

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

MEETING OF THE
ORTHOPEDICS AND REHABILITATION

DEVICES ADVISORY PANEL
P000054

INDUCTOS (RHBMP-2/ACS) FOR ORTHOPEDIC TRAUMA

WYETH RESEARCH

Thursday, November 21, 2002

9:30 a.m.

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

C O N T E N T S

	PAGE
MORNING SESSION:	4
Call to Order	
Dr. Michael J. Yaszemski, Chairperson	8
Open Public Hearing (No Speakers)	9
Sponsor Presentation	
Dr. F. Owen Fields, Worldwide Regulatory Affairs, Wyeth Research	12
Dr. Rod Riedel (Preclinical Data)	19
Dr. Alex Valentin (Clinical Data)	25
Dr. Marc F. Swiontkowski (Relevance to U.S. Practice)	58
FDA Presentation	
Mr. Aric Kaiser (PMA Lead Reviewer)	74
Dr. Barbara Buch (Preclinical)	78
Dr. Chang S. Lao (Statistical)	109
Panel Presentations	
Dr. Sanjiv Naidu (Preclinical)	120
Dr. Maureen Finnegan (Clinical)	127
Dr. Kinley Larntz (Statistical)	139
Open Public Hearing	
Bill Christiansen, on behalf of Orthopedic Surgical Manufacturers Association (OSMA)	149
AFTERNOON SESSION	
Panel Questions and General Discussion	156
Final Sponsor Comments	208
Vote	210

C O N T E N T S (Continued)

General Panel Discussion of Spinal Devices	232
Open Public Hearing:	
Brenda Seidman (Seidman Toxicology Services)	233
Diane Johnson (Medtronic Spinal Dynamics)	238
Dr. Bailey Lipscomb (Medtronic Sophomore Danik)	240
Dr. Rich Jansen (Disc Dynamics, Incorporated)	244
Dr. Britt Norton (Raymedica, Inc.)	248
FDA Presentation	
Dr. Barbara Buch	253
Panel Reviews	
Dr. John Kirkpatrick (Clinical/Preclinical)	268
Dr. John Doull (Preclinical Toxicology/Safety)	279
Discussion of FDA Questions to Panel	281
Adjourn	309

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

2 DR. YASZEMSKI: Good morning, everybody.
3 May I ask that everybody take their seats, and
4 we'll go ahead and get started.

5 Welcome.

6 MR. DEMIAN: Good morning. I would first
7 like to welcome you.

8 We are ready to begin this meeting of the
9 Orthopedic and Rehabilitation Devices Panel.

10 My name is Hany Demian, and I am the
11 Executive Secretary for this panel.

12 I would like to remind everyone that you
13 are requested to sign in on the attendance sheets
14 which are available outside the doors. You may
15 pick up an agenda and information about today's
16 meeting, including how to find out about future
17 meeting dates through the Advisory Panel phone line
18 and how to obtain meeting minutes and transcripts.

19 I will now read two statements that are
20 required to be read into the record. The first one
21 is an Appointment to Temporary Voting Status
22 Statement, and the second one is the Conflict of
23 Interest Statement.

24 "Appointment to Temporary Voting Status.
25 Pursuant to the authority granted under the Medical

1 Device Advisory Committee Charter dated October 27,
2 1990 and as amended August 18, 1999, I appoint the
3 following individuals as voting members of the
4 Orthopedic and Rehabilitation Devices Panel for
5 this meeting on November 21, 2002: Andrew Schmidt,
6 John Doull, and Albert Aboulafia. For the record,
7 these individuals are Special Government Employees
8 and consultants to this panel or other panels under
9 the Medical Device Advisory Committee. They have
10 undergone the customary conflict of interest review
11 and have reviewed the material to be considered at
12 this meeting."

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

16 "Conflict of Interest Statement, November
17 21, 2002."

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

1 prohibit Special Government Employees from
2 participating in matters that could affect their or
3 their employers' financial interest. However, the
4 Agency has determined that the participation of
5 certain members and consultants, the need for whose
6 services outweigh the potential conflict of
7 interest involved, is in the best interest of the
8 Government."

9 "Therefore, waivers have been granted to
10 Drs. Albert Aboulafia, John Kirkpatrick, Kinley
11 Larntz, and Andrew Schmidt for their interest in
12 firms that could potentially be affected by the
13 panel's recommendation. The waivers allow them to
14 participate fully in today's deliberations."

15 "Dr. Aboulafia's waiver involves a
16 consulting arrangement with a competing technology
17 firm. For this unrelated consulting service he
18 receives less than \$10,001 a year."

19 "Dr. Kirkpatrick's waiver involves
20 stockholdings valued between \$5,001 and \$50,000 in
21 competing firms and the parent company of several
22 competing manufacturers."

23 "Dr. Larntz' waiver involves a consulting
24 agreement with a competing technology firm. For
25 his consulting services, he receives less than

1 \$10,001."

2 "Dr. Andrew Schmidt's waiver involves a
3 consulting arrangement with a competing technology
4 firm. For this consulting service, he receives
5 less than \$10,001 a year."

6 "Copies of these waivers may be obtained
7 from the Agency's Freedom of Information Office,
8 Room 12A-15 of the Parklawn Building."

9 "We would like to note for the record that
10 the Agency took into consideration other matters
11 regarding Drs. Maureen Finnegan, John Kirkpatrick,
12 Andrew Schmidt, Michael Yaszemski, and Ms. Karen
13 Rue. They reported interest in firms at issue but
14 in matters not related to today's agenda. The
15 Agency has determined therefore that they may
16 participate fully in all discussions. In the event
17 that the discussions involve any other products or
18 firms not related to today's agenda for which an
19 FDA participant has a financial interest, the
20 participant should excuse him or herself from such
21 involvement, and the exclusion will be noted for
22 the record."

23 "With respect to all other participants,
24 we ask in the interest of fairness that all persons
25 making statements or presentations disclose any

1 current or previous financial involvement with any
2 firm whose product they may wish to comment upon."

3 Before turning this meeting over to Dr.
4 Michael Yaszemski, I would like to introduce our
5 distinguished panel members who have generously
6 given their time to help FDA in matters being
7 discussed today and other FDA staff seated at the
8 table, so we'll just go around the room and
9 introduce ourselves, our affiliation, and our areas
10 of interest.

11 Mike?

12 DR. YASZEMSKI: Michael Yaszemski,
13 Rochester, Minnesota. I am an orthopedic surgeon,
14 and on the research side, I am a chemical engineer.

15 DR. NAIDU: Sanjiv Naidu, Penn State
16 College of Medicine. I am an orthopedic surgeon
17 and a materials scientist.

18 DR. LARNTZ: Kinley Larntz, Professor
19 Emeritus, University of Minnesota School of
20 Statistics. I also work as an independent
21 statistical consultant, and my interest is in
22 biostatistics, clinical design.

23 DR. SCHMIDT: Dr. Andrew Schmidt from
24 Minneapolis. I am on the faculty of the University
25 of Minnesota. I practice primarily in trauma and

1 adult reconstructive surgery, and I am interested
2 in biologic applications to improve the human
3 factors.

4 DR. ABOULAFIA: My name is Albert
5 Aboulafia. I am an orthopedic oncologist at Sinai
6 Hospital in Baltimore and the University of
7 Maryland.

8 MS. WITTEN: Celia Witten. I am with the
9 Food and Drug Administration. I am the Division
10 Director of the division reviewing this product,
11 DGRND.

12 MS. MAHER: Sally Maher. I am the Senior
13 Director of Regulatory and Clinical, Smith & Nephew
14 Endoscopy, and I am the industry rep.

15 MS. RUE: Karen Rue. I am a registered
16 nurse at Lafayette General Medical Center and
17 Acadian Health Care Alliance, and I am the consumer
18 representative.

19 DR. DOULL: John Doull. I am a clinical
20 toxicologist from the University of Kansas Medical
21 Center.

22 DR. KIRKPATRICK: John Kirkpatrick,
23 Associate Professor of Orthopedic Surgery at the
24 University of Alabama Birmingham.

25 DR. FINNEGAN: Maureen Finnegan, at UT

1 Southwestern in Dallas, with a research interest in
2 fracture healing.

3 MR. DEMIAN: Thank you.

4 At this time, I would like to turn the
5 meeting over to our chairman, Dr. Michael
6 Yaszemski.

7 DR. YASZEMSKI: Thanks, everybody, and
8 good morning again.

9 I am Dr. Michael Yaszemski, and I will be
10 the chair for this meeting.

11 Today, we the panel will be making
12 recommendations to the Food and Drug Administration
13 regarding a Pre-Market Approval application for a
14 growth factor soaked in collagen sponge to treat
15 tibial fractures.

16 I would like to note for the record that
17 the voting members present constitute a quorum as
18 required by 21 CFR Part 14.

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

25 And I will ask as a protocol for

1 today--and please bear with me; I know as the
2 discussion goes back and forth, we frequently
3 forget--but I will apologize in advance for
4 interrupting you if you don't introduce yourself so
5 we can have our transcriptionist know who everybody
6 is when they talk.

7 We are requesting that all persons making
8 statements during the open public hearing of the
9 meeting disclose whether they have financial
10 interest in a medical device company. Before
11 making your presentation to the panel, please state
12 your name, your affiliation, and the nature of your
13 financial interest, if any.

14 At this time, is there anyone wishing to
15 address the panel?

16 [No response.]

17 DR. YASZEMSKI: There was a person who
18 asked to be scheduled. Mr. Christiansen, are you
19 here?

20 [No response.]

21 DR. YASZEMSKI: We will now proceed to
22 consider the Pre-Market Approval application for
23 Wyeth Pharmaceuticals, Incorporated InductOs
24 rhBMP-2 Absorbable Collagen Sponge.

25 I would like to remind the public

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

5 We are now ready to begin with the
6 sponsor's presentation. We'll follow that with the
7 presentation by FDA. I would like to ask that each
8 speaker state his/her name and affiliation with the
9 firm before beginning the presentation.

10 Wyeth, please.

11 Sponsor Presentation

12 DR. FIELDS: Good morning. My name is
13 Owen Fields. I am in Regulatory Affairs at Wyeth.

14 I would like to thank FDA for this
15 opportunity to present before the panel, and I
16 would also like to thank the panel members for
17 their time and attention this morning.

18 [Slide.]

19 I will begin by describing the product.
20 The product is a combination of a biologically
21 active protein with a matrix that serves to deliver
22 the protein to its site of action. The protein is
23 known as recombinant human bone morphogenetic
24 protein-2. Understandably, this is often
25 abbreviated as RHBMP-2 or simply as BMP-2.

1 BMP-2 is an osteoinductive protein, that
2 is, it induces bone formation. And the protein is
3 produced by what are now fairly standard biological
4 production techniques.

5 [Slide.]

6 There is a matrix used to deliver the
7 protein. The matrix used to deliver the protein is
8 an absorbable collagen sponge. This product is
9 manufactured by Integra Life Sciences. It was
10 originally approved in 1981 as an implantable
11 hemostatic agent, and when it is placed to the use
12 of the hemostatic agent, it is known by the trade
13 name Helistat.

14 [Slide.]

15 To prepare the BMP-2/ACS product, the vial
16 of protein is first reconstituted with water for
17 injection, and this solution is then applied to the
18 absorbable collagen sponge. For the use that we
19 propose, the combined product is then surgically
20 implanted at the fracture site in this form.

21 Two strengths of BMP-2, .75 and 1.5 mg/ml,
22 have been clinically tested, as you have read in
23 your packages, but only the 1.5 mg dosage form is
24 proposed for marketing, and this is due to the
25 clinical results and the differentiation between

1 the efficacy of the two doses which you will hear
2 some detail about in subsequent presentations.

3 [Slide.]

4 The BMP-2/ACS product is what is known as
5 a "combination product" in that it shares
6 characteristics with both biologicals and devices.
7 It is like a device, and then it is surgically
8 implanted. It is generally used only for a single
9 application, and it acts only at the site of
10 implantation.

11 However, it is also like a biological or
12 drug product in that we had to establish the proper
13 delivery context and the proper dose, and in that
14 it has pharmacological activity.

15 As a result of this, both drug and device
16 development paradigms had to be applied to the
17 product, and in fact globally, the product is
18 regulated as both, specifically. In the U.S., the
19 product is regulated as a device, whereas in
20 Europe, the product is actually regulated as a
21 drug.

22 And as you will see, we conducted a
23 preclinical program involving both drug and device
24 studies whereas we conducted a clinical program
25 more similar to that of the device. And as you

1 might imagine, the manufacturing characterization
2 and work that was done was very typical of a
3 biological product and in fact was fully reviewed
4 by the Center for Biologics.

5 [Slide.]

6 The BMP-2/ACS product has been
7 simultaneously developed in several medical areas.
8 Starting on the left, the product has been
9 developed for spine fusion in combination with a
10 spine fusion cage. Our commercial partner,
11 Medtronic Sophomore Danik, has carried out this
12 development, and the BMP-2/ACS product when it is
13 used for this indication is known by the trade name
14 INFUSE.

15 In addition, the product has been
16 developed by Wyeth for use in orthopedic trauma,
17 specifically for long-bone fractures. The product
18 when it is placed for this use is known by the
19 trade name InductOs.

20 It is important to note here that the
21 rhBMP-2 and the ACS for all of these uses are
22 biochemically identical, and the ratio at which
23 these two components are combined are also
24 identical.

25 [Slide.]

1 Products containing BMP-2/ACS have
2 previously been approved in two different contexts
3 globally. Specifically, in January 2002, this
4 panel recommended approval of the INFUSE/LT-CAGE
5 product, which is a combination of BMP-2/ACS with
6 an already approved spine fusion cage. This PMA
7 was sponsored by Medtronic Sophomore Danik, our
8 corporate partner.

9 The spine fusion product was formally
10 approved by FDA in July of this year, and given
11 this, in our presentation, we will not focus on the
12 manufacturer of BMP-2 and ACS; we will also not
13 focus on the preclinical safety program in that the
14 preclinical safety program supports both uses of
15 the product and was discussed in some detail at the
16 January 2002 panel meeting.

17 [Slide.]

18 BMP-2/ACS, that is, the product without
19 the fusion cage for the use that we propose, has
20 also been approved in the European Union for
21 orthopedic trauma. Specifically InductOs was
22 approved as a drug in the European Union in
23 September of this year. Wyeth was the sponsor of
24 the medicines application that allowed this
25 approval.

1 As is typical for drug approvals, this
2 approval included some post-approval commitments.
3 First, we have preclinical post-approval
4 commitments, which are essentially the same as some
5 of those that have been made for the INFUSE product
6 in the U.S., so the same set of studies that were
7 subject to post-approval commitments for the INFUSE
8 product are also post-approval commitments in the
9 European approval.

10 [Slide.]

11 Second, we will also be conducting a tibia
12 fracture clinical trial to expand experience with
13 the product when it is used with reamed IM nails.

14 Obviously, the approval of InductOs for
15 the orthopedic trauma indication in the U.S. is the
16 focus of the remainder of our presentation.

17 [Slide.]

18 The proposed orthopedic trauma indication
19 is as follows. InductOs is indicated for the
20 treatment of acute long-bone fractures that require
21 open surgical management. InductOs increases the
22 probability of fracture healing, accelerates
23 fracture healing, and decreases the frequency and
24 invasiveness of interventions for delayed union or
25 nonunion.

1 The mechanistic rationale for this
2 indication is fairly simple to understand. We
3 believe that the data indicate that osteoinduction
4 at the fracture site improves the probably and
5 speed of healing and reduces the need for secondary
6 interventions.

7 [Slide.]

8 FDA has placed some specific questions
9 before the panel, and our objective today is to
10 address these questions. We believe we can address
11 each and every question that has been raised by
12 FDA. Toward this end, I will be followed by three
13 speakers.

14 First, you will hear a brief review of the
15 relevant preclinical data from Dr. Rod Riedel.

16 Second, Dr. Alex Valentin will review the
17 clinical data available.

18 Third, Dr. Marc Swiontkowski will review
19 the relevance of the clinical data to U.S.
20 practice.

21 And finally, later today, we will address
22 any questions that the panel may have.

23 [Slide.]

24 In order to help address questions from
25 the panel, we have a wide range of resources

1 available as listed on this slide, and next, you
2 will hear from Dr. Rod Riedel regarding the
3 relevant preclinical data.

4 Thank you.

5 DR. YASZEMSKI: Thanks very much, Dr.
6 Fields.

7 Dr. Riedel?

8 DR. RIEDEL: Good morning.

9 My name is Rod Riedel, and I am a Wyeth
10 employee. I will review several preclinical
11 proof-of-concept studies and preclinical safety
12 results. These data establish a rationale for
13 evaluating rhBMP-2 as a treatment for long-bone
14 fractures.

15 [Slide.]

16 This slide shows the signature biological
17 activity of rhBMP-2, its ability to induce bone
18 formation de novo. In this classic rat ectopic
19 implant assay, BMP-2 is implanted at a non-bony
20 site. The photograph on the left of the slide
21 shows a bone ossicle induced by BMP-2 14 days
22 following implantation.

23 Histological analysis of this new bony
24 tissue, as shown in the photograph on the right,
25 shows extensive formation of trabecular bone,

1 corresponding to the dark pink regions in the
2 photograph on the right, as well as a complete
3 complement of normal, bone-associated cells such as
4 osteoblasts, osteoclasts, stromal cells, and all
5 other bone marrow elements. ments.

6 This bone-inducing activity has been
7 labeled "osteoiduction." It is unique to BMP-2
8 and several other members of the BMP protein
9 family.

10 [Slide.]

11 rhBMP-2 can also stimulate bone formation
12 at an orthotopic site, as illustrated by this
13 radiograph of a rabbit ulnar osteotomy treated with
14 rhBMP-2.

15 The following slide provides additional
16 histological information about the effect of BMP-2
17 at an orthotopic site.

18 [Slide.]

19 As shown at the yellow arrows in the
20 slide, BMP-2 treatment yields increased bone
21 formation and an acceleration of that bone's
22 maturation.

23 [Slide.]

24 BMP-2's ability to induce bone de novo and
25 to stimulate bone formation at an orthotopic site

1 provides rationales for two different types of
2 clinical applications. BMP-2 could first be used
3 to replace a component of standard orthopedic
4 treatment such as autogenous bone graft. Last
5 January, this panel reviewed this specific use of
6 rhBMP-2/ACS in spine surgery and recommended its
7 approval.

8 Alternatively, BMP-2 could be used to
9 augment standard therapy in an effort to improve
10 its outcome. For example, rhBMP-2/ACS could be
11 used as an adjunct to standard fracture fixation in
12 certain fractures. We decided to explore this
13 potential application in a series of preclinical
14 studies.

15 [Slide.]

16 We established a rabbit model to study the
17 effect of BMP-2 as an adjunct treatment. The model
18 uses surgically-generated, mid-diafacial ulnar
19 osteotomies to assess bone repair. The osteotomies
20 do not require instrumented fixation and typically
21 heal within 6 to 8 weeks. It is feasible to
22 perform bilateral osteotomies, allowing the use of
23 within animal controls which greatly decreases
24 study variability.

25 The model allows the use of plain view

1 radiographs, biomechanical analyses, and bone
2 histology as well as the measurement of the local
3 pharmacokinetics of BMP-2.

4 This model does not stimulate the bone and
5 soft tissue damage that occurs in fractures but
6 rather serves as a proof-of-concept system for
7 evaluating bony healing under controlled
8 conditions.

9 [Slide.]

10 We used this model to determine whether
11 BMP-2 could accelerate the process of normal bony
12 healing. In the experiment shown in this slide,
13 normal animals received bilateral ulnar osteotomies
14 and were treated with either BMP-2/ACS, depicted in
15 the yellow bars, or ACS alone, depicted in the
16 orange bars. Each animal received standard
17 surgical treatment on the contralateral ulna,
18 depicted by the gray bars.

19 Normal ulnar biomechanical strength was
20 determined by testing age-matched, unoperated
21 limbs, depicted by the blue bar on the right.

22 The slide shows the results of torsional
23 biomechanical testing to failure at various time
24 points following surgery. BMP-2 treatment
25 accelerated the return to normal strength in this

1 model, yielding significant differences from
2 controls at several time points. Importantly,
3 rhBMP-2 treatment reduced the time to return to
4 fully normal strength by one-third, in this model,
5 from 6 weeks to 4 weeks.

6 The results of this study have been
7 published and form part of the rationale for
8 testing whether BMP-2 could accelerate normal
9 fracture healing in patients.

10 [Slide.]

11 We also studied whether BMP-2 treatment
12 could provide a beneficial effect under conditions
13 of impaired bone healing. To address this
14 question, we modified the rabbit ulna osteotomy
15 model. We administered systemic prednisolone to
16 all animals at doses of this glucocorticosteroid
17 that were sufficient to impair bone healing.

18 This slide shows the result from this
19 study in which the effect of rhBMP-2/ACS treatment
20 can be clearly observed in a plain view radiograph.

21 The results of this study have also been
22 published and form part of our rationale for
23 testing BMP-2 in patients with difficult-to-heal
24 fractures.

25 [Slide.]

1 We have conducted a comprehensive
2 nonclinical safety evaluation of rhBMP-2 and
3 rhBMP-2/ACS as listed on this slide. All these
4 studies were reviewed by the panel last January and
5 established the nonclinical safety profile for
6 BMP-2.

7 In these evaluations, no dose-limiting
8 toxicity was detected in any study at exposure
9 levels that greatly exceed anticipated patient
10 exposure. Furthermore, no systemic effect of BMP-2
11 was observed in any study. We attribute this
12 finding to the extremely rapid clearance of BMP-2
13 from the systemic circulation, resulting in very
14 low, if any, systemic exposure.

15 In summary, we have established a
16 preclinical rationale for evaluating rhBMP-2 as a
17 treatment for long-bone fractures. Our studies
18 showed that BMP-2 can accelerate bony healing under
19 normal conditions and can additionally increase the
20 probability of bony healing in impaired healing
21 conditions.

22 These effects were consistently observed,
23 radiographically, biomechanically, and
24 histologically. The bone formed by BMP-2 contained
25 all the components of normal bone and modeled and

1 remodeled in a manner similar to that of host bone.
2 Additionally, the nonclinical safety profile of
3 rhBMP-2/ACS has been established.

4 In conclusion, our preclinical data
5 support the clinical use of InductOs in fracture
6 patients.

7 I now turn the presentation over to Dr.
8 Alex Valentin, who will review the results of the
9 InductOs pivotal clinical study in open tibia
10 fracture patients.

11 DR. YASZEMSKI: Thanks very much, Dr.
12 Riedel.

13 Dr. Valentin?

14 DR. VALENTIN: Good morning. My name is
15 Alex Valentin. I am an employee of Wyeth Research,
16 and I have been directing BMP-2 clinical research
17 since 1993.

18 [Slide.]

19 I am here today to present the results of
20 our clinical study in patients presenting with open
21 tibia shaft fractures, because the study met its
22 four stated objectives.

23 The pivotal study has shown that InductOs
24 reduced the rate of reintervention for delayed
25 union, accelerated clinical fracture healing,

1 demonstrated an appropriate safety profile, and
2 these results were also corroborated by the
3 independent radiology panel.

4 [Slide.]

5 Before presenting the results of this
6 pivotal study, I would like to say a word here
7 about our clinical program, because this pivotal
8 study actually concludes 10 years of our clinical
9 research.

10 During these years, Wyeth sponsored a
11 number of clinical trials, and many were designed
12 and conducted in collaboration with lead orthopedic
13 surgeons in the United States and abroad. Not
14 including all the studies conducted by our
15 commercial partner, Medtronic Sophomore Danik,
16 Wyeth has enrolled over 1,000 patients, of whom
17 more than 675 were treated with BMP-2.

18 These studies helped us gain important
19 insights into the mechanism of action of BMP-2 in
20 patients and also in its safe use. This
21 information is summarized in the package that we
22 have shared with the panel.

23 [Slide.]

24 Of these studies, the three studies listed
25 here at the bottom of the slide stand out, because

1 they helped us under the U.S. standard clinical
2 practice in patients with open tibia shaft
3 fractures.

4 [Slide.]

5 These studies yielded four important
6 conclusions. First, we learned that about 40
7 percent of the open tibia shaft fractures surveyed
8 in the United States required some form of
9 reintervention to promote fracture healing; second,
10 that surgeons make decisions to reintervene before
11 they can diagnose fracture healing; third, with
12 respect to the definition of study endpoints, we
13 learned that the diagnosis of delayed union was
14 multifactorial. Surgeons made their decision
15 weighing the progression of clinical symptoms and
16 signs of radiographic fracture healing. And
17 finally, we concluded that given the high frequency
18 of interventions to promote fracture healing, their
19 avoidance was a relevant endpoint for the U.S.
20 orthopedic trauma patients.

21 Today this panel will discuss the
22 relevance of our study primary endpoint, and
23 therefore I would like to emphasize that this
24 endpoint was selected on the basis of this
25 preliminary work.

1 [Slide.]

2 I will now review our pivotal study
3 starting with the study rationale and study design.
4 I plan to describe patients' baseline
5 characteristics, the treatment they received. I
6 will then review the key efficacy and safety
7 results and our conclusions supporting the efficacy
8 and safety of InductOs in this patient population.

9 Throughout this presentation, I also plan
10 to address two questions raised by the FDA: Did
11 the protocol design allow the measurement of an
12 objective treatment effect, and are these effects
13 clinically relevant?

14 [Slide.]

15 We have chosen open tibia fractures
16 knowing well that we would be facing a challenging
17 indication. Unlike preclinical experimental models
18 in rabbits, tibia fractures are associated with
19 contaminated wounds and poor vascular supply.
20 Also, the condition requires urgent care adjusted
21 to patients' needs, not leaving surgeons much room
22 to conduct clinical trials.

23 We chose this study nonetheless because
24 open fractures affect the tibia more often than any
25 other bone and represent a very serious condition.

1 For example, despite all the progress made in the
2 treatment of open tibia fractures, 62 percent of
3 ulna unions reported in the United States affect
4 the tibia shaft region.

5 We confirmed our preliminary studies that
6 not only do these patients have a great reduction
7 in functional ability, but they suffer also a
8 dramatic and sustained reduction in their quality
9 of life.

10 [Slide.]

11 So we decided to test if BMP-2 could
12 improve the success of standard treatment in these
13 fractures, and as illustrated by the preclinical
14 results presented earlier, BMP-2 has been shown to
15 induce bone in a variety of preclinical models.

16 We hypothesized, therefore, that BMP-2 may
17 improve fracture healing by stimulating bone
18 formation at the site of a recent fracture,
19 therefore reducing the number of reinterventions
20 required.

21 Let me now describe the study design.

22 [Slide.]

23 The following objectives were selected.
24 The primary efficacy objective was to demonstrate
25 by the end of the study an increased probability of

1 fracture healing reintervention for delayed union.
2 We acknowledge the challenges raised by this
3 choice. The primary objective depends on
4 investigator's decision, and investigators could be
5 biased by their treatment of treatment allocation.

6 I would like to stress here that by
7 choosing to evaluate reinterventions, we selected
8 also an endpoint that required to take the patient
9 back to the OR. And no surgeon or patient makes
10 this decision lightly. We felt, therefore, that
11 the consequences of this decision was a warranty of
12 very careful consideration.

13 In addition, the study had two secondary
14 efficacy objectives. They evaluate what is
15 commonly called clinical fracture healing and
16 radiographic fracture healing. For the purpose of
17 this study and to avoid any confusion, we call
18 radiographic fracture healing fracture union.

19 These two endpoints were evaluated
20 separately. Clinical fracture healing was
21 evaluated by surgeons, whereas radiographic
22 fracture union was evaluated by an independent
23 radiologic panel blinded to treatment allocation.

24 Finally, the study also addressed the
25 safety of BMP-2 use in these patients.

1 [Slide.]

2 The study was a prospective, randomized,
3 controlled evaluation of BMP-2 in patients
4 presenting open tibia shaft fractures. Patient
5 randomization was stratified based on the Gustilo I
6 severity to assure a balanced distribution of this
7 important factor among treatment groups.

8 [Slide.]

9 The study was single blind. Patients were
10 not aware of the treatment allocation. And in
11 addition, a panel of three radiologists reviewed
12 radiographs to assess fracture union.

13 For the purpose of the panel evaluation,
14 union was prospectively defined as being at least
15 three or four cortices being breached on orthogonal
16 viewed.

17 We validated the methods of radiographic
18 review and trained the radiologists prior to the
19 study initiation.

20 X-rays were reviewed by the radiologists
21 of the Osteoporosis and Arthritis Research Group at
22 UCSF under the direction of Professor Harry Genent.

23 To clarify a question raised by the FDA,
24 no x-ray was withheld from the panel interpretation
25 on grounds that the patient was deemed a treatment

1 failure.

2 The panel and the surgeons have reviewed
3 the same patients and the same x-rays.

4 To facilitate outcome evaluation, no more
5 than one limb could be treated per patient, no more
6 than one BMP-2/ACS could be used, and repeat
7 treatments were not allowed. Patients were
8 followed for a total of 12 months postoperatively,
9 at seven prescheduled visits.

10 [Slide.]

11 In the interest of time, I will not review
12 here all the patient inclusion and exclusion
13 criteria. They are detailed in the panel's
14 briefing package. I will focus, however, on our
15 exclusion criteria which are relevant to the FDA
16 comment on prophylactic use of bone graft.

17 Such prophylactic treatment was indeed
18 excluded from this study. This exclusion criterion
19 is justified by our prior findings as well as
20 current experience that prophylactic bone grafting
21 is very rarely prescribed in patients with open
22 tibia shaft fractures treated with an IM nail.

23 Accordingly, should this product be
24 approved, patients requiring prophylactic bone
25 grafting should be excluded by the label.

1 [Slide.]

2 Having addressed the exclusion criteria, I
3 would like now to review the actual standard of
4 care administered in this study. This is an
5 important point since the panel will review its
6 adequacy and its relevance to the U.S. practice.

7 Wound irrigation and debridement had to be
8 promptly performed and repeated as many times as
9 required. The initial fracture reduction and
10 stabilization were to be conducted within 24 hours.
11 Definitive wound closure and fixation of the
12 fracture was conducted no later than 14 days after
13 the injury, and definitive fracture stabilization
14 required the use of an IM nail.

15 Reflecting the absence of national or
16 international consensus on the type of nail to use
17 in open tibia shaft fractures, investigators were
18 authorized to use either reamed or unreamed nails
19 of a brand familiar to them.

20 [Slide.]

21 Let me now review the definition of the
22 treatment groups. Patients were randomly allocated
23 to three treatment groups. And please note that in
24 this study, BMP-2 was not tested as a replacement
25 of bone graft but as an adjuvant to the standard

1 treatment.

2 The study was designed to demonstrate
3 superiority of at least one of the two BMP-2
4 concentrations tested as compared with control
5 patients. So patients randomized to the control
6 group received only standard care, while patients
7 randomized to BMP-2/ACS received the standard care
8 and the test article.

9 Two concentrations were tested, either .75
10 mg/ml or 1.5 mg/ml.

11 [Slide.]

12 BMP-2 was implanted at the time of
13 definitive closure of the fracture-related wound,
14 and like in this diagrammatic example, the product
15 was positioned so that it breached the region of
16 comminution, making good contact with the major
17 proximal and distal tibial fragments.

18 [Slide.]

19 I will conclude the review of the study
20 design with comments on the standardization of
21 investigator assessments, which was one of FDA's
22 concerns.

23 We believe the study has been as
24 standardized as possible considering the context of
25 this orthopedic trauma condition.

1 Investigators were trained with the same
2 protocol and the same study guidelines. The
3 protocol included a common definition of fracture
4 healing. There is no commonly-accepted definition
5 of delayed fracture union, but to the extent a
6 definition was available, that definition was
7 provided. And the protocol also had a definition
8 of non-union.

9 Now, more importantly, investigators were
10 prospectively required to report at each follow-up
11 visit the presence or absence of fracture
12 tenderness upon palpation, weight-bearing status,
13 and fracture union. These are the cardinal signs
14 used everywhere to diagnose fracture healing, and
15 as with other clinical conditions, there is no set
16 of signs or symptoms that is always present in each
17 and every patient defining delayed union or
18 healing. The intent of prospectively collecting
19 this information was not to force what we
20 considered an artificial definition of fracture
21 healing or delayed union, but to use a common set
22 of symptoms and document the soundness of the
23 investigator's decision.

24 [Slide.]

25 A word about patient enrollment. The

1 study was to our knowledge the largest clinical
2 study in this patient population. It involved 49
3 centers in 11 countries.

4 [Slide.]

5 Enrolling 450 patients achieved the study
6 objective, and as pointed out on this slide, we
7 noted that during the study conduct, three patients
8 died, one in each treatment group, and seven others
9 withdrew at their request or that of the
10 investigators.

11 Of the 440 remaining patients, 93 to 97
12 percent were actually evaluated at the last
13 follow-up visit at 12 months. Furthermore, more
14 than 90 percent of all patients were evaluated at
15 all visits, and this number includes the evaluation
16 of all protocol-required efficacy and safety
17 outcomes and in our opinion is a strong indication
18 of good compliance with the clinical protocol.

19 [Slide.]

20 Let me now describe the main baseline
21 conditions and the standard care. We have in total
22 assessed seven demographic variables and 29 other
23 covariables such as baseline comorbidities,
24 fracture and injury characteristics, treatment
25 administered before and after definitive wound

1 closure, rehabilitation prescribed for the region
2 under study.

3 This comprehensive review was conducted to
4 ensure that study results were sufficiently
5 comparable among all sites to justify pooling them
6 together and compare outcomes across treatment
7 groups.

8 I will now summarize some of the findings
9 in my next slides.

10 [Slide.]

11 Overall, patient demographics were very
12 comparable across treatment groups. The small
13 difference in median age is not clinically
14 meaningful. And in all respects, study subjects
15 reflected well the general patient population with
16 open tibia fractures--mostly young males who
17 suffered a high-energy trauma such as motor vehicle
18 accident.

19 Smoking, which is a non-risk for delayed
20 union, was noted equally in all treatment groups.

21 [Slide.]

22 The distribution of the fracture
23 characteristics was also very comparable among
24 treatment groups. Although the majority of
25 fractures were isolated to the tibia under study, a

1 substantial proportion of patients in all three
2 treatment groups presented multiple fractures.
3 This is typical of the presentation of patients
4 with open tibia fractures.

5 And fracture severity categorized
6 according to the AO classification, which is very
7 comparable to the OTA classification, was
8 comparable among treatment groups. So was wound
9 severity according to the Gustilo-Anderson
10 classification. For example, Gustilo IIIB
11 fractures, which have a very poor fracture
12 prognosis, were observed in 11 to 18 percent of the
13 cases involved.

14 [Slide.]

15 With respect to the mode of fracture
16 reduction and fixation, we noted that all but one
17 percent of the patients enrolled were actually
18 treated using IM nail, and most patients received
19 statically locked nails. In agreement with the
20 protocol design, a few patients equally distributed
21 across treatment groups received dynamically locked
22 nails or unlocked nails. About two-thirds of the
23 patients received unreamed nails, while the rest of
24 the patients received reamed nails.

25 We found an imbalance in the distribution

1 of reamed and unreamed nails which approached
2 statistical significance. We have investigated the
3 cause of this imbalance, and our analysis, which
4 was included in the panel's briefing package, shows
5 this imbalance was a consequence of a centralized
6 randomization procedure.

7 So, to summarize, with two exceptions,
8 demographic characteristics, risk factors, fracture
9 presentation, and fracture management were found
10 sufficiently similar across all centers to justify
11 the pooling of the data and among treatment groups
12 to justify the treatment effect analysis.

13 [Slide.]

14 Let me now review the study results.

15 The primary efficacy objective of this
16 study was to demonstrate an increased probability
17 of fracture healing. At study completion,
18 treatment success was based on the number of
19 fractures being healed by the investigator in the
20 absence of other intervention to promote fracture
21 healing.

22 Secondary procedures to promote fracture
23 healing and also reported screw breakage leading to
24 fracture self-dynamization were deemed indicative
25 of treatment failure.

1 [Slide.]

2 The primary efficacy objective of this
3 study was met. BMP-2 increased treatment success,
4 and in patients receiving BMP-2/ACS 1.5, the
5 success rate was increased by one-third.

6 Conversely, there was a 41 percent decrease in
7 failure rate. This is a clinically substantial
8 improvement, and the overall difference among
9 treatment groups was highly significant.

10 Furthermore, BMP-2 was dose-dependent, and
11 we believe that the dose-dependency of the
12 treatment effect further supports our conclusion
13 that this effect was unbiased.

14 [Slide.]

15 As I pointed out on the study endpoints,
16 treatment failures account for two categories of
17 event--secondary interventions and
18 self-dynamizations. With respect to secondary
19 interventions and in the spirit of an
20 intent-to-treat analysis, all procedures, whether
21 prescribed or preformed, were counted. In
22 addition, in some cases, the inadvertent breakage
23 of locking screw led to fracture self-dynamization.
24 These occurrences were counted as treatment
25 failures because self-dynamization affects fracture

1 healing.

2 It is noteworthy that self-dynamization
3 appeared to be treated more frequently in control
4 patients and in BMP-2 treated patients. This
5 difference approached significance.

6 These hardware failures are observed in
7 the presence of delayed union. Self-dynamizations
8 are not subject to investigative bias because they
9 occur without intervention from the investigator.
10 In this case, the difference observed in
11 self-dynamizations independently suggests that
12 patients treated with BMP-2 healed faster and
13 reduced their exposure to this risk.

14 [Slide.]

15 We have also assessed the number of
16 interventions to identify interventions that may
17 have been done in the same patients either
18 concurrently or sequentially. This analysis
19 complements the previous one, which counted the
20 number of patients with secondary intervention.
21 The number of procedures was counted only in
22 patients who actually received the treatment they
23 were randomized to and had evaluable outcomes. We
24 call these patients the evaluable population.

25 Supporting the results observed in the

1 primary efficacy endpoint, in this patient
2 population, the number of interventions was found
3 significantly decreased in the 1.5 mg/ml treatment
4 group as compared to the control group.

5 [Slide.]

6 Accounting for the number of
7 interventions also allows us to characterize and
8 evaluate their invasiveness.

9 Noninvasive procedures represent
10 ultrasound, electrical stimulation, or magnetic
11 field stimulation. Less invasive procedures
12 represent nail dynamization or addition of a
13 functional brace.

14 [Slide.]

15 And finally, the most invasive procedures
16 represent procedures such as bone graft, exchange
17 nail, tibial osteotomy or bone transport.

18 Half of the procedures conducted in
19 control patients were categorized as most invasive,
20 whereas invasive procedures represented only 37
21 percent of the procedures undertaken in patients
22 treated with BMP-2 1.5.

23 Consequently, in these evaluable patients
24 receiving InductOs, the number of the most invasive
25 interventions was found significantly decreased as

1 compared to control patients.

2 [Slide.]

3 A secondary efficacy objective of this
4 study was to demonstrate an accelerated fracture
5 healing. This endpoint was the number of fractures
6 clinically healed without a secondary intervention
7 as determined by the investigator 26 weeks
8 post-injury.

9 As I mentioned earlier, to determine
10 fracture healing, investigators assessed clinical
11 parameters such as tenderness upon fracture
12 palpation, patient's weight-bearing status, and
13 reviewed the orthogonal radiographic views of the
14 fracture.

15 The 6-month time point for this evaluation
16 was suggested to us during the 1996 review of the
17 protocol by FDA. We have adopted it for this
18 study, and in addition, fracture healing was also
19 reported at all other preceding and following
20 visits.

21 [Slide.]

22 As illustrated on this slide, the
23 cumulative rate of fracture healing indicates that
24 the secondary efficacy objective was also met.
25 Twenty-six weeks post-injury, InductOs increased

1 the number of patients healed without secondary
2 intervention by 53 percent as compared to control
3 patients, thus suggesting an accelerated fracture
4 healing. This increase was highly statistically
5 significant.

6 Similarly, the number of patients healed
7 after treatment with InductOs was significantly
8 increased at every other visit starting at the Week
9 14 follow-up and lasting until the end of the
10 study.

11 [Slide.]

12 This accelerated healing was confirmed by
13 this Kaplan-Meyer evaluation of probability of
14 healing as a function of time. According to this
15 evaluation, patients treated with InductOs healed
16 significantly faster than control patients. The
17 median time to healing for InductOs patients was 39
18 days shorter than for control patients, a
19 clinically and statistically significant
20 difference.

21 [Slide.]

22 Another secondary efficacy objective of
23 this study was to demonstrate accelerated fracture
24 union. We are referring to this outcome as
25 "fracture union" rather than "fracture healing"

1 because the endpoint was based solely on
2 radiographs.

3 For this objective, the endpoint was the
4 number of fractures with radiographic healing
5 assessed 6 months after the fracture, and the
6 result was also reported at all the other visits.

7 For the purpose of this endpoint, patients
8 united after a second intervention were counted as
9 treatment failures.

10 This time, the endpoint was measured
11 independently by three trained radiologists from
12 UCSF who were blinded to patients' treatment
13 allocation and patients' clinical presentation.
14 And as I mentioned already, the radiographic
15 assessments used the same x-rays that were used by
16 the investigators, and all radiographs from all
17 patients that were reviewed by the surgeons were
18 also reviewed by the panel.

19 [Slide.]

20 As indicated on this chart, this efficacy
21 objective was also met. The radiology panel
22 blinded to treatment allocation and patient
23 symptoms independently confirmed that BMP-2
24 treatment effect. At 26 weeks after the fracture
25 in the InductOs group, the number of patients with

1 fractures united was 65 percent higher than in the
2 control group. This clinically significant
3 increase was also statistically significant.

4 The difference in union rate between
5 InductOs and control patients was still significant
6 at the 50-week visits, when 34 percent more
7 patients had their fractures united in the InductOs
8 group as compared to the standard care.

9 [Slide.]

10 As pointed out by FDA, the Kaplan-Meyer
11 evaluation of radiographic union failed to identify
12 the difference between treatment groups. We
13 believe in this case that radiographic fracture
14 union is best evaluated using the cumulative rate
15 of union by visit rather than the Kaplan-Meyer
16 display. And in my next slides, I will attempt to
17 explain why.

18 [Slide.]

19 As illustrated on my previous slides, the
20 radiology panel diagnosis of fracture union
21 occurred at a later time point than investigators'
22 assessment of clinical fracture healing. This lag
23 time is not unusual.

24 In the absence of guidance provided by
25 patients' clinical science, it reflects the

1 difficulties of transforming the progressive
2 callous mineralization into a dichotomous decision
3 of success and failure.

4 We verified this explanation in a separate
5 study where a group of orthopedic surgeons were
6 requested to determine fracture union without
7 clinical information. Furthermore, similar
8 observations were made and published by many other
9 authors.

10 [Slide.]

11 So, as an example of lag time observed
12 sometimes between investigators and radiologists,
13 this slide illustrates the case of a 29-year-old
14 male who suffered a Gustilo IIIB left tibia
15 fracture following a motorcycle accident. His
16 fracture was treated with an unreamed nail and
17 BMP-2/ACS 1.5.

18 As illustrated on these AP views, the
19 fracture progressed toward healing, and at 20 weeks
20 post-injury, the patient had no tenderness upon
21 palpation, was full-weight-bearing, and was deemed
22 healed by the investigator. In this case, the
23 diagnosis of fracture union was confirmed at the
24 following visit by the independent radiology panel,
25 but the delay varied from patient and patient.

1 [Slide.]

2 Overall, the delay observed between
3 investigators and radiologists is illustrated on
4 this slide which shows side-by-side the two
5 evaluations for the same patients. For the purpose
6 of this example, only the control patients were
7 selected.

8 The study was designed to maximize
9 clinical evaluation in the first 6 months of
10 patient follow-up. The delay between clinicians
11 and radiologists resulted in pushing the evaluation
12 of radiographic union to the second half of the
13 study, in the last 6 months, where only two
14 follow-up visits were planned.

15 [Slide.]

16 So it is important to understand that for
17 most patients, clinical fracture healing was
18 established by the investigators in the first 6
19 months of the study. In contrast, the independent
20 panel observed radiographic union about 3 months
21 later, in the second half of the study.

22 As a result, clinical fracture healing
23 could be assessed by the investigators at one of
24 four follow-up visits planned in the first 6
25 months, and in contrast, the second half of the

1 study, radiographic union could be assessed by the
2 panel only at two follow-up visits.

3 The paucity of time points available in
4 the second half of the study has hindered the
5 Kaplan-Meyer evaluation of fracture union, and it
6 resulted in what can be called an "interval
7 censoring" of data.

8 It is for this reason that we prefer
9 instead to express the radiographic union results
10 as a cumulative proportion of patients united by
11 visit.

12 [Slide.]

13 We believe that the independent of
14 fracture union by the radiology panel is most
15 appropriate to corroborate the investigators'
16 findings in a different manner. In cooperation
17 with the FDA, we constructed a composite index
18 called Combined Clinical and Radiographic Endpoint,
19 or CCRE.

20 As shown on this slide, this composite
21 index assigns patients to four groups reflecting
22 the clinical assessment of healed/not healed, and
23 the radiographic assessment of united or not
24 united. It can be viewed as a way of separating
25 true positive results, shown here on the first

1 line, from false positive, false negative, and true
2 negative results shown here on the following three
3 lines.

4 If you would allow me to draw your
5 attention to the second line, showing patients
6 healed but not united, I would like to make the
7 following observation. If the study results were
8 affected by investigator bias, one would expect to
9 see the number of patients healed without
10 radiographic substantiation of union being
11 different among treatment groups; but that is not
12 what the data show.

13 In the control group, there were 16 such
14 patient, in the BMP groups, there were 21 and 19.
15 This small numeric excess is not only statistically
16 insignificant, but also very small compared to the
17 size of the treatment effect.

18 So one must concluded that the healed but
19 not united patients are best explained by a lag in
20 the radiographic findings happening equally in all
21 three treatment groups and not due to investigator
22 bias.

23 [Slide.]

24 By using this composite index, we further
25 analyzed BMP-2 treatment effects. This slide

1 presents the results of this analysis.
2 Conservatively, we scored as treatment successes
3 only patients clinically healed and
4 radiographically united. Even by using this
5 conservative assessment, we still found that 36
6 percent more patients in the InductOs group were
7 healed and united as compared to the control group.
8 This difference remains clinically and
9 statistically significant.

10 [Slide.]

11 In their review, the FDA has expressed the
12 concern about the heterogeneity of the study
13 population which may have founded study results.
14 As I have pointed out in my presentation, the
15 review of seven demographic criteria and 29
16 covariables led us to conclude that the
17 randomization process was generally successful in
18 generating comparable treatment groups.

19 To further address the question, we
20 conducted additional analysis using prospectively
21 defined patient categories. These categories
22 reflect fracture severity such as isolated versus
23 fractures are multiple skeletal locations, Gustilo
24 classification, risk factors such as smoking,
25 patient enrollment at different research centers or

1 countries, and the type of nail used.

2 Our conclusion has been that no specific
3 patient category as defined above influenced the
4 overall efficacy results. These findings further
5 justify the data-pooling.

6 [Slide.]

7 Another question in front of the panel
8 today concerns the potential investigator bias made
9 possible by the knowledge of treatment allocation.
10 To address this issue, we conducted several
11 post-hoc evaluations to determine the consistency
12 of treatment failure or success assessments across
13 centers and treatment groups. We concluded that
14 success and failure criteria were applied
15 consistently.

16 For example, investigator prescription of
17 secondary intervention with a diagnosis of fracture
18 healing were concordant with patients' clinical
19 status.

20 Additionally, reintervention decisions
21 were made at comparable time points across
22 treatment groups. That means that no patient was
23 given extra time to achieve healing before a
24 reintervention was decided. The time from injury
25 to prescription of reintervention was consistent

1 with patients' condition and, most importantly,
2 comparable across all three treatment groups.

3 Also, the clinical status of patients
4 diagnosed as healed did not deteriorate.

5 These findings made us conclude that no
6 evidence of investigator bias could be detected and
7 that the study was conducted with appropriate
8 standardization to earn the review of its results.

9 [Slide.]

10 Let me now review the BMP-2/ACS safety.
11 This objective was based on clinical, radiographic,
12 histologic, and lab evaluations and on the
13 detection of antibody titers to BMP-2, bovine, and
14 Human Type 1 collagen.

15 As a background to this safety review, let
16 me remind you that we have generated a database
17 including over 1,000 patients from all Wyeth BMP-2
18 studies. These results were summarized in our
19 investigator brochure which was included in the
20 panel's briefing package.

21 The safety data collected in this pivotal
22 study support our general conclusion that BMP-2/ACS
23 can be safely used in patients. We found that most
24 adverse events were consistent with the trauma
25 setting. Generally, the treatment groups have the

1 same frequency and the same severity of adverse
2 events.

3 [Slide.]

4 Let me now review some of these
5 parameters, in particular those of interest to
6 orthopedic surgeons. I will start with the
7 incidence of infection.

8 The introduction of a foreign body in this
9 potentially contaminated wound always poses the
10 question of an increased infectious risk, so we
11 monitored very carefully the occurrence of
12 infections in this pivotal study, and we have
13 conservatively recorded all declared infections,
14 whether superficial or deep, whether confirmed or
15 not by bacteriologic analysis. And this reporting
16 rule explains a relatively high incidence of
17 infectious events reported here. However, the
18 incidence of infections was found comparable among
19 all three treatment groups.

20 And, as expected, most infections occurred
21 in patients who suffered the most severe fractures,
22 the Gustilo IIIA and IIIB, and furthermore, to
23 track the most severe infections, we identified all
24 the cases of deep-bone infection requiring the
25 surgical procedure. And this is the infectious

1 event typically reported in orthopedic research
2 publications.

3 Again, the incidence of deep-bone
4 infections was comparable with data previously
5 published in the U.S. and is strictly comparable
6 across treatment groups, suggesting that BMP-2 did
7 not increase patients' exposure to infection.

8 [Slide.]

9 Another safety variable important to
10 orthopedic surgeons is the occurrence of hardware
11 failure. In this study, hardware failure includes
12 most broken or bent locking screws and in two
13 cases, a broken nail.

14 Hardware failures occur with decreasing
15 frequency across the three treatment groups--21
16 percent, 17 percent, and 11 percent. These
17 decreased incidences of hardware failure in
18 BMP-2-treated patients was observed whether
19 patients were treated with a reamed or an unreamed
20 nail.

21 [Slide.]

22 Because of the osteoinductive properties
23 of BMP-2, we have monitored all signs of
24 exaggerated or abnormal bone formation. Such
25 events include calcification of remote sites, which

1 we called ectopic, and calcification in the
2 fracture vicinity, which we have called
3 heterotopic.

4 Conservatively, heterotopic callouses in
5 tibia/fibula synostosis were added to the
6 heterotopic calcifications.

7 No ectopic calcification due to BMP-2 was
8 reported, and overall, heterotopic calcification,
9 hypertrophic callouses, and tibia/fibula synostosis
10 included, were rarely observed in this study.

11 While not statistically significant, treated
12 patients with BMP-2 had an increase in the number
13 of such reports compared to control
14 patients--respectively, eight, four, and four.

15 [Slide.]

16 Patients enrolled in this pivotal study
17 were also monitored for the development of
18 antibodies to BMP-2 and to Type I collagen, and
19 serum samples were collected at baseline 6 and 20
20 weeks post-treatment.

21 We have detected anti-BMP-2 antibodies in
22 a small number of patients. This human response
23 was always marked by a low and transient titer.

24 Anti-bovine Type I collagen antibodies
25 were also detected in nine of the control patients

1 and in 22 and 29 BMP-2/ACS patients. There was no
2 cross-reactivity, and none of these patients
3 presented an immune reaction to Human Type I
4 collagen.

5 The presence of antibodies to BMP-2 or to
6 bovine collagen was not associated with lower
7 treatment efficacy or associated with any
8 accompanying symptoms of immune reaction or
9 allergy.

10 [Slide.]

11 The other safety evaluations are
12 summarized on this slide.

13 [Slide.]

14 So, to summarize my presentation, we found
15 that InductOs may offer new therapeutic options in
16 the treatment of open tibia fractures which are
17 serious orthopedic trauma conditions.

18 In this study, the product has
19 consistently demonstrated safety and efficacy
20 irrespective of fracture severity, documented risk
21 factors, type of nail used, investigational center,
22 or country where patients were treated.

23 [Slide.]

24 BMP-2 effective and safety sue was
25 supported by results observed in regard to all four

1 study objectives.

2 First, BMP-2/ACS reduced the rate of
3 reintervention for delayed union; in addition,
4 BMP-2 accelerated clinical fracture healing; the
5 evidence of efficacy was corroborated by the
6 independent panel evaluating radiographic fracture
7 union; and finally, InductOs safety profile was
8 deemed appropriate.

9 I thank you for your attention and wish
10 not to turn the presentation Professor Marc
11 Swiontkowski, who will discuss the relevance of
12 these results to the U.S. trauma population.

13 DR. YASZEMSKI: Thanks very much, Dr.
14 Valentin.

15 Dr. Swiontkowski, welcome.

16 DR. SWIONTKOWSKI: Good morning. My name
17 is Marc Swiontkowski, and I am from the University
18 of Minnesota Department of Orthopedic Surgery,
19 where I have been privileged to serve as chairman
20 of that department since 1997.

21 I practice in two Level I trauma centers
22 in the Twin Cities. I also co-direct the Clinical
23 Outcomes Research Center for the University of
24 Minnesota School of Medicine.

25 Prior to my arrival in Minneapolis, I was

1 the Chief of Orthopedic Surgery at Harbor View
2 Medical Center in Seattle, Washington, also a Level
3 I trauma center.

4 I have spent my entire 17 years of
5 clinical practice in the management of severely
6 injured patients, and based on my research
7 interests have a particular interest in improving
8 the knowledge base on which we have managed these
9 patients.

10 I have been involved with the rhBMP-2
11 series of studies since 1991. I have participated
12 in the initial discussions regarding the selection
13 of the clinical indication to study through the
14 conduct of the 12-patient safety study in the
15 United States, the 60-patient trial in the United
16 States, and as an advisor to the pivotal trial
17 which we are discussing today.

18 I have no financial interest or ethical
19 conflicts regarding the study we are discussing
20 today, although I am an active paid consultant with
21 Wyeth, who has paid my way here today.

22 [Slide.]

23 This morning, I will address some of the
24 questions that FDA has raised to the panel. I will
25 review the relevance of the study data to clinical

1 practice both in the United States and
2 internationally. I will comment on the selection of
3 the clinical indication and the primary efficacy
4 endpoint secondary intervention to promote fracture
5 healing.

6 I will also comment on the study design
7 and conduct and how the study findings are relevant
8 for patients with tibial fractures in the United
9 States. I will compare the data collected from the
10 pivotal study with that of an identically-designed
11 FDA-approved trial of 60 patients conducted in the
12 United States.

13 Finally, I will address how the pivotal
14 study findings are of utility to surgeons managing
15 patients with long-bone fractures.

16 [Slide.]

17 Open tibia shaft fractures were selected
18 as the clinical indication because of the high
19 medical need for improving outcomes. These
20 fractures have a high rate of delayed union and,
21 among common fractures, the highest rate of
22 non-union. As a stringent model, results from
23 these fractures can be readily applied to other
24 less severe long-bone fractures with more
25 biologically friendly tissue conditions.

1 In other words, if the protein works in
2 this setting of severe muscle damage from
3 high-energy blunt injury, it will work anywhere.

4 As part of the panel discussion today, you
5 have been asked to evaluate the definition of
6 standard care described by the sponsor for this
7 patient population. The question is what role bone
8 grafting plays in the management of these
9 fractures.

10 As a practicing orthopedic traumatologist,
11 I will reiterate the sponsor's previous statements
12 that prophylactic bone grafting is not standard
13 care, either in the U.S. or internationally, for
14 the management of the fracture type studied in this
15 trial.

16 [Slide.]

17 I base my statements about the standard of
18 care not only on my experience in clinical practice
19 but also from investigation of worldwide standards,
20 including data collected by Wyeth and information
21 in the literature.

22 Wyeth conducted two separate U.S.-based
23 investigations of patients with tibial shaft
24 fractures. These include a retrospective chart
25 review of 484 patients conducted in 1993 and a

1 prospective natural history study of 86 patients
2 conducted in 1994. Both studies demonstrated a low
3 incidence of bone grafting, revealing that early
4 prophylactic bone grafting is not commonly
5 practiced in the management of these fractures.

6 Regarding the literature, when early
7 prophylactic bone grafting has been advocated, its
8 use has been strictly limited to those fractures
9 with substantial bone loss. Patients with
10 substantial bone loss are a different type of
11 patient population and were excluded from this
12 pivotal study.

13 In general, surgeons seek to avoid bone
14 grafting whenever possible, because there is a 9 to
15 10 percent incidence of major complications and 20
16 to 30 percent incidence of persistent pain and
17 disability.

18 [Slide.]

19 This pivotal trial was designed in
20 consultation with over 20 of my peers who staff
21 Level I trauma centers around the United States and
22 Canada, in four separate meetings. During these
23 meetings, we discussed the merits of individual
24 skeletal injuries and debated the aspects of the
25 study design amongst ourselves and with Wyeth.

1 Ultimately, we recommended the open tibial fracture
2 model.

3 In addition to medical need, its merits
4 include that the ACS could be implanted at the time
5 of wound closure, which allowed adequate time for
6 patient and family consent. This is a key
7 consideration in the trauma population.

8 We felt that these fractures were
9 consistently managed with staged wound closure. We
10 argued the pros and cons of a blinded trial and
11 ultimately decided upon an open-label trial design
12 as the majority of practicing participating
13 surgeons stated with confidence that they could not
14 ethically place a plain collagen sponge in an open
15 fracture wound, as it would have little potential
16 benefit to the patient and could expose the patient
17 to the risk of infection in a potentially
18 contaminated wound environment.

19 Further, they believed that their ethics
20 committees would not approve such a trial-blinding
21 strategy.

22 [Slide.]

23 After reaching agreement on the open
24 tibial fracture model and open label study design,
25 this group of orthopedic traumatologists

1 extensively debated the pros and cons of the
2 primary efficacy endpoint.

3 We felt that revision surgery--secondary
4 intervention--was a measurable endpoint that held
5 the most relevance from a clinical perspective.
6 Failure was defined as the need for any secondary
7 intervention with a stimulatory effect on healing.
8 This is a highly conservative definition which
9 includes not only surgery but also other less
10 invasive interventions.

11 The endpoint used in this trial is
12 consistent with other control trials, both past and
13 present, conducted within the orthopedic trauma
14 community.

15 [Slide.]

16 The panel has been asked to evaluate the
17 clinical relevance of the primary efficacy endpoint
18 used in this trial. In making the pivotal trial as
19 directly applicable to clinical practice as
20 possible, the clinician's assessment of fracture
21 healing, based on a combined assessment of clinical
22 and radiographic findings, was favored over a
23 purely radiographic assessment of efficacy.

24 This is consistent with clinical practice
25 where treatment decisions are routinely made based

1 on the combined clinical presentation of the
2 patient and radiographic appearance of the
3 fracture.

4 As the sponsor has previously described,
5 the key variables in the assessment of fracture
6 healing are lack of fracture site tenderness upon
7 manual palpation, ability to be
8 full-weight-bearing, and radiographic fracture
9 union.

10 [Slide projector malfunction.]

11 DR. SWIONTKOWSKI: I'm not sure we need
12 the slides.

13 DR. YASZEMSKI: That will be up to you,
14 Dr. Swiontkowski, if you want to proceed.

15 DR. SWIONTKOWSKI: Yes; I don't mind. I'm
16 really not sure you need them, anyway.

17 This trial was hypothesis-driven.
18 Specifically, an expected rate of secondary
19 intervention was established from the prospective
20 natural history study conducted by Wyeth, and these
21 data were used to support the hypothesis and sample
22 size for this pivotal study.

23 Because of the practical nature of
24 conducting a trial within busy trauma centers, the
25 study was designed to minimize the disruption of

1 care and to be compatible with day-to-day clinical
2 practice. The design was acceptable to the
3 clinical investigators in the United States, and
4 then, as the sponsoring agency went international,
5 the trial design, which had been piloted in the
6 United States, was acceptable to investigators in
7 numerous countries.

8 This study designed passed all human
9 subjects committee reviews, which spoke to our
10 consideration of patients and their families in the
11 trial design.

12 [Slide.]

13 What we have here in this three-arm,
14 450-patient, randomized control trial of patients
15 with open tibial fractures is the largest
16 orthopedic trauma clinical trial that I am aware
17 of. It was conducted at high-quality centers and,
18 as a part of my advising role to Wyeth, I helped
19 identify these centers. As a part of my academic
20 career, I have traveled to many centers in the UK,
21 South Africa, and Germany. I have visited the
22 majority of these sites. I knew that the quality
23 of care in the operating room and postoperatively,
24 as well as the implants available and the surgeon
25 training, was basically equivalent to United

1 States' standards. Many of these surgeons had in
2 fact trained at our center in Seattle or in other
3 U.S. or Canadian centers with which we are all
4 familiar.

5 Over 90 percent of the centers involved in
6 this trial have published their clinical outcomes
7 for treatment of long-bone injuries in the
8 peer-reviewed literature. This further confirms
9 their commitment to delivering a high standard of
10 care.

11 The fact that we chose the right centers
12 is revealed in the fact that we had over 90 percent
13 patient follow-up at one year across all centers
14 and countries. The quality of this study has been
15 certified by high-profile podium presentations at
16 the Orthopedic Trauma Association, CCOT, and the
17 American Academy of Orthopedic Surgeons. It has
18 also been accepted for publication by the Journal
19 of Bone and Joint Surgery, which is widely
20 considered to be the premier peer-reviewed
21 publication in the field of orthopedic surgery.

22 [Slide.]

23 As the sponsor has previously described,
24 definitions for key study outcomes were provided to
25 investigators participating in this trial. These

1 include definitions for delayed union, non-union,
2 and secondary intervention for delayed union or
3 non-union. Recognizing the need to define these
4 key variables, the sponsor provided radiographic
5 and clinical definition that not only conformed to
6 the assessment methods commonly described in the
7 orthopedic literature, but also to governmental
8 guidelines including HCFA and FDA.

9 The definitions provided are appropriate
10 in that they are consistent with clinical practice.

11 [Slide.]

12 To address the relevance of the pivotal
13 study data to the U.S. population, I will review a
14 number of variables collected as part of the
15 FDA-approved 60-patient U.S. study in patients with
16 open tibia fracture, compare it to that of the
17 pivotal study.

18 It is important to note that the U.S.
19 study was a randomized controlled trial that used
20 the same endpoints, decisions for healing, and
21 radiographic assessment as the international
22 pivotal study.

23 Among these two studies, the U.S. and the
24 pivotal trial, the population of patients included
25 is comparable overall. As you can see, the

1 demographic and baseline profile of the patients in
2 both trials in terms of age, gender, smoking
3 history, and extent of injury are very similar,
4 with no significant differences.

5 Similarly, there were no differences in
6 the distribution of fracture patterns by AO/OTA
7 classification, Gustilo wound type, or mechanism of
8 injury. Over 90 percent of patients in both the
9 U.S. and international cohort were injured by a
10 blunt mechanism.

11 [Slide.]

12 Again, the relevance of this pivotal study
13 to the U.S. population is demonstrated by the
14 consistent standards of fracture and wound
15 treatment that were applied among the centers
16 involved in the two trials. State-of-the-art
17 implants were used and, with few exceptions, were
18 manufactured by one of four major implant
19 companies, all of which are FDA-approved for use in
20 the United States.

21 The patients had repeat irrigation and
22 debridement with delayed wound closure in many
23 cases, and consistent muscle flap/skin graft
24 coverage for larger wounds, the Gustilo IIIB
25 classification.

1 I should note that there was a small
2 number of Type IIIB fractures in the international
3 cohort which were treated with skin grafts, whereas
4 in the United States cohort, all patients with IIIB
5 fractures received muscle flaps. In each case that
6 a muscle flap was not used, the investigator
7 verified that the fracture grade was indeed Gustilo
8 Type IIIB.

9 [Slide.]

10 The pivotal study design did not randomize
11 by reamed versus unreamed technique of nail
12 insertion. At the time the study was conducted,
13 and even today, the use of reamed versus unreamed
14 nails in the management of open tibial shaft
15 fractures remains an unresolved controversy.

16 A meta-analysis published in the Journal
17 of Orthopedic Trauma by Bhandari et al. has failed
18 to confirm an advantage or disadvantage for reamed
19 or unreamed nailing in this setting. Given that
20 this issue remains unresolved, the sponsor's
21 decision to include both types of nail insertion
22 techniques in the pivotal trial was appropriate.

23 In comparing the U.S. and international
24 studies, one observes differences in use. The
25 issue of reamed versus unreamed nailing is now

1 being specifically addressed through a randomized
2 control trial of 900 patients in the U.S. and
3 Canada, funded collaboratively between the National
4 Institute of Arthritis and Musculoskeletal Skin
5 Diseases at the NIH and the Canadian Institute for
6 Health.

7 This trial, the Sprint trial, for which I
8 am the principal investigator, utilizes the same
9 clinically-relevant endpoint of secondary
10 intervention as judged with the surgeon, with
11 patient exam and radiographic review, as was used
12 in this pivotal trial. As sometimes happens, the
13 study data show an imbalance for nail insertion
14 technique.

15 [Slide.]

16 Finally, the most important outcome--the
17 rate of secondary intervention. Again referencing
18 our 60-patient U.S. trial, the data from the
19 international pivotal study supports similar
20 decisionmaking used in these different settings.
21 The rates of secondary intervention in the standard
22 of care arm verified the hypothesis that this is
23 not an uncommon outcome and confirmed what we
24 learned from the natural history study conducted by
25 Wyeth, which revealed a 41 percent rate of

1 secondary intervention among patients with open
2 tibial shaft fractures treated with IM nailing.

3 The types of secondary interventions were
4 not significantly different between trials, with IM
5 nail dynamization being most common, followed by
6 exchange nailing and bone grafting procedures.

7 An important measure of quality of
8 care--infection--utilizing the strict definition
9 outlined by Dr. Valentin was 18 percent in the U.S.
10 cohort and 22 percent in the international cohort.

11 Another important measure--the time to
12 decision for reintervention--was also comparable
13 across the two trials, peaking between 10 and 20
14 weeks post-injury, time points consistent with
15 those reported in the orthopedic literature.

16 The decision as to when to intervene was
17 within 2 days for patients in the three trial
18 treatment arms in both studies, confirming a lack
19 of bias in this decisionmaking.

20 [Slide.]

21 Last, I will comment on the utility of the
22 pivotal study findings to other surgeons managing
23 patients with long-bone fractures.

24 As we have seen today, the trial findings
25 are consistent with the preliminary data collected

1 in the natural history and pilot studies conducted
2 in the U.S. The standards applied in the
3 international study in terms of definitions
4 utilized and treatments administered are compatible
5 with U.S. practice.

6 The primary efficacy endpoint of secondary
7 intervention was a clinically meaningful measure
8 and being consistent with U.S. clinical practice is
9 directly applicable to the care of patients here in
10 the U.S.

11 Most importantly, through the significant
12 reduction in secondary intervention, the study
13 results represent a substantial clinical benefit to
14 patients with these types of severe injuries.

15 Finally, I must reiterate that this
16 fracture model represents the most harsh biologic
17 environment in which to test the impact of rhBMP-2.
18 I am confident and comfortable with the conclusion
19 that the protein will definitely work in other
20 settings.

21 [Slide.]

22 In conclusion, to my knowledge, this is a
23 controlled trial of the highest quality yet
24 performed in the orthopedic trauma community. The
25 study shows a significant decrease in the rates of

1 secondary intervention which are highly relevant to
2 patients with these injuries, as well as the
3 physicians treating them.

4 As an orthopedic traumatologist, I am
5 comfortable with the conclusion that rhBMP-2 with a
6 collagen sponge is safe, that it accelerates
7 healing in long-bone fractures, and will be a
8 useful adjunct to my care of these patients.

9 I am proud to have played a small role in
10 the conduct of this trial and, along with the Wyeth
11 representatives, would be pleased to answer any
12 questions that the panel may have.

13 Thank you.

14 DR. YASZEMSKI: Thanks very much, Dr.
15 Swiontkowski.

16 We're going to proceed now with the
17 presentations by FDA. Aric Kaiser, the lead
18 reviewer, will present first.

19 FDA Presentation

20 MR. KAISER: Good morning. I am Aric
21 Kaiser, the lead reviewer for this PMA.

22 We are going to be discussing InductOs,
23 the rhBMP-2/ACS device from Wyeth Pharmaceuticals.

24 [Slide.]

25 I would also like to introduce the

1 collaborator for this project, Peter Hudson, who
2 was the lead preclinical reviewer; Barbara Buch,
3 the clinical reviewer; and Chang Lao, our
4 statistical reviewer.

5 [Slide.]

6 In addition to those three, we also had a
7 number of people from CDRH as well as CBER and CDER
8 who provided valuable input on reviewing the
9 information provided by the sponsor.

10 [Slide.]

11 As described by the company, this is a
12 two-component combination product consisting of a
13 growth factor, rhBMP-2, and a carrier for that
14 protein, the ACS absorbable collagen sponge.

15 [Slide.]

16 One of the things I want to point out is
17 that in the clinical presentation that we will be
18 giving, we are reviewing only the tibia data that
19 was generated as a result of the clinical trial.
20 We did not review and we are not presenting any of
21 the data that was summarized in the study that
22 related to the use of the product either in other
23 orthopedic applications or in dental applications.

24 This leads into a discussion that we are
25 going to have you participate in this afternoon,

1 looking at the indication for product, whether it
2 is the indication that was actually studied by the
3 company, the acute open tibia fracture stabilized
4 with IM nails, compared to the proposed indication
5 which is listed up here that includes both an
6 indication for the product as well as some claims
7 about the behavior of the product.

8 [Slide.]

9 A little history about this PMA. The
10 original PMA was issued a not approvable letter,
11 and the basis for this letter was our belief that
12 there were some critical deficiencies in the design
13 of the trial that would have prevented the company
14 from developing data to fall in the category of
15 valid scientific evidence.

16 The sponsor, after reviewing that
17 information, believed they could address our
18 concerns and submitted a response to that letter
19 where they re-analyzed their data and then tried to
20 address what we had identified as the critical
21 issues as well as some other issues of a clinical
22 and statistical nature that had been identified in
23 that letter.

24 [Slide.]

25 We are not going to go into a discussion

1 of the preclinical information. As the sponsor
2 mentioned, this was previously discussed by the
3 panel at the January meeting.

4 All I want to identify from a preclinical
5 standpoint is that as a result of that meeting,
6 there were some issues that were identified as
7 being outstanding preclinical issues, and as the
8 company has said, they are conducting some
9 additional in vitro and in vivo evaluations to
10 address those concerns, having to do with the
11 potential ability of the protein to promote tumor
12 formation as well as the impact--the potential
13 impact--of the protein on fetal development.

14 The company is also working on some new
15 ELISA assays that are more sensitive.

16 We are going to focus today on clinical
17 and statistical issues that were outstanding from
18 our review of the resubmission of the product.
19 That would lead us to the end of this discussion,
20 where we are going to have you provide some comment
21 on four questions that we are going to pose--one
22 having to do with the study design, some questions
23 having to do with the ability of the data to
24 demonstrate safety and effectiveness, and then,
25 finally, this labeling question that I alluded to

1 having to do with the indications.

2 With that, I would like to introduce Dr.
3 Barbara Buch, who was the clinical reviewer for
4 this product and will present some issues having to
5 do with the clinical trial design as well as the
6 resulting clinical data.

7 DR. YASZEMSKI: Thanks, Mr. Kaiser.

8 Dr. Buch?

9 DR. BUCH: Good morning.

10 My name is Dr. Barbara Buch, and I am an
11 orthopedic surgeon in the Orthopedic Device Branch
12 of the FDA, and I thank you for your attention and
13 endurance today.

14 The sponsor has already presented the
15 summary of the international investigation quite
16 nicely. It is not my intent to repeat the summary
17 of safety and effectiveness which has already been
18 so well-presented by the sponsor.

19 What I do want to do is bring your
20 attention to some major issues that may have
21 impacted on the study outcomes and made our
22 evaluation and interpretation of this study and its
23 results quite challenging.

24 The issues involve primarily aspects of
25 study design, general clinical relevance, but it

1 also involves aspects of interpretation and
2 analysis and questions raised when evaluating the
3 safety of this device.

4 Before we can even look at study results,
5 we should evaluate the strength of the study
6 itself--what are the confounding variables, how
7 were the patients assessed, what data was
8 collected, and how was the data analyzed.

9 Clinical trials often differ from clinical
10 practice, as they are intended to specifically
11 define the therapeutic effect and safety profile of
12 a specific treatment without question.

13 Ideally, when comparing two or three
14 groups, it is preferable to have them as much alike
15 as possible except for the treatment variable being
16 studied. This allows us the most confidence that a
17 difference in outcome is due to that treatment.

18 [Slide.]

19 As has already been mentioned, this is a
20 difficult task to accomplish, especially in a
21 trauma population, as there are multiple
22 confounding variables that influence the final
23 outcome--variables such as the energy of the
24 initial injury, the environment in which the
25 initial injury occurs, and the contamination of the

1 fracture, prior medical health and nutritional
2 status, the number of associated injuries, the
3 number and type of fractures, and the amount of
4 bone and soft tissue loss, especially after
5 irrigation and debridement, all affect fracture
6 healing.

7 In this study, there were multiple
8 confounding variables. The most striking is the
9 choice and type of IM nail technique chosen for
10 definitive fracture fixation. The choice of an
11 unreamed or reamed nail was left up to the surgeon
12 and not specified in the protocol.

13 While the effect of this is an ongoing
14 debate, there are varying thoughts as to the effect
15 of this on fracture healing and the risk of
16 infection depending on the nail technique used.

17 In this study, there was a statistically
18 significant difference between the standard of care
19 group and the groups receiving the rhBMP-2
20 treatments. The two treatment groups had greater
21 numbers of patients receiving reamed nails as
22 compared to the standard of care group. Although
23 it is not statistically different, it may be
24 clinically significant that patients in the
25 larger-dose rhBMP-2 group received a slightly

1 higher percentage of larger-diameter, unlocked
2 nails.

3 There were other more subtle but possibly
4 confounding variables associated with this study.
5 For example, all fracture types, fracture
6 locations, and patterns were considered
7 collectively. It is well-known that the purpose
8 for using classification systems is to direct
9 treatments so that as patients fall into these
10 categories would be expected by experience to have
11 different outcomes and risks of adverse events.
12 Yet in this study, all fracture types and patterns
13 were considered together. This is exemplified by
14 the fact that patients with Gustilo Types I, II,
15 and IIIA were considered as one group. This
16 contradicts the concept of the classification
17 system.

18 In addition, patients with isolated
19 fractures of the tibia were grouped with patients
20 with multiple and varied other injuries. Both of
21 the rhBMP-2 groups had lower numbers of patients
22 with associated multiple injuries and more patients
23 with isolated tibia injuries.

24 As a minor point, the protocol allowed for
25 less than a full sponge to be implanted if the

1 fracture defect or configuration did not allow the
2 implantation of the full sponge. Therefore, not
3 all the patients received the same dose of rhBMP,
4 although a majority did receive a full sponge.
5 Whether this had any effect on the rate of healing
6 is not known.

7 Finally, trauma physicians have different
8 philosophies for the treatment for different
9 fracture types, which may differ significantly
10 across different parts of the world and across the
11 United States, East and West Coasts. Cultural and
12 geographic differences across the world influence
13 patient expectations for treatment outcomes, which
14 also may affect study outcomes.

15 It is also well-known that experience can
16 play a role in the decisionmaking process and the
17 patient outcome in trauma. In this study, larger
18 centers with greater numbers of patients may have a
19 different experience than smaller centers with
20 fewer trauma patients.

21 Although the differences for these
22 variables discussed were not large enough to
23 establish statistical significance, such as in the
24 case of the choice of nailing techniques, when
25 considered collectively, there remains a concern

1 that many variables impacted clinically on the
2 final outcome.

3 [Slide.]

4 Because of the divers cultural
5 expectations, treatment philosophies and geographic
6 locations of the investigational sites, the
7 poolabilities of these patients and the
8 applicability of this population to the U.S.
9 population was an issue.

10 As seen in this chart, approximately 50
11 percent of the patients were enrolled in two of the
12 countries. South Africa contributed 138 patients,
13 and Germany, 83. The remainder of the countries
14 contributed fewer than 40 patients, with several
15 site contributing fewer than 10 patients each.
16 Centers with few patients were pooled with centers
17 contributing large numbers of patients.

18 As has been stated, often, larger trauma
19 centers have different experiences in outcomes as
20 compared to centers who do not have large numbers
21 of trauma patients.

22 [Slide.]

23 Patient characteristics actually did
24 differ from country to country. For example, the
25 proportions of patients who smoked varied in each

1 of the countries, ranging from 31 percent in the
2 Scandinavian countries to 64 percent in South
3 Africa. Fewer patients with isolated fractures
4 were enrolled in Australia and Israel. The numbers
5 of isolated fractures ranged from 49 percent in
6 Germany to 75 percent in South Africa.

7 The types of fractures treated in each
8 country were also varied. For example, there were
9 no Gustilo IIIB fractures in France, but there was
10 a great incidence, about 38 percent, of Gustilo
11 Type IIIB fractures enrolled in the Scandinavian
12 countries. Some of the centers used reamed nails,
13 and others used unreamed nails. This difference
14 was also noted among the treatment groups.

15 When results are reviewed by
16 investigational sites, differences in outcome are
17 apparent from site to site. The ability to
18 extrapolate the patient population to the U.S.
19 population was not clearly validated in this
20 submission.

21 Although the sponsor did not consider the
22 differences in these populations to be clinically
23 relevant, the multiple differences bring into
24 question the ability to pool these patients and
25 distinguish between the confounding factors to

1 establish a treatment effect.

2 [Slide.]

3 Now let's look at the assessment methods
4 used.

5 Patients were assessed by investigators
6 both clinically and radiographically, and their
7 x-rays were assessed by an independent radiology
8 panel. These were then combined in the CCRE or the
9 Combined Clinical and Radiological Endpoint.

10 Now let's consider this aspect of study
11 design in detail. Clinical assessments by the
12 investigators included an assessment of fracture
13 site tenderness, an assessment of healing status by
14 x-ray, and the patient's weigh-bearing status.

15 [Slide.]

16 Our concern about the pain assessment is
17 as follows. Pain was assessed by each investigator
18 who had to interpret the patient's subjective
19 report of pain upon direct palpation of the
20 fracture site by the investigators. There was no
21 standardized or objective measurement scale used to
22 quantify this parameter. In fact, there were no
23 standardized objective methods to define the
24 intensity of pain and compare it to initial
25 fracture site tenderness or differentiate fracture

1 site pain from referred pain from other injuries or
2 soft tissue injury.

3 [Slide.]

4 This is an example of the case report form
5 that investigators filled out for each patient. As
6 you can see in the top portion of the slide,
7 fracture site tenderness was documented as either
8 "absent," "not evaluated" or "present."

9 You can see in the bottom portion of the
10 slide that weight-bearing status was also
11 determined by the investigator, but the progression
12 of status from non-weight-bearing to touch-down to
13 partial weigh-bearing and then to full
14 weight-bearing was not based on any objective or
15 standardized criteria.

16 [Slide.]

17 This slide shows the criteria for
18 radiographic union that the independent radiology
19 panel used to determine whether a fracture was
20 united. The objective criteria as seen in the
21 slide consisted of three or four cortices
22 demonstrated cortical bridging and/or the complete
23 disappearance of fracture lines and was delineated
24 in detail in the independent radiology case report
25 form along with other radiographic determinations

1 including hardware failure.

2 [Slide.]

3 However, on this slide, as can be seen in
4 this case report form the investigators filled out,
5 there is no indication of how the decision of union
6 was made and whether the decision of radiographic
7 healing was based on any objective criteria.

8 In a subsequent submission, the definition
9 for radiographic healing was provided in the second
10 submission.

11 [Slide.]

12 The difficulty in interpreting results
13 without precise criteria for all evaluators is
14 demonstrated by looking at this case study provided
15 by the sponsor in the submission of a Grade IIIA
16 tibia fracture which was treated with a sponge
17 soaked in the .75 dose of rhBMP-2. There was a
18 clear and significant discrepancy between the
19 determination by the investigator and the
20 independent radiology panel, as seen in this slide.

21 [Slide.]

22 You will note that the investigator
23 considered this Grade III fracture united at only
24 10 weeks, while the independent radiology panel
25 considered this fracture healed at 26 weeks. You

1 will note that the postoperative radiograph and the
2 6-week radiograph are not provided here.

3 [Slide.]

4 The definition of a healed fracture was
5 specified in the protocol, as it is here. However,
6 whether all three criteria were expected in order
7 to consider a fracture healed was not. Although
8 provisions were made for patients with different
9 weight-bearing status due to other injuries, it is
10 not specified whether all three criteria had to be
11 satisfied to be considered a healed fracture.

12 The distinctions between delayed union
13 based on time or other criteria and a healing
14 fracture were not defined well in the original
15 protocol. A post-hoc analysis states that every
16 patient recommended for secondary intervention
17 failed to meet at least one of three criteria
18 defining fracture healing.

19 [Slide.]

20 This is the definition of delayed union
21 that was provided in the protocol: "A fracture is
22 considered a delayed union if insufficient fracture
23 healing was observed as determined by the
24 investigator's radiographic and clinical
25 assessment."

1 This definition of delayed union is vague.
2 There are no objective criteria specified in the
3 protocol that defined what was to be used to make
4 the decision of delayed union. For example, there
5 is no delineation of the time or interval course to
6 establish that a fracture was delayed in healing,
7 nor are there clinical and radiographic criteria to
8 make this decision provided.

9 This is not clearly differentiated from
10 fracture non-union. How the decision was made to
11 recommend a secondary intervention based on this
12 definition is not specified in the protocol.

13 [Slide.]

14 It is not clear what criteria the decision
15 by investigators to recommend a secondary
16 intervention was actually based on. The ambiguity
17 can be seen in this table which shows that
18 secondary interventions were based on the failure
19 of one or two or three of the clinical criteria.

20 In addition, the sponsor provided data
21 tables that showed that patients may be considered
22 healed based on one or two or three of these
23 criteria.

24 [Slide.]

25 So the question still remains how was the

1 decision to recommend a secondary intervention
2 made. The imprecise guidance of the protocol and
3 lack of standard criteria for assessing patients,
4 coupled with the fact that investigators were
5 unblinded to the treatment in determining which
6 patients should receive this secondary
7 intervention, are subject to potentially
8 significant investigator bias.

9 [Slide.]

10 Next, the choice of control group should
11 be considered. All the different types of
12 fractures and different types of wounds were
13 treated with the same treatment protocol.
14 Fractures are graded differently because different
15 types are expected to have different prognostic
16 rates for healing and adverse events. Therefore,
17 they may need different treatment regimens.

18 For example, the incidence of infection
19 differs between Gustilo Type I and Gustilo Type III
20 in the literature. In this investigation, the
21 population of fractures was comprised of 40 to 45
22 percent Gustilo Type IIIA and B fractures. Whether
23 the standard of care is applicable to all grades of
24 fractures and wound types is not clearly justified.

25 As we have already heard, the use of

1 prophylactic bone graft may be considered
2 controversial. There are authors who do recommend
3 the addition of autologous bone graft, recommending
4 evaluation for this at 2 to 6 weeks following wound
5 closure. This literature review was provided for
6 you in the panel pack.

7 The use of prophylactic bone grafting has
8 been shown to enhance healing and may be associated
9 with a reduced risk of infection in some studies.
10 The inclusion criteria as stated by the sponsor
11 stated that patients with anticipated treatment
12 plans which included additional procedures to
13 promote fracture healing, such as bone graft, were
14 excluded.

15 This decision, however, was only relevant
16 to that considered at the time of definitive wound
17 closure, when in practice, this may often not be
18 made until the wound is closed and the initial
19 fracture progress has been assessed.

20 Regardless of this controversy, I would
21 like you to consider that while the treatment
22 groups in this investigation received a substance
23 that would potentially increase bone formation or
24 enhance bone healing--namely, rhBMP-2--the control
25 group did not.

1 All of this raises the question of whether
2 the standard of care group was treated comparably
3 to the rhBMP-2 treatment groups and therefore
4 whether the study results between the treatment
5 arms can effectively be compared.

6 [Slide.]

7 The clinical relevance of the endpoints
8 was also considered. These are placed on this
9 slide for your convenience and memory. These are
10 the primary and secondary endpoints that were
11 specified in the protocol. Realize that the
12 primary endpoint consists of four subgroups.

13 [Slide.]

14 What is important in fracture healing
15 studies, though? Fracture healing. This should be
16 the primary focus. A review of the literature
17 shows that the commonly determined outcomes include
18 the incidence of union and nonunion as a function
19 of time, the incidence of infection, and the time
20 to healing, usually comparing one method of
21 fixation to another, or between fracture types.

22 The importance of some of these
23 effectiveness endpoints are secondary in this
24 investigation.

25 [Slide.]

1 The combined clinical and radiographic
2 endpoint was intended to support the observations
3 made by the treating surgeons with those made by
4 the independent radiology panel. However, this
5 combination has not been validated as an analytical
6 method.

7 There are several potential problems with
8 using this method of corroborating investigators'
9 assessment. First, the CCRE is composed of
10 potentially biased subjective assessment compared
11 with a more objective assessment.

12 Second, the CCRE combines two dissimilar
13 assessments--a clinical assessment with a
14 radiologic assessment--instead of comparing two
15 radiologic assessments.

16 Lastly, patients with secondary
17 interventions were not treated the same as patients
18 who did not have secondary interventions. Patients
19 with secondary interventions were paired with the
20 results of independent radiology review at the time
21 the decision for secondary intervention was made,
22 while the patients with no secondary interventions
23 were paired with the independent radiology
24 evaluations at 12 months.

25 [Slide.]

1 The treatment of missing data related to
2 the success and failure was inconsistent in some
3 cases, and this may also affect the result.

4 The number of patients who met the
5 criteria for treatment and follow-up defined in the
6 evaluable patients, was 404 patients out of the
7 total 450 patients, or 89 percent.

8 When evaluating results, missing patients
9 or missing data were treated differently in three
10 cases that I will give examples of. For the data
11 analysis of the rate of secondary interventions,
12 patients with no data or with no outcome were
13 considered in the category of patients with no
14 secondary interventions. This may falsely elevate
15 the number of patients and the rates of success.

16 In another case, in the analysis of the
17 independent radiology panel results, 44 patients or
18 10 percent with missing 6-month data for united
19 fracture assessment had data carried forward from
20 previous visits. About two-thirds of the patients
21 were in rhBMP-2 treated groups. This practice may
22 have overestimated the not united rates in this and
23 subsequent visits.

24 In the third case, when reporting the
25 summary of combined clinical and radiographic

1 endpoint results, missing patients with no clinical
2 outcome or no radiographic outcome were included in
3 the category of no secondary intervention/not
4 united. Again, the failures may have been
5 overestimated in this particular case.

6 [Slide.]

7 Therein lies the dilemma. All of these
8 factors related to study design and protocol make
9 evaluation of the results of the study and the
10 confidence that the results are truly an effective
11 treatment quite a challenge.

12 The fundamental issues include the fact
13 that investigators were unblinded; they made the
14 assessments related to the determination of the
15 primary endpoint with imprecise, not specifically
16 spelled-out guidelines for making their decisions.
17 While this may be acceptable for clinical practice,
18 it may not be appropriate for a controlled clinical
19 trial.

20 Even the attempt to support the
21 investigators' assessment, the CCRE, is partially
22 based on the investigators' assessment as well.

23 Additional design issues of the protocol
24 that led to uncertainty that the protocol provided
25 rigorous and explicit guidelines were provided to

1 all investigators are listed here. These include
2 the fact that no time course was defined to
3 distinguish delayed healing from aggressively
4 healing fractures. There were no precise
5 radiographic or clinical criteria to separate the
6 healing fracture from one that was considered to
7 have delayed healing.

8 How the patients with delayed healing
9 fractures were recommended for secondary
10 interventions is imprecise. The sponsors did not
11 provide adequate evidence to provide a confidence
12 that the extent to which patients were recommended
13 for secondary intervention were guided by the same
14 criteria across all investigational sites.

15 [Slide.]

16 Looking at the effectiveness results has
17 also raised some issues to bear in mind if one gets
18 past the issue of study design. Depending on which
19 analysis is reviewed, different results may be
20 reported. These analyses include the primary
21 endpoint, the rate of fracture healing, the time to
22 event analysis, and the 50 percent probability of
23 healing, as well as the incidence of non-union.
24 Each of these will be considered.

25 [Slide.]

1 The overall rate of secondary
2 interventions is highest in the control group.
3 Recall, however, that in addition to the number of
4 interventions recommended and performed, the
5 overall rate of secondary interventions included
6 the number of self-dynamizations or screw
7 breakages, the number of secondary interventions
8 recommended but not performed, and the number of
9 secondary interventions not recommended but
10 performed anyway.

11 The 0.75 mg/ml dose treatment group had
12 the most patients in the latter category. If the
13 self-dynamizations or hardware failures are
14 excluded, the differences between the groups is
15 reduced. It is not clear why patients were
16 included who had secondary interventions
17 recommended but not performed, or those who had
18 secondary interventions with no recommendation were
19 included. This quandary further underlines the
20 problem with this primary endpoint.

21 [Slide.]

22 If we look at the rate of fracture healing
23 at 6 months or 26 weeks, this was also a secondary
24 endpoint in the study. This rate differs depending
25 on whether the investigator or the independent

1 radiology panel made the determination, as seen in
2 this slide.

3 The rate determined by the radiology panel
4 was significantly lower, and the differences
5 between groups was lower than by the investigators'
6 assessments. The low success rate indicates that a
7 choice of 6 months may not have been an appropriate
8 endpoint for this study. The discrepancies at 39
9 weeks and 50 weeks are progressively less, as has
10 already been discussed.

11 [Slide.]

12 The time to healing yields yet another
13 result. On this graph, the red line represents the
14 course of the 1.5 mg/ml dose rhBMP; the yellow line
15 represents the 0.75 mg/ml group, and the black line
16 represents the standard of care group.

17 It is obvious that there is little
18 difference between the control and the lower dose
19 of rhBMP throughout the time course of the study.
20 However, we should look at two example probability
21 points.

22 The sponsor has already reported that the
23 50 percent point of probability of healing
24 represents that lower line that traverses
25 horizontally across the graph. There is a

1 difference between the groups at this point.

2 However, this may not be a point that clinicians
3 will consider relevant.

4 If we look at the 75 percent probability
5 of healing or the 80 percent probability of healing
6 which is represented by the horizontal line that is
7 above that, there are no differences between the
8 groups.

9 [Slide.]

10 This is clearly demonstrated on this
11 chart. Although there is a difference between the
12 standard of care and the higher doses of rhBMP at
13 the 50 percent probability of healing, there is
14 little difference in the days to healing at a point
15 where there is 75 percent probability of healing.
16 They are virtually the same between the groups.

17 [Slide.]

18 Now let's look at the same type of graph
19 as shown by the determination of the independent
20 radiology panel. If there were indeed a difference
21 between the treatment groups, this would be
22 expected to be carried out by the detection of the
23 independent radiology panel.

24 I would like to draw your attention to the
25 180-day mark on the lower asymptote [phonetic] of

1 the graph, which corresponds to the 25 percent
2 probability of fracture healing. At this time
3 point, there was no difference between the groups.

4 [Slide.]

5 This is clearly evident on this table,
6 which shows that the days to healing at either the
7 25 percent, 50 percent, or 75 percent probability
8 are almost identical for each group, regardless of
9 the probability chosen.

10 [Slide.]

11 Lastly, I would like to discuss the issue
12 of nonunion. Overall, at 12 months, the nonunion
13 rates as determined by the independent radiology
14 panel were 53 percent of the patients in the
15 standard of care group, 48 percent in the 0.75
16 mg/ml group, and 38 percent in the 1.5 mg/ml group.
17 These rates are slightly lower by the
18 investigators' assessment.

19 By either assessment, these rates appear
20 high, and perhaps one explanation may be that the
21 results reflect the diverse fractures treated in
22 this study or other multiple factors previously
23 mentioned.

24 Patients with secondary interventions were
25 an interesting group to review. These patients who

1 actually had a secondary intervention to promote
2 healing had similar nonunion rates whether they
3 were treated with the rhBMP-2-impregnated sponge or
4 not.

5 [Slide.]

6 This is clearly demonstrated on this
7 graph. It is of interest that the rate of nonunion
8 in patients with secondary interventions is clearly
9 demonstrated by--again, the black line is standard
10 of care, and the red is the 1.5 mg/ml dose.

11 Patients treated with rhBMP-2-impregnated
12 collagen sponge who required a secondary
13 intervention were considered healed later than
14 patients who did not. This is shown in this graph
15 and noted in the chart previously.

16 [Slide.]

17 Let's move on to the safety issues that
18 concerned us. There were no apparently
19 life-threatening safety concerns. However, there
20 are some issues which are not explained and whose
21 clinical significance remains unclear. I will
22 briefly touch on each of these issues and the
23 questions that were raised.

24 [Slide.]

25 The first issue deals with serology

1 results. The rates of authentic antibody response
2 to rhBMP-2 and Type I bovine collagen are higher in
3 this study than in published data in other rhBMP-2
4 in collagen sponge investigations. The rate of
5 authentic antibody responses to rhBMP-2 in treated
6 patients in a recently published study using
7 rhBMP-2 and the collagen sponge in an anterior
8 lumbar spine fusion study was 0.7 percent. In this
9 study, 12 patients had an authentic immune
10 response. In the 1.5 mg/ml rhBMP-2 group, the rate
11 of authentic responses was 6 percent and one
12 percent in the control population. This is an
13 increased rate as compared to the previous study.

14 What the contribution of the trauma
15 setting is to these results is not clearly known.
16 The fact that there are antibody responses is the
17 concern, especially since we don't know what the
18 clinical significance of these results is. The
19 numbers of patients may also be too small to make
20 any sound conclusions, however.

21 There were 60 patients who developed
22 antibodies to Type I bovine collagen and
23 approximately half of the patients had persistently
24 elevated antibody titers 20 weeks or longer. In
25 the rhBMP-2 lumbar fusion study, the

1 investigational patients had a similar rate of
2 authentic positive immune responses to Type I
3 bovine collagen.

4 Again, the clinical significance of this
5 is difficult because the small respective numbers
6 and the respective significance is unknown. In
7 both cases, however, the analysis of the adverse
8 events did not seem to correlate with the presence
9 or absence of immune response.

10 [Slide.]

11 The rate of hardware failure was
12 relatively high in this study. There were 48 screw
13 breakages or bending noted in the standard of care
14 group, 31 in the middle dose, with two nail
15 fractures in this category, and 24 screw breakages
16 in the 1.5 mg/ml dose. There is a typo in this
17 slide; sorry.

18 Hardware failure consisted mostly of
19 bending or breaking of locking screws. Whether
20 this hardware failure is a function of the hardware
21 used to treat the fracture, the type and size of
22 nail used and thus the screw size used, or a
23 function of the high degree of ununited or
24 non-healed fractures is unclear.

25 [Slide.]

1 The one adverse event listing in which
2 there was a statistically significant difference
3 between the control and the investigational groups
4 is the rate of abnormal lab values related to liver
5 and pancreatic function--specifically, elevated
6 amylase and hypomagnesemia.

7 There were 30 patients in the rhBMP-2
8 treated groups with elevated amylase as compared to
9 five in the SOC group. There were two patients in
10 each of the standard of care group and the
11 higher-dose rhBMP group compared to 11 patients in
12 the middle-dose rhBMP group with a finding of
13 hypomagnesemia.

14 Although the sponsor states that the
15 patients had no overt manifestations of
16 pancreatitis, the concern stems from published
17 preclinical data that showed pancreatic cell
18 lines, showed increased cellular proliferation when
19 exposed to rhBMP-2. The significance or
20 association to this population is not clear.

21 Coincidentally, one patient in the
22 previously-conducted study using rhBMP-2 in the
23 spine was diagnosed with pancreatic cancer during
24 the duration of the study.

25 The remaining liver functions were

1 elevated in a large number of patients, but this
2 could possibly be explained by soft tissue trauma
3 and not due to the biologic that was added.

4 Whether any of this is clinically
5 significant due to trauma or the exposure of
6 rhBMP-2 is unclear, but it should not be dismissed.

7 [Slide.]

8 A total of 17 patients experienced at
9 least one event classified as heterotopic or
10 ectopic ossification or callous.s The patients in
11 the 1.5 mg/ml rhBMP-2 group had the highest number
12 and percentage of patients with heterotopic
13 ossification, but no action was required to treat
14 any of these heterotopic ossification-related
15 events.

16 I would like to point out, however, that
17 according to the sponsor, heterotopic and ectopic
18 ossification was not a significant concern.
19 Although the sponsor stated that no ectopic
20 ossification was reported, the table in the
21 submission includes a patient in the category
22 titled, "Ectopic ossification/other sites."

23 Additionally, it is not clear how the
24 sponsor ruled out heterotopic ossification in other
25 areas of the tibia. Sponsor had told us that no

1 additional radiographic physical exam or serum
2 testing was done to observe heterotopic bone
3 formation in other areas away from the fracture
4 site studied. We believe it would be difficult to
5 determine the presence of heterotopic bone or even
6 distinguish it from myecitis ossificans secondary
7 to trauma on history alone. It would be difficult
8 to determine whether the ectopic ossification was
9 due to trauma to the soft tissues or bone in the
10 area was an effect of increased bone formation in
11 response to rhBMP-2.

12 With the limited surveillane that was
13 done in the study, one cannot comment on the
14 existence of distant ectopic ossification in other
15 sites of the body.

16 [Slide.]

17 The overall infection rates were
18 comparable between the three groups when the
19 denominator is the intend-to-treat population, with
20 the standard of care group experiencing slightly
21 more infections both overall and in the region
22 under study.

23 The figures for the leg tibia category do
24 not include skin infections noted as wound
25 dehisants, gangrene, inflammation or necrosis.

1 Overall, these rates seem somewhat higher than in
2 other multiple fracture and single fracture
3 comparison studies reviewed in the literature.
4 When broken down by Gustilo classification, the
5 rates are also high. Especially concerning are the
6 rates in the Gustilo Types I and II fracture
7 categories. It is not really clear why these rates
8 are so high.

9 Although the small sample size may be a
10 factor in these rates, one should consider what
11 other factors may also play a part in these higher
12 rates. Although some of these safety uncertainties
13 may be consistent with the trauma population
14 studied or may be in too low of a sample size to be
15 of statistical significance, these issues should
16 still be considered when evaluating this device.

17 [Slide.]

18 In conclusion, we agree that trauma
19 patients represent a difficult population to study
20 even in a well-controlled trial. This is due to
21 the multiple confounding factors. This trial was
22 no exception.

23 It is difficult to make comparisons
24 between this study and the literature because of
25 the multiple varied factors that confound or

1 influence the outcome. Other additional factors
2 contribute to the challenge of evaluating this
3 device in this study. On our part, this is mainly
4 centered on factors related to study design.
5 Objective criteria for making assessments were no
6 clearly defined, and therefore, the judgments that
7 were made were not clearly defined.

8 The protocol was not specific in
9 instructions to the investigators, especially
10 regarding the distinction between a healing
11 fracture and delayed union. There is some debate
12 as to whether the control group represents the
13 standard of care for all the fracture and wound
14 types described in the patients in the study.
15 Endpoints commonly found in the literature were not
16 considered to be primary endpoints. For the
17 primary endpoint chosen, how the investigator came
18 to the determination to perform an intervention was
19 not specific.

20 In the study, more importantly, there was
21 no clear substantiation that all investigators used
22 the same criteria for making the decision for
23 secondary interventions and that pooling across so
24 many different sites was justified.

25 When looking past the design issues at the

1 effectiveness results and some aspects of the
2 safety profile, further questions were raised. All
3 these factors caused considerable uncertainty as to
4 the actual treatment effect and the safety profile
5 of this device.

6 Thank you for your attention.

7 DR. YASZEMSKI: Thanks, Dr. Buch.

8 Dr. Lao?

9 DR. LAO: Good morning. My name is Chang
10 Lao, and I am a statistician at FDA. I have been
11 working at FDA for the Center for Drugs and Devices
12 for a long time.

13 Today, my presentation will concentrate on
14 the statistics evaluation of the primary endpoint,
15 which is the proportion or rate of secondary
16 intervention.

17 [Slide.]

18 I will concentrate on three major issues
19 for this PMA. The first issue is pooling of the
20 multi-clinic data or multi-national data; the
21 second issue is the reproducibility study, intra-
22 and inter-observer agreement; the final issue is
23 the survival analysis, time-specific, versus crude
24 event, which is secondary intervention,
25 probability.

1 [Slide.]

2 As you can see, on the first issue,
3 pooling of data, I have three charts. The first
4 one shows ideal conditions--the two lines are
5 parallel--between Center 1 and Center 2. In both
6 of them, the high dose is better than control in
7 terms of the percent of secondary intervention
8 success.

9 The one in the middle is acceptable--we
10 call it quantitative center by treating
11 interaction. The distance is not parallel, but at
12 least they go in the same direction between the two
13 sites.

14 The last one, the crossover, which is
15 questionable, we call qualitative interaction. The
16 primary endpoint varies from the opposite direction
17 between Center 1 and Center 2.

18 [Slide.]

19 This is a hypothetical example of wrong
20 pooling of the data. In Site 1, you can see two
21 success and failure proportions between high dose
22 and control are identical--33 percent each. In
23 Site 2, they are also the same--67 percent--and the
24 P value in both of them equals one. Chi-square
25 equals zero. So if the P value equals one, it is

1 not significant.

2 But what happens if we pool the other
3 numbers together or the observations together? You
4 see the last table, where percent success is 58
5 percent for high dose and 45 percent for control.
6 Chi-square equals 5.56, and P value is 0.018, which
7 is significant.

8 So the question here is can you add all
9 the numbers together and do the pooling of the
10 data. So this kind of pooling, adding some of the
11 observations together, is statistically invalid.
12 We should use a better approach here.

13 [Slide.]

14 This is [inaudible] pyramid data, which is
15 the estimated difference, high dose minus control
16 in percent success if we have secondary
17 intervention, and the exact 95 confidence interval
18 by regrouped investigator sites. We have a total
19 of about 30 regrouped sites here. By definition,
20 "regrouped" means any country in which the number
21 of patients is less than nine patients across
22 regrouped were pooled into a combined site.

23 As you can see, in this chart, the
24 confidence interval, which was based on exact
25 binomial distribution because of smaller sample

1 size with each regrouped site-- about seven or
2 eight of them, the point estimate, which is the dot
3 on the left of the zero, which means the point
4 estimate of difference between the two success
5 proportions in favor of the control. There are 22
6 or 23 in favor of the high dose--but this is just
7 point estimate based on the data. We have to
8 consider the uncertainty of the estimate, because
9 we have to deal with the sample size. That is what
10 the 95 percent confidence interval tells you.

11 You can see the width of the confidence
12 interval is wide in most cases because of the
13 smaller sample size. Almost 29 out of 30 of them
14 include zero. So statistically speaking, none of
15 them is significantly different from zero between
16 control and high dose.

17 [Slide.]

18 The second chart is a different data base.
19 It is the combined clinical radiological endpoint
20 or CCRE patients. Pretty much you see a similar
21 pattern. About 10 or 11 of them go in the negative
22 direction, to the left side of zero, and about 20
23 of them go to the right side of zero. But the
24 confidence interval, again, about 29 of them
25 include zero.

1 So if you were to predict success by site,
2 none of them can stand alone in favor of the
3 device.

4 Now, what happens--can we combine them?

5 [Slide.]

6 Okay. There are two statistical models
7 used here, what we call the meta-analysis. The
8 meta-analysis is a very big issue in clinical
9 trials. If you do a MedLine search, there are
10 probably over 1,000 articles dealing with
11 meta-analysis.

12 Here, I present two models. One is the
13 fixed model. The assumption in the fixed model is
14 that each center has the same clinical effect,
15 considering within-center variability only.

16 Random effect is assumption of very
17 diverse nature in study design, methods among sites
18 and heterogeneity among sites, so we consider both
19 within-center and between-center variability.

20 So which ones are not appropriate in here?
21 From the previous two charts, you can see some
22 things, but we can do a formal statistical test.

23 [Slide.]

24 Here, the meta-analysis is of 30 regrouped
25 investigator sites. In our analysis, we excluded

1 three regrouped sites because they had zero
2 variance in the difference of the two proportions.
3 It means you have both zero percent success or 100
4 percent success in the control and high dose.

5 So our analysis included 27 regrouped
6 sites, and we used the method of moments suggested
7 by DerSimonian and Laird in their Statistics in
8 Medicine 1986 paper.

9 [Slide.]

10 Here are the results of the meta-analysis
11 for 27 regrouped sites. For the fixed effect, the
12 mean difference--meaning difference being
13 proportion success--which is high dose minus
14 control, equals about 11 percent difference.

15 Standard error of estimated difference is
16 0.04.

17 P value is significant, less than 0.01.
18 We just divided by the mean difference divided by
19 standard error, which is a T statistic with 26
20 degree of freedom.

21 And the 95 percent confidence interval,
22 which does not include zero, is in favor of the
23 high dose, 0.039, 0.194.

24 But what happens if we allow the random
25 effect? We consider not only within-center

1 variability but also between-center variability,
2 which is a mean difference of about 12 percent.
3 Standard error is larger because we include
4 between-center variability here. The P value is
5 not significant, and the 95 percent confidence
6 interval was inclusive, from minus 0.04 percent to
7 plus 0.28 percent.

8 And at Chi-square equal 97, which is
9 highly significant, less than 0.005 P value, what
10 that means is reject the null hypothesis, which is
11 between-center variance equals zero.

12 So by this test, it means there is
13 significant variability from center to center. We
14 would prefer the random effect model in this
15 example.

16 [Slide.]

17 The second chart for the CCRE data pretty
18 much has the same conclusions as the regrouped
19 investigator sites, as you can see here.

20 The random effect in the 95 percent
21 confidence interval does include zero also. The
22 Chi-square test is very highly significant and
23 rejects the null hypothesis of no difference in
24 terms of variability among sites.

25 [Slide.]

1 The second issue here that I am going to
2 discuss a little bit is the reproducibility study
3 intra- and inter-observer agreement.

4 In the PMA, we have a total of 60 patients
5 from 10 U.S. trauma centers. Please remember that
6 this is not from PMA data, not from the pivotal
7 study; this is from a different protocol, from a
8 previous protocol study.

9 So the two teams of multiple raters--three
10 raters, actually--fracture union, between observer,
11 inter-observer, Kappa statistics--I am going to
12 explain what Kappa means. Kappa says that the
13 higher the number, the better; 1.0 is perfect
14 agreement. Zero is no agreement at all. So 0.87
15 for the inter-observer agreement and 95 confidence
16 interval of 0.7 to 1.0, based on 20 patients.

17 The last two were intra-observer, with the
18 same observer, the first study and the second
19 study, about 0.5, but the confidence interval, the
20 lower and upper bounds are quite wide. The reason
21 is because of a smaller sample size, 20 patients,
22 and some observed predicted proportion of
23 agreement.

24 [Slide.]

25 This chart just gives reference to general

1 guidance about what Kappa statistics mean. This is
2 from Professor Gary Koch, 1977 Biometrics paper.
3 He is a professor at the University of North
4 Carolina Chapel Hill.

5 This is general guidance. The one in the
6 middle, 0.4 to 0.6, is moderate; clinical
7 interpretation is moderate agreement. For the
8 intra-, with the same observer, in the last table,
9 we have two of them at 0.5. So the [inaudible] is
10 like flipping a coin, 50 percent each. So this is
11 just to give you general information here.

12 [Slide.]

13 The general question for the
14 reproducibility study here is on sample patient
15 selection. Twenty patients out of a total of 60
16 patients, which is not from the PMA data.

17 And the random sample, is it
18 representative to the reproducibility study, to the
19 PMA data, or are they masking?

20 And for time comparability--time is
21 important. And you have multiple raters per team
22 here. I think that between-observer Kappa 0.87,
23 that sounds higher than the intra-observer Kappa
24 0.50. I think the reason is because it is based on
25 majority rule. If you had two out of three raters

1 agree, that is considered agreement; that is what I
2 think.

3 [Slide.]

4 The final topic is survival analysis
5 versus crude secondary intervention event
6 probability.

7 The life-table or Kaplan-Meyer analysis,
8 we just recently received for the final three
9 analyses--first, fracture healing assessed by
10 investigator; second, radiographic assessment of
11 fracture union by independent radiology panel; and
12 the last was the CCRE study.

13 [Slide.]

14 On survival analysis in this PMA, for a
15 long time, we hadn't seen the patient follow-up
16 data and the survival analysis, so we did not know
17 what patients were censored, lost to follow-up,
18 missing, or at risk of secondary intervention at
19 different time points.

20 Also, we had to assume censoring
21 independent of treatment.

22 And if you look at the proportion of
23 success to failure, we always consider what time
24 you are talking about. Are you talking about 12
25 months, are you talking about 6 months, 3 months,

1 whatever?

2 The crude secondary intervention event
3 probability is always less than time-specific
4 cumulative SI event probability by survival
5 analysis, unless all patients had completed the
6 entire follow-up study, or all patients with
7 secondary intervention. This is not a very
8 practical situation in clinical trials.

9 [Slide.]

10 In conclusion, first, with study design.
11 Heterogeneity among centers--I would think that
12 random effect for combined analysis is not
13 appropriate; and that direct adding up all numbers
14 and the corresponding analyses is not valid;
15 survival analysis is required due to patients
16 censored or lost to follow-up; and questionable
17 reproducibility studies.

18 Finally, in the survival analysis, we
19 think the assumption here sounds like the whole
20 dataset comes from one center, not adjusted for
21 center differences. But including a center in the
22 model is also not easy, because we have too many
23 regrouped sites here--30 of them. You have to cut
24 down that number to include in the model.

25 So the survival analysis here assumes data

1 from one site, all the numbers together.

2 This is the end of my talk. Thank you
3 very much.

4 DR. YASZEMSKI: Thanks very much, Dr. Lao.

5 Right now, we're going to take a break for
6 5 minutes, and we're going to come back after the
7 break and have the presentations from the panel
8 reviewers, which will begin with Dr. Naidu's
9 assessment of the preclinical studies.

10 We'll see everybody in 5 minutes.

11 [Break.]

12 Panel Presentations

13 DR. YASZEMSKI: I'll ask Dr. Naidu to give
14 his presentation now on the preclinical studies.

15 Dr. Naidu?

16 DR. NAIDU: Thank you.

17 My charge was to provide the panel and the
18 audience here with a summary of preclinical
19 results.

20 I derived most of my information from the
21 first volume issued by the sponsor. The sponsor
22 has already gone over some of the preclinical
23 results, especially in an animal model, with the
24 New Zealand adult rabbits.

25 However, in the volume provided, there are

1 various other animal models in which the BMP was
2 tested, which included the Rhesus monkey model, the
3 canine model, in addition to the rabbit osteotomy
4 model, and also a goat tibia fracture study was
5 performed. So I will touch on the fracture models
6 that were not addressed by the sponsor in their
7 presentation initially.

8 Of course, this is in a long-bone fracture
9 healing model, and with regard to the Rhesus radial
10 defect studies, unilateral radial defects 3.5 cm in
11 size, four times the diameter of the bone, were
12 created. These were internally fixed with a
13 fixation plate.

14 From this, the sponsor reaches the
15 conclusion that the bone-bridging was highly
16 variable, inconsistent, no dose response was
17 discernible. The only thing that one could
18 conclude from this Rhesus radial defect study was
19 that the antibody responses to rhBMP-2 were higher
20 in the treated group, whereas none of the control
21 animals showed any of these antibody titers.

22 These were low antibody titers, and they
23 were detected in 35 percent of the treated animals.
24 This was with the ELISA assay.

25 With the Rhesus ulna defect study, the

1 size of the defect was not clearly defined in the
2 material provided. Presumably, the ACS rhBMP-2
3 sponge was placed at the site of the defect, and
4 the negative control was buffer with the ACS
5 sponge.

6 What the sponsor concluded was that the
7 BMP-2/ACS sponge was replaced with a dense
8 population of spindle-shaped cells, presumably
9 capable of continued bone formation. However,
10 considerable compression of muscle into the center
11 of the defect was noted, limiting the volume of
12 potential bone formation.

13 My conclusion--nothing happened.

14 Therefore, in the primate study and the
15 preclinical studies, as designed by the sponsor, I
16 could not conclude much except for the fact that
17 the antibody titers to rhBMP-2 were apparent in 35
18 percent of the Rhesus monkeys.

19 The next study that I want to touch on is
20 the canine radial defect study. Bilateral radial
21 osteotomies in mature hound-type dogs with 2.5 cm
22 diafacile [phonetic] critical-size segmented
23 defects were stabilized with external fixation.
24 One limb received the rhBMP-2/ACS or the ACS and
25 buffer as the negative control. The contralateral

1 limb received autogenous bone graft harvested from
2 the humeral head.

3 The rhBMP-2 concentration studied with
4 0.05, 0.2, 0.8 mg/cc. In all concentrations of
5 rhBMP-2, radiographic union was achieved at 12-week
6 time point. Trigonal failure of all three rhBMP-2
7 dose groups were equal to the contralateral limb
8 treated with the autologous bone graft. It was
9 superior in the 0.05 and 0.8 mg group, but there
10 was no difference in the 0.2 mg group.

11 In conclusion, the radial density in the
12 period from 4 to 12 weeks was essentially
13 equivalent in the rhBMP-2 treated defects and
14 defects treated were autographed. The total
15 energy-to-torsional failure of three dose groups
16 was equal to in one group and superior to the
17 contralateral limbs treated with auto bone graft in
18 two of the dose groups, especially in the 0.05 and
19 0.8 mg.

20 There was a longer-term follow-up for 24
21 weeks in some of these animals, and at 24 weeks,
22 biomechanical testing demonstrated no significant
23 differences between the rhBMP-2 group and the
24 autogenous bone graft group. Of course, the
25 buffer, the negative control group, did not heal.

1 Therefore, the rhBMP-2 is equivalent to
2 the autogenous bone graft group in this canine
3 radial defect study.

4 Going on to the canine femoral intercalary
5 allograft incorporation study, the goal was to
6 compare the effect of augmentation of the host bone
7 allograft junctions with rhBMP-2 and compare this
8 to the augmentation with autogenous bone graft.
9 Six-centimeter midshaft femoral defects in 21
10 mixed-breed dogs were fixed with frozen allograft
11 stabilized with an interlocking nail. Host
12 allograft junction was augmented with rhBMP-2/ACS
13 at a dose of 1.15 mg total dose or buffer ACS, and
14 of course, the last group was the autogenous
15 cantelas bone graft. This augmentation was done at
16 the proximal site and also at the distal site.
17 Animals were euthanized at 24 weeks post surgery.

18 At the proximal junction, the BMP/ACS
19 torsional strength was significantly greater than
20 the cantelas bone graft group or the buffer group.
21 However, at the distal junction, there was no
22 difference between the BMP group and the cantelas
23 graft group.

24 Both the BMP and cantelas bone graft
25 groups were torsionally better than the negative

1 control group at both the proximal and distal
2 junctions.

3 These are all mechanical studies, and
4 these are the conclusions reached from the
5 mechanical studies.

6 The next is the goat tibial fracture
7 study. This was a closed fracture model.
8 Bilateral closed midshaft tibial fractures were
9 created using a three-point bending jig.
10 rhBMP-2/ACS combination or buffer/ACS combination
11 was placed at the fracture site in one limb, either
12 by wrapping it or by doing as an onlay. And the
13 contralateral limb served as a surgical control.
14 The tibia was stabilized with an ex-fix. This was
15 a closed fracture model again.

16 X-rays at 6 weeks showed that all three
17 groups had healed, and differences are hard to
18 discern by x-ray. Biomechanical testing showed
19 that fractures that were treated with rhBMP-2/ACS
20 had greater torsional toughness relative to the
21 untreated controls at P equals 0.017.

22 However, fractures treated with buffer/ACS
23 group, the so-called negative control group, also
24 showed a trend toward increased torsional
25 toughness, albeit with a slightly lower P value.

1 So you can't conclude anything.

2 On the other hand, [inaudible] showed that
3 torsional toughness in the rhBMP-2/ACS fractures
4 wrapped with the sponge was significantly higher
5 than those treated with an onlay. Whether they
6 contained BMP or not did not make a difference.

7 Who knows what one can conclude from this?
8 I'll let Dr. Kinley Larntz comment with regard to
9 stats.

10 Lastly, the rabbit ulna osteotomy model,
11 which was shown by Dr. Riedel from the sponsor--he
12 showed a beautiful radiograph which showed that it
13 had healed; he showed a nice histology slide which
14 showed bridging callous albeit not complete healing
15 in the standard treatment group.

16 But here are the numbers. Of course, the
17 mechanical testing of this fracture is the gold
18 standard. On Volume 1, page 35, the bar graphs are
19 quite clear with regard to torsional strength
20 testing. In this bilateral mid-ulna osteotomies
21 group, in 72 male rabbits with one millimeter
22 defect, there were three treatment
23 groups--rhBMP-2/ACS onlay; buffer/ACS onlay; and no
24 treatment.

25 Torsional loading was performed in treated

1 limbs at 2 weeks, 3 weeks, 4 weeks, and 6 weeks.
2 Failure torque was no different at 2 weeks for any
3 of the groups--of course, that is reasonable. It
4 was significantly higher in the BMP-2/ACS group at
5 3 and 4 weeks. But at 6 weeks, again, there was no
6 difference between any of the three groups tested,
7 and at 6 weeks, in fact, no matter what you did to
8 it, it was similar to the intact group.

9 That is my summary on the preclinical
10 animal trials. In conclusion, the preclinical
11 animal trial studies are highly variable, mixed.
12 My gut feeling is that the rhBMP-2 does enhance
13 bone formation, but practical clinical use is going
14 to be very tough to show, based on the preclinical
15 data.

16 Thank you.

17 DR. YASZEMSKI: Thanks very much, Dr.

18 Naidu.

19 We're now going to proceed to Dr. Finnegan
20 and her clinical review.

21 Dr. Finnegan?

22 DR. FINNEGAN: I have been asked to do the
23 clinical review, and as I started into my homework,
24 I realized two things--one, I needed to figure out
25 whom I had annoyed, and two, I needed a large

1 bottle of aspirin.

2 You are going to hear some repetition, but
3 I think some of that repetition is important.

4 Reviewing the material for clinical
5 trials, the initial trial was 12 patients who were
6 open-label, as was discussed. The dose there was
7 0.43, which is much lower than was in the pivotal
8 trial. This was done for safety and efficacy, and
9 there was no difference between healing and no
10 adverse effects.

11 The next study, actually, that is
12 mentioned, which was not presented by the sponsors
13 was a study using open tibial shaft fractures and
14 an external fixeter, with the same doses that they
15 presented in their pivotal study, and this was
16 terminated because of patient recruitment problems.
17 That brought them to the pivotal study, which is
18 classed as a Phase 3 multi-center prospective,
19 randomized but single-blind, that being the patient
20 only, and all of the Gustilo grades that you have
21 heard. These were treated definitively with IM
22 nailing.

23 The control was labeled standard of care,
24 and this was limited to wound coverage and an IM
25 nail.

1 The experimental--and from now on, I am
2 going to call this the "composite"--is the Helistat
3 absorbable collagen sponge with the recombinant BMP
4 in the two doses that have been described.

5 According to the sponsors, the BMP has
6 left the site at 4 weeks, and the sponge is gone at
7 8 weeks. They define the material as
8 osteoinductive, stating that it produces trabecular
9 bone, and I think you saw that fairly nicely on
10 their histology slides.

11 However, this is not the normal bone for
12 this diafacial [phonetic] region, and there does
13 not appear to be much work done on the process of
14 remodeling afterward.

15 In the material that I received, the
16 sponsors outlined very nicely five objectives, and
17 what I would like to do is outline those
18 objectives, and at the end of my talk, I will
19 discuss whether I think they were met or not met.

20 The first objective was to increase the
21 likelihood of healing with the composite. The
22 second was to define the safety of the composite.
23 The third was to document that this increased
24 healing was actually present at 6 months. The
25 fourth was to document that radiographic union was

1 observed earlier in the composite group. And the
2 fifth was to evaluate the potential economic
3 benefit of treatment with the composite as compared
4 to the control.

5 Really interesting for the exclusions to
6 their patient group which they did not bring up in
7 their presentation was that they excluded any
8 history of exposure to silicon or injectable
9 collagen as well as hypersensitivity to monoclonal
10 antibodies or gamma globulin.

11 Their protocol as they have discussed had
12 some interesting components to it. The first is
13 that although at initial assessment, a Gustilo
14 grade was given the final grade was not done until
15 their definitive wound closure, which needed to be
16 carried out within 14 days.

17 As has been previously discussed,
18 intermedullary rodding was allowed to be picked by
19 the investigator whether it was reamed or not
20 reamed, and this was not controlled.

21 Also what is interesting is that a very
22 small percentage of the patients received their IM
23 rodding at their first intervention, although the
24 largest number of the patients were Grade I and
25 Grade II Gustilo class. And I respect Dr.

1 Swiontkowski immensely, and I have known him for a
2 long time, but I actually do not think this is
3 standard of care in the United States.

4 As well, I did not find any definition of
5 acceptable bone loss for patients who would be
6 allowed in this study.

7 Failure was described as requiring a
8 second intervention, and that included
9 self-dynamization, and I think that's a significant
10 problem with trying to define the results of this
11 study.

12 The nonunion and delayed union definitions
13 have already been covered.

14 Follow-up was defined as at the 12-month
15 or one-year period and involved both the clinical
16 evaluation, the chemistry, the serology, the
17 radiographs, and health resources consumption.

18 As we have discussed, this is a
19 multi-center study. Initially, there were actually
20 59 investigators, of whom 10 evidently contributed
21 no patients whatsoever; and this occurred in 11
22 countries. Nineteen of these principal
23 investigators are said to have had a portion of
24 their training in the U.S. This portion is not
25 defined, and given the licensing difficulties in

1 most of the States, my concern is that a good
2 portion of these would have been either in a
3 research lab or in observation only.

4 The sponsors state actually several times
5 that there are basically no treating differences
6 between any of the countries, and my first problem
7 with that statement is the fact that there were no
8 Grade III fractures in France--and with apologies
9 to anybody here who actually might be from France,
10 I have first-hand seen their driving, and I do not
11 believe that there are no Grade III tibial
12 fractures in France.

13 So the question is what happened to these
14 fractures, and it would suggest to me that the
15 protocol was not the standard of care for the
16 French for treating Grade IIIB fractures. As well,
17 both the CCOT organization and the combined
18 English-speaking organizations have meetings on a
19 regular basis, and I think that it is fairly
20 obvious that the standard of care around the world
21 is different. Some of this is based on culture,
22 some of it is based on health care resources and
23 economy, and some of it is based on training.

24 The German and South African groups, as
25 was discussed, had the largest number of patients

1 contributing. What I found very disturbing was
2 that there were some very capable countries that
3 had very few patients contributed, and I think this
4 calls to several questions.

5 The first one is was this study protocol
6 actually not standard of care for the various
7 countries that were involved. Did the patients
8 actually self-select themselves out, suggesting
9 that perhaps there were other reasons why they did
10 not get involved in the study? Or do these centers
11 actually truly see very few open tibial fractures,
12 and if that's the case, one would be concerned
13 about the patients that they did contribute as far
14 as their experience in both judgment and technique
15 is concerned.

16 When you look at the results, there are
17 actually a couple of areas that have been touched
18 on but not really elaborated. First is that the
19 standard of care group or the control group
20 actually had a larger number of unreamed nails.
21 And if you look at the failure rate in the first 30
22 to 60 days, you will see that there is a very high
23 number in the standard of care. A 9 mm unreamed
24 nail in an otherwise healthy young male has a
25 fairly high incidence, which has been reported in

1 the literature, of self-dynamizing by fracturing
2 the screws. So one would wonder if in fact these
3 patients went on to heal very nicely, and that the
4 implant used was not appropriate for study
5 conditions--it would be appropriate for treatment,
6 accepting that the screw would break, but perhaps
7 not appropriate for the study.

8 As well, although not statistically
9 significant, there were more patients with multiple
10 fractures in the standard of care group than there
11 were in the other group.

12 For the 1.5 composite, there was a higher
13 number of younger patients, and there was also a
14 higher number of reamed rods. And I was very
15 delighted to see that the European Union has asked
16 that this be addressed, because as I was reading
17 through this, this is one of the areas where I
18 said, "Hello?"

19 There is no question that--and you can see
20 this with the American study that Marc showed when
21 they used exchange nails--that the concept of the
22 philosophy is that you are putting stem cells or
23 some osteogenic potential at the fracture site when
24 you do this process. I think that that definitely
25 affects the results.

1 And actually, to expand on that, if you
2 look at the research or the philosophy of promoting
3 fracture healing, you will see that most people
4 consider three concepts--osteoiduction,
5 osteoconduction, and osteogenic potential.
6 Although the sponsors state that this is
7 osteoinductive, if you read their investigators
8 brochure, they actually state that the collagen
9 sponge needs to contact both the distal and the
10 proximal ends of the fracture, suggesting that
11 probably there is some osteoconduction, and if you
12 then add osteogenic cells, you have a fairly potent
13 fracture promotion.

14 If you go to their evaluation, I agree
15 with both the statistician and the clinician from
16 the FDA in that the CCRE has no validation
17 associated with it whatsoever. In spite of that,
18 if you look at the 75 percent of patients healed,
19 it is within 48 hours for all three groups, and if
20 you look at the radiological evaluation, it is
21 exactly the same. There is some fallout at the 50
22 percent healing results, but I don't think it is
23 significant.

24 What is really interesting is that at the
25 12-month or one-year level, all the groups had more

1 than 25 percent of their fractures not united, and
2 this is using either the sponsor's numbers, of
3 which the lowest is 26, or the FDA numbers, where
4 the lowest is 38.

5 The other thing--and this is probably not
6 totally fair--but if you take all of the secondary
7 procedures in the control group and you take all of
8 the secondary procedures in the BMP group, in fact,
9 there is a larger number of patients who received
10 BMP--there is also a larger number of patients who
11 received BMP, but there is a larger number of
12 patients who underwent a secondary procedure.

13 Looking at side effects, the local side
14 effects are really minimal. There is 17 percent
15 reported hypesthesia with the 1.5 composite as
16 compared to single digits for the other two groups.

17 My biggest concern is the antibodies to
18 the recombinant BMP. There is one in the control
19 and nine in the 1.5 composite. As has been
20 previously discussed, this is significantly higher
21 than previously noted. And the sponsors actually
22 pulled out the numbers for antibodies for all of
23 their experimental groups, and it rounds out to
24 just slightly more than 3 percent if you put all of
25 their studies together.

1 My problem with this is that nobody
2 understands what this actually means. There has
3 been no long-term data, although there have been
4 more than 1,000 patients receiving BMP, as noted by
5 the sponsor.

6 The other thing that concerns me is that
7 the investigator brochure states that the safety
8 and efficacy of repeat use is unknown, and it
9 probably is not in the public interest if a key
10 trauma surgeon puts the sponge on a Grade I tibial
11 fracture in a 32-year-old motorcycle rider who,
12 years later at the age of 47 or 50, needs titanium
13 cage and is unable to get healing promotion because
14 he has antibodies.

15 So if we go back to reviewing the
16 objectives which they discussed in the beginning,
17 the increased likelihood of healing with the
18 composite, I think this study has way too many
19 variables, and you can't come to a conclusion, but
20 the answer is probably borderline.

21 Defining the safety, I do think they have
22 shown that it appears to be safe at least in the
23 short term.

24 Documenting increased healing with the
25 composite at 6 months--I agree with the FDA

1 evaluator; there is too much subjective data in the
2 clinical investigation to be able to state that.

3 I think the documentation that the
4 radiographs healed earlier is a definite "No".

5 And the potential economic benefits--if
6 100 of the 300 BMP patients had to have a second
7 procedure, then it is unlikely there are
8 significant economic benefits to this.

9 So in conclusion, the studies suggest that
10 it is safe. This pivotal study is such a potpourri
11 that it is unable to tell us much except that it
12 does not appear that this material interferes with
13 healing, nor does it appear that it has a
14 deleterious effect.

15 I have several questions for the panel.
16 What was the scientific reasoning behind having
17 such an eclectic group studies where the variables
18 were going to be so multiple? Can you explain the
19 lack of Grade III entrances in France? Why did you
20 not have a more specific protocol for the
21 investigators, including not only the reaming
22 versus unreaming, but also using scales to measure
23 weight-bearing and other more objective means of
24 clinical outcome?

25 The fourth question is why did you include

1 Grade I's at all, as most people consider these to
2 be pretty close to closed fractures.

3 My last question--and I may actually be
4 wrong in interpreting the data, because it was a
5 little hard to pull some of the wheat out of some
6 of the chaff in this--but it appeared to me that in
7 some of the patients--I think it is three--with BMP
8 antibodies, actually, three of them had delayed or
9 nonunions or some kind of intervention.

10 That's the end of my discussion.

11 DR. YASZEMSKI: Thanks very much, Dr.
12 Finnegan.

13 We're going to move now to Dr. Larntz for
14 his statistical presentation.

15 Dr. Larntz?

16 DR. LARNTZ: I have a number of comments,
17 and they are a mixed bag, my comments, and I'm not
18 sure I have them very well-organized, but I'll try
19 to tell you a few things that I found out and what
20 I learned by doing this, looking at this, playing
21 with this, enjoying the data very much.

22 First of all, I think it is very
23 interesting that the rate of secondary
24 intervention, at least as measured by the sponsors,
25 does show an effect. It does; there is no

1 question. What they measured shows an effect, the
2 rate of secondary intervention. By showing an
3 effect, I mean the 1.5 dose has a lower rate of
4 measured secondary intervention in numbers of
5 patients to the control. So that seems to be
6 there.

7 There is a question about poolability of
8 that, and I appreciated Dr. Lao's analysis, and I
9 appreciate--actually, the sponsor did a similar
10 analysis in materials that they provided that they
11 did not report, at least, not in the same detail.

12 What is interesting is that the analysis
13 of poolability depends a lot on scale. Now, let's
14 see--how many of you want to know about logid
15 versus probability scales--you can all raise your
16 hands. Whoops--I don't see any. Well, that's too
17 bad, because I'm going to tell you a little bit
18 about it.

19 What we are looking at is probabilities
20 which are proportions, numbers of successes over
21 numbers of total attempted, or numbers of failures
22 over numbers of total attempted.

23 What is interesting about the probability
24 scale, which you all remember from your first
25 course in statistics, is that the variability of

1 that scale depends upon where you are in the scale,
2 and in fact, when you are at very low proportions,
3 you have very small variability, or if you are at
4 very high proportions, you have very small
5 variability. If you are in the middle, you have
6 higher variability.

7 The long and short of that is that
8 statisticians like me prefer to analyze the data
9 for the most part in the logid scale, which is the
10 log odds, whatever that is. Odds are proportion
11 fore over proportion--well, I guess everyone knows
12 about odds. Don't they have lotteries in this
13 country now--not lotteries, but casinos. Okay. So
14 it is proportion for versus proportion against, and
15 then, to make that work statistically,
16 mathematically, you take the log of that. That's
17 the logid scale.

18 Now, if you do the poolability analysis in
19 logid scale, which the sponsors actually did do in
20 the materials, it turns out that you need to think
21 about some of the same issues that Dr. Lao talked
22 about, which are random effects versus fixed
23 effects. It is very clear--it is very clear--that
24 random effects are necessary. What does that mean?

25 That means the rate of secondary

1 intervention differed considerably by site. There
2 is no question about that. The rate of secondary
3 interventions differed considerably by site. That
4 doesn't mean you have anything wrong. I would
5 expect that. I'm a statistician. If they didn't
6 vary by site, I wouldn't have enough to do, right?
7 So they vary by site.

8 And if you account for that and take
9 account of that variability by site in the
10 probability scale, which is what Dr. Lao did, you
11 would adjust out and find that in fact there was no
12 significant difference, no significant effect, in
13 terms of secondary intervention.

14 However, if you do that in the logid
15 scale, which in my opinion is the correct scale to
16 use, if you do that in the logid scale--the
17 sponsors tried to do that and used some statistical
18 package from what they called "SAS"--is that the
19 one you used--I don't know if anyone has ever heard
20 of that package or not, but it's a very major
21 package. That package has difficulty handling the
22 kind of data that they had. And Dr. Lao had some
23 difficulty handling that, too. He omitted three
24 sites because they had zero failures, I think.
25 Well, those sites might be useful, don't you think?

1 Zero failures is a pretty good number, do you
2 agree? Should you throw out data like that? Well,
3 I wouldn't.

4 And I wouldn't use the kind of package
5 that SAS does. I would do a Bayesian
6 analysis--some of you who have been here before
7 have heard me talk about that. if I do a Bayesian
8 analysis in the logid scale--sorry for the long
9 shaggy dog story here--if you do a Bayesian
10 analysis in the logid scale, it turns out that you
11 don't have total poolability of sites, but what you
12 do have is a significant effect with respect to
13 numbers of reinterventions.

14 So in fact in the Bayesian analysis, you
15 do random effects, you do get a statistically
16 significant effect, so I'll just say that now.
17 That's the first story.

18 By the way, I am going to comment slightly
19 about those Kappas and reliability. The sponsor
20 provided that data--Kappas based on 20 evaluations.
21 And again, this is technical--20 is too few to talk
22 about, so I'll stop talking.

23 The next point--do we need survival
24 analysis? Do we need to use those Kaplan-Meyers?
25 There is a difference in the sponsors saying, well,

1 maybe the crude rates are better. Maybe the
2 Kaplan-Meyers are not the right thing. And of
3 course, the Kaplan-Meyers, depending on where you
4 draw the line, as was shown by the FDA, you might
5 get different answers with respect to conclusions.

6 An important aspect of the Kaplan-Meyers
7 is a censoring of data--that is, the number of
8 patients for whom you don't have a data after a
9 certain point. One of the assumptions, basic
10 assumptions, is that in fact that censoring does
11 not depend on eventual outcome. It doesn't depend
12 on eventual outcome. And you would think that that
13 might not depend much on treatment group as well.

14 Let me tell you what I learned from data
15 that actually arrived Saturday by FedEx--how is
16 that for the way we got our information? In that
17 data that arrived on Saturday by FedEx, I found out
18 that there actually was censoring. I sort of heard
19 that there was not much missing data, but then, the
20 censoring with respect to radiologic assessment or
21 with respect to even investor assessment is
22 considerable.

23 For instance, with respect to radiologic
24 assessment--remember, we are trying to go out 6, 9,
25 12 months--it was easy, because there was a table,

1 and I took it out of the table, to look at it at 50
2 days. That's not quite the 6 months, I think--you
3 have to realize that I am a statistician, and the
4 calendar maybe different for me--but at 150 days,
5 the rate of censoring for the control group was 34
6 percent. That means that there were no data for
7 radiologic assessment--no data that could be used
8 for radiologic assessment for 34 percent of the
9 patients after 150 days.

10 Remember, I said it should be the same for
11 the different groups, approximately, if things seem
12 okay, if there is not something different about
13 they way they are doing things?

14 For this 0.75 BMP group, the rate of
15 censoring was 25 percent. Do you see what I'm
16 saying? And for the BMP 1.5 group, the one that we
17 have thinking would have an effect, the rate of
18 censoring was 16 percent.

19 So in fact, there is more radiologic
20 assessment missing for the control group. There is
21 more radiologic assessment missing for the control
22 group, at least if I understand the information
23 provided to me on Saturday, okay?

24 The same thing goes with respect to
25 fracture healing by the investigator--37 percent

1 have no investigator assessment of fracture healing
2 in the control group after 150 days. That is,
3 within 150 days, 37 percent of the individuals are
4 censored within the first 150 days.

5 Excuse me--that sounds like a large
6 number. What is interesting is if you--I'll skip
7 to the 1.5 BMP group--in the 1.5 BMP group, the
8 rate is 19 percent. So there is a vast difference
9 in the censoring rates for these measures that we
10 are worried about--a vast difference in the
11 censoring rates. That concerns me, that concerns
12 me.

13 So, even if we make adjustments for
14 that--I assume there is nothing funny about the
15 amount of censoring--if we make adjustments, if we
16 look at the radiologic assessment of time to union,
17 there is no difference between the three groups if
18 we make adjustments for the amount of censoring.

19 As I said, with respect to secondary
20 interventions, there does seem to be a difference;
21 it is clear. That is the primary endpoint, and
22 there does seem to be a difference.

23 What else do I want to say? On the IM
24 nail issue, there are differences in the rate of
25 reamed versus unreamed, if that's the right term.

1 If you in fact make an adjustment--and buried in
2 one of the reports is an adjusted analysis for just
3 that--the effect of that on secondary
4 intervention--actually, the effect that we see for
5 the 1.5 versus control--is decreased considerably.
6 It is still statistically significant. So there
7 does seem to be some effect. If you make a
8 covariate adjustment for the IM nail--I didn't have
9 the data for that; I just found the analysis--if
10 you have the data on the IM nail, it looks like if
11 you make a statistical adjustment for that, you
12 reduce the effect that you see. It is still
13 significant, but it is not--what was it, .0036 as
14 the P value? It is not that big; it is smaller.

15 Finally--maybe not finally, but finally on
16 this page, anyway--I am confused by something that
17 was said about the fact that the investigators and
18 the radiologic panel had access to the same x-rays.
19 That's fine, but what you didn't tell me was did
20 they have access to all of the x-rays that were
21 taken. And I don't know that. I can't figure that
22 out. I would have expected assessment to be made
23 of all x-rays by the panel. If that is true, that
24 they had access to all of them, that's fine, but I
25 still worry about the amount of missing data that

1 is implied in the Kaplan-Meyer analyses.

2 And if you will just bear with me for a
3 second--I'll stop there.

4 Thank you.

5 DR. YASZEMSKI: Thanks very much, Dr.
6 Larntz.

7 What I'd like to do now is go over the
8 order for the rest of the meeting. We're going to
9 proceed with the second of three open public
10 sessions now, and I'll call for folks who might
11 want to speak in just a moment.

12 Then, we're going to take lunch. I'll ask
13 the panel to stay here for a working lunch, and
14 everyone else is free to have lunch where they
15 would like to. We're going to take a half an hour
16 for lunch from the time that we break, and we'll
17 come back at that time and ask the FDA to put up
18 the questions that they have for us, and we'll have
19 a discussion of those questions and a vote.

20 So now, we're going to proceed with
21 another open public session hearing.

22 I would ask again as I did before that
23 persons addressing the panel come forward, speak
24 clearly into the microphone, and state their name
25 and affiliation.

1 We are requesting all persons making a
2 statement during this open public hearing to
3 disclose whether they have financial interest in
4 any medical device company.

5 Is there anyone at this time who would
6 like to address the panel? I'll ask again--we had
7 one listed presenter. Mr. Christiansen, if you are
8 here and would like to speak, now is an okay time.

9 Good. Welcome.

10 MS. WITTEN: By the way, Dr. Yaszemski,
11 can I just clarify?

12 DR. YASZEMSKI: Yes, ma'am.

13 MS. WITTEN: We are actually having a
14 nonworking lunch; is that right?

15 DR. YASZEMSKI: Is that correct? Did we
16 not do that?

17 MS. WITTEN: Yes. It's actually a
18 nonworking lunch.

19 DR. YASZEMSKI: Okay, fine. That's fine.

20 MS. WITTEN: And then we'll reconvene
21 shortly.

22 DR. YASZEMSKI: Yes. Thank you, Dr.
23 Witten.

24 Open Public Hearing

25 MR. CHRISTIANSEN: Thank you, Dr.

1 Yaszemski, and I'm sorry I wasn't here for the
2 morning session. I misjudged the traffic
3 conditions here in the D.C. area.

4 My name is Bill Christiansen. I am a
5 full-time employee of Depuy Acromad, and I am
6 speaking here today representing the Orthopedic
7 Surgical Manufacturers Association, otherwise known
8 as OSMA.

9 OSMA is a trade association with over 30
10 member companies, and we welcome the opportunity to
11 provide general comments at today's Orthopedic
12 Advisory Panel meeting. OSMA's comments should not
13 be taken as an endorsement of the products being
14 discussed here today. We ask instead that our
15 comments be considered during today's panel
16 deliberations. These comments represent the
17 careful compilation of the member companies' views.

18 OSMA was formed over 45 years ago and has
19 worked cooperatively with the FDA, the American
20 Academy of Orthopedic Surgeons, the American
21 Society for Testing Materials, and other
22 professional medical societies and standards
23 development bodies. This collaboration has helped
24 to ensure that orthopedic medical products are
25 safe, of uniform high quality, and supplied in

1 quantities sufficient to meet national needs.

2 Association membership currently includes
3 over 30 companies who produce over 85 percent of
4 the orthopedic products in clinical use in the
5 United States today.

6 OSMA has a strong and vested interest in
7 ensuring the ongoing availability of safe and
8 effective medical devices.

9 The deliberation of the panel today and
10 the panel's recommendation to the FDA will have a
11 direct bearing on the availability of new products.
12 We make these comments to remind the panel of the
13 regulatory burden that must be met today. We urge
14 the panel to focus its deliberations on the
15 product's safety and effectiveness based on the
16 data provided.

17 The FDA is responsible for protecting the
18 American public from drugs, devices, foods, and
19 cosmetics that are either adulterated or unsafe or
20 ineffective. However, FDA does have another role
21 to foster innovation. The Orthopedic Devices
22 Branch is fortunate to have available a staff of
23 qualified reviewers, including certified orthopedic
24 surgeons, to evaluate the types of applications
25 brought before this panel.

1 The role of this panel is also very
2 important to the analysis of the data in the
3 manufacturer's application and to determine the
4 availability of new and innovative products in the
5 U.S. marketplace. Those of you on the panel have
6 been selected based on your training and
7 experience. You also bring the view of practicing
8 clinicians who treat patients with commercially
9 available products.

10 OSMA is aware that you have received
11 training from FDA on the law and the regulation,
12 and we do not intend to repeat that information
13 today. We do, however, want to emphasize two
14 points that may have a bearing on today's
15 deliberations.

16 One is reasonable assurance of safety and
17 effectiveness, and two, valid scientific evidence.

18 The first point--reasonable assurance of
19 safety and effectiveness. The definition in the
20 law is that if there is a reasonable assurance that
21 a device is safe when it can be determined that the
22 probable benefits outweigh the probable risks.

23 Some important caveats associated with this
24 oversimplified statement include valid scientific
25 evidence and proper labeling and that safety data

1 may be generated in the laboratory, in humans, or
2 in animals.

3 There is a reasonable assurance that a
4 device is effective when it provides a clinically
5 significant result. Again, labeling and valid
6 scientific evidence play important roles in this
7 determination.

8 The regulation and the law clearly state
9 that the standard to be met is a reasonable
10 assurance of safety and effectiveness.

11 "Reasonable" is defined as "moderate, fair, and
12 inexpensive."

13 The second point is valid scientific
14 evidence. The regulation states that while
15 controlled investigations shall be the principal
16 means to generate data that are used in the
17 effectiveness determination, the following
18 principles are cited in the regulation as being
19 recognized by the scientific community as
20 essentials in a well-controlled investigation--a
21 study protocol, a method of selecting subjects,
22 methods of observation and recording results, and a
23 comparison of the results with the control.

24 To conclude, the panel has an important
25 job today. You must listen to the data presented

1 by the sponsor, evaluate the FDA presentations, and
2 make a recommendation about the approvability of
3 the sponsor's application. We speak for many
4 applicants when we ask for your careful
5 consideration. Please keep in mind that the
6 standard is a "reasonable assurance" balancing the
7 benefits with the risks. The regulatory standard
8 is not proof beyond the shadow of a doubt. Please
9 be thoughtful in weighing the evidence.

10 Today OSMA thanks the FDA and the panel
11 for this opportunity to speak. Our association
12 trusts that its comments will be taken in the
13 spirit offered--to help the FDA decide whether to
14 make a new product available for use in the U.S.
15 marketplace.

16 OSMA members are present in the audience
17 to answer any questions during the deliberations
18 today.

19 Thank you.

20 DR. YASZEMSKI: Thanks very much, Mr.
21 Christiansen.

22 We're going to break for lunch now. I
23 have 20 minutes to one; we'll start up again at
24 1:10.

25 Thanks everybody.

1 [Whereupon, at 12:40 p.m., the proceedings
2 were recessed, to reconvene at 1:15 p.m. this same
3 day.]

1 study design.

2 DR. FINNEGAN: Actually, we had asked for
3 this one first, because we think it can be dealt
4 with quickly.

5 MS. WITTEN: Oh, okay. That's fine.

6 DR. YASZEMSKI: Is that okay with FDA, Dr.
7 Witten?

8 MS. WITTEN: Oh, absolutely. If that's
9 your intention, that's fine.

10 DR. YASZEMSKI: Okay. Thank you.
11 What we'll do is go around the table and
12 ask every panel member, voting and nonvoting, if
13 they have a comment on this question. The panel
14 members are free if they would like to request
15 information from the sponsors; they may request,
16 and then I'll ask the sponsors to come up and
17 answer the specific questions posed to them.

18 Dr. Finnegan, let's start with you and go
19 clockwise.

20 DR. FINNEGAN: I actually agree with the
21 sponsors. I do not think that there is a
22 significant difference between the tibia and any
23 other long bones, and in fact I would think that
24 the labeling is more critical related to the grade
25 of open fracture than it is to the specific long

1 bone that is involved.

2 DR. YASZEMSKI: Thank you, Dr. Finnegan.

3 Dr. Kirkpatrick?

4 DR. KIRKPATRICK: I'm sorry, I thought we
5 were going counter-clockwise.

6 At any rate, I also agree with the
7 sponsors. The question that I would raise is do we
8 need to expand indications where it may not be
9 needed at all.

10 DR. YASZEMSKI: Thank you.

11 Dr. Doull?

12 DR. DOULL: I have no comment on that.

13 DR. YASZEMSKI: Thank you.

14 Ms. Rue?

15 MS. RUE: I have no comment.

16 DR. YASZEMSKI: Ms. Maher?

17 MS. MAHER: I have no comment at this
18 point.

19 DR. YASZEMSKI: Dr. Aboulafia?

20 DR. ABOULAFIA: Yes, I hate to dissent,
21 but I think, in keeping with Dr. Kirkpatrick, I
22 still think it is a broad jump to say that one
23 situation begets another and that while the data,
24 which we will get to in the study design, may or
25 may not support its use in open tibial fractures,

1 so to extrapolate it to other long-bone fractures
2 may be also problematic and dependent on how those
3 fractures are healed, whether it is primary or
4 secondary healing, whether it is a plate versus a
5 rod.

6 So I think it becomes a little bit too
7 broad.

8 DR. YASZEMSKI: Thanks, Dr. Aboulafia.

9 Dr. Schmidt?

10 DR. SCHMIDT: I generally agree with the
11 sponsors on this issue. I agree that they really
12 have chosen the most severe model for fracture
13 healing, which would be an open tibia fracture. A
14 femur typically does not have trouble healing, but
15 even in that regard there can be problems. So in
16 general, I am comfortable with the more broad
17 indication, but I think that we do need to see some
18 data at some point to demonstrate that.

19 DR. YASZEMSKI: Thank you.

20 Dr. Larntz?

21 DR. LARNTZ: No comment.

22 DR. YASZEMSKI: Thank you.

23 Dr. Naidu?

24 DR. NAIDU: I concur with the sponsor as
25 far as the labeling.

1 Thank you.

2 DR. YASZEMSKI: Thank you, Dr. Naidu.

3 Dr. Witten, the panel feels that in
4 general, the sponsor's decision about labeling is
5 appropriate. There is some concern that it may not
6 directly extrapolate and that more data down the
7 line will be necessary, but there don't seem to be
8 any major disagreements with the labeling.

9 Have we adequately discussed FDA's
10 questions regarding the labeling?

11 MS. WITTEN: Yes.

12 DR. YASZEMSKI: Thanks very much.

13 We are now going to move on to the study
14 design.

15 Ms. Witten?

16 MS. WITTEN: Actually, let me just ask a
17 follow-on question, although you may be planning to
18 discuss it when you talk about effectiveness.

19 The comments from the panel have related
20 to the first part of it, that is, the treatment of
21 acute long-bone fractures that require open
22 surgical management. The rest of it--probability
23 of fracture healing, accelerates fracture healing,
24 decreases frequency and invasiveness of
25 interventions--I think we would appreciate a

1 comment on that specifically either now or when you
2 discuss the question on effectiveness.

3 DR. YASZEMSKI: If it would be acceptable
4 to FDA, I think we'll do it with the effectiveness
5 question.

6 Mr. Kaiser, we'll go to the study design.

7 "Study Design. Discuss the impact of the
8 following on the ability of the study to collect
9 clinically valid data: 1) definition of standard
10 of care in view of the multiple confounding
11 factors; 2) clinical relevance of rate of secondary
12 interventions required to promote healing as a
13 primary endpoint; 3) reliability of interpretation
14 of the terms 'union', 'healing', 'delayed union',
15 and 'delayed healing' at various sites."

16 Please start again, Dr. Finnegan.

17 DR. FINNEGAN: Well, this is sort of
18 beating a dead horse, but anyway, I think that we
19 have talked about the standard of care. The
20 standard of care that was used in the study is one
21 that is an acceptable standard of care worldwide.
22 By that, I mean that patients were not denied
23 treatment that would have been appropriate, and
24 patients were not given treatment that was
25 inappropriate.

1 However, I am not sure that it is
2 up-to-date standard of care, but I think it is
3 probably acceptable.

4 Then, I would go to the last point on the
5 definitions of "union", "healing", "delayed union",
6 and "delayed healing". I think there are a number
7 of problems with the study design, both
8 subjectively for the investigators as well as the
9 fact that the blinding was not double and that, as
10 Dr. Larntz has shown very nicely, there does appear
11 from statistics to probably have been some
12 investigator enthusiasm for the study material.

13 On the clinical relevance of the rate of
14 secondary interventions, my problem with this is
15 the use of the small, unreamed nails which will
16 have hardware problems, and I think that that is
17 not a sign of a delayed union at the fracture site,
18 it is a sign of mechanical forces on the implant
19 that the implant probably can't handle. So I think
20 that that does have relevance as far as the study
21 design and the implications of the sponsor are
22 concerned.

23 DR. YASZEMSKI: Thanks, Dr. Finnegan.

24 Dr. Kirkpatrick?

25 DR. KIRKPATRICK: Mr. Chairman, would it

1 be appropriate to ask a question of the sponsor at
2 this point about a specific issue within the study?

3 DR. YASZEMSKI: Yes.

4 DR. KIRKPATRICK: Thank you.

5 I would like the sponsor to tell me,
6 because I don't recall seeing the data separated
7 out, how many of the fractures in each group had
8 the fibula fracture fixed.

9 DR. VALENTIN: This is Alex Valentin.

10 I would like to get back to you on this
11 question. We have this number, but we need to
12 check exactly the listing, and I think we can get
13 back to you on this.

14 DR. YASZEMSKI: Dr. Kirkpatrick, would
15 that be okay to come back to you with that when
16 they have it?

17 DR. KIRKPATRICK: That would be fine.

18 DR. YASZEMSKI: Do you have other
19 questions or comments regarding the study design?

20 DR. KIRKPATRICK: No.

21 DR. YASZEMSKI: Dr. Doull?

22 DR. DOULL: I also had a question and it
23 had to do with using the worldwide data as a
24 predictive basis for the U.S. population.

25 When Dr. Finnegan was discussing

1 confounders there, I wondered--I didn't find in the
2 data that you gave us specific information about
3 diet and smoking and ethnicity and so on, about
4 those specific confounders in that worldwide study.
5 I am wondering whether I missed that, or if that is
6 not available.

7 DR. VALENTIN: We have collected a certain
8 number of variables at baseline and provided this
9 information in the package. For example, we
10 provided the ethnicity, we provided the percent of
11 patients with a history of smoking, which is a
12 known risk of delayed union. We have in total
13 identified 27 covariables at baseline in addition
14 to seven demographic characteristics .

15 In choosing our covariables, we were
16 intent to select those that were identified as
17 having an effect on the outcome, and we are
18 satisfied that we did that. We have no knowledge
19 of other covariables that might have affected the
20 outcome.

21 Have I answered your question?

22 DR. DOULL: Yes. I guess my question
23 would be whether, if you just used the U.S., for
24 example, and lost all that worldwide data, the EU
25 would still have pretty much the same database.

1 DR. SWIONTKOWSKI: This is Marc
2 Swiontkowski from the University of Minnesota.

3 What I tried to allude to in m
4 presentation was that those covariates were not
5 distinctly different between the U.S. population
6 and the worldwide population.

7 DR. DOULL: Okay; that's reassuring.
8 Thank you.

9 DR. YASZEMSKI: Thank you, Dr. Doull.

10 Ms. Rue?

11 MS. RUE: I don't have anything. Thank
12 you.

13 DR. YASZEMSKI: Ms. Maher?

14 MS. MAHER: I actually have a follow-up
15 question to Dr. Doull's question, and that is
16 questions were raised about whether the standard of
17 care is applicable to the U.S. and whether their
18 data was applicable. I was wondering if you could
19 comment on that in a more general term.

20 DR. SWIONTKOWSKI: This is Marc
21 Swiontkowski again.

22 I appreciate Dr. Finnegan's analysis. I
23 think there was some confusion about whether or not
24 the nail was placed at the time of the initial
25 procedure. You mentioned that the majority of

1 patients did not have the nail placed at the
2 original--that's incorrect.

3 I think what you are reading is a table
4 that looked at supplemental cast or splint
5 fixation. That is in addition to the IM nail. The
6 only patients who did not get an IM nail at the
7 time of the original presentation had an ex-fix,
8 and that was less than 10 percent in which is was
9 exchanged at the time. So I think you have a
10 misinterpretation.

11 So in summary, the standard of care, as I
12 said in my comments, is very close, if not
13 equivalent, to the care rendered in the United
14 States.

15 DR. YASZEMSKI: Thanks, Dr. Swiontkowski.
16 Dr. Aboulafia?

17 DR. ABOULAFIA: I think there is a pattern
18 emerging of what the concerns are from panel and
19 from FDA, and a lot of my concerns have already
20 been expressed by Dr. Finnegan and Dr. Buch.

21 I'll start with the positive. Before
22 being critical, you have to also think what could
23 be done better, and for things like radiographic
24 analysis and clinical analysis, although it may be
25 subject to some criticism, if it is the best we can

1 do, that criticism goes away.

2 The same thing with standard of care
3 issues, and I want to make clear that I don't have
4 any issues with either standard of care or clinical
5 or radiographic assessment, excepting the fact that
6 there is a margin of error and that it is the best
7 we can do. So I'll take those out of the equation.

8 The other things to some extent are
9 repetition and may be just saying the same thing
10 over again, but in my own words. The issue of
11 reamed versus unreamed nails is not only relevant
12 as it relates to mechanical failures but also the
13 effect on decision for secondary surgery or
14 secondary interventions. Are surgeons more likely
15 to go back and do an exchange nailing in a patient
16 who was initially treated with a small-diameter
17 nail, who may be heavysset, and they are reluctant
18 to allow that patient to weigh-bear because of risk
19 of mechanical failure?

20 Also, one of the monitors or measures of
21 secondary outcomes was the effect on weight-bearing
22 or what the weight-bearing status is.
23 Weight-bearing status is determined not necessarily
24 by fracture healing, but also the diameter of the
25 nail. Even though some of the smaller,

1 solid-diameter nails biomechanically have allegedly
2 the same strength as a larger, non-solid nail or
3 hollow nail, the screws that are used to lock those
4 nails are different sizes, and they are subject to
5 different mechanical failures as a result. So what
6 effect did the choice of whether it was a reamed or
7 unreamed nail have on those secondary things such
8 as weight-bearing status?

9 The decision--and this obviously relates
10 to study design and was brought up by Dr. Buch and
11 FDA--the decision of how secondary interventions
12 were determined was very, very subjective, and that
13 is reflected again by the diameter of the nail.

14 Also, there is no mention of whether
15 secondary procedures were related to nail reduction
16 or errant screw placement. In one of the example
17 in Volume 2, I think, on page 346, one of the
18 distal interlocks is going into the fibula, and you
19 can see some radiolucency around the fibula. While
20 that patient didn't have secondary intervention,
21 errant screw placement or problems with the screw
22 may have influenced the decision to go ahead with
23 an exchange nailing; how was that separated out?

24 It has already been mentioned that the BMP
25 group had larger-diameter nails, and many of those

1 were unlocked. You obviously cannot have
2 mechanical failure of the interlock if there is no
3 interlock, so it biases that secondary variable
4 because the "N" is smaller.

5 The fact that censoring differences took
6 place, as pointed out by Dr. Larntz, raises the
7 issue whether physicians were treating patients
8 differently in the two groups. What I mean by that
9 is why would there be such a difference between the
10 group that received BMP and the control group in
11 terms of censoring.

12 Were physicians more interested or had a
13 certain level of enthusiasm for the BMP patients?
14 The reason that becomes an important issue is again
15 if it leads to secondary intervention.

16 Some people put a small-diameter unreamed
17 nail, get over as an initial internal splint, sort
18 of with the idea of going back and doing an
19 exchange nailing if there is no evidence of
20 radiographic healing in a 6-week period of time.
21 Would a physician who knew that the patient had BMP
22 be less inclined to take that patient back for an
23 exchange nailing, saying, "Well, maybe the BMP will
24 start working"?

25 So I think that physicians who were not

1 blinded did handle those patients differently.

2 I said in the beginning that if you can't
3 find a better way to do it, you can't be too
4 critical. I think you can find a better way of
5 doing it and have very defined criteria of what
6 constitutes secondary intervention, whether someone
7 goes back for an exchange nailing or not.

8 And while the sponsor says that
9 prophylactic bone grafting was not allowed,
10 exchange nailing might be considered a type of bone
11 grafting. It is not the typical post- [inaudible]
12 bone grafting or open autogenous bone grafting that
13 we normally talk about, but secondary interventions
14 were done at an average of 108 days or in that
15 range, between 100 and 110, and that is not the
16 definition of a delayed union. Certainly there are
17 high-risk fractures, and no one would say that that
18 is a violation of standard of care, but it is a
19 form of prophylactic intervention used to encourage
20 bone healing.

21 Then, there was also a little bit of an
22 issue--and I don't know what the magnitude of this
23 was--but there was variation in the dose, and some
24 patients didn't get the dose that are listed under
25 their labeling of 1.5 or not.

1 So those were issues in the study design
2 that I think are confounding variables that
3 actually can be controlled and make for a better
4 scientific experiment.

5 DR. YASZEMSKI: Thanks, Dr. Aboulafia.

6 Dr. Schmidt?

7 DR. SCHMIDT: I agree with most of the
8 comments that Dr. Aboulafia just made and have a
9 few more of my own to add.

10 There are significant differences in the
11 standard of care from country to country, and that
12 has been alluded to. For instance, in Germany,
13 there are still a number of surgeons who will
14 basically use small-diameter unreamed nails in most
15 open tibia fractures, and in some areas of the
16 United Kingdom, for instance, a reamed tibial nail
17 will be used in every, single patient. And that
18 local standard of care is going to influence
19 management. Surgeons who use reamed nails are
20 going to have a far less dramatic problem with
21 hardware failure than the surgeons in Germany who
22 may be accustomed to seeing a lot of their
23 interlocking screws break. So there is going to be
24 a bias from country to country or center to center
25 in the threshold for recommending a secondary

1 intervention, and I think that that is a
2 significant problem with how things worked out with
3 this particular study, where we have centers that
4 are dramatically different in their practice, and
5 this may reflect some of the variation that was
6 seen in the data.

7 I wish there had been a little more
8 uniformity among the centers that were studied in
9 terms of their underlying treatment protocols. One
10 question that came up was is the control group an
11 appropriate control group, and no one has really
12 discussed that.

13 I think what the study is looking at is
14 whether this growth factor accelerates fracture
15 healing, which is different from using it as a bone
16 graft to fill in a defect.

17 There are other methods available right
18 now to accelerate bone healing, for instance,
19 ultrasonic or electrical bone stimulation. Those,
20 even though they are available, I would say that
21 they are not the typical standard of care. I don't
22 use them much in my own practice, yet those methods
23 are available. I think perhaps it would have been
24 nice to have had another group that had a
25 noninvasive method of bone healing acceleration

1 studied.

2 But given those factors, I agree with what
3 Dr. Finnegan said, that the global standard of
4 care, that appropriate treatment was provided and
5 inappropriate treatment was withheld, was met by
6 this study.

7 Are we going on to discuss all of these
8 bullet points now, or just the--

9 DR. YASZEMSKI: All the bullet points
10 under study design.

11 DR. SCHMIDT: I also have some comments
12 about the secondary intervention, and this has been
13 brought up as well.

14 The breakage of interlocking screws is
15 very common, and it is a marker that a fracture has
16 not yet healed. Obviously, a healed fracture is
17 not going to have hardware failure. But the point
18 is that a broken screw is also a method of
19 treatment. For instance, when a screw breaks, the
20 fracture becomes dynamized, and more often than
21 not, it is a clinically irrelevant incidental
22 finding that you see after a fracture has healed.
23 So to count that as one of the determinants of the
24 primary endpoint I think needs a little bit of
25 further discussion.

1 I would be interested to see what the
2 analysis is if you threw out that group of patients
3 and really just looked at secondary interventions
4 that were invasive to the patient--for instance,
5 the need to exchange the nail or to perform a later
6 bone graft.

7 Another question I had--and this relates a
8 little bit to safety--was the high infection rate
9 in all three cohorts of patients. That seems to
10 indicate that there may have been a systematic
11 problem compared to what we have in the United
12 States. Our infection rate--we did a study at my
13 hospital of tibial nails, and we had an infection
14 rate of about 5 percent. I know that the sponsor
15 was trying to be very careful to include every
16 possible infection, and that is going to make it a
17 little bit higher, but it still seems higher than
18 it should be.

19 One question I had--and this may be a
20 ticklish point to bring up in front of the FDA--but
21 were antibiotic beads typically used in this study?
22 I know that they are very commonly used in Europe,
23 and I would submit that they represent a standard
24 of care.

25 DR. YASZEMSKI: Dr. Valentin?

1 DR. VALENTIN: The antibiotic beads were
2 used when necessary during the initial phase of one
3 treatment, and they had to be removed at the time
4 of definitive wound closure upon implantation of
5 BMP-2/ACS.

6 DR. SCHMIDT: That raises another question
7 that I have, which is is there any animal data that
8 suggests there might be a difference in efficacy
9 when this composite is used immediately after there
10 has been an antibiotic bead in the same defect.

11 DR. YASZEMSKI: Dr. Valentin?

12 DR. VALENTIN: It is our experience that
13 there is no apparent interaction between BMP-2 and
14 antibiotics. As a matter of fact, all animal
15 studies have systematic antibiotic treatment at the
16 same time as BMP-2 treatments. We haven't seen any
17 deleterious effect there.

18 DR. YASZEMSKI: Thanks, Dr. Schmidt.

19 Dr. Larntz?

20 DR. LARNTZ: I have a question. I would
21 just like to understand a little better the
22 decision to have a radiologic evaluation. If I
23 understand right--maybe I didn't understand--it
24 wasn't done at all visits for all patients. Is
25 that correct? You can answer "yes" or "no" for

1 that.

2 DR. VALENTIN: The answer is no, it is not
3 correct.

4 DR. LARNTZ: So you did do radiologic
5 evaluation?

6 DR. VALENTIN: Of all patients at all
7 visits.

8 DR. LARNTZ: For all patients at all
9 visits.

10 DR. VALENTIN: Correct.

11 DR. LARNTZ: And all those were evaluated
12 by your panel?

13 DR. VALENTIN: That is correct.

14 DR. LARNTZ: Okay--all patients, all
15 visits. There wasn't any exclusion based on--

16 DR. VALENTIN: No--except for x-ray lost
17 in the mail--

18 DR. LARNTZ: I understand that, I
19 understand that.

20 DR. YASZEMSKI: For the transcriptionist,
21 that discussion was between Dr. Valentin and Dr.
22 Larntz.

23 DR. LARNTZ: That's fine.

24 DR. YASZEMSKI: Thank yo.

25 Dr. Naidu?

1 DR. NAIDU: I have several comments and
2 also several questions.

3 First of all, with regard to standard of
4 care, Dr. Schmidt has clearly stated that standard
5 care is different from country to country. My
6 question to Dr. Swiontkowski is were you dictating
7 this fracture care, or was the surgeon calling it?
8 I mean, you stated that you trained all of these
9 people. Could you clarify that?

10 DR. SWIONTKOWSKI: Yes. The protocol
11 defined the standard treatment, which was
12 irrigation and debridement, and then, prophylactic
13 antibiotics and insertion of an IM nail.

14 DR. NAIDU: Okay. So it appears as if the
15 standard of care is variable, and I do concur with
16 Dr. Schmidt with regard to that.

17 DR. SWIONTKOWSKI: Which aspect?

18 DR. NAIDU: With regard to the reaming,
19 unreaming, and the treatment in various countries
20 that Dr. Schmidt clearly cited, that the cultural
21 differences are there. So therefore, in my
22 opinion, the standard of care was different, and
23 that is a big issue.

24 The second issue is the clinical relevance
25 of the primary endpoint and the rate of secondary

1 interventions required to promote healing. You
2 know, we are looking at the efficacy of a drug.
3 This is classified as a drug in Europe. It is
4 classified as a device. Even though Dr.
5 Swiontkowski clearly states to us that there is an
6 NIH-sponsored trial of reamed versus unreamed
7 nailing underway with secondary intervention as the
8 final endpoint, we are not testing a new product in
9 the sense that this is a different drug. Like the
10 European Union--EU stated that this is a drug.

11 Therefore, I have a problem with this
12 clinical relevance of the primary endpoint being
13 the rate of secondary interventions, even though
14 there may be an NIH-related protocol that is
15 approved. When one judges the safety and efficacy
16 of a drug/device, I'm not sure this is a good
17 enough primary endpoint.

18 Finally, the reliability of the
19 interpretation of the terms "union", "healing",
20 "delayed union", "delayed healing" at various sites
21 is completely nebulous.

22 Thank you.

23 DR. YASZEMSKI: Dr. Finnegan?

24 DR. FINNEGAN: Dr. Swiontkowski, in Volume
25 IB, page 59, Table 4.2.4-1, it says the number of

1 patients who received preliminary external fixation
2 or intramedullary nail fixation by treatment group,
3 and there are significantly small numbers receiving
4 external fixation IM rod, and the patients without
5 preliminary fixation number at least 130 in each
6 group.

7 DR. VALENTIN: This is Alex Valentin
8 taking that question, if you don't mind.

9 DR. YASZEMSKI: Go ahead.

10 DR. VALENTIN: I would like to clarify
11 this table, and I agree it may be a little bit
12 confusing in that table.

13 What we meant to say is that initially,
14 the patients had casts or splints in addition to
15 their primary treatment by an IM nail. The
16 external fixiter was used, as indicated there, in
17 about 7 percent of the patients, and I believe
18 there were two patients--one in the standard of
19 care and one in the 1.5--who initially received an
20 IM nail, and there was an exchange of that IM nail.
21 The other patients, the 7 percent, received an
22 external fixiter, which was then changed to an IM
23 nail. And the remaining patients all received an
24 IM nail as their primary care. In addition, they
25 received a cast and other sorts of treatment that

1 are indicated there.

2 DR. FINNEGAN: So the following page has
3 the following table which says "Days from injury to
4 definitive fracture fixation with IM nail," and the
5 standard is 2.6, 2.7, 2.9, and the maximum is 13 or
6 14 days.

7 DR. YASZEMSKI: This information is
8 correct as well. It does not contradict the first
9 information. These patients were initially treated
10 for the vast majority with an IM nail, in a few
11 cases by external fixiter, and then moved to an IM
12 nail; and in two cases, an IM nail exchange.

13 DR. FINNEGAN: Thank you.

14 DR. YASZEMSKI: Dr. Aboulafia?

15 DR. ABOULAFIA: I was just going to add,
16 again related to study design, two small comments.
17 One of the things that is missing is Winkquist
18 [phonetic] classification, which impacts on
19 weight-bearing status. There are patients whom you
20 allow immediate weigh-bearing--"on the way to the
21 recovery room" is the euphemism I use--and it has
22 to do more with fracture pattern than it does
23 anything else. So when you look at that secondary
24 endpoint, weight-bearing status, and don't include
25 data related to degree of comminution and cortical

1 contact and the things associated with Winkquist
2 classification, it does a disservice. And whether
3 that is corrected by randomizing them, you would
4 want to know if treatment groups were different in
5 the allocation of those with severe comminution
6 versus those without severe comminution.

7 And there was one other thing--I'll leave
8 it there.

9 DR. YASZEMSKI: Thank you.

10 Dr. Witten, we have had a discussion now
11 about the study design. There are some strengths
12 and weaknesses that have been identified. In
13 general, the standard of care was deemed acceptable
14 with some caveats, and those caveats included that
15 local standard of care, specifically in other
16 countries, may have affected the choice of the
17 initial nail, and also the differences in different
18 countries perhaps had effect on the infection rate.

19 It was brought up that other noninvasive
20 means of accelerated fracture healing such as
21 electrical or ultrasound means may have been
22 appropriate additions. It was also brought up that
23 since some of the patients didn't get the full
24 sponge that perhaps there was some dose variability
25 among the three groups.

1 The small nails were considered to perhaps
2 be a factor, but in general, given the strengths
3 and weaknesses as discussed, there didn't appear to
4 be any discussion of any critical flaws in the
5 study design as brought up by the members of the
6 panel.

7 Have we adequately addressed your
8 questions on this issue?

9 MS. WITTEN: Yes.

10 DR. YASZEMSKI: Thank you.

11 Mr. Kaiser, could we move on, please, to
12 effectiveness?

13 For effectiveness, the FDA is asking us:
14 "Accounting for trial design, resulting data and
15 statistical analyses, discuss the adequacy of
16 effectiveness in terms of the decrease in the
17 number of secondary interventions required to
18 promote fracture healing, and accelerated fracture
19 healing determined by the fracture healing at 6
20 months assessed by the investigator and the
21 radiographic evidence of fracture union assessed by
22 the independent radiologist.

23 Dr. Schmidt, could I ask that we start
24 with you?

25 DR. SCHMIDT: Yes. As we have heard

1 discussed this morning, this is a very complicated
2 study and very difficult to just answer those in a
3 "yes" or "no" manner.

4 I think I should state my personal bias,
5 which is that I know that these compounds are
6 effective. There have been ample animal models in
7 the literature, some of which were reviewed today,
8 that BMPs to promote bone healing.

9 I guess the question, though, is does it
10 accelerate bone healing in human beings with an
11 open tibia fracture.

12 I have to defer to the statistical
13 analysis that was presented by Dr. Larntz, and it
14 sounds like that answer is true, although it is
15 still a little bit difficult and perhaps a bit
16 nebulous and depends to some degree on how you
17 analyze those statistics, and even that may not be
18 perfectly clear.

19 I don't really think they have truly shown
20 that there is an increased rate of union at 6
21 months, and I think you could argue about is the
22 6-month important or some different time frame, and
23 it appears that the results are different at the
24 different time frames, so I am less comfortable
25 with that assertion. And I am also concerned about

1 the issues with the radiographic analysis that we
2 heard discussed.

3 DR. YASZEMSKI: Thank you.

4 Dr. Larntz, can we come around to you?

5 DR. LARNTZ: Sure. I believe that the way
6 secondary interventions were measured, there is
7 clearly a significant effect in that variable with
8 respect to whether or not there was a secondary
9 intervention. And I think that that is true
10 accounting for the diversity of the sites, which I
11 understand some people might think that's a
12 disadvantage. As a statistician, I think diversity
13 of sites is actually quite good and useful--but I
14 may be in a minority with respect to pure study
15 design.

16 With respect to time to healing, we are in
17 a more problematic state, and clearly, the
18 radiologic assessments, however that was done--and
19 if you look at that Kaplan-Meyer analysis, the
20 curves are on top of each other, so what can you
21 say? I once had someone try to tell me there was a
22 difference in a subset based on that, and I walked
23 out of the room. They are just on top of each
24 other.

25 With respect to the investigator

1 evaluation of time to healing, it seems like there
2 probably is a slight advantage for the 1.5 BMP with
3 respect to the investigator time to healing. But
4 again, I worry about--well, I'll just say that as
5 recorded, I would say that that is probably there.
6 The P values in the Kaplan-Meyer are slightly
7 different for the log rank Wilcoxin [phonetic]
8 test; they give slightly different indications--but
9 I think there probably is something in the time to
10 healing with respect to the investigator version of
11 that.

12 With respect to the radiologic evaluation
13 by the panel, there is nothing there.

14 DR. YASZEMSKI: Thanks, Dr. Larntz.

15 Dr. Naidu?

16 DR. NAIDU: With regard to the first
17 bullet point, whether the sponsor has shown a
18 decrease in number of secondary interventions
19 required to promote fracture healing, I will rely
20 some of my conclusions on Dr. Larntz' statistical
21 analysis, and it seems as if they have shown that.

22 But as far as accelerated fracture healing
23 as determined by fracture healing at 6 months, Dr.
24 Larntz clearly went through the numbers in
25 detail--in the standard of care group without any

1 BMP, 37 percent of the x-rays at 150 days were
2 censored; in the 1.5 group, only 19 percent
3 censoring was there. Based on all these numbers
4 presented, I am not sure that accelerated fracture
5 healing can be concluded at 6 months as assessed by
6 the investigator.

7 Thanks.

8 DR. YASZEMSKI: Thanks, Dr. Naidu.

9 Dr. Finnegan?

10 DR. FINNEGAN: I would concur--do you want
11 us to address labeling at the same time, or no--the
12 question that Dr. Witten had?

13 DR. YASZEMSKI: I think that, with the
14 permission of FDA, since they asked for additional
15 comment on labeling after our discussion of that
16 question, if you have something to add to it at
17 this point, please do so.

18 DR. FINNEGAN: I would suggest that the
19 label probably should not contain "accelerates
20 fracture healing" and "decreases the frequency and
21 invasiveness of interventions," the reason being
22 that I really do think that there are so many
23 confounding variables that certainly, there is no
24 deleterious effect, but I really don't think that
25 even for secondary interventions, given the

1 mechanical properties of the small nail, that we
2 can draw any large conclusions.

3 DR. YASZEMSKI: Thanks, Dr. Finnegan.

4 Dr. Kirkpatrick?

5 DR. KIRKPATRICK: Has the sponsor been
6 able to get the fibula data for me?

7 DR. VALENTIN: Yes. The fibula data were
8 collected on 437 patients, and there were 17
9 patients in the standard of care, 10 patients in
10 the 0.75 and 10 patients in the 1.5, who received
11 additional treatment of their fibula.

12 DR. KIRKPATRICK: So roughly 10 percent of
13 your control group had the fibula fixed, and less
14 than that--somewhere around 5 or 6 percent--of the
15 other two groups. Was that looked at with
16 statistics as well?

17 DR. VALENTIN: From what standpoint--if it
18 is comparable across treatment groups?

19 DR. KIRKPATRICK: Did you do any
20 statistical analysis on whether that had an impact
21 on the results?

22 DR. VALENTIN: No.

23 DR. KIRKPATRICK: I would just like to
24 point out one concern with regard to effectiveness.
25 If the control group, which had a lower rate of

1 healing, so to speak, had a higher rate of fibula
2 fixation which may act as a distraction device on
3 the fracture, then the normal biology of the
4 fracture healing may have been disrupted somewhat,
5 so it may not be a true indicator of the actual
6 effectiveness.

7 That's all the comment I have on that.

8 Thank yo.

9 DR. YASZEMSKI: Thanks, Dr. Kirkpatrick.

10 Dr. Doull?

11 DR. DOULL: I am a little confused about
12 definitions. It seems to me that when you defined
13 heterotopic and ectopic, you defined that as local
14 and distant, and your rate for ectopic was zero.
15 But what would you define as increased bone growth
16 further up on the tibia? Is that heterotopic?

17 DR. VALENTIN: Thank you.

18 We would define this as heterotopic. I
19 would like first of all the clarify that we have
20 reported two ectopic calcification. In my
21 presentation, I stated that no calcification
22 related to BMP-2 was reported. We had two
23 calcification observed, one in the femur and one at
24 another side I can't remember now, and neither case
25 was attributable to the BMP treatment.

1 With respect to heterotopic ossifications,
2 I show the numbers. We had four, four, and eight
3 patients with heterotopic ossification. That
4 assessment was for the region under study, which
5 was the full limb we followed for the fracture.

6 DR. DOULL: Okay, thanks.

7 DR. YASZEMSKI: Thanks, Dr. Doull.

8 Ms. Rue?

9 MS. RUE: No further comment.

10 DR. YASZEMSKI: Ms. Maher?

11 MS. MAHER: I actually have two questions.
12 One, there was a question raised earlier, and maybe
13 it was answered, and I didn't get it, in which case
14 I apologize. That is, were all x-rays reviewed by
15 both the panel and the investigators?

16 DR. VALENTIN: Yes. The answer is yes to
17 both. We addressed this question earlier.

18 MS. MAHER: Okay. And my second question
19 is that I heard questions raised by Dr. Larntz
20 regarding the censoring and radiologic assessment,
21 and I was wondering if you all could comment on the
22 questions he raised.

23 DR. VALENTIN: This is a very important
24 question, and thank you very much for asking this.

25 We would like to clarify here the process

1 we have followed. The first question we had for
2 the primary endpoint was the avoidance of secondary
3 intervention. The second question we had for the
4 secondary endpoints was for the patients who do not
5 have a second intervention, do we see further
6 acceleration of fracture healing or fracture union.

7 So by definition, the patients who had a
8 second intervention had to be removed from that
9 analysis. So this censoring was done on purpose,
10 and the different numbers pointed to earlier in
11 this analysis reflect in fact the number who had
12 second interventions.

13 So in order to answer the question was
14 there an acceleration of fracture healing in the
15 other patients, those who did not require second
16 intervention, we had first of all to remove the
17 patients who had one. This is dealt with in
18 different ways, with different types of analysis.
19 For instance, in the Kaplan-Meyer display, this is
20 handled by way of censoring, and we actually agree
21 with your analysis that this weakens the
22 Kaplan-Meyer analysis in that respect. That is why
23 we also pointed out in my presentation that we
24 believe the rate of healing or of union by visit
25 where the patients second interventions were

1 accounted as failures, not healed or not united,
2 was a more powerful evaluation of these data.

3 DR. YASZEMSKI: Thank you.

4 Ms. Maher, does that answer your
5 question--Dr. Valentin, if you are not done, please
6 go ahead.

7 DR. VALENTIN: I'm sorry. I just wanted
8 to add, therefore, that the censoring of the data
9 in each treatment group, therefore, just to restate
10 it, is a reflection of the success of the
11 treatment. More patients were censored in the
12 standard of care because more patients required a
13 second intervention; less patients were censored in
14 the 1.5 group because less patients required second
15 intervention.

16 Thank you.

17 MS. MAHER: Thank you. I actually have
18 one follow-up question. I was wondering if you all
19 could comment on your opinion on the
20 appropriateness of pooling the data from these
21 various centers.

22 DR. VALENTIN: I would like to take the
23 first stab at this question; this is clearly one
24 that was very hotly debated, and many people have
25 given their opinion here.

1 I would like to give you the perspective
2 of a clinician. We have selected 59 centers, of
3 which 49 have participated with patients. First of
4 all, I would like to point out here that we
5 selected these 49 centers out of 400 that were
6 screened. So we were very careful to make sure
7 that the centers participating in the study had
8 common criteria--using, for example, the same types
9 of surgical procedures, the same type of
10 practice--so that we could compare the centers. It
11 was not done out of the Yellow Pages.

12 The second part of my answer is that we
13 have monitored quite a large number of variables to
14 make sure that indeed these centers have
15 contributed patients treated in the same manner,
16 and as I was pointing out, seven demographic
17 criteria, 27 covariables were checked, and we
18 didn't find a difference between them.

19 We have also run statistical analyses to
20 look at center by treatment interaction, and in our
21 analysis, there was no interaction, and that has
22 justified the treatment analysis that we have
23 conducted.

24 At the end of the day, I'm saying that we
25 want to have a population that reflects the general

1 trauma population. If we are too selective, we
2 will finish with all patients having had exactly
3 the same fracture, the same treatment, the same
4 nail, and that may be a very narrow application
5 than other treatments. So it was our intent to
6 have a balanced application.

7 DR. YASZEMSKI: Thank you.

8 Does that answer your question, Ms. Maher?

9 MS. MAHER: Yes. Thank you.

10 DR. YASZEMSKI: Dr. Aboulafia?

11 DR. ABOULAFIA: Addressing the issue of
12 effectiveness, the OSMA spokesperson made the point
13 that our task here is to look at a reasonable
14 assurance of safety and efficacy and sponsor
15 innovation, and I would clearly support that. And
16 I certainly share Dr. Schmidt's enthusiasm about
17 biological modifiers and recombinant BMPs as a
18 group and other things to promote fracture healing,
19 and I think it is a noble cause.

20 Having said all that, I think some of that
21 enthusiasm is based on both preclinical and
22 clinical data in sites other than the tibia, of
23 course. So then, the question or the weighing on
24 the other side of that teeter-totter is are the
25 conclusions supported by the data, and that relates

1 to study design, and there are issues with that.

2 One of the things I neglected to mention
3 about study design is whether subsets of patients'
4 proximal, distal and middle third fractures were
5 equally spread out. We know that healing
6 potential, rates, complications, depending on the
7 anatomic site, is significant within the tibia
8 itself and that the proximal tibia and the distal
9 tibia are not the same bone in many respects.

10 So I have less enthusiasm for whether the
11 sponsor has proven effectiveness based on the data
12 presented as it relates to the tibia in this study.

13 DR. YASZEMSKI: Thanks, Dr. Aboulafia.

14 Dr. Naidu?

15 DR. NAIDU: I do have an additional
16 comment about the censoring business, because Dr.
17 Larntz clearly made it clear that at 6-month time
18 point, 34 percent of x-rays at the 6-month group
19 was missing.

20 Now, if you go back to the definitions of
21 heal fracture, the three criteria--absence of
22 tenderness upon manual palpation at the fracture
23 site; radiographic fracture union as assessed by
24 the investigator; and full weight-bearing
25 status--and if you look at the number of patients

1 with secondary intervention recommended and
2 patients meeting the criteria of delayed union, all
3 three criteria were used in only 26 percent of the
4 patient population; two criteria were used in 52
5 percent; one criterion was used in 23 percent.

6 Therefore, this issue of censoring does
7 become important. We should not dismiss that.

8 DR. YASZEMSKI: Thanks, Dr. Naidu.

9 Are there further comments?

10 [No response.]

11 DR. YASZEMSKI: Dr. Witten, we have
12 discussed the issue of effectiveness and the FDA's
13 questions regarding it. We previously discussed
14 the study design and offered you our opinions about
15 the strengths and weaknesses of it, so these
16 comments will be issues of effectiveness for the
17 study design as presented in the application by the
18 sponsors.

19 Dr. Larntz indicated that with respect to
20 secondary interventions, there clearly was an
21 effect demonstrated by these data. The time to
22 healing, the investigator evaluation, and the
23 radiologist evaluation were less positive in their
24 strength with respect to demonstrating an effect.
25 Although there could have been an effective with

1 the time to healing, it was most weak with the
2 radiologist interpretation.

3 There were questions with respect to the
4 two points that FDA has asked, that although the
5 decrease in the number of secondary interventions
6 is shown by the data, there is some question as to
7 whether the accelerated fracture healing has been
8 shown by this data, and there are arguments on
9 either side of that, as you have just heard.

10 Have we adequately discussed this
11 question?

12 MS. WITTEN: Yes, but I do have a
13 follow-on question based on the answers to this
14 question and the answers to the previous question.

15 DR. YASZEMSKI: Please go ahead.

16 MS. WITTEN: I would like to know whether
17 anybody on the panel would like to comment on the
18 relevance of the effectiveness shown by these data
19 on the study performed outside of the U.S. to
20 effectiveness in U.S. patients.

21 DR. YASZEMSKI: Panel members, the
22 question is does the data gathered on patients
23 outside of the U.S. apply to the care of patients
24 within the U.S. Would anyone like to comment on
25 that?

1 Dr. Finnegan?

2 DR. FINNEGAN: I think that one of the
3 nice parts about working in the melting pot of the
4 world is that, yes, the world will produce the same
5 patients that you have in your patient population.

6 DR. YASZEMSKI: Other comments?

7 Dr. Kirkpatrick?

8 DR. KIRKPATRICK: I would agree. I have
9 even been in Third World countries that would
10 manage tibias in a similar fashion and get them
11 acutely debrided, irrigated and stabilized with an
12 IM nail.

13 DR. YASZEMSKI: Dr. Schmidt?

14 DR. SCHMIDT: I agree, and a lot of the
15 practice variation that I alluded to earlier, we
16 see within our own country, even in the State of
17 Minnesota, perhaps. So I don't have any real
18 concerns about that.

19 DR. YASZEMSKI: Dr. Witten, have we
20 adequately addressed this?

21 MS. WITTEN: Yes. Thank you.

22 DR. YASZEMSKI: Thanks so much.

23 Mr. Kaiser, could we go to the next
24 question, please?

25 The next question from the FDA regards

1 safety: "Accounting for trial design and resulting
2 data, discuss whether or not the sponsor has
3 provided a reasonable assurance of device safety in
4 view of the rate of authentic antibody response to
5 rhBMP-2 and to bovine Type 1 collagen; rate of
6 hardware failure; rate of infection; rate of
7 abnormal liver function lab values."

8 Dr. Doull, can we start with you, please?

9 DR. DOULL: Yes. There are four
10 questions--the antibody response, the rate of
11 hardware failure and infection, and the abnormal
12 lab values.

13 I wasn't really too concerned about the
14 antibody until Dr. Finnegan raised the possibility
15 that those antibodies might in fact influence the
16 subsequent response of that patient to another
17 episode. It seems to me that that is a question
18 which could be resolved by animal experimentation,
19 and I would think that's certainly something
20 worthwhile doing.

21 I found the data regarding the hardware
22 failure and rate of infection lacking a causal
23 relationship to some adverse effect of rhBMP or the
24 sponge.

25 And finally, then, the abnormal liver

1 function values--what you really didn't tell us
2 there was how long they persisted and whether that
3 was the same in your control population and in the
4 two treatment groups that you talked about.

5 DR. YASZEMSKI: Dr. Doull, shall we ask
6 the sponsors to comment on that?

7 DR. DOULL: Yes, could you tell us?

8 DR. YASZEMSKI: Dr. Valentin?

9 DR. VALENTIN: So if I understand the
10 question, you would like to know if the incidence
11 of liver function abnormalities was comparable
12 across treatment groups?

13 DR. DOULL: Right, both for the amylase
14 and for the magnesium.

15 DR. VALENTIN: With respect to amylase, we
16 have seen an increase in the number of patients
17 reporting anomalies in the 0.75 mg group as
18 compared to the control group, and an elevation at
19 1.5 compared to control group. In other words, you
20 have--I am citing from memory here--I think four
21 patients in the control group, 10 patients in the
22 1.75, and 6, I think, in the 1.5--and please bear
23 with me; I am trying to remember the exact numbers.
24 But we didn't find an exact dose response, and we
25 think that by just having the battery of 200 tests,

1 with every adverse event tested, it was likely that
2 some would be elevated and irregularly elevated
3 between the three treatment groups.

4 I personally don't think there is a
5 relationship between BMP and increased amylase. I
6 think it translates the status of trauma of these
7 patients. However, we stated the numbers as they
8 are, and there is a statistical difference between
9 0.75 and control.

10 DR. DOULL: Dose response is a hallmark of
11 toxicity, and I would agree with you that if you
12 don't see dose response, you have to ask that
13 question.

14 DR. VALENTIN: And I would like to add
15 that for hypomagnesemia that the same thing was
16 true--the 0.75 was more elevated at 1.5, and both
17 were slightly more elevated than control. Again,
18 we couldn't see a clearly relationship between
19 these elevations in very few patients, by the way,
20 and the treatment with BMP.

21 DR. DOULL: I would like to point out that
22 we have previously reviewed the tox database for
23 this material and agreed that it was adequate. I
24 am impressed with the fact that in this
25 presentation, you are using the term "safety" more

1 than you are using "toxicity." The tox database
2 which you use to support this application are
3 really safety studies. You are showing that at
4 various levels--1,000 times anticipated dose and so
5 on--you are seeing no adverse effects, but you do
6 not characterize toxicity with safety studies. All
7 you do is show that at that dose, it is safe. In
8 order to characterize toxicity, you have to
9 demonstrate adverse effects, and you have to show
10 the dose required to produce those kinds of adverse
11 effects, and in all the studies you did--the acute
12 tox, the 28-day tox, the teratology, the
13 reproduction--those are all safety studies.

14 So that I can't help but wonder what is
15 the true toxicity of rhBMP, and I guess we haven't
16 answered that question, and we may not need to,
17 because in terms of the safety, if you do a range
18 of safety or a margin of exposure, you have huge
19 factors here.

20 Thank you.

21 DR. YASZEMSKI: Thanks, Dr. Doull.

22 Dr. Kirkpatrick?

23 DR. KIRKPATRICK: I also would concur with
24 Dr. Finnegan's concern about a secondary challenge
25 from an immune-converted or antibody-positive

1 animal model, so to speak, a secondary challenge
2 sometime in the future. I don't think we can
3 answer that in humans, obviously. I think if we
4 could come up with a reasonable way with an immune
5 study, which I have no expertise in, it would be a
6 reasonable assurance--and fairly simply, I would
7 hope--that a future challenge would not result in a
8 catastrophic immune response or autoimmune
9 response.

10 DR. YASZEMSKI: Thanks, Dr. Kirkpatrick.

11 Dr. Finnegan?

12 DR. FINNEGAN: The only thing I would add
13 to that is that you have a huge number of patients
14 out there, and you could do a natural history on
15 the antibodies to see if they persisted or not for
16 the patients you have given this to over "x" number
17 of years.

18 I have no concern about the hardware
19 failure, but that just means I do this operation
20 more than once a week.

21 Dr. Schmidt's comments on infection are
22 interesting; I did not pick that up, and I'm not
23 exactly sure what the effect of that is. And I
24 would defer to Dr. Doull for the liver function.

25 DR. YASZEMSKI: Thank you.

1 Dr. Naidu?

2 DR. NAIDU: I do have a problem with the
3 authentic antibody response to rhBMP-2. Doctor, as
4 the FDA clinician presented--and I sat here at the
5 previous INFUSE meeting--the previous spine
6 approval, the antibody response was only 0.7
7 percent. This is almost 10 times as much. I don't
8 know exactly what the clinical relevance is, but it
9 is significant, and therefore, I would concur with
10 Dr. Finnegan with regard to this.

11 The rate of hardware failure, I'm not too
12 concerned--it breaks. And high rate of breakage is
13 noted in the unreamed group. That is not
14 surprising.

15 The rate of infection is high, but these
16 are high-energy open tibia fractures, so you're
17 going to expect it to be high. But I did find Dr.
18 Schmidt's comments very interesting in that in his
19 institution, it is about 5 percent. But the rate
20 of abnormal lab values with regard to liver
21 function, I will defer to our toxicologist on the
22 panel.

23 DR. YASZEMSKI: Thanks, Dr. Naidu.

24 Dr. Larntz?

25 DR. LARNTZ: I have nothing to add.

1 DR. YASZEMSKI: Thanks.

2 Dr. Schmidt?

3 DR. SCHMIDT: I don't know what more to
4 add about the issue of the immune response. I do
5 have a question about why it may be higher in this
6 group than it was in the spine group. It may be a
7 reflection of the different immune response for a
8 traumatized patient as opposed to someone
9 undergoing surgery. I do think that is something
10 that probably ought to be looked at.

11 The comments I made earlier about the
12 infections stem from my knowledge that previous
13 studies looking at acute bone grafting in open
14 tibia fractures have shown a high infection rate.
15 There was one study--the most recent one I am aware
16 of was published over 10 years ago, and granted,
17 things have changed since then in management of
18 these cases--but acute bone grafting of open tibia
19 fractures has a dramatically higher infection rate,
20 and what we know from clinical experience is that
21 you need to wait until the soft tissues have
22 healed, typically, 6 to 8 weeks, before you add an
23 autogenous bone graft to a patient who has had an
24 open tibia fracture. If you do it before then, the
25 infection rate is high, and the graft often just

1 resorbs and isn't effective.

2 That raises the issue of is this type of
3 composite device going to be effective before the
4 soft tissues have really restored themselves and
5 regained their vascular supply and that sort of
6 stuff, and that is what the study was looking at.

7 In terms of the other issues, I'm not too
8 worried about the hardware failure; I think that
9 may just represent the small-diameter nails. One
10 point I would like to make, though, is that the
11 term "BMP" is really a misnomer. These are
12 generic morphogenetic proteins. There are
13 cell-[inaudible] models that are active throughout
14 development; they affect the whole body. They
15 affect DNA transcription, and I think it is a
16 mistake to think that these are just a simple
17 protein that is only going to act on the bone.
18 They have potential, far-reaching side effects, and
19 I think that patients who receive this should be
20 followed.

21 I think there is data that some tumors do
22 respond to these prostate and pancreatic cancers.
23 Tumor lines, I think, have shown responsive to
24 BMP-2. I just think that's a small but theoretical
25 concern that needs to be addressed with long-term

1 studies.

2 DR. YASZEMSKI: Thanks, Dr. Schmidt.

3 Dr. Aboulafia?

4 DR. ABOULAFIA: Briefly, I do not have any
5 concerns related to safety of the product and
6 actually feel that the development of antibodies is
7 probably less of an issue than some members have
8 expressed.

9 DR. YASZEMSKI: Thanks, Dr. Aboulafia.

10 Ms. Maher?

11 MS. MAHER: I have nothing further to add.

12 DR. YASZEMSKI: Thank you.

13 Ms. Rue?

14 MS. RUE: I have nothing further to add.

15 DR. YASZEMSKI: Thank you.

16 Dr. Witten, we have discussed safety in
17 terms of the questions that the FDA has posed to
18 us. There seem to be no issues with respect to
19 hardware or infections, and the infections seem to
20 be accounted for by the nature of this injury.

21 There have been a few comments made,
22 however, about the nature of the antibody response,
23 that it did greater than previously documented and
24 perhaps warrants looking at these patients over a
25 longer period of time.

1 It was noted that the trauma may in fact
2 be an effect and hence this be a manifestation of
3 the injury that these people have undergone.

4 There was also a question that we should
5 be cautious about the unknown but potentially
6 theoretic effect of a tumor in the future.

7 However, in general, I think the tenor of
8 the conversation was that this device is safe, as
9 shown in the data from the study presented by the
10 sponsor.

11 Have we adequately discussed this from
12 FDA's perspective?

13 MS. WITTEN: Yes. Thank you.

14 DR. YASZEMSKI: Thanks, Dr. Witten.

15 That will conclude our discussion. We are
16 going to proceed now with another open public
17 hearing session, and I would ask again if anyone in
18 the audience would like to address the panel,
19 please come forward to the microphone, state
20 clearly your name, affiliation, and financial
21 considerations.

22 Would anybody like to address the panel at
23 this time?

24 [No response.]

25 DR. YASZEMSKI: Seeing no one, I would

1 like now to ask the sponsor if any of your members
2 have any final comments and would like to address
3 the panel in any way before we proceed with voting.

4 Dr. Swiontkowski?

5 Final Sponsor Comments

6 DR. SWIONTKOWSKI: There are two areas
7 that I'd like to comment on. One is on Dr.
8 Schmidt's concern regarding the infection. I tried
9 to point out in my third-to-last slide that using
10 the strict definition in this trial where
11 basically, any redness, whether culture-proven or
12 not, was infected, by that definition in the U.S.
13 60-patient trial, it was 18 percent, and in this,
14 it was 22 percent.

15 So I think it is related to the strict
16 definition, not really a different outcome as a
17 result of the care.

18 The other area I would like to comment on
19 is the study design and the endpoint selection. I
20 have to beg the panel's indulgence for a minute,
21 because I think that the decision here could
22 potentially affect the ability to study trauma
23 patients in general for any condition in the
24 future.

25 When we discussed the whole issue of which

1 model to use with our potential clinician
2 investigators, they were adamant about the fact of
3 not having a control, and some of the panelists
4 commented that it would be nice to have a control.
5 They really felt that it was an ethical issue of
6 not putting a sponge into a potentially infected
7 environment. And as Dr. Schmidt just pointed out,
8 maybe that environment where you have acutely
9 injured soft tissue affected the basic ability of
10 the protein to stimulate healing, which I agree
11 with. I think this is the most severe model.

12 Second, regarding the endpoint, I
13 appreciate Dr. Naidu's comment about we are using
14 the same endpoint in a randomized controlled trial,
15 but this is different. We are talking about a
16 drug. But I would submit that this is a decision
17 to take a patient back to the operating room. It
18 is not to discontinue a drug therapy or something
19 like that. And if there were a bias, you should be
20 able to see it in the days to decision to
21 intervene, and they were within 2 days in all three
22 of the groups. So there was no bias there.

23 I would also point out that in the
24 randomized control trial that we are conducting
25 now, we have a rule that you can't intervene within

1 6 months, and 25 percent of the surgeons are
2 violating that rule. That is because as surgeons,
3 we are always going to act in what we believe is
4 the best interest of the patient, and I think that
5 that is why we have the design that we have here
6 today, because we are dealing with surgeons who are
7 making real decisions that are major decisions to
8 intervene, and it is not a trivial intervention.

9 Thank you.

10 DR. YASZEMSKI: Thanks very much, Dr.
11 Swiontkowski.

12 I would now like to ask Mr. Demian to read
13 the voting instructions for the panel.

14 Vote

15 MR. DEMIAN: I will now provide you with
16 the panel recommendation options for premarket
17 approval applications.

18 "The Medical Device Amendments to the
19 Federal Food, Drug, and Cosmetic Act require that
20 the Food and Drug Administration obtain a
21 recommendation from an outside advisory expert
22 panel on designated medical device pre-market
23 approval applications that are filed with the
24 agency."

25 "The PMA must stand on its own merits, and

1 the recommendations must be supported by safety and
2 effectiveness data in the application or by
3 applicable, publicly available information."

4 "Safety is defined in the Act as
5 reasonable assurance, based on valid scientific
6 evidence, that the probable benefits to health
7 under the conditions of use outweigh any probable
8 risks."

9 "Effectiveness is defined as reasonable
10 assurance that in a significant portion of the
11 population, the use of the device for its intended
12 uses and conditions of use when labeled will
13 provide clinically significant results."

14 "Your recommendation options for the vote
15 are as follow: 1) Approval. There are no
16 conditions attached. 2) Approvable with
17 conditions. You may recommend that the PMA be
18 found approvable subject to specified conditions
19 such as a resolution of clearly identified
20 deficiencies which have been cited by you, the
21 panel, or FDA staff. All the conditions are
22 discussed by the panel and listed by the panel
23 chair and then voted on one by one. For example,
24 you may specify what type of follow-up information
25 the panel or FDA should evaluate prior to or after

1 approval. Panel follow-up is usually done through
2 homework assignments by one or two panel primary
3 reviewers or to other specified members of this
4 panel. A formal discussion of the application at a
5 future panel meeting is not usually held."

6 "If you recommend a post-approval
7 requirement to be imposed as a condition of
8 approval, then your recommendation should address
9 the following points: The purpose of the
10 requirement, the number of subjects to be
11 evaluated, and the types of reports that should be
12 submitted."

13 The third option is not approvable. Of
14 the five reasons the Act specifies for denial of
15 approval, the following three reasons are
16 applicable to your panel deliberations: The data
17 to not provide reasonable assurance that the device
18 is safe under the conditions of use prescribed,
19 recommended, or suggested in the proposed labeling;
20 reasonable assurance has not been given that the
21 device is effective under the conditions of
22 prescribed use recommended or suggested in the
23 labeling; and based on a fair evaluation of all
24 material facts in your discussions, you believe the
25 proposed labeling to be false or misleading."

1 "If you recommend that the application is
2 not approvable for any of these stated reasons,
3 then we ask that you identify the measures that you
4 think are necessary for the application to be
5 placed in approvable form. Traditionally, the
6 consumer representative and the industry
7 representative do not vote, and Dr. Yaszemski, as
8 panel chairman, votes only in the case of a tie."

9 Dr. Yaszemski?

10 DR. YASZEMSKI: Thank you very much, Mr.
11 Demian.

12 Before beginning the voting process, I
13 would like to make a point of procedure that was
14 brought up to me, that the sponsors are not
15 supposed to be at the presenters' table during the
16 vote. I recognize the chairs are all tight, but
17 could I just ask you to perhaps back up a little
18 bit or move the table up a little bit? If that's
19 okay with FDA, we'll just do it that way.

20 Thanks very much.

21 The other point is that I'd like to
22 mention both for the panel's benefit and for the
23 record that votes taken are votes for or against
24 the motion made by the panel. Votes are not votes
25 in favor of or against the product.

1 At this time, I would like to ask if there
2 is a motion to be made.

3 MS. MAHER: Just before the motion.

4 DR. YASZEMSKI: Okay, before the motion,
5 Ms. Maher.

6 MS. MAHER: I would just like to clarify
7 one thing that I have heard twice now and I'm a
8 little concerned with.

9 Dr. Naidu brought up the fact that this is
10 a drug. In fact, it is not a drug. Under U.S.
11 law, it is regulated as a device, which means we
12 are looking for reasonable assurance of safety and
13 effectiveness, as opposed to the drug standard. As
14 we are moving forward to the vote, I would like the
15 panel to remember that.

16 DR. YASZEMSKI: Thank you for that point
17 of clarification, Ms. Maher.

18 Dr. Finnegan?

19 DR. FINNEGAN: Mr. Chairman, you were
20 looking for a motion.

21 DR. YASZEMSKI: Yes, ma'am.

22 DR. FINNEGAN: Actually, I think this is
23 part of my job description. This was fairly
24 difficult, but taking into account what Hany has
25 just outlined, I think there is reasonable

1 assurance that this is safe. I am less sure that
2 there is reasonable assurance that it is very
3 effective, but it certainly is not deleterious.

4 So my motion is that it be approved with a
5 boatload of conditions.

6 DR. YASZEMSKI: Thank you.

7 DR. LARNTZ: Second.

8 DR. YASZEMSKI: The motion has been
9 seconded.

10 Before we go to discussion, I'm going to
11 mention another point of protocol. We will
12 entertain, after Dr. Finnegan's conditions which
13 she will read, a discussion regarding addition of
14 conditions or deletion of conditions; we will
15 discuss and vote on each of them independently, and
16 after we have had that discussion, we will re-read
17 the motion as it stands with conditions that have
18 already been voted for inclusion or exclusion and
19 then vote on that motion.

20 Dr. Finnegan, may we hear your conditions?

21 DR. FINNEGAN: Do you want all of them, or
22 one at a time?

23 DR. YASZEMSKI: Let's hear all of them,
24 because they constitute your motion. Then, we'll
25 ask others if they want to add or subtract.

1 DR. FINNEGAN: All right. My first
2 condition is that this should be limited to Grade
3 III open fractures which have been stabilized and
4 the material placed at definitive wound closure.

5 My second condition is that the users
6 should be educated on the potential benefit of
7 adding osteogenic material to this composite.

8 My third condition is that labeling in
9 very large letters needs to deal with unknown
10 factor of repeat use and that perhaps this also be
11 education for the users.

12 My fourth condition is that there need to
13 be two studies on the antibodies just so we have
14 the knowledge. I think part of the problem is that
15 we don't have any knowledge. I think there could be
16 a natural history study done on the 1,096 patients
17 who have already received this material, and then a
18 prospective study, either animal or human or
19 perhaps both, and I would leave that up to the
20 sponsor and FDA to work out.

21 And my last condition is that I think it
22 is mandatory that there be post-market
23 surveillance, and what are the things they need to
24 answer for that?

25 DR. YASZEMSKI: Thank you.

1 Those are the five conditions.

2 Dr. Witten?

3 MS. WITTEN: I was going to answer Dr.
4 Finnegan's question, but perhaps Hany already did.

5 DR. FINNEGAN: My right hand already did.
6 Okay.

7 The purpose of the requirement is to
8 further define the efficacy of the implant. The
9 reason for choosing the Grade III opens is that it
10 will limit undue exposure to the antibodies until
11 we know the antibody history, and these are also
12 the patients who require the maximum help to get
13 their fractures to heal.

14 The number of subjects to be evaluated I
15 think is a number that would produce statistically
16 useful information, and again I would leave that up
17 to the sponsor and the FDA. And the types of
18 reports that should be submitted I would think
19 would be a composite of this study perhaps with the
20 design improved per the recommendations of the
21 panel and the FDA clinical reviewer.

22 You are looking rather perplexed.

23 MS. WITTEN: Can you just explain the
24 objective of the study again?

25 DR. FINNEGAN: The purpose of the study?

1 MS. WITTEN: Yes.

2 DR. FINNEGAN: It would be to--how am I
3 going to word this--to further elucidate the
4 potential effectiveness of this composite. Okay,
5 you don't like that.

6 MS. WITTEN: It's your motion.

7 DR. FINNEGAN: But I want you to buy
8 it--that's the problem.

9 MS. WITTEN: It's your motion.

10 DR. FINNEGAN: Thank you.

11 Dr. Kirkpatrick has it--to clarify the
12 effectiveness of this material as it has been
13 somewhat muddy to the panel.

14 DR. YASZEMSKI: That's the motion as
15 stands.

16 Discussion for modifications, additions,
17 deletions?

18 Dr. Aboulafia?

19 DR. ABOULAFIA: I think to limit it to
20 just Grade III open fractures may have a
21 theoretical advantage that you are going to try to
22 help most those who need it the most. But I think
23 the truth of the matter is that a problem fracture
24 or a high-risk fracture is not simply just a Grade
25 III fracture. Again, we talked about issues of

1 comorbidities, diabetics, steroid users, distal
2 third fractures versus proximal third fractures,
3 and I think we need to leave that up to the
4 judgment of the treating physician to define what
5 he or she considers to be a potential problem
6 fracture or a patient who may benefit from this
7 project if we're saying there is a theoretical
8 advantage to using this product to promote fracture
9 healing in long bones treated with intramedullary
10 nails.

11 DR. YASZEMSKI: Is your motion to modify
12 or delete one of Dr. Finnegan's conditions?

13 DR. ABOULAFIA: I would modify it with
14 saying that the indications would be those patients
15 for whom intervention is thought to be beneficial.

16 DR. YASZEMSKI: There is a motion to
17 change Dr. Finnegan's condition of limitation to
18 Grade III open fractures--and I'm going to
19 paraphrase, Dr. Aboulafia, so you tell me if I say
20 it right--to those open fractures of any grade that
21 in the opinion of the treating surgeon represent a
22 problem fracture that could benefit from the
23 device.

24 DR. ABOULAFIA: Dr. Aboulafia is nodding
25 yes.

1 DR. YASZEMSKI: Is there a second to that
2 motion?

3 DR. LARNTZ: I'll second.

4 DR. YASZEMSKI: Okay. Dr. Finnegan--

5 DR. KIRKPATRICK: Is that tibia only?

6 DR. YASZEMSKI: This is tibias, yes, sir.

7 Okay. We're going to go around and vote
8 on Dr. Aboulafia's modification, Dr. Finnegan, to
9 your motion.

10 Do you have commentary on that?

11 DR. FINNEGAN: Well, yes. Actually, I
12 think we already previously said for labeling that
13 this could be any fracture, so this is not just the
14 tibia--Grade III open fracture of any long bone.

15 DR. YASZEMSKI: Dr. Aboulafia, would that
16 be okay with your motion--any Grade III open
17 fracture that the clinician considers a problem?

18 DR. ABOULAFIA: I don't know. Does the
19 panel want to extrapolate the data?

20 DR. YASZEMSKI: If you make that motion,
21 we'll vote on it.

22 DR. FINNEGAN: My motion was not to limit
23 it to tibias. My motion was to limit it to Grade
24 III open fractures.

25 DR. ABOULAFIA: Okay, yes.

1 DR. YASZEMSKI: Okay. We're going to go
2 around the vote. We're going to vote on a change
3 in Dr. Finnegan's first condition. Her first
4 condition was that this device approval, condition
5 of approval, be that the device be limited to Grade
6 III open fractures.

7 Dr. Aboulafia has made a motion to change
8 that condition to any open fracture that in the
9 opinion of a treating surgeon is a problem fracture
10 that could benefit from use of the device.

11 Dr. Doull, yes or no?

12 DR. DOULL: Yes.

13 DR. YASZEMSKI: Dr. Kirkpatrick?

14 DR. KIRKPATRICK: Yes.

15 DR. YASZEMSKI: Dr. Finnegan?

16 DR. FINNEGAN: No.

17 DR. YASZEMSKI: Dr. Naidu?

18 DR. NAIDU: No.

19 DR. YASZEMSKI: Dr. Larntz?

20 DR. LARNTZ: Yes.

21 DR. YASZEMSKI: Dr. Schmidt?

22 DR. SCHMIDT: Yes.

23 DR. YASZEMSKI: Dr. Aboulafia?

24 DR. ABOULAFIA: Yes.

25 DR. YASZEMSKI: The motion passes. So

1 Condition 1 of Dr. Finnegan's motion for approval
2 with conditions is that this device be limited to
3 any open fracture that in the opinion of the
4 treating surgeon is a problem fracture and would
5 benefit from the use of the device.

6 Are there any other motions for additions,
7 deletions, or changes to Dr. Finnegan's conditions?

8 DR. KIRKPATRICK: I have a question of
9 clarification.

10 DR. YASZEMSKI: Go ahead, Dr. Kirkpatrick.

11 DR. KIRKPATRICK: When you talk about
12 safety on the immune response, are you talking
13 about a secondary challenge once someone has
14 converted positive, or an animal has converted
15 positive?

16 DR. FINNEGAN: That is why I said I would
17 leave the study up to the sponsor. I think it
18 probably needs to be a combination of an animal and
19 perhaps a person over a period of time, especially
20 if the natural history shows that the antibodies
21 seem to disappear fairly quickly.

22 DR. KIRKPATRICK: So basically, if the FDA
23 consults with an immunologist and feels that a
24 secondary challenge study is not necessary, we
25 would go with that.

1 DR. FINNEGAN: Yes.

2 DR. YASZEMSKI: Dr. Doull?

3 DR. DOULL: Well, in that case, then, if
4 you do that study, will you do the history of the
5 antibody response and you determine in people and
6 in animals what that means, then you don't really
7 need the labeling requirement--

8 MR. DEMIAN: Speak into the mike, please.

9 DR. DOULL: The labeling requirement which
10 says do not repeat--once you have that information,
11 you would no longer need that labeling requirement?

12 DR. FINNEGAN: That is correct, but that
13 would be withdrawn down the road, because this is
14 going to take some time.

15 DR. DOULL: Okay.

16 DR. YASZEMSKI: Thank you.

17 Other motions for additions,
18 modifications, or deletions to Dr. Finnegan's
19 conditions?

20 DR. KIRKPATRICK: Yes.

21 DR. YASZEMSKI: Dr. Kirkpatrick?

22 DR. KIRKPATRICK: One further condition.
23 I would like the sponsor and the FDA to work out
24 assurances of a statistical nature that the fibula
25 fracture fixation had no effect on either the

1 primary or secondary endpoints and also was not
2 utilized in more fractures that were more severely
3 comminuted, for example, in other words, the AOCs
4 as opposed to the AOAs. If they can provide that
5 information to the FDA, and everybody feels that
6 that is statistically fine, I would say that we
7 could proceed with approval.

8 DR. YASZEMSKI: This is a motion for the
9 addition of a condition regarding looking at the
10 presence of the fibula fractures in the study and
11 that the sponsor would get this data together for
12 the FDA.

13 Is there a second, first, before we
14 discuss it?

15 DR. LARNTZ: I'll second.

16 DR. YASZEMSKI: There is a second.

17 Discussion, Dr. Larntz.

18 DR. LARNTZ: If it would be all right with
19 Dr. Kirkpatrick, I would like to expand that to the
20 use of reamed and unreamed nails also, as a
21 covariate to the study.

22 DR. YASZEMSKI: If everybody is okay--Dr.
23 Kirkpatrick, it is your motion. If you are okay
24 with adding that to it--

25 DR. KIRKPATRICK: I would prefer the two

1 issues remain separate.

2 DR. YASZEMSKI: Okay. We're going to keep
3 it separate.

4 Discussion?

5 [No response.]

6 DR. YASZEMSKI: Let's vote.

7 Dr. Aboulafia?

8 DR. ABOULAFIA: In favor of Dr.
9 Kirkpatrick's motion.

10 DR. YASZEMSKI: Dr. Schmidt?

11 DR. SCHMIDT: In favor.

12 DR. YASZEMSKI: Dr. Larntz?

13 DR. LARNTZ: Yes.

14 DR. YASZEMSKI: Dr. Naidu?

15 DR. NAIDU: Can I abstain?

16 DR. YASZEMSKI: Yes, you may abstain.

17 DR. NAIDU: I abstain.

18 DR. YASZEMSKI: Abstention.

19 Dr. Finnegan?

20 DR. FINNEGAN: Yes.

21 DR. YASZEMSKI: Dr. Kirkpatrick?

22 DR. KIRKPATRICK: Yes.

23 DR. YASZEMSKI: Dr. Doull?

24 DR. DOULL: Yes.

25 DR. YASZEMSKI: The motion passes.

1 There is now a sixth condition.

2 Any other discussion, additions,
3 deletions?

4 DR. ABOULAFIA: Can you repeat each one?

5 DR. YASZEMSKI: Seeing none, we're going
6 to do this. I'm going to go over Dr. Finnegan's
7 motion as it is now with the conditions and then
8 call for a vote, unless there is any further
9 discussion that anybody would like to bring up.

10 DR. KIRKPATRICK: Excuse me. Just a point
11 of order. There was a suggestion about looking at
12 nonreamed and reamed nails.

13 DR. YASZEMSKI: I asked for another motion
14 and heard none.

15 DR. KIRKPATRICK: Okay.

16 DR. YASZEMSKI: Thank you.

17 The motion is for approval with
18 conditions. There are six conditions--number one,
19 that the use of the device be limited to open
20 fractures that in the opinion of the treating
21 surgeon represent a problem fracture that would
22 benefit in his or her clinical judgment from the
23 use of the device; number two, that there be user
24 education regarding this device; number three, that
25 the labeling include a statement that the factor of

1 repeated use is at present unknown with respect to
2 antibodies; number four, that there be two studies
3 on antibodies, one, a natural history study of the
4 1,096 patients who already have been in the study,
5 and number two, either an animal or a human study
6 as determined by the sponsor and the FDA; number
7 five, that there be post-market surveillance to
8 clarify the issue of acceleration of fracture
9 healing; number six, that the sponsor and the FDA
10 will work out the statistics regarding the presence
11 of a fibula fracture and whether, when accounted
12 for, that fibula fracture had any effect on the
13 results as presented.

14 This is the motion. Would anybody like to
15 discuss it further?

16 DR. KIRKPATRICK: The motion was fibula
17 fracture fixation.

18 DR. YASZEMSKI: Thank you for that
19 clarification, Dr. Kirkpatrick. Fibula fracture
20 fixation. Thank you.

21 Further discussion?

22 [No response.]

23 DR. YASZEMSKI: We're going to vote.

24 Dr. Aboulafia?

25 DR. ABOULAFIA: In favor.

1 DR. YASZEMSKI: Dr. Schmidt?

2 DR. SCHMIDT: In favor.

3 DR. YASZEMSKI: Dr. Larntz?

4 DR. LARNTZ: Yes.

5 DR. YASZEMSKI: Dr. Naidu?

6 DR. NAIDU: No.

7 DR. YASZEMSKI: Dr. Finnegan?

8 DR. FINNEGAN: Yes.

9 DR. YASZEMSKI: Dr. Kirkpatrick?

10 DR. KIRKPATRICK: Yes.

11 DR. YASZEMSKI: Dr. Doull?

12 DR. DOULL: Yes.

13 DR. YASZEMSKI: The motion passes.

14 Thank you.

15 Mr. Demian?

16 MR. DEMIAN: We are going to go around the
17 room and ask people why they voted the way they
18 did.

19 DR. YASZEMSKI: Thank you.

20 Dr. Witten, thank you for reminding us of
21 this important function.

22 What we are going to do for the benefit of
23 the FDA and the sponsor and the public at-large is
24 poll the panel and ask each of them why they voted
25 the way they did and what they consider the

1 positives and negatives that affected their vote.

2 Dr. Aboulafia?

3 DR. ABOULAFIA: I think this is one of
4 those things where sponsor may not appreciate my
5 help. I think a large portion of this decision was
6 based on the safety, which I think it is a safe
7 product.

8 I think the issue of effectiveness is at
9 best weakly demonstrated. And my hope is that with
10 the power of some of the coinvestigators who have
11 national and international reputations both in
12 fracture management and in study design, they may
13 be able to better design a study that will clearly
14 demonstrate the effectiveness of this product, and
15 that what I am really allowing is fair market or
16 free society to determine whether the cost-benefit
17 analysis is worthwhile or not.

18 DR. YASZEMSKI: Thanks, Dr. Aboulafia.

19 Dr. Schmidt?

20 DR. SCHMIDT: I agree with Dr. Aboulafia's
21 comments whole-heartedly and have no other ones to
22 add.

23 DR. YASZEMSKI: Thank you.

24 Dr. Larntz?

25 DR. LARNTZ: I believe this product is

1 safe. I believe they have shown effectiveness with
2 respect to secondary intervention. With respect to
3 other endpoints, I think it is quite questionable.

4 DR. YASZEMSKI: Thanks, Dr. Larntz.

5 Dr. Naidu?

6 DR. NAIDU: I said "no" mainly because in
7 my opinion, the preclinical data is mixed; the
8 clinical data has too many confounding factors, as
9 previously presenters have clearly demonstrated;
10 x-ray data was not complete. Healing criteria was
11 varied for secondary intervention groups, and I
12 just did not feel right voting "yes" for it.

13 Thank you.

14 DR. YASZEMSKI: Thanks, Dr. Naidu.

15 Dr. Finnegan?

16 DR. FINNEGAN: I have to sort of agree
17 with Dr. Naidu in that I do think that both the
18 sponsor and some of the investigators are capable
19 of a much better study, and I agree with Dr.
20 Aboulafia that I hope that will in fact occur.

21 But I do think it is safe, and I do think
22 there are patients who will actually benefit from
23 its use.

24 DR. YASZEMSKI: Thanks, Dr. Finnegan.

25 Dr. Kirkpatrick?

1 DR. KIRKPATRICK: I think the
2 effectiveness data is borderline. I hope that the
3 fibula does not cause any change in my opinion that
4 I think it is marginally effective, or does offer
5 some improvement.

6 I think with the condition that we have on
7 the safety issue with regard to the antibody
8 response, if that is satisfactory, then I think it
9 is a reasonable decision to go approval.

10 DR. YASZEMSKI: Thanks, Dr. Kirkpatrick.

11 Dr. Doull?

12 DR. DOULL: The issues are safety and
13 effectiveness, and as a clinical toxicologist, I am
14 of course influenced primarily by the safety issue.
15 But I think the arguments presented for efficacy,
16 weakly efficacious, are satisfactory to me.

17 DR. YASZEMSKI: Thanks, Dr. Doull.

18 Dr. Witten, have we adequately discussed
19 this to FDA's satisfaction?

20 MS. WITTEN: Yes. Thank you.

21 DR. YASZEMSKI: Thanks very much, Dr.
22 Witten.

23 Thanks, everybody on the panel.

24 We're going to take a 5-minute break now,
25 and then reconvene.

1 [Break.]

2 General Panel Discussion of Spinal Devices

3 DR. YASZEMSKI: I'll ask everyone to
4 please take their seats, and we're going to get
5 started with the spinal portion of today's meeting.

6 We are going to have a general panel
7 discussion regarding spinal devices this afternoon.
8 FDA has provided us with a list of preclinical and
9 clinical questions related to the evaluation of
10 fusion and nonfusion spinal devices.

11 We are going to have an open public
12 hearing session regarding this general discussion
13 on spinal devices, and we have had six persons who
14 have requested speaking time.

15 I will mention to the folks in the
16 audience that these folks have put handouts outside
17 the door, if anybody is interested in getting them.

18 We are going to ask the speakers, please,
19 in the interest of keeping on time, to limit your
20 comments to 5 minutes. Each of the six speakers
21 will have 5 minutes to speak.

22 I would ask that all persons addressing
23 the panel come forward and speak directly into the
24 microphone, as the transcriptionist is dependent on
25 this means for providing an accurate record of the

1 meeting. And we request again that all persons
2 making statements during the open public hearing
3 disclose whether they have financial interest in
4 any medical device company.

5 Before making your presentation to the
6 panel, please state your name, your affiliation,
7 and the nature of your financial interest, if any.

8 The first person will be Mr. Antonio
9 Valduvit [phonetic].

10 Are you here, sir?

11 [No response.]

12 DR. YASZEMSKI: Not in attendance.

13 The next person who has asked to speak is
14 Ms. Brenda Seidman.

15 Is she here? Thank you. Welcome.

16 Open Public Hearing

17 DR. SEIDMAN: My name is Dr. Brenda
18 Seidman, of Seidman Toxicology Services. I am
19 both a general and neurotoxicologist and an active
20 participant in six ISO 10993 committees. ISO 10993
21 is the international standard on the biological
22 evaluation of devices.

23 I have served as a consultant to
24 orthopedics manufacturers over the last several
25 years. Today I represent myself.

1 My purpose in speaking today is to respond
2 to FDA's proposal to include a requirement for
3 particle injection studies in its spinal implant
4 guidance documents.

5 As a participant in the ISO 10993
6 standard-setting process, I suspect the agency may
7 be confusing foreign body reactions with
8 chemically-induced toxicity. Foreign body
9 reactions are inflammatory reactions that appear to
10 be related to the loosening of orthopedic implants.
11 Such reactions are responses to the physical
12 properties of a material, such as size, shape, and
13 surface properties.

14 Chemical toxicity related to a device is a
15 biological response to its chemical leachates.

16 ISO 10993 currently addresses chemical but
17 not foreign body reactions. As such, ISO 10993 is
18 the most appropriate mechanism for addressing
19 chemical toxicity. For those unfamiliar with the
20 standard, it addresses the chemical toxicity of
21 materials from finished devices by several means,
22 including chemical characterization, clinical
23 history of use, the scientific literature, and in
24 vitro and in vivo testing on both extracts of the
25 material and on the material itself.

1 Potential chemical toxicity related to
2 wear debris can and should be addressed using ISO
3 10993.

4 The agency may be concerned that fatigued
5 materials might be chemically different than
6 non-fatigued materials. Although I am personally
7 unaware of such changes, manufacturers would need
8 only to demonstrate that chemical differences do
9 not exist in order to rely on their ISO 10993
10 evaluations of their devices' non-fatigued
11 materials from their finished devices.

12 Next transparency, please. I'll go on for
13 the sake of time.

14 Now with regard to testing for foreign
15 body reactions. The agency appears to have made
16 the assumption that in vivo testing is the only or
17 most suitable means of testing for foreign body
18 inflammation. To my knowledge, neither ISO nor
19 ASTM have developed or validated a test method in
20 vitro or in vivo for an evaluation of foreign body
21 effects.

22 Therefore, it makes sense to consider the
23 possible use of in vitro test methods. In vitro
24 tests have the potential be more sensitive and
25 focused, raise no animal welfare issues, could be

1 performed in a shorter period of time, and would be
2 less costly and burdensome to industry.
3 Furthermore, it may not be reasonable to assume
4 that a device's wear debris from an animal model
5 will be sufficiently similar to that generated
6 after implantation in humans. Wouldn't there be
7 different wear and load scenarios that would be
8 difficult if not impossible to replicate using an
9 in vivo model?

10 Second, with all due respect to FDA and
11 the panel, isn't there value in developing proposed
12 biological testing methods within larger consensus
13 groups, such as relevant ISO and ASTM working
14 groups? In the interim, is there value in
15 requiring manufacturers to develop and perform
16 nonvalidated tests with objectives not carefully
17 articulated by the agency?

18 Third, should the agency's goal be to use
19 the medical device industry as a methods incubator?
20 While methods need to be developed to characterize
21 the risks associated with wear debris, it is
22 unlikely that forcing the development of methods
23 into the submissions process is scientifically
24 justifiable, effective, consistent with animal
25 welfare regulations, or otherwise ethical.

1 I have provided the panel with numerous
2 technical questions regarding proposed testing, and
3 those are made available outside on the table.
4 Unfortunately, these questions are impossible to
5 fully present within my allotted time.

6 To summarize, however, my questions relate
7 to the following: The rationale for performing
8 foreign body evaluations when no wear debris is
9 generated under physiological conditions; the
10 characteristics of wear debris we consider relevant
11 to foreign body reaction; the dynamic aspects of
12 particle generation; the possible role of
13 pre-existing pathology; and the considerations for
14 selecting the most appropriate model for either an
15 in vitro or in vivo test.

16 Last, given the need for basic
17 research--not research as part of a submissions
18 process; they are two different things--I would
19 like the panel to come up with suggestions on what
20 the agency and industry can do to satisfy debris
21 safety concerns while validated methods are being
22 developed. In other words, how do we get from here
23 to there?

24 Thank you.

25 DR. YASZEMSKI: Thanks very much, Dr.

1 Seidman.

2 Next, Diane Johnson.

3 MS. JOHNSON: My name is Diana Johnson. I
4 am a full-time employee of Medtronic Spinal
5 Dynamics.

6 With respect to one of the questions posed
7 by FDA, Spinal Dynamics is requesting that the
8 advisory panel specifically consider FDA's position
9 on durability testing and its relationship to wear
10 particulate testing.

11 In the questions, FDA suggests durability
12 testing should be conducted and the loads and
13 motions utilized in the testing should be
14 justified.

15 In a related question, FDA is also
16 requesting information related to the biologic
17 effects of particulate that is generated by devices
18 following implantation.

19 Spinal Dynamics is requesting that the
20 panel consider the following specific questions.

21 Simulation testing for hips and knees is
22 conducted utilizing loads and motion representative
23 of activities of daily living, as opposed to
24 maximum loads and motions. This approach is based
25 on 20 years of research which shows that explanted

1 devices show wear similar to that produced during
2 simulation testing conducted at the ADL load and
3 motion profile. This testing methodology is
4 currently recommended in ASTM testing methodologies
5 for hips and knees, which indicate that loads and
6 motions should be those associated with walking.

7 In light of the correlation that is
8 clearly established for other joints, is it
9 appropriate to perform simulation testing for
10 functional devices at activities of daily living or
11 at maximum loads and motions at some time suggested
12 by FDA?

13 If the biologic effect of particulate is
14 approximated using simulator-generated particulate,
15 should the particle size and distribution and
16 quantity be determined using a load and motion
17 profile associated with the activities of daily
18 living?

19 If the biologic effect of particulate is
20 approximated using particulate generated in an
21 animal model, there is likely to be some level of
22 nonphysiologic loading, especially if a quadruped
23 is utilized. This may result in the production of
24 particles that would not be generated in humans
25 under physiologic loading.

1 Does the generation of particulate due to
2 nonphysiologic loading necessarily invalidate the
3 model in terms of the evaluation of effects of
4 particulate that is wear-generated in the model?

5 Thank you.

6 DR. YASZEMSKI: Thank you very much.

7 Next, Dr. Bailey Lipscomb.

8 DR. LIPSCOMB: Members of the panel, my
9 name is Bailey Lipscomb, and I am Vice President of
10 Clinical Affairs at Medtronic Sophomore Danik in
11 Memphis, Tennessee. We appreciate the opportunity
12 to make a few comments concerning issues that
13 affect our IDE clinical studies both for nonfusion
14 and for fusion spinal implants.

15 First, after having sponsored numerous
16 clinical trials on spinal implants, we believe that
17 Oswestri [phonetic] pain success should be based on
18 a percent improvement from baseline rather than the
19 current FDA-mandated 15-point improvement. This
20 recognizes that preoperative scores have a
21 substantial range and that it is easier for a
22 patient with a preoperative score of 80 to improve
23 15 points as opposed to a preoperative score of 40.

24 We recommend a success for Oswestri
25 [phonetic] or its cervical counterpart, the MDI, be

1 a 20 percent improvement form baseline.

2 Second, we are concerned about FDA's
3 recent condition on assessing neurological status
4 in IDE clinical study patients. This is a very
5 important consideration, since neurological status
6 is one of the components of the overall success
7 criteria which is the primary outcome variable.

8 Along with neurological success, you have
9 fusion, you have pain success, and you have no
10 serious device-related safety issues. These are
11 the components of overall success. Therefore,
12 anything affecting neurological success directly
13 impacts the overall success rate and ultimate
14 conclusions from the study.

15 Heretofore, the premise for classifying a
16 patient as a neurological success is that their
17 overall neurological condition after surgery is no
18 worse than it was before surgery, and there were
19 means for summarizing the approximately 40-plus
20 assessments of sensory, motor function, and
21 reflexes to make this determination.

22 Recently, FDA has required that
23 neurological success be based on no worsening of
24 any single measurement in the entire neurological
25 assessment. Stated another way, if any one of the

1 40 post-operative measurements is worse than the
2 preoperative measurement, then the person is a
3 neurological failure and therefore an overall
4 success failure for the study.

5 Stated another way, a person could be
6 fused, have dramatic pain relief, no adverse event,
7 and intact both in terms of sensory and motor
8 function, but could be a neurological and an
9 overall failure because one reflex measurement
10 after surgery was worse than the preoperative
11 measurement. And that is in light of the fact that
12 other reflex measurements could have improved.

13 We believe that FDA's current requirement
14 for interpreting neurological results exceeds the
15 prior intent of discerning whether a patient is as
16 neurologically intact after surgery as before. We
17 believe this new directive may misrepresent the
18 true neurological status of study patients and will
19 inappropriately lower study success rates.

20 The third point pertains to unnecessarily
21 large clinical study sizes. As you are aware, many
22 spinal implant studies are noninferiority trials in
23 which investigational treatment is compared to a
24 standard of care control. Sample sizes for these
25 studies are primarily impacted by two factors--one,

1 the overall success rate for the study, and two,
2 the noninferiority margin. I will not dwell on the
3 overall success rates, even though their
4 multi-component nature drives their values toward
5 50 percent in higher sample sizes. Rather, I want
6 to focus on the selection of the noninferiority
7 margin, or delta.

8 The impact of delta selection is dramatic.
9 A difference of one percentage point can add 100
10 patients to an overall study size. Presently, FDA
11 advises that delta not exceed 10 percent regardless
12 of the success rate. We believe that this
13 one-size-fits-all approach is inappropriate and
14 that delta should vary with the success rate. For
15 example, in a range of success rates between 50 and
16 95 percent, the delta could vary between 12-1/2 and
17 7-1/2 percent, respectively. Statistical
18 literature supports our proposal.

19 The deltas described above will yield a
20 sample size of about 450 patients in a two-arm
21 study, adequate enough to characterize the safety
22 and effectiveness of a spinal implant. Otherwise,
23 the sample sizes can approach 700 patients.
24 Clinical studies of this magnitude are very
25 burdensome, delay the availability of new

1 technologies to surgeons, discourage the pursuit of
2 new treatment modalities, and most importantly, are
3 unnecessary.

4 If you are concerned that you may approve
5 a device that is observed to be more than 10
6 percent worse than the control, the reality is that
7 this won't happen. Even with a delta of 12-1/2
8 percent and a sample size of 450 patients,
9 noninferiority could not be claimed if the observed
10 control success rate were 60 percent versus a 55
11 percent rate for the investigational group--only 5
12 points different.

13 In conclusion, we appreciate the panel
14 considering these three points and would like to
15 thank FDA for the opportunity to make these
16 comments.

17 Thank you.

18 DR. YASZEMSKI: Thanks very much.

19 Dr. Jansen?

20 DR. JANSEN: My name is Rich Jansen. I am
21 Vice President of Regulatory and Clinical Affairs
22 at Disc Dynamics, Incorporated.

23 Disc Dynamics is an early-stage medical
24 device company in the Minneapolis area, developing
25 a disc nucleus prosthesis.

1 I would like to comment on three issues
2 being discussed here today. First, I would like to
3 suggest that the radiographic endpoint of measuring
4 fusion or motion on flexion and extension films
5 should be a secondary success criterion. I have
6 talked with many surgeons who have argued that
7 patients do not come to their offices requesting a
8 fusion. Their concern is that they have
9 intolerable pain, they cannot go to work, they
10 cannot pick up their kids, and other activities of
11 daily living.

12 Study success should be measured as
13 clinical improvement such as pain and function. We
14 should measure and report range of motion using
15 flexion and extension films, but this should be a
16 secondary endpoint.

17 Regardless of the final radiographic
18 results, it is the patients that we should be
19 concerned about, and patients will consider their
20 surgery a success if they have manageable pain, can
21 go back to work and function in their usual daily
22 activities.

23 Secondly, I would like to point out that
24 we have been unable to find an acceptable model for
25 a disc nucleus prosthesis. With regard to the

1 baboon, which is the most frequently suggested
2 model, this may be a good model for fusion devices
3 or for total disc replacements, but not for disc
4 nucleus replacements.

5 We conducted the study using a baboon
6 model and found several limitations with this
7 model, with less than desirable results. The disc
8 space is so narrow that even in the hands of a very
9 good and experienced surgeon doing animal research
10 with this model, many of the endplates were damaged
11 during surgery in both the sham-operated level and
12 the nucleus-implanted level, indicating that this
13 was a result of the discectomy procedure, not the
14 device.

15 In addition, the nucleus cavity in the
16 baboon is so small that the portal of entry to gain
17 access to the nucleus is about the same size as the
18 implant, leading to a high rate of extrusion. This
19 is not at all the case in humans, where the nucleus
20 cavity and implant size are many times larger than
21 the access port needed to implant the Disc Dynamics
22 device.

23 Finally, we found extensive heterotopic
24 ossification in both the sham-operated levels and
25 the implanted disc levels at 3 months. These

1 issues make this model unsuitable for mechanical
2 evaluations.

3 We have also tried the mini pig model and
4 found the same limitations with that as we did with
5 the baboon model.

6 So unfortunately, we do not believe that
7 there is an adequate model to address disc nucleus
8 prostheses at this time.

9 The third issue I would like to address is
10 a statement made in the draft questions for this
11 meeting. these are the draft questions dated
12 11-12-02. There is one sentence in here that I
13 would like to read.

14 "Because devices not intended for fusion
15 are intended to stabilize the spinal motion segment
16 and retain functional motion, they must be designed
17 to last the lifetime of the individual rather than
18 until fusion has occurred."

19 Total disc replacements and disc nucleus
20 replacements are frequently referred to as spine
21 arthroplasty devices. If we look at our orthopedic
22 counterparts at hip and knee arthroplasty, we know
23 that they are not expected to last the lifetime of
24 all patients. Based on the type of spine
25 arthroplasty device, there are some devices that do

1 not preclude reasonable and appropriate follow-up
2 surgical procedures if required.

3 I would like to suggest that we look at
4 each type of device before concluding that all
5 spine arthroplasty devices must be designed as
6 lifetime implants.

7 Thank you for the opportunity to consider
8 these issues.

9 DR. YASZEMSKI: Thank you.

10 Dr. Norton?

11 DR. NORTON: My name is Britt Norton, and
12 I am Vice President of Research and Development
13 with Raymedica in Minneapolis.

14 Mr. Chairman, distinguished members of the
15 panel, thank you for the opportunity to speak with
16 you.

17 We agree with the objectives and many of
18 the concepts in the spinal guidance document and
19 draft questions, but there are a few areas that we
20 feel merit further discussion.

21 [Slide.]

22 In developing test methods for prosthetic
23 disc nucleuses, which I am going to focus on today,
24 the fundamental differences between the nucleus
25 replacement and fusion must be recognized.

1 Specifically, nucleus devices are intended to
2 maintain segmental motion and perform their
3 stabilization in that manner. Fusion devices, of
4 course, are intended to eliminate segmental motion.

5 Nucleus devices are intended to function
6 in concern with the surrounding tissues of the
7 endplates, the annulus, the ligaments, and the
8 facette joints. Fusion devices, of course,
9 generally render the surrounding tissues more
10 nonfunctional.

11 [Slide.]

12 These differences in approach to
13 stabilization are reflected in device function and
14 the component materials as well. Nucleus devices
15 are intended to mimic load-deformation behavior of
16 a normal disc, while fusion devices replace that
17 normal disc with solid bone mass.

18 Current designs for nucleus devices
19 utilize elastomeric polymers, which have a high
20 strain capability and high energy absorption
21 capability. Of course, fusion materials are rigid;
22 the metals are polymer composites possessing low
23 strain and are more energy-transmitting than
24 absorbing.

25 Elastomeric materials used in nucleus

1 devices have high fatigue durability, more metals,
2 and fusion devices are prone to embrittlement
3 following fatigue.

4 With these things in mind, I would like to
5 very briefly talk about the tests described in the
6 questions proposed. Compression fatigue,
7 durability/shear testing, I will lump together;
8 migration, expulsion, creep and stress, relaxation,
9 and potential for generating wear debris.

10 [Slide.]

11 With regard to compression fatigue
12 testing, the proposed test is more appropriate for
13 metallic than elastomeric constructs.

14 Specifically, an asymptotic endurance limit as
15 proposed is typically used to describe strain
16 hardening and embrittlement of metals due to
17 fatigue, whereas elastomers can accommodate
18 relatively large strains, thereby reducing the
19 value of this test for testing nucleus devices.

20 It is also mentioned that the proposed
21 requirement for an appropriate control device
22 should be reconsidered as for this type of device,
23 one does not currently exist.

24 [Slide.]

25 With regard to durability testing, the

1 proposed test is more appropriate for total disc
2 replacement, especially regarding wear debris.
3 With the total disc replacement, segmental motion
4 results in relative movement of the rigid device
5 components offering a large shear component within
6 the device. With nucleus devices, segmental motion
7 results in more focal compression of the
8 elastomeric device, with much smaller amount of
9 shear compression.

10 [Slide.]

11 With regard to shear testing, we suggest
12 that a single fatigue compressive shear test could
13 satisfy the intent of compression fatigue,
14 durability and shear test for this kind of device.

15 Compressive testing using angled platens
16 can provide both compressive and shear forces
17 similar to the lordotic geometry of the lumbar
18 spine. We propose evaluating device functionality
19 following fatigue rather than determining
20 asymptotic endurance limits, and also propose that
21 tests be performed in simulated physiologic
22 environment, in saline solution, and the solution
23 can then be evaluated for particulates following
24 the test.

25 [Slide.]

1 With regard to migration and expulsion
2 testing, there is a basic concern here that the
3 mechanism responsible for migrations and expulsions
4 seen clinically in some devices has not been
5 documented. Development, then, of a bench test to
6 evaluate this would not be validateable.

7 Should animal testing be considered, the
8 differences in loads and disc geometries between
9 human and animal lumbar discs would prevent the use
10 of this test data to predict migration and
11 expulsion in humans.

12 Should simulated use testing in cadaver
13 tissue be considered, for instance, using cyclic
14 complex motion, the natural degeneration at even
15 room temperature of this type of material would
16 really limit the applicability of this type of
17 test.

18 So the best evaluation for migration and
19 expulsion is controlled clinical study. The risks
20 associated with clinical migration and expulsion so
21 far appear to be no greater than reherniation
22 following discectomy.

23 [Slide.]

24 With regard to creep and stress relaxation
25 testing, it is important to note that the choice of

1 test parameters such as load or load duration must
2 be made based on the objectives of the test.
3 Physiologically relevant test conditions should be
4 used when evaluating finished devices.
5 Nonphysiologically relevant test conditions can be
6 used to evaluate component materials, but cannot be
7 used then to predict in vivo device performance.
8 The value of such a test would then become
9 questionable.

10 [Slide.]

11 Lastly, potential for generating wear
12 debris, and specifically to the question of using
13 animal models. The viability of a functional
14 animal model is unproven. Animal models are not
15 adequately functional with regard to a prosthetic
16 nucleus, again, a device designed to maintain
17 motion and biomechanical function of the disc.

18 Specifically, there are significant
19 disparities between humans and animals with regard
20 to load-generating activities, posture, and ranges
21 of motion. Specifically for quadrupeds, their
22 spines generally lack biconcave endplate shapes in
23 humans. Combining these provides a great potential
24 for device expulsion, requiring the use of an
25 unacceptable number of animals, to then gain

1 questionable results.

2 [Slide.]

3 Animals that possess some bipedal ability,
4 such as baboons, have small disc spaces that will
5 require miniaturized devices. The problem with
6 this is that proportional scaling of these devices,
7 especially those that are composite in nature, with
8 expansion-limiting components, the proportional
9 scaling will likely have a nontrivial effect on
10 device performance due to material and geometric
11 nonlinearities.

12 To develop such a device for a baboon,
13 say, the test would effectively become an
14 evaluation of a device designed for that animal
15 rather than one designed for humans.

16 [Slide.]

17 In summary, prosthetic nucleus devices,
18 total disc replacements, and fusion devices all aim
19 to stabilize the spinal segment but do so in
20 completely different ways. The tests used to
21 evaluate these devices must recognize these
22 differences and be specifically designed for each
23 type of device.

24 I also want to mention that the
25 appropriate patient groups for each type of device

1 may not be the same, and as such, any one type of
2 device will likely not be an appropriate test
3 control for another type of device.

4 Thank you.

5 DR. YASZEMSKI: Thank you.

6 May I ask one more time if Mr. Valduvit is
7 here?

8 [No response.]

9 DR. YASZEMSKI: No. Before we conclude
10 the open public session, would anyone else like to
11 address the panel?

12 [No response.]

13 DR. YASZEMSKI: Seeing none, we will
14 proceed with Dr. Buch and the FDA lead
15 presentation.

16 FDA Presentation

17 DR. BUCH: Hello again. My name is Dr.
18 Barbara Buch, and I am an orthopedic surgeon and
19 member of the FDA's Orthopedic Devices Branch.

20 At the outset, I'd like to stress that
21 this discussion is not related to any specific
22 device, nor is it related to any one specific
23 preclinical or clinical trial related to any
24 specific device.

25 It is my fervent hope that this discussion

1 will endeavor to provide the panel with provocative
2 questions to stimulate a discussion which may
3 ultimately provide information to aid and update
4 our current thinking regarding guidelines for
5 clinical trials which strive to prove the safety
6 and effectiveness information for many spinal
7 devices.

8 This will include both preclinical and
9 clinical aspects of clinical trials and will focus
10 on the study of emerging spinal technologies.

11 Just by way of background, in January of
12 2000, the FDA issued the Guidance Document for the
13 Preparation of IDEs for Spinal Systems. Prior to
14 its issuance, ORDB presented a preliminary
15 background document to the Orthopedic and
16 Rehabilitation Devices Panel. During the October
17 8, 1998 panel meeting, input was received from
18 panel members and the public which resulted in the
19 current guidance document which is available to the
20 public.

21 At that time, the FDA requested some input
22 on nonfusion devices which are not intended to
23 facilitate fusion of the spine. Unlike fusion
24 devices, these devices allow some functional motion
25 through various levels of the spine. These include

1 device that provide stability while continuing to
2 allow some percentage of normal or functional
3 motion, devices which allow motion and growth, and
4 devices which stabilize vertebral body and spinal
5 fractures.

6 Examples of these devices were included in
7 the references enclosed in the panel package.

8 The current spinal guidance focuses
9 primarily on spinal fusion devices for various
10 etiologies, with brief guidance on such nonfusion
11 devices as vertebral body replacements and disc
12 replacements.

13 While the FDA guidance for spinal implant
14 510(k)s issued September 27, 2000 outlined in
15 detail devices intended for fusion, and there is a
16 voluntary testing standard available for pedicle
17 screw systems and intervertebral body fusion
18 devices, these being ASTM 1717 and ASTM 2077,
19 respectively, many sponsors have chosen to modify
20 versions of these two testing standards to address
21 different types of spinal systems.

22 Because there a\re currently testing
23 standards in development, the FDA has asked
24 sponsors to contact appropriate standards bodies,
25 including ASTM and ISO, for additional information.

1 As the scope of spinal devices expands,
2 the FDA recognizes that the need to update the
3 spinal guidance to include additional clarification
4 and suggestions for preclinical testing, clinical
5 assessments, endpoints, and success determinations
6 related to emerging spinal technologies is
7 necessary.

8 Therefore, I will begin with what is
9 typically our current recommendations to companies.

10 Currently, the FDA guidance for spinal
11 implant 510(k)s, which extensively covers devices
12 intended for fusion, recommends various static and
13 fatigue testing for spinal devices. Because
14 devices not intended for fusion are intended to
15 stabilize the spinal motion segment and retain
16 functional motion, they must be designed to last
17 the lifetime of the individual rather than until
18 fusion occurs. This corresponds to the definition
19 of a spinal implant as stated in the guidance.

20 Therefore, the current testing typically
21 requested for devices intended for nonfusion may
22 not be adequate. In addition, the current testing
23 for fusion devices made of other materials than
24 stainless steel and titanium may also not be
25 adequate.

1 The FDA currently requests the following
2 testing for spinal devices. For fusion devices,
3 for example, devices intended to stabilize by
4 fusing motion segments, those being pedicle screw
5 systems, intervertebral fusion devices, and
6 vertebral body fusion devices, fatigue testing is
7 requested.

8 This should involve a minimum of six
9 samples of the worst-case construct to generate
10 stress or load versus the number of cycles in a
11 curve that characterizes the asymptotic endurance
12 limit compared to an appropriate control device.

13 The rationale for components chosen as the
14 worst-case scenario should be provided by the
15 sponsor.

16 The interconnection mechanisms or systems
17 may be tested in the same set of constructs, or
18 each in a separate set of constructs. Each
19 interconnection mechanism should be tested, or an
20 adequate rationale for not testing the
21 interconnections is asked to be provided.

22 Additionally, testing should be performed
23 out to a minimum run of 10 million cycles for
24 intervertebral body replacement devices intended
25 for tumor patients, because these patients may

1 represent a great difficulty in achieving fusion.
2 Therefore, this device is acting more like a
3 stabilizer in this condition.

4 The second test that is required is a
5 static test. This should involve a minimum of five
6 samples of the worst-case construct. As with
7 fatigue testing, the components tested and the
8 loading mode should be justified.

9 Examples of these types of construct
10 testing typically performed for a given type of
11 spinal system in order to establish relative safety
12 are as follows. For lumbar and thoracic pedicle
13 screw systems that are intended for fusion, both
14 static and fatigue testing as well as bending
15 testing should be provided, this in accordance to
16 ASTM Standard 1717.

17 For cervical, pedicle, or lateral mass
18 systems intended for fusion, static and fatigue
19 testing should also be provided. The loading mode,
20 either torsional or bending, is dependent on the
21 design and the material.

22 For intervertebral body fusion devices,
23 static and fatigue testing again should be
24 provided. The loading mode, which may be axial,
25 torsional, bending, or shear, is dependent on the

1 design, the material, and the levels and number of
2 levels of use.

3 Finally, for vertebral body replacement
4 devices, static and fatigue testing in bending and
5 torsional loading modes should be provided.

6 Now let's look at nonfusion devices.
7 These are devices intended to stabilize the spine
8 yet retain some kind of functional motion over a
9 wide range. These might be things like disc
10 nucleus replacements, intervertebral disc
11 prostheses, and screw- or hook-based stabilization
12 spinal systems that do not attempt to afford a
13 fusion.

14 These are some of the items that the FDA
15 believes might be appropriate to consider. The
16 first is compression fatigue. This fatigue testing
17 should involve a minimum of six samples of the
18 worst-case construct to generate a stress or load
19 versus the number of cycles curve that
20 characterizations the asymptotic endurance limit,
21 which is then compared to an appropriate control.

22 The rationale for the components chosen as
23 worst case again should be provided.

24 The next testing is durability testing.
25 Durability testing should involve cyclical loading

1 testing in several loading modes--for example, in
2 flexion-extension, lateral bending, and axial
3 rotation. And it should involve a minimum of six
4 samples of the worst-case construct carried out to
5 10 million cycles.

6 This test can either be combined to
7 incorporate all testing directions to one test or
8 separated into each loading mode.

9 Durability testing establishes loading
10 direction, the stability of the device, and wear
11 generation potential. Clinical justification for
12 the loads and angles chosen are asked to be
13 provided.

14 Static compression testing should involve
15 a minimum of five samples of the worst-case
16 construct. As with fatigue testing, the components
17 tested and the loading mode should be justified.

18 Other potential tests that are not as
19 clearly defined might be: migration and expulsion
20 testing, static and dynamic shear testing, creep,
21 and stress-relaxation testing.

22 Examples of the types of construct testing
23 typically performed for a given type of spinal
24 system in order to establish relative safety are as
25 follows for these nonfusion-type devices.

1 For vertebral disc replacement, static and
2 fatigue testing in multiple-load modes should be
3 provided out to 10 million cycles.

4 For stabilization pedicle screw systems
5 intended for nonfusion, dynamic shear testing and
6 torsion testing would be provided.

7 For nucleus replacements, expulsion
8 testing is requested. For nucleus replacements as
9 well, fatigue compression testing on new and aged
10 devices should be provided.

11 For devices with polymer components, creep
12 and/or stress-relaxation testing should be
13 provided.

14 Depending on the design of the system, the
15 sponsor may need to perform different tests in lieu
16 of those identified above, perform additional tests
17 in different testing modes, and provide testing on
18 individual components of the subject system.

19 While there is a voluntary standard
20 available for pedicle screw systems intended for
21 fusion and for intervertebral body fusion devices,
22 many sponsors have used modified versions to
23 address different types of spinal systems relative
24 to their device. Because there are testing
25 standards in development for these devices as well,

1 sponsors are advised to contact appropriate
2 standard bodies for information regarding test
3 setups and parameters for their specific device.

4 Now, having this background, we'll get to
5 the questions at hand.

6 The first question deals with preclinical
7 issues. We would like the panel to please comment
8 on the currently-recommended preclinical mechanical
9 debris and wear testing to evaluate new materials,
10 device properties and integrity, and the wear
11 debris for fusion and nonfusion devices. Within
12 this, we would like you to discuss what additional
13 testing, if any, should be added to current testing
14 recommendations for the following devices, and we
15 would like to ask you to make your comments for
16 each of the following subcategories of nonfusion
17 devices--intervertebral disc or joint replacements
18 that can be placed in the cervical or
19 thoraco-lumbar areas; stabilization devices for
20 nonfusion; intervertebral disc nucleus
21 replacements, and devices manufactured out of new
22 materials.

23 The second preclinical issue is this. The
24 FDA is currently requesting information for any
25 device used in the area of the spinal cord and

1 nerve roots that has the potential to generate
2 debris regarding local and systemic effects. For
3 those incorporating new materials such as polymers
4 or composites or other designs for both fusion and
5 nonfusion, the FDA currently recommends that
6 manufacturers perform wear simulations and fatigue
7 tests to evaluate the potential for the device to
8 generate wear debris.

9 The FDA believes that the wear debris
10 generated from these tests should be collected and
11 characterized. For those devices where this may be
12 an issue, the FDA has suggested two options based
13 on current literature and methods employed in
14 spinal research studies. These include an
15 injection study of various-size particles into the
16 spinal cord area of small animals and functional
17 animal models.

18 Because of the limitations of the current
19 testing methods and models, should devices made of
20 new materials and/or those intended to retain
21 motion be tested for local and systemic effects
22 independent of the type of material or the amount
23 of wear debris generated?

24 If you suggest that testing be performed,
25 please describe the testing that you would

1 recommend. For example, discuss the viability and
2 usefulness of injection animal studies, including
3 the amount and distribution of sizes and shapes of
4 wear debris that should be injected into the
5 animal, which can then predict what may occur
6 clinically for the life of the implant.

7 Second, discuss recommendations and the
8 viability and usefulness of a functional animal
9 model in predicting what may occur clinically for
10 the life of the implant, or discuss any
11 alternatives you may have.

12 Next, I would like to get to the clinical
13 issues and some questions that we would have for
14 the panel.

15 For spinal assemblies not intended to fuse
16 motion segments, as I have just delineated, the
17 goals of treatment may be to stabilize the spine,
18 maintain normal or functional motion, or treat
19 disease early in its course to prevent further
20 progression and to conserve motion instead of
21 fusing segments of the spine to alleviate pain and
22 restore function.

23 These types of devices provide challenges
24 in choosing the best methods to evaluate safety and
25 effectiveness.

1 Our current spinal guidance describes
2 methods to assure that data collected provide
3 adequate characterization of the safety and
4 effectiveness of devices.

5 A copy of the spinal guidance was provided
6 to all panel members, and as I have stated before,
7 is available to the public on the Web, and these
8 sections will not be repeated here. However, I
9 would direct your attention to the appropriate
10 patient inclusion and exclusion criteria, the
11 effectiveness evaluations, safety evaluations, and
12 patient and study success criteria.

13 The FDA believes that the populations and
14 goals of treatment may be different for devices
15 that maintain functional motion. Therefore, we
16 will ask you to please discuss study designs which
17 may be better-suited to evaluate nonfusion spinal
18 devices. In your discussion, we would like you to
19 please comment on enrollment criteria, patient
20 populations, controls, success criteria, and goals
21 of the study, each of these that would be suitable
22 for these types of nonfusion spinal devices.

23 Devices intended to stabilize the spine
24 yet retain functional motion are expected to have
25 an upper limit of motion beyond which one would

1 consider the device to be unstable and a lower one
2 below which one would consider the device to have
3 inadequate motion or possibly even consider the
4 segment to be fused.

5 Therefore, we are going to ask you to
6 please discuss the amount of motion and on what
7 scale to define a patient as a functional and
8 clinical success--for example, a clinically
9 significant improvement in the condition for each
10 of cervical, thoracic and lumbar levels for
11 nonfusion spinal devices.

12 Those are all the questions we are putting
13 before you.

14 DR. YASZEMSKI: Thanks very much, Dr.
15 Buch.

16 We are now going to begin the pane lead
17 reviews, and I'll ask Dr. Kirkpatrick to start with
18 his preclinical and clinical reviews, and then
19 we'll ask Dr. Doull to follow on with the
20 toxicology review.

21 Dr. Kirkpatrick?

22 Panel Reviews

23 DR. KIRKPATRICK: Thank you.

24 My distinguished colleagues on the panel,
25 our FDA friends have invited the guy from Alabama

1 to address the preclinical and clinical issues, so
2 I need to paraphrase the questions to better
3 understand them.

4 In essence, we are being asked to
5 recommend mechanical testing of unknown devices
6 when there is no current validated or consensus
7 method to test them.

8 We are being asked to recommend test
9 methods for devices for a wide range of designs and
10 intended use with no specifics known to us yet.

11 We are asked to recommend toxicology and
12 biocompatibility for unknown materials and debris
13 with no validated test methods.

14 We are asked to recommend clinical
15 evaluations where the indications, intended use,
16 controls, and safety concerns are not specific.

17 Now, if that's not enough for us, I'm
18 worried about the time that we have. At any rate,
19 I would like to also give a brief comment on some
20 of the concerns that were raised by industry and
21 independent representatives from the public, and
22 that is from the standpoint of the panel, my
23 discussion is going to be what we would like to
24 see, not necessarily what we would accept. In
25 other words, we always work from compromise, so

1 from the standpoint of being an incubator for
2 testing, yes, we will ask for the companies to
3 satisfy the burden of some of the questions we have
4 with regard to safety and effectiveness, and there
5 may not be current test methods to do so.

6 We also may recommend that the extensive
7 nature of the tests may be pretty high, but that is
8 where compromise comes in in working with the FDA
9 reviewer panel.

10 With regard to preclinical questions, I
11 believe that these devices require mechanical
12 characterization; they should be loaded in all
13 intended and anticipated modes of load and motion
14 to mechanical failure to characterize what amount
15 of load will bring a failure. They should have
16 durability testing at a physiologic load and motion
17 with anticipated length of service--I am concerned
18 that the 10 million cycles currently recommended is
19 a little bit low if we think of a 40-year-old, like
20 my neighbor, who rose every morning, 5 days a week,
21 and rode a couple of miles, that is a lot of load,
22 a lot of motion, and a lot of repetition of that
23 motion, and I don't think 10 million cycles would
24 represent a very long period of time for him if we
25 are looking at a 40-year-old with hopefully a 10-

1 to 15-year life span of the disc replacement, for
2 example, similar to what a joint replacement would
3 be expected to do.

4 I do think that physiologic load needs to
5 be considered very seriously. Physiology for a
6 grandmother as far as loading her lumbar disc is
7 very different from the physiology of my neighbor
8 loading his lumbar disc.

9 In addition, I think that mechanical
10 characterization should include device changes
11 after durability testing, and that includes looking
12 at the wear, the characterization of debris,
13 plastic deformation, geometry changes, and any
14 mechanical changes of polymeric or other type
15 materials that we may not be reviewing yet.

16 As far as potential tests, I agree that
17 migration and expulsion are important to consider
18 with nuclear replacements. I think that static and
19 dynamic shear testing may also be important,
20 depending on the design and intended use of the
21 implant. Creep and stress relaxation for viscal
22 elastic designs are important as well. I think we
23 all know that when we stand, our disc spaces shrink
24 during the day. And I also think that evaluation
25 of bone implant interface may be required,

1 depending on the specific design of the implant.

2 Overall, I think that each of these
3 devices that is intended to preserve motion, we
4 should define those motion limits, and I think the
5 best way to do that in current literature is
6 stability testing. We should compare to a quote
7 "normal" and a quote "expected" based upon the
8 device. We should characterize the neutral zone
9 and elastic zone of these devices and characterize
10 the failure at the extremes of motion for these
11 devices, as many times, a patient may be in an
12 accept and have to extend more or flex more than
13 they would do under physiologic loading.

14 With regard to new materials, I think
15 biocompatibility and toxicology are important, and
16 I will defer that to our other panel members.

17 We do need to characterize any corrosion,
18 wear, or biologic response to such debris, and I
19 think shelf life and in vivo degradation are
20 important in some of the polymeric devices and
21 materials that may be coming down the pike.

22 Nuclear replacements, I think they require
23 mechanical characterization as well, and I would
24 include creep and stress-relaxation, expulsion
25 testing, stability testing. If simpler tests can

1 be validated, I think it is appropriate to use
2 them.

3 I think that the insertion site repair of
4 disc nuclear replacements should also be tested.
5 In other words, to get something into the disc
6 site, into the nucleus, you have to go through the
7 annulus. Whether they are using the place where
8 the disc herniated already or if they are doing it
9 in a degenerative condition, there may be some type
10 of repair of the annulus, and that needs to be
11 tested as well.

12 We also need to look again at degradation
13 and deterioration of properties over time if they
14 are nonmetallic implants.

15 With regard to particulate debris, it is
16 unknown for the spine. I think we could follow the
17 total joint arthroplasty lead, and perhaps we could
18 add somebody with that expertise to the panel who
19 has a particular interest in particulate debris and
20 testing.

21 Animal models do appear to provide us with
22 the best guess at present as to the effect of these
23 particulates. Particulates in joints may differ
24 from the non-joint sites. Unless we are using a
25 facette joint replacement, the spine may react

1 completely differently than the total joint
2 arthroplasty. But right now, it again is a best
3 guess.

4 As far as debris around the dura and
5 whether there is a neurologic effect, we don't know
6 that, either, and I think it warrants some
7 investigation. Perhaps an animal model would be
8 the most appropriate first guess at that.

9 Basically, sa far as particulate debris in
10 the spine, there are no established methods.

11 Moving on to clinical issues, with regard
12 to inclusion and exclusion, I think the criteria
13 placed for fusion are appropriate. However, as we
14 noted in the earlier presentation today, I would
15 like to see the indications refined and specific as
16 opposed to fairly broad. We talked about--for
17 those not available for most of the day--we had
18 four different fracture classifications of severity
19 of the fracture combined with four different open
20 wound classifications, and as such, that creates a
21 very complex and heterogeneous dataset.

22 I would urge investigators to consider
23 making it as refined as possible for disc
24 replacements or nonfusion devices. I would also
25 suggest that we consider the philosophy of the

1 implant in picking the populations. When I say
2 that, there are some issues with regard to disc
3 replacement, such as the adjacent segment
4 degeneration. That has been proposed as a very
5 serious problem, and that is why we are developing
6 these disc replacements. I think that that is not
7 exactly an easy thing to say, that the degeneration
8 occurs at the adjacent segment just because of the
9 fusion. It may actually be happening because of
10 the natural history of the spine.

11 Biomechanics has shown that your load on
12 the adjacent segment is similar to the load at the
13 affected segment, and other segments farther away
14 from that adjacent segment are also subjected to
15 the same increases in load and motion,
16 biomechanically. So the question is is that really
17 making a big difference.

18 As far as primary measures on what to look
19 at for clinical success, radiographic measures are
20 challenging at best. Validated pain measures and
21 specific function measures I think are appropriate.
22 The challenge of course remains as to how much
23 change do we need to see in those to call it a
24 success.

25 Specifically on radiographic criteria, the

1 range of motion--again, flexion-extension views
2 give us very poor reproducibility and are very
3 challenging to interpret. It may involve having to
4 add extra implants to the patient such as beads to
5 be able to actually do good motion measurements.

6 I think the absence of bridging bone is a
7 reasonable thing; if we are trying to preserve
8 motion, we should not have bridging bone result.
9 The bone implant interface needs to be evaluated in
10 those that are supposed to be fixated. We should
11 not have radiolucencies develop.

12 The implant position should be evaluated
13 radiographically. That would detect subsidence and
14 migration.

15 The implant geometry, to detect where; the
16 disc height, again to detect where and add to the
17 implant position issue; and adjacent segment--if we
18 are agreeing with the philosophy that we are
19 sparing the adjacent segment from degeneration, we
20 can't see progression of the adjacent segment
21 degeneration in the clinical trial.

22 As far as safety, I think some key things
23 clinically we need to evaluate include what are the
24 revision options for these implants. Is
25 replacement of the device appropriate, or is the

1 only option fusion after removal of a failed
2 device? Are there other procedures that could be
3 done following this?

4 If fusion after failure is the intended
5 treatment once an implant fails, is that success
6 equal to a primary fusion? That should be included
7 in our evaluation of the success of the implant.

8 And of course, we have also heard about
9 neurologic effects. I personally believe that all
10 neurologic effects should be reported, and the
11 panel should be given the opportunity to determine
12 whether they feel it is caused by the device itself
13 or whether it is a surgical complication.

14 Patient success measures--I think specific
15 radiographic criteria should be developed. It is
16 going to be implant-dependent. Specific
17 improvement in pain and function--I don't know how
18 much improvement we should look for. Should it be
19 50 percent improvement? Twenty-five percent?
20 Seventy-five percent? It is a very difficult thing
21 to pin down.

22 From the reading of the FDA regulations,
23 it sounds like if we have 5 percent improvement and
24 can demonstrate it, that is enough to satisfy the
25 efficacy. I am not so sure, clinically, that I

1 would put somebody through a major operation for a
2 5 percent improvement.

3 And then, what risk is acceptable for what
4 benefit? That's what the bottom line is on that
5 discussion.

6 On study success, what are the controls
7 going to be? Should we look at nonoperative
8 controls to demonstrate an improvement over the
9 natural history? That would seem to be a logical
10 measure, especially in a nonfusion device that is
11 preserving motion.

12 Should we look at traditional operative
13 management to compare pain and function scales? We
14 obviously cannot compare radiographs there, but
15 pain and function may be appropriate.

16 And then, what sort of follow-up should we
17 look at? Is 2 years adequate? Personally, I don't
18 feel that 2 years is adequate for some of these
19 studies. I think 5 to 10 would be better if we are
20 trying to look at a longevity-producing implant.

21 And then, how much improvement relative to
22 other treatments, as I mentioned before, is a very
23 difficult question to answer.

24 In general as a summary, I would suggest
25 that nonfusion devices require more extensive and

1 complex evaluations, both preclinical and clinical;
2 longer in vitro testing; different endpoints; and
3 environmental exposure should be evaluated in the
4 in vitro testing, as well as stability testing.

5 Debris and particulate matter should be
6 characterized and determined whether it is toxic or
7 induces an immune reaction. Degradation should be
8 evaluated as well. And we should have extensive
9 clinical data to be able to make our judgments.

10 In short, like my teenage daughter around
11 Christmas time, she'll ask for the world--but as
12 far as the others in the household are concerned,
13 we will adjust to some specific requests, look for
14 rational and justifiable compromise, and then work
15 together as a team to serve our patients.

16 Thank you very much.

17 DR. YASZEMSKI: Thanks, Dr. Kirkpatrick.

18 Dr. Doull, can we ask you to present your
19 preclinical toxicology review?

20 DR. DOULL: Well, I'm pleased that Dr.
21 Kirkpatrick included the mechanical testing as part
22 of the efficacy. That means I don't have to deal
23 with that since I am going to deal with safety.

24 The safety issue, as one of the commenters
25 mentioned, boils down to whether the wear and tear

1 debris has a chemical or a toxic effect or whether
2 it has a physical adverse effect, and how one sorts
3 that out.

4 There is no real basis that I know of for
5 concluding that simply because you reduce the size
6 of the material, that you induce some special kind
7 of toxicity. It is a question of dose, and as you
8 reduce the dose, you reduce the toxicity.

9 Whether the physical state of the material
10 can in fact induce some special kind of toxicity I
11 think is something that needs to be explored, and
12 certainly that is one area where animal testing
13 would help.

14 I think we have a strong background in
15 that area, however, and that comes from our studies
16 with solid-state tumor agenesis. We know a lot
17 about elastomers, silicone elastomers, asbestos,
18 metals, and so on, about solid-state tumor
19 agenesis, and I think that gives us a good head
20 start on how we might approach the area here.

21 By and large with solid-state tumor
22 agenesis, as one reduces the size of the particle,
23 you reduce the propensity of that material to
24 produce tumor, and hopefully, one would have
25 similar effects here.

1 The specific kind of neurological testing
2 that one might do to look for particle size effects
3 I think is a challenge, and I am not aware of
4 really good animal models in fact that would help
5 us with that, and I think clearly, we are going to
6 have to develop some good models in order to get a
7 handle on this.

8 And I'll leave the clinical areas to my
9 colleagues.

10 Discussion of FDA Questions to Panel

11 DR. YASZEMSKI: Thanks very much, Dr.

12 Doull.

13 What I would like to do now if it would be
14 acceptable to FDA, Dr. Witten, is to put the
15 questions up in the order that Dr. Buch presented
16 them to us, and let's discuss them one at a time.

17 Thanks, Mr. Melkerson.

18 The first slide discussed the preclinical
19 issues, and I think there are probably a few
20 questions embedded in here, so we'll have to
21 separate them out a little bit, and I am open to
22 discussion of my method of separation if somebody
23 thinks they can do it better.

24 The first bullet point, perhaps we can
25 take as a question: "Please comment on the

1 currently recommended preclinical mechanical,
2 debris, or wear testing to evaluate new materials,
3 device properties integrity and wear debris for
4 both fusion and nonfusion devices."

5 We all have the list that Dr. Buch gave us
6 of three slides of current recommendations.

7 Would anybody care to start, and then
8 we'll go around and discuss the current
9 recommendations?

10 DR. NAIDU: Sure, I can start.

11 DR. YASZEMSKI: Dr. Naidu.

12 DR. NAIDU: The current recommendations
13 for fusion devices and nonfusion devices have been
14 specified by Barbara pretty well. The problem is
15 that major area where it lacks is nonfusion
16 devices.

17 The nonfusion devices can come in many
18 flavors. They could be thermoplastic elastomers,
19 they could be lightly crosslinked elastomers, they
20 could be highly densely crosslinked elastomers,
21 they could be crystalline polymers, they could be
22 amorphous polymers. They could be many things.

23 The problem is that depending on the
24 material that you choose, they will age, and
25 obviously, what you can't do is just base yourself

1 on all these plain, old, simple mechanical testing.
2 You are going to have to do some sort of viscal
3 elastic testing, whether it involves generating
4 enthol-B [phonetic] curves and studying
5 crystallinity, whether you are going to use DMA or
6 thermal analysis, depending on the mode of loading
7 that you want to do, and depending on whether you
8 want to use torsion pendulum tests.

9 There are many varieties of tests. We can
10 sit down and discuss this issue forever here. I am
11 not exactly sure that we can reach a consensus,
12 because these materials are so variable. Like I
13 said, it ranges all the way from thermoplastic
14 elastomers to crosslinked to non-crosslinked to
15 crystalline to semi-crystalline to amorphous.

16 So I think that this is a very involved
17 topic. I'm not sure that we are going to reach a
18 consensus at this point within the next hour or
19 two, and therefore, I think that all these issues
20 should be addressed individually with the people
21 who are actually producing these devices.

22 When you start talking about things like
23 peak, you have got to start thinking about whether
24 it is pure peak, neat peak, is it a composite peak,
25 is it peak-on-peak. There are many things. So

1 suffice it to say that there is a lot to be
2 discussed.

3 DR. YASZEMSKI: Thank you.

4 Let's come around this way. Dr. Finnegan,
5 do you have anything that you would like to add to
6 Dr. Naidu's comments?

7 DR. FINNEGAN: The only two things I would
8 add are that I would like to reinforce the fact
9 that the longevity issue and the properties after a
10 length of time on the shelf do need to be tested,
11 because the total joint supported demonstrated that
12 that is a problem.

13 The other issue I would bring up is the
14 method of sterilization, because again, if it is
15 gamma radiation, and you have those kinds of
16 polymers, you will also have an effect. So that
17 also needs to be tested.

18 DR. YASZEMSKI: Thanks.

19 Dr. Kirkpatrick?

20 DR. KIRKPATRICK: I think conceptually,
21 most of the things have been addressed. I would
22 suggest once again that wear testing and
23 characterization of wear debris would be
24 appropriate.

25 DR. YASZEMSKI: Thank you.

1 Dr. Doull?

2 DR. DOULL: Nothing more.

3 DR. YASZEMSKI: Thanks.

4 Dr. Aboulafia?

5 DR. ABOULAFIA: Nothing specific to add.

6 DR. YASZEMSKI: Thanks.

7 Dr. Schmidt?

8 DR. SCHMIDT: I don't have a lot to add.

9 I am not a spine surgeon and not too up-to-date on
10 a lot of the testing methods we're talking about,
11 but I do know a little bit about wear particles in
12 total joints, and I know that a combination of wear
13 debris and motion has been shown to be a bad
14 combination. So I think that that is something
15 that needs to be studied.

16 I think we need to work with the
17 regulatory agencies to define standards, and it is
18 going to need to be a long, involved process with
19 all the different players here to come up with
20 something.

21 DR. YASZEMSKI: Thank you.

22 Dr. Larntz?

23 DR. LARNTZ: Just a couple of specific
24 comments. In the current guidelines, there are
25 some numbers, like "N" equals 6 for SN curve. I

1 have actually done a little bit of work with those,
2 and boy, I can't imagine what we find out with N
3 equals 6.

4 I am a statistician--I am not an engineer,
5 where everything is perfect and where everything
6 works perfectly--but then, when I come in and see
7 engineers do more than 6, they say, "Wow, I didn't
8 expect that to break out there."

9 So we have to be very careful with
10 specific numbers, very careful, and I think we have
11 pretty inadequate characterization from some of the
12 standards that are set by so-called standards
13 agencies--excuse me for being a heretic on that.

14 And as far as things like cycles,
15 actually, I decided to do a little calculation. I
16 worry about my knees because I am a bicyclist, and
17 I just figured out that in 2 years, I do 10 million
18 cycles on my bicycle. I have nothing else to do,
19 so that's nice, but I would like my knees to last a
20 long time, and if I have to do something else, I
21 would like those other things to last a long time.

22 So we have to be very careful when we set
23 upper limits. I agree with Dr. Kirkpatrick's
24 comment. Many of the bounds that we are talking
25 about are low--I'm sorry, I'm no speaking as a

1 statistician now; I am speaking as a potential
2 consumer, okay--but as a statistician, I remember
3 doing this stuff with wire or raw material, and the
4 engineer said, "It never breaks, it never breaks,"
5 and I said, "Let's just try it." He put the thing
6 over the weekend, and he was surprised to come back
7 and find half the specimens broken that he thought
8 were going to be perfect.

9 So things to happen, and we have to be
10 very careful.

11 As far as other materials, obviously,
12 innovation is important, and testing is critical,
13 and people have to have incredible intimate
14 knowledge of these materials to develop the
15 appropriate tests. And I do believe there are
16 going to be a lot of very specific, very different
17 kinds of tests developed, and I do think we have to
18 not underestimate--I'm going to put a plug in for
19 my own field--the variability in the results of
20 tests that we often do.

21 Thank you.

22 DR. YASZEMSKI: Thanks, Dr. Larntz.

23 Dr. Witten, as we go over this round of
24 discussion, I'm going to note that although the
25 first bullet of the first question is what I

1 started out with, I think that the discussion
2 extended into additional testing, so if it is
3 acceptable to FDA, I think I'll summarize on the
4 first slide both current and new testing.

5 I think we probably will lend more
6 heterogeneity to the slide than currently exists,
7 because there really is no consensus as to where
8 this is all going to go. And I think what I am
9 hearing from the panel members is that that is
10 probably okay right now, because these are new
11 devices in a new field, and we can perhaps learn
12 some things from problems that have occurred with
13 existing devices from other fields.

14 They include that there will be a variety
15 of materials as there were for joints when joints
16 came up, and some commonalities were that wear
17 debris has been a problem, so that we should
18 probably look at wear debris in these new
19 materials.

20 The sterilization effect will be an issue,
21 especially in light of the fact that some of these
22 new materials perhaps will be combination products
23 in which the effect of sterilization on biologics
24 associated with devices will really have to be
25 taken into account.

1 Longevity and shelf life is important,
2 because we will have to know how long in advance
3 and what the demand is for these, and we'll have to
4 get some idea for how long they will last on the
5 shelf before we put them in and maintain those
6 properties that we are talking about testing.

7 Several references have been made to the
8 voluntary standards organizations, the ASTM and the
9 ISO, and perhaps as per Dr. Naidu's comment, we can
10 learn from the testing that exists under ASTM,
11 usually Section (b), for polymeric materials used
12 for mostly nonbiologics, non-human devices, and
13 apply some of those, the thermal tests and the
14 dynamic mechanical analysis that he mentioned, to
15 the various polymeric devices that will occur here.

16 And I guess as a summary, what I have
17 heard from everybody is that each different
18 material may need a different set of tests, and all
19 the people who are part of this--the FDA, the
20 investigators, the companies, and the patients--are
21 going to have to work together and work this out.

22 It's not a very clear answer, but have we
23 addressed the issue to your satisfaction?

24 MS. WITTEN: yes. Thank you.

25 DR. YASZEMSKI: Thank you.

1 We're going to move on to the next
2 question, then. Dr. Buch, thank you.

3 Question 2 concerns preclinical issues.

4 "For those incorporating new
5 materials--polymers, composites--or designs, both
6 fusion and nonfusion, the FDA recommends that
7 manufactures perform wear simulations and fatigue
8 tests to evaluate the potential for the device to
9 generate wear debris. The FDA believes the wear
10 debris generated from these tests should be
11 collected and characterized. For those devices
12 where this may be an issue, the FDA suggests two
13 options--injection study of various-sized particles
14 into the spinal cord area of small animals, and
15 functional animal models."

16 If I may start, I think we have already
17 discussed in the last question that we believe wear
18 debris testing is important, so we'll say that that
19 should be included.

20 I would ask the panel members please to
21 comment now on the type of wear debris testing.
22 The two that are mentioned here, spinal cord
23 particulate and injection, and what would
24 functional animal models be--would anyone like to
25 comment on the animal models?

1 Dr. Kirkpatrick?

2 DR. KIRKPATRICK: My comment on the animal
3 model was this talks about into the spinal cord
4 area. I don't think that's very specific. I would
5 suggest that the particles or particulates that are
6 produced through wear testing of the device that is
7 made should be placed in the area of intended use
8 adjacent to the dura. In other words, if we are
9 looking at a ligament replacement that is going to
10 be posterior for lumbar spine only application, it
11 should just be posterior on the dura. If we are
12 looking at a disc replacement that produces wear
13 debris, it should be placed anterior to the dura.
14 If it is for cervical disc, it should be in the
15 cervical spine of whatever the animal is, so we
16 could represent whether there is a root effect or a
17 cord effect or both.

18 DR. YASZEMSKI: Thank you.

19 Ms. Maher?

20 Ms. MAHER: My only comment on this is
21 that if we are going to be generating wear testing
22 on wear debris, the wear testing should be under
23 physiological loads, not under the maximum load.

24 DR. YASZEMSKI: Thanks.

25 Dr. Doull?

1 DR. DOULL: Let me add to that that the
2 focus should be on the physical adverse effects
3 rather than the chemical adverse effects, which can
4 be tested in the conventional approaches. If we
5 are developing new technology, it ought to be for
6 physical adverse effects.

7 DR. YASZEMSKI: Thank you.

8 Dr. Kirkpatrick?

9 DR. KIRKPATRICK: If I could just add two
10 caveats to what was just said, one is the
11 physiologic loading of the most vigorous patient
12 anticipated for the device would be appropriate as
13 opposed to maximal loading. We also should look at
14 the immune response to the particulate debris,
15 because that is the main problem in total joints.

16 DR. YASZEMSKI: Thank you.

17 Dr. Larntz?

18 DR. LARNTZ: If I can just comment a
19 little bit further, the testing at physiological
20 load or even at maximal load is if you do it right
21 and think about it is near impossible. Accelerated
22 testing is absolutely necessary, and modeling of
23 those accelerated tests is the key to making sure
24 that they apply to the physiological load or the
25 maximal physiological load. Testing at

1 physiological load means that you will never get
2 your test done. You don't want that. You want to
3 be able to get your test done, you want to be able
4 to get it done quickly, and accelerated testing is
5 the way to do that.

6 DR. YASZEMSKI: Thank you.

7 Dr. Naidu?

8 DR. NAIDU: The particle size is also
9 important, and just to reflect Dr. Larntz'
10 suggestion that accelerated testing is needed,
11 along the same lines, a barrage of particles, you
12 have to put those particles at the site, like Dr.
13 Kirkpatrick suggested, at the site of implantation,
14 and reaction to such particles should be studied,
15 because as suggested, before accelerated testing,
16 these debris particles are going to be small, and
17 we don't know what the response is going to be.

18 It is the same thing in total joint
19 literature with polyethylene particles--you really
20 can't predict, but there is definitely a
21 correlation with size. So you have to do a
22 dose-response type study, implanting such particles
23 in intended areas of use.

24 So I do concur with all the other panel
25 members as far as that goes.

1 Thank you.

2 DR. YASZEMSKI: Thank you.

3 Dr. Kirkpatrick?

4 DR. KIRKPATRICK: Just one further comment

5 on particle size. I don't think that the
6 manufacturer should be required to produce
7 particles of a size that is not produced by wear
8 under physiologic conditions. In other words, I
9 don't think we should arbitrarily ask for certain
10 size of particles. It should be justified by the
11 particles produced by that device.

12 DR. YASZEMSKI: Thank you.

13 Ms. Maher?

14 MS. MAHER: I also want to emphasize that
15 we need to be careful not to place the burden so
16 high on the manufacturers that they decide not to
17 develop in this area, because while wear debris in
18 joints is a problem, prior to having total joint,
19 it was a bigger problem. So I think we need to
20 balance the risk and benefit of what we are asking
21 for.

22 I understand all the science that we are
23 bringing out in everything we have learned, but if
24 people say, fine, we aren't going to develop any
25 artificial discs because the burden is too high,

1 then I think that as a whole, the public has lost
2 out.

3 DR. YASZEMSKI: Thank you.

4 DR. NAIDU: Can I just make an additional
5 comment on that?

6 DR. YASZEMSKI: Dr. Naidu, go ahead.

7 DR. NAIDU: I understand that the burden
8 may be high, but we are also talking about high
9 stakes. These are neurological tissues--the spine.
10 Total joint, you have the bone, and you have to
11 consider that, too.

12 Thank you.

13 DR. YASZEMSKI: Thank you.

14 Dr. Aboulafia?

15 DR. ABOULAFIA: I have nothing to add.

16 DR. YASZEMSKI: Dr. Doull, may I ask you
17 with respect to toxicology--the FDA has asked us
18 about alternative animal models, and they mentioned
19 functional small animal models. From a toxicology
20 perspective, are studies performed in certain types
21 of animals directly expandable to humans?

22 What do we need to know from a toxicology
23 perspective about the type of animal we recommend
24 to FDA and to industry?

25 DR. DOULL: There are two cardinal rules

1 in toxicology. The first is the dose makes the
2 poison, and the second is results in one species
3 are predictive for another species when properly
4 qualified.

5 So all we have to do to use animal studies
6 is properly qualify them.

7 In terms of the neurological testing, Food
8 and Drug, EPA, and a number of agencies have put
9 together some guidelines for testing for
10 neurological effects, and for new substances, new
11 polymers, new elastomers and so on, clearly, those
12 are the kinds of things one ought to do first,
13 because that is going to characterize the chemical
14 toxicity of the material, and we can do that before
15 we do any wear and tear debris studies up front, in
16 a sense, and much simpler.

17 DR. YASZEMSKI: Thank you.

18 Would anybody else like to make a comment
19 on this issue, which will include both of these
20 slides--thank you, Mr. Melkerson, for putting them
21 up.

22 [No response.]

23 DR. YASZEMSKI: Seeing none, Dr. Witten,
24 we have had a discussion that I think has tended
25 toward suggesting we balance the risk and benefit

1 to patients and to industry's interest in pursuing
2 this. Particles, once generated, will probably
3 show a spectrum of particle size distribution, and
4 the recommendation has been that we ask industry
5 only to test those particle sizes that will occur
6 in a specific device.

7 Dr. Doull has let us know that if someone
8 recommends a certain device that it would be
9 prudent to test the material first, before putting
10 it in a device, to assess its chemical toxicity and
11 then to check its physical effects after it has
12 been put in the device. We should use physiologic
13 loads and accelerated testing, and again, be
14 flexible given the new and novel nature of these
15 devices.

16 We have also heard that we need to be
17 concerned about the immune response to these
18 particles.

19 Have we discussed this adequately?

20 MS. WITTEN: Yes. Thank you.

21 DR. YASZEMSKI: Thanks, Dr. Witten.

22 Let's go on to clinical issues, please,
23 Dr. Buch.

24 "FDA believes that the populations and
25 goals of treatment may be different for devices

1 that maintain functional motion. Therefore, we are
2 asked to discuss study designs which may be
3 better-suited to evaluate nonfusion spinal
4 devices."

5 We are asked to comment on enrollment
6 criteria, patient populations, controls, success
7 criteria, and study goals that would be suitable
8 for nonfusion spinal devices.

9 These are devices, on the next slide,
10 "intended to stabilize the spine yet retain
11 functional motion. They are expected to have an
12 upper limit of motion beyond which one would
13 consider it to be unstable, a lower limit beyond
14 which one would consider it to have inadequate
15 motion or possibly consider the segment to be
16 fused."

17 We are also asked to discuss the amount of
18 motion and on what scale to define a patient as a
19 functional and clinical success.

20 Comments from the panel members on
21 this--nonfusion devices, clinical studies,
22 exclusion/inclusion criteria, ranges of motion.

23 Dr. Kirkpatrick?

24 DR. KIRKPATRICK: Go ahead.

25 DR. ABOULAFIA: I was going to sort of

1 echo what Dr. Kirkpatrick said earlier. One of the
2 ideas behind using these nonfusion devices is that
3 you may alter degenerative changes at adjacent
4 segment. And hopefully, any study design would
5 compare possibly a level and similar cohort of
6 patients, groups who have been fused at a
7 particular level, to see if there is a difference
8 in the natural history at the adjacent segment by
9 not fusing the treatment level.

10 DR. YASZEMSKI: Dr. Kirkpatrick?

11 DR. KIRKPATRICK: Just again reiterating
12 what I said earlier about inclusion criteria, I
13 think what is there is fine; however, the
14 investigators or the sponsors should seriously
15 consider what indications they want applied to
16 their device. I don't think it would be
17 appropriate for them to consider studying a nuclear
18 replacement, for example, in a Grade II
19 spondylolisthesis unless they felt it was
20 distracting and reducing that particular disorder.
21 Otherwise, there are going to be too many
22 conflicting issues.

23 Similarly, for a disc replacement, they
24 need to consider whether they are looking at
25 deformity to correct. I think that would unduly

1 compound their analysis and may alter their
2 results. So the cleaner the indication, the
3 better.

4 DR. YASZEMSKI: Ms. Rue?

5 MS. RUE: From a consumer's perspective, I
6 think that success criteria should definitely
7 include improvement of pain and functional capacity
8 and not just no digression in it, and to what
9 degree will have to be determined.

10 DR. YASZEMSKI: Thank you.

11 Dr. Larntz?

12 DR. LARNTZ: Just a couple comments to
13 follow up. I think I hear something about
14 homogeneity of population for indication. I think
15 devices are typically used across a broad range of
16 patients. I think we have to make sure that we are
17 not afraid of testing them across a broad range of
18 patients. I hear that a lot. People are worried
19 about--I have heard that recently--sites being
20 different. I think that's actually an advantage.
21 We want to find out if things work across a range,
22 because they are used across a range. Even if it
23 is past recommended, labeled with an indication, we
24 have got to recognize that that indication may not
25 be totally limiting.

1 With respect to patient success, I think
2 we have had a lot of trouble at different times
3 defining "patient success," and I think that should
4 be--I understand the reason for that--I think that
5 patient success, of course, is a
6 multivariate--multivariate--construct, for want of
7 a better term--heaven forbid, I thought I'd never
8 use that word.

9 At any rate, what we need to do is think
10 hard about comparing patients, which patient is
11 doing better than another. I think that's a great
12 way to do things, and I have argued that for many
13 years, that what we need to do is try to get scales
14 that compare patients and who does better than
15 another one, and I would argue that that kind of
16 thinking has been missing. What we are doing now
17 is success/failure, and our successes have been a
18 broad range of patients, and our failures have been
19 an even broader range of patients. So we are
20 lumping them into a dichotomous--we are losing tons
21 of information by doing that. We are making sample
22 sizes larger than necessary to do that. I think it
23 is very important when we do comparative studies,
24 which I think most of these should be comparative,
25 although sometimes we have to think about--the

1 question up there about controls is difficult,
2 right, because in some of these things, we aren't
3 sure what the alternative is; particularly for some
4 new therapies, there may not be much of an
5 alternative, so that is interesting to think about.

6 But I think it is important to think about
7 ways of doing these so that we can reduce sample
8 size to get the information out that we need. I
9 think the old dichotomy of looking at patient
10 success/failure and just doing that is very
11 dangerous. I think we lose tons of information by
12 doing that.

13 DR. YASZEMSKI: Thanks, Dr. Larntz.

14 Other comments?

15 Dr. Kirkpatrick?

16 DR. KIRKPATRICK: Getting back to the
17 second slide on clinical issues which talked about
18 the different motions which would be appropriate,
19 basically, I don't think we should set a level of
20 motion that is required for this, because if we
21 have a patient who gets a nonfusion device, and
22 they end up doing, functionally and painwise, much
23 better than they would have without it, I think it
24 is reasonable that it is an efficacious device much
25 like our colleague just mentioned a few moments

1 ago.

2 If we put arbitrary definitions on must
3 have so much motion at that segment to be
4 considered a success, we are not going to be able
5 to do it. If you want to have a guide for how much
6 motion is what is there, or should be there, I
7 think the White and Punjabi [phonetic] data is
8 pretty well-accepted as being fairly close to what
9 we would expect to be a physiologic range of
10 motion, and whether you can duplicate that with a
11 device remains to be seen.

12 And--there was one other thing that just
13 escapes my mind.

14 DR. YASZEMSKI: As you are thinking about
15 it, I'm going to ask some others to think about two
16 additional issues. Please offer commentary if you
17 have it on the devices that are primarily nonfusion
18 devices in the anterior portion of the spine--that
19 is, either a disc replacement or a nucleus
20 replacement--would there be any consideration
21 regarding the number of levels for an ideal
22 patient? We are asked about enrollment criteria.
23 Would an ideal patient for this study be one, for
24 example, with single-level disease, or would it be
25 just as appropriate to consider persons with

1 multilevel disease?

2 Comments?

3 Dr. Kirkpatrick?

4 DR. KIRKPATRICK: I think that gets back
5 to my earlier comment. If you are looking at using
6 a disc replacement because it spares the adjacent
7 segment, then multiple levels are going to
8 eliminate a rational analysis of that. It depends
9 on their rationale for recommending the device.

10 DR. YASZEMSKI: So again, study-dependent.

11 DR. KIRKPATRICK: However, if we are
12 looking at being able to serve patients with
13 multilevel degenerative disease or multilevel
14 pathology of similar circumstances, I think one or
15 two levels would be reasonable, although again, it
16 would take away from the cleanliness of the data to
17 be able to analyze it.

18 I did remember the other issue I wanted to
19 bring up, and that is measurement of motion on
20 flexion-extension views, as I mentioned in my
21 earlier presentation, is very difficult to do as
22 far as a standardized method. It is probably going
23 to require the addition of beads in there so we can
24 do stereophotogrametry techniques, basically, and
25 look at whether the motion is real or parallax.

1 So I think we are going to have to
2 consider whether that is something that is going to
3 be critical or not, because that does add some
4 added implant risk and surgical morbidity.

5 DR. YASZEMSKI: Thank you.

6 Another thing I'd like to ask the panel
7 members for comment on for those devices, i.e.,
8 disc replacement and nucleus replacement, that are
9 anterior, is what if any information should we know
10 and/or ask about the status of arthritis in the
11 facette joints at the level we are putting the
12 anterior device in when evaluating the anterior
13 device?

14 Comments?

15 Dr. Aboulafia?

16 DR. ABOULAFIA: I wonder if that won't be
17 addressed by the indications for the product.

18 DR. YASZEMSKI: Dr. Kirkpatrick?

19 DR. KIRKPATRICK: I would suggest we
20 ignore the condition of the facettes from the
21 standpoint of the testing, because if the companies
22 find that if they have significant facette
23 pathology, and the patients continue with
24 significant pain and limited function, they are
25 going to eliminate that indication on their own.

1 DR. YASZEMSKI: Thank you.

2 Dr. Witten, we have talked about clinical
3 issues, the inclusion and exclusion criteria, and I
4 think the discussion indicated that we should study
5 a wide range of disease diagnoses, that the
6 indications for replacement versus fusion would be
7 an important aspect of any study design. We would
8 need to assess the adjacent segments and decide as
9 one of the outcome variables whether nonfusion
10 interventions would have any effect on adjacent
11 segment progression of degeneration and arthritis.

12 Success criteria should include pain and
13 functional improvements as reported by the patient,
14 and with respect to the ranges of motion question
15 asked, that the White and Punjabi data regarding
16 neutral zone, physiologic zone, and trauma zone
17 would be good guidelines, but that range of motion
18 in and of itself should not exclude--range of
19 motion considerations should not exclude projects
20 that otherwise have merit and could benefit
21 patients.

22 Have we discussed this adequately from
23 FDA's perspective?

24 MS. WITTEN: You have, except that I have
25 one little follow-on question.

1 DR. YASZEMSKI: Please go ahead.

2 MS. WITTEN: Basically, you have discussed
3 the range of motion question with respect, I would
4 say, to effectiveness, that is, if there is limited
5 range, the goal of the range shouldn't be
6 considered to be the goal of treatment success.
7 But is there an upper limit beyond which there
8 might be a safety concern--or, perhaps you have
9 answered that by referring to--

10 DR. YASZEMSKI: Yes. I think that
11 actually, Dr. Kirkpatrick covered that, and I am
12 going to ask him to comment on the White and
13 Punjabi transition between physiologic zone and
14 trauma zone.

15 I think you covered that; would you care
16 to comment again?

17 DR. KIRKPATRICK: I think it will be
18 addressed partly in the preclinical issues, because
19 they are going to have to characterize how much
20 motion is there. If you find out that it is 50
21 percent over what the White and Punjabi data is,
22 you are going to question it seriously, and so will
23 we as a panel. If it is within 10 percent of it,
24 we may not question it, because once it is
25 implanted, the scar tissue may correct for that.

1 Clinically, if you are going to measure
2 that, again, if it is going to fail, it is going to
3 demonstrate radiographic failure with either motion
4 of the component, a deformity developing in the
5 spine, that sort of thing--assuming the preclinical
6 stuff looks okay.

7 Does that address what you are wondering?

8 MS. WITTEN: Yes.

9 DR. YASZEMSKI: Thank you.

10 Dr. Finnegan?

11 DR. FINNEGAN: As he was discussing the
12 materials and the stiffness of the material, I am
13 wondering if the concern about a created spinal
14 stenosis by retropulsion of any of the materials
15 and how the stiffness of the material will affect
16 the area of the spinal canal and also the effect on
17 the cord and how much it will react to that. That
18 might be something that needs to be added.

19 DR. YASZEMSKI: Thank you.

20 Mr. Demian?

21 MR. DEMIAN: I would like to thank the
22 panel for their time and effort and energy today in
23 reviewing the material and for their participation
24 on this panel.

25 At this time, I would like to remind all

1 panel members that if you want the material
2 destroyed, just leave it in front of you.

3 And the last thing--this meeting is
4 adjourned.

5 Thank you.

6 [Whereupon, at 4:23 p.m., the proceedings
7 were concluded.]

8 - - -