UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

DENTAL PRODUCTS PANEL

MEDICAL DEVICES ADVISORY COMMITTEE

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MEETING

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THURSDAY, NOVEMBER 9, 2006

The meeting came to order at 8:30 a.m. in the ballroom of the Gaithersburg Holiday Inn, Two Montgomery Village Avenue, Gaithersburg, Maryland, RICHARD G. BURTON, Chairman, presiding.

PRESENT:
RICHARD G. BURTON, D.D.S., Chairman
SALOMON AMAR, D.D.S., Ph.D., Voting Member
WILLIAM J. O'BRIEN, M.S., Ph.D., Voting Member
YIMING LI, Ph.D., Non-Voting Member
MASON DIAMOND, D.D.S., Industry Representative
KURT C. GUNTER, M.D., Industry Representative
MICHAEL FLEMING, D.D.S., Consumer Representative
JANINE E. JANOSKY, Ph.D., Temporary Voting Member
MARK R. PATTERS, D.D.S., Ph.D., Temporary Voting Member
JOHN R. ZUNIGA, Ph.D., D.M.D., Temporary Voting Member
MICHAEL J. RYAN, Executive Secretary

I-N-D-E-X

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

(8:33 a.m.)

CALL TO ORDER

OPEN SESSION -- WELCOME AND

INTRODUCTORY REMARKS

CHAIRMAN BURTON: Good morning. I am Dr. Richard Burton from the University of Iowa. I would like to welcome all of you to this meeting of the Dental Products Panel and to the CDRH Medical Devices Advisory Committee. I am the Chairman of the Dental Products Panel at this time, and I would like to call this meeting to order.

We are gathered here today to discuss the premarket approval application for the InFuse bone graft sponsored by Medtronic Sofamor Danek. This device consists of recombinant bone morphogenic protein, rhBMP-2, combined with a bovine collagen sponge.

I would like to go around the table, starting over here on the left, and have each of the members introduce themselves.

MEMBER GUNTER: My name is Kurt Gunter. And I'm the non-voting industry representative.

MEMBER FLEMING: My name is Mike Fleming. I am the non-voting consumer representative on the Dental Products Panel.

MEMBER DIAMOND: My name is Mason Diamond. I am the industry representative to the Dental Products Panel.

MEMBER AMAR: Good morning. My name is Salomon Amar. I am professor of periodontology at Boston University. I am a voting member.

MEMBER O'BRIEN: Bill O'Brien, professor of biologic and material sciences at the University of Michigan School of Dentistry. And I am a voting member of the panel.

MEMBER LI: I am Yiming Li, professor of restorative dentistry at Loma Linda University. I also serve as the Director for Center for Dental Research. I am

a member of the Dental Products Panel.

MEMBER ZUNIGA: Good morning. My name is John Zuniga. I am a professor of oral and maxillofacial surgery at the University of Texas Southwestern Medical Center at Dallas. And I am a voting member of the panel.

MEMBER JANOSKY: Janine Janosky, an associate professor at the University of Pittsburgh School of Medicine. And I am a consultant.

MEMBER PATTERS: Mark Patters. I'm the Associate Dean for Academic Affairs and professor of periodontology at the University of Tennessee.

DR. LIN: Good morning. My name is Chu Lin. I am the Director of the Division of Anesthesiology, General Hospital Infection Control and Dental Devices in the Office of Device Evaluation, CDRH, FDA.

CHAIRMAN BURTON: Thank you.

The Executive Secretary will make some introductory remarks at this time.

EXECUTIVE DIRECTOR RYAN: Thank you, Chairman Burton.

My name is Michael Ryan. I am the Executive Secretary of the panel. I'll now read into the record the deputization of temporary voting member statement and the conflict of interest statement.

"Pursuant to the authority granted under the Medical Devices Advisory Committee charter dated October 27, 1990, as amended on April 20, 1995, I appoint the following consultants as voting members of the Dental Products Panel for the joint meeting to be held on November 9th: Janine E. Janosky, Mark R. Patters, John R. Zuniga.

"For the record, these individuals are special government employees and are consultants to this panel under the Medical Advisory Committee. They have undergone the customary conflict of interest review. They have reviewed the material to be considered for the meeting." This memo was signed by

Daniel G. Schultz, M.D., Director of Center for Devices and Radiological Health, FDA.

The conflict of interest statement is as follows, "Food and Drug Administration is convening today's meeting of the Dental Products Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

"With the exception of the industry representative, all members and consultants of the panel are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

"Following information on the status of this panel's compliance with federal ethics and conflict of interest laws covered by but not limited to those found at 18 USC section 208 are being provided to participants in today's meeting and to the public.

"FDA has determined that members

and consultants of this panel are in compliance with federal ethics and conflict of interest laws. Under 18 USC section 208, Congress has authorized FDA to grant waivers to special government employees who have financial conflicts when it is determined that the agency's need for particular individual services outweighs his or her potential financial conflict of interest.

"Members and consultants of this panel who are special government employees at today's meeting have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their employer, spouse, or minor child related to the discussion of today's meeting.

"These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

"Today's agenda involves the review of a premarket approval application for the InFuse bone graft. This device is a combination product which features a collagen sponge that incorporates a recombinant bone morphogenetic protein.

"The device is indicated for the following oral maxillofacial bone grafting procedures as an alternative to autogenous bone graft for oral maxillofacial bone grafting procedures, sinus augmentation, and ridge augmentation at extraction socket sites.

"Particular matters during the meeting or specific matters related to PMA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the panel members and consultants, no conflict of interest waivers have been issued in connection with this meeting.

"A copy of the statement will be available for review at the registration table during this meeting and will be included as

part of the official transcript.

"Dr. Mason Diamond is serving as the dental device industry representative, acting on behalf of all related industry, and is employed by TyRx Pharma, Incorporated.

"Dr. Kurt Gunter is serving as the biologics industry representative, acting on behalf of all related industry, and is employed by Hospira, Incorporated.

"We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, participants need to exclude themselves from such involvement. And their exclusion will be noted for the record.

"FDA encourages all other participants to advise the panel of any financial relationships that they may have with any firms at issue. Thank you."

If you have not done so already, I

would like to request that everyone in attendance please take the opportunity to sign the attendance sheet that's available at the door. I would also like to request that everyone turn off their cell phone ringers.

Transcripts of today's meeting will be available from Neal Gross and Company, Incorporated. Information on purchasing videos of today's meeting can be found on the table outside the meeting room.

Presenters to the panel who have not already done so should provide FDA with a hard copy of their remarks, including overheads. Ms. Annemarie Williams will collect these for me at the podium.

With that, I will turn the meeting over to Chairman Burton. Chairman?

CHAIRMAN BURTON: Thank you.

I would like to note for the record that the voting members present constitute a quorum, as required by 21 CFR part 14. We will now proceed with the agenda.

OPEN PUBLIC HEARING

CHAIRMAN BURTON: This is the first of two open public hearing sessions for this meeting. The second open public hearing session will follow the panel discussion this afternoon.

At these times, public attendees are given the opportunity to address the panel, to present data or views relevant to the panel's activities.

I would like to remind public observers at this meeting that while this portion of the meeting is open to the public for observation, public attendees may not participate except at the specific request of the Chair. You will be given no more than ten minutes for your presentation.

Both the Food and Drug Administration and the public believe in a transparent process for the information-gathering and decision-making process. To ensure such transparency at the

open public session of the Advisory Committee meeting, the FDA believes that it is important to understand the context of each individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the Committee of any financial relationship that you may have with the sponsor; its product; and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of our statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

I would ask at this time that persons addressing the panel come forward to the microphone and speak clearly as the transcriptionist is dependent upon this as a means of providing an accurate transcription of the proceedings of the meeting. If you have a hard copy of your presentation, please provide it to the FDA staff for use by the transcriptionist to help provide an accurate record of the proceedings.

Okay. The first speaker is Vivian Roblin.

MS. ROBLIN: My name is Vivian Roblin, and I am speaking on behalf of Medtronics. Ten years ago, at the age of 62, I had no teeth, no upper teeth, and I have no bone.

If I laughed, I sneezed, or I coughed, the denture fell out. No amount of sticky stuff would hold the denture in. I was limited to soft food. And it was a very depressing time.

I was referred to Dr. Spagnoli in October of '96. He put the InFuse in my mouth. Six months later, they were able to put in eight implants. I had had that much bone growth.

I have minimal discomfort from the surgery. Would I do it again? Yes, I would. Fortunately, I don't have to. I hope this product will be available worldwide for people that have my problem because, really, with people living longer, it gives you a quality of life that I did not have ten years ago.

That's my story. If you have any questions, I would be happy to answer them.

MEMBER O'BRIEN: Where was the surgery performed: Dr. Spagnoli's office?

MS. ROBLIN: Yes.

MEMBER O'BRIEN: Where is he located?

MS. ROBLIN: Charlotte, North Carolina.

MEMBER O'BRIEN: Thank you.

CHAIRMAN BURTON: Do you have other than your overall results any comments you would like to make about your clinical course in terms of problems you had or didn't have during the course of treatment?

MS. ROBLIN: Yes. I did not have any problems. Everything went just as Dr. Spagnoli thought it would. I never dreamed that I would be able to eat anything I want, but I can now. It's a fabulous product.

CHAIRMAN BURTON: Thank you very much for your input.

MS. ROBLIN: Thank you.

CHAIRMAN BURTON: Thank you for coming.

That was the only preregistered speaker that we had at this time. Are there any others who wish to speak during this time frame?

(No verbal response.)

CHAIRMAN BURTON: Hearing none, we'll move on to the presentation by the

sponsor. Medtronic Sofamor Danek will now give their presentations on this PMA. And we have three listed speakers that are Dr. Chin, Dr. Marx, and Dr. Cochran. I don't know if you care to stay in that order. Is that correct? Okay. Dr. Edward Chin?

PRESENTATION BY THE SPONSOR -

INFUSE BONE GRAFT (P050053)

DR. CHIN: Good morning, members of the panel, the Dental Products Advisory Panel. My name is Ed Chin. And I am the Group Director of Regulatory Affairs of Medtronics Spinal and Biologics in Memphis, Tennessee.

We have the pleasure to present to you the results of decades of research and development of rhBMP-2 for use in oral and maxillofacial procedures. The InFuse bone graft product is the combination of work of hundreds of scientists and clinicians who have worked over the years. And I would like to acknowledge their efforts to make this product

available to the surgeons and their patients.

Today you will hear from two investigators who participated in IDE clinical trials. Dr Robert Marx of the University of Miami will present the clinical problem that patients face and the clinical data of InFuse in sinus augmentation surgery.

Dr. Marx will be followed by Dr. David Cochran of the University of Texas Health Sciences Center in San Antonio, Texas. Dr. Cochran will present the clinical data of InFuse in extraction socket augmentation surgery as well as the overall safety data developed in our clinical trials. I will then return for closing remarks.

We have also assembled here today many of the scientists who performed their preclinical research and some of the investigators who participated in the clinical trials as well as scientists and experts, members of the clinical and regulatory staff of Medtronic, Wyeth, and Allquest, who are

available to answer questions from the panel.

I would especially like to acknowledge Dr. Philip Boyne from Loma Linda University, who is one of the recognized pioneers of rhBMP-2 research in oral and maxillofacial surgery and who wrote the seminal paper on sinus lift procedures.

Discovery of osteoinductivity of BMP was first made by Dr. Marshall Urist in 1965. In his landmark research, Dr. Urist found that certain proteins, which he later termed "bone morphogenetic proteins," BMPs, stimulated the formation of new bone when placed into a non-bony site of a rat. Thus, the term "osteoinductivity" was coined to describe this phenomenon.

Only BMPs have been demonstrated to be osteoinductive. In the 1980s, researchers of Wyeth Bioforma developed a method to synthesize the osteoinductive bone morphogenetic proteins commonly referred to as rhBMP-2 using recombinant methods. We are

also fortunate to have here today scientists who cloned the BMP-2 and performed this work, Dr. John Wozney from Wyeth.

As shown on this slide, rhBMP-2 production cells are grown in a bioreactor that contains a well-defined nutrient media free of human or animal-derived components. The protein of interest is separated from process stream components by a streamed series of three chromatography steps resulting in rhBMP-2 of very high quality and purity.

For added assurance of viral safety, each batch is processed through a nanofilter. Throughout the production process, quality control testing is performed to assess the consistency of the sample, the processing and safety, purity and activity of the resulting rhBMP-2 protein.

rhBMP-2 that has met the established quality criteria is sterile filtered; freeze dried in vials; and then further tested for consistency, safety, and

activity, involves meeting specification of subsequently assembled into InFuse kits.

InFuse is commercially available in four kit configurations containing either 4.2 milligrams or 12 milligrams of rhBMP-2. The vials contain a free stripe powder that has been reconstituted at the time of surgery with sterile water to a final concentration of 1.5 milligrams per ml. The solution is then applied to a type I bovine absorbable collagen sponge referred to as ACS in this presentation.

The ACS localizes the activity of rhBMP-2 and that provides the scaffolding for bone formation. The absorbable collagen sponge is a commercially available product that is manufactured by Integra LifeSciences. FDA approved this hemostatic sponge in a PMA application in 1981. The product for which we are seeking approval is the same product currently on the market.

RhBMP-2 is a specific

concentration, combined with ACS, is the commercial product called InFuse bone graft, which will from this point forward be referred to as InFuse, and this is the product we are discussing today.

The safety and effectiveness of InFuse has already been demonstrated in two previous PMA approvals. The first PMA approval was in 2002 for interior lumbar spinal fusion. The second PMA approval was granted in 2004 for open tibia fractures.

There were 437 patients who received InFuse in IDE clinical trials for these indications. In addition, over 1,200 patients received InFuse or rhBMP-2 on other carriers in clinical trials that are in various stages of completion. Thus, our clinical experience under rigorously controlled, FDA-approved clinical trials is very extensive.

Over the years, research sought to find a bone grafting agent that is truly

osteoinductive. That search ended with the approval of InFuse, providing surgeons with the long-sought osteoinductive product to help their patients.

The therapeutic benefits have been available for patients requiring spinal fusions or tibia repair. Today we are here to seek a third therapeutic benefit for our patients who need oral and maxillofacial treatments to replace teeth.

Similar to other PMAs, we are seeking a third indication for InFuse bone graft. This is an oral indication where InFuse bone graft again induces bone formation that leads to a patient therapeutic benefits, in this case to replace teeth.

The models studied in this PMA are sinus augmentation supported by three studies and extraction socket with buccal wall defects augmentation supported by two studies.

BMP is one of the most studied of all bone-forming agents. This graph

illustrates the large body of knowledge that exists for BMP. The red line graphs the cumulative number of publications over the last 30 years.

Over 5,000 articles have been published, and research continues. The blue line shows 31 regulated clinical studies of rhBMP-2 products conducted over the last 13 years, in which over 1,700 patients have been enrolled.

In the oral and maxillofacial space, early preclinical safety studies provided the foundation for rhBMP-2 development. Preclinical studies were conducted in lower to higher animal species, as shown here, enabling human clinical trials to begin in 1994.

Human experiences from five prospective clinical studies provide the evidence to unquestionably support an approval recommendation for InFuse in oral and maxillofacial bone grafting procedures.

Medtronic is seeking approval for the following indications. InFuse bone graft is indicated as an alternative to autogenous bone graft for sinus augmentations and localized alveolar ridge augmentations for defects associated with extraction sockets.

InFuse has already been proven to be safe and effective for two orthopedic uses. We will present evidence from multi-centered, prospective controlled clinical trials that provide valid scientific evidence to support that InFuse is safe and effective to, one, regenerate bone; two, that that bone supports dental implant placement; and, three, that the restoration is stable over time.

This research has been recognized by professional societies as outstanding high quality work. The American Academy of Oral and Maxillofacial Surgeons Journal editorial board awarded the 2005 Daniel M. Laskin Award for the most outstanding article published in the Journal of Oral and Maxillofacial

Surgeries to Dr. Boyne and others for their article, "De Novo Bone Induction by rhBMP-2 in Maxillofacial Sinus for Augmentation."

The American Academy of Periodontology Foundation bestowed the 2005 Tarrson research award in oral plastic surgeries to Drs. Florellini and others for their paper, "Randomized Study Evaluating rhBMP-2 for Extraction Socket Augmentation."

Today we have the privilege of having several of those authors present. Dr. Robert Marx and Dr. David Cochran of those award-winning research papers will present these clinical results, which is the basis for this PMA.

First, I would like to introduce Dr. Robert Marx, who will present the clinical need for InFuse in oral and maxillofacial surgery and the first part of the clinical data that is the foundation of this PMA.

Thank you.

DR. MARX: Good morning, panel

members. My name is Dr. Robert Marx. I am an oral and maxillofacial surgeon and Chief of the Department of Oral and Maxillofacial Surgery at the University of Miami, Miller School of Medicine.

I have no direct financial interest in the product under review today. I am a consultant for Medtronic, which is covering my expenses for attending this meeting. I participated in the IDE clinical trials of this device as a clinical investigator since its inception in 1994.

My colleague, Dr. David Cochran, and I have been asked to present the data from the clinical studies of InFuse as an alternative to autogenous grafts for maxillofacial conditions, specifically sinus augmentation and localized alveolar ridge augmentations for defects associated with extraction sockets. Autogenous bone grafts will be referred to in this presentation as bone graft.

I would first like to describe the clinical needs that require a bone graft. The essential need occurs when individuals lose teeth and thereby lose bone. There is a need to replace bone loss due to disease, such as this, due to trauma, and due to congenital absence of bone.

We will show you that the use of InFuse will provide bone support to replace missing teeth and in doing so restore structure and function as well as the appearance of the individual.

These photographs show an extreme example of an individual who lost significant amounts of bone, which has resulted now in the loosening of her dentures. She is representative of a totally dentureless patient enrolled in the sinus augmentation study.

She did not have enough bone to comfortably wear dentures or to have dental implants placed. As you can see, this

correlates to a facial collapse that affects her speech and her eating abilities. It also affects her appearance.

To regenerate enough bone to support facial contours and to allow either the placement of dental implants or the wearing of dentures, this patient would require an extensive bone harvest and a grafting procedure.

The current standard of care is autogenous bone grafting. It has certain advantages. It is the patient's own bone. And, therefore, it does not have any risk related to transmissible diseases. It has proven effectiveness as well.

However, autogenous bone grafts such as these have also significant disadvantages, mainly donor site morbidity of pain, blood loss, and permanent scars. It also extends the surgical time and the anesthesia time. And its availability in some patients is very limited.

Because of the risks associated with extending operating time, postoperative pain, infection, and even sensory bone loss, many clinicians would prefer not to harvest bone from their patients. And patients prefer not to undergo this additional painful procedure.

There are a number of disadvantages to the bone graft. Today we will show you that InFuse overcomes these disadvantages. There is certainly a clear need to grow bone with a product that doesn't have the risks and morbidity associated with such a bone harvest.

Bone grafting is also not a benign procedure. Patients often will continue to suffer from pain or numbness or sensory nerve loss at the donor site long after the oral surgery has healed. Patients will often have permanent numbness at this site. There is also significant blond loss and a significant risk of donor site infection.

Because of the risk associated with extended operating time, postoperative pain, infection, or sensory loss, many clinicians would prefer not harvest bone from their patients. And many patients avoid needed procedures due to their fear of bone graft harvest and the pain associated with it, essentially denying themselves access to care.

Ullman, et al., reported the complication rates associated with iliac crest bone grafts in this Journal of Bone and Joint Surgery publication. They found that patients had an average of over 200 milliliters of blood loss, a 3 percent instance of hematomas, an 8 percent sensory loss, of which 5 percent was a permanent sensory loss with associated numbness. They also had two percent with chronic pain.

The proposed indications for InFuse as an alternative to the autogenous bone graft, there are a number of disadvantages to bone grafts, as you can see.

Today we will show you that InFuse overcomes these disadvantages.

The oral and maxillofacial surgery program objectives were to demonstrate effectiveness of rhBMP-2/ACS in the following: one, regenerate or grow normal physiologic bone; two, to provide an adequate amount of good quality bone to support dental implants and dental restorations; three, to produce bone that remains stable under long-term functional loading, providing a durable result; and, finally, four, to demonstrate a safety profile in the maxillofacial indications.

The clinical studies were designed to collect evidence to prove these. Bone density measurements, bone biopsy, histologic studies were accomplished. And CT scans were performed to accomplish all of these objectives.

The evidence for this PMA is derived from two clinical models. The first

that I will present is for the sinus augmentation indication illustrated here, where an opening is made into the lateral wall of the maxillary sinus, the membrane is elevated, and bone or InFuse is placed.

The second will be the extraction socket defect augmentation, in which this lateral or buccal wall is lost and represents a true critical-sized defect.

The science augmentation studies were prospective, controlled, clinical trials. These data provide a high level of clinical evidence. After completion of pre-clinical studies, a pilot study was initially performed to assess the feasibility of using rhBMP-2/ACS in sinus augmentation procedures utilizing a concentration of 0.43 milligrams per milliliter. That's this one.

Although bone formed in this study, it was not optimal for dental implant placement. Therefore, a randomized dosing study was then conducted which evaluated 0.75

milligrams and 1.5 milligrams per milliliter concentrations, which were selected based on data from the preclinical, pharmacokinetic, local bioavailability, and pharmacologic studies.

Data from the dosing study demonstrated the ability of rhBMP-2/ACS to successfully induce an adequate amount of bone in this surgical procedure for dental implant placement and found that 1.5 milligrams per milliliter concentration to be the most effective concentration used.

To confirm these observations, a randomized pivotal study was conducted with the 1.5 milligrams per milliliter concentration. The data demonstrated that InFuse could safely and effectively induce new bone, which could receive dental implants that could then be functionally loaded and maintain their functional loading over a long period of time.

The data to be presented today and

which was submitted in the PMA is an analysis of subjects receiving 1.5 milligrams per milliliter rhBMP-2/ACS in the sinus dosing study and the sinus pivotal study. These data were pooled following statistical justification that they were homogeneous populations with respect to demographics, baseline characteristics, and clinical outcomes.

By agreement with the FDA and with similar justification, the autogenous bone graft subjects in the sinus dosing study and the sinus pivotal study were also pooled. The primary efficacy endpoint for these analyses was the same as that approved for the pivotal study, which was the rate of functional loading of the implant-borne restoration at six months.

The target success rate calculated for this study was 73 percent. This predetermined target was selected based upon data from the dosing study and a review of the

literature at the time.

The investigators determined that 70 percent was the minimum clinically acceptable and meaningful success rate for rhBMP-2/ACS success. And this target value was adopted in the study design. The target was then set at 73 percent for this statistical consideration and sample size requirements. This success rate was submitted in the IDE protocol and approved by the reviewers within the FDA.

The primary objectives of the sinus augmentation study were to evaluate the effectiveness of InFuse to induce adequate bone to successfully support implant-borne restorations after six months of functional loading and to evaluate the safety of rhBMP-2/ACS compared to a bone graft.

The secondary objectives of the sinus augmentation studies were to evaluate the overall quality of the bone from CT scans, histology, and functional loading results of

InFuse compared to those of the bone graft.

This slide illustrates the sequence of events in our sinus augmentation studies. Testing performed in each study period is shown across the bottom of this line. Following the baseline period with the initial CT scans and other studies, patients underwent the sinus lift procedure in which InFuse was implanted under the sinus membrane to induce new bone.

At approximately four to six months, each patient was evaluated by CT scans to determine whether or not a dental implant could be placed. After implant placement, a periapical radiograph was also taken. Core biopsies of the bone for also taken for histologic assessment.

If the clinician determined that there was adequate quality and quantity of bone, the dental implant was placed. Following osseointegration of the dental implants, the implants were then uncovered. A

dental prosthesis was fabricated and then placed. Then functional loading of the prosthesis began.

A third CT scan was taken at either six months post-dental implant placement or at six months post-functional loading depending upon the study. The patients were then assessed at six-month intervals through 24 months post-functional loading, which was approximately 36 months following the original placement of rhBMP-2/ACS.

Now, the initial cohort of the sinus dosing study patients were randomized to 0.75 milligrams per milliliter rhBMP-2/ACS or the bone graft.

After acute safety was established, patients were randomized between 1.5 milligrams per milliliter rhBMP-2/ACS or the bone graft itself as the second cohort. In the sinus pivotal study, patients were randomized to receive either InFuse or bone

graft.

The clinical data were collected in three separate prospective controlled IDE clinical trials. Patients were treated with various concentrations of rhBMP-2/ACS or a bone graft. In these studies, bone graft is defined as either autogenous bone alone or a combination of autogenous bone and allogenic bone, consistent with the current standard of care.

Two hundred twenty patients were enrolled in the sinus augmentation studies at 21 different study sites. The effectiveness data subset consists of 82 patients from the pivotal study and 17 patients from the dosing study, for a total of 99 patients, all of whom were randomized to be implanted with the 1.5 milligram per milliliter concentration of rhBMP-2/ACS plus collagen response, which is the product of InFuse.

I will now present the results. This representative slide is a preoperative

panoramic CT scan view of the lower portion of the sinus cavity. As you can see here, the sinus is hyperpneumatized and there is insufficient bone to place an implant.

The lower CT scan now, taken from the patient at 16 weeks post-InFuse placement, shows a large amount of de novo bone formation, new bone formation formed beneath the sinus membrane on each side of the maxilla. Indeed, InFuse was shown to induce new bone in this indication.

On this next slide, CT scans from another sinus augmentation patient are shown. The height of bone is measured from the level of the alveolar crest to the floor of the maxillary sinus, as illustrated by this thin yellow line. This patient had only 3.9 millimeters of bone at baseline, certainly an insufficient amount to place a dental implant.

On this CT scan, you can see first the opening of the lateral sinus window used to place the InFuse, which is right here. At

6 months now, 16 millimeters of bone was present, a fourfold increase in the bone height, which is suitable now for a dental implant placement.

On this bar graph, the bone height gained for 98 patients who received InFuse in the sinus augmentation study is displayed. Nearly all patients great significant amounts of bone. And most patients grew a substantial amount of bone.

The clinical trial data show that InFuse induced a substantial amount of new bone in sinus augmentation procedures as a conclusion. InFuse averaged a gain of 8.2 millimeters of bone in the sinus, quite comparable to the current standard of treatment of a bone graft, which had a slightly higher average in bone gain at 9.7 millimeters.

At six months following InFuse implantation, patients were eligible to receive dental implants. Per the protocol,

only those patients who received a dental implant without further augmentation were considered successful and allowed to be followed for functional loading. If they were not, they were considered treatment failures.

82.8 percent of the InFuse patients were considered successful in this study. 79.8 percent of patients went on to receive a prosthesis and were evaluated for the primary objective.

The combined results from the sinus augmentation studies exceeded the target success rate of 73 percent, achieving 79.6 percent success at 6 months of functional loading. This was also seen in the separate by study analyses.

One of the trial's secondary objectives was to compare functional loading success over time between InFuse and the bone graft. In this slide, the by patient functional loading success rates of the bone graft and InFuse groups are compared. Note

that both treatments are highly successful at the patient level and the results are maintained all the way out to 24 months.

In this slide, the by implant functional loading success rates of the bone graft and InFuse groups are compared as well. Note that both treatments are also highly successful at the implant level, with 87 percent and 86 percent of implant target sites receiving implants and a prosthesis.

After 6 months of functional loading, 81 percent of the InFuse target sites remained functionally loaded compared to 84 percent in the bone graft. This difference is not statistically significant. As shown here, the results are maintained once again out to 24 months with no statistical difference.

In summary, once the dental implant is placed, almost all patients continued to have a successful prosthesis placement and long-term functional loading in both groups.

Bone density was measured on CT scans in a subset of sinus augmentation patients treated with bone graft and InFuse. At four months, dense mature enough bone to receive dental implants in both groups developed.

The higher bone density in the bone graft group is probably due to the residual mineral density of the bone graft, rather than new bone, which is the nature of autogenous bone.

From the time of surgery to six-month post-functional loading, which is 10 to 12 months from the first density measurement, the bone induced by InFuse becomes much more dense with loading of the dental implant.

The bone densities now are comparable in each group. These results demonstrate that bone induced by InFuse responds as normal physiologic bone and increases in density when loaded as

anticipated by physiologically normal bone.

The histologic assessments demonstrated that there were no clinically significant differences in histologic parameters between InFuse and the bone graft-induced bone. Patients in these studies had a core biopsy taken, which is represented by this at the dental implant placement site. That's why it is cylindrical in shape.

These core biopsies were used to make qualitative and quantitative histologic assessments. This representative specimen, as you see here, is taken from a patient who received InFuse. It has been prepared with the Goldner stain.

Native bone is seen at the base of the longitudinal section of the core biopsy, which is here. This is the native bone of the maxilla that's note induced by either a bone graft or InFuse. And new bone is seen above this level.

The histologic assessment

demonstrates that there are no significant differences in histologic parameters between InFuse and the bone graft-induced bone. Both resulted in significant formation of new trabecular bone comparable in density and structure to native bone. Sufficient bone was generated for osseointegration with the implant.

Essentially this Goldner stain shows the green to be bone, the red here to be marrow spaces. You see end osteo, osteoblasts. You see thick trabecular connectivity here, which is ideal for dental implant placement.

By everything we measured, radiographs, histology, bone density, implant placements, we have demonstrated that InFuse induces growth of normal physiologic bone.

On this next slide, we show representative samples from a patient who received a bone graft and another who received InFuse. The bone graft is here. Again, these

are core biopsies. And, therefore, they're cylindrical and the InFuse-induced bone on this side.

Autogenous bone and InFuse grafted sites resulted in significant formation of new trabecular bone comparable in density and structure to the host site. Both show similar trabecular bone volume as the amount of bone in this total volume space, accounting for narrow spaces, and bone thickness. And both had a 90 to 95 percent lamellar bone architecture, indicative of mature bone. Only a small amount of residual immature bone was present in each group.

Although statistically somewhat different, perhaps due to the residual and lamellar bone fragments in bone grafts, the difference did not affect clinical outcomes.

Patients were administered subtherapeutic doses of tetracycline and doxycycline in order to label the new bone that was formed. The early osseoinductive

event of InFuse is easily demonstrated on the far right in this pair of micrographs. This is the InFuse. This is a bone graft at ten days. The early yellow/green fluorochrome label shows all the new bone at ten days post-grafting.

In comparison, the fluorochrome label on the pair on the left shows 80 percent residual allograft and autograft fragments incorporated into only about 20 percent new de novo bone. Essentially the yellow fluorochrome, as you see here, is indicative of new bone.

The remaining darker bone particles are nonviable, residual bone particles from the graft itself; whereas, the rhBMP-2/ACS-produced bone at ten days, shows a remarkable amount of new de novo bone formation, as illustrated by the fluorochrome labeling.

Dr. Stephen Cook, a bioengineer and professor of orthopedics at Tulane

University with over three decades of experience in bone histology, independently reviewed the data from this PMA. He concluded, and I quote, "Autogenous bone and rhBMP-2/ACS grafted sites resulted in significant formation of new trabecular bone comparable in density and structure to the host site. The bone that formed was biologically and structurally normal."

It is well-established that InFuse leads to bone growth where it is surgically implanted. Logically it should follow that the treatment sites have sufficient bone with InFuse will lead to bone growth; and, in turn, will allow for dental implants and successful functional loading after a prosthesis is placed.

The data presented here were derived from prospective, randomized clinical trials to confirm this is the oral and maxillofacial population with a protocol to find success definition with an agreed-upon

predetermined success rate.

The data collected from the sinus augmentation studies indicate that InFuse induced new bone growth. The 79.6 percent success rate in the InFuse group exceeded the 73 percent target success rate for implantation and long-term functional loading. The evidence we presented here supports the efficacy of InFuse in the sinus augmentation procedure.

This concludes the sinus augmentation presentation. I thank you for your attention. I now would like to introduce my colleague, Dr. David Cochran, who will present the extraction socket data and the safety profile.

Thank you.

DR. COCHRAN: Good morning, panel members. My name is Dr. David Cochran. And I am a periodontist and the Chairman of the Department of Periodontics at the University of Texas Health Science Center in San Antonio.

I have no direct financial interest in the product under review. I am a consultant for Medtronic, who is covering my expenses for attending this meeting. I participated in the IDE clinical trials of this device as a clinical investigator.

It is my pleasure to present why there is a clinical need for extraction defect augmentation with InFuse bone graft, the clinical data from this IDE clinical trial and the safety data that supports the entire PMA.

When a patient becomes edentulous, the alveolus or alveolar ridge can collapse or remodel through the resorption of bone to such an extent that the patient is unable to have dental implants placed or receive other dental restoration.

Dentists want to augment these extraction defects with a bone graft that can induce new bone formation and preserve or restore the height and width of the extraction socket or ridge.

If you look in this picture on the left over here, as Dr. Marx pointed out, this is an extraction socket area, where half the buccal plate is missing. So the defect exists, particularly on the facial side here, where this bone is gone.

On the right side here is the collagen sponge, or ACS as we refer to it in the trial here. And what that is, is, in this case either the sponge alone or the sponge with the BMP placed in that sponge. We were blinded as investigators. And I'm not sure which case this is.

When we place a dental implant, we need to have a sufficient volume of bone so that the bone can completely surround the cylindrical implant. The implant is normally 3.5 millimeters in diameter. So we have to have a sufficient volume in here.

And when you take these teeth out, this bone tends to collapse here. And we don't have enough width, particularly from the

palatal to the buccal side, to place our implants. So we normally need some sort of grafting material to bulk out this area and form new bone.

The clinical data was derived from a prospective randomized controlled 80-patient human clinical trial. This trial design is considered a high level of clinical evidence.

Patients were eligible for inclusion if they had a buccal wall defect at least 50 percent of the extraction socket depth for maxillary teeth from the bicuspids forward.

Other criteria were similar to the sinus program, including no active nicotine use or disease or medications that affected bone metabolism. The efficacy endpoint was the formation of adequate alveolar bone formation similar to the sinus augmentation study. Safety was also evaluated similar to the sinus augmentation program.

This is the sequence of events in

our extraction defect augmentation study. You will notice that it's very similar to the sinus augmentation studies. Testing performed in each study period is shown again across the bottom of this line here.

Following the baseline period extraction of the tooth and collection of the initial CAT scan or CT, rhBMP-2/ACS was implanted in the extraction defect to induce bone.

Approximately four months after surgery, each patient was evaluated by CT scans to determine whether sufficient bone formation had occurred.

The surgeons then reentered the surgical site. We took the core biopsy here for histological evaluation. And then we placed our dental implants. There was then a period of time to allow for osseointegration of the implant.

After the dental implant was integrated, an abutment and prosthesis was

placed on the implant and loading of the prosthesis began. The patients were assessed at six-month intervals through 24 months, which was approximately 36 months following rhBMP-2/ACS placement.

Two clinical trials were conducted under the extraction socket IDE. And first I want to mention about the pilot study: at the same time as the sinus pilot study, a two-center pilot study was conducted to assess the feasibility of rhBMP-2/ACS in horizontal ridge augmentation in six patients and extraction socket augmentation also in another six patients utilizing this concentration of 0.43 milligrams per ml.

Filling of the extraction sockets was seen in this study, but it was not optimal for dental implant placement. So we progressed, then, to a dosing study, which was then conducted similar to the sinus dosing study.

In the first cohort on the bottom

down here, patients were randomized to receive implantation of 0.75 milligrams per ml concentration of rhBMP-2, the ACS sponge alone down here, or unfilled extraction defects.

In the second cohort, which is up on the right here, patients were randomized again to receive implantation of the 1.5 milligram per ml concentration of rhBMP-2, the ACS sponge alone, or unfilled extraction defects.

The clinical data were collected in these two separate prospective clinical trials. Ninety-two patients were enrolled, including the randomized dosing study of localized alveolar ridge augmentation with buccal wall defects, referred to throughout this PMA as extraction defect augmentation studies. And this was conducted at eight different clinical study sites.

The effectiveness data set consists of 21 patients from one study who were treated with InFuse bone graft. The

other patients in these studies received lower concentrations of rhBMP-2/ACS; no treatment, which is referred to as the unfill control; or the ACS alone. Let's now review some representative CAT scan data.

This image is a pre-implant CAT scan showing an extraction socket after the tooth has been removed. This is where the tooth was located right here. Here you see the palatal wall of the extraction socket that's fairly prominent and a buccal wall that's not very prominent.

In fact, the buccal wall is missing in this area here. Normally the extraction socket would be down here. So you're missing the buccal wall and all of the space where the tooth was removed.

You will see that this radiolucency makes this a much more challenging defect because we're missing this buccal wall. So we need bone fill in a vertical direction as well as in a horizontal

direction here.

This next CT scan shows bone growth after 16 weeks following InFuse placement. De novo bone exists between the missing buccal wall and the palatal wall. So all of this is new bone formation here. So you see the palatal wall and then the new buccal wall here. Thus, horizontal and vertical ridge augmentation has occurred.

Now, this is really an exciting picture when you think about it because we have really never seen pictures like this before. And we don't see a lot of residual graft particles or anything like that, that we have had to use in the past. This is all induced bone by an osseoinductive protein.

And when this amount of new bone is formed, particularly at the coronal aspect of this, the surgeon can be very confident that a dental implant can be placed in this patient.

This slide is another

representative CAT scan for an InFuse patient, both at baseline and 16 weeks post-placement. Note again the nearly absent buccal wall. You just see a wisp of this bone. This bone is always very thin in this area, but we're completely missing the remainder of the buccal wall, both in a vertical and horizontal direction. And then after InFuse placement, we see bone has grown and completely filled this area.

In contrast, on this next slide, we show a set of CT scans from a patient with the critical size defect that was left unfilled. So the tooth was in this area here. This is just a radiographic marker where the implant -- we would like to place it in this site here. There is just a wisp of buccal plate here. Here's palatal wall.

Once again, the buccal wall is barely present. And with no treatment, continued resorption takes place over the 16 weeks such that a dental implant cannot be

placed. There's just no fill in this defect, just a little residual amount in this area, certainly not enough bone to place an implant.

So in this slide, we compare the unfilled and the InFuse-treated CT scans. The InFuse treatment on the right provided clinically significant results, allowing for dental implant placement, which is shown on this next slide for this same patient. So the patient therapeutic benefit is demonstrated here by showing this dental implant that's now placed in this vertically enhanced bone growth with the InFuse product.

Now, one of the challenges we faced designing this trial was that no one had evaluated extraction socket defects in the healing over time from the radiographic point of view.

So we collaborated with leading radiologists and determined before the trial began how to evaluate the fill of these defects. We took serial section CT scans and

established where the baseline was and where the most coronal extension of the bone occurred.

So here you can see in this schematic the tooth was in this area. The base of the extraction socket is down here. And the most coronal aspect is right here.

Following the bone augmentation surgery, we repeated this process. And then we evaluated the change in vertical height, which is represented by this green line, which is D-1 plus D-2. So it's this vertical line going through here.

And we also evaluated the width of the defect at the one-quarter, one-half, and three-quarter positions to allow us to look at the width of the bone that's grown. It's better to look at it over here. So there's missing bone here we could evaluate what the dimension of the new bone growth was.

On the next three slides, I will show you the results of our extraction defect

augmentation study for the unfilled, the ACS only, and the InFuse bone graft treatment.

In this slide, we are looking at change in bone height. And we demonstrated that in an unfilled defect, which is this green bar here, the alveolar ridge height in the extraction defect was lost. And with the ACS only, the height of the extraction socket was comparable to the unfilled defect.

What you are looking at here is change in bone height. So here you see a 1.17-millimeter change in bone height, which means that you started here, but then you went down about 1.17 millimeters. When you had the collagen only or the ACS, we still lost about a millimeter of bone.

So in both these situations, we resulted in loss of bone, which is important for the model system, demonstrating that these are indeed critical size defects that do not heal when left alone.

With InFuse bone graft, the height

of the extraction socket was preserved. In other words, there's no change, really, in height of the extraction socket, which means that essentially it filled in all the way and preserved the height of that ridge. These differences confirm that InFuse bone graft leads to highly significant improvements in bone height.

Now, on this next slide, we are switching from bone height to the bone width. The change in the width at the one-quarter position is shown for each of the treatments in this slide.

Here one sees another significant gain in bone growth with InFuse bone graft versus the unfilled and the collagen only-treated patients. Bone growth at the socket crest is significantly greater for InFuse than with either the unfilled or the ACS only treatment. So you see here a very significant difference, which at the one-quarter point is the most important point for us clinically to

place an implant.

If we don't have the width up here at the coronal area, then we can't place the implant because the implants are generally about 3.5 millimeters in width. So we're looking at this area right here.

Patients with InFuse bone graft experience an average of 2.7 millimeters additional width gain where it counts the most compared to patients with unfilled defects and an average of 2.45 millimeters additional width gain compared to patients treated with ACS only.

This is not only significant, but it is clinically relevant because bone is needed here to place the implants and/or support aesthetic restorations for our patients; similarly, if we see another significant gain in bone width at the one-half position of the extraction defect, again with the InFuse bone graft compared to the unfilled or the ACS only.

Patients with InFuse experience an average of 2.35 millimeters additional width gain compared to patients with unfilled and an average of 2.18 millimeters additional width gain compared to patients treated with the sponge only. As mentioned previously, this bone is required to clinically support the dental implant restorations.

In summary, InFuse is significantly more effective than both unfilled and ACS only in terms of the change in alveolar ridge height and in width at the one-half and one-quarter measurement positions. This is clinically relevant for our patients because the more bone, the better the chance of implant placement and/or prosthesis success in long-term function of the dental restoration.

So the take-home message is that over time InFuse induced bone growth in significant and sufficient quantities to place dental implants in this study.

Now, the previous slide showed the effectiveness of InFuse for promoting bone growth. This slide shows the relationship between bone growth and implant success. So we're looking at the relationship between that bone growth that occurred and the success of implant placement.

The data demonstrate that the amount of bone growth is strongly associated with successful dental implant placement. Bone width gained at the one-half and one-quarter positions and the increases in bone height are all significantly associated with implant success. Only at the three-quarter position is there no association in bone width in either treatment with implant success.

In summary, greater bone growth is associated with greater implant placement, a logical conclusion, but this was proven in this controlled clinical trial.

This slide shows the comparison of

dental implant, prosthesis placement, and functional loading by patient for the unfilled, ACS, and InFuse patients. The important time points are the dental implant placement along this line here and the six-month evaluation point along that line. On the next two slides, we will look more closely at these two time points.

When we compare dental implant placement, prosthesis placement, and functional loading by patient for unfilled, ACS, and InFuse patients, we find significant differences between the groups. Of the patients that reached this phase of the study without the need for further augmentation, 86 percent of the InFuse grafted patients received a dental implant versus only 59 percent in the ACS only patients and 47 percent of the unfilled patients.

The greater bone growth achieved with the use of InFuse bone graft led to a significantly greater number of patients

receiving dental implants without an additional augmentation procedure.

Focusing on the functional loading at six months, functional loading at six months, we find that a significantly greater percentage of patients in the InFuse group, 74 percent, remained functionally loaded than those in the unfilled group at 38 percent.

Similarly, a higher percentage of the InFuse patients remained functionally loaded at six months compared to those in the ACS only group at 50 percent, although this difference is not statistically significant.

The conclusion from these effectiveness data is that InFuse bone graft successfully outperformed both ACS only and unfilled groups.

In this next slide are representative core biopsies taken at the time of dental implant placement from both the extraction socket augmentation study, which is on the left here; and the sinus augmentation

studies on the right.

This shows the new bone induced by InFuse is nearly identical in every measurable parameter to the native bone in terms of trabecular volume, thickness, and number. And this is the same, whether it's in the sinus augmentation or in the extraction defect augmentation studies.

This higher magnification section shows the normal mix of lamellar and immature bone pattern, which is indicative of maturing bone produced by InFuse bone graft.

On this slide, the density of the induced bone is compared in the extraction, augmentation, and sinus augmentation studies, the sinus on the right, extraction on the left.

For the infused patients, the purple bars, which we're looking at here, the purple bars, on the right side of this slide, in the sinus study, the density was 137 milligrams per cc at 4 months post-grafting

and 508 milligrams per cc 6 months post-functional loading.

On the left, this graft shows a mean density of 343 milligrams per cc at 4 months post-grafting in the extraction socket augmentation study. The density achieved in the extraction socket study was well on its way to being comparable to the sinus study results.

In summary, the clinical data from the extraction defect augmentation studies demonstrate that InFuse bone graft induces new bone growth that leads to successful dental implantation and long-term functional loading. InFuse was most clinically effective following tooth extraction for augmentation of the alveolar ridge and dental restoration.

InFuse provides a new treatment modality and a treatment alternative since bone growth is stimulated by this osteoinductive protein and really gives us another option for our patients.

Now let's turn our attention to the overall safety of InFuse bone graft. One of the things that is prominent when you look at the data related to the InFuse product is that there is an extensive safety profile. There are already two approved PMAs. And over 300,000 InFuse bone graft kits have been distributed. Four hundred thirty-seven patients support InFuse safety and effectiveness in the two PMAs.

InFuse has more level I clinical evidence than any other bone grafting agent. There are 1,070 patients enrolled in rigorously controlled FDA clinical trials. InFuse has an established safety profile.

The oral and maxillofacial safety data set consist of patients who were implanted with any concentration of rhBMP-2 plus ACS sponge and sinus augmentation or extraction defect studies.

The population includes 129 patients from the sinus augmentation studies

and 55 patients from the extraction defect studies, for a total of 184 patients at all concentrations of rhBMP-2/ACS. Of these, 120 represent the InFuse patients.

The table on the next two slides shows the adverse events which occurred in more than ten percent of the patients who received InFuse or bone graft in the three studies.

The majority of the events were expected in oral surgical patients or patients who undergo bone harvest procedures. They included oral, facial, and general edema, infection, mouth pain, arthralgia, and abnormal gait. These events resolved in short order.

When all of these categories of adverse events in these two groups were compared, only the AEs presented on this slide were significantly different in the two patient populations. These included arthralgia, abnormal gait, hypothesia,

erythema, general edema, infection, pain, and hyperglycemia. All were significantly less frequent in the patients treated with InFuse bone graft.

This table shows the number of adverse events reported in the IDE studies, the percentages of patients who experienced at least one adverse event, the relatedness of the events to InFuse bone graft, plus the number of grade 3 and grade 4 events.

The collection of adverse events was very conservative and documented every conceivable AE that patients experienced. As you can see, virtually every patient reported at least one adverse event. And there was no difference between the InFuse and bone graft groups.

The incidence of adverse events related to InFuse was 17 percent and 24 percent in the 2 indications. These were predominantly facial edema, oral edema, mouth pain, and oral erythema, which rapidly

resolved.

The adverse events related to autogenous bone graft were not recorded as a part of this study, but I will present the data related to the donor site in just a moment.

The majority of adverse events were grade I or grade II. The rates of grade III or IV adverse events in both groups was low. None of the grade III or IV adverse events was related to InFuse bone graft.

There was one death among the 312 participants in these studies. The patient was a 43-year-old woman at my site in San Antonio who underwent an extraction socket augmentation procedure. The operation was uneventful and only had some expected mild facial swelling in the immediate postoperative period and no significant other adverse events. The patient died three years postoperatively. The cause of death was judged not related to the study treatment by

the investigator, which was me.

Antibody titers were measured preoperatively and postoperatively in 184 patients who received rhBMP-2/ACS in 91 autogenous bone graft patients to monitor for immune reactions to the components of InFuse. There was no incidence of positive anti-rhBMP-2 antibodies in the autogenous bone graft and a 2.2 percent incidence in the InFuse group. The titers, however, were low and transient.

There was a 20 percent incidence of antibodies to bovine collagen in the InFuse patients. But, interestingly, the autogenous bone graft group had an even higher incidence at 31 percent, presumably due to exposure from other bovine sources. Some titers continued into the follow-up period.

Antibodies to human type I collagen were not detected in either group of patients. The presence of antibodies to rhBMP-2 or bovine collagen was not associated

with immune-mediated adverse events, such as allergic reactions.

As previously mentioned, there were 91 patients who received autogenous bone graft. And that bone graft was predominantly harvested from three different areas: the Iliac crest, the tibial plateau, and an intra-oral bone site.

The pain and morbidity associated with the harvest site is shown in this table. Significant pain is experienced in a high percentage of patients with all three bone harvesting techniques.

Iliac crest harvesting is associated with significant donor site pain and gain disturbance out to ten days. Sensory loss was present in 11.1 percent of these patients, even at 6 months.

Even in the tibial plateau site, there was significant pain and associated gait disturbance, with pain present in 3.1 percent of the patients out to 6 months.

At 2 days, 27.6 percent of patients experienced local sensory loss in the perioral region, the gingiva, the lip, or in the teeth, which can become nonviable due to the harvesting of the intraoral bone. Sensory loss was still present in 17 percent of these patients at 6 months.

In summary, there is a large percentage of patients that have problems with these donor sites. The use of InFuse will eliminate the morbidity associated with autogenous bone graft harvesting.

This graph shows the time line of the harvest site adverse events. The majority of events occurred in the first 20 days after the harvest procedure and dropped off precipitously by 60 days with some morbidity extending beyond 180 days. This was not relevant to the InFuse group as these patients did not undergo a harvest procedure.

In summary, InFuse bone graft has an established safety profile through two

previous PMA approvals in more than 1,000 patients enrolled in rigorous FDA prospective randomized human clinical trials.

In addition, the clinical data from three prospective randomized IDE trials that specifically evaluated its use in oral and maxillofacial applications demonstrated that there were significantly fewer adverse events with InFuse bone graft than with autogenous bone graft.

The use of InFuse as an alternative to autogenous bone graft eliminates the significant morbidity associated with autogenous bone harvesting. We believe that there is reasonable assurance that InFuse is safe for these indications for use.

I would now like to turn the podium back to Ed Chin from Medtronics to conclude our presentation.

DR. CHIN: Thank you, Dr. Cochran.

Members of the panel, based on the

information presented to you today and the information submitted in the PMA application, we have demonstrated that there is a reasonable assurance that the safety and effectiveness for the use of InFuse bone graft as an alternative to autogenous bone graft for sinus augmentations and localized alveolar ridge augmentations for defects associated with extraction sockets.

Both indications are supported by clinical data from prospective randomized controlled FDA-approved clinical trials. We believe our studies demonstrate that these patients share a common clinical problem; that is, the need to grow sufficient bone to support the dental implant borne restoration, bone that will respond to physiologic loading over time.

Our studies of both the sinus augmentation and extraction socket indications demonstrated that InFuse induces significant amounts of bone. The bone is histologically

normal bone. The bone was sufficient to allow the dental implant and subsequent functional loading over time. We believe that InFuse produced nearly identical results.

When reviewing these studies and analyzing the numbers, it is sometimes easy to forget the significant clinical benefits these patients derived from this technology.

This patient lost teeth and subsequently the supporting bone. Reconstruction using InFuse provided the bony support for dental implantation and eventual prosthetic restoration. This was accomplished by eliminating the autogenous bone graft harvest procedure and the associated pain and morbidity with the harvest.

These non-restorable teeth were extracted and the sockets were grafted with InFuse, as shown in this slide. This aesthetically pleasing and functional result is only possible when adequate bone is grown in the extraction socket, again eliminating

the bone harvesting, the pain, and morbidity.

InFuse was effective in inducing new bone in sinus augmentation and extraction socket with buccal wall defects augmentation procedures.

Our clinical studies demonstrated that InFuse induced normal bone where no bone existed before and this bone was histologically and physiologically normal. This bone responded to functional loading stresses and supported dental implants under physiologic loading conditions out to three years.

The clinical data demonstrate that InFuse is clinically effective in a significant portion of the patient population and has been shown to be an effective alternative to bone graft.

We believe that we have established that InFuse is safe. The multitude of preclinical in vitro and in vivo studies and extensive human clinical trials

performed on the product attest to the established safety profile of InFuse.

Clearly the risks associated with the use of InFuse are outweighed by the benefits of the device, particularly when the use of the device avoids the significant morbidity associated with bone harvesting procedures and/or the general anesthesia.

As clearly demonstrated in these presentations and the information submitted in the PMA application, a reasonable assurance of safety and effectiveness of InFuse has been provided. Functional animal model testing, clinical data from two previously approved PMAs, two large-scale IDE studies demonstrate InFuse safety stimulates the formation of bone.

The data are consistent. The data are compelling. They are convincing. InFuse can safely grow normal bone where none existed before and is an effective alternative to a bone graft. These data provide a reasonable

assurance that the device is safe and effective for its intended use, the main criterion for PMA approval.

We ask that you as members of the panel acknowledge the significance and validity of the information and make this breakthrough technology available to surgeons and their patients by recommending approval of this PMA application.

This concludes Medtronic's presentations. And we are available for further questions.

CHAIRMAN BURTON: Thank you, Dr. Chin, Dr. Cochran, and Dr. Marx.

At this time I would like to ask the panel if there are any points of clarification that they would like to have from the three presentations that they would like to have or we can also call them back during our discussions later this morning and in the afternoon, but I would certainly like to entertain any questions at this time while

the information is fresh. Yes, Dr. O'Brien?

MEMBER O'BRIEN: You may have covered this already in your presentation, but do you use antibiotics as part of the InFuse procedure? Is that necessary for the procedure or do you have any adverse effects that you would like to avoid with antibiotics or are they helpful in preventing adverse effects?

DR. MARX: As per the protocol, the individual site investigators were allowed to use their standard antibiotic regimes in both the bone graft groups and in the treatment groups. No adverse reactions were reported to the antibiotics related to the study.

CHAIRMAN BURTON: Dr. Zuniga?

MEMBER ZUNIGA: I will address this to Dr. Marx. In your presentation, you introduced the tetracycline staining protocols. Can you clarify, was that done in the dosing study or the pivotal study? And

was there any quantitative analysis of that tetracycline staining?

DR. MARX: The tetracycline staining was done in both the dosing study and the pivotal study, more in the pivotal study because there were greater numbers. They were given to a subset of the individuals.

The quantitation of that was not recorded. There was mainly a qualitative study with that only.

CHAIRMAN BURTON: Yes, Dr. Amar?

MEMBER AMAR: Was there any attempt to look at a demineralized core biopsy in terms of looking at the mineral content of a recombinant human BMP-2 graft site, as opposed to either original sites or site grafted with DFDBA? I guess my question is, was there any attempt to look at mineral content and how would that progress over time?

DR. MARX: That was not part of the original protocol to look at mineral content. So that was accomplished in a few

patients, but it was not part of the original protocol. Therefore, that data was not presented.

MEMBER AMAR: Is there any data to support that mineral content remains over there? Because from what I saw, it is the only demineralized section. Am I correct?

DR. MARX: Dr. Cook is behind me, who was the histologic investigator. I think he can address that question better than I.

DR. COOK: Yes. I'm Stephen Cook. I'm a bioengineer. I'm professor of orthopedic surgery at Tulane University. I am a consultant for Medtronic, who are paying my expenses to attend this meeting. I acted as an independent histologic reviewer of the sections and reports from all of these studies. And that was my role in the project.

If I can go back maybe to your first question, which was related to the tetracycline labeling protocol. There was quantification done on acquisition rates as

part of the quantification of the sections in the sinus pivotal study.

So there is data from the tetracycline labels that was used more than just looking at the change over time of the mineralization, but also there was actually some quantitative data that was performed. And I believe that was in the packet of information.

The second question was on mineralization of the bone. And there were bone density-type measurements that were shown in the presentations by Dr. Marx and Dr. Cochran based on CT examination of bone density. And what that showed was that earlier, at the four-month time period, when the CTs were formed, mineralization was slightly lower in the rhBMP-2 group.

But you have to remember that in the autogenous bone group at four months and indeed in the histologic sections, from the biopsies that were generally 6 to 12 months

after placement of the graft, there was still a significant amount of graft present in the sections themselves.

So in the CT examination of bone density, you're getting a false sense of mineralization of new bone because you're picking up the information, the mineralization from the residual bone graft.

So although there were differences at four months, as you got into later time periods, as both the bone matured in both groups, bone graft was reincorporated, they became equivalent.

CHAIRMAN BURTON: Dr. Janosky?

MEMBER JANOSKY: I will direct my questions to Dr. Cochran. You presented some data about extraction socket studies. Am I correct that the n is 21 that's in those studies?

DR. COCHRAN: For the 1.5 milligram per ml concentration. It was an 80-patient study --

MEMBER JANOSKY: Exactly.

DR. COCHRAN: -- with multiple arms, yes.

MEMBER JANOSKY: Okay. For the patients the n equals 21, what could you tell us about either the provider data and/or the patient data? I'm very interested in the mix of providers and who provided that, training and level, as well as patients.

You didn't present any data today that shows us the heterogeneity of either the patients or the providers. So what could you tell us about that n equals 21, please?

DR. COCHRAN: I think that data was analyzed between the different sites. I think that's really what you're asking about. Of the eight different sites that were involved, what was the statistical variation between the eight different sites? I have to refer that to the statistical evaluator to do that.

From a clinical investigator,

ourselves, we did do training as a group of investigators. So we did get together on multiple occasions. And we did standardize the procedure as much as we possibly could. So the standardization from an investigator training point of view was done in group meetings.

I'll have to get the statistician to give you the variability between the sites.

MEMBER JANOSKY: I'm also interested in the n for each of those. So if you have n equals 21, how many providers did that represent?

DR. COCHRAN: Yes. I don't know that information. Do you? Yes. We'll have to get that. We'll look it up and get it back to you.

CHAIRMAN BURTON: Dr. Li?

MEMBER LI: My question is for Dr. Marx. The results of your pivotal study showed that the success rate for the bone graft group was fairly stable between the 6

months and 24 months, which was 90.8 throughout that period. But for the rhBMP-2/ACS group, it declined slightly but fairly consistently, which was 79 percent down to 76 percent. It's slight, but each period was a little bit lower.

Do you have any data beyond 24 months which indicates any trend that continued or --

DR. MARX: The study concluded at 24 months. We don't have data beyond 24 months. The patients who declined were a mixture. Many of them were dropouts whom we couldn't get back for follow-up. And so although the success rate declined, they were successful up until the point we lost them to follow-up. That explained a number of them.

But beyond 24 months, the study was extinguished. So we don't have regular follow-up on those. Many of them were followed up outside the study, but that could not be recorded.

MEMBER LI: Okay. Thank you. And I have a second question for Dr. Cochran. For the extraction socket study, the completion rate was 37.5 percent. You started with 80 subjects, right, total. Then the majority of them dropped out or did not complete.

Do you have any thoughts on that, the possible impact on the results?

DR. COCHRAN: Unfortunately, I can probably tell you why that happened. The problem was we provided the treatment up front. We gave these patients new teeth, in these cases really nice implant restorations. And they were very satisfied with that restoration. So they didn't like coming back for the follow-up exams because they were pretty satisfied. And that's a problem in these studies, especially when you're stretching it out pretty far.

And we saw these patients a lot. I mean, we wanted to make sure that there were no adverse events. And so Wyeth or Medtron --

at that point it was Wyeth was very on top of the study to make sure that we were following these patients as much as possible.

But a lot of them, we wrote letters. We sent certified letters to the people. We would call them. And after a while, they were pretty happy. And they, unfortunately, didn't come back too often.

MEMBER LI: Thank you.

CHAIRMAN BURTON: Dr. Zuniga?

MEMBER ZUNIGA: I need to make a follow-up question to Dr. Cook, I believe, who earlier mentioned something about the mineralization in tetracycline studies.

I thought I heard that both of these analyses were done at the dosing and the pivotal study. And, if so, was there a quantitative difference between the two dosages? And were there standard error or standard deviation variances between the autogenous bone graft in either of the BMP --

DR. COOK: In the earlier studies,

which the dosing was with much smaller numbers, they were qualitative assessments made, rather than quantitative, in the pivotal study when they n's were approximately 90 in each group is where the quantification actually took place and statistical evaluations were performed. Qualitatively assessments were done on a zero to three type of scale in the pilot study as well as in the dosing study.

MEMBER ZUNIGA: Was there much variance, then, in the 1.5 milligrams per ml in the autogenous bone graft comparators in this scale?

DR. COOK: There's a vast difference in the way the bone is formed in the rhBMP group. It's a de novo bone formation occurring very early. As you saw in the slide that was presented, I believe, in Dr. Marx's presentation, the ten-day stain, the ten-day label, there was extensive networking of new bone formed at that early

time period; whereas, in the autogenous group, it was more of a connection of the bone fragments to each other so that it formed a network connecting the fragments themselves, rather than a new network of de novo bone formation; again, forming bone where there was none present versus connecting pieces of viable fragments.

CHAIRMAN BURTON: Dr. Patters?

DR. COCHRAN: Hang on one second, Mark, if you don't mind. We found the data for the 21 patients that you asked about a little bit earlier.

Two of the sites had five patients in that group each. Two sites had three patients. Two sites had two patients. One site had one patient. And one site didn't have any patients in that group.

MEMBER JANOSKY: So am I correct in there were 6 diverse sites representing 21 patients?

DR. COCHRAN: Seven, I believe.

MEMBER JANOSKY: Seven. And the largest number of patients treated at any one site was?

DR. COCHRAN: Five.

MEMBER JANOSKY: Was five.

DR. COCHRAN: At two different sites.

MEMBER JANOSKY: Okay. Thank you.

MEMBER PATTERS: Question for Dr. Chin and Dr. Cochran. Dr. Chin, the proposed indications that you have revolve around that InFuse is an alternative to autogenous bone grafts.

DR. CHIN: Yes.

MEMBER PATTERS: And you provide direct data comparing autogenous bone grafts and InFuse sinus augmentation with the pivotal study.

DR. CHIN: That is correct.

MEMBER PATTERS: But that data seems to be lacking with regard to extraction sockets. And that's more implied, rather than

shown with the pivotal study. So what is the justification for lumping those two together under the indication of an alternative to autogenous bone graft?

DR. CHIN: Okay. There are some statistical implications there. So I would maybe get some assistance there. But the data for the sinus and the extraction socket are looking at the 1.5-milligram concentration, which is the commercial version of that product today. So the analyses are done comparing the 1.5 concentrations for that efficacy.

DR. COCHRAN: I think I can address that as well. In the sinus studies, what we wanted to do was to take the standard of care that existed at that time and compare the treatment of InFuse bone graft to that standard.

So at the times that we were doing these studies, the standard there was autogenous bone graft procedures mixed

occasionally with DFDBA as an extender or some other type of material. So that was the standard that we were trying to go against to see what we could do as far as the standard of care.

In the extraction socket defects, the standard of care doesn't include bone graft procedures, particularly at that time. Most of the time when teeth are extracted, there is nothing done in those cases. And so that's why we did the comparison to the unfill treatment because, really, that is the standard of care.

We thought it was important to have also as a control the carrier alone for the BMP-2. So we had the unfilled cohort. And then we had the collagen treatment alone because we thought that was the most scientific rigorous way to do that in the carrier plus the protein. And, really, the data showed exactly what we had hoped it did, that the unfilled didn't form bone and that

the collagen formed a little bit but not significantly. And it was very clear that the BMP presence made a significant difference in the outcome of that trial.

MEMBER PATTERS: Thank you, Dr. Cochran.

I think I appreciate that. My concern is really the indications as stated here. I think that your data would clearly show that InFuse has advantages over the collagen carrier, but my question is, is there any direct data to show that it has advantages over autogenous bone being that's the indication that the sponsor is looking for?

DR. COCHRAN: Yes. I would again say that we didn't do that in the trial. So we don't have that. But we can certainly speculate on that. And I would speculate that if you look at the histological specimen and you look at the CAT scan data, you see the growth of new bone in those areas.

People that do use some type of

grafting material in extraction sockets, most of the data indicates that in those cases, these other materials, these osteoconductive or really alloplastic materials, actually get in the way of bone formation if you take biopsies of that. And so that material will stay around in the extraction defects. And, really, it's not an optimal treatment for placing implants.

The beauty of using a biological growth factor like this is that you induce de novo bone formation. So you don't have those residual particles in that.

I thought the histology was really nice with the fluorochrome stablin that showed the particles of the autogenous bone stayed in that area. And we really don't want to put our implants in that type of bone.

Thanks.

CHAIRMAN BURTON: Dr. Diamond?

MEMBER DIAMOND: Thank you.

Dr. Cochran, don't sit down yet.