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FOOD AND DRUG ADMINISTRATION

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ORTHOPEDICS AND REHABILITATION DEVICES
ADVISORY PANEL

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PUBLIC MEETING

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THURSDAY, JANUARY 10, 2002

The Advisory Panel met at 9:30 a.m. in the Walker/Whetstone Room of the Gaithersburg Holiday Inn, Two Montgomery Village Avenue, Gaithersburg, MD, Dr. Maureen Finnegan, Acting Chair, presiding.

PRESENT:

- Maureen Finnegan, M.D.
- Barbara D. Boyan, Ph.D.
- Betty Diamond, M.D.
- John Doull, Ph.D., M.D.
- Edward N. Hanley, M.D.
- John Kirkpatrick, M.D.
- John Kostuik, M.D.
- Kinley Larntz, Ph.D.
- Leon Lenchik, M.D.
- Stephen Li, Ph.D.
- Sally Maher, Esq.
- Richard K. Miller, Ph.D.
- Sanjiv H. Naidu, M.D., Ph.D.
- A. Hari Reddi, Ph.D.
- Karen Rue
- Gene P. Siegal, M.D., Ph.D.
- Rocky Tuan, Ph.D.
- Hany Demain, M.S.

Acting Chair

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

Executive Secretary

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

(9:41 a.m.)

1
2
3 MR. DEMIAN: Good morning, everyone. I
4 would first like to welcome you to this meeting.
5 We're ready to begin this meeting of the Orthopedic
6 and Rehabilitation Device Advisory Committee. My name
7 is Hany Demian, and I'm the Executive Secretary of
8 this Committee.

9 I'd first like to remind everyone that
10 you're requested to sign in on the attendance sheets
11 which are available outside the doors. You may also
12 pick up an agenda and information about today's
13 meeting, including how to find out about future
14 meeting dates through the advisory panel phone line
15 and how to obtain meeting minutes or transcripts

16 I will now read two statements that are
17 required to be read into the record. The first one is
18 the appointment to temporary voting member status and
19 the conflict of interest statement.

20 "Appointment to Temporary Voting Status;
21 pursuant to the authority granted under the Medical
22 Device Advisory Committee Charter, dated October 27th,

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1 1990 and as amended August 18th, 1999, I appoint the
2 following individuals as voting members of the
3 Orthopedic and Rehabilitation Device Panel for this
4 meeting on January 10th, 2002; Kinley Larntz, Sanjiv
5 Naidu, Leon Lenchik, Gene Siegal, John Kirkpatrick,
6 Barbara Boyan, John Doull, Betty Diamond, and Hari
7 Reddi. For the record, these individuals are special
8 government employees and consultants to this panel or
9 other panels under the Medical Device Advisory
10 Committee.

11 They have undergone the customary conflict
12 of interest review and have reviewed the material to
13 be considered at this meeting. In addition I appoint
14 Dr. Maureen Finnegan to serve as acting Chairperson
15 for the duration of this meeting", and this is signed
16 by David Feigal, Director of CDRH.

17 "Conflict of interest statement; The
18 following announcement addresses conflict of interest
19 issues associated with this meeting and is made part
20 of the record to preclude even the appearance of any
21 impropriety. To determine if any conflict existed the
22 agency reviewed the submitted agenda for this meeting

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1 and all financial interests reported by the
2 committee's participants. The Conflict of Interest
3 Statute prohibits special government employees from
4 participating in matters that could effect their or
5 their employer's financial interests.

6 However, the agency has determined that
7 the participation of certain members and consultants,
8 the needs for whose services outweigh the potential
9 conflict of interest involved is in the best interests
10 of the government. Therefore, waivers have been
11 granted for Doctors Stephen Li, Kinley Larntz, Edward
12 Hanley and John Kirkpatrick for their interest in
13 firms that could potentially be effected by the
14 panel's recommendations.

15 The waivers permit them to participate in
16 all matters before today's panel. Copies of these
17 waivers may be obtained from the agency's Freedom of
18 Information Office, Room 12A-15 of the Parklawn
19 Building. We would like to note for the record that
20 the agency also took into consideration other matters
21 regarding Doctors Li, Larntz, Maureen Finnegan,
22 Barbara Boyan and Gene Siegal.

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1 Each of these panelists reported current
2 or past interests in firms at issue but are not
3 related to today's agenda. The agency has determined,
4 therefore, that they may participate fully in all
5 deliberations. Dr. Hanley has a past involvement with
6 matters that are related to today's agenda. The
7 agency has determined, however, that he may
8 participate in the panel discussions.

9 We would like to also note that Doctors
10 Rocky Tuan and John Kostuik are guests at this meeting
11 and have reported interests in the firms at issue. In
12 the event that the discussions involve any other
13 product or firms not already on today's agenda, for
14 which an FDA participant has a financial interest, the
15 participant should excuse him or herself from such
16 involvement and the exclusion will be noted for the
17 record.

18 With respect to all other participants, we
19 ask in the fairness -- in the interest of fairness
20 that all persons making statements and presentations
21 disclose any current or previous financial involvement
22 with any firms whose products they may wish to comment

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1 upon".

2 Before turning this meeting over to Dr.
3 Finnegan, I would like to introduce our distinguished
4 panel members for generously giving their time and
5 effort to help FDA in matters being discussed at
6 today's meeting and other FDA staff seated at this
7 table. So we'll go around the room and give your name
8 and affiliation and your current areas of research.
9 Dr. Finnegan?

10 CHAIRPERSON FINNEGAN: Maureen Finnegan,
11 I'm an orthopedic surgeon at Southwestern Dallas and
12 I do -- my research is mainly fracture repair.

13 DR. KIRKPATRICK: I'm John Kirkpatrick.
14 I'm an orthopedic surgeon and spine surgeon from the
15 University of Alabama at Birmingham.

16 DR. SIEGAL: I'm Gene Siegal, also from
17 the University of Alabama at Birmingham and I'm an
18 anatomic pathologist.

19 DR. HANLEY: Edward Hanley, orthopedic
20 spine surgeon, Carolinas Medical Center, Charlotte,
21 North Carolina.

22 DR. DIAMOND: Betty Diamond, Albert

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1 Einstein College of Medicine. I'm an immunologist and
2 rheumatologist. I'm on sabbatical at NIH.

3 DR. DOULL: I'm John Doull. I'm a
4 clinical toxicologist from the University of Kansas
5 Medical School.

6 DR. LI: I'm Stephen Li. I'm interested
7 in biomechanics and biomaterials. I'm current
8 president of Medica Device Testing Innovations located
9 in Florida.

10 DR. WITTEN: Celia Witten. I'm the
11 Division Director of the Division of General
12 Restorative and Neurological Devices which is the
13 reviewing division for this product for FDA.

14 MS. MAHER: Sally Maher. I'm with Smith
15 and Nephew Endoscopy and I'm the industry
16 representative.

17 MS. RUE: I'm Karen Rue. I'm an R.N. I'm
18 consumer representative.

19 DR. LARNTZ: Kinley Larntz, Professor
20 Emeritus, Statistics, University of Minnesota and I'm
21 a statistician interested in clinical trials.

22 DR. LENCHIK: Leon Lenchik,

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1 Musculoskeletal Radiologist from Wake Forest
2 University in Winston-Salem, North Carolina.

3 DR. REDDI: I'm Hari Reddi. I'm a student
4 of bone morphogenetic proteins.

5 DR. BOYAN: Barbara Boyan. I'm a
6 professor at the University of Texas Health Science
7 Center at San Antonio and my specialty is bone and
8 cartilage cell biology.

9 DR. NAIDU: Sanjiv Naidu. I'm an
10 orthopedic surgeon at Penn State College of Medicine
11 in Hershey and my interest is in biomechanics and
12 orthopedic surgery.

13 MR. DEMIAN: In addition, I'd like to
14 introduce our three guests who are seated over here,
15 Dr. Richard Miller, Rocky Tuan and John Kostuik.

16 CHAIRPERSON FINNEGAN: Thank you, Hany.
17 As I previously stated, I'm Maureen Finnegan and I
18 will be the chair for this meeting. Today the panel
19 will be making recommendations to the Food and Drug
20 Administration regarding a pre-market approval
21 application for a spinal fusion cage with a growth
22 factor soak in a collagen sponge use to treat lumbar

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1 degenerative disc disease.

2 I need to note for the record that the
3 voting members present constitute a quorum as required
4 by 21 CFR Part 14 and we will now proceed with the
5 open public hearing session of this meeting I would
6 like to ask at this time that all persons addressing
7 the panel come forward and speak clearly into the
8 microphone. The transcriptionist is dependent on this
9 as a means of providing an accurate record of this
10 meeting.

11 We would request that all persons making
12 statements during the open public hearing of the
13 meeting disclose whether they have financial interests
14 in any medical device company. Before making your
15 presentation, please state your name, affiliation and
16 the nature of your financial interest if you have any.
17 There's obviously someone who wishes to address the
18 panel.

19 MS. TRISLER: Good morning, my name is
20 Patsy Trisler and I'm a regulatory consultant at
21 PharmaNet, Incorporated, a contract research
22 organization. As an employee of PharmaNet, I have

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1 several clients who are orthopedic product
2 manufacturers but I have no financial interest in any
3 of them.

4 CHAIRPERSON FINNEGAN: Ms Trisler, you had
5 made a request to make an oral presentation.

6 MS. TRISLER: Yes.

7 CHAIRPERSON FINNEGAN: What we would like
8 to do is ask those people who had not made such a
9 request, we do have two -- a request for oral
10 presentations which we have put into the program and
11 that's the next part of the program, so we would ask
12 those people who had not made such a submission if
13 they would like to make a presentation.

14 MS. TRISLER: All right, I apologize.

15 CHAIRPERSON FINNEGAN: So if you'd give us
16 one second. Is there anyone else other than the two
17 parties who had made a formal request to make an oral
18 presentation?

19 (No response)

20 CHAIRPERSON FINNEGAN: All right, if not,
21 then we have had two requests. One is from Osteotech
22 and one is from Striker Biotech and we will start with

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1 Ms. Trisler. Go ahead.

2 MS. TRISLER: Thank you and I apologize
3 for jumping the gun. As I indicated, I'm an employee
4 of PharmaNet, Incorporated which is a CRO. I would
5 like to thank the Chairperson and the FDA Executive
6 Secretary for providing the opportunity to speak to
7 you today.

8 The purpose of my brief presentation is to
9 express some concerns in the form of potentially
10 unanswered questions relating to the combination
11 products of the type under review today by this
12 committee. As you know, there have been several
13 spinal fusion cages or systems approved by the FDA
14 over the last five years. These products approved for
15 treating degenerative disc disease are to be used with
16 autogenous bone grafts.

17 Papers are being published reporting the
18 successes observed with the use of the cages. It is
19 clear also that there remains some problems or issues
20 such as subsidence. The focus of my comments, though,
21 is not on the cages but rather on the biologic
22 component of the device, the bone morphogenetic

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1 protein or BMP.

2 As I'm sure you are aware even though BMPs
3 have been under evaluation clinically now for about 15
4 years, only one has been allowed into the marketplace
5 by the FDA. The approval is a limited one in the form
6 of a humanitarian device exemption for treating long
7 bone, non-unions when alternative treatments have
8 failed. That product is human recombinant BMP-7 and
9 bovine bone derived collagen.

10 This PMA before you today represents an
11 important advance in medical device technology. BMPs
12 and other growth factors are potent compounds that
13 offer significant promise in many therapeutic areas.
14 Further, the potential of BMPs or other growth factors
15 combined with traditional medical devices is
16 significant. However, before the first combined
17 product of this type achieves market approval, it's
18 very important to be certain all the appropriate
19 questions have been addressed, have been both raised
20 and addressed and as I indicated, this is the reason
21 I'm speaking.

22 I do not know the full extent of Medtronic

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1 Sofamor Danek safety and effectiveness data. However,
2 I do know this is a reputable company and my comments
3 are by no means meant to challenge the capabilities,
4 integrity of the data or quality of the studies
5 performed by them. While we recognize that Center for
6 Biologic staff participates in reviews of products of
7 this type along with the Devices Center, the issues
8 posed by the biologic component are quite different
9 from the issues typically presented to this committee.

10 The standard of proof is different for
11 drugs and biologics than for devices. Thus, the
12 guidances provided by the FDA in those areas are
13 different. The issues that prompt the following
14 questions, in fact, are not covered in the devices
15 guidance document for spinal systems. As a member of
16 the public, I ask that you consider these questions in
17 your deliberations.

18 My first point is related to cancer
19 promotion. Cancer promotion by cytokine growth
20 factors is well known, particularly when circulating
21 blood levels are greater than normal or baseline as in
22 the case of recombinant BMP. My question is, is

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1 enough known about the cancer promoting capability of
2 BMPs. I question the status if this growth factor,
3 BMP-2 as a cancer promoting compound.

4 In my review this morning of the panel
5 briefing materials, my very quick review, I was
6 surprised that FDA has agreed that certain non-
7 clinical safety studies may be conducted post-
8 approval. If transformed cells or other adverse
9 events are seen after this implant has been released
10 to the market, what is the surgeon to tell the
11 patient?

12 I noted in the BMP-7 product that is
13 approved, that patients with a cancer history are
14 contra-indicated for the current -- for that product
15 approval. Will it be necessary to similarly contra-
16 indicate this BMP that is before you today or is the
17 risk to benefit fully profiled?

18 My second point relates to the immunology
19 area. Circulating antibodies to both Type I collagen
20 and BMPs are reported. I know the FDA has dealt with
21 this matter in the collagen area for many years. Are
22 enough data available to demonstrate there is no

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1 correlation between these antibodies and health or
2 medical events? Is the safety risk greater if a BMP
3 is inappropriately and perhaps inadvertently applied
4 directly to the spinal canal? Has the autoimmune
5 reaction potential been fully evaluated?

6 My third point relates to cardiovascular.
7 Cardiac adverse events and increased blood pressure
8 and body temperature have been reported in animal
9 studies. The effects reported are dose dependent. Is
10 there sufficient assurance that benefits of the use of
11 the BMP collagen mixture in a sensitive body area are
12 outweighed by the potential risk to the cardiovascular
13 system? The other BMP approved for orthopedic use and
14 this one are provided with collagen as a carrier.

15 While I realize this may -- this question
16 may not be particularly important, since there are
17 potentially greater risks with the use of a growth
18 factor in the spine than there are at a long bone non-
19 union site, are data available to show that collagen
20 alone is not effective in improving the rate of spinal
21 fusion?

22 I believe this next point deserves

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1 particular attention. As is well-known, the early
2 work of Dr. Urist demonstrated the ability of a bone
3 inductive extract from adult bone to induce new bone
4 formation at ectopic sites. Have the studies
5 published since that time sufficiently looked at the
6 quality of the bone produced and at the risk of
7 uncontrolled growth of bone in the immediate and
8 surrounding region of the implant? I have heard of
9 one case in which bone grew into the spinal canal
10 although I'm unaware of the extent of the problem.

11 Has a full enough evaluation been
12 performed to be reasonably sure that if a large amount
13 -- if a larger amount than indicated is applied in the
14 spinal fusion area, the risk of in-growth won't occur.
15 There is one final issue relating to a problem that is
16 not limited to orthopedic devices, the expanded or
17 off-label use in the medical community of a product
18 approved for a very limited indication.

19 While I believe the medical community, not
20 the government, should control the practice of
21 medicine, in this case it seems the risk is
22 significant for off-label use of the BMP component of

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1 this device system. Because of this, I feel that it
2 is important for the panel to, perhaps, give more
3 consideration than is usually done to this issue. As
4 I noted earlier, many of the reported adverse events
5 were dose dependent.

6 Since BMPs are potent compounds that have
7 systemic effects and this particular product is the
8 first of a kind for this use, I am concerned that the
9 pharmacodynamics may not be fully understood. After
10 this product type is out in the marketplace, if it is
11 misused or misapplied, the potential for patient harm
12 is great.

13 In closing, I ask the panel to give
14 special attention to the potential for off-label use.
15 I realize I have just scratched the surface of a
16 number of areas and have not provided you with
17 substantive information or data and that others,
18 perhaps, will raise some more concerns. I am hoping,
19 though, that none of these topics remain issues after
20 today's review. This concludes my comments. Thank
21 you for this opportunity.

22 CHAIRPERSON FINNEGAN: Thank you for

1 having the interest. I did interrupt you when you
2 were going through your financial interest. Would you
3 mind reviewing those?

4 MS. TRISLER: Yes. No, I would not mind.
5 I am employed by PharmaNet, which is a contract
6 research organization. As such, I have clients in
7 many areas. I have several clients in the orthopedic
8 product area. I have no financial interest in any of
9 them.

10 CHAIRPERSON FINNEGAN: So you're a
11 consulting firm.

12 MS. TRISLER: Yes.

13 CHAIRPERSON FINNEGAN: Okay. And I
14 believe our next presenter is from Striker Biotech.

15 DR. McCULLOUGH: My name is John
16 McCullough and I'm an orthopedic spine surgeon from
17 Denver, Colorado. I am not from Striker Biotech. I'm
18 here to offer an opinion regarding today's discussion
19 on the BMP-2 interfex threaded fusion cage PMA and I
20 thank the panel for granting me permission to speak.
21 My travel has been paid for by Striker Biotech. I
22 have no financial interest in the company and I'm not

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1 a paid consultant.

2 I've participated in the Striker Biotech
3 pilot study using BMP-7 in the human lumbar
4 intertransverse interval for which my institution
5 received research funds to cover the cost of the
6 study. Contrary to questions by my colleagues prior
7 to this meeting, I am here in a positive relationship
8 with BMP, not a negative relationship.

9 Studies of BMP-2 and BMP-7 have shown
10 great promise as potential osteo inductive
11 replacements for iliac crest autograft for bone
12 healing in appendicular and spinal fusion
13 applications. In working with BMP-7 in the lumbar
14 inter-transfers interval, I am impressed with its
15 effectiveness, but I'm also impressed with the
16 meticulous technique required to increase the
17 likelihood of a solid fusion.

18 It is a much less forgiving milieu for
19 fusion than the interbody interval mainly because it
20 is a soft tissue bed on which the body never intended
21 bone to form. A solid anterior lumbar interbody
22 fusion is a relatively easy outcome to achieve but

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1 it's a technically demanding surgical approach fraught
2 with serious complications. The lumbar
3 intertransverse fusion is just the reverse. It's an
4 easy, safe, posterior surgical technique but obtaining
5 a solid fusion is much more difficult.

6 As an example, allograft bone will often
7 successfully incorporate in an interbody fusion model
8 but it is useless in the adult intertransverse
9 interval. The success of fusion with BMP-2 in a
10 collagen sponge with the interfixed threaded fusion
11 cage, the subject of today's discussion, is well
12 established by the research of Boden's Zdeblick, Sandu
13 and Hine.

14 The researchers, the brave patients who
15 submitted themselves to this largely successful pilot
16 study and the company supporting the research are to
17 be congratulated. It is not my purpose today to call
18 into question the efficacy of BMP-2 and its use in an
19 interbody fusion with the interfixed threaded fusion
20 cage. My concern, as with the last speaker's last
21 point, is the potential off-label use of BMP-2 soaked
22 in a collagen sponge.

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1 There is a potential for surgeons to take
2 an off-label approach if the panel does not carefully
3 consider the labeling and packaging considerations
4 available with this product and provide the option
5 that will prove to be the best direction and control
6 of the product and its potential off-label use. One
7 off-label use for this BMP-2 collagen sponge model is
8 the lumbar intertransverse interval. My concern for
9 such usage is found in the research work done by
10 Martin Boden, et al in the posterior lateral
11 intertransverse fusion non-human primate model.

12 The efficacy of the BMP soaked in a
13 collagen sponge, in this particular intertransverse
14 fusion application was negatively impacted by the soft
15 tissue and muscle compressing the sponge and thereby,
16 compressing the growth factor out of the sponge. This
17 led to an unexpectedly high failed fusion rate. It is
18 easy to conclude that this scenario would conclude in
19 humans with BMP-2 and a collagen sponge carrier. In
20 this setting the potential is for the muscle to
21 compress the collagen sponge and leak the BMP-2 away
22 from where the bone is intended to form.

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1 To induce new bone formation, it is not
2 currently feasible or practical to apply BMP directly
3 into a bone void for the purpose of bone growth. A
4 carrier is needed for a number of reasons. One of the
5 main reasons is for the containment of the growth
6 factor at a site where bone growth is needed. A
7 carrier is also needed for stem cell attachment and to
8 provide a structural matrix for bone growth.

9 Well, BMP-2 and BMP-7 have been shown to
10 be two of the most effective BMPs in the bone healing
11 cascade, the carriers used by these BMPs and
12 ultimately the orthopedic application site in which
13 they are placed can effect their efficacy regardless
14 of their potency. BMP-2 and the studies being
15 discussed today has been used with a fibular
16 hemostatic collagen sponge carrier placed in the
17 interfix titanium threaded interbody cage.

18 In this application, liquid BMP-2, a
19 combination of BMP and sterile water, is applied into
20 the collagen sponge inter-operatively and allowed to
21 soak into the sponge. The sponge is then rolled and
22 placed into the cage. In this application it is

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1 important to note that the BMP collagen sponge
2 combination is protected by the structure of the
3 titanium cage.

4 In the intertransverse interval, this same
5 BMP-2 soaked collagen sponge would enjoy no cage
6 protection. Rather as Boden et al suggested, its
7 compression by muscle would possibly lead to extrusion
8 and dissipation of the BMP-2 and a failed bone
9 induction.

10 Bone morphogenic protein research
11 represents an exciting and new opportunity for
12 surgeons and patients alike that over time may
13 revolutionize the way we treat our patients. Getting
14 rid of the bond graft harvest is an exciting concept
15 and could possibly overrun the relative lack of
16 knowledge amongst my colleagues about this technology.
17 There may be a temptation to push the envelope when it
18 comes to indications and applications. With this new
19 opportunity, also comes the responsibility and
20 challenge of not only appropriate patient selection
21 but also appropriate product labeling.

22 My strong assertion and belief is that we

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1 need to make every effort possible to insure the
2 health and benefit of our patients through appropriate
3 labeling in regards to this PMA. The BMP-2 collagen
4 sponge device has been tested in an IDE study for
5 specific spine pathology with a specific type of
6 branded cage in the interbody interval.

7 If approved, I hope the indication for use
8 will be for this particular combination of BMP carrier
9 and cage product. Since this product was tested as a
10 combination product cage with BMP, the requirement
11 that they be packaged together the way they are
12 intended to be used is reasonable and logical. This
13 provides an additional and important opportunity to
14 further insure that the use of the growth factor will
15 be used in an application where efficacy has been
16 proven.

17 Off-label use in areas such as the
18 posterolateral intertransverse fusion will not be
19 eliminated as an option to my colleagues, but
20 packaging the BMP and cage together will limit the
21 product's use in an unproven and potentially flawed
22 application.

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1 In concluding, I defer to commenting on
2 the final approvability of this product. I am an
3 enthusiastic supporter of the BMPs but in the event it
4 is voted to be approved, I would recommend that the
5 combination of the interfixed cage and BMP-2 be
6 specifically required to be ordered together and
7 packaged together to insure the product is used as has
8 been tested. I would also recommend that off-label
9 use of BMP-2 and the collagen sponge in areas outside
10 of the application such as the intertransverse
11 interval be addressed in the product labeling.

12 Thank you.

13 CHAIRPERSON FINNEGAN: Thank you. Dr.
14 Witten.

15 DR. WITTEN: We also need to ask the prior
16 speaker who paid her way, whether she paid her way or
17 whether her way was paid for.

18 CHAIRPERSON FINNEGAN: Okay, I'll have her
19 come back. Dr. McCullough, thank you very much. Ms.
20 Trisler, is she still with us? While she's coming up,
21 are there any other persons who would wishy to make a
22 comment? Go ahead.

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1 MS. TRISLER: I'm sorry, what was the
2 question?

3 CHAIRPERSON FINNEGAN: Who paid your way
4 to the meeting?

5 MS. TRISLER: As a consultant Osteotech
6 has.

7 CHAIRPERSON FINNEGAN: Has paid your way
8 to the meeting?

9 MS. TRISLER: Well, yeah, I live here but
10 they paid my time.

11 CHAIRPERSON FINNEGAN: Thank you. All
12 right, if there are no other people wishing to make
13 comments, Mr. Demian has received eight letters
14 regarding this meeting and he will now read them into
15 the record.

16 MR. DEMIAN: I've receive eight letters
17 and seven of them are from spinal surgeons, all
18 letters regarding the use of BMP. The first letter is
19 from Dr. Regis Haid.

20 "I am currently the chief spine surgeon
21 for the Department of Neurosurgery at Emory University
22 in Atlanta, Georgia. I have no vested financial

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1 interest in the product being discussed before the
2 panel. I've developed products for cervical spine for
3 various companies, including Medtronic, Codman and
4 Spinal Concepts. These may be considered by some to
5 constitute an indirect conflict of interest. I've
6 received no remunerations for my interest in BMP.

7 Our group has been involved in the use of
8 BMP. We have been given presentation on fusion
9 techniques at national and international meetings and
10 have briefly discussed the experimental use of BMP.
11 We have actually published a paper in the Neuroscience
12 Focus on the use of BMP. From my knowledge of the
13 studies and presentations I've heard presented by
14 other spinal surgeons, I do believe that BMP offers a
15 significant advantage in the practice of spine.

16 It is very clear from my experience that
17 the literature in neurosurgery and orthopedics state
18 that autograft sites do present a well array of
19 complications. It is also commonly known that
20 harvesting the autograft iliac crest adds time to
21 surgery and expense in the operating room and pain to
22 the patient is always part of the harvesting autograft

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1 iliac crest.

2 I would ask the panel to recommend to the
3 FDA to expedite their approval of this product. This
4 would prevent further suffering of patients that occur
5 with every autograft bone harvest as well as
6 potentially decreasing the time in the operating room
7 and, thus, potentially decrease the total cost to the
8 patient. Having reviewed the data from the academic
9 perspective, it seems very clear to me its efficacy is
10 clear-cut in the use in lumbar interbody anterior
11 devices and that the product should be made available
12 to the American public.

13 Although I'm not an expert on the FDA, it
14 is my belief that FDA required a small pilot study for
15 this device under review and this was done before a
16 large pivotal study could begin. If this is indeed
17 the case, I believe this was unnecessary and prompted
18 a delay of the release of this product which
19 definitely benefits patients. I would suggest that
20 the Orthopedic Advisory Panel recommend to FDA not to
21 require these types of pilot studies for similar
22 issues in the future".

1 The second letter is from David Malone.
2 "I would like to add some information to the pre-
3 market approval application for a spinal fusion cage
4 with growth factors soaked in a collagen sponge
5 intended for treatment of lumbar degenerative disease.
6 I took part as one of the investigators in the
7 posterior lumbar interbody fusion BMP trial sponsored
8 by Medtronic Sofamor Danek Corporation.

9 Dr. Frank Tomecek was the lead
10 investigator for our small group. There were a number
11 of patients that were treated with the PLIF. Two of
12 the patients had significant posterior bony over-
13 growth impinging on their nerve roots requiring
14 additional surgery. One patient, who was my patient,
15 required two surgeries to clear excessive bone growth
16 from his spinal canal. He has had no new bone growth
17 over the past year. I am unsure as to whether or not
18 this data has been included in the application to the
19 FDA.

20 I've been told that the posterior lumbar
21 in a body fusion cage trial was halted. I assume it
22 was because of this bony overgrowth problem. With

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1 regard to the patients with bony overgrowth, I
2 personally experience -- my personal experience in re-
3 operation on both of these patients, the bone quality
4 from the BMP is robust and excellent. The fusions are
5 solid. I do feel that the BMP is a useful adjunct to
6 bony spinal fusion.

7 However, BMP may lead to excessive bone
8 growth and may cause significant neural impingement if
9 placed in posterior lumbar interbody type of device.
10 There does need to be at this point in time some type
11 of barrier between the area where the bone can
12 overgrow and the neural elements. I note that Dr.
13 Frank Tomecek and Sofamor Danek did further
14 experimental studies on the PLIF model but I do not
15 have the data. I know the data does exist and may be
16 helpful if you are considering approval of this
17 material for a posterior lumbar interbody fusion type
18 of approach.

19 If BMP is approved for spinal fusion, and
20 I feel that it would be useful adjunct, the caveat is
21 that it must be placed in such a manner that bony
22 overgrowth cannot grow into the spinal canal as I

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1 think this would cause significant problems for a
2 proportion of the patients whom it is used in".

3 The next letter is from Dr. Robert Banco.
4 "As chief of the spine section of the New England
5 Baptist Hospital, my colleagues and I are pleased to
6 have participated in the rhBMP-2/ACS/LT open clinical
7 trial. Serving as the principal investigator, two co-
8 investigators and myself are members of the Boston
9 Spine Group, four orthopedic surgeons and one
10 physiatrist with a practice dedicated solely to spine.

11 As a group we perform over 400 spinal
12 fusions annually many of which are accompanied by
13 iliac crest harvesting. As you know, harvesting
14 patients with iliac crest increases the risk of
15 complications, including but not limited to infection,
16 nerve damage and possible damage to the muscles and
17 vessels. Donor site pain is by far the most common
18 complication and patient complaint.

19 BMP-2 supplants the need for harvesting
20 the iliac crest and therefore, negates the risk of
21 these complications. We at the Boston Spine Group
22 have heard many presentations and have read the

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1 literature regarding BMP-2. We are excited by the
2 reported outcomes. We are anxious for this product to
3 get out of the lab and into the clinical practice and
4 are looking forward to the use of InFUSE™ in the
5 clinical setting".

6 The next letter is from Dr. Paul
7 McCormick. "I'm a full time faculty member at
8 Columbia University of Physicians and Surgeons. My
9 practice is exclusively limited to the evaluation and
10 surgical management of patients with spinal disorders.
11 By the way of disclosure, I have no financial or other
12 vested interest in the products that are being
13 discussed before the panel.

14 As a full time spine surgeon at a major
15 academic center, I'm well aware of active research
16 that has been conducted for years regarding biological
17 enhancement of spinal fusion. Like many other spine
18 surgeons, I look forward with great anticipation when
19 effective agents will be commercially available for
20 the utilization in spinal fusion. Spinal fusion is an
21 important technique for many patients who have lost
22 their mechanical integrity of their spinal elements

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1 through trauma, degenerative changes, neoplasm, or
2 disc herniations in prior surgery.

3 A major problem related to the spinal
4 fusion is the harvesting of the autograft which is
5 usually required for a vast majority of spinal fusions
6 currently performed. The pain and morbidity
7 associated with autograft harvest can be considerable.
8 Often this pain persists over time and may be
9 permanent.

10 Further, despite significant advances in
11 fusion techniques and spinal instrumentations, a
12 measurable number of patients continue to suffer from
13 failed fusion or pseudoarthrosis. Therefore, any
14 useful adjunct that can be utilized to facilitate and
15 enhance spinal fusion would be of tremendous benefit
16 to patients with spinal disorders requiring this type
17 of surgery. In essence, there's a tremendous need for
18 biological fusion enhancers such as BMP that diminish
19 the reliance on autograft harvesting as well as
20 enhancing the rate and the success of spinal fusion.

21 I'm also well aware of the research that
22 is currently being conducted at numerous centers

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1 regarding BMP. To my critical review, BMP has shown
2 exciting promise in enhancing spinal fusion and bone
3 incorporation. I fully appreciate the
4 responsibilities of the FDA in general and of your
5 panel in particular in acting in the public interest
6 through oversight on the approval and introduction of
7 these devices and agents. I would respectfully
8 request that such evaluation be carried on in an
9 expedited fashion so that if BMP satisfies the FDA
10 requirements for approval, we can utilize this
11 substance in a timely manner.

12 Such an expedited approval would likely
13 reduce the pain and suffering of future patients that
14 are requiring spinal fusion".

15 The next letter is from J.J. Abitol. "I'm
16 a practicing spinal surgeon, also a current board
17 member of the North American Spine Society where I
18 have been a past scientific program chairman.
19 Although there is no current official position
20 statement from the Society, I would like to express my
21 opinion about bone morphogenetic proteins or BMPs.
22 Being familiar with the research in this area, I can

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1 say with certainty that BMP has been one of the most
2 heavily researched subject matters in all of
3 orthopedics.

4 Since the late Dr. Marshall Urist first
5 discovered these proteins over 30 years ago, and
6 unprecedented amount of publications and research
7 efforts have been dedicated to studying these
8 proteins. For all practical purposes, all of these
9 studies have demonstrated to the research and medical
10 community that safe and new alternative to taking
11 autograft is now at hand.

12 I strongly urge this panel to approve
13 these desperately needed proteins and make Dr. Urist's
14 dream of having bone graft in a bottle a reality. It
15 is time to take these type of proteins out of research
16 and make them available to surgeons to use in our
17 clinical practice to treat patients".

18 Our next letter is from Dr. John Pelorza.
19 "I'm a nationally recognized spine expert with a
20 tertiary specialty practice in Dallas, Texas. In my
21 practice I perform many spinal fusion procedures on
22 all levels of the spine from the skull to the sacrum.

1 These fusions are done from an anterior, posterior and
2 sometimes combined approach.

3 I'm often challenged by difficult spinal
4 reconstruction problems secondary to disease processes
5 including spinal deformity, degeneration, trauma,
6 tumor and infection. My team and I have been and are
7 presently involved in multi-center studies evaluating
8 spinal surgical implants minimally invasive and non-
9 surgical technologies as well as biological
10 technologies for the treatment of spinal disorders.

11 I'm an authority on bone morphogenetic
12 protein from my experience as a clinical investigator
13 with rhBMP-2, professional presentations, knowledge of
14 the scientific literature, national and specialty
15 meetings and think tanks. I have direct experience
16 with the impressive clinical results on my own
17 patients utilizing this protein.

18 Presently we have a number of bone graft
19 alternatives. The gold standard is the patient's own
20 bone or autograft. It is osteogenic, contains viable
21 bone cells at transplantation, osteo inductive,
22 actively promotes or enhances bone formation and osteo

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1 conductive, acts as a structural framework or scaffold
2 for bone formation. Unfortunately, it is in limited
3 supply, e.g. the patient's iliac crest.

4 In many cases we have very little or no
5 autograft at all. Additionally, the bone graft
6 harvest surgery contributes significantly to post-
7 operative pain that can be permanent and can lead to
8 other complications. When autograft is not available
9 or inadequate, surgeons use allograft, bone bank or
10 cadaver bone. Allograft bone is mainly osteo
11 conductive, weakly osteo inductive and has no
12 osteogenetic properties.

13 Depending on the surgical construct,
14 allograft fusion rates are lower than autograft and
15 take much longer to heal. Due to the massive demand
16 for bone graft worldwide, allograft bone is also in
17 limited supply. Additionally, allograft bone has a
18 risk of disease transmission. Modern bone processing
19 is effective in eradication of bacteria and viruses.
20 However, prions are very difficult to detect and no
21 processing has been validated for their removal.

22 After autograft and allograft, surgeons

1 can use bone graft extenders, demineralized bone
2 matrix. These products are mainly osteo conductive,
3 poorly osteo inductive if at all, and not osteogenic.
4 They are the last line of bone graft material and
5 informed surgeons have little confidence in their
6 efficacy in obtaining a solid fusion.

7 Recombinant human bone morphogenetic
8 protein is an attractive infusion surgery for many
9 reasons. The fusion rates in animal models and in
10 human trials is the same or better than the gold
11 standard autograft. With a production facility there
12 would be an unlimited supply of rhBMP. RhBMP will
13 eliminate the need for bone graft harvesting surgery
14 which will eliminate the associated pain, potential
15 complications and cost.

16 There will be no chance of disease
17 transmission. The major cost of sponsored surgery is
18 when the surgery fails. This can occur secondary to
19 a major complication such as infection but the most
20 common reason for failed surgery is the failed fusion
21 or pseudoarthrosis. This is a problem that vexes all
22 spinal surgeons.

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1 A product that markedly enhances our
2 ability to heal bone with few documented side effects
3 is an extremely powerful tool in the treatment of
4 spinal disorders. RhBMP is a breakthrough product
5 that represents the best of our research and advances
6 technologies. It has been thoroughly tested in animal
7 models and human trials. It has consistently proven
8 better and safer than our present alternatives. It is
9 time to get rhBMP into the clinical arena where it is
10 desperately needed for the optimum care of people.

11 Finally, I would like to state I have no
12 financial interest in the product rhBMP-2 nor do I
13 have a financial interest in the company that is
14 sponsoring rhBMP-2".

15 Second to the last letter from a trio,
16 Stephen Papadopoulos, Curtis Dickman and Volker
17 Sonntag. "We practice primarily spine surgery at the
18 Barrow Neurological Institute in Phoenix, Arizona.
19 Our practice consists of regional and national and
20 international referrals. We have no vested financial
21 interest in the specific product being discussed
22 before the panel.

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1 We have been aware of the field of BMP
2 research for several years through peer review,
3 publications and scientific presentations. We
4 strongly believe the clinical availability of this
5 product in the United States will significantly
6 enhance patient care. Graft site complications from
7 autograft harvest are well described and documented.
8 The availability, quality and healing issues related
9 to allograft is also well known.

10 Fusion failure may result in chronic pain,
11 deformity and the need for additional spinal
12 reconstructive procedures. We believe that the
13 approval of BMP will provide a significant advance in
14 the patient outcome and satisfaction".

15 The last letter is from Dr. Doug Morrow.
16 "It is my understanding that you are about to discuss
17 and vote on approval or rejection of rhBMP. I want my
18 voice to be one that you may not otherwise get in the
19 sense that I am both a physician and a patient waiting
20 on the approval of this enzyme to fuse my lumbar
21 spine. I have rather an unusual set of circumstances
22 wherein I got an infected disc in my lower back

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1 because of an injection called a discogram.

2 The infection all but destroyed two lumbar
3 vertebrae, leaving me in constant pain for the
4 instability associated with the deformity. I've been
5 keeping up with all the literature on the subject and
6 especially this enzyme which speeds up the natural
7 healing process of growing bone. I'm a perfect
8 candidate for this material to be used in surgery on
9 my back. I've been waiting for its use for some time
10 delaying my surgery because of it.

11 I have back pain every day all day. I
12 urge you prompt approval of this material so that my
13 doctor can then use it on me as soon as possible.
14 There are many people just like me who need help.
15 Please help us. I beg you and thank you from the
16 bottom of my heart".

17 That's it.

18 CHAIRPERSON FINNEGAN: Thank you, Mr.
19 Demian. You may get an award for that. We will now
20 proceed to the presentation of the pre-market approval
21 application P000058, Medtronic Sofamor Danek InFUSE™
22 bone graft/LT-cage lumbar tapered fusion device. I

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

6 We will proceed first with the sponsor's
7 presentation followed by the FDA presentation. I
8 would like to ask each speaker to state his or her
9 name, their affiliation and I would ask everyone to
10 please speak into the microphone so that people in the
11 back of the room can hear you but also most
12 importantly so that transcriptionist can hear you.
13 The sponsors, if they would like to come up, could
14 start.

15 DR. LIPSCOMB: Members of the Orthopedic
16 and Rehabilitation Devices Advisory Panel, my name is
17 Bailey Lipscomb and I'm the Vice President of Clinical
18 Affairs at Medtronic Sofamor Danek in Memphis,
19 Tennessee. We have the pleasure and the long awaited
20 privilege to present to you the results of decades of
21 research, development, and clinical studies. At the
22 outset, we would like to thank literally thousands of

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1 people who have worked over the years to make these
2 presentations possible. For the next 90 minutes we
3 will present for the first time to an FDA advisory
4 panel the culmination of work arising from a discovery
5 made by Dr. Marshall Urist in 1965.

6 Dr. Urist found that certain proteins
7 which he later terms as bone morphogenetic proteins,
8 stimulate the formation of bone and these proteins can
9 literally make bone where bone did not exist before.
10 In the early 1980's researchers of Wyeth-Genetics
11 Institute in Cambridge, Massachusetts developed a
12 method to synthesize several of these bone
13 morphogenetic proteins using recombinant methods.

14 The BMP-2 yields from these methods are
15 much greater in quantity and much purer in nature than
16 can be obtained from natural sources. The bone
17 morphogenetic protein that will be reviewed today is
18 recombinant human bone morphogenetic protein 2 or more
19 commonly known in its abbreviated form as rhBMP-2 and
20 this is made by Wyeth-Genetics Institute.

21 The rhBMP-2 is supplied as a sterile
22 freeze-dried powder that is reconstituted at the time

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1 of surgery with sterile water to a concentration of
2 1.5 milligrams per milliliter. The solution is then
3 applied to absorbable collagen sponge. The sponge
4 provides the matrix to retain the rhBMP-2 in the
5 desired location sufficiently long to stimulate the
6 formation of bone cells.

7 The absorbable collagen sponge is a
8 commercially available product that is made by Integra
9 Life Sciences of Plainsboro, New Jersey. FDA approved
10 the PMA application for the absorbable collagen sponge
11 back in 1981. Medtronic Sofamor Danek has named the
12 combination of rhBMP-2 with the absorbable collagen
13 sponge as InFUSE™ bone graft. This PMA application
14 for InFUSE™ covers this use with Medtronic Sofamor
15 Danek's LT-cage lumbar tapered fusion device, not the
16 interfix device that Dr. McCullough mentioned but the
17 LT-cage device.

18 The LT-cage device is a hollow fenestrated
19 titanium alloy threaded interbody fusion device. FDA
20 approved the PMA application for this device over a
21 year ago. Typically two cages are inserted in
22 parallel from an anterior surgical approach in lumbar

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1 spinal fusion procedures. In current medical practice
2 bone graft is harvested from the iliac crest, is
3 packed into the LT-cage devices. This is stipulated
4 in the labeling of the device.

5 Autogenous bone graft augments the fusion
6 of the treated segment and it is now considered a
7 standard of care graft material. Today, however,
8 we're seeking an approval recommendation from this
9 panel to use infused bone graft instead of autogenous
10 bone graft to pack the central cavities of the LT-cage
11 devices. Let's focus more closely on what is at issue
12 here today.

13 It is not the LT-cage device. This
14 product is commercially available for the same medical
15 indication, that is symptomatic degenerative disc
16 disease, and for the same manner of use, anterior
17 antibody lumbar fusion procedures. It is not the
18 absorbable collagen sponge that has been FDA approved
19 as an implantable hemostatic agent. It has a long
20 history of safe and effective use dating back over 20
21 years. The real issue today is the safety and
22 effectiveness of rhBMP-2 when used with the two

1 previously approved products and whether it is a
2 suitable replacement for autogenous bone graft, the
3 gold standard, in antibody fusion procedures.

4 We believe the years of basic research and
5 development of this product have yielded considerable
6 evidence to support the safety and effectiveness of
7 the product. Further, the infused bone graft LT-cage
8 device is supported by clinical data arising from a
9 large multi-centered prospective randomized clinical
10 trial, a desirable scientifically valid study design,
11 but one that is rarely used for orthopedic implants in
12 the United States due to its difficulty in execution.

13 This study embodies an idyllic scientific
14 research. Eliminate as much of the variation as
15 possible except for the variable being studied. In
16 this study that's exactly what occurred. Patients met
17 the same study entrance criteria and received the same
18 interbody fusion cage. The only variable was the
19 50/50 chance that a patient would receive either
20 infused bone graft or would receive autogenous bone
21 graft in their surgery.

22 It is our opinion that this study

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1 presented today overcomes virtually all of the
2 objections to study trial designs that have been
3 voiced over the years by this orthopedic advisory
4 panel. These clinical data as well as the pre-
5 clinical test results, manufacturing information, and
6 labeling were submitted to FDA as a modular PMA
7 application with the first module being submitted in
8 April of 2000. The PMA application has been under
9 review by FDA since then and presenting this
10 information to this advisory panel is part of the
11 review process.

12 As typical for these meetings, we plan to
13 present overviews of the relevant information
14 contained in the PMA application. Dr. Gerard Riedel,
15 the senior project director of the rhBMP-2 program at
16 Wyeth-Genetics Institute, will make the first
17 presentation and he will cover the origin and biology
18 of rhBMP-2 and the pre-clinical safety studies. Dr.
19 Riedel will be followed by Dr. Scott Boden, an
20 orthopedic surgeon from Emory University. Dr. Boden
21 will discuss the results of pre-clinical testing of
22 infused bone graft in animal studies as well as the

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1 results of the pilot trial involving infused bone
2 graft with the LT-cage device and that study supported
3 the initiation of the larger pivotal trials.

4 Dr. Hallett Matthews, an orthopedic spine
5 surgeon from Richmond, Virginia, will review the
6 results of the large scale pivotal IDE trial of the
7 infused bone graft with the LT-cage device. Dr.
8 Matthews was an investigator in the open surgical
9 approach study. I will then return to the podium for
10 concluding remarks.

11 In addition to these speakers, we have
12 assembled here today a group of physicians and
13 scientists who should be able to answer the questions
14 you may have about the product under review. These
15 experts include several clinical investigators, the
16 inventor of the cage, radiologists and immunologists,
17 an OB/gyn physician, a histologist, a statistician,
18 basic scientist and the discoverer of the rhBMP-2 that
19 has been used in the study.

20 So without further ado, I will now turn
21 the podium over to Dr. Riedel.

22 DR. RIEDEL: Thank you, Bailey. Good

1 morning. My name is Gerard Riedel. I'm employed by
2 Wyeth-Genetics Institute, a pharmaceutical company,
3 that collaborates with Medtronic Sofamor Danek in the
4 development of BMPs in spine surgery. In my
5 presentation I will briefly describe the origin and
6 the biology of recombinant human bone morphogenetic
7 protein 2. I will also summarize the pre-clinical
8 studies we have conducted that compliment the pre-
9 clinical studies conducted by Medtronic Sofamor Danek.

10 As a reminder, the letters rhBMP-2
11 represent recombinant human bone morphogenetic protein
12 2. Scientists at Genetics Institute use molecular
13 biology techniques to isolate the human gene in coding
14 BMP-2. This gene was inserted into a chromosome of an
15 industry standard mammalian cell line and this cell
16 line was subsequently engineered to enable it to
17 produce high levels of rhBMP-2 protein. This cell
18 line can grow in large vessels and synthesize the
19 protein as it does so. RhBMP-2 is purified from the
20 media, filled into sterile vials and subsequently
21 freeze-dried.

22 RhBMP-2 is a member of a large protein

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1 family whose members all have activities associated
2 with the growth and differentiation of tissues.
3 Endogenous rhBMP-2 plays a key role in bone repair and
4 embryonic development. Recombinant human BMP-2 is a
5 homodimeric glycosylated molecule with a molecular
6 weight of approximately 30,000 Daltons. The protein
7 is highly conserved and active across species. This
8 conservation allows the use of recombinant human BMP-2
9 in all of the animal studies I will present rather
10 than having to prepare specie specific versions of
11 this protein.

12 Finally, the biological activity of rhBMP-
13 2, that is the basis for its therapeutic development,
14 is its ability to induce bone in both animals and
15 humans.

16 This slide demonstrates that bone
17 induction activity of rhBMP-2 in the classic in vivo
18 assay known as the rat ectopic implant assay. This
19 assay was originally developed in Dr. Reddi's
20 laboratory. In this assay, rhBMP-2 is implanted at a
21 non-bony site. Typically bone is induced at this site
22 within seven to 14 days following implantation. The

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1 photograph on the left shows the gross appearance of
2 an ossicle of bone induced by rhBMP-2 in the
3 subcutaneous space of a rat's thorax. Histological
4 analysis of this new bony tissue reveals extensive
5 formation of trabecular bone corresponding to the dark
6 pink regions in the photo micrograph on the right, a
7 complete compliment of bone associated cells such as
8 osteoblasts, osteoclasts and stromal cells and a
9 highly vascularized structure with all bone marrow
10 elements corresponding to the light pink regions in
11 the photograph on the right.

12 This activity in this rat model has been
13 labeled osteo induction. Only rhBMP-2 and several
14 other bone inducing BMP proteins exhibit this
15 biological activity. No other protein or drug has
16 demonstrated this activity in this model. Some of the
17 biological events comprising bone induction have been
18 identified. Following the implantation of recombinant
19 human BMP-2 cells initially migrate to the site and
20 undergo several rounds of cell replication.

21 Subsequently, fibroblasts appearing
22 mesenchymal cells differentiate into osteoblasts.

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1 Bone is formed, initially as woven trabecular bone and
2 subsequently remodeled by the combined action of
3 osteoclasts and osteoblasts into lamellar bone.

4 The newly induced tissue is highly
5 vascularized as demonstrated by the numerous blood
6 vessels in the photo micrograph on the left. The
7 entire sequence of events induced by rhBMP-2
8 recapitulates the physiologic process of bone
9 formation.

10 Considerable information has also been
11 published about the mechanism of rhBMP-2 action.
12 Responsive cell types and major cell surface receptors
13 have been identified. Additionally, elements of the
14 signal transduction pathway have been identified by
15 which rhBMP-2 exercises its effects on cells.
16 Finally, and very importantly, it has been shown that
17 it is necessary to apply rhBMP-2 locally in order to
18 obtain bone induction in vivo.

19 To facilitate the local application of
20 rhBMP-2, the protein is combined with a biomaterial
21 that is generally called a matrix. The use of a
22 matrix with rhBMP-2 enables its surgical placement at

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1 the treatment site, facilitates retention of rhBMP-2
2 at that site and ideally provides an environment that
3 is compatible with bone induction.

4 The matrix selected for clinical
5 development in this specific program is an absorbable
6 collagen sponge, abbreviated as ACS. This sponge was
7 selected after screening dozens of matrix candidates.
8 The sponge is a commercially available product
9 marketed in the United States since 1981 as a
10 surgically implanted hemostatic agent and has an
11 extensive commercial experience of safe use. The
12 sponge is composed of bovine tendon- derived type 1
13 collagen. Its manufacturer meets or exceeds all
14 regulatory requirements.

15 This next slide shows an example of the
16 dry absorbable collagen sponge in its original
17 packaging prior to the addition of rhBMP-2. This
18 diagram describes the preparation of rhBMP-2 ACS. The
19 vial containing the freeze-dried powder of rhBMP-2 is
20 reconstituted with an appropriate volume of sterile
21 water, abbreviated WFI in the diagram. The resulting
22 sterile solution of rhBMP-2 is subsequently applied

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1 uniformly to the dry ACS, generating a cohesive
2 pliable implant that can be readily manipulated in the
3 operating room as depicted in this slide which shows
4 that the wetted sponge can be rolled and subsequently
5 inserted into an LT-cage.

6 I mentioned before that one desirable
7 attribute of a matrix is its facilitation of rhBMP-2
8 retention at the site of implantation. This slide
9 describes one experimental system we used to assess
10 this attribute. We generated rabbit ulnar osteotomies
11 onto which we implanted rhBMP-2 ACS contained
12 radioactively labeled rhBMP-2. Following
13 implantation, we measured the amount of rhBMP-2
14 retained at the implantation site over time by a non-
15 invasive technique of gamma camera scintigraphy.
16 Basically, we measured the radioactivity remaining at
17 the site over time and this method has been validated
18 by several supplementary analyses including direct
19 explant measurement and biochemical characterization
20 of the radio labeled BMP-2 derived from the explants.

21 This slide shows the retention of rhBMP-2
22 in the rabbit ulnar osteotomy model. The Y axis

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1 represents the percent of the rhBMP-2 initial dose
2 remaining at the implantation site and the X axis
3 represents time in days. The graph shows that the use
4 of ACS as a matrix facilitates the local retention of
5 rhBMP-2 at the site, in contrast to the application of
6 rhBMP-2 in buffer depicted by the line with black
7 squares. Significantly more rhBMP-2 is retained at
8 the implantation site when it is applied in
9 combination with ACS depicted by the line with yellow
10 diamonds. Radio-labeled rhBMP-2 can be detected at
11 the implantation site for as long as 14 days in this
12 model.

13 With this background information in mind,
14 I will now discuss the non-clinical safety studies
15 that have been conducted. The safety of rhBMP-2 alone
16 or combined with ACS has been assessed in a variety of
17 studies. Implantation of rhBMP-2 ACS to assess its
18 implant safety has been conducted. The absorption,
19 distribution, metabolism and excretion of rhBMP-2,
20 abbreviated ADME, has been assessed. Finally, the
21 safety of rhBMP-2 alone has been studied in a panel of
22 assessments.

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1 The safety of rhBMP-2 ACS implantation has
2 been evaluated in three anatomic sites, including a
3 spine safety study conducted in Dr. Hanley's
4 laboratory. The results of this spine study have
5 already been published. The two other implant safety
6 studies used rat and canine models with follow-up
7 extending through six or 12 months. In these two
8 studies we used rhBMP-2 dosing that greatly exceeded
9 the species specific therapeutic range and I should
10 explain this.

11 I have previously mentioned that
12 recombinant human BMP-2 is biologically active in all
13 mammalian species. However, different species require
14 different concentrations of rhBMP-2 within ACS for
15 optimal bone formation and specifically the optimal
16 therapeutic concentration of rhBMP-2 is lowest in
17 rodents, higher in canine and even higher in non-human
18 primates and patients.

19 We took advantage of this phenomenon to
20 deliberate exceed the species specific optimal
21 concentrations of rhBMP-2 within ACS in order to
22 assess any toxic effects. The safety results of all

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1 these studies were uniform. There were no systemic
2 effects observed, no gross pathology or histopathology
3 findings, no effects on blood chemistry, hematology or
4 urinalysis and no incidents of bone formation distant
5 from the site of implantation.

6 Furthermore, the local effects observed in
7 these studies were consistent with the bone inducing
8 biological activity of rhBMP-2. We also looked at the
9 biodistribution of rhBMP-2 following its implantation.
10 We used two implantation models in two species. The
11 results are similar. RhBMP-2 is slowly released from
12 the implantation site with a maximum of 0.1 percent of
13 the implanted rhBMP-2 dose detected in the systemic
14 circulation.

15 This slide shows the retention of rhBMP-2
16 at the site of implantation but this time in a rat
17 femur onlay model. RhBMP-2 can be detected at the
18 implantation site for as long as 14 days following
19 surgical implantation in this model. In this same
20 study we measured rhBMP-2 levels in the blood and
21 showed that the maximum amount detected was 0.1
22 percent of the total rhBMP-2 implanted. I've not

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1 graphed those levels on this slide because they would
2 all cluster at zero on this scale.

3 Nevertheless, because some small amount of
4 rhBMP-2 was detected in the systemic circulation
5 following the product's implantation, we studied the
6 fate of rhBMP-2 following systemic administration. We
7 used standard animal models of pharmacokinetics and
8 biodistribution in rats and non-human primates and
9 applied rhBMP-2 protein dissolved in buffer via
10 intravenous administration. In these models we
11 observed that rhBMP-2 is rapidly cleared from the
12 systemic circulation with a terminal half-life of 16
13 minutes in rats to seven minutes in monkeys.

14 The liver is the principal organ of
15 clearance. Subsequently, the protein is rapidly
16 degraded and excreted into -- completely degraded and
17 then the remnants are excreted into the urine. This
18 graph shows the clearance of rhBMP-2 from the systemic
19 circulation following intravenous administration of
20 the protein in rats. The Y axis represents the
21 percent of the rhBMP-2 initial dose remaining in the
22 blood and the X axis represents time but now in

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1 minutes rather than in days as used in the previous
2 graphs.

3 This slide shows that rhBMP-2 is rapidly
4 cleared from the circulation and contrasts
5 dramatically with its relatively slow clearance from
6 the site of implantation. This slide summarizes the
7 net effect of the local and systemic clearance of
8 rhBMP-2. Slow rhBMP-2 release from the site of
9 implantation combined with rapid systemic clearance,
10 results in very low systemic exposure. This low
11 systemic exposure has implications for the safety
12 results described in the following slides.

13 I switch now to a description of various
14 safety assessments of rhBMP-2 alone beginning with
15 studies relevant to tumor formation or proliferation.
16 Published studies have screened many different tumors
17 and identified several tumor types that express either
18 BMP-2 or BMP receptors. These published data do not
19 indicate any role of BMP-2 in the initiation or the
20 promotion of tumor formation.

21 We have also assessed rhBMP-2 in standard
22 assays and determined that the protein is neither

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1 cytotoxic nor mutagenic. Additionally, we performed
2 a thorough histological assessment of the local
3 implantation site in the implant toxicity studies I
4 previously mentioned. We detected no abnormal
5 cellular features at the site of implantation in any
6 study at any time point. For example, in our rat
7 implant study, we implanted concentrations of rhBMP-2
8 on ACS that were 40 times higher than the optimal
9 therapeutic concentration for this species.

10 The histopathology assessment of the
11 implant site revealed no abnormal cellular features at
12 any time point through the one-year follow-up period.
13 These combined data suggest that rhBMP-2 has no role
14 in the initiation or the promotion of tumor formation.
15 To investigate the effect of rhBMP-2 on tumor cells
16 that already exist, we have conducted in vitro
17 studies. We focused our efforts on in vitro
18 assessments because it is possible to achieve
19 relatively high exposure levels to rhBMP-2 in contrast
20 to the very low systemic exposure levels that can be
21 achieved in vivo. These studies are summarized on the
22 following slide.

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1 We have provided FDA with the results of
2 series of studies including our own that investigated
3 the effect of rhBMP-2 on the growth of human tumor
4 cells in vitro. Most of these studies have been
5 published. In aggregate, these studies have assessed
6 51 human tumor cell lines to date. Three lines have
7 shown some growth promotion in the presence of rhBMP-2
8 as compared with growth in the absence of the protein.
9 I will discuss these lines first.

10 Two of these lines were derived from
11 pancreatic tumors. When these lines were cultured in
12 the absence of serum, rhBMP-2 stimulated cell growth
13 by 12 or 25 percent above that of the controls. Both
14 lines carried a mutation and a key component of the
15 intracellular BMP signal transduction pathway. Other
16 pancreatic tumor cell lines were evaluated and showed
17 either no effect or growth inhibition.

18 The third tumor cell line demonstrating
19 increased growth was derived from a prostate
20 carcinoma. This cell line only showed growth
21 promotion in the absence of serum or the absence of
22 androgen. When either of these components was added

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1 back to the medium, rhBMP-2 actually inhibited the
2 growth of this cell line. In the remaining 48 cell
3 lines, the addition of rhBMP-2 had either no effect or
4 resulting in the inhibition of tumor cell growth in
5 approximately 50 percent of the cell lines tested.
6 These lines included many different tumor cell types
7 including seven osteosarcoma lines as well as the
8 three additional pancreatic tumor lines and four
9 additional prostate tumor cell lines.

10 Besides testing rhBMP-2 on established
11 tumor cell lines, the protein has also been tested on
12 primary tumor isolates generally obtained following
13 surgical debulking procedures. Seventy-one
14 independent tumor isolates have been tested to date
15 and all show either no effect or inhibition this time
16 in approximately 25 percent of the isolates tested.

17 Finally although inhibition of tumor
18 growth has been observed most dramatically in the cell
19 lines and primary isolates of multiple myeloma cells,
20 the degree of inhibition is not extensive enough to
21 consider rhBMP-2 for therapeutic applications in
22 patients with these tumors.

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1 Over the course of the review of this PMA
2 submission, we met with FDA on several occasions to
3 discuss additional tumor biology studies that could be
4 conducted. We mutually agreed to perform that
5 additional studies outlined in this slide as a post-
6 approval commitment. These studies are intended to
7 compliment the scientific literature and to more
8 systematically assess rhBMP-2 effects on tumor cells
9 that express the known BMP receptors.

10 The first study is designed to screen
11 tumor cell lines for the levels of messenger RNA in
12 coding each known component of the BMP receptor
13 complex. We are performing the screening activity by
14 using a sensitive polymerase chain reaction assay for
15 each known receptor component and comparing the
16 individual component messenger RNA levels in tumor
17 cells with messenger RNA levels in other cell types
18 known to respond to rhBMP-2. We used this comparison
19 to operationally classify tumor cell lines as positive
20 or negative for BMP receptor RNA.

21 The second cell line evaluates
22 representative tumor cell lines from the first

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1 experiment. If possible, cell lines will be selected
2 that represent a variety of tumor types and different
3 messenger RNA levels of BMP receptor components. The
4 growth of these cell lines will be assessed in vitro
5 in the presence and the absence of rhBMP-2.

6 In the third study, representative tumor
7 cell lines from the second experiment will be assessed
8 if relevant as xenografts in an appropriate mouse
9 model system in the presence and absence of implanted
10 rhBMP-2. As I stated earlier, these additional
11 studies constitute a post-approval commitment in
12 agreement with FDA.

13 I will now discuss additional safety
14 assessments of rhBMP-2 alone that have been performed.
15 We have also conducted formal studies of rhBMP-2
16 safety in well-characterized animal toxicological
17 models. We studied the systemic safety of rhBMP-2 in
18 two species using intravenous administration to apply
19 a single dose or doses repeated daily for 28 days at
20 systemic exposure levels that greatly exceeded
21 anticipated human exposure.

22 Similarly, because indigenous BMP-2 is

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1 active during embryogenesis, we have studied the
2 reproductive safety of rhBMP-2 using repeated
3 intravenous administration in standard rat and rabbit
4 models that assess fertility or teratological effects
5 again at systemic exposure levels that greatly exceed
6 anticipated human exposure. In these formal toxicity
7 studies, we assessed rhBMP-2 effects on clinical
8 signs, ophthalmic evaluations, electrocardiograms and
9 blood pressure, bone marrow and hematology parameters,
10 blood chemistry, urinalysis, growths pathology and
11 histopathology of all major organs.

12 In the reproductive toxicity studies, we
13 additionally assessed rhBMP-2 effects on maternal and
14 paternal mating performance and reproductive
15 parameters, maternal toxicity, embryo lethality,
16 litter size and viability and fetal abnormality. The
17 results of all of these studies were similar. There
18 were no effects observed.

19 Studies were also conducted according to
20 the tripartite biocompatibility guidelines for medical
21 devices and a series of general safety pharmacology
22 studies were conducted using systemically administered

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1 rhBMP-2. The results of these studies were also
2 similar. There were no effects observed.

3 In the course of the review of this PMA
4 submission, we have recently met with FDA to discuss
5 issues related to an immune response to rhBMP-2.
6 Following consultation with FDA, we have mutually
7 agreed to perform the additional studies outlined in
8 this slide as a post-approval commitment. These
9 studies are intended to more thoroughly assess the
10 overall immune response to rhBMP-2.

11 Our first commitment in this area is to
12 develop a broader clinical antibody assay to detect
13 human antibody isotopes in addition to the major IgG
14 isotopes that we currently detect. Our second
15 commitment is to develop a valid assay to assess the
16 ability of antisera to block or neutralize the
17 biological activity of rhBMP-2.

18 Finally, we have also recently begun a
19 discussion with FDA concerning experimental approaches
20 to appropriately assess the potential of maternal
21 anti-rhBMP-2 antibodies to have adverse effects on
22 fetal development during pregnancy. In summary, the

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1 safety of rhBMP-2 ACS has been comprehensively
2 evaluated in a series of non-clinical safety studies
3 that used either local implantation or systemic
4 administration. The overall pre-clinical profile that
5 we have observed in these studies can be characterized
6 as follows.

7 There was no observed systemic adverse
8 effect of rhBMP-2 whether it was administered as an
9 intravenous solution or implanted in association with
10 the absorbably collagen sponge. We attribute this
11 lack of adverse effects to low systemic exposure
12 caused by the gradual release of rhBMP-2 from its
13 implantation site combined with a very rapid clearance
14 of rhBMP-2 from the systemic circulation. Local
15 effects were observed with consistent with the bone
16 inducing activity of rhBMP-2. We have observed no
17 dose limiting toxicity related to rhBMP-2 in our
18 studies at amounts substantially exceeding anticipated
19 human exposure.

20 In conclusion, our pre-clinical safety
21 assessment supports the use of infused bone graft in
22 patients. Thank you for your attention. I'll now

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1 turn this presentation over to Dr. Scott Boden, who
2 will review the data from several pre-clinical spine
3 fusion studies and the results of the infused bone
4 graft pilot clinical study.

5 DR. BODEN: Thank you, Dr. Riedel. My
6 name is Scott Boden and I'm a Board certified,
7 practicing orthopedic spine surgeon in Atlanta,
8 Georgia. I'm also a professor of orthopedic surgery
9 at Emory University. I've written extensively on the
10 subject of bone morphogenetic proteins and I am
11 familiar with the literature in this area. I have no
12 direct financial interest in the product being
13 discussed today before this distinguished panel but I
14 am a paid consultant for Medtronic Sofamor Danek.

15 I also participated in the pilot study for
16 the device being presented today which began five
17 years ago when recombinant human BMP-2 was first used
18 inside the LT-fusion cage device in humans.

19 I'd like to focus my remarks on the pre-
20 clinical studies that led to the design and rationale
21 and evaluation tools for the pivotal clinical trial
22 which you'll hear about shortly. This slide

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1 summarizes four of the key pre-clinical studies
2 looking at the recombinant BMP-2 protein in an
3 interbody spine fusion environment.

4 Before I go into them individually, I want
5 to point out the theme for these studies is that it
6 was done in an animal model where the gold standard of
7 the control had a less than 50 percent success rate in
8 three of those four studies. And the empty cage or
9 without protein had a zero percent success rate in the
10 a fourth of those studies. Similarly or in contrast,
11 the recombinant BMP-2 had a 95 or 100 percent success
12 for inducing bridging bone in each of these
13 challenging animal models.

14 The first study looks at single level
15 interbody fusion with a titanium cage in a sheep
16 model. In this study the cage was either filled with
17 autogenous bone graft or the recombinant BMP-2
18 absorbable collagen sponge device. This slide
19 highlights some of the challenges in non-invasively
20 evaluating the presence or absence of bone formation
21 in the interbody fusion area.

22 In the autograft controls, plain

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1 radiographs measuring lucencies of the primary
2 determinant of presence or absence of fusion suggested
3 that there might be 100 percent successful fusion
4 rate. However, histologic analysis which directly
5 visualizes bridging trabecular bone which is the
6 criteria for a solid fusion, show that only 37 percent
7 of those animals actually had bridging trabecular
8 bone. In the case of BMP-2, again, the plain x-ray
9 showed a very -- or indicated a very high success rate
10 just using the lucency criteria but the difference
11 here was that the histologic analysis showed bridging
12 trabecular bone in each and every animal receiving
13 BMP-2.

14 These pictures illustrate that point.
15 Here is a micro-radiograph of an autograft control
16 where there is clearly bone inside the cage but there
17 are some areas that are not filled with bone and
18 histology demonstrates that this is fibrous tissue
19 shown in the pink color as compared to bone shown in
20 the blue. This can be contrasted with both a
21 radiograph and histology from one of the other animals
22 in that study that had BMP-2 absorbable collagen

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1 sponge inside the cage rather than autogenous bone
2 graft.

3 One of the other relevant questions that
4 has already been raised this morning is what is the
5 mechanical quality of bone that is induced using BMP-2
6 as compared to bone that would be initially formed and
7 remodeled using autogenous iliac crest bone graft?
8 And this study shows that using a variety of
9 mechanical testing modes that the mechanical
10 properties of the bone induced by BMP-2 were
11 comparable comparing the red bar and the green bar to
12 those seen with bone formed by autogenous bone graft
13 from the iliac crest.

14 The second study looks at single level
15 interbody fusion with titanium cage this time in a
16 goat model. The end point was again six months and
17 the two groups were again the same. Cage was either
18 filled with autogenous bone or recombinant human BMP-2
19 on the absorbable collagen sponge. Once again, we see
20 the challenges of using just plain radiographs to
21 assess the presence of bone inside a fusion cage. In
22 this case in the autograft group clearly less than 100

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1 percent but more than the just under 50 percent that
2 had an actual fusion based on histology, were assessed
3 to be fused again using lucency as the primary
4 criteria.

5 In contrast in the case of the BMP
6 animals, although 100 percent lacked lucency on the
7 plain x-ray criteria, only 95 percent, which means all
8 but one animal had continuous bridging bone as
9 measured by histology, the ultimate assessment of bone
10 formation inside the cage.

11 Once again, biomechanical testing show
12 that there was no statistical difference in the
13 stiffness between the fusions that were formed with
14 the autograft or fusions that were induced by the
15 recombinant BMP-2. So, again, bone induced by BMP-2
16 absorbable collagen sponge functionally, inside the
17 cage functioned similar to that of autograft bone.
18 Now, one could argue that the presence of the metal
19 cage might interfere with the ability to truly assess
20 the quality of the bone and for that reason I'll just
21 briefly show some mechanical assessment of bone with
22 recombinant BMP-2 on the same carrier matrix, that's

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1 the absorbable collagen sponge but from a
2 posterolateral fusion model where there's no metal.

3 The advantage of this model, which
4 incidentally the autograft once again fused less than
5 50 percent of the animals and BMP-2 absorbable
6 collagen sponge fused 100 percent of the animals but
7 we can do testing that looks at just the strength and
8 quality of the bone formed in the fusion without any
9 confounding information from metal fixation. Once
10 again, in this case, the mechanical properties of the
11 bone formed with BMP-2 shown in the green bars were
12 essentially comparable to those in terms of relative
13 strength and relative stiffness seen with autogenous
14 bone.

15 Now moving onto the non-human primate
16 studies which are extremely relevant as was mentioned
17 earlier by Dr. Riedel, because of the close parallel
18 of the required concentration of BMP-2 to get efficacy
19 of bone formation in non-human primates and how that
20 translates to human clinical trials. In this case an
21 allografted bone dowel or bone cage was filled with
22 either BMP-2 and absorbable collagen sponge or with

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1 autogenous bone graft and inserted in a rhesus monkey
2 single level, interbody fusions.

3 These two x-rays show an example from a
4 control and you can see that the intervertebral disc
5 space, that black line, is still present and there was
6 no bridging bone or fusion across the segment when the
7 allograft bone dowel was filled with BMP-2. In
8 contrast, in this case you can see that bone has
9 bridged the two vertebral segments completely
10 obliterating the disc space with the allograft dowel
11 was filled with BMP-2 and in addition, the allograft
12 dowel has been remodeled.

13 These microradiographs again highlight
14 this point. Two controls shown on the to, in this
15 case, the remnant of the allograft dowel can be seen
16 but bone is growing into and through it. In this case
17 the dowel has fallen out of the histologic section but
18 you can see that bone has not grown completely through
19 the specimen. In contrast, these are two examples
20 from animals that had BMP-2 with absorbable collagen
21 sponge inside that cage and you can see that there's
22 bridging trabecular bone across the interspace and

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1 remodeling of the allograft bone cage.

2 The last pre-clinical study is the one
3 that most closely simulates what was to take place in
4 human -- in the fact that this time BMP-2 with
5 absorbable collagen sponge was placed into a scaled
6 down titanium fusion cage. This was inserted into
7 rhesus monkey at the lumbosacral junction with a six-
8 month end point and the cage was either filled with
9 the absorbable collagen sponge with buffer only, in
10 other words, no BMP-2 or one of two doses, .75 or 1.50
11 milligrams per milliliter of recombinant human BMP-2.

12 What we found was that the sponge alone
13 did not result in any spontaneous bone formation
14 through the cage in either of those control animals.
15 However, all of the animals that received either dose
16 of recombinant BMP-2 on the collagen sponge had
17 histologic bone formation through the cage as can be
18 seen on these two examples.

19 This slide is important because it leads
20 to the reliance and the importance of using CT scans
21 to assess the presence of bone inside an interbody
22 fusion cage. Here you can see that histologically in

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1 this case there was no bone forming inside the cage
2 and on the CAT scan you can see that this dark area
3 rather than a bright white area suggests that there is
4 not a density consistent with bone inside the metal
5 fusion cage. In contrast, in animals where bone grew
6 through the cage, a CT scan revealed homogeneous
7 bridging trabecular bone through the center of the
8 cage on the CAT scan.

9 The quality of the bone and the normalcy
10 in the non-human primates was as described earlier by
11 Dr. Riedel in rodents and other animal models being
12 entirely normal bone with osteoblast-line trabeculae
13 remodeling and bone marrow elements.

14 Now I'd like to briefly describe the pilot
15 clinical study that was undertaken following that
16 rhesus monkey pre-clinical study as an introduction to
17 validating the evaluation tools. In this study which
18 was done at four investigational sites, the LT-
19 threaded tapered fusion cage was filled with either
20 autogenous bone graft in a small number of patients or
21 with infused bone graft, that is recombinant human
22 BMP-2 in absorbable collagen sponge.

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1 First I'd like to briefly review the
2 surgical anatomy for those who may be less familiar
3 with the spine. The normal spine would have two
4 vertebra adjacent connected by the intervertebral disc
5 cartilage and in the approach that's being put before
6 the panel today which is an anterior surgical
7 approach, two cages are inserted from the front of the
8 spine. It's important to note that there is residual
9 disc or annulus material that serves as a microscopic
10 barrier creating that compartmentalization that Dr.
11 McCullough was asking for earlier preventing gross
12 leakage of BMP-2 and carrier matrix into the area
13 where the neuro elements would be.

14 Looking at this in cross section, we can
15 see here the normal or pre-operative and then post-
16 surgical schematic of two cages inserted side by side
17 again with residual annular tissue serving as a
18 macroscopic barrier. I should point out that while
19 this is a macroscopic barrier and there can be
20 fissures, in none of the animal studies nor in the
21 human studies have we seen formation of bone posterior
22 to the cage outside the confines of the disc space

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1 when the anterior surgical approach has been used
2 which is under consideration today.

3 So the device before it goes in, has the
4 wetted collagen sponge inside the taped fusion cage
5 and in this clinical pilot study, 11 out of 11
6 patients were deemed by independent review of plain x-
7 rays and CT scans to have achieved bridging trabecular
8 bone through and/or around the fusion cages. Two of
9 three of the autograft were shown to have successful
10 bridging bone.

11 Another issue is the impact on clinical
12 outcome. In the Oswestry Disability Index is a
13 disease specific patient derived outcomes measure,
14 which is commonly used in patients with low back
15 problems. In this case having a lower score is
16 desirable or indicative of less symptoms or less
17 disability. In the Oswestry scores from pre-op to 24
18 months, gradually decreased on both groups, in this
19 case it seemed a little bit quicker in the infused
20 group and it nearly reached statistical significance
21 but in the end the clinical outcome was at least as
22 good in patients that used infused and did not have to

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1 have a second site harvest with autogenous bone graft.

2 Lastly, I think showing some
3 representative pictures are really important to bring
4 home the fact that bone is forming in an area where
5 there otherwise wasn't bone. The format of the next
6 several slides will look at a slice through the right-
7 hand cage, the left-hand cage and a coronal view of
8 both cages or frontal view using reconstructed thin
9 sliced CT scans. And the three columns represent
10 different points in time; six months, 12 months and 24
11 months. And you can see from this patient that
12 started with autograft bone, that in fact, there was
13 incorporation of the autograft in this case and there
14 is bridging trabecular bone through the cages both on
15 the lateral and on the frontal view.

16 Here's an example of another autograft
17 patient where you can see that there's less density
18 inside the cage perhaps with resorption of the
19 autograft bone and over time there were lucencies that
20 formed around the cage and absence of bridging bone
21 suggesting a failure of bone formation and fusion.
22 Contrast that with an example of some of the infused

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1 patients keeping in mind that the cage starts out
2 without any bone in it and so when we see white bone
3 growing through the cage, we know that it was induced
4 as a result of infuser BMP-2.

5 You can see here in both cages there's
6 bone growing through the cages and as time progresses
7 you can see secondary ossification which is a normal
8 adjunctive finding in any solid fusion around the
9 cages through the disc space. Another example of an
10 infused patient, again showing an increase in bone
11 density in the cage over time and also the secondary
12 healing around the cage normal for a solid interbody
13 fusion.

14 Another question is what happens to the
15 bone inside these cages over a longer period of time
16 and although this was a pilot study, these patients
17 have continued to be followed and this is an example
18 of one of the autograft patients at 48 months showing
19 that when autogenous bone was put inside the cage,
20 then in fact, it remains bridging through the cage and
21 remodels similar to the density of bone in the
22 adjacent vertebral bodies.

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1 Looking at a patient that received infused
2 we saw this same trend of preservation of bone in the
3 cage, not disappearing of bone, and continuing to
4 mature the adjunctive fusion throughout the
5 interspace. So the bone that's induced with BMP
6 behaves ostensibly the same as bone that was put by
7 autograft bone in the case of inside the fusion cage.

8 And just one other example of a patient
9 with BMP, again with longer term follow-up showing
10 that the fusion is maintained even at four years with
11 bone both through the cage and around the side of the
12 cage. So I think it's important to summarize the
13 goals of the recombinant BMP-2 absorbable collagen
14 device. You've heard much about systemic safety and
15 toxicity in the first talk and I think at this point
16 it suffice it to say very simply that we did not see
17 any bone formation at a distance from the cages or in
18 any place outside the caged in matrix in any of the
19 animals or any of the pilot patients that have been
20 discussed so far.

21 Equally important to safety is
22 effectiveness. And effectiveness for this device

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1 really should be considered the ability to eliminate
2 bone grafting morbidity which is substantial in these
3 patients and to obtain equal or better healing success
4 rate defined as bridging trabecular bone across the
5 interspace and through the cage. In other words,
6 stated more simply the goal of recombinant BMP-2
7 absorbable collagen sponge device is to make bridging
8 bone.

9 So in conclusion, based on a series of
10 detailed pre-clinical and a clinical pilot trial, I
11 believe that recombinant BMP-2 absorbable collagen
12 sponge has shown success in 95 percent or better in
13 four animal studies, substantially better than
14 autograft controls in those models. The bone formed
15 is normal and biomechanically equal to that formed
16 with autogenous bone graft. CT scan analysis
17 correlates the best with the histology of bone and
18 therefore, is an important indicator of the presence
19 of new bone formation by BMP-2 inside fusion cages.

20 And finally, the concentration of BMP-2
21 that was successful in the rhesus monkey pre-clinical
22 study was also successful in the clinical pilot study

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1 with 100 percent success in humans at the same doses
2 that were predicted by the rhesus monkeys. At this
3 point, I'd like to turn the podium over to Dr. Hal
4 Mathews, who will describe the results of the pivotal
5 clinical trial in greater detail.

6 DR. MATHEWS: Distinguished panel members,
7 ladies and gentlemen, good morning. My name is Hal
8 Mathews. I'm a practicing spine surgeon from
9 Richmond, Virginia. My entire clinical focus is spine
10 care. I'm an associate clinical professor of
11 orthopedics and neurosurgery at the Medical College of
12 Virginia in Richmond. I have no direct financial
13 interest in this product under review here today and
14 I'm not being paid for my participation in this
15 meeting. I participated in the open surgical approach
16 study of this device as an investigator.

17 I'm here today to present the results of
18 the InFUSE™ Bone Graft/LT Cage Lumbar Tapered Fusion
19 Cage Device clinical trial. Before I discuss the
20 details, I want to report to this advisory panel and
21 to the audience the top line findings from this open
22 surgical approach study. First and foremost the

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1 primary objective of the clinical trial as stated in
2 the protocol was met, thus establishing the safety and
3 effectiveness of the InFUSE™ bone graft in the
4 treatment of degenerative disc disease.

5 Secondly, the InFUSE™ bone graft
6 stimulates the formation of bone which results in very
7 high fusion rates. Thirdly, the InFUSE™ bone graft
8 patients experience shorter operative times and less
9 blood loss than the control patients. And finally,
10 patients who receive the InFUSE™ bone graft avoided
11 the complications and significant post-operative pain
12 associated with bone graft harvesting in the control
13 group.

14 Let me offer a few additional observations
15 that I believe will bring into sharper focus the
16 clinical trial results. At the end of the day it is
17 our job as physicians to help our patients in the
18 least invasive and least painful ways. For the
19 patients from whom a bone graft was taken from their
20 iliac crest, at the time of discharge, 80 percent of
21 patients registered a score of at least 10 out of 20
22 and nearly 15 percent of these patients had a score of

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1 at least five at 24 months. In addition, six percent
2 of these patients experienced graft site
3 complications, including bone fractures, nerve
4 injuries, infections and hematomas.

5 Given its equivalent performance in
6 achieving fusion, the infused bone graft is clearly
7 the most humane way to treat this painful condition.
8 I will now elaborate on the clinical trial and the
9 results and I will conclude with a brief review of the
10 laparoscopic clinical trial that was also conducted
11 showing equivalent rates of fusion as well as some
12 other potential patient benefits.

13 Let us now discuss the open surgical
14 approach for device implantation. This study had a
15 prospective randomized control design. The
16 investigational treatment patients received the LT
17 cage device filled with the InFUSE™ bone graft.
18 Henceforth, I will refer to these patients as the
19 InFUSE™ group. The control patients were treated in
20 a similar manner with the LT cage device filled with
21 autogenous harvested bone from the iliac crest. These
22 patients will be designated the autograft group.

1 The primary objective for the clinical
2 trial was to determine if the overall success rate for
3 the InFUSE™ is at least as high statistically as the
4 rate for the autograft group. Overall success is a
5 derived variable encompassing primary safety and
6 effectiveness considerations. Secondary objectives
7 focusing on equivalency and superiority of specific
8 end points were also developed.

9 Bayesian methods were used for statistical
10 comparison of study outcomes. Patients admitted to
11 the study had a single level symptomatic degenerative
12 disc disease as noted by back pain of discogenic
13 origin with or without leg pain with degeneration of
14 the disc confirmed by patient history and radiographic
15 studies. There are a number of additional inclusion
16 and exclusion criteria such as age, weight, mental
17 competency, medical history, and existing medical
18 condition.

19 Patients involved in the clinical trial
20 were evaluated pre-operatively, at surgery and post-
21 operatively at six weeks, three, six, 12 and 24
22 months. A total of 143 patients received the InFUSE™

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1 bone graft. There were 136 patients who were treated
2 with autogenous bone graft. Patient follow-up
3 compliance at all post-operative periods exceeded 90
4 percent. Sixteen investigational centers contributed
5 to these patients.

6 Patients in both treatment groups had very
7 similar demographic characteristics and pre-operative
8 medical conditions. This enhances one's ability to
9 interpret the treatment effects since potentially
10 confounding factors did not impact with the results.
11 In terms of surgery results, the mean operative time
12 for the InFUSE™ group was approximately one-half hour
13 less than that for the autograft group and this
14 finding was statistically different.

15 The blood loss for the InFUSE™ group was
16 also statistically lower than that for the autograft
17 group. The mean hospital stays of patients in both
18 treatment groups were slightly more than three days
19 and did not have statistical difference. The results
20 of other surgical variables such as treated level,
21 operative approach and type of orthosis were similar
22 for both groups. The outpatient and inpatient

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1 classification and return to work times were also
2 comparable.

3 For clinical outcomes I would like to
4 emphasize that 24-month data are being used a primary
5 supporting evidence of the safety and effectiveness of
6 treatments. In order to satisfy the FDA's guidance
7 for spinal implant studies, a composite variable
8 termed overall success was created and this variable
9 is the primary end point of the entire study for PMA
10 approval purposes.

11 Overall success is comprised of the
12 effectiveness parameters of fusion, Oswestry success,
13 neurologic success. It is also influenced by two
14 important safety considerations, the occurrence of any
15 serious adverse events possibly associated with the
16 device and the occurrence of a second surgical
17 procedure classified as a failure. The overall
18 success criteria is very demanding.

19 The primary objective of this study was to
20 determine if the overall success rate for the InFUSE™
21 group was at least as high statistically as for the
22 autograft group. As evidenced from this slide, the

1 overall success rates for the two treatment groups at
2 12 and 24 months following surgery are very similar
3 and stable over time. These rates were statistically
4 equivalent at 24 months. Therefore, the primary
5 clinical trial objective was met, thus supporting
6 approval of this product.

7 I will now discuss in detail the safety
8 and the effectiveness parameters that were used in
9 this clinical trial. Safety was assessed as a
10 function of the nature and the frequency of adverse
11 events and second surgery procedures and the formation
12 of antibodies to rhBMP-2 and collagen. Based on these
13 assessments, the infused group was found to be as safe
14 as the autograft group.

15 Now for more details. Reported adverse
16 events in each group were classified by their nature,
17 their severity according to the World Health
18 Organization criteria, and their duration. Also
19 Medtronic Sofamor Danek instructed investigators to
20 report all adverse events that occurred whether or not
21 the event was related to the treatment or the device.
22 This conservative approach led to the reporting of

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1 many unrelated events that were included in the
2 analysis. For the InFUSE™ group only 17 patients or
3 11.9 percent had an event that was possibly related to
4 the device and only 11 of these patients or 7.7
5 percent were the events considered serious.

6 Overall, a total of 113 InFUSE™ patients
7 had at least one adverse event with a substantial
8 majority not being related to the device. As you can
9 see from this slide, these rates are very similar to
10 those rates for the autograft group. Adverse events
11 were also categorized according to their nature and
12 comparisons were made between the two treatment
13 groups. There were no statistical differences for all
14 reported categories of adverse events except for two.
15 These categories in which differences were noted were
16 graft site events and urogenital. Nearly six percent
17 of the autograft patients had graft site
18 complications. These complications included bone
19 fracture, nerve injuries, infection and hematoma.

20 Obviously, there were not graft site
21 adverse events for the InFUSE™ group. This fact
22 clearly supports the use of InFUSE™ bone graft since

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1 it eliminates the need to harvest bone graft.
2 Urogenital complication rates favor the autograft
3 group. The difference in rates was mainly due to
4 urinary retention following surgery and these events
5 resolved in all patients prior to discharge from the
6 hospital.

7 Overall the occurrence of adverse events
8 in the clinical trial were considered typical for a
9 patient population having an anterior lumbar interbody
10 fusion procedure and were not unanticipated. Another
11 component of safety assessment is the number and
12 nature of additional surgical procedures performed
13 after the initial study surgery. This slide lists the
14 classifications of additional surgical interventions.

15 According to the protocol, revisions,
16 removals and supplemental fixations are considered
17 significant procedures at the treated spinal level
18 that effect the assessments of the treatment outcome.
19 Therefore, a patient having one of these procedures is
20 considered a treatment failure for study purposes. On
21 the other hand, re-operations and other surgical
22 procedures that are believed to have no effect on the

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1 treated level are therefore, not considered failures.
2 The second surgery rates for both groups were
3 comparable and there were no statistical differences
4 for any of the additional surgery category
5 comparisons.

6 Because of the proteinaceous nature of
7 both rhBMP-2 and the absorbable collagen sponge the
8 development of antibodies was assessed as part of the
9 IDE clinical trial. Serum samples were taken from
10 each patient pre-operatively to establish their
11 baseline condition and at three months following
12 surgery. These samples were analyzed for the presence
13 of antibodies specific to rhBMP-2 and to bovine type
14 I collagen. If a patient had a positive response to
15 bovine type I collagen, the serum was also tested for
16 antibodies to human type I collagen. Antibody levels
17 were checked in both InFUSE™ and autograft patients,
18 even though the latter group was not exposed to the
19 InFUSE™ product.

20 The rates of antibody formation were not
21 different for the two treatment groups. There was one
22 InFUSE™ patient and one autograft patient who had

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1 authentic positive responses to rhBMP-2. The
2 incidents rates were very low, at less than one
3 percent. There were no adverse events that appeared
4 to be related to these findings.

5 Approximately 13 percent of patients in
6 both treatment groups had authentic positive responses
7 to bovine type I collagen. These antibody responses
8 did not appear to result in any clinical manifestation
9 nor impact the overall success rates of the study.
10 None of the patients who tested positive for bovine
11 type I collagen had a positive result for human type
12 I collagen. These antibody findings are similar to
13 those from other Medtronic Sofamor Danek clinical
14 trials involving the InFUSE™ bone graft.

15 Since I've presented a lot of information,
16 I want to briefly review the impressive safety profile
17 of the use of the InFUSE™ bone graft with the LT-cage
18 device before moving onto the effectiveness results.
19 Adverse events and second surgery procedures for the
20 InFUSE™ treatment were very similar to the autograft
21 treatment. The rates of antibody formation were not
22 different for the two treatment groups. In addition,

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1 any positive antibody response appeared to be without
2 clinical manifestation.

3 The use of the InFUSE™ bone graft
4 eliminated graft harvesting adverse events that
5 occurred in approximately six percent of the autograft
6 patients and significant graft site pain in
7 approximately 80 percent of patients peri-operatively.
8 This finding is significant since it supports a major
9 reason for using the InFUSE™ bone graft.

10 There were also no cardiovascular adverse
11 events associated with the use of the InFUSE™ bone
12 graft. Therefore, based on the data, the InFUSE™
13 bone graft LT-cage device is safe for its intended use
14 in the anterior lumbar interbody fusion procedures to
15 treat degenerative disc disease.

16 Now, we'll focus on device effectiveness.
17 Briefly in summary, these patients received the
18 InFUSE™ bone graft experienced exceptionally high
19 fusion rates, pain relief, maintenance or improvement
20 in neurologic status. Let's review specific
21 effectiveness results in more detail. We consider
22 fusion to be the primary end point since the intended

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1 use of the infused bone graft is to induce bone
2 formation in spinal fusion procedures.

3 For this clinical trial, CT scans and
4 radiographs were used to assess fusion. These films
5 were evaluated at the University of California San
6 Francisco under the direction of Dr. Harry Genant, a
7 board certified radiologist. There were two teams of
8 reviewers who were masked to patient treatment. Each
9 team worked independently of each other. If their
10 overall fusion conclusions differed, a third reviewer
11 would adjudicate the findings. However, this occurred
12 in frequently since the percent agreement between the
13 two primary review teams exceeded 98 percent at all
14 time points.

15 Fusion was based on evidence of bone,
16 spanning the two vertebral bodies of the treated
17 segments, using CT scans and radiographs. In
18 addition, segmental stability and lucent line criteria
19 also had to be met to be considered fused. Patents
20 having second surgical procedures reported by the
21 investigator as due to pseudoarthrosis or non-union
22 were also considered as fusion failures regardless of

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1 independent radiographic findings.

2 This later condition dramatically impacts
3 fusion rates for both treatments. For example, at 24
4 months post-operatively, all non-unions in the
5 InFUSE™ group were due to second surgery criteria and
6 not the radiographic criteria. The fusion rates for
7 both treatment groups were high at 12 and 24 months
8 following surgery. At 24 months following surgery
9 the InFUSE™ fusion rate was 94.5 percent and was
10 statistically equivalent to the autograft rate of 88.7
11 percent.

12 Frankly, for the study the most important
13 aspect of the fusion criteria is whether bone,
14 spanning the two vertebral bodies at the treated level
15 could be detected by the independent radiologist.
16 This would be indicative of whether the InFUSE™ bone
17 graft was effective in stimulating de novo bone
18 formation. It is noteworthy that in all patients in
19 both treatment groups with CT scans available, such
20 spanning bone was detected at 12 and 24 months. CT
21 scans were particularly important in detecting the
22 bone. These findings are considered of prime

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1 importance since fusion cannot exist unless bone is
2 connecting the treated segment.

3 In addition, these findings agree with the
4 data previously presented by Dr. Scott Boden. The
5 Oswestry Low Back Pain Disability Questionnaire was
6 used to measure the effects of back pain on a
7 patient's ability to manage everyday life. The
8 Oswestry Questionnaire has 10 questions and is self-
9 administered. Oswestry scores are expressed as a
10 scale ranging from zero to 100 points with a lower
11 score indicating less pain and disability.

12 As seen with this slide, the mean Oswestry
13 scores for the two treatment groups were very similar
14 at all time periods. At 24 months following surgery,
15 the mean improvements in Oswestry scores from pre-
16 operatively were approximately 29 points for both
17 treatment groups. These findings are quite gratifying
18 and represent an approximate 55 percent improvement.

19 This slide illustrates the distribution of
20 patients demonstrating pre-operative to post-operative
21 improvements in Oswestry scores of at least 15 points,
22 which is a very rigorous condition mandated by the

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1 FDA. This is termed Oswestry success. Like mean
2 Oswestry scores, the Oswestry success rates were
3 similar for both treatment groups. At 24 months
4 following surgery the Oswestry success rates were
5 found to be statistically equivalent with rates of 73
6 percent in both groups.

7 The neurologic status of patients was also
8 assessed pre-operatively and post-operatively and at
9 every follow-up visit and is considered an indicator
10 of safety and effectiveness. The neurologic
11 evaluations consisted of measurements of motor
12 function, sensory, reflex, and degree of straight leg
13 raise producing pain. A successful outcome for each
14 parameter was based on the post-operative condition
15 being no worse than the pre-operative condition.

16 Overall neurologic success for a patient
17 in any given post-operative time period was based on
18 having successful outcomes for all four neurologic
19 parameters. This slide shows the overall neurologic
20 success at 12 and 24 months following surgery for the
21 two treatment groups. The rates are very similar
22 across time and treatment. The 24-month neurologic

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1 success rates for the InFUSE™ and autograft groups
2 were determined to be statistically equivalent.

3 In addition to these end points that
4 contribute to overall success, other effectiveness
5 measurements were made during the course of this
6 study. These measurements included back pain, leg
7 pain, disc height maintenance and general health
8 status via the SF-36 survey. The 24-month results for
9 these parameters were comparable for the two treatment
10 groups and statistically equivalent between treatments
11 was demonstrated for all but two comparisons. They
12 were back pain and mental component summary or MCS of
13 the SF-36.

14 I will not focus on the MCS finding since
15 the difference between the two treatment groups was
16 less than four percentage points and this is not
17 considered clinically significant. For back pain the
18 success rate favored the autograft group and it is
19 believed to be due to arbitrary cut-off assumptions of
20 the analysis, since a mean improvement of back pain
21 scores for the InFUSE™ group was actually higher,
22 showing more improvement than that for the autograft

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