional reconstruction of the retrieved component,  
17 we can see some evidence of what appears to be pit  
18 formation. Based on MicroCT images and digitized  
19 coordinance of the retrieved component, a finite  
20 element measure of the Charite was constructed.

21 Contract was simulated between the end  
22 plates and the polyethylene component as well as

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1 between the metallic ring and the polyethylene.  
2 Polyethylene material properties were based on the  
3 small punch testing described previously. The  
4 inferior edge of the polyethylene was fixed. The top  
5 surface was loaded axially with 800 Newtons and a 10  
6 newton meter extension moment was applied, consistent  
7 with actually the ASTM standard for wear testing.

8 To validate the model, we compared the  
9 orientation under full extension to what we observed  
10 in the patient's radiographs. We found good agreement  
11 between the model positioning and what was observed in  
12 the radiographs. From the finite element results and  
13 full extension, we observed peak tensile stresses at  
14 the edge of contact. That's right there, that red  
15 line right there. The 25 megaPascal fringes  
16 correspond to the true yield stress for polyethylene.  
17 This tensile stress distribution is similar to what is  
18 observed in total knee replacements where the  
19 polyethylene is stretched at the edge of contact.

20 A MicroCT slice here which is taken at a  
21 slightly different axial position shows the transverse  
22 crack at the location or near the location of the high

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1 tensile stresses at the edge of contact. Here is  
2 another photograph of the retrieved Charite implant.  
3 Especially note again the large damage region inside  
4 the rim and here are the transverse cracks. Here are  
5 the minimum principle stress distributions  
6 superimposed on the damage patterns.

7 The high compressive stresses in the model  
8 are located where the end plates pinch the rim. The  
9 polyethylene thickness at this location is only 3  
10 millimeters, which is a concern in this loading mode.  
11 The magnitude of the compressive stress during this  
12 pinching loading mode was comparable to what has been  
13 reported for total knee replacements.

14 In conclusion, the retrieval analysis to  
15 date has shown that low levels of oxidation were  
16 measured at the surfaces of the polyethylene  
17 component, but these were not associated with  
18 substantial reduction and mechanical properties. The  
19 surface damage observed on the core upon retrieval  
20 indicated that the direction of these cracks was not  
21 associated with the magnitude and distribution of  
22 oxidation.

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1           From the finite element analysis, we found  
2 regions of both high tensile and high compressive  
3 stresses in the polyethylene where the rim of the  
4 component was pinched between the end plates under  
5 full extension. The regions of high tensile and  
6 compressive stress in the model corresponded to  
7 locations of transverse cracks or rim damage around  
8 the polyethylene component. The stress results  
9 presented here for the design with the 3 millimeter  
10 rim thickness are expected to be sensitive to the  
11 properties of the polyethylene, the applied loading  
12 and also on the design and the size of the component.

13           Thank you all for your attention.

14           CHAIRPERSON YASZEMSKI: Thanks, thanks  
15 very much, Dr. Kurtz. May I ask Dr. Pelozo to come  
16 forward now and give his presentation? Dr. Pelozo,  
17 you are also scheduled for 10 minutes.

18           DR. PELOZA: Good morning, Members of the  
19 Panel. My name is John Pelozo. I'm a spine surgeon,  
20 orthopedic surgeon, board certified and fellowship  
21 trained with 14 years of clinical experience. I have  
22 also trained fellows and medical students and

1 residents. I'm a member in good standing with all the  
2 academies in various licensing organizations. I've  
3 been a principal investigator for several FDA trials  
4 and I am a principal investigator for the Maverick  
5 Trial in my center, Total Disc Trial. And I would  
6 like to thank you for your time today.

7 Today, my purpose of being here is to  
8 address my concerns concerning the LINK Charite  
9 Implant. Before I do that, I would like to express my  
10 disclosures. I am a consultant for Medtronic Danek.  
11 They paid for my airline ticket, hotel room, but I  
12 don't own any stock in Medtronic. I don't have any  
13 patents, royalties, agreements concerning any total  
14 disc replacements with any company or manufacturer and  
15 again I am an investigator for the Maverick Total Disc  
16 Replacement.

17 I wanted to talk a little bit about motion  
18 technology and then get into my concerns specifically  
19 with the LINK Charite and my opinions based on the  
20 analogous fine literature, biomechanics and 14 years  
21 of experience. Also, I would like to say that my  
22 comments are not meant to disparage any investigator,

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1 engineers or company representatives. I know these  
2 people personally, many of them anyway, and I hold  
3 them in highest regard. Again, it's only to discuss  
4 my concerns with the treating physician with the link  
5 disc.

6 I would like to basically start with an  
7 overview of the properties of a successful disc and I  
8 would like to say first and foremost it has to last  
9 the lifetime of the patient. It has to stand the test  
10 of time. The average age of a person that would be a  
11 candidate for this procedure is about the mid-40s.  
12 Most of the studies with fusions average age in around  
13 mid-40s and it can actually, on the studies, go down  
14 to the age of 18. So it is a completely different  
15 patient population that would be getting a total hip  
16 or knee prosthesis.

17 I think it is critical that these implants  
18 last for the life of the patients, because revision  
19 surgery to remove the implant particular from an  
20 anterior approach will be potentially life threatening  
21 in every case. And at present, there is no  
22 consistently successful strategy to deal with a failed

1 implant. Secondly, Dr. Kurtz has gone over the  
2 material properties of the implant, and again, because  
3 it needs to last approximately 40 years, I think it  
4 precludes the use of high molecular weight  
5 polyethylene.

6 The other issue I have with the implant is  
7 its fixation into the bone. You need immediate  
8 fixation as well as long-term stability and I think  
9 this is inadequate. This would prevent any loosening,  
10 subsidence or migration to the implant, which is a  
11 major issue. If these problems occur, the implant  
12 will fail. It would cause altered motion at the  
13 segment in question as well as the adjacent segments.  
14 It is important to note if that should occur, then all  
15 the advantage of a motion device will be lost and all  
16 the disadvantages of alter kinematics and applied  
17 forces to this segment of surgery and also adjacent  
18 segments would be a problem.

19 The screw pegs and spikes are only  
20 adequate in short-term and will fail under tensile  
21 loading. The other properties of the successful disc  
22 prosthesis would involve range of motion and mobility

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1 and the implant should reproduce near normal range for  
2 motion and stability. And again, if that doesn't  
3 happen, kinematics and loading of the segment is  
4 altered.

5           Regarding the link disc specifically, we  
6 have clinical series in Europe, Australia, United  
7 States that essentially report results equivalent to  
8 fusion in regard to pain relief. The U.S. trial is a  
9 prospective randomized trial with a control, an  
10 Anterior Lumbar Interbody Fusion with a BAK cage  
11 implant. And they have clearly defined outcome  
12 criteria. The U.S. trial produced superior clinical  
13 outcomes to the BAK control, but there are published  
14 studies that show significant re-operation rates  
15 between 5 and 20 percent with complication rates  
16 reported greater than 10 percent. The U.S. study has  
17 shown re-operation rates of 5 percent for implant  
18 failure at 24 month follow-up and no series has  
19 greater than 11 years follow-up.

20           Regarding the materials of the disc  
21 replacement, Dr. Kurtz has talked about the  
22 polyethylene that we explanted. It is clear that I

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1 don't think the polyethylene as they have in this  
2 implant will last anywhere near 40 years or the  
3 lifetime of the patient. Polyethylenes can be cross-  
4 linked. This would significantly reduce wear. It has  
5 been shown in total hip arthroplasty, but that is not  
6 the polyethylene that is in this implant.

7           The forces in the lumbar spine are far  
8 different than in the hip. The loading is different.  
9 The wear properties will be different. I concede that  
10 point. Also, the spine is not a synovial joint, so  
11 some of the things that are problematic for  
12 polyethylene in a hip would not be happening at the  
13 spine. However, we can see that the polyethylene does  
14 break down and potential to cause polyethylene  
15 fragments, which could induce osteolysis or at least  
16 severe inflammatory reactions which make revisions far  
17 more difficult.

18           The fixation of the implant to the bone is  
19 considerably compromised. The metal base is secured  
20 with a press fit with little spikes. This is not  
21 adequate and will predictably fail. Since the implant  
22 in the U.S. study has no porus coding for bony

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1 ingrowth, it really doesn't have any chance to achieve  
2 significant fixation at a later time. So it is  
3 susceptible to loosening. There are reports of  
4 dislocation of polyethylene core as well as metal  
5 implants and incidents of subsidence of the implant  
6 anteriorly, posteriorly and laterally.

7 One of the problems with implanting these  
8 devices is the base plate has to be large enough to  
9 fit the entire rim of the disc. If it doesn't do  
10 that, it will settle into or subside into the soft  
11 portion of the end plate. Therefore, one needs to be  
12 skilled enough to get the exposure to get this implant  
13 in the right position, otherwise, it will be  
14 susceptible to failure.

15 And I guess my last point would be that  
16 the surgeons who would be doing the surgery need to be  
17 skilled at getting that exposure, otherwise there are  
18 going to be problems with the implant. I had some  
19 comments about kinematics. Basically, the implant,  
20 even if it is placed in the exact right position, with  
21 the way the link is designed, it is still anterior to  
22 the incident axis or rotation of disc space, which

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1 would be likely to increase forces at the facet joint,  
2 another area that can cause pain, also it has been  
3 shown that there is increased rotational translation  
4 of this implant, which would again affect the facet  
5 joints.

6 We have evidence that even with the  
7 implant, in, there is a significant amount of facet  
8 degeneration that occurs either before the implant was  
9 placed, and in the case of that patient, or occurred  
10 after the implant was in approximately three years.  
11 I would like to just conclude that because of my  
12 experience revising a failed link, I think that it is  
13 a problem and that the idea that we're just going to  
14 fail -- rescue failed disc replacement with posterior  
15 fusion will probably not work. It didn't work in our  
16 experience and it hasn't worked in published studies  
17 so far.

18 Therefore, we will have to remove them  
19 from the anterior approach and the potential  
20 complication from the anterior approach to the spine  
21 is life threatening in every case, and that only  
22 surgeons with extension training and experience with

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1 anterior lumbar spine surgery and placing of spinal  
2 implants should be involved in the surgery. Thank you  
3 for your attention.

4 CHAIRPERSON YASZEMSKI: Thanks very much,  
5 Dr. Peloza. I'll next ask Dr. Polly to come up. Dr.  
6 Polly is a professor and chief of spine surgery at the  
7 University of Minnesota. Dr. Polly?

8 DR. POLLY: Thank you, Dr. Yaszemski and  
9 Panel Members. You've stated my current job position  
10 and my area of expertise is in spine surgery. My  
11 disclosure statement, I paid my own way for travel to  
12 the D.C. area where I lived until about six months  
13 ago. I drove up on my own from Bethesda. Given the  
14 current cost of gas, that's a different experience  
15 than it was a year ago. In terms of relationships  
16 with companies, in the past years I have conducted  
17 teaching programs for DePuy, Medtronic and Synthes in  
18 an unpaid fashion. Since my departure from the  
19 military, I now have a consulting relationship with  
20 Medtronic.

21 I'm excited about this new technology of  
22 disc arthroplasty. It is my professional hope that it

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1 will allow us to make patients better and to achieve  
2 these results faster than current fusion technology.  
3 This technological advance represents a paradigm shift  
4 in our expectations of spinal implant performance.  
5 Until now, all spinal implants were temporary internal  
6 stabilizing structures serving their purpose until the  
7 biologic solution of fusion was achieved.

8 Disc arthroplasty represents a new level  
9 of demand in that it is expected to function for the  
10 remaining lifetime of the patient. When it succeeds,  
11 it will be a quantum leap forward. When it fails, it  
12 will be a substantial revision challenge. The  
13 challenges facing disc arthroplasty after its approval  
14 will include the challenge of indications, both on  
15 label as approved by the FDA and off label as defined  
16 by clinical use and clinical experience as well as the  
17 challenge of revisions.

18 Revisions of any implant device are  
19 inevitable. These revisions will be due to infection,  
20 dislodgement, malposition and eventually to wear or  
21 wear debris. The initial conventional thought as a  
22 result of our clinical experience with threaded

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1 cylindrical interbody devices, such as the BAK and the  
2 TFC was that for a well-positioned device all that was  
3 needed was an instrumented posterior or post lateral  
4 fusion. This is a relatively low risk procedure and  
5 the benefits of a motion device would certainly seem  
6 worth it.

7           Emerging non-U.S. data suggests that this  
8 unfortunately may not be the case. Specifically, the  
9 series by Cinotti showed that only three of eight  
10 cases established in this fashion has good or  
11 excellent results. Dr. Van Ooij will describe his own  
12 experience in those series with larger numbers.  
13 Professor Frasier from Australia in his experience  
14 with a different motion device found that better  
15 clinical results were achieved with the combined  
16 anterior and posterior salvage strategy. But  
17 unfortunately, this comes at a price.

18           In his series of eight revisions, five  
19 were converted to ALIF where he used a contralateral  
20 anterior approach, and even so there were still two  
21 major vascular injuries. So it is imperative that  
22 implanting surgeons understand the difficulties

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1 associated with revision procedures and that these  
2 revisions are potentially life threatening. They must  
3 then ask themselves if they are prepared to undertake  
4 such revision cases. If they are not prepared to do  
5 so, then they must ask themselves if they ought to be  
6 implanting the device.

7 I know that my current group as a regional  
8 referral center will be facing these difficult  
9 revision cases whether we ever implant a single device  
10 or not, and I expect this will be a daunting task.  
11 Any anterior revision case is high risk. Iridal  
12 injuries come, but we can certainly place iridal  
13 stance to aid identification and facilitate repair  
14 should an injury occur, that's why identification and  
15 mobilization do to scar formation is extremely  
16 problematic. To date, most of the time if the vessels  
17 could not be adequately mobilized, there were  
18 alternative salvage strategies available.

19 Given the bulk of all the current disc  
20 arthroplasty designs, significant vessel mobilization  
21 will be required. If the implant must come out, such  
22 as will be the case for dislodgement or infection,

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1 then the vessels will have to be adequately mobilized  
2 so the revision will be not be able to be  
3 accomplished. Strategies for minimizing vascular  
4 scarring and allowing remobilization will be crucial  
5 for lessening the risk associated with inevitable  
6 revisions.

7 The concept of joint registries has  
8 appeal. Lessons learned from the Swedish Joint  
9 Registry have been helpful in early identification of  
10 problems that otherwise would have taken much longer  
11 to detect. Such a registry could provide early  
12 warning and possible avoidance of significant problems.  
13 However, U.S. experienced today from the American  
14 Academy of Orthopedic Surgeons attempts to develop  
15 such a hip and knee registry has had minimal success  
16 with less than 300 cases having pre and post-operative  
17 data enrolled in the registry to date.

18 This was an effort that initially predated  
19 the HIPAA constraints that make such prospective data  
20 collection even more difficult. Unfortunately, I  
21 suspect that our current legal and regulatory  
22 environment would preclude this from being a

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1 successful venture. In summary, it is in all of our  
2 best interests that this device is used prudently,  
3 trained for intensively and lessons learned  
4 disseminated widely. I look forward to hearing the  
5 presentation of the complete clinical trial data and  
6 the Panel's deliberation. Thank you very much.

7 CHAIRPERSON YASZEMSKI: Thanks very much,  
8 Dr. Polly. I would like to ask now if there is anyone  
9 else present who would like to address the Panel? If  
10 so, please, raise your hand, get recognized and come  
11 forward. Seeing no one, we will now proceed to the  
12 sponsor's presentation on this PMA for the DePuy  
13 Charite Artificial Lumbar Disc intended for spine  
14 arthroplasty in skeletally mature patients with  
15 degenerative disc disease at one level, from L4 to S1.

16 We will have the sponsor and FDA  
17 presentations before lunch. After lunch, the Panel  
18 will deliberate on the approvability of the PMA.  
19 Before the Panel votes, there will be another open  
20 public hearing and a time for FDA and sponsor  
21 summations. I would like to remind public observers  
22 at this meeting that while this meeting is open for

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1 public observation, public attendees may not  
2 participate, except at the specific request of the  
3 Panel.

4 We will begin now with the sponsor  
5 presentations. The first, DePuy Spine Incorporated  
6 speaker is Mr. William Christianson, Vice President of  
7 Clinical and Regulatory Affairs. He will introduce  
8 the other DePuy Spine presenters. Mr. Christianson?

9 MR. CHRISTIANSON: Good morning, Mr.  
10 Chairman and ladies and gentlemen of the Panel. I am  
11 very pleased to be here today to report the results  
12 from the PMA for the Charite Artificial Disc. My name  
13 is Bill Christianson and I am the Vice President of  
14 Clinical and Regulatory Affairs. I am a full time  
15 employee of the sponsor, DePuy Spine.

16 The Charite Artificial Disc is a lumbar  
17 disc prosthesis. It is composed of two cobalt  
18 chromium end plates and an ultra high molecular weight  
19 polyethylene core. The device is indicated for  
20 degenerative disc disease at a single level, at either  
21 L4-L5 or L5-S1 and we're here today to present the  
22 results from our multicenter IDE study with 24 months

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1 follow-up.

2 The presenters today will be myself, I've  
3 already been introduced, Dr. Paul McAfee from Towson  
4 Orthopedic Associates of Towson, Maryland, Bryan  
5 Cunningham from the Union Memorial Hospital,  
6 Baltimore, Maryland, Dr. Scott Blumenthal from the  
7 Texas Back Institute of Plano, Texas and George DeMuth  
8 a statistician from Stat-Tech Services. In addition,  
9 we have a number of other consultants with us who we  
10 may introduce later to answer specific questions that  
11 may be raised by the Panel.

12 This device is different from previous  
13 devices presented before this Panel because it has an  
14 extensive clinical history outside the U.S. The  
15 device studied in our IDE study has been available in  
16 Europe since 1987. You will hear today about the  
17 extensive biomechanical characterizations and animal  
18 studies we have performed on this device and the Level  
19 1 randomized prospective data from our IDE study. We  
20 believe that you will agree with us that the Charite  
21 Artificial Disc is safe and effective after you have  
22 reviewed our data, and we hope that you recommend

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1 approval for this device at the end of deliberations.

2 I am currently passing around an  
3 instrumental model of the Charite Disc and the spine  
4 model and a loose device for you to look at during the  
5 course of our presentations. Now, I would like to  
6 introduce Dr. Paul McAfee.

7 CHAIRPERSON YASZEMSKI: Thanks, doctor.  
8 Thank you, Mr. Christianson. Dr. McAfee?

9 DR. MCAFEE: Thanks very much. I'm Paul  
10 McAfee. I'm the Chief of Spine Surgery at St.  
11 Joseph's Hospital. I'm a consultant with DePuy Spine.  
12 I have a financial interest in the product. I'm the  
13 inventor of a cervical disc replacement made out of  
14 the same biomaterials. Five key points I want to  
15 emphasize.

16 First, the design of often the experience  
17 with two early prototypes. Second, the design mimics  
18 the motion of the intact disc. Third, there are  
19 substantial clinical use outside the USA. Fourth,  
20 there are some minimal reports of adverse events, but  
21 there are good results long-term. The inventor of the  
22 SB Charite Prosthesis, the S is for Schellnack, the B

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1 for Karin Buttner-Janz, two time olympic gold medal  
2 winner in Munich in 1972 and by 1984 she had developed  
3 with Schellnack the world's first artificial disc.

4 There was Type I and Type II, but these  
5 were just experimental prototypes. They were never  
6 commercially available and there is only 58 implants  
7 in 49 patients, so nine of these were double  
8 implantations. The original biomaterial was  
9 manufactured out of non-forged stainless steel,  
10 similar to a bottle cap. It was not inserted by  
11 spinal specialists.

12 The first SB Charite patient is still  
13 doing well. He is playing tennis. He is coming up on  
14 20 year follow-up. He still has eight degrees range  
15 of motion. The current design, it refined by Helmet  
16 Link, a Waldemar Link. It is cobalt chrome cast end  
17 plates, ultra high molecular weight gamma radiated, so  
18 partially cross-linked. It is compression molded from  
19 sheets of 10-20 polyethylene, first released in 1987.  
20 Okay. There are 7,000 implanted worldwide and 700 in  
21 the United States.

22 It was introduced in 1987 and we will be

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1 talking about the same prosthesis in the U.S. IDE  
2 study. It has a 16 year track record. It is the  
3 uncoated version. The design rationale two end plates  
4 and a convex sliding core, which is an intermediate  
5 bearing. There is less stress of the metal bone  
6 interface, decrease incidents of loosening and  
7 decrease wear debris.

8 Now, on the right side of the slide is  
9 anterior, so with normal flexion and normal center of  
10 the nucleus displaces dorsally and this is exactly  
11 what happens with flexion of the artificial disc,  
12 because of the intervening intermediate bearing. Now,  
13 the mobile bearing also allows the rotation and  
14 translation to be independent and it does reproduce  
15 the centrad, the instantaneous mapping of the center  
16 of rotation of the disc.

17 There are actually five different sizes,  
18 five sizes of footprints to match the normal spine.  
19 Four different inclinations of each end plate, 0, 5  
20 degrees, 7.5 and 10 degrees. Now, I do want to go  
21 over reports of adverse events. The first is a report  
22 by Van Ooij, published of 29 patients, but will be

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1 presented later today as 49 patients. These are  
2 infrequent complications. There is one single case of  
3 documented osteolysis in Australia and there is a  
4 single case of a fractured core in a series in Europe.

5 Experience with, we'll call it, 49  
6 patients, since that's what will be presented today,  
7 but I have studied this right from the beginning with  
8 Dr. Van Ooij, I feel these are largely problems due to  
9 improper indications and they are largely approach  
10 related complications. It is from a personal series  
11 of one surgeon. In short, these are technical  
12 complications and I believe they are not problems  
13 inherent in the disc itself.

14 For example, this is a case that was  
15 published as a case of osteolysis, but it actually was  
16 not loose, was not revised and this I interpret to be  
17 a degenerative cyst and this was not histologically  
18 confirmed. This was a histologically confirmed case  
19 which I heard presented at the Spine Society of  
20 Australia. It was a case that would not have been  
21 included in the U.S. study for several reasons.

22 First, the case was performed adjacent to

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1 a fusion at this lower level. Secondly, the  
2 polyethylene was irradiated in air and since 1997,  
3 this has been irradiated in nitrogen in a vacuum. The  
4 case was successfully revised, by the way, with a  
5 post-year fusion in Side 2. This is from Dr. David's  
6 experience, a 42 year-old woman after nine and a half  
7 years she was asymptomatic, but this core fractured.  
8 The important things are: (1) It was successfully  
9 revised with the SB Charite implant after nine and a  
10 half years, and (2) There was no systemic spread of  
11 wear debris and all this material was encapsulated  
12 within a fibrous pseudocapsule.

13 Now, there are some long-term results of  
14 the prosthesis. To date, there are 315 patients with  
15 at least 12 months follow-up in the literature. The  
16 main one is JP LeMaire in Rachis 2002. He reported  
17 107 patients, 146 implants, the mean follow-up of 11.3  
18 years. And what he found was the range of motion at  
19 10 years was 10.3 degrees flexion-extension and 5.4  
20 degrees lateral bending and 82 percent of the patients  
21 were able to return to work.

22 There is one patient that had 9 degrees

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1 flexion, 12 degrees extension for a total of 21  
2 degrees flexion-extension at 10 year follow-up. The  
3 side bending was 8 degrees to each side. So that's a  
4 total of preserved 16 degrees lateral bending after 10  
5 years. Terry David's experience of 43 patients for  
6 the first three years and then in sequences of three  
7 more years. The interesting thing was that he went  
8 from a clinical result of 63 percent excellent and  
9 good to his next series of 82 percent excellent and  
10 good and finally to 93 percent of his patients in the  
11 excellent and good category.

12 So the important take home message is not  
13 only did he technically get better, but he also --  
14 this should be thought of as a learning curve for the  
15 indications, so in the U.S. study we have got the  
16 benefits of the worldwide honing down of the  
17 indications and mainly in our inclusion criteria in  
18 the discogenic back pain, but it is important to  
19 remember that around the world they were also  
20 operating for back pain with sciatica.

21 So the range of motion, the best way to  
22 look at this is the bar on the left, you go flexion,

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1 extension and then lateral bending. This is a bench  
2 top study of the normal disc. This is a bench top  
3 study with the artificial SB Charite in place and this  
4 is JP LeMaire's experience with 100 cases at 10 years  
5 follow-up. And you can see the remarkable  
6 consistency. This is directly from the core  
7 laboratory. Every case was digitized at Union  
8 Memorial Hospital and it does document 2 millimeters  
9 of anterior translation which is afforded in our  
10 patients as a result of the mobile bearing core.

11 So in summary, the design does reproduce  
12 the motion of the intact disc. There is substantial  
13 clinical use outside the United States. The majority  
14 of the long-term data is with the uncoated end plates.  
15 The FDA wanted to do the study on the design with the  
16 most experience. The company will seek approval with  
17 the coated design. This is two layers of titanium and  
18 calcium phosphate that has been used since 1998  
19 worldwide and extensively tested in the lab.

20 There are good results in the literature  
21 and there are anecdotal reports of adverse events and  
22 we have done our best to study these so that we can

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1 make a better prosthesis. St. Joseph's Hospital was  
2 the second largest enrollment in the IDE study and I'm  
3 proud that our clinical nurses are here today. It is  
4 safe and effective. The keys are appropriate patient  
5 selection and it does require specialized surgical  
6 training. And our whole team would recommend it be  
7 approved for use in the United States.

8 Thank you very much and I'll introduce  
9 Bryan Cunningham from Union Memorial Hospital in  
10 Baltimore.

11 CHAIRPERSON YASZEMSKI: Thanks very much,  
12 Dr. McAfee. Mr. Cunningham?

13 DR. CUNNINGHAM: Thank you, Paul, and good  
14 morning. Jack, if you could que my slides? My name  
15 is Bryan Cunningham and I serve as Director of Spinal  
16 Research at Union Memorial Hospital in Baltimore,  
17 Maryland and I have a financial interest in the  
18 Charite Artificial Disc. Preclinical laboratory  
19 investigations on the Charite Disc have focused on  
20 three specific areas, these include mechanical testing  
21 and wear simulation, in-vitro biomechanical modeling  
22 and in-vivo animal modeling. Collectively, these

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1 three areas serve as the framework for the current  
2 presentation.

3 Preclinical mechanical testing of the  
4 device includes the preliminary in-vitro analyses  
5 conducted prior to 1994, as well as the FDA  
6 recommended supplementary testing, which serve to  
7 characterize the intrinsic static and fatigue  
8 properties of the Charite Disc, as well as the wear  
9 characteristics of the implant. The results obtained  
10 from the preliminary dynamic testing indicated an  
11 endurance limit of 3.7 kN based on axial fatigue  
12 loading. This is greater than the estimated 3.4 kN  
13 maximum in-vivo load reported from the literature.

14 Moreover, dynamic compression simulation  
15 indicated the calculated 10 year deformation of the  
16 Charite core to be less than 8 percent under cyclic  
17 loads peaking from 2.5 to 4.5 kN. Supplementary  
18 mechanical testing undertaken to further characterize  
19 the static properties indicated the average yield  
20 strength of the Charite core and axial compression  
21 with flexion and extension to be equal to or greater  
22 than the lumbar vertebral fracture strength which

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1 ranges from 5.0 to 8.2 kN.

2 Axial fatigue testing carried out to 10  
3 million cycles at a peak load level of 3.75 kN  
4 demonstrated a mean deformation of 6.8 percent.  
5 Moreover, compressive shear fatigue loading carried  
6 out to the same number of cycles indicated a mean  
7 deformation of 5.2 percent without evidence of gross  
8 specimen damage in any case.

9 As a third component to the preclinical  
10 mechanical testing, wear simulation with subsequent  
11 particle analysis were performed. The test materials  
12 included a total of nine Charite Lumbar Disc cores and  
13 12 end plates of the smallest configuration to  
14 represent the worst case scenario. Fatigue testing  
15 was carried out and a bovine calf serum had 25 percent  
16 concentration at 37 degrees celsius. The fluid was  
17 replaced every 200,000 to 300,000 cycles. Six of the  
18 test samples served as experimental, while the  
19 remaining three were controls.

20 Under an applied compressive load ranging  
21 from -900 to -1850 N, three of the six test samples  
22 were evaluated under coupled flexion-extension with

1 axial rotation as shown in the left picture. The  
2 remaining three were evaluated under combined lateral  
3 bending and axial rotation. Analysis conducted by  
4 Drs. McKellip and Campbell include particulate  
5 cleaning, gravimetric assessment and dimensional  
6 characterization of the implant core.

7 In plodding the average mass change per  
8 cycles completed, the Charite core indicated an  
9 average mass decrease of 1.1 milligram per 10 million  
10 cycles with a range of .4 to 1.8 milligrams. These  
11 wear rates are considerably less than those reported  
12 in the literature for total joint replacement at  
13 similar load cycles as shown. The Charite core design  
14 permitting both motions of rotation and translation  
15 may account for these findings.

16 Moreover, the lower segmental ranges of  
17 intervertebral motion and loads on the lumbar disc  
18 versus those observed in total hip arthroplasty may  
19 account for these lower wear rates. The wear  
20 particulates average .21 to 1.5 microns in size with  
21 a definitive trend of a decrease in particulate size  
22 with increasing cycles. Particle counts ranged from

1 39 to 264 per sample.

2 Based on preclinical mechanical testing,  
3 the Charite Disc offers high compressive strength  
4 properties adequate to address physiologic demands.  
5 The device provides sufficient resistance to permanent  
6 compressive deformation under fatigue loading  
7 conditions and to that end, afford sufficient fatigue  
8 strength for intended in-vivo use. Based on wear  
9 analysis, the implant generates lower levels of  
10 particulate wear debris compared to arthroplasty  
11 devices utilized in total joint replacement.

12 As a second area of investigation, an in-  
13 vitro biomechanical study was undertaken to quantify  
14 the multidirectional flexibility properties of the  
15 Charite device versus that afforded by conventional  
16 methods of spinal stabilization. A total of eight  
17 human cadaveric spines were utilized in this study.  
18 Following analysis of the intact condition, three  
19 reconstructions were performed at the L4-L5 level.  
20 These included the Charite device, two BAK cages and,  
21 as a final construct, Pedical screws were added  
22 posteriorly to create a 360 degree arthrodesis.

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1           Multidirectional flexibility testing was  
2 performed using a Six-Degree-of-Freedom Spine  
3 Simulator. Loading parameters included axial  
4 rotation, flexion-extension and lateral bending, each  
5 applied at plus minus 8 Newton Meters with peak range  
6 of motion at the operative level quantified using an  
7 optoelectronic tracking system.

8           Based on multidirectional flexibility  
9 testing, flexion and extension and lateral bending  
10 testing indicated similar results in that no  
11 statistical differences were observed between the  
12 intact condition and Charite reconstruction. However,  
13 both conditions afforded significantly more segmental  
14 motion than the BAK device or the BAK combined with  
15 Pedical screws.

16           Axial rotation indicated the segmental  
17 range of motion produced by the Charite as  
18 significantly greater than the intact condition, and  
19 both the intact and Charite were greater than either  
20 method of conventional stabilization. Analysis of the  
21 plain film flexion-extension radiographs indicated  
22 segmental translation at the operative levels

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1 averaging 2.06 for the intact condition, which was  
2 nearly reproduced at 1.9 millimeter for the Charite  
3 reconstruction.

4 Based on the preclinical biomechanical  
5 testing, the Charite reestablishes near normal  
6 kinematics to the operative functional spinal unit  
7 when compared to conventional methods of spinal  
8 stabilization.

9 The third area of preclinical  
10 investigations was based on in-vivo animal modeling.  
11 The first in-vivo project served to determine the  
12 histopathologic response following epidural  
13 application of ultra high molecular weight  
14 polyethylene particles. Histological analyses were  
15 based on review of the epidural structures, spinal  
16 cord, as well as the systemic and reticular  
17 endothelial tissues.

18 A total of 20 New Zealand White Rabbits  
19 were included in the study. These were randomized  
20 into two treatment groups, including operative Sham  
21 and the experimental group of ultra high molecular  
22 weight polyethylene. The animals were randomized into

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1 two post-operative survival periods of three and six  
2 months. In terms of particulate specifications, the  
3 particles ranged from 1 to 10 microns in size with 95  
4 percent of the implanted particles being less than or  
5 equal to 5 microns. Samples were shown to be  
6 endotoxin free based on limulus assays prior to  
7 implantation and total of 3 milligram of particulate  
8 was applied directly to the epidural site.

9 This particulate load represents,  
10 approximately, 38 times the average amount of debris  
11 generated in 10 million cycles when normalized to a 70  
12 kilogram individual. The surgical procedure consisted  
13 of a midline surgical approach followed by resection  
14 of the L6 spinose process, ligamentum flavum.  
15 Finally, we had exposure of the epidural sac. The  
16 particles were applied directly to the epidural site  
17 in dry, sterile format.

18 Postmortem blood chemistry and  
19 cerebrospinal fluid profiles were within normal limits  
20 for all assays at both time periods. Histopathologic  
21 analysis of the local epidural fibrosis using  
22 macrophage staining indicated the presence of

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1 histiocytes. There was no evidence of  
2 polymorphonuclear giant cells, spinal cord lesions or  
3 cellular apoptosis at either the three or six month  
4 post-operative intervals.

5 Based on preclinical neurotoxicity testing  
6 of ultra high molecular weight polyethylene, the  
7 debris elicits can be characterized as a chronic  
8 histiocytic reaction localized primarily within the  
9 epidural fibrosis as evidenced by macrophage  
10 infiltration. There was no evidence of an acute  
11 neural or systemic histopathologic response in any  
12 case.

13 The second in-vivo project served to  
14 evaluate the Charite device using a non-human primate  
15 model. Analyses were based on postmortem radiography  
16 and functional biomechanical testing of the operative  
17 segments, as well as histopathology of the local  
18 tissues. Baboons served as the experimental model.  
19 In this investigation these animals served as a semi-  
20 upright model for both inner body spinal arthrodesis,  
21 as well as total disc arthroplasty.

22 Following a six month survival period,

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1 plain film radiography indicated no evidence of  
2 heterotopic ossification, disc migration or end plate  
3 radiolucencies at any operative level.  
4 Multidirectional flexibility testing compared the  
5 range of segmental motion afforded by the intact  
6 spine, Charite device in blue bars, as well as a  
7 historical fusion control in yellow. No differences  
8 were observed under axial compression between the  
9 three groups. The Charite device permitted more  
10 motion than the intact spine under axial rotation and  
11 slightly less in lateral bending. No differences were  
12 observed in flexion-extension.

13 As a general trend, both the intact and  
14 Charite groups afforded significantly more segmental  
15 motion to the operative level than the autograft  
16 control under each of the three rotational loading  
17 modes. Histopathologic analysis of the local tissues  
18 directly overlying the device indicated no evidence of  
19 ultra high molecular weight polyethylene, cobalt-  
20 chrome wear debris, macrophages or cytokines based on  
21 plain and polarized light microscopic review.

22 Based on preclinical evaluation of the

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1 Charite device using a worst case scenario functional  
2 animal model, the device restored the range of  
3 segmental motion to near intact levels without  
4 evidence of end plate radiolucencies or device  
5 migration. There was no evidence of polyethylene or  
6 cobalt-chrome wear debris based on local tissue  
7 analysis.

8 As an overall summary to the preclinical  
9 investigations conducted on the Charite Artificial  
10 Disc, multiple biomechanical test batteries have  
11 demonstrated the biomechanical performance in safety  
12 margins of the smallest, thinnest, Charite Artificial  
13 Disc under extreme loading conditions.

14 Fatigue wear testing has shown very low  
15 levels of particulate generation when compared with  
16 other arthroplasty devices due to the unique design of  
17 the disc and spinal loading conditions. Cadaveric and  
18 functional animal studies have shown the device to  
19 restore motion at the operative level and, most  
20 importantly, there is no evidence of an acute neuro or  
21 systemic histopathologic response due to wear debris  
22 in the rabbit epidural model or in functional animal

1        characterization.

2                    Thank you very much.    And with that, I  
3        would like to turn the podium over to Dr. Scott  
4        Blumenthal.

5                    CHAIRPERSON YASZEMSKI:   Thanks very much,  
6        Mr. Cunningham.   Mr. Blumenthal?

7                    DR. BLUMENTHAL:   Thank you.   My name is  
8        Scott Blumenthal.   I'm a spinal surgeon at the Texas  
9        Back Institute.   I had the privilege of serving as the  
10       lead investigator.   I do have a financial interest in  
11       the Charite Artificial Disc and I will be presenting  
12       the clinical results.

13                   Some of the key points that we would like  
14       to emphasize is that this study will provide  
15       comprehensive, valid scientific Charite Artificial  
16       Disc is both safe and effective.   The Charite  
17       Artificial Disc is at least as good as an Anterior  
18       Interbody Fusion with BAK cage for treatment of single  
19       level degenerative disc disease and we'll see that in  
20       the study design, and the Charite Artificial Disc  
21       provides several important advantages over Anterior  
22       Interbody Fusion in appropriate patients.

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1           We have 15 centers across the United  
2 States. After agreeing upon a protocol with the  
3 sponsor, physicians and FDA, all local sites, gained  
4 local IRB approval. Each center was allowed five  
5 training cases followed by the randomization schedule  
6 at 2 to 1 Charite to BAK with the targeted enrollment  
7 seen at the bottom of the slide. These were the  
8 principal investigators at all the clinical sites.

9           The objective of the study was to compare  
10 the effectiveness of the Charite Artificial Disc to  
11 Anterior Lumbar Interbody Fusion with BAK cage for the  
12 treatment of single level degenerative disc disease  
13 with the hypothesis that being a non-inferiority  
14 study, that the success rate in the Charite Artificial  
15 Disc group will be at least as good as in the ALIF BAK  
16 group.

17           Key inclusion criteria, age range of 18 to  
18 60, single level degenerative disc disease at either  
19 L4-5 or L5-S1 confirmed by positive provocative  
20 discography. Minimum Oswestry scores and VAS scores  
21 were required, failure of six months or greater of  
22 nonoperative care. These patients had primary back

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1 pain with or without a pseudoradicular type leg pain,  
2 no nerve compression. They have to be judged to be  
3 able to tolerate an anterior surgical approach and  
4 agree to comply with the two year follow-up schedule.

5 Key exclusion criteria includes previous  
6 thoracal lumbar fusion, symptomatic multilevel lumbar  
7 degeneration, non-contained disc herniation,  
8 osteoporosis or other metabolic bone disease,  
9 spondylolisthesis greater than 3 millimeters or  
10 scoliosis greater than 11 degrees, spinal stenosis  
11 manifested as a midsagittal diameter of less than 8  
12 millimeters, positive straight leg rays for  
13 radiculopathy and the other exclusion criteria shown  
14 at the bottom of the slide.

15 Proposed indications for use. The Charite  
16 Artificial Disc is indicated for spinal arthroplasty  
17 in skeletally mature patients with degenerative disc  
18 disease at one level from L4 to S1. Degenerative disc  
19 disease is defined as discogenic back pain with  
20 degeneration of the disc confirmed by patient history  
21 and radiographic studies. These patients may also  
22 have up to 3 millimeters of spondylolisthesis without

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1 a pars defect at the involved level.

2 To judge success criteria we utilized four  
3 primary endpoints, that being the Oswestry Disability  
4 Index improvement of greater than or equal to 25  
5 percent from baseline to 24 months, no additional  
6 surgery at the treated level, no major complications  
7 and maintenance of neurologic status from baseline to  
8 24 months. To be considered a study success all four  
9 criteria need to be satisfied.

10 The secondary efficacy endpoints include  
11 improvement in Oswestry, pain as measured by VAS, SF-  
12 36, change in disc height, displacement of device,  
13 range of motion, duration of hospitalization and  
14 patient satisfaction.

15 Methods utilized to minimize bias included  
16 validated patient self report questionnaires,  
17 independent reviewers of both neurologic results and  
18 the radiographic results and randomization treatment  
19 was assigned the day of surgery, such that the  
20 patients were consented for either procedure and  
21 didn't find out what they got until they woke up.

22 The BAK group was chosen as the control

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1 group after a discussion with the FDA. The surgical  
2 approach is the same with similar morbidity and, at  
3 the time, the BAK was the only accepted state of the  
4 art approved technology, stand alone for the same  
5 diagnosis that we're studying.

6 The enrollment in analysis population.  
7 Enrollment started in March of 2000 and at 25 months,  
8 205 subjects were enrolled into the treatment arm  
9 receiving the Charite 99 into the BAK. Safety data  
10 will be presented on all randomized patients,  
11 effectiveness data on the intent-to-treat group, which  
12 excludes subjects not complete through 24 months,  
13 those not yet due and overdue subjects, and I will  
14 also present additional information on the 71 training  
15 cases. The follow-up status, at all follow-up  
16 intervals the total follow-up was greater than 90  
17 percent.

18 The demographics are shown in this slide  
19 looking at gender, age, age categories greater than or  
20 less than 45 years, body mass index and a target  
21 level, medical history including gait,  
22 spondylolisthesis, baseline activity level before

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1 injury and pre-op activity level were looked at as  
2 well. The summary was that no differences were noted  
3 between the groups in the majority of baseline  
4 characteristics evaluated. Statistical differences  
5 were seen in that the BAK group had a slightly higher  
6 body mass index and had a slightly lower pre-op  
7 activity level. These differences were further  
8 factored into covariate analyses and will be presented  
9 later.

10 This looks at the hospitalization and  
11 operative data with, again, in terms of levels,  
12 surgery time, estimated blood loss, similar between  
13 the two groups with the only difference being the  
14 duration of hospitalization, which favored the Charite  
15 group by, approximately, one half day.

16 As mentioned, the safety data will be  
17 looked at in the all randomized population. In  
18 summary, the Charite Artificial Disc and Anterior  
19 Interbody Fusion with BAK cage have similar adverse  
20 events profiles. These are the adverse events  
21 profiles, and I would like to highlight a couple of  
22 them.

1           There were very few AEs related to the  
2 device in either arm. The neurologic AEs were similar  
3 between the two groups. The approach problems are  
4 pretty close to identical. Obviously, fusion related  
5 issues to the fusion group only. Additional surgery  
6 favored the Charite group and, of note, there was no  
7 device infections in either arm. This further details  
8 the neurologic adverse events.

9           This details the approach in fusion  
10 related events and I would just like to highlight a  
11 couple of them. Retrograde ejaculation, always a  
12 concern in anterior retroperitoneal surgery, was low  
13 in both groups consistent with the literature.  
14 Obviously, donor site complications were seen just in  
15 the BAK fusion group and the instances of  
16 pseudoarthrosis in the BAK was 9 percent. Turn that  
17 around and it's a 91 percent fusion rate, which is  
18 consistent with the BAK IDE data.

19           There were five Charites which fulfilled  
20 the criteria for displacement or migration. Four out  
21 of five remained stable and in place. One out of five  
22 required additional fixation. In terms of the need

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1 for additional surgery, there was a lower rate seen in  
2 the Charite group. The Charite group had two  
3 removals, one early, one late. The BAK group had one  
4 re-op and one revision.

5 Revision strategies and, obviously, that's  
6 an issue here. If there is a need for revision early  
7 in the post-operative period, these can be  
8 repositioned by a repeat anterior approach. If late  
9 revisions are required, if the device is in good  
10 position, a posterior lateral fusion leaving the  
11 device in place can be performed. If the device  
12 position presents a risk, then careful redissection  
13 with repositioning or replacing the device, removing  
14 the device and performing a fusion or repositioning  
15 and fusion with the device in place.

16 The conclusion of this part is the Charite  
17 Artificial Disc is safe when compared to the ALIF with  
18 BAK cages. In the efficacy, in the intent-to-treat  
19 population, the Charite Artificial Disc is at least  
20 equivalent in overall success to the BAK. This  
21 actually shows the clinical success looking at the  
22 primary efficacy endpoints. The Charite Disc is at

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1 least as effective as Anterior Lumbar Interbody Fusion  
2 with the BAK cage with a small P-value indicating a  
3 high degree of certainty. The Charite success rate,  
4 however, is numerically superior. This breaks down  
5 the four primary endpoints with statistical  
6 significance favoring the Charite approaching, but not  
7 yet reached, in the improvement in Oswestry.

8 Other factors were considered in the  
9 covariate analysis, age, baseline, Oswestry, gender,  
10 operative level, hormone replacement therapy, pain  
11 medication, BMI, baseline activity level, sight and  
12 osteopenia. In all cases the equivalence hypothesis  
13 remained highly significant regardless of the factors  
14 considered. Sensitivity analysis was performed to  
15 evaluate the effect of non-completers via a last  
16 observation carried forward with these analyses also  
17 further supporting the primary analysis.

18 This looks actually at the Oswestry scores  
19 over time and at all follow-up intervals, the Charite  
20 group performed numerically superior with statistical  
21 superiority seen at six weeks, three months and six  
22 months. The VAS scores similarly showed numerical

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1 superiority at all follow-up intervals with  
2 statistical superiority seen at the six month.

3 In terms of pain relief, the pain relief  
4 was better in the Charite subjects than the BAK at all  
5 post-op time points, but remember this is a  
6 challenging patient population, those with symptomatic  
7 lumbar disc degeneration. The percentage of non-  
8 responders was similar or lower than prior literature  
9 for all treatment modalities for this particular  
10 diagnosis, and in the non-responders there was no  
11 evidence to implicate the facet joints.

12 The physical component score of the SF-36  
13 showed statistical superiority at all follow-up time  
14 points favoring the Charite. The mental component  
15 score showed equivalence with a change in baseline for  
16 the BAK showing statistical superiority at three  
17 months. The conclusion is that the Charite Artificial  
18 Disc is effective compared to the ALIF with BAK cages.

19 Patient satisfaction data was also looked  
20 at. The Charite outperformed the BAK at both time  
21 periods, 12 and 24 months, with statistical  
22 significance achieved at 24 and when asked whether

1 they would choose the same treatment, the same results  
2 were seen with statistical superiority at the 24 month  
3 follow-up.

4 Radiographic results, we found near  
5 physiological range of motion on flexion-extension for  
6 the Charite patients, good maintenance of disc height.  
7 We talked about the five device displacements and we  
8 also looked at heterotopic ossification. There were  
9 six at 12 months in Charite patients, 11 at 24 months  
10 with an incidence of about 4 percent. Of note though,  
11 the mean range of motion on those patients at 12 and  
12 24 months was preserved to the amount of 4.8 degrees  
13 and 5.9 degrees, respectively.

14 This shows diagrammatically the range of  
15 motion data, which certainly mimics the in-vitro data  
16 showing superiority of the Charite as to be expected.  
17 Disc height also shows that disc height was better  
18 gained and maintained in the Charite patients.

19 We also wanted to look at the all  
20 randomized patients and see how that would affect the  
21 efficacy data. The baseline characteristics were very  
22 similar. Statistical significance superiority was

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1 demonstrated, however, in more of the intervals than  
2 in the intent-to-treat group. The proportion of  
3 patients with 25 percent ODI, which was close in the  
4 intent-to-treat group, achieved statistical  
5 significance in all randomized and at more follow-up  
6 intervals, Oswestry and VAS achieved statistical  
7 significance now at six, three months, six months and  
8 12 months.

9 The SF-36 physical component still favors  
10 the Charite. Patient satisfaction favors the Charite  
11 more strongly. Range of motion and disc height  
12 results, the same as the intent-to-treat, and this  
13 further analysis supports the intent-to-treat  
14 population. This just highlights that one primary  
15 efficacy endpoint, achieving statistical significance.

16 Training cases, a couple brief words on  
17 that. We looked at the demographics and the  
18 demographics were similar between the randomized and  
19 the training cases. The AE events, however, as would  
20 be expected, were higher in the training cases. As to  
21 be expected in terms of operative data, we also found  
22 that the median length of surgery was greater in the

1 training cases, not surprising. What was surprising  
2 is that the training cases in the VAS and Oswestry  
3 outperformed the study patients. So with the same  
4 exclusion criteria, similar baseline characteristics,  
5 we had longer surgeries, higher rates of AEs in the  
6 training cases, but greater average improvement in  
7 pain and Oswestry.

8 So in conclusion, this is Level 1 data,  
9 randomized study design with minimized bias utilizing  
10 validating instruments and independent reviewers, very  
11 robust data with extremely high rates of follow-up and  
12 a high statistical significance supporting the  
13 equivalence. The Charite Artificial Disc provides  
14 advantages over the ALIF in early clinical  
15 improvement, function, pain and quality of life,  
16 shorter mean hospitalization, higher patient  
17 satisfaction and maintains its range of motion through  
18 24 months as well as disc height.

19 So going back to the primary hypothesis,  
20 I believe that we have proven this device, the Charite  
21 Artificial Disc, to be both safe and effective. Thank  
22 you. I would like to introduce George DeMuth.

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1 CHAIRPERSON YASZEMSKI: Thanks very much,  
2 Dr. Blumenthal. Mr. DeMuth?

3 MR. DEMUTH: Thank you. I'm George  
4 DeMuth. I'm a consultant to DePuy Spine and I do not  
5 have a financial interest in the company or the  
6 product.

7 I want to just touch on some statistical  
8 topics and provide some comments. I will start with  
9 the primary efficacy endpoint and the definition, some  
10 study populations of interest and that will lead us  
11 into some sensitivity analyses. After that I just  
12 want to give one slide about the response over time  
13 and then offer some conclusions from a statistical  
14 viewpoint.

15 Here the primary efficacy is one endpoint.  
16 It has four components of success and as we defined it  
17 in advance, anybody that had incomplete information  
18 just in any of the components would be treated as a  
19 failure at 24 months. In the case of this study where  
20 there are some ongoing patients, those patients  
21 obviously have missing data at 24 months, and they  
22 were going to be treated as failures. And if we

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1 include those patients in the analysis under this  
2 rule, that will always lower the response rate and it  
3 may well change the estimate of the treatment  
4 difference depending upon the distribution of the  
5 ongoing patients between the treatment groups.

6 So our ITT population consisted of  
7 completers and discontinued subjects. This is  
8 subjects that we know about their 24 month  
9 information. However, we didn't do the primary  
10 efficacy analysis on all randomized and ITT plus the  
11 overdue patients. FDA pointed that out and I think  
12 that was an oversight on our part, and I would like to  
13 present them in the next slide.

14 So our center line here our ITT analysis.  
15 We get these observed rates, 63, 53 percent in the  
16 groups. If you go up to the top two rows, you see the  
17 all randomized and the all randomized minus the not  
18 yet due, those are subjects that just haven't been  
19 followed quite long enough to make it to the 24 month  
20 window. You can see the observed rates are lower  
21 there. Two sensitivity analyses included in the PMA  
22 was an LOCF based on the all randomized and a repeated

1 measures model for the all randomized population.  
2 Those have similar observed event rates, success  
3 rates, that we saw in the ITT.

4 Most importantly though, I think, here is  
5 the difference between the BAK and the Charite. It  
6 ranges from 9 percent to 11 percent regardless of the  
7 population you choose. And if you look at the 95  
8 percent confidence balance, they are well below the 15  
9 percent barrier or a 10 percent barrier. So they  
10 clearly support a non-inferiority claim here,  
11 treatment differences consistent across the  
12 populations and our ITT population looked like the  
13 LOCF and repeated measures analysis.

14 The FDA offered some other imputations in  
15 the Panel package and only in the most extreme case  
16 where all ongoing Charite patients were failures and  
17 all ongoing BAK patients were successes could the  
18 result be made nonsignificant in terms of non-  
19 inferiority. That's an unlikely result based on what  
20 we know about the data.

21 So I just want to make a few comments on  
22 the response over time we saw in Dr. Blumenthal's

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1 presentation, some significant differences at six  
2 months and three months and six weeks, and more  
3 similar results between 12 and 24 months. We did try  
4 and look at this briefly in the primary efficacy  
5 endpoint in the repeated measures model where we got  
6 a significant difference at six months, an overall  
7 contrast that was different.

8 We also did another life table type  
9 analysis looking for a time to sustained or durable  
10 response. That wasn't significant. So there is  
11 clearly some trends towards the earlier improvement in  
12 the Charite, but we got at least one response where we  
13 didn't get analysis that was significant.

14 So just some conclusions and comments. I  
15 think these results strongly support the non-  
16 inferiority claim. The response profile is consistent  
17 with an earlier response in the Charite subjects. The  
18 all randomized results through 12 months continue to  
19 the trends that we see in the ITT analysis and the  
20 follow-up rates were well-maintained and pretty good  
21 throughout the study.

22 So I think that -- and Dr. Blumenthal

1 touched more on the safety and I wanted to talk about  
2 it, so in conclusion I think the results strongly  
3 support the efficacy and safety of Charite relative to  
4 the BAK. Now, I'm going to return the podium back to  
5 Bill. Thank you.

6 CHAIRPERSON YASZEMSKI: Thanks very much,  
7 Mr. DeMuth. Mr. Christianson?

8 MR. CHRISTIANSON: I'm Bill Christianson  
9 with concluding remarks, full-time employee of DePuy  
10 Spine. Obviously, physician training is going to be  
11 very important for the successful launch of this  
12 product if approved in the U.S., and DePuy Spine is  
13 committed to a very robust and vigorous training  
14 program that will initially start at the Spine  
15 Arthroplasty Institute. It's owned by Ethicon Endo-  
16 Surgery, a sister J&J company to DePuy Spine and a  
17 site where the IDE surgeons will be the primary  
18 faculty.

19 This will be augmented by, after a number  
20 of surgeons are trained to gain experience, regional  
21 centers dispersed around the country who will offer  
22 visitation, case consultation and web based resources.

1 These are some scenes of the Ethicon Endo Institute.  
2 There are both classroom and operating room teaching  
3 facilities, and we will use both to train surgeons in  
4 the post-approval period.

5 The Spine Arthroplasty Institute will  
6 start with 12 training modules. We already have  
7 content developed in all of these areas, including  
8 many of the areas that you have seen presented here  
9 today. The training will be identical regardless of  
10 faculty, because everything is already built and will  
11 be reproduced by all the course faculty and then, in  
12 addition to the didactic, there will be hands-on  
13 training using a Calf Spine Model in an anterior  
14 lumbar surgery simulator.

15 This concludes our presentation. You have  
16 seen a device that has got a long clinical history.  
17 It has been available outside the U.S. since 1987. It  
18 has been thoroughly biomechanically characterized by  
19 our company. You see robust clinical data  
20 constituting valid scientific evidence that the  
21 Charite Artificial Disc is safe and effective, and we  
22 believe you should recommend approval to the FDA

1 today.

2 CHAIRPERSON YASZEMSKI: Thanks very much,  
3 Mr. Christianson. I would like to thank the sponsor  
4 for their presentation. We're going to move next to  
5 the FDA presentation and while Mr. del Castillo is  
6 getting ready, I will ask the Panel. We have adequate  
7 time this afternoon to ask questions of both the  
8 sponsor and the FDA, but if any Panel Members have a  
9 question that they need to ask right now, we'll do it  
10 while Mr. del Castillo is getting ready.

11 DR. NAIDU: I have a quick question. Now,  
12 all the mechanical tests done to date have been on the  
13 polyethylene. Are they on freshly irradiated  
14 specimens or aged specimens? Can anybody answer that?

15 CHAIRPERSON YASZEMSKI: Mr. Christianson,  
16 would a representative from the sponsor care to answer  
17 that question?

18 DR. SERHERN: I'm Hassan Serhern. I am  
19 with DePuy Spine. They are shelf products.

20 DR. NAIDU: Well, what was the shelf life?

21 DR. SERHERN: Around three years.

22 DR. NAIDU: Three years? And what was the

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1 radiation dose that you used?

2 DR. SERHERN: This was 2.7 plus minus .2  
3 megarad.

4 DR. NAIDU: 2.7 megarads. So these are on  
5 three year aged specimens. Am I correct?

6 DR. SERHERN: Correct. They are in a  
7 shelf package, that is vacuumed with nitrogen.

8 DR. NAIDU: Okay. Thank you.

9 CHAIRPERSON YASZEMSKI: Okay. Thanks, Dr.  
10 Naidu. Thank you.

11 MR. DEL CASTILLO: Good morning. My name  
12 is Sergio del Castillo. I'm a biomedical engineer, a  
13 reviewer in the Orthopedic Devices Branch and the lead  
14 reviewer for the Charite Artificial Disc Pre-Market  
15 Approval Application.

16 FDA will provide several presentations for  
17 you this morning. First, I will be presenting a  
18 summary of the preclinical and clinical assessments.  
19 Dr. Jianxiong Chu will present the statistical  
20 analysis of the PMA data. Finally, Dr. Jove Graham  
21 will summarize the wear debris testing conducted.

22 The company who has presented the data has

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1 submitted their pre-market application. Therefore, my  
2 presentation will highlight the preclinical and  
3 clinical analyses that we feel are particularly  
4 important for the Panel to consider today. Specific  
5 to the preclinical data, I will provide a brief  
6 description of the Charite Artificial Disc, highlights  
7 from cadaver and animal testing and a summary of the  
8 mechanical testing conducted. I will also discuss the  
9 clinical study design, adverse events and study  
10 results. After Drs. Chu and Graham have completed  
11 their presentations later on this afternoon, we will  
12 then ask seven specific questions for the Panel's  
13 consideration.

14 Let me begin with a description of the  
15 Charite Artificial Disc, which I will refer to as the  
16 Charite from this point forward. The Charite is  
17 intended for spinal arthroplasty in patients with  
18 single level lumbar degenerative disc disease or DDD  
19 from L4 to S1. The Charite is a multi-component  
20 artificial spinal disc. It is composed of two cobalt-  
21 chrome alloy end plates and an ultra high molecular  
22 weight polyethylene core.

1           The end plates are offered in two  
2 versions, parallel and oblique. The parallel plates  
3 are designed such that the end plate surface is  
4 parallel with the core midline. The oblique end  
5 plates are designed to provide varying degrees of  
6 lordosis, hence the end plate surface is angled with  
7 respect to the core midline.

8           The surgeon is capable of forming various  
9 combinations of these end plates to match the anatomy  
10 of the patient. Although there are some references to  
11 porous coated end plates within the company's  
12 application, please, note that the device for which  
13 the company is seeking approval contains only uncoated  
14 end plates.

15           The sponsor states that the Charite  
16 permits motion at the treated spinal level with up to  
17 a total of 15 degrees bending and flexion-extension,  
18 and lateral bending and axial rotation ranges of  
19 motion that are similar to that observed for the  
20 natural disc. However, do consider that the device  
21 designed, based on the chemical testing, would permit  
22 up to 24 degrees of flexion, 32 degrees of extension

1 and lateral bending and would be unconstrained to  
2 axial rotation.

3 This provides an excellent segueway into  
4 the preclinical portion of my presentation. The  
5 sponsor presented data from several studies utilizing  
6 human cadavers, spinal units and animal specimens to  
7 study range of motion. The sponsor has already  
8 presented the Cunningham Adult Study where the range  
9 of motion in human cadaver spine units were compared  
10 to the range of motion of spine units implanted with  
11 the subject device.

12 I would just like to highlight that the  
13 results of that testing showed that the instrumented  
14 specimens exhibited a statistically significant  
15 increase in axial rotation. However, no statistically  
16 significant differences were observed in flexion-  
17 extension or lateral bending.

18 Similarly, in a study conducted by McAfee  
19 et al, biomechanical analyses were performed on  
20 implanted baboon spinal segments and control  
21 functional spinal units, which the company has also  
22 already presented. I would just like to highlight

1 that there appear to be an increased range of motion  
2 in flexion-extension and a significant increase in  
3 axial rotation for specimens implanted with the  
4 Charite compared to intact functional spinal units.

5 Because the sponsor has already summarized  
6 the mechanical testing quite nicely that was  
7 conducted, I will not elaborate on this testing any  
8 further with the exception of two comments. First,  
9 while the mechanical testing results appear to  
10 represent the expected physiological loads and range  
11 of motion, the correlation of these results to the  
12 clinical performance of the device is not known.  
13 Second, I will refer to Dr. Graham's presentation for  
14 an account of the wear debris testing conducted.

15 I would now like to summarize the clinical  
16 trial used to generate the clinical data presented in  
17 the company's application. The purpose of the study  
18 was to evaluate the safety and effectiveness of the  
19 Charite and compare it to the BAK Interbody Fusion  
20 device, which I will refer to as the BAK from this  
21 point forward.

22 Further, the studies have to demonstrate

1 the non-inferiority of the Charite compared to the  
2 BAK. That is the intent of the study was to show that  
3 the Charite would be at least as good as the BAK  
4 within a non-inferiority margin or delta of 15  
5 percent. This study was not designed to demonstrate  
6 superiority of one group over the other.

7 For the purpose of a comparison, allow me  
8 to provide some background on the control device. The  
9 BAK was approved by the pre-market application process  
10 on September 20, 1996. It is a hollow threaded  
11 titanium alloy cylinder indicated for use with  
12 autogenous bone graft in patients with degenerative  
13 disc disease at one or two contiguous levels from L2  
14 to S1. Two devices are implanted per level.

15 Although the BAK may be implanted by an  
16 open interior or posterior approach, for the purposes  
17 of this study, all control subjects were implanted  
18 with the BAK devices only via an open anterior  
19 approach. It should be noted that the Charite is also  
20 implanted using only this approach.

21 The sponsor conducted a randomized  
22 prospective multicenter clinical trial. The subjects

1 were randomized in a 2 to 1 ratio to either treatment  
2 with a Charite or treatment with a BAK, respectively.  
3 The first five subjects at each investigational site  
4 were treated with the Charite as part of the training  
5 of the surgeons. These training subjects were not  
6 included in the assessment of effectiveness.

7 As stated in the study protocol, the  
8 Charite is indicated for spinal arthroplasty in  
9 skeletally mature patients with degenerative disc  
10 disease at one level from L4 to S1. DDD is defined as  
11 discogenic back pain with degeneration of the disc  
12 confirmed by patient history and radiographic studies.  
13 Study subjects may also have up to 3 millimeters of  
14 spondylolisthesis at the involved level.

15 Subjects were also to have at least six  
16 months of conservative treatments prior to  
17 implantation. These treatments may include  
18 discectomy, laminotomy, laminectomy without an  
19 accompanying facetectomy or nuclear lysis at the level  
20 to be treated.

21 Safety and effectiveness were evaluated in  
22 terms of the complications that arose during

1 implantation and post-operatively, including  
2 infection, thrombosis, migration and subsidence, re-  
3 operation, the incidence of adverse events, the level  
4 of the subject's disability as measured by the  
5 Oswestry Disability Index or ODI and assessment of the  
6 subject's neurological status. Further assessment of  
7 the subjects was conducted radiographically by  
8 measuring changes in disc height, range of motion and  
9 flexion-extension at the involved level, displacement  
10 or migration of the implants and radiolucencies around  
11 the implant.

12 Most measures were conducted at baseline,  
13 six weeks, three, six, 12 and 24 months. This  
14 includes an assessment of the subject's functional  
15 level as measured by the ODI, the subject's  
16 neurological status, any incidence of adverse events,  
17 the subject's level of pain as measured by the Visual  
18 Analog Scale or VAS and the subject's work status.

19 Quality of life as measured by the SF-36  
20 Survey and range of motion were measured at baseline,  
21 six, 12 and 24 months. Patient history and physical  
22 examinations were recorded at baseline and 24 months

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1 only.

2           Within six months of enrollment, all  
3 subjects were measured anteriorly, posteriorly,  
4 laterally and in flexion-extension. These same  
5 measures were repeated at six weeks, three, six, 12  
6 and 24 months.

7           The primary endpoint for effectiveness in  
8 the study consisted of four components, pain in  
9 function as measured by the ODI, any device failures  
10 requiring revision, re-operation or removal, any major  
11 complications and neurological status.

12           An individual subject was determined to be  
13 a success if all of the following conditions were met.  
14 The subject's ODI score increased by at least 25  
15 percent at 24 months compared to the subject's  
16 baseline score. It should be also noted that FDA also  
17 analyzed this component with a success defined as a 15  
18 point improvement compared to baseline. Moving on,  
19 the subject experienced no device failures requiring  
20 revision, re-operation or removal, the subject did not  
21 experience any major complications defined as major  
22 blood vessel injury, neurological damage or nerve root

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1 injury. And finally, the subject's neurological  
2 status should be maintained or improved at 24 months  
3 with no new permanent neurological deficits compared  
4 to baseline.

5 Again, an individual subject is considered  
6 a success only if he or she is a success in all four  
7 components. The study was defined as a success if the  
8 overall success rate of the Charite study group is  
9 non-inferior to the overall success rate of the BAK  
10 group. In this study safety was assessed by comparing  
11 the rate of incidence of all adverse events observed  
12 in the Charite and BAK study groups.

13 The secondary effectiveness endpoints  
14 consisted of all the primary endpoint components,  
15 which I listed previously, which are pain in function  
16 as measured by ODI, device failures requiring a  
17 revision, re-operation or removal, any major  
18 complications and neurological status. Also included  
19 are pain as measured by the VAS, quality of life as  
20 measured by the SF-36 Survey, disc height, device  
21 displacement, range of motion, length of hospital stay  
22 and patient satisfaction, including a satisfaction

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1 with the procedure and whether or not the same  
2 treatment would be chosen in the future. Only  
3 descriptive statistics were used in the assessment of  
4 the secondary endpoints. I would also just like to  
5 point out that range of motion was measured only in  
6 flexion and extension.

7 Overall the subjects in both study groups  
8 were similar demographically in terms of age, body  
9 mass index and baseline ODI scores. It is noted that  
10 a higher percentage of females were enrolled in the  
11 Charite group compared to male subjects with the  
12 opposite trend noted in the BAK group. Pre-operative  
13 activity levels also differed slightly between these  
14 groups. Also of note are the higher percentages of  
15 subjects in both study groups with degenerative disc  
16 disease at the L5-S2 level compared to the L4-L5  
17 level.

18 Adverse event information was collected  
19 from all randomized subjects. Adverse events were  
20 categorized as typical or unusual, severe or life  
21 threatening, device related or not device related,  
22 severe and device related occurring within two days of

1 surgery and by date of onset.

2 This table here presents an account of the  
3 adverse events reported during the study. The  
4 percentages of Charite and BAK subjects experiencing  
5 at least one adverse event is essentially equal.  
6 However, I have highlighted some adverse events  
7 reported for a higher percentage of Charite subjects  
8 compared to the BAK group. These include infection,  
9 abdominal events, device related events and severe  
10 life threatening events.

11 This table shows some of the device  
12 related adverse events reported. It is noted that 7.3  
13 percent of Charite experienced device related adverse  
14 events compared to 4.0 percent of BAK subjects. A  
15 greater percentage of Charite subjects were reported  
16 to have experienced the following adverse events  
17 compared to the BAK group. Back or lower extremity  
18 pain, neurological events, such as numbness, motor  
19 deficit or nerve root injury and additional surgery at  
20 the index level.

21 It should be noted that the rate of  
22 adverse events was higher in the training subjects

1 group compared to the randomized subjects in the study  
2 as the sponsor has already pointed out. In the  
3 training group this may be true primarily to the  
4 slightly higher rates of prosthesis related events and  
5 additional surgeries at the index level. However,  
6 please, note that the training subjects were not  
7 included in the assessment of safety.

8 I will now present assessments of the  
9 primary and secondary endpoints. Unless otherwise  
10 noted, the analysis population, which I will refer to,  
11 which was only used to assess these endpoints, is  
12 referred to as the completers population. It is a  
13 subset of all randomized subjects who are evaluated at  
14 the 24 month time point regardless of when the 24  
15 month measurements occurred. For clarification, I  
16 have included here a table indicating which randomized  
17 subjects are not included in the completers  
18 population. This population contains 86 percent and  
19 79 percent of all randomized Charite and BAK subjects,  
20 respectively.

21 Using the completers population, the  
22 overall success rates for the Charite and the BAK

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1 groups are 64 percent and 58 percent, respectively.  
2 Although these rates differ slightly from what the  
3 company has presented, considering the overall success  
4 rate is within a non-inferiority margin or delta of 10  
5 percent of the BAK overall success rate, it appears  
6 the study has demonstrated the non-inferiority of the  
7 Charite compared to the BAK. Dr. Chu will provide  
8 more details regarding the assessment of overall  
9 success and effectiveness during his presentation.

10 Listed here are the success rates for the  
11 individual components of the composite endpoint. None  
12 that the success rates among the completers are  
13 comparable between the two groups and the ODI  
14 component or ODI score appears to be the major reason  
15 of overall failure at 24 months.

16 A subject was considered improved in the  
17 Oswestry secondary endpoint if the subject's ODI score  
18 had increased by at least 25 percent at 24 months  
19 compared to the baseline ODI score. At 24 months  
20 using the completers analysis population, 72 percent  
21 of Charite subjects had improved compared to 63  
22 percent of BAK subjects.

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1                   Here is a listing of the SF-36 Quality of  
2 Life Survey scores for all randomized subjects who had  
3 data available. 73 percent of Charite subjects and 66  
4 percent of BAK subjects had a 15 percent or greater  
5 improvement in the Physical Composite Score or PCS at  
6 24 months. 50 percent and 55 percent of subjects had  
7 a 15 percent improvement for the Mental Composite  
8 Score or MCS, respectively.

9                   Note that the amount of data used to  
10 assess the PCS and MCS rates of improvement are much  
11 less compared to the number of randomized subjects in  
12 the study. Further, the observed differences in  
13 improvement between the Charite and BAK groups are not  
14 statistically significant.

15                   In the Charite group radiolucencies were  
16 identified in 1 percent of the subjects at 24 months.  
17 Longitudinal ossifications were identified in 6  
18 percent at 24 months. It is noted that in the BAK  
19 group, 5 percent of subjects experienced  
20 pseudoarthrosis at 24 months. Note also that the  
21 interpretations of these radiolucencies are  
22 inconclusive. We believe these data were adequately

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1 captured in the safety analysis. Therefore, we will  
2 not provide any further comment.

3 Neurological status was maintained at 24  
4 months for 77 percent of Charite subjects and 76  
5 percent of BAK subjects. About 5 percent of Charite  
6 subjects experienced slight or significant  
7 deterioration of their neurological status compared to  
8 about 8 percent of BAK subjects.

9 A subject was considered a success in pain  
10 if the individual's VAS score decreased by at least 20  
11 millimeters compared to the individual's baseline  
12 score. Within this definition, 75 percent of the  
13 Charite subjects were considered successes compared to  
14 70 percent of BAK subjects at 24 months. It is noted  
15 that 12 percent of Charite subjects reported only some  
16 pain relief and 13 percent experienced no change or an  
17 increase in pain. The etiology of this unrelieved  
18 pain is unknown. However, the data do demonstrate  
19 non-inferiority of the Charite in terms of maintenance  
20 or improvement in pain.

21 No conclusions can be made regarding the  
22 time to improvement. The study was designed to

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1 demonstrate non-inferiority at the 24 month time point  
2 only. In the Charite group, no subjects had a  
3 decrease in disc height greater than 3 millimeters at  
4 24 months while 4 percent of BAK subjects lost more  
5 than 3 millimeters in disc height. Overall, disc  
6 height is maintained or improved over time in both  
7 study groups with roughly equivalent maintenance of a  
8 24 month time point.

9 Vertebral range of motion was measured on  
10 lateral flexion-extension views using the Cobb Method  
11 at the operating level with measurements recorded at  
12 the three, six, 12 and 24 month time points. The mean  
13 flexion-extension range of motion for subjects with  
14 available data was 4.9, 6.0, 7.0 and 7.4 degrees,  
15 respectively.

16 The histogram shown here displays the  
17 range of values recorded for subjects with available  
18 data at 24 months. Notice the wide range of values  
19 obtained, which range between 0 degrees and 24  
20 degrees. Again, please, note that lateral bending and  
21 axial rotation were not measured in this study.

22 Considering that one of the principal

1 theoretical advantages of disc replacement devices is  
 2 the preservation of segmental motion, FDA considered  
 3 the correlation between overall success and range of  
 4 motion observed. An analysis of these two variables  
 5 was conducted. In this table, success and failure  
 6 rates at 24 months for Charite subjects are compared  
 7 with a range of motion data. It appears that subjects  
 8 experiencing range of motion in the 5 to 7 degrees  
 9 range were more likely to be successful than subjects  
 10 experiencing different ranges of motion. However, the  
 11 association of range of motion with overall success is  
 12 not statistically significant.

13 This concludes my presentation of the  
 14 preclinical and clinical assessments. So allow me to  
 15 highlight the major points we would like you to keep  
 16 in mind as we continue with the remaining  
 17 presentations.

18 The study was designed to demonstrate non-  
 19 inferiority of the Charite compared to the BAK. It  
 20 was not designed to demonstrate superiority over the  
 21 BAK in any of the clinical measures. The Charite  
 22 demonstrated non-inferiority to the BAK with respect

1 to the primary endpoint. Overall, the number of  
2 adverse events in the Charite and BAK groups were  
3 roughly the same with a higher rate of incidence in  
4 only a few categories for the Charite group.

5 The Charite was able to maintain pain and  
6 function up to 24 months. Some subjects reported only  
7 some pain relief and a few experienced no change or an  
8 increase in pain. And finally, it is unclear how  
9 range of motion is related to the clinical outcomes if  
10 at all. I will now turn the podium over to Dr.  
11 Jianxiong Chu who will provide a presentation of the  
12 statistical analysis of the PMA data.

13 CHAIRPERSON YASZEMSKI: Thanks very much,  
14 Mr. del Castillo. Dr. Chu? While Dr. Chu is getting  
15 ready, I will ask my Panel colleagues to remember that  
16 our discussion this afternoon will need to be focused  
17 on answering these questions that the FDA presents to  
18 us and ask that you begin to consider them.

19 DR. CHU: Hi. Good morning. My name is  
20 Jianxiong "George" Chu. I am an a statistician at the  
21 CDRH. I'm glad to have this opportunity to present  
22 some statistical summary for the Charite Artificial

1 Disc and today my talk will focus on the sensitivity  
2 analysis for the primary endpoint, which is patients'  
3 overall success at 24 months followed by my comments  
4 with regard to the sponsor's claim about some of the  
5 secondary endpoints.

6 To demonstrate that Charite provide  
7 equivalent functional improvement and pain relief, as  
8 well as equivalent to the way the device fares  
9 compared to the BAK cage, the study was designed to be  
10 a prospective multicenter randomized controlled non-  
11 inferiority trial. Patients of age 18 to 60 years-old  
12 with single level DDD at L4 to S1 were to be  
13 randomized at 2 to 1 ratio of Charite to BAK.

14 Please, also note that the patients ODI  
15 score have to be at least 30 in order to be included  
16 in this study. After implantation, the patients will  
17 be followed at six weeks, three months and up to 24  
18 months. Please, note that the primary endpoint  
19 individual success rate was evaluated at 24 months.

20 As our lead reviewer has mentioned, the  
21 study's primary endpoint consists of four components  
22 and the patient's overall success rate at 24 months

1 has to meet all the following four criteria, 25  
2 percent at least improvement in ODI score compared to  
3 the baseline, no major device adverse event, no device  
4 failure requiring revision of the operation or removal  
5 and also the maintenance or improvement in  
6 neurological status with no new permanent neurological  
7 deficit.

8 So what does non-inferiority really mean?  
9 To demonstrate that Charite Disc is not worse than the  
10 control, BAK, by more than a certain margin called a  
11 delta with regard to the success rate at 24 months.  
12 So you can think of the delta as a maximum tolerable  
13 inferiority. We are waiting to accept, considering  
14 the other potential benefits, for the Charite  
15 potential benefits.

16 Please, also note the delta was pre-  
17 specified at 15 percent in the sponsor's protocol, but  
18 the FDA believes that 10 percent non-inferiority  
19 margin is more clinically appropriate. So all my  
20 little analysis will use 10 percent delta margin.

21 Corresponding to the study objective to  
22 demonstrate that Charite Disc is not worse than the