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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

ORTHOPAEDICS AND REHABILITATION DEVICES

ADVISORY PANEL

OPEN SESSION

This transcript has not
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Thursday, August 9, 2001

9:35 a.m.

Walker/Whetstone Room
Gaithersburg Holiday Inn
2 Montgomery Village Avenue
Gaithersburg, Maryland 20879

PARTICIPANTS:

Harry B. Skinner, M.D., Ph.D., Chairperson
Haney Demian, Executive Secretary

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Albert J. Aboulafia, M.D.
Edward Y. Cheng, M.D.
Maureen Finnegan, M.D.
Kinley Larntz, M.D.
Stephen Li, Ph.D.
John Lyons, M.D.
Sanjiv Naidu, M.D.
Clayton Peimer, M.D.
Douglas Wright, M.D.

NONVOTING MEMBERS:

Sally Maher, Esq., Industry Representative
Robert A. Dacey, Consumer Representative

FDA:

Celia Witten, M.D., Ph.D.
John Goode, M.S.
Phyllis Silverman, M.S.

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P R O C E E D I N G S

Call to Order

MR. DEMIAN: Good morning, everybody. We are ready to begin this meeting of the Orthopaedics and Rehabilitation Devices Advisory Panel.

My name is Haney Demian, and I am the Executive Secretary for this panel, and I am Acting Branch Chief of the Orthopaedics Devices Branch.

I would like to remind everyone that you are requested to sign in on the attendance sheets at the tables by the door. You may also pick up an agenda and information about today's meeting, including how to find out about future meeting dates and how to obtain meeting minutes or transcripts.

I will read two statements that are required to be read into the record--the Deputization of Temporary Voting Members Statement and the Conflict of Interest statement.

"Appointment to Temporary Voting Status. Pursuant to the authority granted under the Medical Device Advisory Committee Charter dated October 27, 1990 and as amended August 18, 1999, I appoint the following individuals as voting members of the Orthopaedics and Rehabilitation Devices Advisory

1 Panel for this meeting on August 9, 2001: John
2 Lyons, Douglas Wright, Kinley Larntz, Clayton
3 Peimer, and Sanjiv Naidu. For the record these
4 individuals are Special Government Employees and
5 consultants to this panel. They have undergone a
6 customary conflict of interest review and have
7 reviewed the materials to be considered at this
8 meeting."

9 "In addition, I appoint Dr. Harry Skinner
10 to serve as panel chair for the duration of this
11 meeting."

12 This is signed by the Director of Center
13 for Devices and Radiological Health, Dr. David
14 Feigal.

15 Orthopaedic and Rehabilitation Device
16 Panel Meeting, August 9, 2001, Conflict of Interest
17 Statement.

18 The following announcement addresses
19 conflict of interest issues associated with this
20 meeting and is made part of the record to preclude
21 even the appearance of any impropriety.

22 To determine if any conflict existed, the
23 agency reviewed the submitted agenda for this
24 meeting and all financial interests reported by
25 committee participants. The conflict of interest

1 statute prohibits Special Government Employees from
2 participating in matters that could affect their or
3 their employers' financial interests. Due to this
4 prohibition, Dr. Michael Yaszemski will not
5 participate in today's session of this meeting.

6 However, the agency has determined that
7 participation of certain members and consultants,
8 the need for whose services outweighs the potential
9 conflict of interest involved, is in the best
10 interest of the Government. Therefore, waivers
11 have been granted for Drs. Edward Cheng and Stephen
12 Li for their interest in firms that could
13 potentially be affected by the panel's
14 recommendations. These waivers permit them to
15 participate fully in all matters before today's
16 panel.

17 Copies of these waivers may be obtained
18 from the agency's Freedom of Information Office,
19 Room 12A-15 of the Parklawn Building.

20 We would like to note for the record that
21 the agency also took into consideration other
22 matters regarding Drs. Li and Finnegan. These
23 panelists reported interest in firms and issues but
24 in matters that are now concluded and are not
25 related to today's agenda. The agency has

1 determined, therefore, that they may participate
2 fully in all discussions.

3 In the event the discussions involve any
4 other products or firms not already on the agenda
5 for which an FDA panelist has a financial interest,
6 the participant should excuse him or herself from
7 such involvement, and the exclusion will be noted
8 for the record. With respect to all other
9 participants, we ask in the interest of fairness
10 that all persons making statement and presentations
11 disclose any current or previous financial
12 involvement with any firms whose products they may
13 wish to comment upon.

14 Before turning this meeting over to Dr.
15 Skinner, I would like to introduce our
16 distinguished panel members who are generously
17 giving their time to help FDA in matters being
18 discussed today and other FDA staff seated at the
19 table; so we'll go around the room, and you can
20 state your name and your current area of interest.

21 Dr. Skinner?

22 DR. SKINNER: My name is Harry Skinner. I
23 am Professor and Chair of Orthopaedic Surgery at
24 UC-Irvine and Professor of Aeronautical and
25 Mechanical Engineering at UC-Irvine. My interest

1 is in adult joint reconstruction.

2 DR. NAIDU: My name is Sanjiv Naidu. I am
3 an Associate Professor of Orthopaedic Surgery at
4 Penn State College of Medicine, Hershey Medical
5 Center. My area of interest is hand and upper
6 extremity surgery. I also have an adjunct
7 appointment in the Material Science and Engineering
8 Department at the University of Pennsylvania at an
9 assistant professor level.

10 DR. LI: My name is Stephen Li. I am
11 president of a company that is weeks old, called
12 Medical Device Testing and Innovations, located in
13 Florida. My interests are in biomechanics and
14 biomaterials.

15 DR. PEIMER: My name is Clayton Peimer. I
16 am Professor of Orthopaedics at the University at
17 Buffalo for the next ten days and will be Professor
18 of Orthopaedics at Northwestern University and
19 Chair of Orthopaedics at Evanston Northwestern
20 Health Care. My area of interest is in hand and
21 upper extremity, and some of my research has been
22 on implant arthroplasty and consequences.

23 DR. ABOULAFIA: My name is Albert
24 Aboulafia. I am an orthopaedic surgeon with the
25 area of interest of musculoskeletal oncology and

1 reconstruction following tumor resection. I am
2 affiliated with the University of Maryland and the
3 Cancer Center at Sinai Hospital in Baltimore.

4 DR. WITTEN: Celia Witten, Division
5 Director of DGRND at FDA, which is the reviewing
6 division that reviews orthopaedic implants, among
7 other things.

8 MS. MAHER: Sally Maher, Smith & Nephew
9 Endoscopy, Industry Representative.

10 MR. DACEY: Robert Dacey, Boulder,
11 Colorado, Consumer Representative.

12 DR. LARNTZ: Kinley Larntz, Professor
13 Emeritus, University of Minnesota. I am a
14 statistician in the Department of Applied
15 Statistics, and my interest is research design and
16 data analysis.

17 DR. CHENG: My name is Edward Cheng. I am
18 an Associate Professor at the University of
19 Minnesota and an orthopaedic surgeon. My interests
20 are in orthopaedic oncology and adult
21 reconstructive surgery.

22 DR. WRIGHT: Douglas Wright from
23 Baltimore. I am an orthopaedic surgeon, and my
24 area of interest is fracture and foot and ankle
25 surgery. I am affiliated with the University of

1 Maryland.

2 DR. LYONS: John Lyons. I am an
3 orthopaedic surgeon and a biomedical engineer from
4 Erie, Pennsylvania. My areas of interest are adult
5 reconstruction and mechanisms of injury.

6 DR. FINNEGAN: Maurean Finnegan. I am
7 Associate Professor of Orthopaedics at
8 UT-Southwestern in Dallas and an adjunct
9 appointment at UT-Arlington in biomedical
10 engineering. My interest is trauma.

11 MR. DEMIAN: Thank you.

12 At this time, I'd like to turn the meeting
13 over to our chairman, Dr. Harry Skinner.

14 DR. SKINNER: Good morning. My name is
15 Dr. Harry Skinner, and I will be acting chairman
16 for this meeting.

17 I would like to not for the record that
18 the voting members present constitute a quorum as
19 required by 21 CFR Part 14.

20 We will now proceed with the open public
21 hearing session of this meeting. I would ask at
22 this time that all persons address the panel come
23 forward, speak clearly into the microphone, as the
24 transcriptionist is dependent on this means of
25 providing an accurate record of this meeting.

1 We request that all persons making
2 statements during the open public hearing of the
3 meeting disclose whether they have financial
4 interest in any medical device company. Before
5 making your presentation to the panel, in addition
6 to stating your name and affiliation, please state
7 the nature of your financial interest, if any.

8 Is there anyone wishing to address the
9 panel?

10 [No response.]

11 **Open Public Session**

12 DR. SKINNER: We'll move into the open
13 public session now and consider the Premarket
14 Approval application for Ascension's PMA for
15 Semi-Constrained MCP Total Joint Arthroplasty.

16 I would like to remind public observers at
17 this time that while this portion of the meeting is
18 open to public observation, public attendees may
19 not participate except at the specific request of
20 the panel.

21 We are now ready to begin with the
22 sponsor's presentation followed by the FDA
23 presentation. I would like to ask that each
24 speaker state his or her name and affiliation with
25 the firm before beginning the presentation.

1 Sponsor's presentation, please.

2 **Petitioner's Presentation**

3 DR. KLAWITTER: Thank you, Dr. Skinner,
4 distinguished members of the panel, FDA staff, and
5 interested public here today.

6 My name is Jerry Klawitter. I am the
7 founder and president of Ascension Orthopedics. I
8 have an ownership interest in this company and in
9 this product. By way of introduction to my
10 background, I am a ceramic engineer, have B.S.,
11 M.S., and Ph.D. degrees in biomedical engineering,
12 have had faculty positions for 10 years in
13 departments of biomedical engineering and
14 orthopaedic surgery. I spent 10 years from 1980 to
15 1990 developing an artificial heart valve made of
16 carbon, developed that product through innovation
17 through PMA approval. I bring these experiences to
18 the development of this particular product, which
19 for illustration is an all-carbon total joint
20 replacement for the metacarpophalangeal joint of
21 the hand.

22 We have several speakers here. We will
23 try to summarize what we submitted in support of
24 our PMA application to be able to answer your
25 questions so that you can make an informed decision

1 with regard to your recommendation to the FDA.

2 [Slide.]

3 Ascension Orthopedics is located in
4 Austin, Texas. It is a company which started this
5 endeavor in 1996 and has 24 employees. The only
6 activities we do are development of small joints,
7 so that is our entire operation. We are currently
8 24 people. We have engineering design and
9 analysis, laboratory testing, manufacturing and
10 quality systems, clinical and regulatory. We are
11 ISO 9001 certified and have had our pre-PMA QSR
12 inspection.

13 [Slide.]

14 The people presenting today will be
15 myself, presenting preclinical testing. Phil Lavin
16 will talk about clinical data audit, verification,
17 extraction, and statistical analysis. Peter
18 Strzepa will present clinical results. Dr. Robert
19 Beckenbaugh will discuss clinical need and his
20 experience, and Dr. Beckenbaugh has asked Dr. Andy
21 Palmer of Upstate Medical Center and past president
22 of the American Society for Surgery of the Hand to
23 add some clinical perspective.

24 [Slide.]

25 If we look today at MCP joint

1 arthroplasty, we find that the only devices that
2 are available are silicone rubber prostheses.
3 These are single-piece, flexible, interpositional
4 spacers. They are useful in treating late-stage RA
5 in that they mitigate pain and have an improved
6 cosmetic result. They are often not suitable for
7 high-demand patients, in our patients with
8 osteoarthritis, post-traumatic arthritis, and
9 perhaps early intervention in RA.

10 The concerns in these high-demand uses are
11 high fracture rates with the silicone devices,
12 adverse tissue reaction to particulate wear debris,
13 and a long-term loss of joint motion. These will
14 be described more completely by Dr. Beckenbaugh.

15 [Slide.]

16 The device that we are discussing here
17 today is a two-component, semi-constrained device.
18 There is a proximal ball-shaped component that
19 replaces the service of the metacarpal head and a
20 distal cup-shaped component that replaces the base
21 of the first phalanx.

22 This is a total joint replacement. It is
23 noncemented. It achieves fixation by noncemented
24 intramedullary stem, and it is made of a pyrocarbon
25 material construction.

1 [Slide.]

2 The indications for use are for primary
3 MCP total joint arthroplasty resulting from pain,
4 limited motion, subluxation, dislocation, articular
5 destruction, degenerative joint disease involved
6 with osteoarthritis, post-traumatic arthritis, RA,
7 and SLE.

8 We also indicate that there should be an
9 opportunity for soft tissue reconstruction to
10 result in and provide for joint stability.

11 [Slide.]

12 This is an example--and this is a material
13 that perhaps you have not seen before, so I'm going
24 to take a ~~few~~ ~~nan~~ ~~as~~ millimeter of pyrocarbon is

25 radiolucent, so there is this apparent seam which

1 is actually the radiolucent coating of the
2 pyrolytic carbon.

3 One can visualize this in use and from
4 this make assessments of lucency having to pay
5 attention to the fact that it does exist.

6 These devices are stabilized by direct
7 bone apposition up to the stem of the device and
8 provide for long-term stabilization without the use
9 of bone cement.

10 [Slide.]

11 The term "pyrocarbon" involves a genetic
12 class of materials called pyrolytic carbons, the
13 "pyro" meaning heat and the "lysis" portion is
14 breaking apart. These are produced using a
15 chemical vapor deposition technique whereby
16 hydrocarbon gas is heated to a very high
17 temperature, the chemical bonds between the carbon
18 and hydrogen are broken, and then they hydrogen
19 vapor deposits on whatever substrate is there--in
20 this case, it is a graphite substrate.

21 In the past, it was thought that one had
22 also to introduce a silicone-bearing organic gas in
23 it so this was allied with silicone. The process
24 control over the last 10 years or so has shown that
25 this is no longer necessary, and the materials that

1 we are talking about here are pure carbon pyrolytic
2 layers.

3 [Slide.]

4 The manufacturing process, to give you
5 some idea as to how these are produced, is a
6 high-purity, high-strength graphite core which is
7 machined into a pre-shape using a four-axis
8 computer-controlled machine operation. It is then
9 bath-coated in a fluidized bed reaction chamber
10 where hydrocarbon gases are introduced in the
11 bottom. Then, over a period of time, a precision
12 coating is placed on the device. They are removed,
13 the articular surfaces are polished, various
14 quality inspections are done, and the device is
15 packaged.

16 [Slide.]

17 The pyrolytic carbon material itself has
18 some of its characteristics. These materials are
19 very nonreactive in the body and are highly
20 biochemically compatible. The elastic modulus of
21 these materials are essentially equivalent to that
22 of cortical bone, so they are a low-modulus
23 material, which introduces a biomechanical
24 compatibility. They have isotropic mechanical
25 properties. They are high-strength--the flexural

1 strength of these materials is approximately seven
2 times that of cortical bone. They are known not to
3 undergo fatigue failure mechanism as is evident
4 with many of the metals, and they are extremely
5 wear-resistant.

6 [Slide.]

7 When we look at the history of use of
8 pyrolytic carbon in medical devices, they were
9 first used in the late sixties as materials to
10 construct artificial heart valves. Now they are
11 the material of choice. Over the last 30 years,
12 there have been approximately 2 million-plus
13 mechanical heart valves made of pyrolytic carbon
14 with 20 million-plus patient-years.

15 This is an example of an artificial heart
16 valve. There are occluders that have pivot joints.
17 This is a carbon-on-carbon joint. They open and
18 close 40 million times a year. The transvalvular
19 pressures are such that the loading on the small
20 surface areas here are very high. They resist
21 fracture, and they resist wear. These are very,
22 very durable, biocompatible materials. It was the
23 experience in cardiac valves that has brought our
24 interest to transferring this technology to the
25 development of small joints for the

1 metacarpophalangeal joint of the hand.

2 [Slide.]

3 If we look at biocompatibility, in
4 addition to the history, we have conducted tests
5 ourselves conforming to ISO and FDA regs. We have
6 looked at the results of histopathologic sections
7 on animals studies we have conducted. There is an
8 extensive amount of information in the published
9 literature regarding biocompatibility with bone,
10 and in the human finger joint, we have experience
11 which goes past 17 years.

12 [Slide.]

13 I'd like to now address an important
14 portion of our preclinical testing, and that is the
15 biomechanical testing, strength, fatigue and wear.
16 I will indicate that this actually was a
17 challenging portion for us because there is very
18 little work been done in this area in the past that
19 gives us guidance, so we have had to look to both
20 engineering tests that have been used in other
21 joints as well as develop what we think are
22 particular and demanding tests.

23 [Slide.]

24 As guidance, we looked at the biomechanics
25 of the hand. Here, I present some information

1 regarding hand strength. We are looking at the
2 relative strength of fingers, and here is the index
3 and long finger that have what we'll call relative
4 strength of 1.0; the ring finger has a relative
5 strength of about two-thirds of that, and the
6 little finger about half. This is for an adult,
7 healthy male or female, where the female strength
8 is approximately 70 percent of the male, and the
9 strength in the RA or rheumatoid hand can be only
10 10 to 30 percent that of normal.

11 So we find quite a range here in both
12 sizes of fingers and the mechanical demand.

13 In setting up the testing, we have chosen
14 the strengths of the index finger and the long
15 finger to set a very high bar, a very demanding
16 bar, that we use to test against.

17 [Slide.]

18 If we look, then, at the important factor
19 which is the joint reaction force--what are the
20 forces acting on the hand from pinch and grip--our
21 interest is to identify both the magnitude and
22 direction of a demanding load on the hand that is
23 associated with normal function of an adult male.

24 The literature teaches us that the
25 conditions of demand here are with grip with the

1 hand in approximately 60 percent of flexion; under
2 that condition, the joint reaction force is at a
3 dorsal angle of about 20 degrees and results in an
4 internal joint force of about 80 pounds of
5 load--again, the adult male. And this is an
6 isometric function.

7 In hand movement, in dynamic function, the
8 literature also reports that the joint-loading is
9 substantially less and represents something in the
10 order of 4.5 pounds.

11 [Slide.]

12 We have taken this information and then
13 developed a testing system that we use both for
14 strength and for fatigue. This is a modified ASTM
15 1440 test where we have the device in a
16 biomechanically demanding position. This is the 40
17 degrees, which is 60 degrees of flexion minus 20
18 degrees of dorsal angle. On all tests on both
19 components, we leave one-third of the stem
20 unsupported, as is done in fatigue testing of hips.
21 This is to mimic the loss of supporting bone
22 underneath the subarticular collar. It increases
23 the moments on it and looks to be in our estimation
24 a very demanding test.

25 In the fatigue testing, we conducted these

1 at 30 Hz, with an R of 10--that is, 8 to 80 pounds.

2 [Slide.]

3 When we look at the results, then, here
4 are the tests for strength and fatigue. Again, the
5 criterion is an 80-pound load which is seen by a
6 normal adult male hand. These are the components
7 that we tested--sizes 10 through 50. There are
8 five different sizes of this device. We tested
9 10's, 30's, and 50's to bracket the component
10 strength.

11 We find that even with the smallest
12 device, the strength is over two times that of the
13 load anticipated with the normal male hand, where
14 this device would likely be used in a small female
15 hand. So these device strengths are substantial.

16 We also conducted tests of 8 to 80 pounds
17 for 10 million cycles on the smallest size and
18 found no failures.

19 We are really looking here at developing a
20 mechanical testing system to build confidence in
21 the strength of these types of devices. We had to
22 do the same thing in the valve business. We are
23 making heart valves out of pyrolytic carbon,
24 life-sustaining devices. These are extremely
25 durable, and it is possible to design and

1 manufacture high-strength, damage-tolerant types of
2 devices, and I think that that is what we are
3 demonstrating here.

4 [Slide.]

5 We have also looked at wear testing. In
6 doing this, we have an MCP motion simulator which
7 goes through 90 degrees of flexion and extension.
8 In all tests, we used cobalt chrome on polyethylene
9 wear couples as controls. These are subjected to
10 14 pounds of load, which is approximately three
11 times that indicated during the biomechanics during
12 motion. They were done in bovine serum, 10 million
13 cycles.

14 Evaluation methods included optical and
15 scanning electron microscopy, surface profiling
16 using coordinate measurement machine, surface
17 roughness using laser interferometry.

18 [Slide.]

19 This is a picture of one set of our
20 simulator devices. Measurements were done using a
21 coordinate measuring machine where we could map the
22 surface of the device at point zero, and then, at
23 various intervals through the 10 million cycle.

24 [Slide.]

25 This is a map of the curvature of the

1 surface at zero cycles; this is an illustration at
2 2.5 million; and then, by entering this data into a
3 database and subtracting the two, we can tell the
4 difference at each interval.

5 [Slide.]

6 Here, it illustrate a 2.5-million-cycle
7 interval. The accuracy of the measurement was two
8 ten-thousandths of an inch, or approximately 5
9 microns. This particular subtraction shows
10 approximately one ten-thousandth of an inch or
11 unmeasurable wear.

12 [Slide.]

13 When we look at the smallest size device,
14 this is the wear seen with a metal-on-polyethylene
15 specimen. This is the average of the carbon
16 specimens that we ran. I would note that the Axi
17 polyethylene specimen here is a duplicate that we
18 produced of the Ascension Orthopedics MCP. The
19 other device is a device which is commercially
20 available in Europe, the Avanta SR surface
21 replacement. Both of these show continued
22 penetration into the polyethylene where we have
23 unmeasurable wear.

24 This corresponds well with what we have
25 seen in our experiences in heart valves, and I

1 think this is a very wear-tolerant bearing.

2 [Slide.]

3 If we look, then, and draw conclusions
4 from both the material biocompatibility that we
5 gain from our experience with animals, from our
6 experience in humans, and certainly from the
7 extended experience with heart valves as well as
8 the biomechanical testing, I believe that
9 determinations of material biocompatibility and the
10 results of demanding mechanical strength, fatigue,
11 and wear testing demonstrate device durability and
12 safety.

13 [Slide.]

14 That leads us to the presentation of the
15 clinical data. What I want to do here is take a
16 moment to indicate the steps that we have taken to
17 gather data which we feel is scientifically valid
18 and that we present to you in support of device
19 safety and efficacy.

20 This involves retrospective evaluations of
21 patients treated using pyrolytic carbon MCP joints
22 at the Mayo Clinic between 1979 and 1987. In 1996
23 we conducted a long-term patient evaluation looking
24 specifically at pre-op, post-op and last follow-up.
25 The results were submitted to JBJS and published in

1 May of 1999.

2 We took those results to a pre-PMA meeting
3 with the FDA and indicated our intentions of making
4 a PMA application. Based on those discussions, we
5 extended the evaluation to include pre-op through
6 last follow-up, looking at interim information as
7 well as extended the evaluation to examine
8 histopath slides gathered during the course of
9 treatment.

10 In the year 2000, we engaged Boston
11 Biostatistics, a clinical research organization, as
12 an independent third party. The intent here was to
13 audit and verify the clinical and radiographic
14 data, extract and compile all medical information,
15 analyze and summarize data, and conduct a
16 statistical analysis looking at study group
17 outcomes versus literature controls.

18 In addition to this--and this really forms
19 the foundation upon which we built our argument of
20 safety and efficacy as a result of the clinical
21 evaluations--we additionally conducted a case
22 series analysis where we stratified the patients
23 into two groups--osteo and post-traumatic as well
24 as RA. We have a success-failure analysis looking
25 at indications for treatment and outcome, and that

1 will be presented to you here now.

2 The first person I'd like to introduce to
3 you now is Phil Lavin of Boston Biostatistics, to
4 discuss the audit, verification, collection, and
5 analysis of data.

6 DR. LAVIN: Good morning. It is good to
7 be here.

8 I just want to give you a bit of
9 background. Our group provided support for this
10 project under a contract as an independent contract
11 research organization. BBI and myself have no
12 ownership interest or financial interest in
13 Ascension other than doing this work under a
14 contract.

15 I would like to go through with you, as
16 Jerry indicated, the results of the audit and try
17 to locate for you some of the hidden statistical
18 issues that are here and also share with you my
19 confidence in the database and its utility and how
20 it has been used in this submission.

21 [Slide.]

22 First, let me show the types of data that
23 we did in fact have available to us. When BBI
24 first took on the project, we were given several
25 large boxes similar to the type that I think you

1 folks were sent here for review today. We had
2 about four or five such boxes, and in each box,
3 there was anywhere from 200 to 400 individual pages
4 for each of the 53 subjects that were to become
5 part of the database.

6 BBI's role in this was to organize and
7 identify what was in these documents and put them
8 into categories. And to our extreme pleasure, we
9 were able to find a number of forms already in
10 there--such things as hand clinic records, such
11 things as operative reports--probably a third of
12 the data was already onto case report forms in a
13 manner that made it quite easy to be able to
14 identify the sources of information. We also had
15 quite a number of progress note reports, like
16 M.D.-to-M.D. correspondence, M.D.-to-patient
17 correspondence--quite a bit of information.

18 We also discovered an implant registry at
19 the Mayo, and we also discovered a long-term
20 follow-up questionnaire as well. This gave us some
21 real confidence in the volume of data that was
22 there. On average, there were eight different
23 clinical and subjective measures each, comprising a
24 total of 12 different postoperative contacts with
25 the patient, and the average patient had data

1 preceding the implant of approximately 3 to 5
2 years.

3 So this represents a rather complete and
4 comprehensive database in terms of its extent.

5 [Slide.]

6 Now I want to say a few words about the
7 audit. We conducted a 20 percent sample, so given
8 these charts that we had and this material that we
9 had, we wanted to find whether or not there was a
10 larger universe out there. So we went off to the
11 Mayo Clinic with our auditing group, and we went
12 through and identified the larger universe of
13 documents from which the 20 percent sample came,
14 and we are indeed able to verify that all of the
15 information that should have been there for
16 purposes of relevance to the implants was indeed
17 there. And it wasn't just implants--it was data
18 relating to hand surgeries, adverse events,
19 progress reports, and whatever. We verified that
20 everything indeed had been copied. We feel very
21 comfortable in the database that we were able to
22 extract from that, and we granted them an audit
23 certificate.

24 We feel that the database met GCP
25 standards; it was conducted under BBI SOPs, and the

1 database was able to be extracted and built. We
2 all breathed a sigh of relief when that database
3 was indeed able to be established.

4 [Slide.]

5 The processes that BBI set up in order to
6 carry this out were those that you would expect
7 from any type of prospective trial. First, we
8 wanted to confirm that the population of 53
9 subjects was indeed the entire population. That
10 took an extra day of the audit, but we conducted
11 that and verified that all 53 were indeed the 53.

12 We also were able to look at all of the
13 pre-existing forms and to try to organize the
14 database into a manner that could be used for
15 building the database and for doing statistical
16 analyses.

17 We set up CRF completion guidelines. We
18 set up conservative extraction procedures, and we
19 made no such extrapolations on the database. If
20 there was any type of comment of an adverse event,
21 we recorded it, but we would not make any back
22 inferences with respect to the pain of a patient.
23 The patient had to specifically say, or the doctor
24 had to specifically note that the patient had no
25 pain before we would ever record that. This might

1 explain why certain areas of the database were more
2 complete than another. They needed objective
3 information to be there. We would not make any
4 kind of back-inferences for it.

5 We also conducted internal audits at the
6 end of the day to make sure that our abstraction
7 team that worked to fill out our internal case
8 report forms indeed did so properly, and they also
9 passed that internal audit.

10 [Slide.]

11 Here is some of the data that we
12 extracted, and some of this, I believe the FDA will
13 also be addressing. There was quite complete
14 information on demographics the patient clinical
15 assessments, the surgical intervention information,
16 the information on the implants--like why were they
17 revised, why were they removed--and adverse events.
18 In adverse events, I as quite struck by the
19 completeness of the database--whereas when you look
20 at the literature, you are perhaps seeing two or
21 three paragraphs in any one of those papers, in
22 this database, you are seeing adverse events at
23 just about all the reports in terms of commenting
24 about the availability of said information. So
25 this database has really established an

1 order-of-magnitude higher, more complete, in terms
2 of contacts with the patients and the types of data
3 that were available there for analysis.

4 [Slide.]

5 The literature database that we
6 established was with the idea of potentially doing
7 a meta analysis. We had identified 21 papers out
8 of a universe of 70. We had looked at the data,
9 and we had seen many things in there that were
10 potentially what you might have expected.

11 In a database like this, people are pretty
12 consistent with how they might measure arc of
13 motion, extension/flexion, or ulnar deviation.
14 Sometimes the ulnar deviation might come from
15 radiology, sometimes it might come from a clinical
16 exam, one is better than the other. And obviously,
17 you know that there are issues related to the
18 completeness of it as you look through the
19 literature.

20 We found a lot of gaps in the literature.
21 Typically, there would be one paper; a paper would
22 just present the results of the exit, and there
23 would be no in-between data. Only a couple of
24 papers of the 21 that we eventually qualified
25 indeed had that in-between information. So we were

1 left with a situation where we had seven or eight
2 in-between follow-up visits, and we could compare
3 to others individually, but we never had the
4 benefit of the literature database being complete
5 enough in order to make the one-to-one comparisons.
6 So it represented a real challenge to us
7 analytically and put some handicaps, I think, on
8 being able to do the kind of meta analysis they
9 originally thought might have been possible.

10 [Slide.]

11 One thing that is really obvious here is
12 that these patients had much less follow-up in the
13 literature than they had in the Mayo Clinic study.
14 It is quite nice to be able to see the volume of
15 data that we had with the median follow-ups 10
16 years in this study. This is really quite an
17 outstanding database. It has many prospective
18 features, even though we must clearly call this a
19 retrospective trial.

20 [Slide.]

21 The other things that we had going on in
22 the trial--there was an independent radiologist
23 review; there was also an independent
24 histopathologist review of the data. In fact, Dr.
25 Palmer is here to talk to anything about the

1 radiographic review. And we conducted an audit to
2 make sure that all of that information was there as
3 well.

4 [Slide.]

5 One thing that I want to mention is to
6 harp on this point of the follow-up completeness.
7 In this study, there were 53 patients. Thirteen
8 died in the first 10 years of the trial, which is
9 what you might expect in a population with the mean
10 age in the higher 50s. This left a total of 40
11 patients. Of those 40 patients, 29 had follow-up
12 at or beyond 10 years. So we were quite favorably
13 impressed by the completeness of these information,
14 and in many of these patients, half of the
15 information would come from telephone interviews
16 and the other half would come from actual clinic
17 visits, because these patients were typically
18 committed to visiting the Mayo Clinic. So this is
19 a quite strong, comprehensive database, and I think
20 the prospective characteristics of it have made for
21 some very unusual abilities to not compare this to
22 anything in the literature in a very
23 straightforward manner.

24 [Slide.]

25 I want to try to make that point here with

1 this Hansraj survival curve. This is a survival
2 curve--the one and only of the 21 papers was
3 written by Dr. Hansraj. Dr. Hansraj's curve is
4 shown in red at the top--it is for the Swanson
5 silastic spacers--and the Ascension Orthopedics
6 product is the blue curve on the bottom.

7 One of the things that struck me when I
8 first looked at this and first read the Hansraj
9 paper--and I am hoping that some of you have had a
10 chance to look at it as well--is the unusually good
11 successes in the first two years. That is when
12 Hansraj in fact lost half of his subjects.

13 So here we are in a situation where
14 mechanically, we can draw life tables like this,
15 one can look at them and say, gee, those curves are
16 comparable, but in reality, the statistics in our
17 clinical training and disciplines tell us these
18 curves really are not directly comparable. Why?
19 Because there are 50 percent that are lost in the
20 top red curve in the first two years. And this is
21 typical of many of the other endpoints as well,
22 when there is no knowledge in the literature of
23 whether they carry forward observations, when the
24 patient's last visit was--we know when our visits
25 were, but we don't always know when the literature

1 visits were as to when the range of motion
2 assessments were, when the pain assessments were
3 made. So we are very much in a position where we
4 have generally more complete information, and it is
5 hard to make those one-on-one comparisons without
6 introducing certain biases.

7 [Slide.]

8 Now, the Hansraj paper, one might try to
9 do some kind of adjustment to it. I did not try to
10 do that, but I had been tempted. Typically, you
11 would expect a 2 to 3 percent loss per year in
12 terms of the implant failure rates if you look
13 through the literature. Typically, Hansraj, not
14 really having anyone lost in the first two years,
15 might have had a 4 or 5 percent compensation to
16 account for those lost subjects.

17 So that typically, if that were the case,
18 you would have a 90 percent 10-year rate or a 1.0
19 percent failure rate per year, and that would have
20 brought us center-stage with Hansraj.

21 [Slide.]

22 The other point that I want to end up with
23 here is that in the literature, the completeness of
24 the safety data is quite remarkable. The
25 literature, all they will give you is two or three

1 paragraphs. They won't tell you when the adverse
2 events occurred. They won't tell you all the
3 different detail of the adverse events, the things
4 which are just a few noteworthy ones--typically, a
5 subluxation, dislocation, that type of thing--you
6 would be lucky to get that in most of the papers.
7 Whereas our database had 25 to 50 types of adverse
8 events that we prospectively looked for and were
9 able to identify. This level of completeness
10 should not be held against Ascension; in fact, it
11 should be held as a standard of the completeness of
12 the information so that when you are making that
13 risk-benefit assessment, you can see that the risks
14 are really quite capped and quite finite here.

15 In terms of the study findings, the
16 follow-up was quite outstanding; many prospective
17 characteristics of the trial. It gives me the
18 confidence to know that when the survival curve is
19 drawn out there, the confidence intervals and the
20 confidence and the belief that you have in the data
21 are indeed there. So I feel good about that
22 survival curve that we drew; I don't feel good
23 about the literature data. And I think that that
24 is a very important distinction that has to be made
25 here.

1 So in conclusion, much more complete
2 information in our trial than was ever found in the
3 literature. We never had the benefit of individual
4 patient records in the literature. We couldn't do
5 a valid meta analysis. We had many person-years of
6 follow-up, many implant years of follow-up, and I
7 feel confident that when we said there were no
8 fractures that we saw currently in the trial, we
9 didn't have the left censoring [phonetic] that I'm
10 sure Hansraj had to be dealing with.

11 At this point, I'd like to turn things
12 over to Peter Strzepa, and he will share with you
13 some of the results of the clinical trials and some
14 of the methodologies.

15 MR. STRZEPA: Thanks, Phil.

16 My name is Peter Strzepa, and I am Vice
17 President of Science and Technology at Ascension
18 Orthopedics. I oversee preclinical device testing,
19 clinical studies, and regulatory submissions.

20 Aside from being an employee of the
21 company, I have an ownership interest in the
22 company.

23 [Slide.]

24 As Phil and Jerry have mentioned, the
25 clinical data in this PMA is based on a

1 retrospective case history review of 53 patients
2 who received pyrocarbon implants at the Mayo Clinic
3 between 1979 and 1987. In all, there were 147
4 ball-and-cup, semi-constrained pyrocarbon MCP
5 implants implanted in a primary implantation
6 procedure. In addition, there were four non-study
7 pyrocarbon implants which included two revision
8 pyrocarbon implants and two condylar pyrocarbon
9 implants that had a different design on the
10 articular surface.

11 [Slide.]

12 The patients who received these pyrocarbon
13 implants received them on an intent-to-treat basis.
14 The basic criteria used to determine if a patient
15 would receive an implant were that the MCP joints
16 exhibited symptoms of pain, deformity, or limited
17 function; there was radiographic evidence of MCP
18 joint disease; and in the judgment of the
19 physician, the patient would benefit from the use
20 of the device.

21 There were two basic types of patients who
22 received the implants. The first type had a
23 diagnosis of osteoarthritis or post-traumatic
24 arthritis; the second type of patient had a
25 diagnosis of rheumatoid arthritis or systemic lupus

1 erythematosis.

2 [Slide.]

3 Looking at radiographic findings,
4 actually, we analyzed all clinical data in the
5 patient database on an overall basis as well as on
6 the two main patient types. Details of the
7 demographics and follow-up and outcomes will be
8 discussed by our next presenter, Dr. Beckenbaugh,
9 one of the surgeons who implanted the devices and
10 followed the patients at Mayo Clinic. I am mainly
11 going to discuss issues associated with device
12 safety.

13 [Slide.]

14 If we look at implanted joint position at
15 last follow-up, for the OA population, we see 100
16 percent of the implants at last follow-up were in a
17 reduce position; for the RA population, we see at
18 last follow-up that 15 percent were disclosed, but
19 almost 70 percent of the implants were in a reduced
20 position.

21 [Slide.]

22 Looking at component subsidence, of the
23 194 components that had last follow-up greater than
24 one year, we see that 30 of the components had
25 subsidence greater than 4 millimeters. Almost all

1 of those components were in patients with a
2 diagnosis of RA or SLE. In the long-term, only
3 four of those components were removed; two were
4 removed due to loosening, and two were removed due
5 to subluxation of the device.

6 [Slide.]

7 Other significant device safety issues
8 that we saw were that there were no in vivo implant
9 fractures, there were no in vivo bone fractures;
10 there were, however, some intraoperative implant
11 fractures. Four of the 294 components inserted
12 fractured during insertion, and 6 fractured during
13 removal. All 10 of these devices were successfully
14 replaced with either another pyrocarbon implant
15 during insertion or revised to a silastic spacer.

16 The intra-operative bone fractures
17 occurred in one patient. The fractures were
18 grossly stable and did not require any further
19 intervention and resolved of their own accord.

20 [Slide.]

21 Other device safety issues--we did not see
22 any device implant-related infections. There were
23 two cases of superficial wound infections that
24 occurred after revision of the pyrocarbon implants
25 through a silicone spacer. There were no adverse

1 biological reactions noted to the device.

2 In terms of re-operations, there were 11
3 soft tissue reconstruction operations performed on
4 22 of the implants and 11 revision procedures
5 performed on 21 implants. Dr. Beckenbaugh will
6 further elaborate on the implant revisions.

7 [Slide.]

8 We had some histopathological slides
9 available from some of these revision operations.
10 In total, we had slides from 11 implants, 9 of
11 which were study implants and 2 were from non-study
12 implants. In all cases, no reaction to the implant
13 was noted.

14 I want to point out that there was some
15 black staining noted on tissues surrounding 7 of
16 the implants. For 4 of these implants, the black
17 staining was a result of drilling of the component
18 performed in order to remove the implants during a
19 revision operation when the carbon implants were
20 converted to silicone.

21 Black staining was also noted on two other
22 implants that were modified. One of the implants
23 was modified during the primary implantation
24 procedure by cutting off a tip of the stem in order
25 to accommodate a total wrist prosthesis that had

1 already been implanted in the patient. Another
2 black stain was noted for an implant, one of the
3 non-study revision implants, that had fractured 4
4 years after the initial revision surgery.

5 The last observation of black staining was
6 noted on the operative report for an implant that
7 was removed due to loosening. The histological
8 section was available for this particular specimen,
9 and upon reexamination revealed no particulate
10 debris nor any reaction to the implant.

11 [Slide.]

12 If we look at recurrent deformity, types
13 of complications, including ulnar deviation,
14 extension or flexion lag or contraction, or
15 rotational deformities, we saw that 49 of the
16 implants in 20 of the patients were affected by
17 recurrent deformities. Well more than half of
18 these deformities occurred less than 3 months
19 postoperatively and were treated with split
20 adjustments or changes in hand therapy post-op
21 protocol, or with soft tissue reconstruction as
22 necessary.

23 [Slide.]

24 In terms of reoperations, as I said, there
25 were 11 reoperations on 22 of the joints. Ten of

1 those reoperations occurred on RA patients,
2 typically for recurrent deformities associated with
3 soft tissue degradation or imbalance of the soft
4 tissues. Some of the post-op procedures performed
5 included open reductions, intrinsic releases or
6 transfers, extensor relocations or lengthening, or
7 tenosynovectomies.

8 The bulk of these reoperations also
9 occurred within less than one year. There was one
10 procedure at 9 years in one of the OA cases for an
11 intrinsic release.

12 [Slide.]

13 In addition to all the statistical
14 examination we did with the information in the
15 patient database that Boston Biostatistics did, we
16 did a case-by-case effectiveness analysis for these
17 implants. The approach was to first stratify the
18 patients into the two primary groups, the
19 OA/post-traumatic and the RA/SLE. We examined
20 endpoints of joint pain, extension or range of
21 motion, and joint position, and grouped implants
22 into categories of success or failure based on
23 Excellent, Good, and Unsatisfactory outcomes.

24 [Slide.]

25 The specific effectiveness criteria are

1 provided in the panel package you received, I
2 believe at pages 6 through 9, and I will just
3 review them quickly here.

4 Success for an OA required a last
5 follow-up greater than 2 years, a pain-free
6 implanted joint, a reduced implant, and increased
7 range of motion or range of motion greater than 50
8 degrees. This is typical of the types of criteria
9 upon which hips are evaluated.

10 [Slide.]

11 Failure was associated with
12 implant-related pain at last follow-up; loosening,
13 removal, or in situ fracture of the implant;
14 decreased range of motion or range of motion less
15 than 50 degrees; subluxation or dislocation of the
16 implant.

17 [Slide.]

18 There were slightly different criteria for
19 the RA patients. Success was based on a last
20 follow-up greater than one year, indicating that
21 all treatment objectives were met, a pain-free
22 implant, a reduced implant, and that the
23 maintenance of the improvements from the surgery
24 were maintained for at least 5 years.

25 [Slide.]

1 Similar to the OA, failure criteria for
2 the RA group were that the treatment objectives
3 were not met; implant-related pain at last
4 follow-up; loosening or fracture of the implant,
5 and implant removal or dislocation at a time period
6 less than 5 years.

7 Dr. Beckenbaugh will elaborate a little
8 further on the particular outcomes of this
9 evaluation.

10 [Slide.]

11 In summary, I would like to say, just to
12 hit the high points of the critical safety issues,
13 we saw no in vivo implant fractures; there were no
14 adverse biological reactions to the implant; there
15 were no implant-related infections; all of the
16 revised implants were salvageable whether they
17 occurred either during the primary implantation
18 procedure or they had to be revised
19 postoperatively.

20 In summary, there were low and acceptable
21 complication rates presenting no unreasonable or
22 significant risk of illness or injury to the
23 patients.

24 At this point, I'd like to turn the mike
25 over to Dr. Beckenbaugh to discuss further the

1 outcomes of the use of these devices and the
2 clinical need and his experiences.

3 Thanks.

4 DR. BECKENBAUGH: Thank you for the
5 opportunity of coming.

6 My name is Robert Beckenbaugh. I am a
7 professor of orthopedic surgery in the Mayo Medical
8 School and director of the Hand Fellowship
9 Department of the Hand Division of the Mayo Clinic.

10 At this time, I would like to state that I
11 am a paid financial consultant to Ascension
12 Orthopedics.

13 I would like to go over some of the
14 highlights of the long-term follow-up study that we
15 originally performed several years ago and which
16 subsequently has been redone and re-audited, as you
17 have seen in extreme detail by Boston Biomedical.

18 [Slide.]

19 We did have a study population which was
20 essentially 53 patients, 45 of whom were
21 rheumatoid/SLE, and 8 were osteoarthritis and
22 traumatic arthritis.

23 The mean age was pretty much in the
24 middle-50s. You can see we actually had one
25 patient with osteoarthritis who actually had

1 traumatic arthritis, a severe injury to his
2 metacarpophalangeal joint for which there was no
3 salvage of infusion who had the implant. Most of
4 the patients in this group were in their 50s. We
5 had one younger patient with early disease with
6 rheumatoid arthritis, but the majority are right in
7 the middle, where we expect to see our normal
8 patient population. And again, 7 of the 8 patients
9 were males with osteoarthritis trauma, where the
10 majority of patients, 44, in the rheumatoid/SLE
11 group were females.

12 [Slide.]

13 If you look at the actual percentage of
14 implantations, you see that 3 percent of the
15 implants were in osteoarthritis and there were
16 actually 5 in post-traumatic arthritis, and 43
17 implants where in rheumatoid and just 2 in SLE.

18 [Slide.]

19 If we look at our follow-ups, our mean
20 follow-ups are quite long, actually. In
21 osteoarthritis and trauma, 9.0 years, and 8.5 years
22 in the rheumatoid group. This is a very long
23 follow-up study period.

24 If we look at the number of implants
25 again, we can see 9.5 in the total number of osteo

1 implants and 7.5 for the rheumatoid implants.

2 [Slide.]

3 I think this is a very interesting curve,
4 because I don't see this kind of information
5 presented for any other group of patients followed
6 up, and there is really only one group that has
7 been followed for a long time. But if we look at
8 this chart, which you have seen briefly before, and
9 if we start out with the number of patients
10 obviously at zero years, 100 percent of them were
11 followed on the day of surgery. But as we go down
12 the area, we see some drops. But at 2 years, 3
13 patients had died, so that left 50 patients, and we
14 still had follow-up on 41 of these patients, or 82
15 percent at 2 years. And if we go to 10 years, or
16 120 months, we have 14 living patients, follow-up
17 on 29, or 73 percent.

18 So this is, I think, a rather outstanding
19 detailed study that does retrospectively look at a
20 large amount of data in patients whom we have
21 information on.

22 [Slide.]

23 One of the things that was different about
24 this device than the other ones that we have been
25 using is the range of motion. As you can see, this

1 chart shows that we took a lot of patients--we
2 essentially took all comers--patients with severe
3 disease early on and mostly later disease, and we
4 had a range of motion of 47 to 82 degrees. That
5 means that they can't extend their fingers more
6 than halfway up.

7 After surgery, we were able to correct
8 that extensor lag to this degree of motion, but
9 unlike the silicone-type devices, as we looked at
10 these at long-term follow-up which averaged, as you
11 saw, over 8 years, we found that range of motion
12 was actually maintained or slightly increased, and
13 I think all of us who do hand surgery are aware of
14 the fact that we tend to lose motion with time with
15 the silicone devices. So this was rather important
16 information for us.

17 None of these implants had fractured while
18 they were being used. We did occasionally have
19 some problems with insertion and removal. For
20 example, in the very first patient that we utilized
21 this device in, who had osteoarthritis, we did not
22 have the precise instrument that we now have. In
23 this patient, we were trying to make a very tight
24 fit, thinking that this would be necessary for the
25 appositional bone fixation, and when we hammered in

1 the implant, the stem broke off, and we had to
2 drill the stem out.

3 We had this happen on four occasions.
4 When you remove these implants--6 were fractured
5 during removal, 4 of them in one actual patient by
6 another physician--you have to sometimes drill them
7 to get them out because they are affixed to the
8 bone.

9 [Slide.]

10 We did remove this number of implants--21
11 implants total over this entire study period. We
12 moved 3 for loosening. Note we had none removed
13 for fracture; we had none removed for clinical
14 complications that we looked for--we looked for
15 evidence of bone fracture, infection, sensory
16 abnormalities, implanted joint pain, injury,
17 foreign body reaction--none required any surgical
18 intervention for this.

19 The majority of our re-operations were
20 actually fairly early on, and they were soft tissue
21 operations designed to correct the occasional
22 problems we had with these severe rheumatoid
23 patients with early recurrent deformity.

24 What we did when we started this program
25 was we used our normal silicone postoperative

1 protocol, which means that we started the motion
2 immediately within 3 to 4 days within splints. We
3 found with this particular device that the motion
4 we achieved was rather remarkable--we would achieve
5 up to 90 degrees of motion--but as we did that, we
6 would see that there would be evidence of recurrent
7 deformity, because the excess motion would stress
8 the soft tissue envelope, and as a result of this,
9 we would get some recurrent deformities, requiring
10 revisions.

11 In fact, we later on attempted to change
12 the protocol as we would now to allow 2 to 3 weeks
13 of immobilization so that we don't get this
14 excessive motion.

15 With silicone devices, you would never get
16 this kind of motion, so we didn't quite know how to
17 handle it when we first saw it.

18 [Slide.]

19 As we looked at the outcomes study that
20 Mr. Strzepa reported on, we looked at the
21 osteoarthritis outcomes, and these are really
22 rather dramatic--7 of 9 of these patients showed
23 successful, meaning Excellent or Good, results. We
24 had one implant failure in a patient who used it
25 extremely heavily, using hammers and other

1 vibration-type devices. The other patient was
2 indeterminate, and that was a patient who died from
3 ALS at a later period of time, but he was only able
4 to get back to the hand clinic for his half-year
5 evaluation as he was dealing with this disease.

6 So the successful implants had a long-term
7 follow-up period in this group from 3.5 to 17.0
8 years within our statistics. Two of these patients
9 are now greater than 20 years, continuing to
10 function in heavy labor activities like farming and
11 continuing to function with good joints. There is
12 not an arthroplasty with silicone or any other
13 device that I have ever been able to do that will
14 give me that kind of function at this long-term
15 follow-up.

16 [Slide.]

17 As we look at the rheumatoid outcomes, we
18 see that 60 percent of the implants were successful
19 in the longer-term follow-up. Now, this may seem
20 like a low number, but when we are dealing with
21 patients with a significantly progressive disease,
22 I am very happy with a 59 percent successful
23 implant rating. We know that we had failure in 27
24 percent of the implants, and much of this was due
25 to soft tissue disease. We had a number of

1 patients whom we were unable to follow who were
2 indeterminate beyond the one- to 5-year period
3 because many of these patients end up in nursing
4 homes and are unable to come back and be evaluated.
5 We made an effort to see all of them.

6 [Slide.]

7 As I look at it as a clinician from the
8 standpoint of overall safety after dealing with
9 this implant for a period of now 20 years of
10 follow-up, I feel very comfortable with it because
11 of the following, what I would consider overall
12 safety features.

13 First of all, there were no postoperative
14 bone or implant fractures. We saw no biologic
15 reactions to the implant or implant-related
16 infections. All intraoperative implant fractures
17 were able to be successfully removed and replaced
18 with another pyrocarbon implant or a silicone
19 spacer. So if this kind of adverse event happened,
20 we were able to get out of it quite easily. This
21 does not represent a major threat to a patient's
22 well-being.

23 In cases where advancing disease and soft
24 tissue degradation caused joint instability, or in
25 cases of the implant loosening, we were always able

1 to salvage the spacer; there was no unsalvageable
2 situation.

3 [Slide.]

4 The material itself in silicone versus
5 pyrocarbon devices is quite different. We know
6 that pyrocarbon is biologically extremely
7 well-tolerated, whereas we see significant reactive
8 synovitis in many patients with MCP silicone
9 devices.

10 We have a very strong material; we have
11 had no fractures with this in up to 17 years or
12 more of follow-up. Silicone devices still have
13 significant fracture rates--in my practice, they
14 would be close to 30 percent in 2- to 3-year
15 follow-up, not always associated, however, with
16 decreased function.

17 These can be constructed to actually mimic
18 more normal anatomy to act more like a normal
19 joint. The functioning that we have from spacers
20 just doesn't seem to be the case, and while we have
21 patients with both devices in place, they will
22 always volunteer to us that the device with the
23 pyrocarbon implant seems like a normal joint, and
24 the silicone does not.

25 The elastic modulus of this device is

1 similar to cortical bone. I think this has some
2 important ramifications with regard to bone
3 tolerance. It is not as hard a material as perhaps
4 the ceramic might be, and less likely to wear and
5 change its position in the bone.

6 Compared to the soft material which we
7 experience with silicone, which has plastic
8 deformation, this is a very low-friction device.
9 It wears minimally. It has almost no tissue
10 reaction and is biologically fixed by appositional
11 bone growth. I don't know whether that was clear
12 before, but we performed baboon studies as well as
13 the work that Dr. Klawitter did at Tulane
14 University with Dr. Cook, which has shown that
15 these devices are very inert, and bone grows up to
16 them appositionally, and this is the way they fit.
17 It is not by an actual direct contact or cement
18 bond to the device, but rather by appositional bone
19 growth. And we could see this very well on x-ray.

20 [Slide.]

21 The reasons I think we need a different
22 option for implants are the following. This is a
23 patient who has had a Sutter implant, and this is a
24 good device that I continue to use, but at 6 years
25 postoperative, we see a little cyst developing,

1 which looked like a little tumor, and we were
2 worried about it. The patient had pain and
3 swelling in both of these joints.

4 We explored and found that silicone-proven
5 reactive synovitis was occurring at both of these
6 joints--and we do see this with this device.

7 Here is an example of the appearance of
8 the trial. This is the actual shape of the
9 prosthesis--and this is what happened after the
10 6-year follow-up. We see deformation, small
11 fractures developing, and curvature, showing the
12 difficulty of maintaining the shape and absence of
13 the rigid design of the material. That is one of
14 the disadvantages of using silicone.

15 Here is an example of one of the newer
16 types of prostheses on the market which I
17 personally use, and at 9 months in this particular
18 patient, who was moderately active, we have already
19 seen fractures develop in both the small finger and
20 the index finger.

21 [Slide.]

22 This patient has still benefitted from
23 these surgeries, and some revisions are necessary
24 just as they were with ours early on. But the
25 advantage that we have I believe with this design

1 and this material is that we have a material that
2 does not wear and is strong, it functions more like
3 a joint, and affixes physiologically.

4 [Slide.]

5 So as we look at the design
6 considerations, we have a more physiologic design.
7 Silicone spacers do not reproduce joint function.
8 This hard material gives patients an appropriate
9 sense of well-being of a normal joint which is not
10 seen with a silicone spacer.

11 This does require soft tissue
12 stabilization for success. It is ideal in
13 osteoarthritis and traumatic arthritis and very
14 good for early rheumatoid arthritis.

15 In my personal practice, because of the
16 problems with silicone, which I do use, we
17 generally reserve this for the more advanced case
18 as a salvage procedure. It does not work well in
19 osteoarthritis and traumatic arthritis.

20 So from a clinical standpoint, we have
21 something that works well in osteoarthritis and
22 traumatic arthritis, and we basically don't use
23 silicone devices for these problems.

24 The strength approach is normal, as we
25 have seen in our study, in osteoarthritis. It is

1 definitely reduced in clinical use with
2 osteoarthritis with silicone. There is a sense of
3 normal function. It is more stable, and the motion
4 actually increases with time as compared to
5 silicone, where the motion tends to decrease.

6 Now, we do have some potential problems in
7 severe RA with stabilization of this, and in those
8 types of patients with a severe deformity
9 preoperatively, these will still require the use of
10 silicone devices which can correct these severe
11 deformities, albeit limited, with perhaps less
12 function.

13 [Slide.]

14 So as I look at this and offer some of my
15 general comments about the differences between a
16 pyrocarbon MCP prosthesis and what we have
17 available now, recurrent deformity can follow
18 procedures with both of these implants. In
19 silicone implants, we have cold flow and fracture
20 when there are subluxing forces. When we have a
21 pyrocarbon device, there is a possibility of
22 instability with subluxation, and we saw some of
23 this. But in the presence of progressive
24 rheumatoid disease, very long-term follow-up has
25 indicated that the pyrocarbon MCP prostheses are

1 equal to or better than silicone devices with
2 regard to both survival, durability, and function.

3 I have asked a colleague of mine, Dr.
4 Andrew Palmer, to comment on this thoughts about
5 the possible need for this type of device. Dr.
6 Palmer is a Professor of Orthopedics at Upstate
7 Medical University and the Director of Hand Surgery
8 and recent past president of the American Society
9 for Surgery of the Hand and is perhaps one of the
10 most respected hand surgeons in our little field in
11 this country.

12 Dr. Palmer?

13 DR. PALMER: Good morning, ladies and
14 gentlemen. My name is Andrew Palmer, and I am a
15 hand surgeon, as Bob Beckenbaugh just said, from
16 Syracuse, New York.

17 I have no financial interest whatsoever in
18 this company, Ascension Orthopedics.

19 I did train at the Mayo Clinic in the
20 mid-seventies, and at that time, Bob Beckenbaugh
21 and his colleague, Ron Linscheid, were looking into
22 small joint arthroplasties for the hand, and since
23 then, I have followed with interest, at a distance,
24 their work in this area.

25 [Slide.]

1 Since I have been in Syracuse for the last
2 25 years, a large portion of my practice in hand
3 surgery has been the treatment of patients with
4 rheumatoid arthritic conditions. I use silicone MP
5 joint arthroplasties, primarily the Swanson
6 implants, to treat these patients with pain,
7 deformity limited range of motion, and with a
8 cosmetic deformity, and I think we have been able
9 to help a lot of these people, improving their
10 function and relieving their pain.

11 I have found, however, that my patients
12 predictably only get 5 to 45 or 50 degrees of
13 motion compared to the normal 95 degrees that they
14 would normally have; that the deformity of ulnar
15 drift does tend to recur with the silastic implant;
16 that these implants predictably break--Dr.
17 Beckenbaugh used the number of 30 percent, and I
18 think that is probably what I see in my practice,
19 too; and of great concern is the number of patients
20 who have evidence radiographically of particulate
21 synovitis and bone and soft tissue involvement
22 around the MP joint.

23 Because of this, I would say that I
24 reserve silicone implant arthroplasties for my
25 patients who are rheumatoids with severe disease.

1 In fact, in my practice, I follow more patients
2 with rheumatoid arthritis with MP joint disease
3 than I end up operating on because of these
4 concerns. I almost never, because of the problems
5 of fracture, ulnar drift, and the particulate
6 synovitis, use this implant in people with
7 osteoarthritis or traumatic, those people with
8 higher demands on their hands.

9 [Slide.]

10 So in summary, I think there is a real
11 need for something that more closely replicates the
12 biology of the MP joint that has less of a chance
13 of fracture, a lower chance of particulate
14 synovitis and the problems we see with that.

15 I follow this data with interest, and I
16 think it is exciting what it offers to me as a
17 practicing hand surgeon.

18 Thank you.

19 DR. SKINNER: Thank you.

20 Are there any other comments from
21 Ascension?

22 DR. BECKENBAUGH: Yes. We have just a few
23 closing comments which may sum up what our thinking
24 is on the need for a pyrocarbon MCP prosthesis.

25 [Slide.]

1 Basically, hand surgeons today currently
2 reserve arthroplasty for severe disease and salvage
3 because of the limited expectations with silicone
4 devices.

5 The pyrocarbon MCP prostheses utilized in
6 earlier rheumatoid disease and deformities offers
7 greater potential for an improved sense of joint
8 function and strength as well as a delay in the
9 progression of the deformity of the hand, which is
10 significant in dealing with rheumatoid surgery.

11 [Slide.]

12 In osteoarthritis and traumatic arthritis
13 currently, there are no really available
14 satisfactory prostheses. This one is. In
15 rheumatoid patients with pain, early subluxation
16 and early drift, the current devices do not offer
17 improvement in function enough to warrant surgical
18 intervention, and these patients are actually going
19 without treatment.

20 There are really no down sides to the use
21 of this implant. It is salvageable without
22 detrimental effects, and it has a very favorable
23 risk-benefit ratio.

24 I want very much, as many hand surgeons
25 do, to have this in our armamentarium.

1 We thank you for the opportunity to
2 introduce this information.

3 DR. SKINNER: Thank you, Ascension
4 Orthopedics.

5 I'd like to move on now to the FDA
6 presentation.

7 John Goode, would you begin, please?

8 **FDA Presentation**

9 MR. GOODE: Good morning. My name is John
10 Goode. I am a biomedical engineer, a reviewer in
11 the Orthopedic Devices Branch, and the lead
12 reviewer for the Ascension Orthopedics Premarket
13 Approval Application for the Ascension MCP, a
14 metacarpophalangeal joint replacement device.

15 I will be presenting an engineering and
16 clinical analysis, and our statistician, Phyllis
17 Silverman, will discuss the statistical analysis of
18 the PMA data.

19 [Slide.]

20 In my presentation, I will be commenting
21 on the device description, bench testing, device
22 implantation, retrospective data collection and
23 data analysis, including the sponsor's final case
24 series analysis, and discussing adverse events and
25 complications.

1 Then, Phyllis Silverman will discuss the
2 statistical analysis of the PMA data.

3 I will then conclude FDA's presentation by
4 reading the sponsor's Proposed Indications for Use
5 and asking three specific questions FDA has for the
6 panel.

7 [Slide.]

8 The Ascension MCP is a two-component,
9 semi-constrained finger joint replacement device.
10 The proximal component with a ball-shaped articular
11 surface is intended to replace the head of the
12 metacarpal bone, while the distal component, with a
13 cup-shaped articular surface, is intended to
14 replace the base of the proximal phalanx.

15 The device is designed to achieve fixation
16 by being press-fit into the intramedullary canal of
17 the proximal phalanx and metacarpal bones.

18 The Ascension MCP is a modification to the
19 original pyrocarbon device that was used in the
20 animal studies and in the clinical study.
21 Modifications to the device were made to the shape
22 and length of the stems and to the design of the
23 subarticular collar.

24 The sponsor stated that the modifications
25 to the design of the original pyrocarbon device

1 were made to simplify surgical implantation and to
2 increase surgical options with respect to size
3 selection. The Ascension MCP is available in five
4 sizes, while the device that was used in the baboon
5 study and the clinical study was available in three
6 sizes.

7 [Slide.]

8 The surface of the device is composed of
9 pyrocarbon, which is approximately
10 one-half-millimeter thick, surrounding a graphite
11 core. The pyrocarbon material in the Ascension MCP
12 has the trade name On-X carbon and is produced by
13 Medical Carbon Research Institute, while the
14 graphite core is proposed by Poco Graphite and is
15 impregnated with 10-weight percent tungsten. The
16 tungsten causes the device to be radio-opaque so
17 that it can be seen on x-ray.

18 The surface of the original device, which
19 was also pyrocarbon and also approximately
20 one-half-millimeter thick, was made by Carbomedics,
21 Incorporated, with a trade name of Pyrolite.

22 The graphite core of the original device
23 was also made by Poco Graphite, but the devices
24 were made both with and without the tungsten
25 additive.

1 [Slide.]

2 The sponsor performed preclinical testing
3 including a baboon study on the original device;
4 bench testing and a biocompatibility evaluation of
5 the Ascension MCP device design. I believe the
6 sponsor has adequately summarized the preclinical
7 testing in their presentation.

8 I want to make one comment about their
9 wear testing. The sponsor only had a few implants
10 of the original device design in their possession;
11 therefore, they could not perform a wear comparison
12 between the original device design and the
13 Ascension MCP device design.

14 [Slide.]

15 From 1979 to 1987, 151 pyrolytic carbon
16 MCP implants were put into 53 patients at the Mayo
17 Clinic by Drs. Beckenbaugh and Linscheid. Of
18 these, 147 implants were primary, uncemented
19 pyrocarbon implants; 2 were revision-- one
20 uncemented and one cemented; and 2 were condylar
21 pyrocarbon implants. These are implants with a
22 conical-shaped bump in the center of the
23 articulating surface of the distal component that
24 interfaced with a groove on the proximal
25 component's articulating surface.

1 The 53 patients who received 147 primary
2 uncemented pyrocarbon implants represent the case
3 series upon which the clinical data in this PMA is
4 based. The outcome of the other 4 pyrocarbon
5 implants--that is, the 2 condylar and the 2
6 revision--are mentioned in the PMA but are not
7 summarized as part of the clinical data.

8 As the sponsor has stated, a prospective
9 clinical investigation was not performed. There
10 was no prospective protocol for the implantation or
11 standardized case report forms for data collection
12 on the 53 patients.

13 [Slide.]

14 Instead, the sponsor conducted a
15 retrospective study by completely reviewing the
16 medical records of each patient who received the
17 original device at Mayo Clinic. All information,
18 clinical findings and observations recorded in the
19 medical records related to the patients' wrists,
20 hands, fingers, and MCP joints, preoperatively and
21 at all follow-up visits, were extracted from
22 patients' medical records.

23 Patient follow-up data was available
24 starting in 1979 through March of 1999. This
25 information was recently amended to include

1 follow-up of two patients in April of 2001.

2 [Slide.]

3 Once the data had been retrospectively
4 collected, the sponsor described the patients who
5 had received the devices as patients with joints
6 that exhibited pain, deformity and/or limited
7 function and radiographic evidence of arthrosis.
8 The patients consented to receive the implant, and
9 in the physician's judgment, the patient might
10 benefit from the use of the device.

11 [Slide.]

12 The medical records included demographic
13 information including age, gender, and diagnosis.
14 Patients were diagnosed with either RA, lupus,
15 osteoarthritis, or traumatic arthritis.

16 It should be noted that the time from
17 diagnosis to implantation for the RA patients
18 ranged from 3 to 36 years.

19 The treatment consisted of implantation of
20 the original pyrocarbon device in 53 patients, 6
21 bilaterally, for a total of 61 hands, and 147 MCP
22 finger joints.

23 The follow-up time for all patients ranged
24 from a few months to 17 years.

25 [Slide.]

1 Additional data extracted from the medical
2 records included clinical assessments, such as
3 range of motion, active flexion, extension lag,
4 ulnar deviation, grip and pinch strength, pain,
5 patient activity level, patient satisfaction, and
6 cosmesis.

7 Please remember that this was not a
8 prospective study; therefore, not all of this
9 information was recorded for every patient. In
10 fact, as you look at the time portion from the few
11 months to the 17 years, if you categorized that
12 prospectively, in a prospective way, you would have
13 limited follow-up for these types of variables over
14 the time, but each patient, as the sponsor alluded
15 to, did have these types of assessments over the
16 whole period of the clinical analysis.

17 [Slide.]

18 Surgical and radiographic information was
19 also gathered from medical records where available.
20 Radiographic information included a determination
21 of joint position--that is, reduced, subluxed, or
22 dislocated; ulnar deviation; subsidence; migration;
23 and periprosthetic bone changes.

24 Finally, all adverse events and
25 complications were summarized.

1 [Slide.]

2 I will let our statistician provide more
3 detailed comments regarding the sponsor's original
4 analysis of their PMA data in a few minutes, but I
5 have the following general comments.

6 In the sponsor's original analysis, their
7 primary effectiveness endpoint was implant
8 survival. After reviewing the literature articles
9 provided by the sponsor, it became apparent that a
10 finger joint replacement device is typically
11 described as successful if it not only remains in
12 place but also relieves pain, improves function,
13 and maintains stability of the joint.

14 Therefore, FDA recommended that the
15 sponsor modify their primary endpoint to include
16 clinical and radiographic information. The sponsor
17 did this and provided a noninferiority analysis
18 with implant survival, clinical and radiographic
19 endpoints.

20 However, from a statistical perspective,
21 we believe that this analysis was lacking; and the
22 sponsor also alluded to the literature data as a
23 control in that analysis, and some of the
24 limitations of that literature data as well.

25 From a statistical perspective, we believe

1 this data was lacking, but because the sponsor had
2 significant longer follow-up on some patients than
3 is typically seen in a prospective study, FDA
4 suggested a case series analysis as a potential
5 option. The sponsor agreed, and this was their
6 final data analysis.

7 [Slide.]

8 For the sponsor's retrospective case
9 series analysis, they stratified patients into two
10 groups--a rheumatoid arthritis/lupus group and an
11 osteoarthritis/post-traumatic arthritis group. The
12 patients in each group presented with distinct
13 treatment objectives and associated physician
14 expectations. Treatment objectives and physician
15 expectations were derived from preoperative notes
16 and physical exam records.

17 Safety and effectiveness criteria were
18 defined retrospectively, with the treatment
19 objectives and physician expectations in mind.

20 [Slide.]

21 For both groups, the RA and the OA groups,
22 the frequency and severity of the following events
23 were evaluated: intraoperative implant fracture;
24 non-intraoperative implant fracture; unstable
25 intraoperative bone fracture; postoperative bone

1 fractures; implant-related infection; and adverse
2 biological reaction to the implant.

3 The sponsor presented a more complete list
4 of adverse events and complications in their
5 original safety analysis of the PMA data. In their
6 case series safety analysis, only intraoperative
7 implant fracture was identified as a safety issue.

8 We believe that all adverse events and
9 complications should be taken into account in an
10 analysis of device safety. Therefore, I will
11 discuss in more detail near the end of my
12 presentation intraoperative implant fracture and
13 four other types of complications that were
14 identified in the patient medical records,
15 including device removal, post-implantation soft
16 tissue reconstruction, synovitis, and black tissue
17 staining.

18 [Slide.]

19 Device effectiveness criteria and the case
20 series analysis were defined differently for the
21 RA/lupus and the OA/traumatic arthritis groups.

22 The sponsor retrospectively defined
23 implant success and failure and performed two
24 analyses for the RA/lupus group which included a
25 one-to-5-year analysis and a longer-term analysis.

1 For the OA/traumatic arthritis group, the sponsor
2 performed one success/failure analysis. Each
3 implant outcome was categorized as Excellent, Good,
4 Unsatisfactory, or Indeterminate, with Excellent
5 and Good defined as success, and Unsatisfactory
6 defined as failure.

7 As stated earlier, the patients in each
8 group presented with distinct treatment objectives,
9 and physician expectations and the retrospective
10 effectiveness criteria were defined with these
11 treatment objectives and physician expectations in
12 mind.

13 [Slide.]

14 The sponsor defined four possible primary
15 objectives for finger joint replacement in the
16 RA/lupus group: A) in cases with limited
17 extension, that is, 30 degrees or more of extension
18 lag, the primary expectation was to increase
19 extension; B) in cases with pain, the primary
20 expectation was to relieve pain; C) in cases with a
21 destroyed or eroded articular surface, the primary
22 expectation was to replace the eroded surfaces and
23 provide a reduced joint; and D) in cases with a
24 preoperative dislocation, the primary expectation
25 was to provide a reduced joint.

1 In cases presenting with a combination of
2 these conditions--that is, A, B, C, and/or D--the
3 primary objective was to address each of the
4 individual conditions.

5 [Slide.]

6 The sponsor has already presented the case
7 series success/failure criteria, but I would like
8 to make a few additional comments.

9 First, regarding the RA/lupus group 1- to
10 5-year analysis, we are calling this first analysis
11 a 1- to 5-year analysis because a patient can be
12 deemed successful with only one year's worth of
13 follow-up information. And if there were negative
14 information found 5 years or more
15 post-implantation, that information did not count
16 against the device, and the device would be deemed
17 successful.

18 [Slide.]

19 The sponsor has already reviewed their
20 criteria for Excellent, Good, Unsatisfactory, and
21 Indeterminate.

22 [Slide.]

23 I would like to add the following
24 comments. The sponsor defined "reduced implant
25 position" as a device being either reduced or

1 subluxed. Therefore, a subluxed joint would not
2 preclude the implant from being deemed successful.

3 Also, although a one-year criterion was
4 established for the implant to be considered a
5 success, the sponsor emphasized in their PMA that
6 72 percent of the successful implants had greater
7 than 2 years' worth of follow-up information in
8 their medical records.

9 However, to meet this criterion, there
10 only had to be greater than 2 years' worth of
11 follow-up information for just one clinical or
12 radiographic endpoint, and not all. This also
13 means that 28 percent of the successful implants
14 had greater than one year but less than 2 years'
15 worth of follow-up information for all clinical and
16 radiographic endpoints.

17 [Slide.]

18 The sponsor's next analysis was a
19 longer-term analysis. In this analysis, a patient
20 can still be deemed successful with only one year's
21 worth of follow-up information; but if negative
22 information was found 5 years or more
23 post-implantation, including reduction in the
24 treatment objectives, pain, dislocation, or device
25 removal, in this analysis, it is counted against

1 the device, and the device would be deemed a
2 failure.

3 Definitions of Excellent, Good,
4 Unsatisfactory, and Indeterminate for this analysis
5 have already been presented by the sponsor.

6 [Slide.]

7 The sponsor's final analysis was for the
8 OA/traumatic arthritis group. The sponsor stated
9 that the OA/traumatic arthritis patients presented
10 with damaged or destroyed articular surfaces and
11 almost always had pain and limited motion. Most of
12 these patients needed treatment in only one MCP
13 joint; only one patient required treatment in
14 multiple MCP joints. In these cases, the physician
15 had the expectation that the total joint
16 arthroplasty would relieve pain, maintain
17 reasonable joint range of motion and maintain joint
18 reduction.

19 [Slide.]

20 The sponsor has already reviewed their
21 definitions for Excellent, Good, Unsatisfactory,
22 and Indeterminate.

23 [Slide.]

24 Now I will present the results for the
25 RA/lupus group.

1 This table includes results for both the
2 1- to 5-year analysis and longer-term analysis. As
3 you can see, in the 1- to 5-year analysis in the
4 first column, there were 138 implants; 59 percent
5 of the implants were categorized as successful,
6 with 48 excellent and 34 good; 27 percent of the
7 implants were categorized as failures, and 14
8 percent indeterminate.

9 In the longer-term analysis, there were
10 138 implants; 37 percent of the implants were
11 categorized as successful, with 30 Excellent and 21
12 Good; 53 percent of the implants were categorized
13 as failures, and 10 percent Indeterminate.

14 The length of follow-up for patients
15 categorized as successful ranged from one to 16.8
16 years for both analyses.

17 [Slide.]

18 Now I will present the results for the
19 OA/traumatic arthritis group.

20 As you can see, there were 9 implants.
21 Seven of the implants were categorized as
22 successful, with 6 Excellent and one Good. One of
23 the implants was categorized as failure, and one
24 was found to be Indeterminate. The length of
25 follow-up for patients categorized as successful

1 ranged from 3.5 to 17 years. The one failure was
2 due to loosening at 1.1 years.

3 [Slide.]

4 The sponsor presented a complete list of
5 adverse events and complications in their
6 presentation. Therefore, I will only discuss in
7 more detail the following five types of
8 complications that were identified in the patient
9 medical records: device removal, post-implantation
10 soft tissue reconstruction, intraoperative implant
11 fracture, synovitis and black tissue staining.

12 I want to point out that FDA has a
13 question for the panel regarding these topics.

14 [Slide.]

15 A total of 21 implants were removed, or 14
16 percent. Eighteen were removed for deformity
17 associated with disease progression related to RA.
18 Deformities included extensor lag, flexion
19 contracture, ulnar deviation, subluxation or
20 dislocation. Three implants were removed for
21 loosening. Six implants were removed less than one
22 year after implantation, 9 were removed between one
23 and 5 years, and 6 implants were removed at greater
24 than 5 years after implantation, with a range of 5
25 to 11 years.

1 [Slide.]

2 Eleven post-implantation soft tissue
3 procedures were performed on a total of 22 joints
4 in 11 patients. All but one of the soft tissue
5 reconstruction procedures involved patients in the
6 RA/lupus group. Sixteen of the 22 joints were
7 operated on less than one year post-implantation.
8 The sponsor stated that soft tissue procedures are
9 not uncommon because of postoperative disease
10 progression.

11 [Slide.]

12 A total of 10 intraoperative device
13 fractures occurred in 7 of 53 patient, or 13
14 percent. Four of the intraoperative device
15 fractures occurred during primary device
16 implantation of 295 components, or 1.4 percent.
17 All 4 events occurred when removing components
18 intraoperatively because the device was too large
19 or additional soft tissue reconstruction was
20 necessary. Either a new pyrocarbon component was
21 inserted, or in one case, the fractured device
22 fragment was left in situ, and a silicone spacer
23 was inserted.

24 Six of the 10 intraoperative device
25 fractures occurred during revision operations of 42

1 components, or 14 percent. Five of the 6 were
2 revised to silicone spacers. The tip of the stem
3 of the other device fractured and was left in
4 place; the rest of the device was reinserted with
5 bone cement.

6 The sponsor addressed this risk by
7 developing a blunt plastic osteotome to aid in
8 component removal. This surgical technique was
9 also modified to include a section on implant
10 removal.

11 [Slide.]

12 Although the sponsor concluded that there
13 was no adverse tissue reaction to the pyrocarbon
14 MCP joint implant, carbon particles or "fine
15 particle matter" in samples evaluated by the
16 histopathologist, there were reports of black
17 staining of tissue and synovitis. A total of 7
18 implants caused black tissue staining in 4 of 53
19 patients, or 7.5 percent. Four events occurred
20 during removal of implants from each finger on one
21 patient's hand; all four fractured implants were
22 removed by drilling them out of the bone. After
23 the drilling process, black stain tissue was
24 observed in each finger. No tissue samples were
25 taken from this patient.

1 In addition, there were three events
2 observed during operations to remove implants that
3 were potentially loose in 3 patients. Tissue
4 samples from these 3 patients were excised during
5 removal for examination. The histopathologist
6 concluded that the tissue did not reveal any
7 negative tissue reaction, and all implants were
8 revised, 2 to silicone and one with cement.

9 [Slide.]

10 In addition, a total of 24 synovitis
11 events were reported for 10 patients, or 19
12 percent. Tissue samples were available for
13 examination from 5 joints, including samples from 2
14 RA patients and one trauma patient.

15 The histopathologist's review concluded
16 that there was no adverse tissue reaction to the
17 implant, carbon particles or "fine particle matter"
18 in these samples.

19 Now Phyllis Silverman will present a brief
20 discussion of the statistical analysis in the PMA.

21 MS. SILVERMAN: Good morning. I am
22 Phyllis Silverman, the statistical reviewer for the
23 Ascension PMA. My comments will focus on the
24 various ways the sponsor presented the PMA data
25 statistically, starting with the original PMA and

1 ending with the case series as presented in
2 Amendments 3 and 5.

3 [Slide.]

4 As you are well aware, the study was
5 retrospectively constructed from data from 53
6 patients implanted with 147 joints at the Mayo
7 Clinic between 1979 and 1987. There was no pre-set
8 follow-up schedule, although there was follow-up as
9 long as 17 years for some patients.

10 In the original PMA, 22 literature studies
11 which used the Swanson silastic spacer were
12 selected as the historical control. The primary
13 endpoint was implant fracture or implant removal.
14 Secondary endpoints included pain, range of motion,
15 radiographically-determined joint position,
16 cosmesis, activity level, and patient satisfaction.

17 All information was reconstructed from
18 physician notes and patient comments in the
19 clinical records. The sponsor's initial claim was
20 noninferiority to the historical control.

21 [Slide.]

22 A statistical checklist review performed
23 by myself in February of this year identified three
24 major deficiencies--concern over appropriateness of
25 literature controls; failure to define the window

1 of noninferiority, or delta, as some of you know
2 it; and lack of a statistical comparison to the
3 control to support the noninferiority claim.

4 The sponsor was asked to address those
5 three issues and did so with an amendment submitted
6 in March.

7 [Slide.]

8 An attempted statistical comparison to the
9 literature controls concerning implant survival,
10 pain and function raised many concerns with the
11 data analysis and interpretation. Only one of the
12 22 control articles contained a survival curve.
13 Variability was high for many other endpoints, and
14 data were sparse at many of the follow-up intervals
15 for both the Ascension data and the controls.
16 There was potential for selection bias.

17 The sponsor was unable to statistically
18 substantiate their claim of noninferiority for the
19 primary endpoint or most of their secondary
20 endpoints due to a general lack of statistical
21 power.

22 My overall assessment was that I could not
23 give this my statistical blessing.

24 [Slide.]

25 FDA then suggested a different approach

1 based on case studies. Case reports generally
2 constitute the weakest form of clinical evidence
3 because they demonstrate only that an event of
4 interest is possible, such as isolated cases of
5 spontaneous cancer remission. One likely would
6 have little information about all other factors
7 that could have affected the outcome.

8 A case series, which is what the sponsor
9 has provided, is somewhat more helpful than case
10 reports because it carries the weight of some
11 experience, and there are usually underlying common
12 factors among the cases.

13 The down side with case reports and case
14 series is that the investigator does not control
15 treatment assignment, endpoints ascertainment,
16 selection biases, or confounding factors. Case
17 reports and case series are typically used to
18 generate hypotheses, not to test them.

19 [Slide.]

20 I would consider the 53 patients and 140
21 implants to represent a case series. This is a
22 large case series with follow-up more extensive
23 than is typically required in prospective studies.
24 The sponsor stratified the population based on two
25 baseline medical conditions--osteoarthritis and

1 post-traumatic, which I will refer to as the "OA"
2 population for short; and rheumatoid arthritis and
3 systemic lupus erythematosus, which I will refer to
4 as the "RA" population.

5 Twenty-nine of the 53 patients were still
6 being followed after 10 years. All patients were
7 treated by one of two physicians at a single clinic
8 over an approximate 7-year period. Because this
9 case series was retrospectively constructed, there
10 are many holes in the data, and information on pain
11 and function was not available at all time points.

12 However, using their own
13 retrospectively-defined criteria as presented to
14 you this morning, the sponsor was able to classify
15 each implant as a success or failure. Although
16 some missing preoperative pain information was
17 reconstructed from postoperative notes, no
18 postoperative pain assumptions were made from the
19 missing data. The sponsor did not take the "No
20 news is good news" approach.

21 I did not see anything in the
22 classification strategy to make me think this
23 process was slanted or biased. However, this
24 process needs to be evaluated from a clinical
25 perspective.

1 [Slide.]

2 The sponsor presented specific safety and
3 effectiveness data on both a per-patient and
4 per-implant basis. They discussed at length the
5 risks associated with the control device. Limited
6 data on implant fracture, pain, and the incidence
7 of reactive synovitis was given for the control
8 device. The success/failure classification that
9 the sponsor initially used for RA patients was
10 based on the last follow-up; but if an RA patient
11 worsened after 5 years, this did not alter their
12 classification because of the natural progression
13 of the disease.

14 With these classification criteria, 59
15 percent of the RA implants were classified as
16 successful, and 78 percent of the OA implants were
17 classified as successful. Sixty percent of the RA
18 patients had all of their implants considered
19 successful, and 75 percent of the OA patients had
20 all of their implants considered successful. In
21 addition, 72 percent of successful implants in the
22 RA group were followed for more than 2 years, but
23 not necessarily for all endpoints.

24 The sponsor was asked to provide an
25 additional longitudinal analysis so that a

1 worsening of symptoms after 5 year was considered.
2 This concerned the RA cohort only, since the 5-year
3 restriction was not applied to the OA cohort. With
4 the modified criteria, 36 implants moved from being
5 rated Good or Excellent to the Unsatisfactory
6 category. This left 37 percent of the RA implants
7 rated successful. On a per-patient basis, 51
8 percent of the RA subjects had one or more
9 successful implants, and 38 percent had all
10 implants rated successful.

11 The sponsor states that the long-term
12 results represent a potential worst-case analysis
13 since the rate of disease progression and soft
14 tissue degradation is not known. While this may be
15 true, one must also keep in mind that in the case
16 series where information is not systematically
17 sought out, one cannot be certain of its
18 reliability. Therefore, this case series must be
19 considered along with its limitation.

20 [Slide.]

21 In summary, the information presented in
22 support of this PMA has come full circle from a
23 nonstatistical argument to a statistical argument
24 and back again. Since the sponsor's claims cannot
25 be supported on a statistical basis in terms of

1 comparison to any control, I feel that my role in
2 this process is limited. A clinical assessment
3 should be made on this large case series to
4 determine which indications, if any, the data
5 support. The limitations of currently available
6 treatments should be considered.

7 You the panel must look at this data,
8 drawing on your clinical and scientific expertise
9 to make a recommendation to FDA.

10 Thank you.

11 DR. SKINNER: We are going to have Mr.
12 Goode present the panel questions, and then we'll
13 take a break if you would bear with us for a few
14 more minutes.

15 MR. GOODE: Before I present the panel
16 questions, I will continue by reading the Proposed
17 Indications for Use for the Ascension MCP.

18 "The Ascension MCP is intended for use as
19 a total joint replacement for the index, long,
20 ring, and small finger metacarpophalangeal joints
21 that exhibit symptoms of pain, limited range of
22 motion, or inadequate bony alignment, that is,
23 subluxation or dislocation, secondary to articular
24 destruction or degenerative disease related to
25 rheumatoid arthritis, lupus, osteoarthritis, or

1 post-traumatic arthritis, where soft tissue
2 reconstruction provides stabilization."

3 I would like to point out that currently,
4 the indications do not exclude revision procedures,
5 although devices used in revision procedures were
6 specifically excluded from the case series
7 analysis.

8 Now, the panel questions.

9 The first question is with regard to
10 device safety: "Based on the retrospective
11 clinical data in the sponsor's case series which
12 included 53 patients and 147 primary uncemented
13 pyrocarbon implants, do the data demonstrate that
14 there is reasonable assurance that the probable
15 benefits to health from the use of the Ascension
16 MCP for its intended use and conditions of use,
17 when accompanied by adequate labeling, outweigh any
18 probably risks?"

19 We would like the panel to provide
20 additional input on this topic. "Specifically,
21 what is the impact of the following complications
22 and adverse events as they relate to safety and
23 effectiveness of this product: device removals and
24 post-implantation soft tissue reconstructions;
25 intraoperative fractures; and black tissue staining

1 and synovitis."

2 The second question is regarding device
3 effectiveness.

4 "Based on the retrospective clinical data
5 in the sponsor's case series which included 53
6 patients and 147 primary uncemented pyrocarbon
7 implants and the sponsor's retrospectively-defined
8 success/failure criteria and analysis, do the data
9 demonstrate there is reasonable assurance that in a
10 significant portion of the target population, the
11 use of the Ascension MCP for its intended use and
12 conditions of use, when accompanied by appropriate
13 labeling, will provide clinically significant
14 results? Please consider whether the data support
15 each of the proposed indications for use."

16 Finally, with regard to patient labeling:
17 "Please identify what additional information, if
18 any, the sponsor should provide in their patient
19 labeling."

20 Thank you very much.

21 DR. SKINNER: Thank you, Mr. Goode.

22 We will take a 10-minute break, and when
23 we come back, we will have the presentations by the
24 panel members on their reviews of the presentation
25 by Ascension.

1 Please be back in 9-1/2 minutes.

2 [Break.]

3 DR. SKINNER: We will now have the general
4 panel discussion, beginning with presentations by
5 Drs. Li, Naidu, and Larntz. We will have the
6 presentations by those three doctors followed by
7 lunch, and we'll have a panel discussion after
8 lunch.

9 So, let's start with Dr. Li.

10 **Lead Panel Member Reviews**

11 DR. LI: Thank you.

12 The following is a summary of my comments
13 on the Ascension MCP PMA.

14 [Slide.]

15 The focus of my presentation, being the
16 biomechanics and biomaterials person, is focused
17 primarily on the materials, design, preclinical
18 testing, and then I'll summarize my final comments.

19 Overall, from the materials and design
20 standpoint, I thought the PMA was well-planned and
21 well-presented, and I appreciate the efforts that
22 went into that. I also believe that the testing
23 plan for both the static fatigue and wear testing
24 were appropriate.

25 My focus of concern, however, and

1 questions goes to four areas about some fabrication
2 questions, wear issues, fracture fatigue, and the
3 issue of wear debris.

4 There are really two devices that we're
5 talking about here--the original MCP and the
6 Ascension MCP, which is the intended commercial
7 device--and there are some differences in materials
8 and geometry between these two devices.

9 A summary of the materials is that in the
10 original MCP device, there were two possible
11 graphite substrates, one with tungsten, one
12 without; and in the Ascension, just the tungsten
13 graphite apparently was available.

14 There were two pyrolytic carbon coatings
15 identified, one called Pyrolite for the original
16 MCP, and the Ascension had a coating that was
17 designed On-X.

18 [Slide.]

19 As far as substrate differences, they were
20 with and without tungsten, as for materials of
21 construction. There were small changes in static
22 mechanical properties, but these properties did not
23 appear to be particularly large. I did not see any
24 data, though, comparing fatigue and fracture
25 differences with and without tungsten. I did not

1 see any data on potential lot-to-lot variations or
2 validation of how the properties of the starting
3 graphite materials were validated.

4 [Slide.]

5 As far as the pyrolytic carbon coatings,
6 there appeared to be some differences in forming
7 processes, and perhaps the applicants could review
8 some of the differences for me; it was not exactly
9 clear.

10 There were differences in static
11 properties, but again, these differences appeared
12 to be small. Differences, again, in the fracture
13 and fatigue between the two types of coatings were
14 not known. They provided a fracture toughness
15 value--I wasn't sure if it was J or K; I would be
16 guessing it was the K value--only for the On-X
17 coating. And again, lot-to-lot variations were not
18 reported.

19 [Slide.]

20 They did have an interesting table about
21 the On-X pyrolytic coating. This was just two of
22 the entries. But they had one column that was
23 essentially the nominal properties--for instance,
24 the flexural strength at a nominal value of 72--but
25 in the "Requirement" column, they had that that

1 value could be anywhere between 50 and 72.

2 On fracture toughness, they did not
3 provide the nominal property, but they did provide
4 the range of requirements of being somewhere
5 between 1.0 and 2.6, which is a relatively large
6 range of fracture toughness, and it isn't quite
7 clear how the requirement ranges were arrived at,
8 nor is it clear in subsequent testing where in the
9 property ranges the particular devices fell within
10 those ranges. It also raises the question did they
11 test the worst possible combination of properties
12 given that the ranges of requirements in some cases
13 were reasonably large.

14 [Slide.]

15 So the property requirements--what were
16 the properties of the devices actually tested; what
17 was the performance of the worst combination of
18 properties; and how were these requirements
19 determined--would be three questions I would have
20 about that.

21 [Slide.]

22 They used hardness as an indirect
23 indicator of the other mechanical properties.
24 However, clearly, this only assesses the coating
25 and not the substrate of the material.

1 Questions I have: As this is a vapor
2 deposition process over a 3-dimensional object,
3 where and how often was the hardness measured?
4 What was the consistency of the coating over a
5 single device? What was the coating consistency
6 between devices? How were they determined, and
7 how would they validate that in the future? And
8 it was unclear what the relationship of hardness
9 with fracture and fatigue was.

10 [Slide.]

11 There were some geometry differences
12 between the original and the Ascension. The
13 Ascension had a slightly thinner coating, appeared
14 to have larger radial clearances and a wider range
15 of sphericity values; but the clinical relevance of
16 these differences is unclear.

17 [Slide.]

18 For wear testing, I thought the test plan
19 and methodology were both reasonable and clever.
20 They ran two controls--a European device, but I
21 didn't have any comparison to clinical results for
22 that device, so I don't know if the testing
23 protocol actually mimicked the clinical result of
24 that particular European device. The second
25 control was a metal, ultramolecular weight

1 polyethylene construct, which I believe was a model
2 of the Ascension, if I understood correctly, but
3 this was obviously not an approved or cleared
4 device, so again, comparisons to what that would
5 have done clinically are unclear. Also, the
6 polyethylene in this case appeared to be
7 nonsterilized, which would give it off-the-bat a 30
8 to 50 percent higher wear than the
9 metal-on-polyethylene generally expected for, say,
10 a total hip or a total knee system.

11 There also was not a comparison, perhaps
12 for good reason, of wear between the original and
13 the Ascension MCP device, and also, there was no
14 connection to the silicone device which was used as
15 a comparison for the clinical trial where they are
16 trying to decide if they are essentially different
17 from the silicone devices at all.

18 [Slide.]

19 There is virtually no wear on these
20 devices. However, there appeared to be somewhere
21 in clinical cases association with blackened
22 tissue, and there appeared to be some histological
23 reports of seeing some debris particles, although
24 there was no inflammation or biological responses
25 in some of the cases with synovitis.

1 So we have a case of virtually no
2 laboratory wear, but obviously, in some clinical
3 cases, clear presence of wear.

4 [Slide.]

5 So the question is why does this occur,
6 and were there any signs of debris during the wear
7 test. The wear test measurements appeared to be
8 done by mostly their coordinate measuring method.
9 There appeared to be neither a weight check nor was
10 there a check for sub-micron particles within the
11 lubricant used during the test. And were there any
12 measurements of wear from a CMM standpoint from
13 retrieved implants, particularly those in cases
14 that had blackened tissue or synovitis?

15 [Slide.]

16 So were there signs of wear on revision of
17 those cases that did not have synovitis or
18 blackened tissue? How was this determined? How
19 hard did they look? What was the quality of the
20 implant surfaces in those cases with blackened
21 tissue or synovitis? How much did they check on
22 periprosthetic tissue in general, and for those
23 cases where there seemed to be some debris, it is
24 unclear what the morphology of that debris was,
25 especially in terms of size.

1 A reminder here that the blackened tissue
2 and synovitis were obviously determined in cases
3 where there was revision, but for those cases where
4 the joints essentially continued to be
5 satisfactory-performing, it is obviously unclear
6 whether wear is occurring in those devices or not.

7 [Slide.]

8 On fracture properties, there were no
9 fracture properties of the substrate or coating
10 alone, which isn't really a reflection of the
11 quality of the device, but it would be, I believe,
12 an important material descriptor to characterize
13 the materials.

14 There are not comparative fracture
15 materials of the original MCP device versus the
16 Ascension, and fracture does appear to occur
17 intraoperatively.

18 [Slide.]

19 They did try to assess some fracture
20 limits by using finite element modeling, which is
21 used to assess distress, but a reminder that FEM
22 does not directly determine fracture limits, nor
23 does it directly determine fatigue lines.

24 [Slide.]

25 They did, however, using this method along

1 with some contact stress measurements, estimate
2 that the fracture requirements was somewhere
3 between 32,500 and 36,200 psi, and they compared
4 that to the estimated use stresses of somewhere
5 between 2,300 and 5,800 for the original and the
6 Ascension MCP device; yet intraoperative fractures
7 did occur which are clearly not multiple fatigue.
8 So the question is do they actually believe that
9 stresses of 32,000 to 36,200 psi were actually
10 applied to these devices intraoperatively.

11 [Slide.]

12 They did fatigue and endurance tests,
13 which I thought was well-planned and a reasonable
14 test. They reported no failures at 10 million
15 cycles, and again, there were no differences,
16 however, reported or compared between the original
17 and the Ascension devices.

18 I was a little bit offset in that there
19 was no basis of comparison because they didn't
20 actually provide a fatigue limit in the normal S/N
21 fashion, which I think would provide a better
22 characterization of materials and would be critical
23 if changes are made to the material, or changes of
24 sources, methods, manufacturing, or whatever.

25 [Slide.]