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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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ORTHOPAEDIC AND REHABILITATION DEVICES PANEL

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February 19, 2016
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, Maryland

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JEREMY GILBERT, Ph. D.	Voting Member
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LEONARD TOPOLESKI, M.D.	Temporary Voting Member
LYNDA YANG, M.D., Ph.D.	Temporary Voting Member
JOSEPH P. O'BRIEN, M.B.A.	Patient Representative
KATHY TRIER, Ph.D.	Industry Representative
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Patient

INDEX

INDEX

M E E T I N G

(8:00 a.m.)

DR. RAO: Well, good morning everyone. I would like to call this meeting of the Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee to order.

My name is Raj Rao. I'm Chair of this Panel. I am an orthopedic spine surgeon. I'm Chairman of the Department of Orthopaedic Surgery at George Washington University in Washington, D.C.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel members participating in today's meeting have received training in FDA device law and regulations.

For today's agenda, the Panel will discuss, make recommendations, and vote on information regarding the premarket approval application for the DIAM Spinal Stabilization System, sponsored by Medtronic.

Before we begin, I would like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation. And maybe we'll begin with Dr. Trier on that side.

DR. TRIER: Am I on? I am on. Yes. My name is Dr. Kathy Trier, and I am the VP of Regulatory and Clinical Affairs with Corin. I am currently located in Tampa, Florida. My background, I had been an academic for a number of years, went into medical devices. My area of expertise at the time I was in academics was research methods and statistics and healthcare policy. I'm also a nurse by training. And I have been with Corin now for 10

years, working in that capacity in regulatory and clinical affairs.

MS. HARMON: Good morning. My name is Monica Harmon. I am a registered nurse. Public health is my background. I've worked in a number of areas, corrections healthcare, maternal child health, and other areas. Currently I am a senior lecturer at the University of Pennsylvania School of Nursing, and I'm also an associate fellow for the Center for Public Health Initiatives at the university as well.

MR. O'BRIEN: Good morning. My name is Joe O'Brien. I'm President of the National Scoliosis Foundation, serving a community of about 25,000 patients. I am also a patient myself. Over the past 40 years, I've had 40 spine procedures, fused from T4 to L5.

DR. LYNDA YANG: Good morning. I'm Lynda Yang. I'm a neurosurgeon at the University of Michigan, and my subspecialty interest is spine and peripheral nerve.

DR. TOPOLESKI: Good morning. My name is Tim Topoleski. I'm a Professor of Mechanical Engineering at the University of Maryland, Baltimore County, UMBC. My areas of expertise are in mechanics, material science, and biomaterials.

DR. SMITH: Good morning. My name is Harvey Smith. I'm an orthopedic spine surgeon at University of Pennsylvania. I also have an appointment at the Philadelphia Veterans Affairs Hospital.

DR. FINNEGAN: Maureen Finnegan, I'm an orthopedic surgeon at UT Southwestern in Dallas. My expertise is that I'm the token generalist, doing both clinic and research work.

DR. GILBERT: My name is Jeremy Gilbert. I am a Professor of Biomaterials in the Department of Biomedical and Chemical Engineering at Syracuse University, also a member of the Syracuse Biomaterials Institute, Editor-in-Chief of the *Journal of Biomedical Materials*

Research Part B: Applied Biomaterials. And my focus is on biomaterial science and engineering.

CDR ANDERSON: Commander Anderson, I'm Designated Federal Officer for this panel, and I am representing the FDA and the United States Public Health Service. Thank you.

DR. EVANS: Good morning. My name is Scott Evans, Department of Biostatistics, Harvard University. My expertise is in biostatistics and clinical trials.

DR. BLUMENSTEIN: I'm Brent Blumenstein, independent statistician and amateur urologist. I work in Washington, D.C.

DR. GOLISH: I'm Raymond Golish. I'm the Medical Director of Spinal Surgery at Jupiter Medical Center in Palm Beach, Florida. My Ph.D. is in engineering. I'm a member of the AOS Biomedical Engineering Committee.

DR. GRAF: Good morning. My name is Dr. Carl Graf. I am an orthopedic spine surgeon at the Illinois Spine Institute outside of Chicago, Illinois.

DR. CHENG: Good morning. My name is Edward Cheng. I work at the University of Minnesota, in the Department of Orthopaedic Surgery there. I also serve as Editor for the *Journal of Bone & Joint Surgery's Essential Surgical Techniques Journal.* My expertise is in the area of orthopedic oncology and joint reconstruction.

DR. ESKAY-AUERBACH: Good morning. My name is Marjorie Eskay-Auerbach. I'm an orthopedic spine surgeon by training. I'm currently in private practice. I practice nonoperative orthopedics.

MR. MELKERSON: My name is Mark Melkerson. I am the Director of the Division of

Orthopedic Devices, background in mechanical and biomedical engineering.

DR. RAO: Thank you, all. Members of the audience, if you have not already done so, please sign the attendance sheets that are on the tables by the doors.

Commander Anderson, the Designated Federal Officer for the Orthopaedic and Rehabilitation Devices Panel, will now make some introductory remarks.

CDR ANDERSON: Good morning. The Food and Drug Administration is convening today's meeting of the Orthopaedic and Rehabilitation Devices 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.

The 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 U.S.C. 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 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened for potential financial conflict of interest of their own as well as those imputed to them,

including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employees. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss and make recommendations and vote on information regarding the premarket approval application of the DIAM Spinal Stabilization System sponsored by Medtronic. The DIAM Spinal Stabilization System is indicated for skeletally mature patients that have moderate low back pain, with or without radicular pain, with current episode lasting less than 1 year in duration, secondary to lumbar degenerative disc disease, at a single symptomatic level from L2 to L4.

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 accordance with 18 U.S.C. Section 208.

Dr. Kathy Trier is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Corin USA.

We would like to remind members and consultants that if the discussions involve any other products or firms already on the agenda for which an FDA participant has a personal or imputed financial interest, the 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.

A copy of this statement will be available for review at the registration table during

this meeting and will be included as a part of the official transcript.

Thank you.

I will now read the Appointment to Temporary Voting Status.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27th, 1990, and as amended August 18th, 2006, I appoint the following individuals as voting members of the Orthopaedic and Rehabilitation Devices Panel for the duration of this meeting on February 19th, 2016:

Dr. Lynda Yang, Dr. Harvey Smith, Dr. Leonard Topoleski, Dr. Brent Blumenstein, Dr. Scott Evans, Dr. Carl Graf, Dr. Edward Cheng, Dr. Marjorie Eskay-Auerbach.

For the record, these individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at the meeting.

This has been signed by Dr. Jeffrey Shuren, Director of the Center for Devices and Radiological Health, on January 20th, 2016. Thank you.

Before I turn the meeting back over to Dr. Rao, I'd like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting, Incorporated, telephone (410) 974-0947.

Information on purchasing videos of today's meeting can be found on the table outside the meeting room.

Handout of today's presentations are available at the registration desk.

The press contact for today is Kimberly Stark. Please stand up, Ms. Stark.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to the FDA until after the Panel meeting has concluded.

If you would like to present during today's Open Public Hearing session, please register with AnnMarie Williams at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

Finally, please silence your cell phones and other electronic devices at this time.

Dr. Rao.

DR. RAO: Thank you, Commander Anderson.

We will now proceed with the Sponsor's presentation. I would like the Sponsor to approach the podium.

I will remind public observers at this meeting that while the meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

The Sponsor will have 90 minutes to present. You may now begin your presentation.

DR. SIMPSON: Good morning, members of the Panel. My name is Kathryn Simpson, and I'm the Director of Regulatory Affairs at Medtronic Spinal Business in Memphis, Tennessee. We have the pleasure and privilege to present to you the results of years of research, development, and clinical studies for the DIAM Spinal Stabilization System.

The DIAM device is a spinous process spacer intended for use in the lumbar spine to

treat moderate low back pain secondary to degenerative disc disease. It was designed to treat patients that have not progressed down the DDD continuum sufficiently to warrant a more complex, invasive procedure such as disc replacement or fusion.

Currently, the only appropriate treatment option for these patients is conservative care. Note that this indication, as well as the design of the device, is different from other PMA-approved spinous process spacer devices, as will be detailed in later presentations.

The device fits between the spinous processes in the lumbar spine and is intended to provide for a load sharing with the posterior disc, annulus, and facet joints. It's made up of a central silicone spacer wrapped in polyester, along with two polyester tethers used to secure the device.

In our series of presentations today, rigorous clinical and preclinical data will be presented that supports the safety and effectiveness of the DIAM device. We will also show that the benefits outweigh any risk associated with the technology for the proposed indication.

The results from the clinical trial show that the DIAM device is statistically superior to the control group in the primary composite safety and effectiveness endpoint as well as in additional secondary endpoints. The consistency of these results is maintained over time and across multiple patient groups and cohorts.

The DIAM device that will be the subject of this Panel's deliberations was invented by Dr. Jean Taylor, an orthopedic surgeon from France. A slightly modified design of the device is currently in use globally, and the DIAM system has been successfully used for over 16 years outside the U.S. To date, more than 140,000 devices have been implanted in more

than 50 countries.

The proposed indication for the DIAM device is moderate low back pain, with or without radicular pain, secondary to degenerative disc disease at one level from L2 to L5. The presence of DDD is confirmed radiologically, and the DIAM device is implanted in a minimally invasive posterior approach. Please note, FDA has made a comment regarding the indication, but the current proposed PMA wording does reflect the same moderate low back pain secondary to DDD population that was enrolled in the IDE study.

The DIAM device is supported by clinical data arising from a prospective randomized, multi-center U.S. clinical trial conducted under an approved IDE protocol, in which 311 subjects were randomized and 282 subjects were treated at 23 investigational sites.

The IDE patients presented with moderate low back pain secondary to DDD, requiring treatment at a single level, consistent with the proposed indication. The control treatment for the clinical study was a regimen of conservative care, as this patient population is not yet severe enough for more aggressive procedures.

This slide highlights some of the key events throughout the timeline of the IDE study, as well as the cumulative enrollment over time. The IDE was approved by FDA in September 2006. Some changes to enrollment criteria and an increase in the allowed number of sites occurred early in the study. During the course of the study, one notable change that was made was the addition of a Bayesian interim analysis, which was approved by FDA in July 2013. Due to the initially still low enrollment of the study, a significant amount of longer-term data was also collected, and the clinical outcome trends were noted to be stable over time.

The interim analysis, which is the primary analysis for the study, was completed when the first 150 enrolled subjects reached 12-month follow-up. As a result of the change in the analysis plan, the criterion for assessing statistical differences was an increase from 95% to 97.5%.

The full enrollment of the study continued as planned and was not impacted by interim analysis. The final subjects enrolled in late 2013, and the PMA was submitted in April 2014. An updated dataset with additional follow-up data was used for a response to FDA questions that was submitted in August 2015.

In our presentations, we'll provide overviews of the relevant information contained in the PMA application and substantiate the trial design. FDA has raised important questions for the Panel to consider. Throughout the presentations, we will address these questions, and we've highlighted the FDA concerns, as denoted by embedded boxes on the presentation slides. We will demonstrate safety, effectiveness, and a positive risk-benefit ratio of the DIAM device, which has shown a consistent, substantial, and durable clinical effect at the primary endpoint and beyond.

We have a series of speakers that will present to you the disease state, interpretation of the preclinical and clinical results and analyses, and case studies from the IDE. Each speaker will introduce himself upon approaching the podium, and I will then return for concluding remarks.

In addition to these speakers, we have assembled here today a group of physicians and scientists who should be able to answer any questions you may have about the product under review. These experts include clinicians, radiologists, statisticians, engineers, and

other basic scientists. I will now turn the podium over to Dr. Alexander Bailey.

DR. BAILEY: Good morning. My name is Dr. Alexander Bailey, and I enrolled patients into the DIAM study. I will be speaking today about the use of the DIAM device in the degenerative disc disease care continuum. In terms of disclosure, I am a study investigator, and I am receiving consulting time from Medtronic for my participation in this meeting. I do not own stock in Medtronic, nor do I have any financial interest in the DIAM product.

In order to understand the degenerative cascade, it is important to understand the normal healthy spine. The normal spinal unit consists of the vertebra, the intervertebral discs, the posterior facet joints, and the surrounding ligaments. The spinal unit is a dynamically stable architecture that allows for complex motion and load transmission.

The primary component of the spinal unit is the intervertebral disc. It consists of the nucleus pulposus of the annulus fibrosus. Together they act as a shock absorber and a spacer, while allowing for complex motion. The secondary components of the spinal unit are the paired posterior facet joints. These are semi-constrained synovial joints and act as supporting structures to compressive loads, resist abnormal slippage, and also allow for complex motions. The surrounding ligamentous structures add support to the primary and secondary components. The normal spine is pain free.

Low back pain from degenerative disc disease is a major societal burden. Approximately 85% of the U.S. population will experience some form of low back pain. Low back pain is the second most common reasons patients seek medical attention. It is the second most common cause of missed work, after the common cold, and it is the most common cause of disability in those less than 45 years of age.

Fortunately, most low back pain is short-lived, resolves on its own with minimal treatment. The most common cause of continued or sustained low back pain is degenerative disc disease. Degenerative disc disease is a cascade. The first or inciting event may, in fact, not be known. It can be caused by age-related changes, recurrent rotational strains, minor compressive injuries, and/or a genetic predisposition.

Regardless of the inciting event or cause, there appears to be a loss of water content in the intervertebral disc. The hydrostatic properties of the nucleus pulposus become disrupted. Loss of water content and health in these tissues may lead to tears and/or fissures. The outer one-third of the annulus is innervated, and nerve endings become inflamed, leading to pain. If the fissures expand, this further weakens the annulus and can lead to secondary herniated discs.

In response to this process, the chemical composition of the nucleus pulposus changes. This results in a loss of the viscoelastic properties of the intervertebral disc. Disc desiccation and altered viscoelastic properties lead to diminished function and a loss of disc height and volume. As this process continues, the changes in the morphology alter the spine's biomechanics, leading to the potential for painful load transmission and/or instability.

The intervertebral disc changes affect the other components of the spinal unit. Loss of disc height causes mal-alignment and overloading of the facet joints. This, in turn, may lead to synovial reactions and cartilage destruction, all leading to additional pain generator involvement.

If allowed to continue, the degenerative process will reach an advanced or end-stage

condition. At this point, patients can experience complete disc space collapse, advanced arthritic changes, severe joint hypertrophy, large bone spurs, severe stenosis, and/or the potential for adjacent level involvement. It is important to understand that when DDD reaches this level, patients would not be candidates for DIAM but would be more appropriately treated with fusion or total disc replacement.

To summarize, DDD is a multi-factorial and often nonreversible pathologic condition. Degenerative discs may progress to facet degeneration and even disc herniation, spinal stenosis, and/or spondylolisthesis. While these varied conditions may seem heterogeneous, they all occur secondary to disc degeneration that interferes with uniform transmission of load.

Multiple structures are innervated that cause pain. Low back pain can result from discogenic sources and/or secondarily facet sources. Leg pain can result from radiculitis, stenosis, and/or spondylolisthesis.

The FDA has questioned the adequacy of our IDE study population based on their perceived heterogeneity of these patients. In reality, not only are these patients representative of those that we see in our patient clinics every day, but the underlying pathological conditions are all due to the same degenerative mechanism I just described.

Notwithstanding the FDA's question of heterogeneity, for the DIAM study we did, in fact, follow the recommendations and guidelines established by the FDA. In Section 4.1, Degenerative Disc Disease, the FDA suggests the Sponsor consider the following.

"Degenerative disc disease should be defined as back and/or radicular pain, with the degeneration of the disc as confirmed by patient history, physical examination, and

radiologic studies with one or more of the following factors: instability or spondylolisthesis, osteophyte formation, decreased disc height, scarring or thickening of the ligamentum flavum, annulus fibrosus or facet joint, herniated nucleus pulposus, facet joint degeneration and/or vacuum disc phenomenon."

Diagnosing moderate low back pain due to DDD may be complicated by the multi-factorial nature of the disease. A radiologic finding of disc degeneration is alone insufficient as disc degeneration without pain is quite common. Multiple levels of disc degeneration with only one symptomatic level also frequently occurs.

This is why, in addition to their clinical judgment, a surgeon's diagnostic workup includes: the patient's history of the duration, location, and intensity of pain, along with an understanding of any painful positions or activities; a physical examination of the patient, including pain on palpation and straight leg testing; as well as radiologic confirmation of the diagnosis including MRIs, X-rays, and potentially provocative discography in order to isolate the symptomatic level.

In response to the FDA concern over the adequacy of our study population, it is through this systematic approach that the symptomatic level was identified in this study as well as during our everyday clinical practice. Please note that while a certain level of disability threshold was required for inclusion in our study, ODI scores are used for a measurement and comparison of outcomes but are not diagnostic.

The Oswestry Disability Index is a validated tool often used in spine studies to measure and compare outcomes. It quantifies a patient's perception of their disability but does not dictate a specific treatment. It is a useful tool for determining a procedure's

success and return of function. ODI is scored on a score of 0 to 100.

The FDA raised a question concerning our moderate low back pain patient population due to the ODI group labels, specifically the severe label. The Oswestry authors' actual interpretation of the groups are illustrative. The minimal disability group speaks for itself. Usually no treatment is indicated. The 20% to 40%, or moderate disability group, experiences more pain and problems with sitting, lifting, and standing. Personal care, sexual activity, and sleeping are not grossly affected, and the back condition can usually be managed by conservative means.

In the 40% to 60% or severe labeled disability group, pain remains the main problem in this group of patients. But travel, personal care, social life, sexual activity, and sleep are also affected. These patients require detailed investigation. The authors defined the 60% to 80% as crippling, saying, "Back pain impinges on all aspects of these patients' lives, both at home and at work, and positive intervention is required."

The DIAM study included patients with an ODI score of greater than 30 and averaged 50, preoperatively. We believe the categorization and use of the words "severe" and "crippled" are obviously overstated. Taking all things into consideration, the moderate clinical patient falls in the 20% to 60% ODI range.

The current standard of care in the U.S. for non-acute low back pain patients includes a regimen of conservative care tailored to each individual patient. They include patient education, activity modifications, analgesic medications, physical therapy, massage or chiropractic care, acupuncture/acupressure, and/or spinal injections.

The FDA has raised a concern with the adequacy of the nonoperative control group,

since subjects were provided different combinations of nonoperative therapies. However, not only are we ethically bound to provide the optimal mix of conservative therapies for each patient based on their individual needs, but also in order to maximize the potential benefit within the control group. This is the same as what would be done in our clinical practices every day.

In their executive summary, the FDA referenced a paper by Mirza, where four studies compared fusion outcome to conservative care treatments. Unfortunately, three of the four papers reviewed used conservative care treatments far in excess of what could be employed in the United States. These included staying in a specialized back hotel, receiving physical therapy for 25 hours per week for 5 weeks, subsequent home physical therapy and support visits, as well as cognitive behavioral therapy 5 days a week for 3 weeks.

The fourth study reviewed by Mirza was authored by Fritzell, who conducted a much more standard battery of conservative treatments similar to those employed in the DIAM study. These included physical therapy, education, TENS unit, acupuncture and/or injections. Their ODI improvement was 5.8%, which is nearly identical to that of the conservative care arm of our study.

For patients that reached and progressed to the end-stage, advanced degeneration, current surgical options include total disc replacement and/or fusion surgery. These advanced surgical techniques should be avoided until the disease process enters the advanced stages as they are highly invasive, nonreversible, for severe degeneration only, carry important risk profiles, longer recovery times, and long-term consequences such as adjacent level degeneration.

The FDA has asked about the use of the DIAM implant as an adjunct to direct decompression in our patient population. It is important to recognize that direct decompression alone is ineffective for treating primary low back pain due to DDD. Direct nerve root decompression may help relieve neurological pressure in the stenotic patient but otherwise has no or negative effects on low back pain due to DDD. Direct neurologic decompression was not performed in the study.

I would like to now further illustrate the DDD cascade and associated treatments. For this discussion, please note that the MRI images shown are for illustrative purposes only and do not necessarily correlate to a patient's severity of symptoms. Low duration and low severity conditions may simply involve muscular conditions, and nearly universally respond to minimal care. Early degenerative disc disease of low duration and low severity may and often do respond to minor conservative care.

On the other end of the spectrum, severe degenerative disc disease with its inherent secondary and tertiary consequences, long duration and high severity of symptoms often does not respond to conservative care and may benefit from total disc replacement or fusion surgeries.

Moderate low back pain from degenerative disc disease is truly the unmet need for spine surgeons and spine patients. These are patients that have longer duration and moderate severity of low back pain but do not have the qualities that make them candidates for total disc replacement or fusion surgery. This is defined as the treatment gap.

DIAM is designed to fill this treatment gap, to provide symptom relief from

moderate low back pain resulting from DDD. In reference to the study, the choice of conservative care to DIAM was the only option of comparison. Patients in this treatment gap would not be candidates for total disc replacement or fusion surgery. It is overtreatment and exposes them to a procedure that is inappropriate for their stage of disease.

As mentioned previously, low back pain due to DDD is a multi-factorial condition affecting multiple structures. In the disease state there is:

a) DDD, loss of water content, chemical changes of the disc, micro and macro tears of the annulus, and loss of disc height and function;
b) Facet mal-alignments and synovial chondral changes; and
c) Ligamentous laxity in supporting structures.

The DIAM device is placed between the spinous processes, and due to its unique design parameters, it unloads or load-shares with the posterior intervertebral disc, it realigns the collapsed posterior facet joints, and it re-tensions the intact supraspinous process ligament and other supporting structures.

This device is designed and functions different than the other interspinous process devices that have been studied, reviewed, and approved. Other ISP devices have an indication of neurogenic intermittent claudication (leg, buttock, groin pain) due to stenosis, with or without back pain. They block extension or create relative kyphosis. They expand the neural foramen and spinal canal via indirect decompression, and they may relieve leg pain by increasing the foramen and canal dimensions.

The DIAM device is fundamentally different. It has an indication of moderate low

back pain due to DDD, with or without leg pain. It stabilizes but does not block extension. It restores biomechanical integrity and load-shares with the facets and posterior disc. It may relieve low back pain by decreasing pressure on painful structures.

I will now review the DIAM surgical technique. The patient is positioned prone, and the skin is marked centered over the intended treatment level, for a skin incision of 4 to 5 centimeters. Dissection exposes bi-level spinous process to the waist to the lamina-facet junction. Specialized instruments are utilized to prepare the interspinous process space, with particular attention to preserve the supraspinous process ligament. Cutting rongeurs and shavers are standard preparation instruments.

Attempts are made to avoid excessive cortical injury but also to remove most soft tissue in the space. Bony resection in order to seat the device far interior and to optimize placement is allowed, but direct neural decompression does not occur in the surgical procedure.

A distraction device is inserted and hand-tensioned to distract the interspinous process space. Sizing paddles are utilized and appropriately sized implants are chosen. Avoidance of overdistraction or overstuffing is appropriate.

The specialized insertion device compresses one size of the DIAM device for ease of insertion. Choice of implant size keeps in mind distracting the parallel end plates, avoiding segmental kyphosis, and tensioning the supraspinous process ligament. Embedded retention tethers are passed, and the compressed side of the DIAM device is inserted past the spinous process, and the insertion device is disengaged, deploying the contralateral wings.

A tamp may or may not be necessary but is available to further refine the position to be anterior, close to the ligamentum flavum. The retention tethers are passed around the superior and inferior spinous processes, and a crimping tool finalizes the procedure.

Completion of the case includes standard closure and sterile dressing application. Early mobilization is standard and encouraged postop Day 0. Once placed, AP and lateral projections show the device in flexion or distraction, and extension or compression.

This morning we have discussed the normal spinal unit, the degenerative disc disease cascade, the treatment gap for patients with DDD and moderate low back pain, and the mechanism of action of the DIAM device as well as the surgical technique. For patients with low back pain due to DDD at a single level, DIAM provides a safe and effective treatment option, a less invasive, less destructive intervention, a simple, straightforward surgical technique.

The DIAM device provides pain alleviation by reduction of stress through painful load-bearing structures, and it provides a treatment that fills a gap in the current continuum of care. The DIAM device is intended for patients who are not yet indicated for fusion or total disc replacement, and finally, it does not complicate potential future surgical procedures, or no burning of bridges.

I thank you for your attention, and I will now pass the podium to Eric Lange to discuss preclinical testing.

MR. LANGE: Good morning. My name is Eric Lange, and I'm a Director of Product Development at Medtronic. Today I have the privilege of sharing with you the design and testing of the DIAM implant.

As Kathryn mentioned previously, the DIAM device has a very long and successful history of implantation outside of the U.S. We believe this implant's success is due to its very simple yet robust design, which allows it to help establish the biomechanical integrity of the degenerated spinal segment.

The purpose of the DIAM implant is to restore and augment the biomechanical function of the spine. As Dr. Bailey explained, DIAM alleviates pain through the reduction of stress on the painfully overloaded posterior disc and facets. Secondarily, the stability of the segment may be enhanced without the elimination of the segment's mobility.

The mechanism of action of the DIAM device is illustrated in this cross-sectional view. Most importantly, the DIAM implant shares the compressive loading with the facet joints and posterior disc and annulus. Also, due to its location between the spinous processes, the implant can limit excessive loading during extension. Finally, the DIAM implant may enhance the stability of the segment during flexion and extension without eliminating motion.

The majority of the load of the lumbar spine transverses the anterior portions, while about 20% is supported posteriorly. As Dr. Bailey explained, in the degenerated condition, the disc loses its viscoelastic properties to a point where it can no longer support this load. This leads to a painful overloading on the posterior disc and facet joints. With the addition of the DIAM device, however, a portion of the loading is rerouted or load-shared through the DIAM implant, thereby relieving the painfully overloaded structures.

In order to analyze the DIAM implant's load-sharing ability, Bellini et al. created a finite element model of the lumbar spine and subjected it to various loading conditions,

with and without the DIAM implant. With DIAM, their model showed a 27% reduction in disc load during flexion and a 51% reduction in extension, and as you can see in these images, a dramatic reduction in compressive stress on the posterior annulus.

Due to the flexible nature of the DIAM implant, it is able to accomplish its goal without the elimination of motion in either flexion or extension. What I'm showing here is a fluoroscopic video taken during cadaveric range of motion testing of the DIAM implant. As you can see in the video, the DIAM implant stretches in flexion and compresses in extension, allowing motion in both directions.

On the right is a chart showing the graphical results of the flexion and extension testing we just watched. In order to quantify the effect DIAM has on spinal motion, the spine was first tested intact, then destabilized, and then with a DIAM implant in place. What the testing showed was that by the application of the DIAM device, the flexion and extension stability improves back to a level relatively close to that of a normal, intact spine.

As we have shown, the primary function of the DIAM implant is load-sharing with the posterior disc, annulus, and facet joints. Load-sharing is accomplished whether or not significant distraction or motion reduction is achieved. This is clearly shown in the Ha paper referred to by the FDA. The Ha paper, in fact, studied stenosis patients that all suffered from severe neurogenic intermittent claudication and were treated with destabilizing decompressive laminotomies and foraminotomies.

This obviously is an indication and surgical procedure different than that of our study. Nonetheless, this paper was referenced, questioning the adequacy of our 12-month time point since the initial gains in distraction, lordotic angle, and foraminal area in the Ha

study diminished over time.

The conclusions of the authors, however, state that the DIAM actually prevented the further collapse of the intervertebral disc height and that they had no patients with recurrent spinal stenosis, as they would have normally expected. In addition, the study found that the range of motion remained significantly reduced at every time period through final follow-up, averaging over 2½ years, indicating the continued mechanical functioning of the DIAM implant.

As with our study, the most important indicator of continued device function is the sustained improvement in clinical outcomes. The Ha study showed a sustained improvement in maintenance of 39% reduction in VAS back pain scores, a 49% reduction in VAS leg pain scores, and a 29% -- or I'm sorry, a 29-point reduction in the ODI score at final follow-up.

This, by the way, corresponds exactly to the 25-point ODI improvement for our DIAM patients at 1-year postop. As the authors concluded, the clinical conditions of the patients were improved, and the improvement was maintained.

In the DIAM study, we found the intervertebral angles and extensions significantly decreased as compared to baseline, at all time periods up to 24 months and sustained out to 60 months. Furthermore, our data also shows a significant increase in posterior disc height from baseline, at all postoperative time points up to 24 months and then maintained out to 60 months.

As we will present in later presentations, our IDE data also shows coincident maintenance of significant reductions in leg pain, back pain, and ODI scores in the

investigational group out to 60 months. Taken together, this provides very strong evidence that the DIAM device load-sharing, stabilization, and clinical effectiveness does not deteriorate over time, as well as supporting the adequacy of our overall success time point and clinical significance of the angular and translational motion results.

The mechanism of action of the DIAM implant is a direct result of the physical properties used in its manufacture. The main body of the implant is a spinous process spacer, which is molded from a stiff silicone, which is then wrapped in polyester jacket. There are two independent braided polyester process tethers, which are threaded through the core of the device. These tethers are wrapped around the spinous processes and secured via titanium crimps.

A complete series of static and fatigue testing was conducted on worst-case size implants. These tests were conducted at extreme test conditions well in excess of those that could be physiologically imposed on the implant. All mechanical testing results met or exceeded the predefined acceptance criteria.

In addition to the mechanical testing, extensive biocompatibility testing was conducted on a DIAM implant. The first component of our biocompatibility testing was a complete series of ISO 10993 tests. All acceptance criteria were met, and the results were well within acceptable limits.

In addition, two animal studies were conducted. A sheep study was conducted with 12 sheep who were implanted with the DIAM device, with 6 sheep each being euthanized at 6 months and 1 year. Histology of tissues surrounding the implant as well as distant organs showed no signs of reaction, wear debris, or osteolysis. The implants were very well

tolerated and showed no signs of loosening or migration.

A rabbit study was conducted in order to evaluate the potential local and systemic effects of the implant wear debris. Half the rabbits were sacrificed each at 3 and 6 months and showed no systemic response, no osteolytic response, and despite the extreme amount of wear debris implanted, the local inflammatory response was slight.

The overall biocompatibility of the DIAM device has been proven over its long and successful history of over 140,000 implantations worldwide. This is in addition to the 240 DIAMs that were implanted in this IDE study, all of which showed excellent biocompatibility. Eight total IDE devices, two of which came from crossover patients, were explanted, with six available for analysis.

As is seen on the example at the right, our explant analysis found that the fabric cover was infiltrated with tissue, was functional at time of explant, and showed no osteolysis of the spinous processes. Three explants showed presence of wear debris, and the foreign body response was graded as mild or slight, which is normal, and consistent with implanted Dacron fabrics.

In summary, the design and function of the DIAM device is quite simple. It functions by load-sharing with a posterior disc and annulus as well as with the facet joints without the elimination of motion. Our extensive preclinical testing has proven that its biomechanical function enhances load-sharing and stability, that its strength is well in excess of the physiologic loads placed on it, and that it exhibits excellent biocompatibility.

Thank you very much for your attention. I will now turn the presentation over to Dr. Matt Gornet.

DR. GORNET: Hello. My name is Matthew Gornet. I'm an orthopedic surgeon from St. Louis, Missouri. My practice is devoted to spine surgery. I'm the primary investigator for the DIAM IDE clinical trial. I am a consultant for Medtronic. I have no financial interest in this product, and I own no Medtronic stock. Medtronic has paid for a portion of my travel expenses to this meeting.

The key findings of the DIAM IDE clinical trial demonstrate that the primary study endpoint was met. The primary study endpoint is a composite which includes clinically meaningful safety and effectiveness parameters. The primary study objective was also met, and the DIAM device demonstrated statistically superior results to control and overall success at 12 months, 63.9 versus 15.1% in the primary dataset.

There was consistency of primary and secondary endpoints over time and across multiple patient cohorts and subgroups. There was a low rate of serious device-related adverse events and few secondary surgeries.

The study design was prospective, randomized at 23 sites. There was 2:1 randomization ratio. Treatment groups included the investigational group, which received the DIAM device, and the control group, which received conservative care. Total number of subjects treated was 282: 181 in the investigational group and 101 in the control group.

Patients selected for the DIAM trial were designed to mirror clinical practice. This included patients with moderate low back pain, with or without radicular pain, radiographic evidence of degenerative disc disease, a single symptomatic level from L2 to L5. Their current episode of low back pain had to be less than 1-year duration. They must have failed at least 6 weeks of some form of conservative nonoperative care prior to enrollment. And

this was done largely to exclude patients who may have suffered from acute low back pain which tends to resolve spontaneously. Patients also had to be capable of undergoing a minimally invasive posterior procedure.

The conservative care employed in this study was designed to be comprehensive and fit basic patients, giving a maximum opportunity to improve based on their individual needs and pathology. Conservative therapy included NASS-derived patient information regarding low back pain, education on lifting techniques and back strengthening, medications including nonsteroidals, muscle relaxants, non-narcotics, narcotics, neuroleptics, and antidepressants.

Physical therapy was performed by the community standard, which the patient received treatment. Spinal injections were performed at the request of the enrolling physician based on the pathology present and included either epidural steroid injections or facet blocks.

As discussed earlier, the primary study endpoint is a composite which includes clinically meaningful safety and effectiveness parameters. The primary endpoint is overall success at 12 months. To achieve overall success, patients must have an ODI improvement of 15 points or greater, and no serious adverse event related to treatment, and no additional surgical procedure for the DIAM subjects or treatment surgery at the involved level for control subjects. Primary study objective is superiority in overall success at 12 months.

Additional effectiveness endpoints were measured, including Oswestry Disability Index, back and leg pain numerical scores, and SF-36 PCS health scores. Secondary study

objective included superiority in these effectiveness endpoints at 12 months.

The study protocol allowed for patients to cross over to the DIAM device or receive other forms of surgical treatment after 6 months if the following conditions were met: Patients must have completed all forms of conservative, nonoperative care and have an ODI score of 30 or greater and an ODI score improvement from baseline of less than 15 points.

Crossover subjects who received the DIAM device were followed at the same evaluation time points as those originally randomized to DIAM, for instance, 6 weeks, 3 months, 6 months, and 12 months post-surgery.

The results of the data sets will be reviewed: the primary dataset, the all-available dataset, and the crossover dataset. The definitions of these datasets will be described by Dr. Berry in his statistical presentation.

This slide shows the demographic factors for the primary dataset. There is no statistical significant differences in any of the demographics or baseline factors between the two groups, and it demonstrates the homogeneity of the subjects in the two treatment groups.

This slide illustrates the demographic factors in the all-available dataset. As you can see, there are no statistical differences between the groups, and it is consistent with the primary dataset.

I will now present the summary findings for each of these datasets.

To reiterate, the primary endpoint of the study contained parameters of both safety and effectiveness, and the primary endpoint was to achieve overall success.

I believe this slide is probably the most important slide in my presentation. It

demonstrates the percent of subjects who achieved overall success in the primary dataset. We can see that the percent of subjects achieving overall success between 6 weeks and 12 months ranged between 60% and 70% for the DIAM group, compared to the control group. The probability of superiority for the treatment with DIAM over control group at 12 months is essentially 100%. The supporting datasets indicate a consistency of results with the primary dataset. The treatment effect with the DIAM device is maintained over time, and the crossover cohort results are consistent with the DIAM subjects in the primary dataset.

This slide indicates the percent of subjects achieving overall success in the all-available dataset. As you can see, the treatment effect with the DIAM device is maintained over time and is consistent through the 60-month time point. The results are consistent with the primary dataset.

This slide indicates the percent of subjects achieving overall success in the crossover dataset. This compares patients who crossed over to the DIAM device to those originally randomized to the DIAM device. We can see that there are similar rates of overall success in both groups, validating the treatment effect with the DIAM device.

In the next several slides, the effectiveness endpoints will be presented.

This slide illustrates the mean postoperative ODI scores in primary dataset. Again, for clinical perspective, an ODI score between 0 and 20 indicates minimal disability or impairment. A score from 21 to 40 indicates moderate disability or impairment. A score from 41 to 60 indicates severe disability or impairment.

This slide shows that the DIAM subjects achieved clinically significant improvement, with a mean ODI score indicating minimal disability for most DIAM subjects. Again, the

probability of superiority over control was essentially 100%.

This slide illustrates the mean postoperative back pain scores. As you can see, subjects randomized to the control group had little change in their mean back pain scores, but subjects randomized to the DIAM procedure showed clinically significant improvement in their mean back pain score that was sustained through 12 months. Again, the probability of superiority over control was essentially 100%.

This slide illustrates the mean postoperative leg pain scores. These scores are similar to the mean back pain scores and demonstrate that subjects randomized to the control group had little change in their mean leg pain scores and may have even worsened from baseline, while subjects who underwent the DIAM procedure showed significant improvement in their mean leg pain scores that was sustained through the 12-month follow-up. Again, the probability of superiority over the control group was essentially 100%.

This slide illustrates the SF-36 PCS composite quality of life scores in the primary dataset. This again demonstrates that the control subjects showed essentially no improvement, while the DIAM subjects showed clinically meaningful improvement which was sustained through 12 months follow-up. Again, the probability of superiority over the control group was essentially 100%.

The same effectiveness endpoints are analyzed in the all-available dataset.

This slide demonstrates the mean ODI scores in the all-available dataset. The all-available dataset is consistent with the primary dataset and shows the significant results achieved at 12 months continue out through the 60-month time point.

This slide illustrates the mean postoperative back pain scores in the all-available dataset. Again, these results are consistent with the primary dataset and show that the results seen at 12 months are consistent out through the 60-month time period.

This slide illustrates the mean postoperative leg pain scores in the all-available dataset. Again, this is consistent with the other slides, showing the treatment effects and improvement in leg pain scores with the DIAM device is maintained out through 60 months.

This slide illustrates the SF-36 quality of life scores in the all-available dataset. It again shows consistency of results from the 12-month point through the 60-month point and is consistent with the primary dataset.

I will now present the findings for the control subjects who crossed over to the DIAM procedure and compare those to subjects originally randomized to the DIAM device.

This slide demonstrates secondary endpoints in the crossover dataset. As you can see in evaluating mean ODI scores, numerical back and leg pain scores and mean PCS quality of life scores, the results are similar between patients who originally were randomized to the DIAM treatment versus patients who crossed over to the DIAM treatment. I believe this data further validates the treatment effect with the DIAM device.

There are a few more study parameters that I believe are important in interpretation of the study findings.

This slide illustrates the percent of patients satisfied with the DIAM treatment in the primary dataset. As you can see, the majority of subjects randomized to the DIAM device were satisfied with their treatment results, compared to the control subjects, where fewer than one-third of patients listed satisfaction with the treatment at 12 months.

This slide illustrates the percent of subjects using narcotics in the primary dataset. As you can see, there was a significant decrease in narcotic medication used in the DIAM population by 6-week follow-up visit, and this narcotic use continued to decrease through the 12-month follow-up visit. There was no change in narcotic pain medication requirements in the control population.

This slide illustrates that the DIAM subjects required less injections at the index or target level compared to the controlled counterparts. The difference was quite substantial; 13% of the DIAM group required injections versus 45% in the control group at 12 months.

I would now like to present the safety results.

This is a summary of adverse events in the primary dataset. There was a very low rate of serious study- or treatment-related adverse events. Only eight subjects in the DIAM group, or 8.2%, experienced serious study or treatment-related adverse events, compared to 19 subjects, or 35.8%, in the control group.

The total number of adverse events reported in the primary dataset during the course of the study is also presented in this table, but I will focus on and discuss serious treatment-related adverse events.

The FDA communicated that there was a concern that there was higher than expected frequency of serious study- or treatment-related adverse events in the nonoperative group compared to the DIAM group. This slide clarifies this finding.

The adjudication committee was charged with determining the seriousness of any adverse event. An event was considered serious by the committee if there was additional medical or surgical intervention to prevent permanent impairment. The independent

committee felt that 17 of the 19 subjects in this group had worsening back pain to the point that they ultimately required additional medical or surgical intervention. This increase in serious treatment-related adverse events in the control group is an indicator of their lack of improvement in this patient population or cohort.

This slide defines the additional types of surgical treatment in the primary dataset. Additional surgical procedures in the DIAM device include revisions, which is a procedure that in any way modifies or adjusts the original implant configuration; a removal, which is removal of one or more components; a reoperation, which is any procedure at the involved level not classified as a revision or removal, and this could include a decompression or fusion; other is an additional surgical procedure not classified as revision, removal, or reoperation, and this includes lumbar surgery not at the index level.

Additional surgical procedures for the control group are any other index level surgery or surgical procedure designed to treat degenerative disc disease, and this could include fusion, decompression, and so forth.

This table summarizes the additional types of treatment surgeries in the all-available dataset. Throughout the course of the study, which for some subjects includes follow-up through 7 years, the rate of removal of the DIAM device is only 3.3%, and only 9.4% have required reoperations.

The table also shows, to date, about 60% of the subjects originally randomized to control have elected to undergo the DIAM procedure. The results of the primary dataset are consistent with the results shown here in the all-available dataset.

I would now like to present the radiographic observations.

The FDA communicated some concern regarding the clinical significance of the presence of radiographic erosions in the clinical trial. For background understanding, the term "erosion" used in the radiographic assessment form is probably an inappropriate choice of words by the Sponsor and should have been "remodeling." But to assess the presence of radiographic erosions around the DIAM device, the core lab was asked to assess the presence or absence of bone erosion by answering a simple yes/no question on the radiographic analysis form.

For clarification of these findings, the FDA requested additional radiographic analysis. Due to this request, a medical data image review protocol was submitted to the FDA, with supplementary information to classify whether radiographic changes seen were consisted with mechanical contouring or an inflammatory erosion.

The findings demonstrated changes consistent with spinous process remodeling due to altered mechanical loading or pressure on the bone. This type of remodeling is consistent with Wolff's law and is seen commonly with orthopedic implants. In all cases, the initial radiographic findings classified as erosions were determined to be mechanical and not inflammatory. But most important, there was no meaningful impact on clinical outcome measures and no reliable patient demographic or preoperative predictors identified for the occurrence of these contour changes.

The FDA communicated concerns regarding the clinical significance of spinous process fractures. The core lab was asked to assess the presence or absence of spinous process fractures and determine the location of the fracture and the time of occurrence.

The FDA requested additional evaluation of this information and a supplementary

review of any spinous process fractures to assess the anatomic location, displacement, and healing status. The findings indicate that the spinous process fractures occurred in 19 subjects, or 7.9%. Most were observed early, and most were asymptomatic. Most of the fractures seen were posterior to the interface of the spinous process and the device. The majority healed without any intervention. This indicates a lower spinous process fracture rate than other interspinous process devices studied in trials.

The next two slides illustrate radiographic findings that demonstrate the load-sharing seen in the functional spine unit with DIAM treated patients. This first slide illustrates the decrease in mean intervertebral angle in the extension position in the DIAM subjects. It is the position of extension where we believe DIAM will have its greatest effect. It also indicates how the DIAM device continues to maintain an effect on extension out through 24 months.

This slide illustrates the increase in posterior disc height in DIAM treated patients. As you can see, the effective increased posterior disc height is maintained out through 24 months, further illustrating the load-sharing effect of the DIAM device on the functional spine unit.

In conclusion, the DIAM device demonstrated superior clinical performance compared to alternative treatments for this patient population. This was seen not only in overall success, Oswestry Disability Index, back and leg pain numerical scores, and SF-36 PCS composite health scores. Other relevant endpoints show an advantage of DIAM over control in patient satisfaction, decreased narcotic usage, and decreased need for injections.

The DIAM device continued to demonstrate consistency of clinical results for

different patient cohorts, maintenance of treatment effect over time, a low rate of serious device-related adverse events, and few secondary surgeries.

There is substantial clinical evidence to support DIAM as a treatment for subjects with moderate low back pain with or without radicular pain secondary to degenerative disc disease, as measured by objective endpoints, as measured by patient general health status endpoints, as measured by incidence of adverse events. Risks are minimal and manageable. Treatment effect is significant and consistent despite the weaknesses appropriately pointed out by the FDA.

On a personal note, I participated in over 40 FDA IDE clinical trials for evaluating neck and low back pain. The patients treated in the DIAM trial are some of my most happy and satisfied patients. Mr. VanLandingham, a patient you will hear from in the public session, is a perfect example. This treatment fit his condition. It fit his lifestyle, his tolerance for risk. It was low invasive procedure, allowing him to recover quickly. Without the DIAM treatment, he faced two options: either continued low back pain or fusion with rods and screws.

I believe the overall results of this trial support a reasonable assurance of safety and effectiveness of the DIAM device. Thank you very much, and Dr. Berry will give the statistical presentation.

DR. BERRY: Thank you. My name is Donald Berry. I'm from Berry Consultants. I'm a consultant for Medtronic. Medtronic has paid for my travel, and they pay Berry Consultants for my time. I have no other financial association with either Medtronic or the device.

I'm going to tell you about the study design, talk about the interim analysis,

especially the endpoint time for assessment, the analysis populations. I'll discuss the issue of crossovers, intention to treat, and subgroups.

Design, as you've heard, is 2:1. Primary endpoint was overall success at 12 months. The Bayesian model for proportion was used consistent with the FDA Bayesian guidance. It was a pre-specified analysis, using a non-informative prior distribution.

The original sample size was 306 patients. This had 90 percent power. The plans for an interim analysis were discussed along the way, as you've heard from Dr. Simpson, and agreed with the FDA. There was an approval of 150 subjects, defining as Dr. Gornet has indicated the primary analysis set. The superiority criterion was adjusted for the interim analysis to take the so-called statistical penalty.

The three analyses populations that were specified in the protocol were the primary analysis set, the first 150 patients that were treated and analyzed at the interim analysis; the protocol set, which I'm not going to say much about; the all-available, which included all available patients in the entire study and all follow-up times.

This is something that Dr. Gornet presented to you. It's the definition of a subject's success, involving ODI, no treatment-related adverse events, no additional surgery at an involved level. And these were summarizing his presentation. For the primary protocol and all-available, the plot on the right-hand side shows the advantage, the success rate for DIAM minus the success rate for control. And the estimate, the mean estimate is the number on the right-hand side. And the bar with those two flags at both ends indicate the 95% probability interval. The fact that the lower bar is to the right of the zero, the dashed line, vertical line, indicates superiority.

This is a repeat of what I said, but to give the FDA concern regarding the adequacy of the study endpoint and the time point for assessment of overall success, and I'm going to address both of those. I'm also going to address these three issues that the FDA -- or concerns that the FDA raised: The crossover subjects in the nonoperative control group makes the proper interpretation of study results difficult, and we agree with that. I agree with that. In addition, the last observation carried forward for determination of overall success with 12 months is biased. Again, I agree. Consequently, the treatment difference is unclear and should be interpreted with caution. I'm going to describe the biases and address them, concluding that although the treatment difference is indeed unclear at 12 months, the superiority of DIAM is clear.

The crossovers were allowed to cross over after 6 months, not before 6 months, if their ODI was high and they were not a success on the basis of ODI improvement. The analysis was to be, and is, the last observation carried forward, which is the 6-month carried over to the 12-month, which means, of course, that if they crossed over and qualified for crossover, they were failures at the 12-month value. And that's a potential bias.

Why the crossovers were allowed, and even necessary: Practical considerations; asking patients to not have additional therapy for 12 months seemed beyond the pale, regarded by opinion leaders as being almost impossible to enroll in such a study, and inherent adherence to follow-up very difficult.

So I want to tell you what happened in the trial. In the first 6 months, there were no crossovers. In the next 6 months, from Month 6 to Month 12, there were 20 subjects who

crossed over to DIAM, not all at 6 months but gradually over the course of time, 20 crossovers, and out to see, you see 28 months, there were another 6 crossovers.

The crossovers, as I said, were not allowed to cross over before Month 6. There were 41 subjects of the 53 in the control arm who were candidates for surgery at Month 6; 12 were not candidates for surgery and did not have surgery. Of the 41, 20 of those chose to be crossed over to DIAM, and 17 chose no surgery; another 4 had other surgery.

So this is a slide that was not previously presented to the FDA, but they had the data for constructing the slide. It shows the four groups. And I want to focus on -- well, you see the Not Qualified for Crossover had the best results, obviously, by definition, because they were successes on the basis of ODI.

The focus on the patients who were qualified for crossovers, 17 of them chose not to cross over, and another 20 chose to cross over. The fact that the line between Month 6 and Month 12 for the crossovers is flat means simply that they got the same reading at Month 6 at Month 12, and of course, that's because that observation was carried forward.

The crossovers, the patients who qualified for crossovers but did not had about the same observation on ODI as they did at Month 6. So there was no average improvement in those non-crossovers. This was not randomized. I mean, you can't take this to the bank because the patients might have been different than those that decided to cross over and those not.

So these are the patients who had LOCF, the other surgeries, and the crossovers. What would have happened, they crossed over, they got an assessment at Month 12. Let's look at the actual ODI score. What was that? And as you got a hint of at least from the

plots that Dr. Gornet showed, they improved. They improved rather dramatically to Month 12. So these are the ODI scores in what might be called an ITT, intention-to-treat analysis.

This is a slide that you saw from Dr. Gornet. It shows 6 months and 12 months. Six months is protected by randomization, in a sense that there's symmetric endpoint definition. The definition of endpoint at 12 months, however, is not symmetric, and the 12-month value is not protected by randomization. It's biased, as the FDA has indicated.

So I want to address that bias. And I want to do so by several ways. One is to ignore crossovers. Just treat everybody as though they have an analysis at Month 12. They get an ODI score at Month 12 and are successes if they're less than 15, etc. So I'm dropping the LOCF.

This is the observed data for the primary dataset. This is the all data for the primary dataset, where the missing data, the four patients in the DIAM group who had missing data and the six patients in the control arm who had missing data are treated as failures.

This is the not treated. The missing data are failures, but also the patients who had been assigned to the therapy but refused the therapy and went away, there were 14 such patients in the DIAM arm. That's 97 up to 111. And there were three such patients in the control arm. Those are now treated as being failures. So on this basis, there is a 30.9% success differential, and that's a probability of superiority is greater than 99.9%.

This is the same set of analyses for the all-available dataset. And on the right-hand side, which is getting as close as possible to an intention-to-treat analysis with 311 patients, the mean difference was 18.1%, still statistically superior.

This is something that, a plot that Dr. Gornet showed. This is the ODI, mean ODI

score over time for the DIAM patients. And then he showed the crossover patients. I just want to make the point that these crossover patients, the Time 0 is whenever their crossover occurred. And so the Month 0 for DIAM is the true Month 0. The Month 0 for the crossover patients occurs at 6 to 12 months after they had started the study.

And this is the corresponding plot for the all-available.

The FDA had concerns about the adequacy of the study population and impact on interpretation of safety and efficacy results. We agree that the population is heterogeneous. That, to my mind, is a feature. It imitates clinical practice, and that's what clinical trials should do. It reflects degenerative disc disease that presents in clinical practice. Results are robust with respect to these different heterogeneous categories, which I'll present, and DIAM shows efficacy despite heterogeneity.

So this is a complicated plot that shows the various categories of degenerative disc subgroups. Disc herniation, defined as any patient who had disc herniation regardless of whether they had other of these categories; they might have had spinal stenosis in addition, for example, but they are categorized in the disc herniation.

That means that the plots on the right-hand side, showing the advantage of DIAM, these are independent, separate categories. So this is five different analyses. Again, it's like the previous forest plot. The interval on the right-hand side shows the 95% probability interval, and the fact that it's to the right of zero means that this is, this shows superiority according to the trial design.

That means, for example, if the company had chosen to do a study in disc herniation only, any disc herniation plus low back pain, and had accrued 55 plus 25 patients, 80

patients in that group, it would have been a successful trial.

The next level -- this hierarchy was defined by the FDA in an analysis that they asked the company to do. The next level, disc degeneration, then identified patients who did not have disc herniation but had disc degeneration in any of the other categories. And that analysis again showed superiority. All five of these categories showed statistical superiority, which is -- it's as though they did five trials, and all five of the trials were successful.

It means that if you -- one of the things it means, that is if you have a misdiagnosis, that the patient really didn't have disc herniation but had one of the other ones, it's still a successful device. So I'm going to hurry a bit here.

This shows the multi-level versus the single level in a study. It was defined for single level but the -- radiologically, in many of the patients showed that it was multi-level. The benefit of the device is again robust with respect to this issue. And my conclusions, all primary analyses show substantial DIAM effect.

The LOCF for crossovers at Month 12 is biased against control, although the non-crossover outcomes are consistent with the LOCF. The primary analyses at Month 6 is not biased by crossovers. ITT analyses of Month 12 showed DIAM superiority with somewhat lower estimated benefit. The subject population is heterogeneous, but the DIAM effect is consistent across all subsets. DIAM efficacy is durable over the long term.

And I'll turn the podium over to Dr. Scott Kitchel.

DR. KITCHEL: Good morning. I'm Scott Kitchel. I'm an orthopedic spine surgeon from Eugene, Oregon, in private practice. I was indeed an investigator and enrolled

patients in the DIAM study. I appreciate the opportunity to present a couple of patients, to try to add a little color and maybe detail to what we've been speaking about. I think, in combination with the patient you'll hear this afternoon, they'll give you an idea of this patient and the benefit they received from this procedure.

By way of disclosure, I am a paid consultant to Medtronic. Our clinic received study expenses and support from Medtronic. I am not a Medtronic shareholder. They did pay my travel expenses to be here, but I have no direct financial relationship to the DIAM or its place in the market.

The first patient I'd like to present -- pardon me, is a 58-year-old male who presented with low back pain which radiated down into both sides, into their buttocks, with some tingling into both feet, a little bit greater on the left side. The back pain was episodic in its nature. It met the inclusion criteria, but there was not a single specific injury which brought it about.

They, indeed, had undergone the community standard of prior conservative care, including physical therapy, chiropractic care, injections, and medications. The diagnostic criteria, radiographically, that allowed enrollment was a central disc protrusion with a small annular tear at L4-L5, Grade 3 Pfirrmann changes within the disc, Grade 1 facet joint osteoarthritis, also at the L4-L5 level. They, indeed, were enrolled in the study on that basis and were randomized to the DIAM or the investigational group.

This is a look at the preoperative X-ray of this gentleman. I think it brings to light a couple of things. First of all, if you go back and look at his Oswestry Disability, he falls within the severe level of disability, yet when you look at that X-ray, I don't think any of the

spine surgeons in the room would say that you could offer that patient a fusion or a disc replacement. There simply isn't an advanced stage enough of the disease. And yet the alternative is to send him back for more conservative treatment, which again, there's no prospectively randomized Level 1 data that shows that additional treatment in a conservative nature beyond this point will help him. So he falls, I think, quite nicely into that so-called treatment gap that you heard about in the presentations.

This is his MRI scan. And I think, again, it belabors the heterogeneity of these patients. This patient has some central disc protrusion at L4-L5, they have some early degenerative change of their facet joint, they have some hypertrophy of their ligamentum flavum, and they have some mild narrowing of the neural foramen in the exit zone of the nerve. I don't understand how any of us could categorize and say that one of those four should be the enrollment criteria for the patient, but rather it's this cascade of disc degeneration that allows the patient to be enrolled.

This is a look at that patient's outcome parameters over time. As was mentioned, they were enrolled and randomized to the DIAM group. The mean results of the DIAM group are shown in black, and this patient's results are shown in blue. You can see that, indeed, he started with an ODI between 50 and 60, so in that severe group, but that gratefully he improved substantially by the 6-month follow-up, and his improvement was maintained all the way out to 36 months.

This then looks at back pain, and again a similar finding. He had moderate low back pain. He got improvement dramatically in the first 6-month time frame, and that was maintained again out to 36 months, with similar indices for the control group.

You can see here leg pain. Again, we don't believe that DIAM is indicated for the treatment of leg pain, but we did observe, as you saw in the overall results, that a number of these study patients had improvement in their leg pain.

The safety considerations for this patient, he started out with all his neurologic functions being normal except for some abnormal straight leg raising, which fluctuated throughout the course of the data recovery. Postoperatively, his neurologic functions remain normal. He had no adverse events. And in the core imaging laboratory assessment, there was no evidence of migration. There was no spinous process fracture; however, some superior spinous process erosion was noted at 36 months.

This is that 36-month X-ray, and again, in the circled area you can see a radiographic finding which now, in retrospect, the independent radiologist would call remodeling rather than erosion. And this is felt to be a reaction of Wolff's law in that bone, to the fact that motion is preserved and motion is ongoing at that level.

This is his 24-month postoperative MRI scan, again making the point that the DIAM is not curative of degenerative disc disease, but it does appear to have halted the progression in terms of the fact that there's no advancement of the disc bulging. The facets are relatively similarly degenerated, there is still thickening of the ligamentum flavum, and there is still some narrowing of the neural foramen at the level of the nerve root exit zone.

I'd like to go on and present a second patient, who actually was a crossover subject, and discuss their findings and course in the study. This patient is a 48-year-old female. They presented with low back pain which did come on from an acute event in an exercise class. She again had undergone prior conservative treatment, including medications,

independent exercises, chiropractic care, and massage.

Her diagnosis on her radiographic imaging was based upon Grade 4 Pfirrmann changes in her disc, a Grade 2 facet joint change of osteoarthritis, and disc height loss at L4-L5. On that basis she was enrolled and was randomized to the conservative care treatment. She received patient education, eight sessions of physical therapy, heat, ice therapy, and took daily non-narcotic medications and nonsteroidal anti-inflammatories. She also had a single trigger-point injection.

After 6 months of that conservative treatment, she had not achieved an ODI success, meaning she had not dropped 15 points in her Oswestry Disability score, so she was felt to be a candidate and indeed was offered crossover.

This is a look at her preoperative X-ray, again, perhaps with some rotational effect, but the feeling was that this might represent some facet joint arthrosis, but again, very well maintained disc space.

I know there's been substantial discussion about how these patients were chosen and enrolled for this study. I think that question has been answered by Dr. Gornet, but it's based on their history, their physical examination, their imaging studies, and the clinical acumen of the surgeon who is taking care of the patient.

I would also ask you to consider the null hypothesis, that if you look at the data collected, there are 300 patients who are enrolled. That was over 30 study sites, and it took 6 years to enroll those 300 patients. So it's very clear to me that if the investigator could not decide upon the symptomatic level, they simply didn't enroll the patient. And that was indeed the case at our study center.

This is that patient's preoperative MRI, again showing all those findings, hypertrophy of the ligamentum, facet joint hypertrophy, narrowing of the foramen and some bulging of the disc, again, not appropriate to try to segregate any one of those findings out.

This looks at her ODI outcomes. Again, the subject is in the blue, and the vertical line indicates the point of crossover. You can see that with the first 6 months of treatment, she did not have any improvement, actually had increase in her disability and still fell within that severe level of disability. She was then treated with the DIAM device, and indeed had an outcome very similar to those patients who were initially randomized to DIAM and a gratifying ODI improvement that held up out to 18 months.

This looks at her back pain, and the same points apply. No improvement initially with her conservative treatment, but then a very gratifying improvement rapidly once she had undergone the surgical procedure. And again, leg pain, for which we do not feel this is an indication for the procedure, but are gratified that patients seem to get improvement in that as well.

So in terms of her safety profile, all her neurologic function was normal preoperatively and remained so. She had no relevant adverse event. And the core imaging laboratory assessment was negative for migration, focal bone structural changes, or spinous process fractures.

This is a look at her 12-month post-surgery X-ray, so actually 18 months plus into the study. You can see a good -- again, good maintenance of disc height and appropriate positioning of the implant.

This is her 12-month postoperative MRI, again, belaboring the point that DIAM

doesn't reverse these changes but it may slow their progression.

So, in conclusion, at least in my patient population and in those that I've seen the outcomes of, the DIAM presents a viable treatment option to fall into this treatment gap for those patients who do not have severe enough disease to undergo the more technically demanding and invasive procedures of fusion or total disc replacement and, at the same time, still remain moderately to severely disabled in their Oswestry scores and seek further treatment.

Thank you.

DR. SIMPSON: First of all, thank you to both the Panel and the Agency for the preparation and participation in today's meeting. I'd like to summarize some of the key points from our presentations today. It's important for the Panel to understand that Medtronic collected data as predefined in the study protocol.

The primary endpoints and statistical analysis plan were pre-specified and approved by FDA. The quality and integrity of the clinical data collection has been monitored by FDA through inspections at various study sites. At FDA's request, Medtronic did perform some additional post hoc analyses and data collection to address FDA concerns. These efforts were made to provide additional information to FDA for their decision process and do not affect the integrity or quality of the predefined study endpoints.

The study data shows that the DIAM device met the primary composite study endpoint of superiority of overall success at 12 months. The device has an excellent safety profile and a high level of patient satisfaction. In addition, the clinical benefit of the device is consistent and sustained, based on available longer-term data.

We know that, following our presentations, the FDA will pose several questions to this panel. Let me summarize what you have just heard as it relates to some of FDA's questions that will be presented to consider in your deliberations.

FDA has expressed a concern about the adequacy of the study population. As you have seen in earlier presentations, the radiographic findings associated with this population are heterogeneous because of the multi-factorial nature of the DDD cascade. However, regardless of the specific radiographic findings, all subgroups do well, and the proposed indication adequately reflects the patient population that would most benefit from the treatment. In addition, the screening and identification of appropriate low back pain patients is consistent with the current practice of medicine.

FDA also raised a question about the selection and adequacy of the nonoperative control group and therapies. We have justified why the conservative care control is the standard of care for this moderate low back pain population for which fusion is not yet indicated. The conservative care requirements in the study were designed to replicate clinical practice and optimize the treatment of each patient while providing appropriate guardrails.

Some aspects of the study design were necessary based on real-world issues of study enrollment and patient retention. The crossover design was needed to afford those who had exhausted and failed the conservative care regimen another potentially effective option for treatment.

As presented by Dr. Berry, Medtronic has explored the potential biases in detail with different analyses and different approaches to the handling of crossover data, and the

superiority of the DIAM device is clear. In addition, the crossover data is consistent with and further supports the treatment effects seen in the randomized portion of the study.

FDA's concern about the adequacy of the study endpoint and time point for assessment is primarily based upon literature reports. However, both Mr. Lange and Dr. Bailey have presented additional details on these literature reports to put the concerns in perspective. In addition, Medtronic believes that our own randomized IDE data, showing the device is durable and consistent performance to the 12-month endpoint and beyond, provide the best support for the adequacy of the endpoint.

The Panel will be asked to comment on whether there is a confounding effect of the tissue or bone resections performed during the DIAM surgical procedure. Let me emphasize again that direct decompression was not done as part of the study and is not part of the proposed use. Minor bone or tissue removal was allowed to properly seat the implant, but this was not a neural decompression. In fact, as discussed by Dr. Bailey, a direct decompression would not have been indicated to treat the back pain experienced by the patient population in this study.

FDA has also raised a question about some of the radiographic findings from the study. With regards to spinous process fractures, Medtronic initially collected data with respect to the presence and timing of these observations. As the Panel may be aware, this type of radiographic finding has been a topic of discussion for other devices fitting in this same anatomical space. Therefore, FDA asked Medtronic to conduct an additional post hoc review of the radiographs to collect further details on the location and healing status of these events. This review concluded that the fractures are typically asymptomatic,

posterior to the device, and often spontaneously heal.

On the topic of bony erosion, Medtronic initially collected data on the presence or absence of bony erosion. Based on the study data, FDA asked Medtronic to conduct an additional post hoc evaluation, which was done by independent reviewers at the core lab. This review found that the erosions were not inflammatory erosions but instead were mechanical contour changes consistent with remodeling of the spinous process, and they do not have a clinically meaningful effect on study outcomes.

Finally, FDA questioned the significance of the motion measurements. Based on Medtronic's presentation of the data, we can see that the motion and extension and posterior disc height are maintained over time and are consistent with the load-sharing mechanism of the device.

We have presented strong evidence in favor of the safety and effectiveness of the DIAM device. We conducted rigorous preclinical testing, demonstrating satisfactory mechanical performance and biocompatibility of the device. Additionally, we completed multiple animal studies and conducted testing in order to provide instructions on the use of the device in the MRI environment.

Our randomized controlled IDE study, which met its primary endpoint of overall success at 12 months, based on the FDA approved interim analysis plan, provides strong clinical evidence of the safety and effectiveness of the device for its proposed indication. A significant amount of longer-term data was also collected during the trial, which confirms that the results are maintained over time beyond the primary endpoint.

In terms of safety, information related to adverse events and additional surgical

procedures was collected according to the protocol-defined standards. As discussed earlier, determinations of seriousness, severity, and relationship to the study treatment were made by an independent clinical adjudication committee. The DIAM and control groups experienced statistically similar rates of adverse events up to 12 months. In terms of adverse events associated with the study treatment, these were numerically lower in the DIAM group through the primary endpoint. The rate of additional surgical procedures through 12 months was also lower in the DIAM group. These trends were all maintained at later follow-up intervals.

The DIAM group outperformed the control measurements -- control patients in all outcome measures, including the composite overall success variable, ODI success, back pain, leg pain, SF-36 PCS, and patient satisfaction. There is a clear effectiveness advantage with the use of the DIAM device.

Overall, DIAMs patients experienced a clinically significant reduction in pain and disability, high patient satisfaction, decreased narcotic usage, and a decreased need for injections. The DIAM device showed a favorable safety profile with a low rate of serious treatment-related adverse events. There were no clinically concerning radiologic findings.

The DIAM device is a minimally invasive intervention that preserves future surgical options should they be needed. Therefore, the DIAM device not only demonstrates a reasonable assurance of safety and effectiveness, but it also shows additional benefits as compared to the current standard of care for this population.

A physician currently has very few options with this moderate low back pain patient for whom fusion is too overly invasive. The DIAM device fills an unmet need and is an

important option for these patients.

Medtronic is committed to postmarket data collection and has proposed a 5-year follow-up study of the existing DIAM patients. However, the post-approval study design is a topic of ongoing discussion and negotiation with FDA. Medtronic is willing to continue working with FDA to design an appropriate post-approval study.

In conclusion, the IDE study of the DIAM device met its pre-specified and approved study endpoint. The study was conducted in accordance with the pre-specified protocol and analysis plan. The patient population was properly defined and compared to the correct control group. The time point for assessment was appropriate. The device showed a favorable safety profile and superior effectiveness, and these trends were also reflected in the long-term data. Therefore, the DIAM device is safe and effective as a primary therapy for moderate low back pain secondary to DDD.

Thank you for your time and attention.

DR. RAO: Thank you very much, Doctor. You had 27 seconds left out of your 1½ hours.

(Laughter.)

DR. RAO: I would like to thank the Sponsor's representatives for their presentation, for their timely presentation.

If anyone on the Panel has any clarifying questions for the Sponsor, this is the time to ask. Please remember that we'll also have time this afternoon to ask questions and get more clarification from the Sponsors.

Let me get this started off. Just I had a couple of quick questions on how you

selected patients for the study. Dr. Bailey, you talked about some of the FDA guidelines for lumbar degenerative disease, and one of those guidelines says translation of 3 mm. Did you measure preoperative translation, either on static films or flexion-extension films?

And the second question, which also relates to inclusion criteria in the study, is one -- I think one of your radiographic criteria was that the disc height at that level -- and it's not specified whether it's anterior or posterior disc height, but one of the disc heights should be less than -- 2 mm less than an adjacent level. But when I look at Dr. Kitchel's X-rays, the L4-5 disc, both anterior and posterior discs, particularly in case 1, looked roughly similar or maybe even taller than 3, 4, and 5 ones. So if you could either clarify now quickly, or you can give me more clarification in the afternoon.

DR. BAILEY: In some of the measurement aspects, we can certainly give greater details this afternoon. But in terms of the disc height when looking at degenerative disc disease, one of the exclusion criteria is to rule out advanced stage abnormalities, is 67%, compared to adjacent levels. When it looks at the inclusion criteria, we're looking for that moderate low back pain patient population from degenerative disc disease with primary low back pain.

DR. RAO: Correct. Exclusion was 67%, but inclusion was greater than 2 mm loss of height, greater loss of height. And so my question was specifically about the 2 mm aspect, not the 67% aspect.

DR. BAILEY: Yes. Preoperative X-rays and MRI scans were sent off to lab for that analysis.

DR. RAO: Yeah. And it didn't look like it was more than 2 mm at L4-5. So you can

respond to that this afternoon. And how about the first part of the question with the 3 mm at translation? Did you use the FDA guidelines for 3 mm at translation to suggest part of the complexity of lumbar disc disease, and did you measure translation on all patients that were included in the study? And you don't have to answer it right now. You can get back to me this afternoon.

DR. SIMPSON: Sure, we can provide that. Okay. Yes. Dr. Kitchel has a --

DR. KITCHEL: Excuse me, Dr. Rao. I think I can address that fairly quickly. If you look at the inclusion criteria in the protocol, the inclusion criteria require one or more of the following findings. One of those is disc height loss greater than 2 mm compared to the adjacent event.

DR. RAO: Thank you.

DR. KITCHEL: But the other two or's are scarring or thickening of the ligamentum flavum or herniation or protrusion of the nucleus pulposus.

DR. RAO: Thank you very much.

DR. KITCHEL: And all patients did meet those criteria.

DR. RAO: Dr. Blumenstein?

DR. BLUMENSTEIN: I'm interested in the definition of your primary endpoint. So the second bullet point on your definition is about adverse events, and particularly when you have a nonoperative treatment, you say that adverse events, other than surgeries and so forth, apply only to the control arm. And so what I'm wondering is like if a patient in the experimental arm gets some of the noninvasive interventions, such as injections or pain meds or whatever, the adverse events associated with those are not counted as adverse

events? Is that correct?

DR. SIMPSON: That's, you know, certainly can be a confusing issue with this type of protocol, so we can present some backup material on that to describe that in more detail after the break, at that time.

DR. BLUMENSTEIN: Well, that's a yes or no. I mean, in other words, if you have an SAE associated with, say, injections, and you're in the intervention arm, in the experimental arm, that would not be counted against the experimental arm; is that correct?

DR. SIMPSON: Right. Dr. John Tillman is going to explain this.

DR. TILLMAN: Hi. I'm John Tillman. I'm a Director of Clinical Science for Medtronic. In the definition, if there is a SAE that is considered treatment-related in the control group, it is a part of the success, overall success definition. So if they did have a treatment-related serious adverse event, it is counted against the control. So it would be a failure.

DR. BLUMENSTEIN: Yes. But what about in the experimental arm. If you had a --

DR. TILLMAN: Yes. If they had a --

DR. BLUMENSTEIN: -- SAE from a noninvasive, say the same kind of thing that's prescribed --

DR. TILLMAN: Yes. If they had any treatment or device-related serious adverse event, it's counted against the investigational group as well.

DR. BLUMENSTEIN: That's not the way it reads in the briefing book. So I mean, it says, and it has little parentheses, you know, non-surgery arm only and surgery arm only.

DR. TILLMAN: Those were for, like for example, in the control group, if they had a treatment surgery in the control, then -- like if they had to go on to get a fusion, then that

would be considered a failure. And also if the investigational group had a surgery, secondary surgery -- but see, in the investigational group, it's a secondary surgery. So it would be counted as a failure.

DR. BLUMENSTEIN: Well, but that's not the way it reads. And I would like for you to make the -- reword that in such a way that I understand. My main concern is whether or not the same kinds of interventions being used in the control arm can induce adverse events that disqualify a patient from being regarded as a success when they happen in the experimental arm.

DR. SIMPSON: I think we can clarify that. But I think one aspect here, and I don't have the definition in front of me, but we did call them treatment-related events in the control group, whereas in the investigational group, because they had had a surgical procedure, the wording there was procedure-related. So that may be one aspect of the clarification.

DR. RAO: If you -- I think that's an important point. And if you can just help Dr. Blumenstein out this afternoon when you come back --

DR. SIMPSON: Sure.

DR. RAO: That'll be great. Dr. Yang had a question?

DR. LYNDA YANG: Yes, Lynda Yang. So as a spine surgeon coming from a neurological background, to me the lumping together of these patients with leg pain and back pain is somewhat concerning. I'm also worried about the potential implications of a device like this being used to treat radiculopathy.

The -- on Slide 68 and on Slide 69, you show the back pain and leg pain scores of

these patients to start with. However, there's no -- I mean, obviously, most of these patients will have back pain. But I don't know how many of these patients had leg pain to start with. Is it all of them? Is it 50% of them? Also, how wide is the distribution, or how tight is the distribution, the range of the leg pain, and were these patients in these potentially separate groups? Because to me, again, clinically, I treat my back and leg pain patients very different than I treat my back pain only patients.

So were the results analyzed by those patients with potentially back and a lot of leg pain, and back and just a little leg pain? Because as far as I could tell from the materials we were provided, they were all analyzed together.

DR. SIMPSON: So, first of all, let me clarify, from the protocol standpoint, all patients that were enrolled in the study had back pain. Some of them had leg pain. But we can certainly get you more detail on that.

DR. LYNDA YANG: Understood. No, I understand that. But I'm -- again, I'm -- you know, from a clinical standpoint, I think those are two very different groups of patients.

DR. RAO: Thank you. Dr. Finnegan has a --

DR. SIMPSON: Okay. I believe Dr. Tillman has some additional details that he can provide on that now.

DR. RAO: Let me just get through some of the questions, and maybe if we have time, we can get the answers. But please remember to answer that important question this afternoon. Dr. Finnegan?

DR. FINNEGAN: Two questions. The first one is, you just defined the ODI groups as 20 to 40, and then 40 to 60. How many of your experimental patients fell in the 39 to 45

group as compared to the 55 to 60 group?

And then my second question has to do with injections. Are all these injections epidural, or are they all sorts of injections?

DR. SIMPSON: I believe it's a mix, as it was presented.

DR. FINNEGAN: And then the second --

DR. SIMPSON: It combines all.

DR. FINNEGAN: The second question is, for the control group, you had injections as part of their treatment. And then you showed a slide that said they had way more injections than the experimental group. Did that exclude their injections as part of their control treatment, or is that all of their injections?

DR. SIMPSON: That would be all of their injections.

DR. FINNEGAN: That's apples and oranges. If injection's part of their treatment, then if you're going to compare how many injections they had as compared to the experimental, it should be what they had after their treatment.

DR. SIMPSON: During their -- it's cumulative, during the course of post-treatment. So we can explain that as well.

DR. RAO: But that kind of goes towards Dr. Blumenstein's question a little bit, because if they received three and then they received a fourth, does that count as an adverse effect, or is that part of the treatment? So maybe you could clarify that for us. Dr. Graf has a question.

DR. GRAF: I have a very broad question that was covered by many of the presenters, but in my mind, as an orthopedic spine surgeon, this device is intended -- you know, there's

been a lot of discussion on unloading and load-sharing. But if you look at your data you've presented, the disc height, which is initially obtained, essentially returns back to normal within 1 year. So then if we're measuring our overall success of these patients at 1 year, what's the long-term outcome? I know your long-term outcomes at 60 months appeared good, but in my mind, biomechanically, that makes no sense.

DR. SIMPSON: Sure. So we did specifically focus on the posterior disc height and showed that was maintained out to the length of the study, and we believe that all of our radiographic measurements are supportive of that load-sharing mechanism. And Dr. Kitchel can describe this more for you.

DR. KITCHEL: I think, just as a fellow clinician, I would urge you to think about the difference. You're talking about distraction, and you're talking about load-sharing. Those are not synonymous terms. You can load share without distraction. You probably can't distract without achieving some load-sharing. But we believe the success and the mechanism of the device is based on load-sharing and not on distraction.

DR. GRAF: Just as a response to that, there was specifically mentioned unloading of the posterior disc, and that's what I was referring to. So unloading of the posterior disc would be by essentially a segmental kyphosis at that level.

DR. GORNET: As the slide I presented, just brief discussion for that, remember that there was an increase in posterior disc height compared to the baseline that was maintained out. So it does continue to show an effect out through not only 24 months but 60 months in the measured posterior disc height in the neutral position. And so it does not show a falloff in that posterior disc height. It maintains its effect through time.

DR. GRAF: Okay, I'm specifically referring to Slide 35, our handout page 9, bottom left. If you can explain that later, then -- because that graph doesn't reflect that.

DR. SIMPSON: We'll do that.

DR. RAO: Dr. Cheng had a question?

DR. CHENG: Yes. Thank you for your presentation. I want to express my appreciation. I know the level of -- having tried to do clinical trials myself, the level of difficulty and the time and effort that goes into these is tremendous for everyone, the Sponsor and the clinicians.

As a orthopedic surgeon who's not doing these operations, I'm -- had several observations, though, and am wondering if these are correct or incorrect, and would appreciate the input from either your spine surgery experts or those on the Panel, we can discuss this afternoon.

So these observations pertain to the study design. You've positioned this as a treatment for patients where there's no other available treatment because the other surgical treatments are too invasive, that is, fusion or disc replacement. But my observation's a little different. So for the -- if I look at the degenerative disc subgroups that you sequentially defined and were presented in this statistical summary, some of those subgroups might have alternative treatments.

For example, the herniated disc group, why wouldn't one consider a microdiscectomy for this group, which is less invasive? It could be argued as maybe the same level invasiveness as your procedure and does not involve a fusion or disc replacement. For the -- and certainly a lot of those patients had herniated discs. According

to the numbers here, it's about a third. And a lot of patients did have leg pain, as was asked earlier.

The second subgroup would be the spinal stenosis group. I believe -- I know it's a small percentage as I see here, about 1%. But certainly a limited decompression might be a consideration there as an alternative treatment, other than the fusion and disc replacement. So there's another comparative group that one might have considered.

And then for the rest of the patients that supposedly fall into this treatment gap, why wouldn't you include a placebo control? We know that for low back pain, in which the results are so variable and difficult to assess, the placebo control in some studies shows that -- at least for drug control studies, 20% to 50% of patients have a reduction in their pain scores by that amount.

So it would seem to me that for a study design, for those patients, you would want to include a placebo control as to just no procedure. And I think that shows in your results, because in the crossover, almost half the patients elected to have something done because they felt they were having a lot of pain but the nonsurgical treatment was not effective in addressing that. So a lot of patients decided to have something else done.

So I see this a little bit differently and am open to hearing what your thoughts are.

DR. RAO: Thank you. Thank you, Dr. Cheng. I think we'll wait for your response on that specific important point after --

DR. SIMPSON: Sure. That's good. Thank you.

DR. RAO: -- during the second session. The core question relates to the basic premise that this is addressing a target group of patients with back pain for which there, for

whom there's no other treatment options. So I'd like a little more clarification on that concept, which is part of the basic premise.

Another quick concept maybe you can respond to after the deliberations relates to your biomechanical testing. The sense I get, reading your materials, is that the bulk of the testing was carried out with regards to the device itself. Was there any testing carried out with regards to the cables or the crimps? Could they loosen? Could they detach, like they did detach in some of the patients? Did you do any strength testing of the cables with cyclical testing with the cables and crimps loaded? So you could maybe perhaps respond to that after the break.

We're out of time for this brief clarification session. If anyone has any quick questions? No.

Marjorie, you have a quick -- Dr. Auerbach?

DR. ESKAY-AUERBACH: In conjunction with the things that Dr. Yang mentioned, I guess from a clinical perspective, the term leg pain to me as a clinician is very broad and doesn't distinguish between, for instance, posterior thigh pain, which is very common, and radicular symptoms. And I didn't see a distinction between those things in the information that was available to us.

DR. SIMPSON: Sure. We can add that to our detail this afternoon.

DR. RAO: Thank you very much, everyone. We will now take a 15-minute break, plus 27 seconds.

(Laughter.)

DR. RAO: Panel members, please do not discuss the meeting topic during the break

amongst yourselves or with any member of the audience. We will resume at 10:15 sharp. Thank you.

(Off the record at 10:02 a.m.)

(On the record at 10:18 a.m.)

DR. RAO: It is now 10:18 a.m., and I would like to call this meeting back to order. The FDA will now give their presentation.

I would like to remind public observers at this meeting that while the meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

FDA will also have 90 minutes to present. FDA, you may now begin your presentation.

MR. O'NEILL: Good morning, distinguished Panelists and members of the audience. My name is Colin O'Neill, lead reviewer of the DIAM Spinal Stabilization Premarket Approval Application P140007, sponsored by Medtronic. We are seeking input of the Orthopaedic and Rehabilitation Devices Panel on this PMA application as it's being reviewed by the Agency.

I would like to take a moment to recognize the FDA Project Team that is currently reviewing the DIAM PMA. The Agency's presentation on the DIAM PMA will follow the outline as shown. Please note that the Panel questions will be presented in the afternoon.

I will now introduce the purpose and rationale of this Panel meeting, briefly describe the DIAM investigational device and its proposed indications for use, intended use, and briefly review the nonclinical studies provided in support of this PMA application.

The purpose of this meeting is to obtain input from the Panel on the safety and effectiveness results of the DIAM Spinal Stabilization System for its proposed indications for use. In addition, the Agency is seeking Panel input on concerns related to the study population, control group, primary endpoint and time of assessment, role of the DIAM as a primary therapy or adjunctive therapy with direct spinal decompression, and radiographic outcomes reported in the study.

These concerns introduce questions about the poolability of the study population and the lack of clinical equipoise between the investigational and control groups. The Agency is concerned about the impact of the interpretation of the study results for the purpose of evaluating safety and effectiveness of the DIAM Spinal Stabilization System and is seeking feedback from the Panel on these issues.

The DIAM Spinal Stabilization System is a polymeric, H-shaped interspinous device that is secured in place and using the attached polymer cables and crimps. The Sponsor describes the investigational device as intended to alleviate pain through the reduction of stresses on the overloaded posterior disc and facet joints, while it re-tensions the supraspinous ligament and other ligamentous structures.

The Sponsor's proposed indications for use for the DIAM Spinal Stabilization System are shown here. Please note that the Sponsor originally indicated the DIAM for treatment of moderate DDD and has used this rationale at this time of the study and informed consent. However, proposed indications for use were revised to reflect moderate low back pain in an attempt, according to the Sponsor, to more closely align with indications for use of the study population, end study population.

Proposed contraindications, warnings, precautions for the DIAM device are described in your Panel pack.

The DIAM IDE clinical trial that collected the data to be discussed at this panel meeting was fully approved on June 23rd, 2006. However, in the IDE approval letter, the Agency's conveyed concerns related to the study population and control group may appear as future considerations.

As an aside, please note that Medtronic registered a clinical trial for the DIAM intended to treat lumbar spinal stenosis, but the study was terminated due to slow subject enrollment or recruitment.

Medtronic provided the nonclinical study results shown here in their PMA application. After review of the nonclinical data provided, the Agency does not have any significant concerns with the information provided. It is not seeking Panel input on the nonclinical study results to the DIAM at this time.

I would like to introduce Dr. Panox, the medical officer assigned to this PMA application, who will present the clinical background information as well as the FDA review of the study results.

DR. ADEGBOYEGA-PANOX: Good morning. My name is Elizabeth Panox, and I am an orthopedic surgeon and the Medical Officer in the Division of Orthopedic Devices, the Anterior Spine Devices Branch. I would like to thank the Panel members for their time and input.

Degenerative disc disease, which is the clinical indication being discussed today, is a broad and incompletely understood condition. It is also inconsistently defined.

Degenerative disc disease is considered to be multi-factorial in etiology. These factors include the normal aging process, the influence of environmental factors such as trauma, and genetic predisposition. Degenerative changes may or may not be symptomatic.

The treatment of and clinical study designed for mild to moderate degenerative disc disease was the topic of a September 9th, 2005 Orthopaedic and Rehabilitation Devices Panel meeting. The Panel could not definitively define degenerative disc disease and recommended study designs be determined on a case-by-case basis.

The work of Kirkaldy-Willis et al., published in 1978, describes the degenerative cascade as disrupting the function of the three-joint complex or functional spinal unit, most commonly at L4-L5. The FSU consists of the intervertebral disc and facet joints of adjacent vertebrae as well as the spinal ligaments and adjacent neurostructures.

Kirkaldy-Willis also demonstrated that degeneration in the lumbar spine is a progressive process, with different clinical syndromes being expressed at different stages of progression. They describe a spectrum of degenerative change that leads from minor strains to marked spondylosis and stenosis.

The rate and manner of progression is variable. Haldeman et al. demonstrated that several structures in each functional spinal unit are innervated and may be the source of pain. They also demonstrated that back pain may originate from structures external to the lumbar disc.

A report from the Combined Task Forces of the North American Spine Society, the American Society of Spine Radiology, and the American Society of Neuroradiology recommended nomenclature for degenerative disc based on radiographic findings. A

degenerative disc is described as having any of the following: desiccation, cleft formation, fibrosis, gaseous degradation of the nucleus; mucinous degradation, fissuring, and loss of the integrity of the annulus; defects in and/or sclerosis of the end plates; and osteophytes at the vertebral apophyses.

The task force also recommended a definition of degenerative disc disease as follows: "A condition characterized by manifestations of disc degeneration and symptoms thought to be related to those degenerative changes. Causal connections between degenerative changes and symptoms are often difficult clinical distinctions. The term 'degenerative disc disease' carries implications of illness that may not be appropriate if the only or primary indicators of illness are from imaging studies, and thus this term should not be used when describing imaging findings."

The FDA has published a number of definitions related to degenerative disc disease in various documents. In the Spinal Systems IDE guidance, the FDA describes degenerative disc disease with one or more of the following radiographic findings as shown on this slide.

In the Spinal System 510(k) guidance, degenerative disc disease is described as being of discogenic origin, and in the FDA Summary of Safety and Effectiveness Data, for a previously approved spinal device PMA, subjects are described as having no more than Grade 1 spondylolisthesis at the involved level.

Degenerative disc disease presents clinically with either back pain, radicular pain, or both. Back pain in degenerative disc disease is variable in intensity. It may be constant or intermittent. It's located at the involved segment and may originate from multiple pain generators. Radicular pain occurs from neural compression by disc herniation or

osteophytes, or compromise of the neural structures by narrowing of the neuroforamina from loss of disc height.

The FDA recognizes that according to the current medical literature, primary treatment for the majority of patients with degenerative disc disease is nonoperative and that patients treated with surgery are selected from the population that has failed nonoperative treatment. Treatments for degenerative disc disease are generally symptomatic and not curative.

Surgical treatment options for degenerative disc disease include fusion procedures, total disc arthroplasty, decompression procedures in subjects with neural compression in the setting of degenerative disc disease.

Please note that the device under discussion today is the first-of-a-kind interspinous process, non-fusion device indicated for the treatment of degenerative disc disease.

Now I will present some details regarding the clinical trial conducted to study the DIAM device.

The details of the study design are shown in this slide. While the study was randomized, a nonoperative control group was used. There was no blinding, the primary endpoint was evaluated at 12 months, and subjects were permitted to cross over from the control group to the investigational group if certain criteria were met.

The Sponsor provided a justification for the study. The investigation examined a group of patients with moderate low back pain secondary to lumbar degenerative disc disease. Currently, the standard of care for this group of patients is limited to nonoperative care.

While surgical alternatives such as spinal fusion and total disc replacement may be considered for more advanced stages of degenerative disc disease, these more invasive procedures, which entail significant potential risks and cannot be reversed, are not indicated for moderate low back pain.

The DIAM Spinal Stabilization System was evaluated as a potential alternative treatment for moderate low back pain secondary to degenerative disc disease in which a spinal fusion or total disc replacement is not yet indicated.

The objectives for the study were to evaluate the safety and effectiveness of the DIAM Spinal Stabilization System; to evaluate the ability of the investigational device to relieve pain and improve function as evaluated using the Oswestry Disability Index; evaluate secondary assessments of clinical outcomes, including the SF-36 Physical Component Summary, back and leg pain success as defined by the Sponsor, and subject investigative questionnaires. Ultimately, it was hoped that this study would demonstrate superiority of the DIAM investigational device as compared to the control group.

The target population for the study was subjects with moderate low back pain secondary to lumbar degenerative disc disease for which spinal fusion or total disc replacement is not yet indicated. The Sponsor had originally described a population with moderate degenerative disc disease in its indications for use. This was changed to moderate back pain secondary to degenerative disc disease, and the Sponsor's rationale was that this more closely aligned with the enrollment criteria.

Key inclusion criteria are shown in this in the next slide.

The next few slides show the exclusion criteria that were utilized for study

enrollment.

The investigational cohort was treated with surgical implantation of a single DIAM device between two adjacent spinous processes via a posterior approach. In addition, some subjects received elements of nonoperative control therapy, as deemed necessary by the investigator. Finally, study subjects were permitted to pursue non-study treatments, such as acupuncture and massage.

Nonoperative treatment for the control group consisted of patient education plus one or more of the following: physical therapy, medications, spinal injections. Similar to the investigational cohort, control subjects were permitted to pursue non-study treatments such as acupuncture and massage.

Patient education consisted of spinal mechanics and ergonomics, and explanation of the anatomy, pathology, and pathomechanics of degenerative disc disease to the study subject.

Control subject received at least one prescription for any and all of nonsteroidal anti-inflammatory drugs, muscle relaxers, oral corticosteroids, neuroleptics, and antidepressants. Medications were not prescribed according to standard protocol, and there was no requirement that subjects take the medication prescribed.

The physical therapy component of control treatment was administered by non-investigative personnel upon referral, who then determined a patient-specific regimen, which could include adjunct therapies such as TENS or ultrasound. Physical therapy was not administered in accordance with a predefined standard protocol for the content, duration, or frequent of treatment. Study subjects were considered to have completed treatment if

they attended an initial assessment plus one session of treatment.

The final component of nonoperative treatment, spinal injections, were also administered upon referral by the investigators. Study subjects received up to three injections.

This study allowed for one-directional crossover of control subjects to receive the DIAM Spinal Stabilization System as a treatment if the following criteria were met:

- Six months of nonsurgical treatment has proven ineffective;
- An ODI score that is equal to or greater than 30 points (based on the initial ODI inclusion criteria for study) after 6 months of nonoperative treatment;
- ODI score improvement of less than 15 points (ODI success criteria) after 6 months of nonoperative treatment;
- Investigator determines that subject has a medical need for additional treatment beyond that provided by the control treatment.

Subjects were evaluated preoperatively for screening and baseline evaluations on the day of operation and assessed for adverse event at discharge, 0 to 7 days, and assessed with a standing AP and lateral lumbar X-ray, neurologic status, pain, as well as for adverse event, and full postoperative evaluations at 6 weeks and 3, 6, and 12 months. Overall success was evaluated at 12 months.

The primary study endpoint as defined by the Sponsor is shown in this slide and includes an assessment of the subject's ODI score as well as absence of any treatment-related serious adverse events or additional surgical procedures.

While the definitions of ODI and treatment-related adverse event success are the

same for both treatment groups, the designation of additional surgery and therefore failure had very specific criteria that differed between the two groups. For the investigational subjects, the definition was any revision procedure necessary to adjust or modify the original implant, any removal procedure to replace the device components or to explant components of the device, or any procedure indicated for pain relief, such as denervation or rhizotomy.

For the control group, additional surgery was defined as a surgery subsequent to poor response to nonoperative care, which was considered necessary to effectively treat the originally diagnosed degenerative disc disease.

The Sponsor defined overall success of the study as statistically superiority of the investigational group as compared to the control group at 12 months. If this success endpoint was met, the device was considered to be safe and effective.

The presentation will now continue with the results and observations of the study: 421 subjects were screened for inclusion, of which 110 did not meet the criteria and were considered screening failures; 311 subjects were randomized. Of these, 26 investigational and 3 control subjects did not complete treatment, resulting in 181 investigational and 97 control subjects, which constitute the all-available dataset.

The primary analysis dataset, comprised of the first 150 subjects to reach the 12-month time point with at least one evaluation of overall success, was derived from the first 167 eligible subjects. There were 10 protocol deviations in the primary analysis dataset.

The two study arms were very similar in terms of demographic variables, with the exception of race. There was an equal distribution of Caucasians. Hispanics were

disproportionately higher in the investigational group, while blacks represented a larger percentage of subjects in the control group.

There was no statistical difference in baseline assessment between the two groups. However, please note the baseline ODI scores close to 50 points in both investigational and control groups, which will be discussed later.

Surgery and hospitalization details for the DIAM subjects are shown in this slide. Mean blood loss was 32 milliliters, and the mean hospital stay was 0.9 days. Most DIAM surgeries occurred at the L4-L5 levels, and all surgeries utilized a posterior approach.

This table demonstrates the nonoperative interventions received by the control group from the 6-week time point through the study endpoint at 12 months. This table includes both study and non-study treatments. The data demonstrates the subjects received variable combinations of nonoperative treatment. Physical therapy and non-study treatment data were not collected in the investigational group.

This table demonstrates the number of injections received by study subjects. In all cohorts, the number of injections and subjects receiving injections increased over time. The majority of injections given were unspecified epidural injections. The data demonstrate that numerically greater numbers of subjects received injections in the nonoperative control group than in the investigational group. This finding is not surprising given that injection therapy was a component of the treatment for this group. No statistical analysis was performed to determine the significance of this finding.

The data also demonstrate an increasing trend of injections provided to investigational and crossover subjects after receiving the DIAM device. Since injection

therapy is a treatment for pain, the administration of such injections to investigational and crossover subjects may be expected to potentially confound the outcomes observed during the study, especially of pain outcomes.

This table demonstrates medication use by study subjects over time. Medication use appears numerically greater in the control group. Different methodologies were used to collect medication data in the study cohorts. Investigational and crossover subjects were asked to provide a listing of medications they were taking and to specify frequency of usage, while the nonoperative control patients were asked if they had been prescribed any medication since the last visit, and if so, were asked to provide a list of medications. This difference in methodology makes meaningful comparison challenging. The potential confounding of outcomes by the use of medications is also difficult to assess.

I will now present on the safety assessments of DIAM.

When making an assessment of safety, the Agency considers adverse events, reoperations or post-treatment surgeries, and neurologic status. Any clinically adverse sign, symptom, syndrome, or illness not already being measured in the trial that had onset or worsens during the trial, regardless of causality, was deemed an adverse event. Expected clinical sequelae related to recent surgery were excluded. Adverse events were collected, categorized, and reported by the study investigations. Subsequently, a clinical adjudication committee evaluated each adverse event for severity, seriousness, and association with study treatment.

This table demonstrates the adverse event rates reported in this study. Overall adverse event rate, severe adverse event, and serious events were greater in the

investigational group than in the control group. Serious events associated with treatment were reported to be greater in the control group.

This table provides the categorization of the serious adverse events which occurred in the study. Rather than focusing on the details of this table, we would like to share concerns that we have regarding the adverse event categories and classification. The event categories were reported in alphabetical order, giving equal weight to systemic adverse events and local events.

This organization is more applicable to a trial in which the investigational product is administered systemically. Many adverse events could be categorized in more than one of the categories, thus providing an inaccurate and indeterminate safety profile for the device. It appears from the table that a pain event could be categorized in one of several categories, for example, musculoskeletal events, trauma, accidental injury, muscle strain, spinal event, pregnancy, or other. Some definitions given for the categories are not specific enough and make it challenging to allow for accurate categorization, for example, accidental injury, muscle strain, and trauma.

The rates of treatment-related serious adverse events were higher for the nonoperative control compared to the investigational group. This is an unexpected finding as it would not be expected that nonoperatively treated subjects would experience a greater number of treatment-related adverse events and treatment-related serious adverse events compared to subjects who had operative treatment. These results further suggest that the nonoperative treatment carries a greater risk than the investigational treatment.

Post-treatment surgical procedures occurred in both the investigational group and

nonoperative control group. The definitions of post-treatment surgeries differ between the two groups, as shown on the next two slides.

Subsequent secondary surgical interventions in the investigational group were classified as revisions, removals, reoperations, or other interventions, according to the definitions shown on this slide.

In the nonoperative control group, any surgical intervention after initial treatment was identified as a treatment surgery. A nonoperative control subject could cross over to receive implantation with the DIAM device. Nonoperative control subjects could also undergo surgical interventions other than implantation with the DIAM device. Any surgical procedure performed at a location other than the involved level was deemed other.

In the investigational group, 13 DIAM subjects underwent secondary surgical procedures, and there were 3 removals. No subjects required revision of the device. Ten DIAM subjects required 11 reoperations to treat symptoms of degenerative disc disease at the index level; the majority of these reoperations was spinal decompression procedures with or without fusion.

For the nonoperative group, there were 29 subjects who received a treatment surgery. This includes 23 subjects who crossed over to receive the DIAM device. Six control subjects received other surgery, which included decompression alone, decompression with fusion, radiofrequency ablation, disc replacement, and rhizotomy.

The neurologic status assessments and success definitions are shown on this slide. There was no difference between the two groups in the neurologic success rate at 12 months.

I will now present on the effectiveness assessments of the DIAM device.

(Off microphone comments.)

DR. ADEGBOYEGA-PANOX: Sorry.

In summary, the rate of any adverse event and rate of serious adverse events were numerically higher in the DIAM subjects as compared to the control subjects in the primary analysis dataset through 12 months. The rates of serious adverse events associated with treatment were numerically higher in the control subjects compared to DIAM subjects in the primary analysis dataset through 12 months.

The rates of treatment surgeries for the nonoperative control group was nearly four times higher than the rates of secondary surgeries in the DIAM group in the primary analysis dataset through 12 months.

Neurologic status, as assed by the Sponsor's neurologic success definition, was similar between the DIAM subjects and the control subjects in the primary analyses dataset through 12 months.

The Agency will be asking the Panel a voting question on whether a reasonable assurance of safety has been demonstrated for the PMA device for its proposed intended use.

Now I will present on the effectiveness assessment of DIAM.

As noted previously, this slide shows the primary study endpoint used to determine overall success. The overall success rate for the DIAM subjects was 63.9%, and the overall success rate for the nonoperative control subjects was 15.1% at 12 months; 69.1% of the DIAM subjects and 17% of the nonoperative control subjects reported greater than or equal

to a 15-point improvement in ODI score at 12 months. Four of the DIAM subjects and none of the control subjects were determined to be secondary surgery failures at 12 months.

Eight DIAM subjects and 19 control subjects were determined to have experienced a pre-specified treatment-associated serious adverse event through 12 months. The effectiveness results were similar in the other analysis datasets, but longer-term success was difficult to assess given the significant loss to follow-up.

Secondary outcomes included leg and back pain, and the physical component of overall health status. In all these categories, aside from the ODI, the outcomes at 12 months were compared to baseline, and any amount of improvement was considered a success by the Sponsor, although the clinically meaningfulness of any amount of change is unclear. In all of these categories, the investigational group had better success rates than the control group.

Additional secondary outcomes included patient satisfaction, perceived treatment effect by the subjects and the investigators, and work status. With the exception of work status, success rates in all of these categories were greater in the investigational group.

Radiographic assessments in this study included assessments related to spinous process erosions, spinous process fractures, sagittal plane angular motion, sagittal plane translational motion, disc height, disc/endplate changes, and implant location.

The original radiographic protocol required that the core lab assess the integrity of the spinous processes at the target level by observation for signs of fracture, erosion, sclerosis, or bony reactor change. The original radiographic protocol did not include a definition of spinous process erosion. A separate group of independent imaging core lab

radiologists developed criteria to assess the type, extent, and location of spinous process erosions and performed a supplemental review of positive erosion cases based on results from the original independent radiologic reviewers in order to classify the bony changes of the spinous processes that occurred after implantation.

Two categories were developed by the radiologists: mechanical contour change and inflammatory erosion. It should be noted that the classification criteria shown were based on observations noted in the Sponsor's imaging studies. These classification criteria were created by the Sponsor, and the adjudication of the data was conducted by the Sponsor. The Agency is not aware that this classification scheme has been validated.

The majority of the erosions involved in the DIAM bone --

(Off microphone comments.)

DR. ADEGBOYEGA-PANOX: Spinous process bone erosions were noted starting at the 3-month postoperative follow-up assessment and occurred more frequently in the superior spinous process compared to the inferior spinous process. The non-cumulative rate of occurrence of spinous process erosion was noted to increase with time following implantation of the DIAM device up to 36 months. At the 36-month time point in the all-available dataset, 37.2% of subjects were observed to have had erosions of the superior spinous process while 15.1% of subjects were observed to have had erosions of the inferior spinous process. A total of 44% of subjects were observed to have had an erosion at either the superior or inferior spinous process or at both locations.

All erosions were characterized as mechanical, using the Sponsor's characterization definitions. However, explant analyses were available from four subjects and documented

a variety of findings in these cases, including polyethylene terephthalate fibers, particulates surrounded by fiberglass, foreign body giant cells, and fibrous connective tissue.

A chronic inflammatory host response consisting of macrophages as well as foreign body giant cells was reported as consistent with the generation of particulate debris by wear mechanisms in arthroplasty.

Spinous process erosions were also characterized in terms of magnitude and location. The majority of erosions involved the DIAM bone spinous process interface and involved between 15% and 30% of the spinous process area at all time points.

This table compares all overall success between those subjects who were observed to have had spinous process erosions and those that did not, at 12, 24, and 36 months. At 12 months, a slightly lower 12-month overall success rate was observed in those subjects with spinous process erosions. Lower success in the subjects with spinous process erosions was also present at 6 weeks.

This table demonstrates the non-cumulative observed spinous process fractures over time in the all-available dataset.

This table reflects the spinous process fractures in the primary dataset at 12 months, as observed by the core laboratory and as reported on case report forms by the investigators. Of note, there is a considerable discrepancy between these numbers, and only one of the fractures was identified by both the core laboratory and the investigators.

Of the 14 fractures identified by the core laboratory, all were located in the superior spinous process. Approximately half, or 57.1%, were considered displaced. The majority, or 85.7%, had the primary fracture line posterior to the interface between the spinous process

and the investigational device. Overall success at the last available time point was observed in 9 of these 14 subjects.

At each evaluation, the angular range of motion was obtained. The angular range of motion was determined using later flexion-extension radiographs and is defined as the absolute value of the angular difference between flexion and extension. Results of angular motion obtained at the index and at the superior and inferior adjacent levels were averaged to obtain the resulting value reported.

The mean angular motion results with subjects in the primary analysis dataset through 24 months are shown in this table. At 6 weeks and 3 months, DIAM subjects were reported to have a significant decrease in angular range of motion of 2.28 degrees at 6 weeks and 1.49 degrees at 3 months, although the mean results at longer time points appear to be numerically similar compared to baseline for DIAM subjects. No decreases at 6 weeks and 3 months were reported for the mean angular motion of the control group.

Translational motion was also determined at each time point. At 6 weeks, the DIAM subjects were reported to have had a decrease in translational motion of 0.3 mm, although the mean results at longer time points appeared to be numerically similar to baseline for the DIAM subjects. No decrease at 6 weeks was reported for mean translational motion of the control group, and results were similar through 24 months.

There were no reported differences in disc height or disc/endplate changes between the two groups. No migrations of the DIAM implant or crimps were reported.

I would now like to introduce Dr. Ying Yang --

(Off microphone comments.)

DR. ADEGBOYEGA-PANOX: In summary, the DIAM subjects reported better outcomes as compared to the control group in the primary and secondary effectiveness assessments. The DIAM subjects reported better outcomes as compared to the control group in the other endpoints, with the exception of work status, which favored the control group.

Spinous process erosions and spinous process fractures were observed in DIAM subjects throughout the course of this clinical trial. The sagittal plane angular and translational motion results identified short-term reduction in motion for DIAM subjects at 6 weeks and 3 months, which returned to baseline over time. No differences in disc height, disc/endplate changes were observed between the two groups. No DIAM migrations were reported.

The Agency will be asking the Panel a voting question on whether a reasonable assurance of effectiveness has been demonstrated for the PMA device for its proposed intended use.

I would now like to introduce Dr. Ying Yang who will present the statistical summary.

DR. YING YANG: Good morning. My name is Ying Yang. I'm a mathematical statistician in the Division of Biostatistics. I will present the FDA statistical review of this PMA application.

In this presentation, I will talk about the study design and the study results for the effectiveness endpoints.

As described previously, the study was designed as a randomized superiority study. Subjects were randomized at a ratio of 2:1 for DIAM to nonoperative control. Subjects in

the DIAM group could also receive the aforementioned nonoperative treatments. Therefore, the effect of a DIAM could be confounded with the effects of a nonoperative treatments. Subjects in the nonoperative control group were allowed to cross over to DIAM or other surgical device after the completion of 6 months of treatment. Subjects were followed at 6 weeks, 3, 6, 12, and 24 months, and annually thereafter. The study subjects and the personnel were not blinded to treatment assignments.

As described previously, the primary study endpoint as shown here was used to determine overall success.

The study hypotheses were to test whether DIAM was superior to the nonoperative control in terms of overall success rate at 12 months. The study was analyzed using a Bayesian approach, and superiority could be claimed if the posterior probability that the difference in the overall success rates between the DIAM and a nonoperative control was greater than zero, given the data is at least a 95%.

204 subjects in the DIAM group and 102 patient subjects in the nonoperative control group were required to demonstrate the superiority, based on the following assumptions. The true overall success rates are 60% for DIAM group and 40% for the nonoperative control group. The one-side significance level is 5% and the power is 90%; the attrition rate is 15%.

No interim analysis was planned at the IDE stage; however, the Sponsor requested to add an interim analysis in June 2013. The interim analysis plan was approved by the Agency in July 2013.

The interim analysis included the first 150 subjects who were treated and had

reached the 12-months follow-up with at least one post-treatment overall success evaluation at or after 6 weeks. After taking into account the multiple looks where maintaining overall Type 1 error rate at 5%, the superiority of a DIAM could be claimed if the posterior probability that the difference in overall success rates between the DIAM and the nonoperative control was greater than zero, given the data is at least 97.5% at the interim and the final analysis. Enrollment continued as originally planned at the time the interim analysis plan was approved.

This PMA is based on the interim analysis, which included the first 150 subjects who were treated and had reached 12 months of follow-up with at least one post-treatment overall success evaluation at or after 6 weeks. 207 subjects were randomized to a DIAM group, and 181 of them were treated. 104 subjects were randomized to the nonoperative control group, and 101 of them were treated. The Sponsor defined an all-available dataset, which included the subjects who were treated and had at least one post-treatment evaluation. Three subjects in the nonoperative group did not complete their treatments; therefore, 181 subjects from DIAM group and 97 from nonoperative control group consisted of the all-available dataset. Among 97 subjects in the nonoperative control group, 59 of them crossed over to DIAM after finishing 6 months of treatment.

The primary analysis and the hypothesis testing were based on the primary analysis dataset. It included the first 150 randomized and treated subjects who had reached a 12-month follow-up with at least one post-baseline overall success status evaluation. 97 subjects from DIAM group and the 59 subjects from nonoperative group were included in the primary analysis dataset. Among 59 subjects in the nonoperative group, 23 of them

crossed over to the DIAM after 6 months of treatment.

The most frequent reason for not being treated after randomization was the subjects did not meet the inclusion/exclusion criteria according to the new information.

The primary analysis, based on the primary analysis dataset, missing data, for example, ODI score, neck pain, back pain, etc., due to loss to follow-up or crossover in the primary dataset, followed the following rules:

- Last observation carried forward approach was used to impute the missing data due to loss to follow-up;
- Last observations before the first surgical treatment were carried forward for nonoperative control subjects who crossed over to receive surgical treatment at the index level;
- DIAM subjects who received additional surgical procedure or intervention were considered as failures; their last observations before additional surgical treatment were carried forward.

As I showed earlier, 64% of DIAM subjects achieved overall success, compared to 15% of the nonoperative control subjects in the primary analysis dataset at 12 months. The superiority of DIAM could be claimed. For the individual components, 69% of DIAM subjects achieved ODI success, while 17% of nonoperative control subject achieved ODI success.

Moreover, more nonoperative control subjects experienced treatment-related serious adverse events. Similar results were obtained for the all-available dataset. Since the subjects in the DIAM group could also receive nonoperative treatments, the potential

confounding effect of a nonoperative treatment in the DIAM group cannot be differentiated. Consequentially, we ask the Panel to interpret these results with caution.

To assess the impact of the last observation carried forward approach and the subjects who were randomized but not treated, the overall success rate intent-to-treat analyses are shown here for the primary analysis dataset and all-available dataset. Subjects who were lost to follow-up and subjects who were randomized but not treated were considered as failures. For the crossover subjects, the overall success status in Month 12 was based on observed ODI at that time point. Superiority of DIAM was achieved in all four analyses.

We ask the Panel take into account the potential sources of bias in this study when you interpret the study results. These potential sources of a bias include:

- Non-adherence of randomization;
- The confounding effect of DIAM subjects being able to receive nonoperative treatments;
- The use of a nonoperative treatment that may have been utilized by a subject prior to study enrollment;
- The absence of blinding of investigators and subjects; and
- Observer and reporter bias.

In summary, the effectiveness and the results show subjects in the DIAM group had a statistically significantly higher overall success rate as compared to the control group. However, these results should be interpreted with caution due to the potential sources of a bias and other observations about to be presented.

Now, I would like to turn this presentation back to Dr. Elizabeth Panox.

DR. ADEGBOYEGA-PANOX: I will now present observations noted by the Agency that impact the ability to interpret the results of this study and will then present a benefit-risk assessment of the DIAM investigational device.

First, I will present some observations related to the study population.

Heterogeneity.

This clinical trial was intended to enroll subjects with moderate low back pain secondary to lumbar degenerative disc disease. This patient population may potentially include subjects with various types of disc displacement abnormalities commonly referred to as herniated discs, spinal stenosis, facet joint degeneration, degenerative spondylolisthesis, and mixed types of degenerative spinal pathologies.

As these different spinal pathologies lead to specific clinical syndromes which vary with respect to natural history, prognosis, and standard of care approach to surgical treatment, a population that includes these different spinal pathologies is heterogeneous. Heterogeneity was also introduced into the study population by the inclusion of subjects with single-level and multi-level pathology, subacute and chronic duration of symptoms, and new onset and recurrent symptoms.

Data with regard to the different diagnostic subgroups were not collected during the trial. In response to the Agency's request to stratify the results of the study population into clinical subgroups, the Sponsor conducted a post hoc analysis using subject pretreatment MRI imaging data only to stratify subjects according to different types of spinal pathology. Clinical diagnostic data, which could be used to assist in identification and definition of

these subgroups, was not collected.

This table demonstrates the distribution of the different diagnostic subgroups in the primary analysis dataset and the all-available dataset. The Agency has concerns with establishing poolability of the subgroups by outcomes alone, and consequently, the outcomes by subgroup are not shown. Despite the limitations of the post hoc analysis, this table illustrates that there was heterogeneity in the composition of the study population.

The Agency also identified postoperative diagnoses documented in the operative reports that extended beyond degenerative disc disease or low back pain, with or without reported annular tears, and described diagnoses including disc herniation, spinal stenosis, spondylolisthesis, and facet pathology.

These reported observations also indicate heterogeneity in the composition of the study population. In some cases, the extent of spinal pathology identified in the operative reports appears to exceed that of the targeted population.

The Agency is asking for the Panel to provide input on the following concerns: ODI severity. The rationale provided by the Sponsor for proposing a moderate back pain population for the investigational device was that spinal disease in these subjects was not sufficiently severe to warrant a standard of care surgical intervention such as lumbar fusion or total disc arthroplasty.

The Sponsor identified a threshold for study entry, which included an ODI score greater than or equal to 30 and a pain score greater than or equal to 8. The literature describes ODI scores in the range of 20 to 40 as representing a moderate population. However, investigational subjects entering into this clinical trial had a mean ODI score of

49.1, and control subjects entering into this trial had a mean ODI score of 49.9.

The Agency conducted a post hoc analysis to determine the proportion of subjects falling into a particular ODI score range during enrollment in this IDE trial. As shown in this table, approximately 65% of subjects in the primary analysis dataset and the all-available dataset in both the investigational and nonoperative control cohorts had an ODI score greater than 40 at the time of enrollment. Furthermore, nearly 25% of subjects had an ODI score that was greater than 60 at study enrollment.

This suggests that the study enrollment included subjects that did not have moderate pathology, despite the Sponsor's target population. Moreover, these ODI scores of enrolled subjects are more consistent with scores reported in the literature as severe pathology, for which surgical treatments such as spinal fusion and total disc arthroplasty may be considered.

Post-treatment surgical interventions. Review of the post-treatment surgeries that occurred in this study further demonstrate heterogeneity and concerns about the severity of pathology in the study population. Specifically, some of the investigational and nonoperative control subjects were subsequently treated with surgery at adjacent levels or surgery involving more than one spinal level.

This suggests the study enrollment was not adequately conducted to isolate the target population of moderate low back pain at a single symptomatic level as subjects may have had multi-level disease upon entry into the clinical trial. The varied nature of the secondary surgeries and treatment surgeries is suggestive, in itself, of heterogeneity in the composition of the study population, for example, discectomies indicated for the treatment

of radiculopathy, a distinct clinical syndrome. In contrast, interbody fusion, posterolateral fusion, and total disc replacement, according to the Sponsor, are typically considered for more advanced stages of degenerative disc disease.

The screening algorithm. The screening algorithm for the IDE study attempted to identify potential subjects with low back pain secondary to single level moderate degenerative disc disease with or without radicular pain, with current episode of less than 1-year duration. However, it remains unclear that the screening protocol adequately identified a clinically discrete population.

For example, it is unclear how the symptomatic level was identified in subjects with multi-level degenerative disc disease and/or facet joint degenerative changes diagnosed on radiographs or MRI scans and how such subjects were either included or excluded from participation.

The proportion of the identified population who experienced subacute low back pain versus chronic low back pain remains unclear. The study screening algorithm did not specify whether the subjects included in the study were subjects who experienced a first-time episode of low back pain in the absence of prior episodes of low back pain, subjects with a history of chronic low back pain who experienced a recurrent back pain episode within 1 year of study entry, or a mixture of these groups. As populations with recurrent back pain differ from populations with a primary episode of low back pain, this information is important for interpretation of the study data.

I will now present some observations related to the nonoperative control and nonoperative therapies.

(Off microphone comments.)

DR. ADEGBOYEGA-PANOX: The Agency will be asking the Panel to comment on the study population and the effect of the observations noted on the interpretation of the study results.

I will now present some observations related to the nonoperative control and nonoperative therapies.

Heterogeneity of the nonoperative control treatment. Subjects in the nonoperative control group were provided with variable combinations of nonoperative therapies as well as different intensities and durations of treatment. There was no limit to the amount of nonoperative treatment that could be received. In addition, there was a lack of information collected regarding the details of the nonoperative therapies prescribed in this clinical trial. These observations suggest that there was heterogeneity in the nonoperative control treatment.

The potentially confounding effect of nonoperative treatment in the investigational group. Subjects randomized to the DIAM device group were allowed to undergo elements of the same nonoperative treatment as the control group, at the discretion of the investigator. Details of the nonoperative therapy for the investigational subjects was incompletely collected. As a result, the effect of the DIAM device is potentially confounded with the effect of these nonoperative treatments and cannot be determined because of the lack of information. This limits the comparability of safety and effectiveness in the outcomes between the investigational and the nonoperative control groups.

The potentially confounding effect of non-study treatment. All study subjects, both

investigational and control subjects, were free to pursue nonprescription therapies, such as massage and acupuncture, in addition to the treatment provided by the study therapies in each group. Details of these non-study, nonoperative therapies were not collected for the investigational subjects.

The effects of the DIAM investigation device and the nonoperative study treatments in the control group are potentially confounded with the effect of these non-study treatments, cannot be determined because of the lack of information. This limits the comparability of safety and effectiveness outcomes between the investigational and the nonoperative control groups.

The success rates of the control group observed. The overall success rate of the nonoperative control group at 12 months was reported to be 15.1% in this trial. A systematic review of studies comparing surgical and nonsurgical treatment of discogenic back pain conducted by Mirza and Deyo concluded that there was a modest difference between surgical and nonsurgical treatments for discogenic back pain with regard to function outcomes at 1 and 2 years. This contrasts with the large difference in overall success reported in the current study between the DIAM investigational surgical device and nonoperative treatments.

The limitations associated with a one-directional crossover study design. Investigators could consider the implantation of the DIAM device as a treatment option for nonoperative control subjects who had a demonstrated medical need for additional treatment after the completion of the initial 6 months of nonoperative care, if certain criteria were met.

The rates of crossover in the study were 60.8%, which is more than half of the nonoperative control subjects. This crossover rate resulted in a control group that was significantly smaller than the original 2:1 randomization. The Agency's concerned this crossover rate limits the ability to determine differences between the investigational and control treatments and reduces the effective randomization in this IDE clinical trial.

Due to the proportion of subjects in the nonoperative control group that crossed over to the DIAM investigational group, the estimate of the treatment effect may be biased. Consequently, the treatment difference is unclear and should be interpreted with caution.

Not all nonoperative control subjects eligible to cross over to the DIAM investigational group actually did so. And it remains unclear to the Agency if there were specific factors that contributed to the decision of those subjects who elected to cross over as compared with those that did not. A few subjects who did not meet the criteria also crossed over. The Agency will be asking the Panel to comment on the nonoperative control group and nonoperative therapies and the effect of the observation noted on the interpretation of study results.

I will now present some observations related to the study endpoints and time points for assessment.

Clinical literature reports that although the DIAM device increased spinal canal size, intervertebral foramen sizes, local kyphosis, and posterior disc height at implanted segments immediately after surgery, these parameters returned to their preoperative levels during follow-up, starting at 12 months after surgery.

It has also been reported in the literature that the greatest mean improvement in

back and leg pain function occurred around 3 months following surgery involving the DIAM Spinal Stabilization System, beyond which a trend for gradual deterioration occurred.

Nonoperative control subjects who received surgical treatment were not automatically deemed failures for overall success. Rather, ODI scores before surgery were carried forward to determine overall success status.

In the context of the proposed target population, as well as the Agency concerns pertaining to the study population and nonoperative control group, it is unclear if the definition of the primary effectiveness endpoint and the assessment of overall success at 12 months are adequate.

The Agency will be asking the Panel to comment on study endpoint and time point for assessments and the effect of the observations noted on the interpretation of the study results.

I will now present some observation related to the implantation of the DIAM device. The surgical technique for the DIAM implant directs surgeons to preserve the ligamentum flavum, apophyseal joint capsules, and the supraspinous ligament, and consider resection of lamina or spinous process only in the situation where these structures are overlapping or hypertrophic and resection is required to insert the DIAM implant.

According to the Sponsor, the DIAM device serves as a primary treatment for spinal pathology at the index spinal level, and no direct surgical decompression of the dural sac or spinal nerves is included in the study protocol. However, in certain investigational subjects, the operative notes as summarized by the Sponsor describe soft tissue and bone resections that could potentially be considered a spinal decompression.

Example terms from the operative notes are shown on this slide. Based on the descriptions noted here, it is unclear if the DIAM Spinal Stabilization System served as a primary therapy or rather as a surgical adjunct to spinal decompression in subjects whose surgical treatment included removal of laminar bone, spinous process bone, or ligamentum flavum during the insertion of the device.

It remains unclear whether an observed positive treatment effect is attributable to the use of the device, the resection of bone or soft tissue during implantation of the device, or a combination of these factors.

The Agency will be asking the Panel to comment on the significance of these soft tissue and bony resections and the impact of the observations on the interpretation of study results.

I will now present some observations related to the radiographic outcomes.

The Agency understands that the DIAM Spinal Stabilization System is dependent on the integrity of the spinous processes to produce this treatment effect. Accordingly, it is reasonable to consider that a facture or erosion involving the spinous process at the operative level would impact the safety and effectiveness of the device.

Spinous process erosions were observed as early as 3 months and increased in magnitude and number over time. The majority of these erosions were observed at the superior spinous process. At 36 months, 44% of subjects were observed to have had an erosion at either the superior or inferior spinous process or at both locations. Post hoc analyses comparing outcomes in subjects with and without erosions were conducted by the Sponsor, and the Sponsor concluded that these radiographic findings have no clinical

relevance.

Please note that the classification criteria previously described were based on observations noted in the Sponsor's imaging studies, were created by the Sponsor, and the adjudication of the data was conducted by the Sponsor. The Agency is not aware that this classification scheme has been validated. While the Sponsor characterized all spinous process erosions as mechanical in nature, explant analyses demonstrate a chronic inflammatory response.

Spinous process fractures. From the Agency's perspective, the clinical significance of the observed spinous process erosions remains unclear. Spinous process fractures were observed in subjects treated with the DIAM device. The incidence of spinous process fractures was reported by the investigators and independent radiologists, and the findings were discrepant.

The findings of location, displacement, and healing of the fractures were not included in the study protocol and were developed post hoc by a consultant radiologist, who provided training for the core laboratory radiologists. The use of this methodology for characterizing the fractures potentially introduces bias.

Published literature suggests that plain radiographs may lack sensitivity for detection of spinous process fractures. Consequently, the Agency is concerned that the Sponsor may not have captured all spinous process fractures with their current imaging procedures, which relied primarily on plain radiography.

Sagittal plane angular and translational motion. According to the Sponsor, the investigational device is intended to provide stability during flexion and extension motions,

and the device is designed to stabilize yet preserve motion at the treated level. The DIAM device appears to have a transient effect with sagittal plane angular motion reduced in the investigational group at only the 6-week and 3-month time points. Similarly, sagittal plane translational motion in the investigational group was reduced at only 6 weeks but becomes similar to baseline and the nonoperative control group at subsequent follow-up time points.

These data regarding sagittal plane angular and translational motions suggest that an initial motions restriction provided by the DIAM device is subject to degradation over time. In addition, the results reported for sagittal plane angular and translational motion are likely within the range of measurement error for this radiographic data.

The Agency will be asking the Panel to comment on the radiographic outcomes and the effect of these observations noted on the interpretation of study results.

I will now present the Agency's assessment of the benefit-risk profile of the DIAM investigational device. When making a determination of the benefit-risk profile of a device, the Agency considers benefits, including the type of benefits, the magnitude of benefits, the probability of a patient experiencing one or more benefits, and the duration of the effect; risks, including the types, number, and rates of harmful events associated with the use of the device (device-related serious, device-related non-serious, and procedure-related adverse events), the probability of a harmful event, and the duration of a harmful event; additional factors are also considered in the benefit-risk assessment, including uncertainty, characterization of the disease, patient tolerance for risk and perspective on benefit, availability of alternate treatments, risk mitigation, postmarket data, and novel technology addressing unmet needs.

In general, the primary, secondary, and other effectiveness assessments favored the DIAM investigational device, with the exception of work status. These benefits should be interpreted in the context of the additional benefit-risk considerations to be discussed.

Over the course of the study, risks were identified. These risks should be interpreted in the context of the additional benefit-risk considerations that will be discussed. The overall rate of any serious adverse event in the primary analysis dataset through the 12-month post-treatment with DIAM was numerically higher compared to the nonoperative control. The overall rates of any serious adverse event in the all-available dataset through 12 months post-treatment with the DIAM was numerically higher compared to the nonoperative control. Superior spinous process fractures were observed by the core laboratory in 7.7% of the DIAM subjects in the all-available dataset at 12 months post-treatment. Forty-four percent of subjects were observed to have had an erosion at either the superior or inferior spinous process or both locations at 36 months.

The following issues raised by the Agency should be considered in assessing the benefits and risks just presented:

- The study population;
- The nonoperative control group and nonoperative therapies;
- The study endpoint and time point of assessment;
- The role of the DIAM device as a primary treatment versus adjunctive therapy with direct spinal decompression;
- The radiographic outcomes of spinous process erosion, spinous process fracture, sagittal plane angular and translational motion;

- The adverse event presentation and results;
- The method of data collection analyses, for example, the use of unvalidated assessment instruments and incomplete collection of data.
- Other considerations that should be taken into account when assessing the benefit-risk profile are the limitations of a post hoc analysis, the lack of clinical equipoise between the treatment cohorts, sources of bias, and subjectivity of some of the assessment tools.

The Agency is seeking Panel input on the impact of the additional factors described above on the interpretation of the safety and effectiveness results in this clinical trial. The Agency will also be asking the Panel a voting question on whether a favorable benefit-risk has been demonstrated for the PMA device for its proposed intended use.

I would now like to introduce Nadine Sloan, who will present the post-approval study considerations.

MS. SLOAN: Good morning. My name is Nadine Sloan. I'm a biomedical engineer. I'm the epidemiology reviewer of this PMA submission within the Division of Epidemiology, Office of Surveillance and Biometrics. I will be presenting the post-approval study (PAS) considerations.

Before I begin, I would like to remind the Agency -- or I would like to remind everyone of the following. The discussion of a PAS prior to FDA determination of device approvability should not be interpreted to mean FDA is suggesting that the device is safe and effective. The plan to conduct a PAS does not decrease the threshold of evidence required by FDA for device approval. And last, the premarket data submitted to the Agency

and discussed today must stand on their own in demonstrating a reasonable assurance of safety and effectiveness and an appropriate benefit-risk balance.

Based upon the Agency's review of the premarket study data, should the DIAM device be approved, the Agency believes it will be necessary to evaluate the long-term safety and effectiveness of the device compared to a clinically appropriate control or controls, particularly taking into account the radiographic findings as presented earlier by Dr. Panox.

Specifically, the Agency has identified the following that may need to be assessed in a PAS for the DIAM device:

- Address concerns related to spinous process erosions observed to increase in magnitude and number over time in the premarket study by evaluating the incidence of spinous process erosions long-term, their relationship to adverse events, and the possibility of a corresponding diminishing effectiveness;
- Address concerns related to the true incidence of spinous process fractures reported through 60 months in the premarket study by evaluating the incidence of spinous process fractures long term, their relationship to adverse events, and also the possibility of a diminishing effectiveness; and additionally
- Address concerns related to a possible transiency in motion restriction, whereby in the premarket study, sagittal plane angular and translational motion returned to baseline after 3 and 6 months, by evaluating motion restriction as well as corresponding clinical outcomes associated with the

DIAM device long-term.

Next I'd like to briefly mention the main elements of the Sponsor's single proposed post-approval study.

The Sponsor proposed to conduct an extended follow-up of the premarket study, with a study objective to estimate the 5-year overall success rate as defined within the IDE study. Secondary objectives are to estimate the success rates of individual effectiveness endpoints and neurological success rate at 5 years and to estimate the event rates of adverse events and secondary surgery at the index level through 5 years.

The Sponsor has proposed to enroll up to 100 subjects that were previously enrolled in the premarket study. The sample size was not statistically determined. DIAM as well as crossover subjects with less than 60 ± 3 months follow-up after DIAM surgery are proposed for enrollment, with a follow-up duration of 5 years upon receiving the DIAM device.

Since the original control subjects are not planned to be followed, statistical analysis will be limited to descriptive statistics of the treatment groups at 5 years. No inferential statistical comparisons between the treatment groups are proposed as there is no hypothesis being tested. Survival analysis will be conducted to estimate the event rates for the adverse events and secondary surgeries at the index level.

The Agency has identified concerns with the Sponsor's proposed extended follow-up post-approval study, and these stem from concerns with the IDE premarket study. These have been discussed in detail by the FDA review team and with regard to the Sponsor's proposed PAS, include concerns related to the following:

- Heterogeneity in the study population that may impact the ability to study a

homogenous target population for meaningful long-term evaluation of the device;

- Study confounders associated with treatment non-uniformity that may impact the ability to assess the long-term treatment effect of the device;
- Lack of comparison to a control, which may limit the ability to analyze the long-term results of the device; and additionally
- Reliance on plain films for evaluation of spinous process integrity, though the clinical literature reports under-detection with this imaging modality compared to other imaging techniques such as CT.

During initial review of the PMA, and in light of the premarket study design concerns, FDA interactively expressed concerns to the Sponsor regarding their proposed continued enrollment study and recommended a new enrollment PAS that would include a more homogenous target population as well as an appropriate control or controls for evaluation of clinically relevant safety and effectiveness endpoints, including bony erosion and spinous process fracture over an extended follow-up period.

Taking into consideration the Agency's concern with the Sponsor's proposed continued follow-up study, we will be asking the Panel to comment on the adequacy of the Sponsor's proposed PAS. If the Panel does not believe the Sponsor's proposed PAS is adequate, the Agency will be requesting specific feedback toward developing a PAS, including comment on the appropriate study population, control group or control groups, the duration of follow-up, and the overall study design that is deemed necessary for developing an appropriate PAS for the DIAM device.

This concludes my presentation of the postmarket study considerations. And thank you. This concludes the Agency presentations, and we're now available to answer any questions the Panel may have.

DR. RAO: Thank you.

I would like to thank all the FDA speakers for their presentation.

Does anyone on the Panel have a question for the FDA? Yeah, Dr. Smith.

DR. SMITH: Regarding the primary analysis dataset, could you please remind me how infection was defined? There was a 12.4% infection rate in the surgical group, and I don't recall if that's a surgical site infection or if it included postop urinary tract infections or something else of that nature. It was on page 17, Slide 51, serious adverse events.

DR. ADEGBOYEGA-PANOX: This is Elizabeth Panox.

Infections were classified using the CDC protocol for classifying infections.

DR. SMITH: So they were all surgical site infections?

DR. ADEGBOYEGA-PANOX: Yes.

DR. SMITH: Thank you.

DR. GRAF: To follow up on that question, I had the same question. It actually is classified in Medtronic's data, if you go back, which was not presented, that it was broken down into other non-wound infections and then surgical site infections. Because it does appear to be much lower than is represented on the FDA's presentation of the percentage of actual infections.

DR. FINNEGAN: My question has --

DR. RAO: Dr. Finnegan, please, if you could announce your names before you ask

your questions, the transcriptionist will have an easier time with that.

DR. FINNEGAN: Sure. Maureen Finnegan.

My question has to do with the definition of SAEs. I don't mean this to sound as obnoxious as it's going to sound, but in my world, we'd have to have two more classifications, very serious adverse events and really, really serious adverse events. So it's my understanding that you classify what's a serious adverse event. Do you do it differently for every project, or do you have the same definitions for all projects?

DR. ADEGBOYEGA-PANOX: The definitions for adverse events are usually pre-specified in the protocol, and we do have guidance with regard to that. But guidance is not binding.

DR. FINNEGAN: Because your control group had more serious adverse events than your surgical group, which the surgeons love, but that doesn't actually really make sense.

DR. ADEGBOYEGA-PANOX: That's correct.

DR. RAO: Dr. Yang, please.

DR. LYNDA YANG: Lynda Yang. Along in the same vein, it says that neurological and spine events are two of the biggest categories here. What's the -- what are some of these? I tried to find it in the information that we were given, but what are these neurological events? I mean, there's a big difference between a slight, you know, numbness and tingling versus death, which both could be neurological, I suppose. And then spine events, I just don't know what that means.

DR. ADEGBOYEGA-PANOX: I'll probably have to get back to you after the break to give you -- we do have pre-specified definitions that Sponsor had in their protocol.

DR. RAO: Mr. Melkerson.

MR. MELKERSON: I just want to point out the slide that you're referring to, if I'm not mistaken, was presented by the Sponsor, so some of these questions may actually be better answered by the Sponsor.

DR. RAO: Dr. Golish.

DR. GOLISH: We will get to Slide Number 87 from Dr. Yang's presentation, overall success at 12 months. So to get to Mr. Melkerson's point, is this the FDA analysis? Because the previous slide says Sponsor's Results. So is that the FDA's results and analysis of the Sponsor's data?

DR. YING YANG: Yes. That's based on the Sponsor's results.

DR. GOLISH: Yeah. And so, just to clarify, you agree that with ITT analysis for all four of these data subsets, the results are statistically significant with your cutoff criteria, even though the effect sizes are smaller than the Sponsor's analysis? These are all significant.

DR. YING YANG: Yes.

DR. GOLISH: Okay. Thanks.

DR. YING YANG: They are for all the -- can be claimed for all the four analyses.

DR. GOLISH: Okay. Yeah, thanks.

DR. RAO: Dr. Blumenstein.

DR. BLUMENSTEIN: So this is Brent Blumenstein.

I want to know the basis of the first line here, where it says the primary analysis dataset, 150 subjects. As I'm interpreting this table, you're classifying that as an ITT analysis?

DR. YING YANG: That is a -- in order to gather these 150 subjects, the Sponsor had a cutoff date to gather that dataset. So that's including 167 subjects, which included 17 patients who were not included in the primary analysis because they were randomized but not have post-start evaluation data.

So the ITT here means, there's two things, one, the last observation carried forward approach was not used. We based it on the ODI, observed ODI, the 12 months, to evaluate the overall success status. That's one thing. Another thing, we want to include the patients who were randomized but not treated into the analysis.

DR. BLUMENSTEIN: But the primary -- the 150 subject line in this table excludes subjects who did not receive the study intervention; is that correct?

DR. YING YANG: Yes.

DR. BLUMENSTEIN: So that's not an ITT analysis, not by any stretch of the imagination, in my book. Is that correct? I mean, do you agree with that, or are you calling that an ITT analysis?

DR. YING YANG: Here, ITT are more for the 150 subjects. The ITT more refer to the patients who did not have ODI at 12 months but have missing data we can -- or cross over, based on the observed at the 12-month evaluation.

DR. BLUMENSTEIN: But I'm trying to get at the patients included in the analysis. And so the 167, I can see where you could argue that that would resemble an ITT analysis because you have patients who did not receive -- who were randomized but did not receive the intervention, study intervention, are included in that analysis; is that correct?

DR. YING YANG: Yes.

DR. BLUMENSTEIN: But the 150, as I understand it from what I've read, that those are the patients who had the intervention, the first 150 patients, who actually had the intervention. And therefore I don't know how you can classify that as an ITT analysis.

DR. YING YANG: Yeah. I agree that in some sense, it's not a strict ITT analysis. But here, though I just put it there, just for one thing, say that for the crossover patients, we used the ODI, observed ODI at 12 months to determine their overall success status at 12 months, just in that sense.

DR. BLUMENSTEIN: Yeah. Well, I mean, that's another issue. But I'm just trying to get at the inclusion, the inclusion criteria. So you're calling -- I'm trying to figure out if you're calling that first line an ITT analysis or not.

DR. YING YANG: Strictly speaking, no. But here I just considered as a modified ITT. Yeah, that I consider as a modified ITT.

DR. BLUMENSTEIN: Okay. Well, I've always figured that -- all right. Thank you.

DR. RAO: Dr. Golish?

DR. GOLISH: Just to follow up on Dr. Blumenstein's point, do you agree that the last line, all randomized subjects, would be perhaps closest as to what is conventionally considered an ITT analysis and what we understand has been presented?

DR. BLUMENSTEIN: Well, I mean, I have a real problem with eliminating patients who were randomized, period, end of story. I mean, I worship at the altar of randomization, and to me, a violation like that just in no way should have the term ITT associated with it.

DR. GOLISH: Yes, sir. May I -- does FDA agree that if you were to do a true full ITT

analysis on a randomized two-arm superiority trial with one-way crossover, that that would be a estimator reasonably biased towards the null hypothesis and therefore some kind of a worst-case analysis? Does that question make sense?

DR. YING YANG: Yes. We do have a worst-case analysis in the backup slide. We can show that in the afternoon.

DR. GOLISH: So that's what we're trying to get at here.

DR. RAO: Just a quick question. I think I know the answer, but one of your slides, you mentioned four spinous process fractures noted by the core lab and one by the investigator in the control group. I presume all five of these were control patients who had crossed over?

DR. ADEGBOYEGA-PANOX: Those, yeah. Those are crossover patients.

DR. RAO: Those are all crossover? So that shouldn't really be -- I don't know why it should be -- you know, it doesn't make too much sense to put it in the control group.

I don't know if this is appropriate to ask, but you talked about primary versus adjunct treatment, of the use of the device as a primary device for primary treatment versus an adjunct treatment to a secondary surgical procedure in the spine. And I don't know whether it was you or the Sponsor that talked about the extensive use of this device in Europe prior to the submission of this study. So I just did a quick search, and in Europe, I believe it's being used as an adjunctive device. Did you have any thoughts on that, or should that be better addressed by the Sponsor?

DR. ADEGBOYEGA-PANOX: I think -- I have not reviewed the data. I have read some of the literature. So I think probably the Sponsor.

DR. RAO: Mr. Melkerson.

MR. MELKERSON: The indication for use is not as an adjunct, if I'm understanding correctly. I defer to the Sponsor, but I believe that your indication was not as an adjunct.

DR. RAO: In this study here, you mean?

Dr. Finnegan.

DR. FINNEGAN: Maureen Finnegan.

Can you clarify, for Slide 66, Dr. Panox, every so often you have spinous erosions. Are those new ones or at each interval, or are they, in fact, the same number and some have healed?

DR. ADEGBOYEGA-PANOX: This is Elizabeth Panox.

It's non-cumulative.

DR. FINNEGAN: I'm sorry?

DR. ADEGBOYEGA-PANOX: It's on the --

DR. FINNEGAN: Is each interval a new set of erosions, or are those the same numbers you're looking at and some of them have healed so the number's gone down?

DR. ADEGBOYEGA-PANOX: For the erosions?

DR. FINNEGAN: Yes.

DR. ADEGBOYEGA-PANOX: No. It's cumulative. It's non-cumulative, sorry, at each time point.

DR. RAO: Mr. Melkerson.

MR. MELKERSON: I believe, if you're looking at the number going down, not all the patients had gotten out to 48 or 60 months. So the number that is shown is what was

reported at that time point, and the numerator is not necessarily the same out throughout the 60 months.

DR. RAO: In the FDA analysis of the preclinical biomechanical testing studies, was there any testing that was done to determine where the wear particles may be coming from? Were they -- was all the testing restricted to the device itself, to the body of the device? Or was there any testing that could determine whether there was any fraying, fretting at the junction between the cable and the device, or between the crimp and the cable, with movements?

MR. O'NEILL: I think the Sponsor would be better to answer that question.

DR. RAO: Thank you.

Dr. Topoleski.

DR. TOPOLESKI: Tim Topoleski.

To follow up, I had a similar question. The preclinical testing was all done prior to the start of the clinical investigation, correct? Was there any concern or question on the FDA's part about the tether itself? Because the tether is in tension, and the Sponsor did tensile fatigue, but they didn't, for example, do tensile creep, or examine the long term, any long-term effects of the tether, which also may be fraying against the bone. And maybe the Sponsor would be better, best to answer that later, but does the FDA have any information on that?

MR. O'NEILL: This device was originally tested in, I believe, 2005 and 2006. I was not the original reviewer. So I think the Sponsor would be best to answer that question in terms of concerns.

DR. RAO: Ms. Harmon.

MS. HARMON: Yes, excuse me. Monica Harmon.

Just a question for clarification on Slide 51, under the serious adverse effects. Under psychiatric disorders, can you clarify what those disorders were and if it was treatment related, or was there a underlying psychiatric disorder before the treatment?

DR. ADEGBOYEGA-PANOX: So these -- you're asking me to define what the psychiatric was?

MS. HARMON: Yes, please. Yes.

DR. ADEGBOYEGA-PANOX: So I can't do that because I don't have it here, but there is, there was definition in the categorization. We can give you that later.

MS. HARMON: Okay.

DR. RAO: Thank you.

Dr. Gilbert, please.

DR. GILBERT: Jeremy Gilbert.

Just to follow up with Dr. Topoleski's question, so I'm wondering maybe two points. First, in the animal study, was there any histology done of bone in immediate contact with the device to see what form of damage was going on? I didn't see any -- I see the particle studies in the rabbit, but I don't see if there was histology done to try to understand if abrasion of the implant against the bone was inducing damage to the bone and the inflammatory processes you describe with the clinical trial.

And then the second part is, in the post-approval study, is there any intent to retrieve devices and investigate them for damage, to identify potential long-term damage

modes that were not identified in this initial study?

MR. O'NEILL: Retrieval analysis can be a part of a post-approval study. And in terms of the animal study results and findings, I defer to the Sponsor to discuss that.

DR. RAO: I believe there was some histological analysis done in sheep, if I'm not mistaken. But the question I would ask you back is, do you think a sheep model would be adequate to test this, when the sheep's kind of like on four legs and the device is not really being subject to as much compression? It's more a distraction type mechanism between the -- so I defer to the biomechanics folks, you and Dr. Topoleski, to see if you have any thoughts on that.

DR. GILBERT: Well, certainly the mechanics are different, unless we all decide to walk on our hands and feet. I would still be interested to note sort of the damage that arises at the junction of the device and the bone, both in terms of what's going on with the device and in terms of what's going on with the bone, and comparing that to what we see in the clinical trial.

DR. RAO: Thank you. Any other questions for the FDA at this time?

Dr. Golish.

DR. GOLISH: On Slide Number 95, there's FDA observations about the study population ODI severity. I just wanted to clarify, was the FDA's thesis here that the ODI severity in the nonoperative control group is sufficiently high that they would be considered surgical candidates for some other surgical procedure? Did I understand that correctly, or was it something else?

DR. ADEGBOYEGA-PANOX: It's Elizabeth Panox.

Our position, with regard to the ODI, is that it reflects a population that is more severe than is indicated for this device.

DR. RAO: Dr. Trier, please.

DR. TRIER: Yes. This is Dr. Trier.

I'd like to ask the question of FDA, the study success criteria that are called out here and are used for the primary analysis and will be used for the determination of safety and effectiveness, is this the same set of success criteria that were approved by FDA at the time the IDE was approved?

DR. ADEGBOYEGA-PANOX: Yes.

DR. RAO: Dr. Cheng.

DR. CHENG: Just a question for the FDA as to whether or not the silicone in this device has been -- of the same material has been used in other FDA-approved devices. I'm thinking of the upper extremity, for example, the elbow and the forearm and wrist and hand.

MR. O'NEILL: I'm not intimately aware with non-spinal devices in terms of my review practice, so I don't know if the exact silicone was used in different devices. We can investigate that further for the afternoon.

DR. RAO: Well, any more questions?

(No response.)

DR. RAO: Well, thank you very much to the FDA as well as the Sponsors for very timely presentations.

We will now break for lunch. Panel members, please do not discuss the meeting

topic during lunch amongst yourselves or with any other members of the audience. We will reconvene in this room at exactly 1:00 p.m. I will ask that all Panel members please return on time. Please take any personal belongings with you at this time. The room will be secured by the FDA staff during the lunch break. You will not be allowed back into the room until we resume.

(Whereupon, at 11:58 a.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:02 p.m.)

DR. RAO: It is now 1:02, and I would like to resume this Panel meeting, if everyone could take their seat. Who are we missing? Dr. Cheng? Dr. Topoleski?

We will now proceed with the Open Public Hearing portion of this meeting. Public attendees are given an opportunity to address the Panel, to present data, information, or views relevant to the meeting agenda.

Commander Anderson will now read the Open Public Hearing disclosure process statement.

CDR ANDERSON: Good afternoon. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, 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 any company or group that may be affected by the topic of the meeting. For example, this financial information may include a company or a group'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 your 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. Thank you.

DR. RAO: For the record, we have received two requests to speak for today's meeting. Each scheduled speaker will be given 5 to 10 minutes to address the Panel. We ask that you speak clearly to allow the transcriptionist to provide an accurate transcription of the proceedings of this meeting. The Panel appreciates that each speaker remains cognizant of their speaking time.

The first speaker is Kevin Stevens. Mr. Stevens is Associate Director of Regulatory Affairs, DePuy Synthes Spine, speaking on behalf of the Orthopedic Surgical Manufacturers Association.

Mr. Stevens.

MR. STEVENS: Thank you. DePuy Synthes has paid for my travel to be here so I could speak on behalf of OSMA. I have no other disclosures.

Good afternoon. My name is Kevin Stevens, and I speak here today representing the Orthopedic Surgical Manufacturers Association, or OSMA. OSMA, a trade association with approximately 30 member companies, welcomes this opportunity to provide general comments at today's meeting of the Orthopaedic and Rehabilitation Devices Panel.

OSMA's comments should not be taken as an endorsement of the product being discussed today. We ask instead that our comments be considered during today's panel deliberations. These comments represent the careful compilation of the member companies' views.

OSMA was formed over 50 years ago and has worked cooperatively with the FDA, the American Academy of Orthopaedic Surgeons (AAOS), the American Society for Testing and Materials (ASTM), and other professional medical societies and standards development

bodies. This collaboration has helped to ensure that the orthopedic medical products are safe, of uniform high quality, and supplied in quantities sufficient to meet national needs. Association membership currently produces over 85% of all orthopedic implants intended for clinical use in the United States.

Like the American public, OSMA has a strong and vested interest in ensuring the ongoing availability of a safe and effective orthopedic devices. The deliberations of today's Panel and the Panel's recommendation to the FDA will have a direct bearing on the availability of new products designed to improve the quality of life of patients treated in the United States.

We urge the Panel to focus its deliberations on the product's safety and effectiveness on the data provided. The FDA is responsible for protecting the American public from drugs, devices, food, and cosmetics that are either adulterated or are unsafe or ineffective. However, FDA has another role: to foster innovation. The Orthopedic Device branch is fortunate to have an available staff of qualified reviewers, including a board-certified orthopedic surgeon, to evaluate the types of applications brought before this Panel.

The role of this Panel is also very important to the analysis of the data and the manufacturer's application and determine the availability of new and innovative products to treat patients in the United States. Those of you on the Panel have been selected based on your expertise and training. You also bring the view of the practicing clinicians who treat patients with commercially available products.

Our objective here today is to emphasize two points that will have a bearing on

today's deliberations: (1) reasonable assurance of safety and effectiveness, and (2) valid scientific evidence.

Point 1, reasonable assurance of safety and effectiveness. There is reasonable assurance that a device is safe when it can be determined that the probable benefits to health outweigh the probable risks. Some important considerations associated with this standard include valid scientific evidence and proper labeling and that safety data may be generated in the laboratory, in animals, or in humans.

There is a reasonable assurance that a device is effective when it can be determined based on valid scientific evidence that a device provides a clinically significant result in a significant portion of the target population. Labeling in the form of adequate directions for use and warnings against unsafe use play an important role in this determination.

Point 2, valid scientific evidence. Valid scientific evidence consists not only of well-controlled investigations, but also partially controlled studies, studies and objective trials without matched controls, well-documented case histories, and reports of significant human experience with a marketed device.

While a well-controlled investigation may be the highest order of evidence used to determine safety and effectiveness, OSMA respectfully reminds the Panel that other types of valid scientific evidence may provide a reasonable assurance of safety and effectiveness. In addition, while the scientific community recognizes that among the essentials of a well-controlled investigation are the methods of selecting subjects, of observation and recording results, as well as comparison of the results with treatment of control, including historical control, OSMA also urges the Panel to recognize that a clinical study with some but not all

of these essentials may yet be a higher order of valid scientific evidence than other types of evidence which can provide a reasonable assurance of safety and effectiveness.

The Panel has an important job today. You must listen to the data presented by the Sponsor, evaluate FDA's presentations, and express an opinion on the safety and effectiveness of the Sponsor's product. We speak for many applicants when we ask for your careful consideration. Please keep in mind that the standard is a reasonable assurance, balancing the benefits with the risks. A greater degree of certainty is not required.

When considering making the recommendation for further studies, remember that FDA takes these recommendations seriously, often as a consensus of the Panel as a whole, and a recommendation for additional studies may delay the introduction of a useful product or result in burdensome and expensive additional data collection. Therefore, you play an important role in reducing the burden of bringing to market new products which you and your colleagues use in treating patients. Please be thoughtful in weighing the evidence. Remember that the standard is a reasonable assurance of safety and effectiveness, and that there's a broad range of valid scientific evidence to support that determination.

OSMA thanks the FDA and the Panel for the opportunity to speak today. Our association trusts that its comments are taken in the spirit offered, to help FDA decide whether to make a new product available for use in the U.S. marketplace. OSMA members are present in the audience and available to answer questions anytime during the deliberation today. Thank you.

DR. RAO: Thank you, Mr. Stevens.

There was another speaker that requested speaking time, Mr. Tom VanLandingham.

MR. VANLANDINGHAM: My name is John T. VanLandingham. People call me Tom. I'm a patient of Dr. Gornet's and received the DIAM device in the IDE study. Medtronic has paid me -- has paid the travel expenses and lodging for me to participate in this meeting. I do not own Medtronic stock, nor do I have any financial interest in the DIAM project.

I should also explain that I'm a principal in an architectural firm that specializes in planning and design for healthcare. So the Venn diagram of what I do in our planning practice and the nature of this proceeding overlap just a tiny bit.

What I want to do for you today is to put a face on all of the information that you've gotten in this meeting by comparing my life before and my life after surgery. In making notes for this meeting, I had the realization that changes in the quality of life and my activity were driven, in part, by the pain that I was experiencing, both the permanent, chronic pain and also the intermittent pain.

Decisions about what to do and what not to do were also being based on the fear of pain, that a common activity like getting into a car or a cab or reaching across a table for a drawing could lead to hours or days of misery. Actual pain was causing time off from work, cancellation of family outings. The fear of doing something that would trigger a painful episode was causing activities like those not to be planned in the first place.

I like to hike. Missouri has beautiful locations to hike, but the prospect of not being able -- of having a slip and not being able to walk back to the trailhead took most of our favorite locations off of my list. Work activities like attending conferences or leading client meetings were getting reduced, particularly if they involved travel. Friends and family would get together for school events, like theater or sports. My wife and I have a daughter

who was in high school when I had surgery. I was the dad that wasn't able to sit with the group but instead stood next to the back door of the theater or at the top of the row of bleachers. We declined social invitations. My wife eventually volunteered to mow the yard.

What I was willing to attempt was contracting based on the fear of pain. I consumed many hours, copays, and deductibles on rounds of all of the nonsurgical alternatives that have been discussed this morning. Nothing produced more than short-term relief for me. And once the insurance company's limits on physical therapy or injections are released, you're pretty much stuck.

I had gotten some good advice from a client over lunch. Dr. Mark Adams, who's an orthopedic surgeon with his practice in Columbia, Missouri, observed that I had stood for most of the morning's meetings and asked if my back bothered me. I confessed. He offered this, and it was good advice for me to follow. Exhaust everything else first. Surgery is irreversible and should be your last option.

I followed that advice but got to my limit when I simply couldn't get a night's sleep. Lots of things can reduce job performance, but for me, lack of sleep was devastating. I was on a downward spiral for real. Everything, family, work, relationships were being diminished.

I finally discussed surgery with the surgeon who was treating me. Based on his assessment, fusion was the only option. For me that was no option. I was offered a choice between fusion, which I didn't want, and a set of nonsurgical options that simply had not proven to work over a number of years. So I asked him for the names of surgeons that

might offer alternatives, and Dr. Gornet's name was on that list.

I do know the length, the longevity of my ancestors. I am interested in genealogy. And so I was looking at this decision -- this is the, little bit the planner in me, I was looking at this decision as being a 40-year decision for me because that's what I would expect to have as a lifespan after surgery.

Dr. Gornet evaluated me, decided that I fit the criteria, explained that it was a randomized trial. I might be on one track or the other track. Regardless of that, I was open to the possibility, and I saw some distinct pluses in what he was offering me in the trial. One was that surgery would be a 23-hour stay rather than an inpatient stay, and as a healthcare planner, I know the difference between the two.

Motion of the joint would be retained. That was very important to me. I didn't want -- you know, I've had friends, I've had associates that have had fusion. It works for many people, but I had a fear that losing movement of the joint would have consequences. And lastly, if there were adverse effects, the procedure was potentially reversible.

In addition to that, the concept of the device had an elegant simplicity to it that aligned with what I think represents a thoughtful design. And I noted earlier, a couple of you on the Panel have engineering backgrounds, so maybe you have an appreciation for that.

Recovery from surgery was fast. I could care for myself the following day. And very quickly there were signs that all of these barriers and constraints that the fear of pain had caused me to put in place were going to come down. They were starting to come down. A few days after returning to work, a longtime employee stopped me in the hall and told me,

it's good to see you smile again, it's been a long time. And I have to concede that I choked up at that.

In the ensuing 4 years, the barriers and constraints have continued to drop. I'm more productive. I'm more active. I'm more engaged with everyone that's around me. So, in closing, I don't know quite how my story fits into your considerations. It's obviously very important to get the science right on this. But I hope that there's an element of this that's subjective and about quality of life that's important to you, because it's important to me. Thank you.

DR. RAO: Thank you very much, Mr. VanLandingham.

Does anyone in the audience wish to address the Panel at this time? If so, please come forward to the podium and state your name, affiliation, and indicate your financial interests. You will be given 3 minutes to address the Panel.

(No response.)

DR. RAO: Okay. Are there any questions from the Panel for the Open Public speakers?

(No response.)

DR. RAO: I now pronounce the Open Public Hearing to be officially closed.

We will now continue the Panel deliberations. As a reminder, although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel Chair. Additionally, we request that all persons who are asked to speak identify themselves each time. This helps the transcriptionist identify the speakers.

Is the Sponsor now prepared to respond to the Panel's questions and themes of

discussion that came up this morning? And/or is the FDA prepared to respond to those issues?

MR. O'NEILL: The FDA is prepared to respond to some of the questions from this morning.

DR. RAO: Okay. Let's please go ahead.

MR. O'NEILL: Sure. There was a question about the animal study findings and analysis of the device's interaction with the bone. A sheep study was conducted and histology was performed and did not find any abnormal tissue reactions or tissue necrosis, and to our knowledge, no wear in this animal study was collected.

DR. RAO: That's not exactly what the Sponsor said. The Sponsor said something different to my recollection.

MR. O'NEILL: I defer to the Sponsor. They're more aware of the details of the testing.

DR. RAO: Yeah. The Sponsor talked about some chronic inflammatory cells, if any --

MR. O'NEILL: The explant analysis involved some of that analysis.

DR. RAO: There was nothing with the -- there were two animal studies, right? The sheep and the rabbit.

MR. O'NEILL: Sheep and a rabbit.

DR. RAO: So the sheep had --

MR. O'NEILL: I'm referring to the sheep study.

DR. RAO: The sheep study? Okay. Thank you.

MR. O'NEILL: Preclinical testing on the cables and crimps was completed. Static and

dynamic testing on the crimped cables was conducted. No creep testing was conducted in tension, and no wear debris for the fatigue dynamic tension test was conducted. However, for the compression tests, wear and creep was conducted.

For the explant analysis, a chronic inflammatory response was found that is consistent with wear response seen in arthroplasty. And for the silicone question, biocompatibility testing per ISO 10993 was conducted prior to the initiation of the trial, and this material has been used in other devices approved by the FDA.

DR. ADEGBOYEGA-PANOX: I'm responding to the question about adverse events categorization. And I need to clarify that the adverse event tables and the definitions of adverse events were provided by the Sponsor. And we did express our concern with those categories and the presentation of them, such as the example that we provided in our presentation. So we're deferring to the Sponsor to provide you those definitions.

Oh, sorry. That was Elizabeth Panox.

We'd also like to clarify that we're aware that the DIAM is used as an adjunctive therapy in out-of-the-U.S. countries. Our concern and question of the Panel is the issue of the soft tissue and bone resections that were performed in conjunction with the device and which confound the treatment effect of DIAM.

And then to Dr. Golish's question on the ODI severity, our post hoc analyses suggest that most of the study population in both of the study groups are severe, and some of those greater ODI scores are consistent with those reported for surgical candidates.

DR. YING YANG: My name is Ying Yang. Regarding my Slide 87, Dr. Blumenstein's question on ITT analysis, I agree, you're right. It is not strict ITT. Instead, I would like to ask

the Panel to focus on these analyses as a sensitivity analysis to assess the impact of missing due to loss to follow-up, crossover, and the subjects who are randomized but not treated.

Regarding Dr. Golish's worst-case analysis, I would like to show them my backup slide.

In this slide, please look at the last row. The missing data -- missing and the crossover and the randomized not treated was considered as a failure for the DIAM group but as a success for the control group. So the posterior probability of superiority is 96.3%, which is lesser than the 95.7%. So the superiority of DIAM cannot be claimed.

The same worst-case analysis was done for the all-available dataset. So please look at the last row as well. And then the -- again, the worst-case analysis shows that the superiority of DIAM cannot be claimed.

DR. RAO: Could you just go over those last two slides one more time, please? Just to clarify the -- go back to the previous slide. I think -- I'm not sure I understood fully exactly what you were saying. Could you just repeat what you said on the slide?

DR. YING YANG: So for the primary dataset here, the ITT, we considered the patients who are missing, has missing, overall success status at the 12 months, and also the patients who were randomized but not treated as a failure in the device group but had considered them as a success for the control.

So these worst-case analyses showed that the posterior probability of superiority is 96.3%, which is lesser than the 97.5%. Therefore, the superiority of DIAM cannot be claimed.

DR. RAO: Thank you.

Dr. Yang.

DR. LYNDA YANG: Maybe I'm just missing a point here, but worst-case scenario for intent-to-treat would include not just the missings in the control but also the crossovers, correct? But that's not there, right?

DR. YING YANG: The crossover is included in the control group.

DR. LYNDA YANG: The crossovers were included in the control with that?

DR. YING YANG: Yes.

DR. LYNDA YANG: Okay.

DR. RAO: Any other questions?

Dr. Evans.

DR. EVANS: I just want to clarify. If they were included in the control group, that wouldn't be a worst-case scenario because worst case would be that your -- you know, it's bad for the control if you include them, so --

DR. RAO: Yang, you have a response to that?

DR. LYNDA YANG: No. That's okay. I defer to Dr. Evans on statistical matters.

DR. RAO: Any other questions for the FDA? Dr. Finnegan.

DR. FINNEGAN: I have a couple. One is, is there a consideration for having third party do the analysis so you can eliminate some of that bias? Is that part of your regular scenario, or does the Sponsor have to come up with that? You know, there's a lot of bias. You talked about bias in your presentation. And if you had a third party, an unrelated third party doing the appraisal, then you might eliminate some of that bias.

DR. ADEGBOYEGA-PANOX: The Sponsor did, they did use a core laboratory of

independent radiologists, and they also used a clinical assessment committee to adjudicate the adverse events.

DR. FINNEGAN: Okay. And then my other one is, given that almost all of the orthopedic devices today that are going to spectacularly fail do so at between 3 and 5 years out, was there a reason why you picked 12 months?

DR. ADEGBOYEGA-PANOX: The study endpoint and time point of determination is part of what we're asking the Panel input in.

DR. RAO: Thank you, Dr. Finnegan.

Any other questions for the -- Dr. Trier?

DR. TRIER: Yes. This is Dr. Trier.

Just again for clarification, was the 12-month endpoint part of the approved IDE protocol?

DR. ADEGBOYEGA-PANOX: It was a study -- it was an advisory. But yes, it was approved as part of the protocol.

DR. TRIER: I guess I need to add a comment at this point. And, you know, I am the Industry Representative. So one of the things that I think it's important for me to state at this point is that, you know, in our discussions and in our development of devices, we interact with FDA on a regular basis. And so as a sponsor with an approved protocol from FDA, that is the guidance that we conduct the studies under. And I would pose that question to Medtronic when they -- or the Sponsor comes to the stand.

DR. RAO: Mr. Melkerson.

MR. MELKERSON: Mark Melkerson, FDA.

In this study, the study was approved based on safety, similar to the FDASIA that went into effect in 2012. The issues associated with the study design and protocol were identified as future considerations, so there was no impact on safety, but not necessarily on the impact on evaluating the relative safety and effectiveness or risk-benefit.

So we're going to be seeing this more and more in future panel meetings where the study is approved, but depending on how strongly the wording is included in the approval letter as we see these things as critical, we see these things as future considerations, are going to be things that are going to be coming up to the panel, saying yes, they did a study, it was approved based on safety, but not necessarily to allow one of the previous criteria prior to the FDASIA, which was you could disapprove an IDE based on valid scientific evidence.

So when you're talking about yes, it was approved, but there are -- even in the -- and again, it's starting in 2012, but this was approved with that same concept in mind.

DR. RAO: Mr. Melkerson, when the study was approved, what exactly was approved?

MR. MELKERSON: We quoted -- the study was based on the safety -- in FDA's exec pack, it'll actually identify the exact wording that was conveyed to the Sponsor when the study started.

DR. RAO: Dr. Golish.

DR. GOLISH: Just a comment on that point. Looking at similar devices that come before a panel and therefore have public information that anybody can access, the most recent interspinous process device to come before a panel had 24-month follow-up. The

most recent spinal fusion device to come before a panel, which the Sponsor will recollect, a 24-month follow-up.

DR. RAO: Dr. Cheng.

DR. CHENG: Just to clarify, Mark, are you saying -- so we have situations where the Panel, not just this Panel but other panels have had some disagreements with regards to either the study design, methodology, or the endpoints used, or the follow-up time period? But those were all completed, of course, once data comes to the Committee. So what does the Committee do when they feel that the, those issues were, what would I say, either suboptimal or inadequate, I suppose you could look at the two extremes. But what's the Committee to do in that situation?

MR. MELKERSON: That goes back to the point of how does it impact your risk-benefit analysis and how does it impact your interpretation of relative safety and effectiveness.

DR. CHENG: Well, that's a difficult -- you'd like to have data to make a judgment on that, to give you the question you're asking the Panel. But if the Panel or the Panel member feels that, well, I don't have that data, that's a problem. And I know, during the design of the study, there is a give and take between the industry and the FDA as to what's acceptable or not accepted.

I think the one question I heard here was Maureen asking about the 12-month time point. I'm sure that it was not just Medtronic's decision on the 12-month time point. I'm sure there was some discussion previously about that.

That's just one issue. There are other issues, of course, too.

MR. MELKERSON: And again, I will defer back to the Office director who signed the approval order for the product. In the -- we tried to quote directly what the company was advised. In other words, there were no patient safety issues associated with the study proposed, but there were issues related to study population, duration, and other things that were listed as future considerations.

Welcome to -- what it will now become after studies that started in 2012, that has actually become law, and not just on a case-by-case basis when a product is approved or a study is approved.

DR. RAO: So would it be fair to say --

DR. CHENG: These are difficult questions, that it puts the Panel in the same situation we are as, yes, you've approved a study that poses no safety risk to the patient, but at the same token may or may not answer the questions that we would like to see. So in a -- after FDASIA, all the issues related to study design are no longer reasons to disapprove an IDE study.

And actually our Deputy Office Director can walk in --

DR. RAO: Would it be fair to say, while the Deputy Officer is moving up to the podium, would it be fair to say that the FDA approved or okayed the study going forward, but did not necessarily approve the design of the study?

DR. BROCKMAN: Hi. I'm Randy Brockman. I'm the Chief Medical Officer and now the Acting Clinical Deputy Director in the Office of Device Evaluation.

I guess there are two issues we could talk about. I don't want to get too heavy into the issue about FDASIA of 2012. I think, moving forward, you will be hearing more about

that and the need for you to think and offer constructive criticism on study design.

For this particular study, and also moving forward, I think, if you have feedback for us, positive or negative, about the study design, the endpoints, the duration of follow-up, we would love to hear it. In one respect, I guess what I'm saying is, don't simply accept the study design at face value because it's an FDA-approved IDE. You know, we approved the IDE with some history to it. But if you have feedback for us on the design, the endpoints, or the duration of follow-up, we would be very interested to hear that feedback.

Is that helpful?

DR. RAO: I think that's acceptable. The issue, I think, some of the Panel members, the sense I get, is if the study design does not allow a Panel member or the Panel to come up with a decision on safety or efficacy or risk versus benefit ratio, is that an option for us to say that it's not necessarily that it's safe or unsafe, or that the data does not allow us to provide an answer to a question? Is that a third option?

DR. BROCKMAN: We are going to ask you to vote at the end of the day.

DR. RAO: Yeah.

DR. BROCKMAN: If you see advantages or limitations in the study design, I think that's part of what I'm saying that you can give us feedback on.

DR. RAO: Okay. So the vote will be either a yes or a no, or will it be a yes, no, or not enough information?

DR. BROCKMAN: I think you do have the option to abstain, but we would prefer as much feedback from you as we can get. We need help from this Panel.

DR. RAO: Okay.

DR. BROCKMAN: Thank you.

DR. RAO: Any further questions for the FDA?

Dr. Smith.

DR. SMITH: Harvey Smith.

A quick question going back. The last hour we had discussed the spinous process fractures. And on the slide you had presented, you had shown that at each year it was a new incident spinous process fracture, but then the size of the cohort was dropping, I guess, as individuals were lost to follow-up at further dates; is that correct?

There was a slide where you showed at any given year there was an *n* for number of spinous process fractures. That *n* was decreasing over time, and the question was, had the fractures healed? And the answer was that, well the *n* was dropping because, I guess, 60 months, there were fewer people in that cohort. And I guess the question is --

(Off microphone comments.)

DR. SMITH: Yeah. And so I'm not sure I fully understand, what was the incidence of spinous process fracture? Because at 36 months, there's 13 spinous process fractures inferiorly. At 60 months, it's *n* equals 4. I don't understand. Does that mean that the other 13 were -- there's 4 that we've seen, and the other ones, there are 9 that we know happened but those patients were somehow lost to follow-up at 60 months or?

(Off microphone comments.)

DR. SMITH: So the inferior spinous process fractures at 36 months, *n* equals 13 is highlighted. At 60 months, it's *n* equals 4. And what I don't -- there's a slide you just had. What I don't understand is, where are the other nine spinous process fractures? Or is that

four new spinous process fractures?

DR. ADEGBOYEGA-PANOX: These -- you're talking about the spinous process erosions then? And --

DR. SMITH: Yeah, the erosion. Excuse me, erosions, yes.

DR. ADEGBOYEGA-PANOX: At 36, *n* is 32 for the superior, and *n* is 13 for the -- that's the one you're talking about?

DR. SMITH: Yes. I'm sorry. I was saying fractures. I meant erosions. So at 36 months, there's 13 patients that had inferior spinous process erosions. At 60 months, the *n* equals 4. And where I'm confused is what exactly does that mean? Does that mean that in nine of those patients, the erosions are no longer seen? Or were individuals lost to follow-up, and at 60 months you see four erosions, and then the other nine that were at 36 months are not in that dataset? Or are these new incidences?

DR. ADEGBOYEGA-PANOX: These are the observation at that particular time point.

DR. SMITH: I'm sorry, the --

DR. ADEGBOYEGA-PANOX: This is the observation at that particular time point, so --

DR. SMITH: So what --

DR. ADEGBOYEGA-PANOX: -- the number of patients that they saw and then the number of erosions that they saw at that time point.

DR. SMITH: So is it safe, then, for me to infer that that means that 9 of the erosions seen at 36 months were not seen in that same patient at 60 months? The erosions, for lack of a -- were no longer observed in the same patient?

DR. ADEGBOYEGA-PANOX: No, you can't assume that because it's possible that

some of the patients that were seen at follow-up at 36 months were also seen at 60 months. So this is just the observation at that time point. So they saw this number of patients and this is what they -- this is -- these are the number of erosions that they identified.

DR. SMITH: I'm sorry, but I don't understand. So if 13 patients at 36 months were observed, and they had significant radiographic erosions on the inferior spinous process.

DR. ADEGBOYEGA-PANOX: Thirteen patients.

DR. SMITH: Now we go out to 60 months.

DR. ADEGBOYEGA-PANOX: Right.

DR. SMITH: And four were observed. And what, I guess what I'm not clear on was, were the same individuals observed at 36 months and 60 months and you didn't see that erosion, or were there individuals that were lost to follow-up in that cohort?

DR. RAO: That's a good question.

Mr. Melkerson.

DR. ADEGBOYEGA-PANOX: So this -- go ahead.

MR. MELKERSON: Dr. Panox, this is Mark Melkerson. What we're trying to say is they took a snapshot in time. So not all patients enrolled were out to 48 months or out to 60 months. So the number that's identified for each time point is the observation for those that had data available at that time point.

DR. SMITH: That's my point. It's difficult for me to interpret that, but I think that's a -- we were discussing a few minutes ago about we're not worrying about safety issues. That's a significant safety issue if I can't understand that data.

DR. RAO: If we could maybe hold this slide and have the Sponsors -- if the Sponsors, number one, agree with the data on the slide. And if they agree with the data on the slide, if they could be prepared to respond to Dr. Smith's question in a few minutes, that would be great, if we could pull this slide up later.

Dr. Finnegan, you had a question?

DR. FINNEGAN: I was just going to say, I agree with him. And my concern is that there's so much intent-to-treat in the statistics that if we can't figure out who are new and who fell out because they weren't followed up, then we're lost.

DR. RAO: So I think it sounds like we may need -- does the FDA have clarification for Dr. Smith and Dr. Finnegan's questions? I guess the question is, is that number 4 less than the number 13 because all those patients were just lost to follow-up and not available at the 60-month time point? Is that a new 4? Is that an existing, pre-existing 4? We just don't know right now. So did the FDA investigate exactly how these numbers play out?

DR. ADEGBOYEGA-PANOX: This is the data that we were given to review.

DR. RAO: So this is the Sponsor's data?

DR. ADEGBOYEGA-PANOX: Yes.

DR. RAO: So if the Sponsor agrees with the data, if they could please respond to Dr. Smith and Finnegan in a few minutes, would that be satisfactory?

(No response.)

DR. RAO: Any other questions from the Panel for the FDA?

(No response.)

DR. RAO: Okay. We'll move on. Is the Sponsor prepared to respond to some of the

themes and questions that came up this morning during the deliberations?

DR. SIMPSON: Yes. Kathryn Simpson.

So a lot of the -- there were a lot of questions this morning. We'll do the best we can to answer all of them, including the additional ones. If there's any we don't get to, we're happy to provide that answer to FDA.

So just to start, very quickly, Dr. Blumenstein had asked the question about how the AEs were treated for the non-op treatments in the DIAM group. We agree with you. It's vague in the protocol, but we want to assure you that the rule was applied the same way in both groups. So those were counted as failures in the DIAM group as well.

DR. BLUMENSTEIN: Well, let me just make sure I understand, because this is, to me, very important. So that if a patient in the surgery arm was getting injections and had a serious adverse event as a result of getting the injection, then that was counted as a treatment-related --

DR. SIMPSON: It would have been an implant/surgical procedure associated event, which would have, if it was serious, would have led to a failure.

DR. BLUMENSTEIN: But that doesn't seem like implant or surgery. It just seems like an injection.

DR. SIMPSON: Right. So that's what I'm saying. I think the nomenclature in the protocol is a little bit confusing, but that's how they were handled, and they were handled the same way in both groups.

DR. BLUMENSTEIN: So that -- let me just be absolutely explicit because I have a bunch of other questions that are pinned on this. So if a patient in the surgery arm had

some kind of a serious adverse event, that was similar -- a result of something that was, might have been done in the control arm, then that serious adverse event counted against that patient having success, just as it would in the control?

DR. SIMPSON: Yes. Yeah, that's correct. Okay.

So with that clarification, then I'm going to ask Dr. Matt Gornet to come up and speak to some of the clinician questions.

DR. GORNET: Matthew Gornet, St. Louis, Missouri.

I wanted -- I owed Dr. Graf explanation of the slide. He asked a good question. In short answer, I think we were both right. You correctly pointed out that the Ha slide did not show a change in disc height. And I think you were correct on that. The reason why I made the statement as -- if we have the slide, Nick, for disc height for our data; do we have that?

NICK: It's coming.

DR. GORNET: It's coming. This was our data. And again, even this slide, I think, is somewhat confusing, Dr. Graf, but this is change from baseline. So what it does show is that there was change from baseline in posterior disc height. And this is maintained out through 24 months, and I believe we also have data out through 60 months. So I hope that that clarifies your answer. So I believe you were correct.

The next response I have is to Dr. Finnegan, and I believe you asked some appropriate questions. One of it -- and it may pertain to you also, Doctor, on adverse events. Realize that this is an independent adjudication committee, and they are independent of the Sponsor. And they are charged with determining adverse events. And I think it's helpful for all the Panel if I just read the definition very quickly.

"An adverse event means any clinical adverse sign, symptom, syndrome, or illness that occurs or worsens during the treatment periods of the trial, regardless of causality, that is not otherwise being measured in the trial."

And then this gets to the seriousness, which is also determined, and obviously whether it's device-related.

An event that meets the following criteria will be considered serious:

- Led to a death;
- Led to serious deterioration in the health of the subject;
- Resulted in life-threatening illness or injury;
- Resulted in permanent impairment of body structure or body function;
- Required an in-patient hospitalization or prolongation of an existing hospitalization;
- Resulted in medical and surgical intervention to prevent permanent impairment of the body structure.

So, in short, I can tell you that I believe there is -- I think you asked whether there's variations in committees in how they interpret that. I believe that that is, based on my understanding of doing different trials, I can't account for that, but that's been my experience.

The next question you asked is regarding injections. For injections -- and I gave a cumulative point at 12 months in the primary dataset. I listed it as 13% versus 45. I think it's important to understand that once a patient is enrolled, even if you're in the DIAM group, you can still have an injection. And I had patients who were mine that had

injections. They were not barred from having injections.

The patients who went in the conservative care arm were not required to have injections. If they went on to want to cross over, they were required to have at least one injection, but at the max was three. So it wasn't that they were required to have injections as part. So what you're seeing is systemic data collected across the entire study that just shows cumulative injections, and hopefully that answers your question regarding injections.

The final one I wanted to answer first was to Dr. Cheng. Thank you for acknowledging this is a hard job for clinical trials. I appreciate that. It answers to the placebo effect. I agree with you. There could be a placebo effect as part of this study. I think we have to acknowledge that. That's a potential bias. But from a personal standpoint, I am not aware of any surgical trial that has a placebo effect out through 60 months. And so -- I'm just not aware of it. And so that's the first part.

The second part is in answer to randomized trial or sham. In talking about this, I don't believe, one, we would have been able to get patients to enroll in a clinical trial that would give them a sham surgery. The only appropriate sham would be to do a deeper dissection, similar to what we would have to do in DIAM, and I don't think patients would do that. And so it was felt to be not only difficult to enroll but unethical.

The final point is, is not only do -- I don't believe that there is a potential placebo effect that can last 60 months, but just like the data that we showed here, there still seems to show a maintenance of effect of the DIAM device in posterior disc height, as Dr. Graf pointed out, and also a reduction in extension.

So we see that there is some effect of the device radiographically, as measured by

objective terms, out through 60 months, which seems to also indicate, again, some method of action of load-sharing that goes along with the clinical result.

DR. RAO: Dr. Auerbach had a question?

DR. ESKAY-AUERBACH: Marjorie Eskay-Auerbach.

I guess, when I read through the information -- actually, this is for you, Dr. Gornet. Sorry. There really is no description of which injections are done for which criteria. And it seems to me that any center, the treating physician could have different criteria or different thresholds for doing injections. I mean, there are evidence-based recommendations, for instance, for epidurals or facet injections, but I don't see any of that. None of those are distinguished or identified specifically in the information that we had available.

DR. GORNET: I believe that there could be a potential bias or variation from center to center. It was obviously done at the request of the enrolling physician based on the pathology. There are different types of injections that were performed, so you are correct. And I think that's an appropriate bias.

Nonetheless, those are systemically collected data across all groups, and it did show a significant increase in the control group versus the DIAM group. So even the DIAM patients, their treatment was felt that they didn't really require further injections. But your point is well taken.

DR. ESKAY-AUERBACH: Thank you.

DR. RAO: Dr. Smith.

DR. SMITH: Harvey Smith.

A quick question for clarification. Am I correct in understanding, then, that in the

control group, no individuals were required to get an injection? If you cross over from the control group to the treatment group, you're required to get at least one injection, which implicitly implies you're now selecting for people that are averse to any injection are mandated to only be in -- cannot cross over.

And then in the treatment group, you must be willing, you crossed over, to undergo what I presume is an epidural injection. And then presumably those individuals are then allowed to get continued epidural injections after the procedure. And then many of those individuals had coexisting radicular buttock and leg pain. Is that correct?

DR. GORNET: Well, that's a multi-part question, but I'll try my best to answer it.

First, you are absolutely correct. To cross over, you had to have at least one injection. The point of that was to determine and let the patients know that they have failed -- or let us know they have failed all forms of what we knew to be comprehensive nonoperative care, education, injections, community-based physical therapy, and all of the parameters.

And then as far as why the injections were performed, obviously a facet block would not necessarily, as you would know, be performed for radicular pain. A transforaminal steroid injection or an epidural would. So I think I could provide a list, potentially, of how many injections were performed in each group. But that's the best answer I could give for you.

DR. RAO: Just to follow up on that, Dr. Gornet.

DR. GORNET: Yes.

DR. RAO: You termed this comprehensive nonoperative care --

DR. GORNET: Yes.

DR. RAO: -- to receive at least one injection. But at the same time, as I interpreted your materials, not in the slides today, but in the materials submitted earlier, the control group had to receive education, which subsequently was modified to even include handing out a booklet, and one of the three other options, which was either physical therapy, medications, or injection.

So the control group, their comprehensive nonoperative care was a booklet plus some medications, injections, or physical therapy, whereas for this group that was crossing over, they had to -- why was the comprehensive nonoperative care definition different for the two groups?

DR. GORNET: Well, it a --

DR. RAO: Or did I misinterpret it?

DR. GORNET: No. I think you're correct. And the reason why we say comprehensive, in the sense, if a patient is doing well with lifting, education, NASS-derived education guidelines or a 6-week course of physical therapy, I feel it would be wrong to force them into an injection that they didn't need. And so from that standpoint, the comprehensive therapy was tailored toward the individual patient need and their individual response to treatment.

So it escalated to the point of maximum, but it wasn't -- the maximum was not required of all. And you can clearly see, there was a group of patients in the control group that did well, did not qualify for crossover, and obviously wouldn't have required all of the comprehensive there.

DR. RAO: I think your answer's valid. And there's a couple of questions, but I just want to follow up on that. I think you're absolutely right that if they don't need it, we shouldn't move forward with additional treatments. But it sounds like this control group, there was something about them where a lot of them crossed over to ask for surgery. So the comprehensive nonoperative care just wasn't working for a large percentage, at least 60% of them that actually stayed on.

So if 60% of them did not respond, how can we say that the comprehensive nonoperative care was working well? So there's a little bit of a miss -- disconnect somewhere in there. And I don't know if you'd be able to really respond to that. But it just comes across as a little bit of a disconnect.

DR. GORNET: I think your point is taken, but again, in trying to do this to mirror clinical practice, these are decisions that we are faced with every day as clinicians. This is what we have to offer our patients.

The one study that pointed out the back hotel, with 25 hours of physical therapy per week and cognitive therapy, we don't have that. We would never be able to employ this. So what we tried to do was allow patients with their coverage to get the maximum of treatment that's offered in our everyday practice. And so your point is well taken.

DR. RAO: Thank you very much.

There's a couple of questions here. Dr. Smith had his hand up earlier. No. Dr. Topoleski.

DR. TOPOLESKI: Tim Topoleski.

I just have a quick one. At what point do the enrollees know that eventually they

may have the -- the controlled enrollees know that they may have the option to cross over?

DR. GORNET: I believe they knew from the very beginning. Once they enrolled, that was part of the protocol that they signed, that they knew. Yes, sir.

DR. TOPOLESKI: So does that mean that -- so they have a subjective score for pain, and they're told at the beginning, if this doesn't work, you're going to have the option for a surgical treatment that we think is going to be better?

DR. RAO: After 6 months.

DR. TOPOLESKI: Later?

DR. RAO: After 6 months.

DR. TOPOLESKI: After 6 months, but --

DR. RAO: They had to have --

DR. GORNET: Yes.

DR. TOPOLESKI: But they know that the criteria for crossing over or not working is based on their subjective scores. Is that true? Okay.

DR. GORNET: Well, I don't know if they know specifically that. They know that if they fail -- I don't know if they're really familiar with Oswestry or numerical back or leg pain scores or SF-36. What I would say is, they are aware that they can cross over if they fail.

But then I would point you to look at the 17 patients who were eligible to cross over and then did not receive the device. And they continued to do poorly in spite of being eligible. So even though there may be this perceived bias, as you say, of wanting to get surgical treatment, there was a group that didn't, and they continued to do poorly.

DR. RAO: Dr. Gilbert?

DR. GILBERT: Jeremy Gilbert.

Like Dr. Cheng, I want to say, I appreciate how difficult and challenging these sorts of clinical studies are. It's a daunting task. But I also have to say, I feel a little bit like a fish swimming in the Potomac River. Every now and then I get to a stream and I can see, and I think I understand. And then I swim a little bit further, and I'm into cloudy and confusion. And so I'm trying to make sense of what I'm hearing, and I'm having a hard time of it. So let me see if I can ask a couple of things.

One confusion I have is, the selection criteria said moderate, 20 to 40 on the ODI, but we were well above that. And then the data actually shows there are some that were well above that cutoff point, up into the 60s. And so I just wonder, for instance, did anybody do an analysis of the delta ODI against ODI?

In other words, if you were a 60, did you come down to a 20? Or is there some systematic change in ODI as a function of where you started? And as a corollary to that, if I'm a 65, and I get a 15-point increase, I'm down to a 50, which is still pretty severe, and so while it's a success according to the study, I'm not sure a 50 in an ODI would be deemed a success. And so can you help me understand some of these?

DR. GORNET: Well, I think there's two parts of your question, and I'll try to answer the clinical part, and I'll defer to those behind me that I think can better answer the statistical part, because that's not my area of expertise.

One is, from our perspective, again the ODI classification -- and I agree that's moderate, 21 to 40, isn't indicative of not only -- there's no predictor on radiographic pathology. It doesn't correlate. This is again subjective based on the patient's perception

of what they're doing. And it may have no, again, correlation with, again, their actual function beyond that.

And so what happens is, is those are the verbiages that we are stuck with, with the ODI, and it doesn't necessarily fit with where we believe the moderate range is. Again, if you would look at Mr. VanLandingham, he's working, he's doing things every day, but yet -- and he's in that area of target population.

As far as whether, you know, a group of patients improve 50 points and then some didn't, I'd have to defer that, and maybe they can get that answer for you, because I think that's an appropriate question. But again, if you look at the overall mean improvement from the entire group in the primary dataset, obviously it was considered superior to the control, for a mean improvement.

DR. RAO: Dr. Graf.

DR. GRAF: Just to go back for a second to the discussion that Dr. Rao was having, I was a little confused on one of the inclusion and the exclusion criteria. Because if you look at number 5, exclusion criteria, was that a patient that has had all of the following nonoperative treatments, medications, physical therapy, spinal injections within the past 6 weeks, were excluded, though the inclusion number 5 was that they had been treated nonoperatively, including bed rest, physical therapy, which those contradict each other.

DR. GORNET: Let me see if I can pull up the inclusion criteria. In other words, they had to fail the entire -- if they had had all of those forms in the prior 6 weeks, then they were excluded, right, because then that would be not someone who could be obviously improved at all, because they've already had it in 6 weeks.

As far as the other point, I don't have the inclusion criteria in front of me.

DR. GRAF: So you're saying that they were excluded if they have had all those modalities before they were brought into the study then?

DR. GORNET: I'm trying to answer.

Do we have that inclusion sheet, guys? Thank you. That's what I wanted.

I'm sorry, Dr. Graf, it was point 5?

DR. GRAF: Yes.

DR. GORNET: Okay, point 5.

DR. GRAF: Your Table 9.1.

DR. GORNET: Yes. Has had all of the following nonoperative treatments: medications, active physical therapy, injections within the past 6 weeks. So they were excluded. So if they had all forms of what we determined comprehensive conservative care, they were not allowed to enroll in the study.

And then there was a second number you had asked about?

DR. GRAF: Well, it was the inclusion criteria, also number 5, which, you know, the wording can be confusing because you are almost including the ones that should be excluded.

DR. GORNET: That has been treated -- I understand your point.

DR. GRAF: Do you understand what I'm saying?

DR. GORNET: No, I understand your point. It was --

DR. GRAF: Because we're including -- we're excluding ones who have had all the treatment.

DR. GORNET: Right.

DR. GRAF: That would allow patients to fit into your study.

DR. GORNET: Correct. But the enrollment criteria we used, I could tell you is they had to have at least one form of nonoperative care. But I understand how that wording could be confusing.

DR. GRAF: Because it would seem to me that you're excluding the patients who have been treated with everything and have had zero improvement, but you're including patients who might have had one or two things.

DR. GORNET: I think, again, the purpose to include at least one type of nonoperative care was to eliminate those patients, as you know, in the clinic that you see that come in with terrible back pain, and within 6 to 8 weeks, they're dramatically better. And so the point was to exclude those acute low back pain patients and have at least one form, so in other words, to not enroll them the first day of their episode of pain.

DR. GRAF: I understand what you're saying. What I'm saying is that almost -- you know, this whole discussion of degenerative disc disease that we might not be able to define if we sat here for many hours would basically be defined by somebody who has failed all of these means nonoperatively. So we're excluding those patients from a study for a product that's designed to treat degenerative disc disease.

DR. GORNET: We're excluding the patients who had had all forms in the last 6 weeks, so in other words, patients -- their current episode of back pain had to be less than 1-year duration.

DR. GRAF: Correct.

DR. GORNET: And so there are patients who have had moderate symptoms. I think the case presentation today is a perfect example, where in the past, he may have had episodes of care where he'd had 6 weeks of therapy or an injection. And this may be spread out of a period of time. But again, the point was if they had had it in the 6 weeks prior to enrollment, we didn't feel it was appropriate to enroll those patients because they would already be failures.

I think Dr. Berry has the answer to your question on ODI. Is that correct?

DR. RAO: There's a couple of questions. I know Dr. Blumenstein is next. And Mr. O'Brien is after Mr. Blumenstein. But go ahead.

DR. BERRY: Should I just --

DR. RAO: Please respond anyway.

DR. BERRY: So could I have Slide F-11, please.

Dr. Gilbert, this addresses partly your question. It shows the effect on the ODI success that is a greater than 15-point drop as a function of the original ODI. And it goes from, you know, high to low. And so the results are very comparable across.

Part of your question was, is there a bigger drop for the bigger baseline? And the answer is yes. It's not reflected here because this just looks at the 15-point drop. But for example, Case Study Number 1 that Dr. Kitchel presented started at 57 and dropped to 10 by 12 months. So that kind of a drop, a 47-point drop, obviously couldn't be possible in the lower ODI range in starting. If you're less than 40, you're not going to drop 47. So there were -- there is a gradient. It's not huge.

DR. RAO: Please go ahead.

DR. GILBERT: Jeremy Gilbert.

On the flip side, did you do any analysis on sort of the worst end of the tail to see, with treatment, how many or how severe of an increase or an unchange in ODI you would see with these different starting severities?

In other words, looking at the tail of the distribution, where you have those that aren't responding well, is there any distinction one can draw between the different groups in how not responsive they were?

DR. BERRY: You mean in -- so if you're looking at the tail of the distribution, this shows a little bit, you know, if you're less than 40, what the proportion drop is, and it's comparable to the other. Are you talking about identifying those patients beyond the ODI, as to which patients are going to be successes?

DR. GILBERT: I suppose I'm interested in knowing, in the case of lack of success, are there common features of those cases that one can learn from?

DR. BERRY: Yeah. So we've looked at this, and the short answer is no. I mean, it's the holy grail, really, in treating. And speaking from someone from the cancer world, it's what everybody's trying to do. And we're doing it badly there. We're doing actually better here. But there are no characteristics that we've seen that would predict which patient is going to respond, including the diagnostic categories that we've presented.

DR. RAO: Thank you.

Dr. Blumenstein.

DR. BLUMENSTEIN: Yes. I'd like to see -- unfortunately, looking at this handout, I can't tell the slide numbers. It is your first slide after the safety result header, the big

header that says, Safety Results, the first slide afterward. Could I see that?

DR. SIMPSON: We're looking for that. Just a second.

DR. BLUMENSTEIN: Twenty, page 20. So it would be 19 times 4.

(Laughter.)

DR. BLUMENSTEIN: I'm not --

DR. SIMPSON: 70-something.

DR. BLUMENSTEIN: I'm not very good with --

DR. RAO: He's only a statistician.

DR. BLUMENSTEIN: That's it.

DR. RAO: He's not a mathematician.

(Laughter.)

DR. BLUMENSTEIN: I'm terrible at arithmetic.

So I want to focus on the last two rows, last two columns. So here we have 80 patients in the experimental arm that have serious adverse events. Let me preface this just a little bit. I'm really looking at criterion number 2 for your primary endpoint, where what you have done is identified that if a patient has serious adverse events, that's a bad thing and keeps them from being a success. That's an intent to --

DR. SIMPSON: Serious related.

DR. BLUMENSTEIN: Well, okay. That's my point. So what you're trying to do here is say that whichever arm you're talking about is going to get penalized if a patient is having serious adverse events. And you've already defined serious adverse events as something I would not want to have, period. Not at all.

And so if we look at this slide here, the bottom from the second to last row, second to last column, there are 80 patients in the experimental arm that have serious adverse events. And if we go over to the left a little bit, there are 340 serious adverse events among those 80 patients. That seems a prodigious impact of patients in this arm where something bad is happening to them.

And I'm not talking about attribution at this moment. I'm talking about just the fact that there are a prodigious, I think, a prodigious number of adverse events. And that -- of serious adverse events. And then if we go to the control arm, there are 87 serious adverse events among 34 patients.

And then you, when you defined your primary endpoint in that, according to that second criterion, you go to attribution. And the attribution is apparently judged by this committee that you've set up.

And so one of my questions is, this committee was blinded as to the treatment the patient was getting, or not?

DR. SIMPSON: Let me -- I don't want to give you a wrong answer to that question, so I'd like to confirm that. You're asking whether the CAC was blinded to the --

DR. BLUMENSTEIN: To the arm.

DR. SIMPSON: To the treatment arm, okay.

DR. BLUMENSTEIN: You're shaking your head. Was that yes or no, or confirming that yes, that was my question?

DR. SIMPSON: Sure. April Bond is going to confirm that.

MS. BOND: April Bond, Medtronic.

So the adjudication committee was not blinded to the original treatment arm because the protocol dictated different relationships based off of the treatment received. So when you had the surgical arm versus the nonsurgical arm, the relationship titles, which caused the level of confusion earlier, were different. So they needed to know what the original treatment was to choose the correct association.

DR. BLUMENSTEIN: Okay. All right. So this whole attribution thing had to do with, something to do with -- it was dependent on which arm they were in, in other words, right? It had elements of what treatments were being regarded, how -- and so forth. And so classifying an adverse event or a patient as having an adverse event that was related depended on the arm they were in?

MS. BOND: For the causality, that's correct.

DR. BLUMENSTEIN: All right. And so what you have here is that you have really a great deal of patients in the control arm relative to the experimental arm. I'm looking at the last row, last two columns, 19 versus 8 patients who had been -- who have had attributable serious adverse events, whereas what you have is that there's a lot more adverse events and a lot more patients in the experimental arm that have serious adverse events.

So this gives me terrific pause about the whole process by which you have defined your primary endpoint. And it means that this whole business about seriousness is somehow or another judgmental with respect to what the -- what did you call it, the CAC? And so what I would request here is could you please redefine your primary endpoint as any serious adverse event and recompute your serious adverse event -- that component of your

primary endpoint and recompute your primary analysis based on that -- and ignoring attribution?

MS. BOND: So you're saying eliminate causality and look at seriousness only?

DR. BLUMENSTEIN: Yes.

MS. BOND: Okay. Just a moment.

DR. SIMPSON: Dr. Berry can explain this a little bit more.

DR. BERRY: So I don't know explain, but at least to give you some comfort. What I just presented, for example, about the ODI and the ODI success, that ignores all of the SAEs.

DR. BLUMENSTEIN: I understand that. We'll come back to that.

DR. BERRY: You'll come back to that?

DR. BLUMENSTEIN: I'm talking about your primary endpoint, the basis on which you folks are bragging that you've passed the study criterion, that I have serious doubts as to whether that primary endpoint is defined in such a way that makes me believe it. And so what I'd like to see, a sensitivity analysis that takes the serious adverse events and ignores attribution.

DR. BERRY: So we're also bragging on the intention to treat.

DR. BLUMENSTEIN: Well, that --

DR. BERRY: Not the worst case, but we're bragging on the intention to treat. And as we went along there, we were dropping various kinds of things except for the ODI. And as I said, the ODI success is clear.

DR. BLUMENSTEIN: Well, the -- yeah. But you've got the crossover and other things like that going on.

DR. BERRY: Well, even counting the crossovers --

DR. BLUMENSTEIN: Yeah. No, I under --

DR. BERRY: Even taking -- you know, pay me now or pay me later, get DIAM now or DIAM later, it turns out that at 12 months, it's not much different. But we're taking and diluting the effect of DIAM and still get success.

DR. BLUMENSTEIN: Yeah. But we also have a question before us that has to do with cost versus benefit or --

DR. BERRY: Yes. I understand. I understand your concern about these issues.

DR. BLUMENSTEIN: So, anyway, is that possible that you could recompute the primary analysis based on no attributions with the serious adverse events?

DR. BERRY: Yes. We've done part of that, but we will do the rest.

DR. BLUMENSTEIN: And that --

DR. BERRY: Some of --

DR. BLUMENSTEIN: What do you -- go ahead.

DR. BERRY: Some of these adverse events are adjudicated as being pain. And so the reason for the discrepancy is partly because of very serious adverse effects that are causing patients to get additional therapy and steroids and whatever to alleviate the pain. And hence the discrepancy between is largely that.

DR. BLUMENSTEIN: Well, I understand. In the control arm, there is a lot more of a tendency, I'm sure, to do systemic type intervention, and they may lead to serious adverse events as well, and so forth. But that's not reflected in the count of adverse events. The count of adverse events is still highly unfavorable in the surgery arm.

DR. BERRY: Yeah. So we will do this --

DR. BLUMENSTEIN: Serious adverse events.

DR. BERRY: We will do this analysis and try to get it to you this afternoon.

DR. BLUMENSTEIN: Okay. And then how are you going to handle -- and doing this as an intent-to-treat analysis, how are you going to handle the patients who don't get the surgery? Did you record the serious adverse events for those patients?

DR. BERRY: You mean don't get the surgery that were assigned to surgery?

DR. BLUMENSTEIN: Yes.

DR. BERRY: I would -- there's a lot of analyses that we've done, and to do that, we would include them as failures. But we would probably include as failures the same in the control group. You know, it doesn't --

DR. BLUMENSTEIN: Oh, that's right. You -- okay.

DR. BERRY: It makes no sense to me.

DR. BLUMENSTEIN: That's fine.

DR. BERRY: This worst-case analysis where you're assuming that patients who don't get the control therapy are all 100% success.

DR. BLUMENSTEIN: Well, now, you don't have to do it as the worst-case imputation.

DR. BERRY: Okay. Okay.

DR. BLUMENSTEIN: No. Just do it as a --

DR. BERRY: So we'll do just that one analysis of --

DR. BLUMENSTEIN: Just redefine your endpoint. And I understand now that I was mistaken. Yes, if they didn't get the surgery, in an intent-to-treat analysis, they're counted

as a failure.

DR. BERRY: Right. Okay.

DR. BLUMENSTEIN: Thank you.

DR. BERRY: We will try to get that to you.

DR. RAO: Thank you.

We had Mr. O'Brien. Then we have Dr. Smith and Dr. Evans.

MR. O'BRIEN: I have some follow-up for Dr. Gornet.

DR. GORNET: Matthew Gornet.

MR. O'BRIEN: Joe O'Brien, sir. First of all, I would absolutely agree with you that in 40 years of discussing with thousands of patients, we have never sat around and discussed our ODI scores or our SF-36s, our SF-22s or any other outcome instrument. Certainly, by and far as you see in the clinic, what we're interested about is quality of life, activity, doing things as Mr. VanLandingham, with touring or socializing, etc.

And certainly with the ODI scores, it's been brought up, some discrepancies that we see in that, both in terms of the ODIs for the population that was selected, the level of it, and also the seeming discrepancy compared to the successive outcomes in this particular study versus what's in the published literature versus the two.

But getting back to it, the other thing I just wanted to get clarification of, it seems also to be a discrepancy between the working ratio. In fact, their control group increased their percentage of work while the investigative group went down on their percentage of work. And I was curious if you'd just respond to that.

DR. GORNET: I don't have that data in front of me, but I would have to look at the

time period, whether they're --

MR. O'BRIEN: Well, this is at 12 months.

DR. GORNET: At 12 months.

MR. O'BRIEN: It went from 69.1% to 63.9% for the investigative group. And then the control group, it went from 74.5 to 77.4 at 12 months, that endpoint.

DR. GORNET: As far as the reasons why that occurred or --

MR. O'BRIEN: Yeah. Why would that increase? If you got such a discrepancy on an ODI but you have, in fact, an increase in working, which is one of the basic activity. You would -- had mentioned, for Mr. VanLandingham, that's one of the things.

DR. GORNET: Sure.

MR. O'BRIEN: He was able to work. Now, granted, I give you there's -- you know, there's work and work. And you can work with a smile and work with not a smile, but you work. So -- and that's certainly one of those most important economic components that we have that we look at in terms of burdens of a particular issue so -- and benefits that -- so I'm just curious as to why that is, particularly with such a discrepancy in the ODI. I find a hard time --

DR. GORNET: Sure. And I'll have to look for that data and see if we have it broken down. We may or may not. But obviously, as you know, one explanation would be patients who are retiring, patients who have different change in occupation. There may be other factors of why they're not at work that may be in the data that I just don't know off the top of my head. So we'll see if we can get that for you, because I think the point's valid.

MR. O'BRIEN: I think that's an important consideration. The other -- to that point

also, in the initial baseline demographics you had indicated the workmen's comp was 12.4% in the investigative group and 13.2% in the control group. But I could not find any 12-month demographic data to tell me what it was at the end of that period of time. Do we have that data?

DR. GORNET: Whether the workers' compensation --

MR. O'BRIEN: Workmen's comp. What the workmen's comp status was at the end of 12 months.

DR. GORNET: You mean, did they still have an active ongoing case with workers' comp?

MR. O'BRIEN: Yes, they -- or new cases, either one.

DR. GORNET: Or new cases? Yes.

MR. O'BRIEN: As a result of surgery.

DR. GORNET: Right. That, I do not know the answer. I'm not sure we collected new workers' compensation cases during that interval, but that could obviously be another --

MR. O'BRIEN: Another indication.

DR. GORNET: -- factor that plays why they're not returning to work. I think that's a point well taken.

MR. O'BRIEN: Okay. The next point, I'd like to switch just to the nonoperative. In the standard of care, we identify nonoperative treatments with a list of five or six of them, including chiropractic.

DR. GORNET: Yes, sir.

MR. O'BRIEN: But I was interested to see that in the study, what you actually did is

you narrowed it down, excluded chiropractic as a treatment, and identified physical therapy, injection, and medication. And the first question was, was that decision based on an evidence-based study that indicated the efficacy of those over any other type of nonoperative treatment?

DR. GORNET: No. I'm not aware of, for instance, any Level 1 data that would support one type of nonoperative care over another. I think, in large part, the answer to that question is, is that CMS as a whole doesn't honor chiropractic or reimburse for that, so there was some concern about including that in the study. And I think that's where the real impetus came from. Personally, I may have done that differently, but that's where I think the impetus came from.

MR. O'BRIEN: To that extent, I would just add that it's very interesting because standard of care changes all the time. We saw it with Ponseti, with clubfoot. We saw it with Mehta and serial casting for --

DR. GORNET: Right.

MR. O'BRIEN: -- EOS. And we're seeing it now in this country with physical therapy, Schroth therapy, scoliosis-specific exercise therapy, which is now becoming a standard of care that existed 60 years in Europe.

DR. GORNET: Right.

MR. O'BRIEN: So to the extent we dismiss nonoperative care because it's not available necessarily for patients, I would just say it's very important if you're going to inform a patient, to inform him, because they may decide to go to Spain or Italy or --

DR. GORNET: Sure.

MR. O'BRIEN: -- whatever the case may be. So just not to give them as an option to do that. I just want to address one other thing. To the 17 patients who did not choose to go to surgery in your -- in the clinical practice, I mean, obviously there are different situations. Some patients, no matter what their condition, they're not going to go to surgery.

And do we know that? And do we know if some patients are opioid-addicted and don't want another treatment because they're getting the treatment they want?

DR. GORNET: Yes.

MR. O'BRIEN: That's there. So there's a number of different scenarios that -- and some of them, to the extent they're actually getting successful treatment. Do we know, within that 17 patients, how many actually may have -- ultimately, regarding that, what their breakdown is or what their category is?

DR. GORNET: Ultimately, in that --

MR. O'BRIEN: Either they're satisfied --

DR. GORNET: -- that group that were eligible for --

MR. O'BRIEN: -- or they're on medication and very -- they're choosing that particular surgery, or just don't want surgery no matter what the case.

DR. GORNET: They're choosing narcotic medicines over an operative --

MR. O'BRIEN: Right. Exactly.

DR. GORNET: I'm not -- I don't have that data off the top of my head. I don't know if we have that information. Yes. I think we could probably get that for you.

MR. O'BRIEN: Okay.

DR. GORNET: Yes sir, I think that's an excellent point.

MR. O'BRIEN: Thank you.

DR. RAO: Thank you. We have Dr. Evans, Dr. Smith, and then Dr. Trier.

Dr. Evans.

DR. EVANS: So let me begin by thanking the Sponsor and the FDA for their thoughtful presentations. I understand the complexities of the issues associated with today's proceedings, and I appreciate the efforts to understand the data.

I think the challenge today is that we have data from a trial that suggests positive effects of the DIAM device. And this is supported by some consistency of the effects across different analysis populations and sensitivity analyses to analysis strategies. But the primary study had a myriad of issues that can create bias and call into question these apparent effects. And we're sort of in a situation where we're asking ourselves, does the apparent magnitude of the effect sort of make up for the trial design and conduct issues that might threaten the validity integrity of this result?

The key issues, from my perspective, are -- first of all, there's been quite a bit of discussion around this topic but -- and I had some confusion, as I read the description. But the criteria or the "bar" for success, as I read it, appears to different -- differ between arms.

Now, if the criteria for success differs between the arms, then how do we interpret a between-arm comparison of success rates? Now, theoretically, this violates a fundamental tenet in clinical trials, that each arm should be held to the same standard and evaluated using some common consistent methodologies.

Now, one might argue that they're not that different, and we're spending a little bit

of time trying to unravel that. But clearly Slide 37 of the FDA sort of alludes to differing definitions of success rates, and it's the way I read the protocol. Now, there seems to be some debate about whether this was the intention or this is the way it read. I know this was the way that I read it. And I'm worried that if I read it this way, then people who implemented the protocol read it this way, and this is the way the study was implemented.

Now, utilization of this aspect of intervention-specific associated AEs and definitions have a lot of complexities. First of all, this study's not blinded. And the non-blinded nature of the study can threaten the reliability of adjudication of relatedness or associated with the intervention.

Secondly, the DIAM arm also allowed nonoperative treatment. And if you're going to count AEs associated with nonoperative treatment in the control arm, then those same AEs should be counted in the DIAM arm. You can't count them for one arm and not another.

Now, there's some confusion about whether that's the case or not, but in looking closely at the data, one questions whether there was sort of uniform collection of that information because it appears to happen more in one arm than another.

The other bigger issue is, there's sort of a subtle distinction between causality and relatedness to treatment. Causality is measured by a contrast of randomized interventions, not by relationship adjudication. Adjudication's helpful for understanding special cases, but a contrast of randomized interventions is the definition of what a treatment effect is, and so this concern about whether such definition of the endpoint is selective.

Now, somewhat related to that is the crossover issue. The issue is that the control

arm has more opportunities to fail than the DIAM arm. If ODI is not improved during some interim, that may be okay for the DIAM arm, at some interim time point. But it may not be okay for the control arm, who gets evaluated, if they choose so, gets operated on. That value gets last observation carried forward, and they fail. So there's more opportunity to fail, which brings up the question about whether similar patients who have similar characteristics in the DIAM arm should also be considered failures.

Now, lastly, there's been talk about the whole intent-to-treat issue. And frankly, given analyses that have been presented, I don't think we should be using the term at all. We randomized -- this study randomized 311 patients. The primary analysis was conducted on 150. That's less than half. Now, there might be reasons for this, but it does bring up concerns about representativeness and generalizability and selection. That selection may not be intentional. But I have questions about why we ended up at 150, and let me break that into two pieces.

Now, part of that might be because there was an interim analysis that was conducted on the first 150 patients. There might be a concern that if those interim analysis results are released, that taints whatever we see afterwards, and therefore let's stick with the 150 that's a little bit cleaner. But you still have the issue about where we've thrown out more than half of the patients that were randomized in this trial.

Now, this interim was conducted in 2013, or at least that's when it was approved to be conducted. I'm wondering where some of this data might be. The second issue is even if we -- now, we might say that the patients after the 150 are only censored administratively, that this is unrelated to treatment assignment, so it's not necessarily biasing what we're

seeing. And that might be true. But even the 150 that we're left with is not intent-to-treat either.

The definition of a primary analysis dataset was also conditional upon post-randomized data. They had to have at least one overall success evaluation. This is excluding patients without this. There's more selection. This is not intent-to-treat either.

So I think there are issues around or at least still questions remaining in my mind about the definition of the endpoint and potential selection of subjects in deciding upon analysis sets. Thank you.

DR. RAO: Thank you, Dr. Evans.

If the Sponsor has a response to that.

DR. SIMPSON: Yes. Dr. Berry's going to address this.

DR. BERRY: So there's a lot of stuff in what you say, Dr. Evans. And much I agree with, and in fact, that was many of the things that you mentioned were precisely my reaction when I saw the data in the study.

In my presentation, I tried to address these questions. I'm from a -- my personal reaction was, initially I said, you know, this is not a good study. This is not the design that you should have done, and I'm not sure how you're going to do.

As I got into it and I saw what happened to the crossovers, what happened to those that chose not to be crossed over that had exactly the same values that they had had at 6 months, that the 6 month, in my presentation, all of the issues that you were worried about, if you focus back to 6 months, are gone.

They were symmetrically treated. The two treatments, the two endpoints were

identical up until 6 months. And that's why I said, the 12 months is -- in big red letters, this is not protected by randomization, and then tried to address, how do we get out of this?

One way was to ignore the crossovers to give the control group the benefit of having the device later. That, I think, is the most important thing to do to equalize the bias or to get rid of as much of the bias as possible. And so that showed really quite a positive result.

The issue of the non-blinding, I mean, I'm like you, like to have blinded studies with placebo or sham. In this instance, I take the opinion leaders to say that we absolutely couldn't do it.

The issue of the nonoperative AEs in the experimental arm, in the DIAM arm, we addressed that with Dr. Blumenstein. Those were treated exactly the same.

The issue of could there be a bias with the nonoperative therapy in the treatment arm and the DIAM arm, that might -- first of all, we wanted to, the company wanted to have something that was superiority, so add to standard of care. It is conceivable that standard of care could change, and there could be biases associated with the nonoperative therapy in one group that might be more intensive or better than in the other group. That is completely possible in an unblinded study. We saw from Dr. Bailey's presentation that these historical results of the benefits of nonoperative therapy are minimal in terms of ODI, with a 5.8% effect, for example.

The issue of the 150 versus the 311, if you remember from Dr. Simpson's presentation, she showed a time chart. And the time chart showed that when the interim analysis was performed, 150, there were almost 300 patients accrued in the trial. By the time it was accepted, as the interim analysis had been done, the trial stopped with 311

patients; that was actually a few more than the 306 that was targeted originally.

I, like you, focus on the all-available. And so -- but we've done both. We've done what the FDA and the company agreed to as the primary dataset, but we've also done the all-available dataset, which were followed as meticulously as the primary dataset.

So this business about, that you ended up talking about, the more opportunity to fail, I agree, but I think we've accounted for it. And certainly at 6 months we've accounted for it. But at 12 months, through this -- forgetting about the crossovers, making them so that they're not failing, give them the opportunity to get the DIAM as a rescue, something that in fact was effective for them and turned them into successes, I think it's a positive study.

DR. RAO: Thank you, Dr. Berry.

Dr. Smith.

DR. SMITH: As a quick question for clarification, my understanding, in the control group, if an individual had continued pain and needed or received an injection, that was considered an adverse event. Is that correct?

DR. SIMPSON: I don't -- an injection alone was not considered an adverse event.

DR. SMITH: It was said there was some wording, there were some comments made. There were -- if someone was in debilitating pain or suffering in the control group, then that was considered an adverse event, I had thought. It was the impression I got.

DR. SIMPSON: Increasing pain would be considered an adverse event.

DR. SMITH: So if an individual's -- so I don't know if we have the exact answer, but I guess I get the impression, and it raises a scenario where if an individual's in a control

group, was in a lot of pain and they went and got an injection, it may have been considered, maybe was considered an adverse event for some of them.

So the follow-up to that question would be, if an individual underwent surgery, and let's say 6 months after surgery they were in pain, and they got a facet injection or an epidural injection after the surgery, was that considered an adverse event?

DR. SIMPSON: So in that case, again, the act of the injection itself would not be an adverse event. Increasing pain could be an adverse event, and they might receive an injection.

DR. SMITH: Okay. Thank you.

DR. RAO: Dr. Trier.

DR. TRIER: Yes, Dr. Trier here.

I was actually going to also ask about bias. Thank you, Dr. Evans, for bringing that up. As you were speaking, if I could speak with Dr. Berry, or pose this question to Dr. Berry.

In your presentation, you addressed the issue of the bias of crossover. You addressed, just now you addressed the differences in the treatment. The one that is in your presentation that you haven't addressed has to do with the last observation carried forward. And I know that you've done a lot of analysis to clarify or to take a look at those biases. And I wondered if you could also speak to that as well, or other analyses that you did to look at bias.

DR. BERRY: So this is from the FDA's concerns.

DR. TRIER: Yes.

DR. BERRY: And they're very closely tied together, the issue of crossover and LOCF.

The way it's written is, if you cross over, then the ODI is carried over from 6 months. It's also written that -- and so you could theoretically be a success at Month 12. If you were a failure -- if you chose to cross over, but then it says that you get this last observation carried forward. What does that do? It means you're a failure.

So, in effect, if you qualify for crossover and you choose to cross over, then you're automatically a failure because of the LOCF. So the two things are very closely tied together, and in one sense, are one and the same.

DR. RAO: Thank you.

Dr. Cheng.

DR. CHENG: Thank you. I just want to respond to Dr. Gornet's comment, and maybe he or the other Sponsors in the room can help me understand.

Why is it that you prepositioned this -- the premise of your device is that it's for that treatment gap. But why isn't a microdiscectomy a treatment alternative for people with herniated discs, as about a third of the people are in your study, and why isn't it a limited decompression an option for those with spinal stenosis?

DR. SIMPSON: Sure. Dr. Kitchel is going to address it.

DR. CHENG: And the other thing is the placebo effect. I appreciate that we could argue all day whether or not a sham surgery is ethical. And it clearly does make doing a study more difficult. There's no question about that. However, you've also positioned this as minimally invasive surgery, and that's been done, for thoracoscopy, for example. For a major surgery, of course, we're not going to do a sham surgery, but one could actually do that for this type of device, which is minimally invasive. So I think that is an alternative that

shouldn't be just dismissed out the window.

DR. SIMPSON: Sure. Dr. Kitchel.

DR. KITCHEL: Scott Kitchel.

I'll try to take on your second question first because it's freshest in my mind. If you remember Dr. Bailey's technique guide, this is about a 5 cm incision, so I will agree with you that minimally invasive is in the eye of the beholder. But a 5 cm incision, to have a sham operation, I or if I were advising my family member or a patient, I would have a real ethical problem with that. I think that that -- you know, the risk of infection is substantial, and there are many reasons I think you would even have trouble getting that through our IRB at my institution.

Your second question is about why we didn't consider other potential surgical controls, or why these patients would be appropriate for decompressive surgery. There's a couple of things to that. I think the first one is, you have to remember that the number one inclusion criteria is moderate back pain.

When I see a patient with back pain who tells me they have back pain greater than leg pain, about the time they get that out of their mouth, for 90 plus percent of them, I don't think they need a decompressive operation. If I'm going to do anything to their back pain with a decompressive operation, I'm likely to make it worse.

The second one is, if you think about going back to the case examples we showed, it's a very broad categorization of disc protrusion. If you look at the amount of disc bulging in those two patients we showed, they both would have technically qualified under the subcategorization as disc protrusion patients. But that's the classic thing my grandpa told

me, you would have never got your bait back if you'd have gone and done a lumbar discectomy on them. There's not any nerve or compression. There's nothing you're going to make better by taking that piece of disc out that's causing the problem.

The last one, I guess, is the question about spinal stenosis surgery and the narrowing of the foramen. Again, if that patient says, I've got leg pain that's 8 out of 10 and back pain that's 2 out of 10, or my leg pain is 70% and my back pain is 30%, I'm certainly going to think about that. But that isn't the group of patients that we're treating. The group of patients in the inclusion criteria is people who have predominant back pain that may or may not have accompanying leg pain.

DR. CHENG: Well, thank you. I appreciate that the -- I'm just wondering. I mean, it appears that, as I look at this, despite the statistical arguments that are being made, there appears to be something going on. I'm not sure what it's due to, and I'm trying to define in my own mind the patient population that this is for. But it certainly seems like that this is not a panacea. It does something. But a lot of the patients are having injections again, and 10%, approximately 10% in each in the control arm and in the patient group had additional surgeries at the index level. So there's still problems going on with these patients.

DR. KITCHEL: And I think we would completely agree, especially with the part that it's not a panacea. And also I think we've tried to emphasize the fact that this doesn't reverse degenerative disc disease. This doesn't eliminate that degenerative cascade. It continues to go on. You could make a point that perhaps this device is just prolonging the inevitable, and that 10 years down the road they're going to need that decompression or they're going to need that fusion.

But I think even if you -- if that's the best-case scenario, if you get a 10-year delay, that would be a tremendous clinical improvement in my practice.

DR. RAO: Thank you, Dr. Kitchel and Dr. Cheng.

Just a little offshoot of the same points that Dr. Cheng has raised of a placebo effect and Dr. Evans raised earlier about the study design, Dr. Blumenstein's point about the study design.

We've talked about maybe Dr. Kitchel feels a placebo effect thing would be unethical to carry out, but what about this nocebo effect where this group that was placed in the control group, in the control arm for the first 6 months, has the same level or slightly higher level of pain going into that arm. They're told, you can't have this. You got to keep doing what you were doing previously, and they're treated nonoperatively. All of a sudden at the 6-month mark, there's a rush of patients switching over to the DIAM group. Could there be some negative effect of the treatment expectations in that 6-month group, and could that potentially skew the results of the study in some way?

Dr. Berry, do you have any thoughts?

DR. BERRY: So I think the clinicians who work with patients probably would have some thoughts to it. It's hard for me to imagine that a patient who signed on to this study and agreed to be, to accept the standard care for 6 months, that somehow would fake things, would say things differently about what their pain was and what their disability was. And the --

DR. RAO: Where did that come from now? I don't -- I'm not sure I understand where that came from.

DR. BERRY: Well the --

DR. RAO: Why would they have to fake things?

DR. BERRY: I'm not sure you were suggesting that --

DR. RAO: No.

DR. BERRY: -- but others in the Panel have suggested that maybe you could bias the results of the report that you give to your physician because you know that if you are a failure at Month 6 --

DR. RAO: No, I'm not actually --

DR. BERRY: -- you could qualify for -- okay.

DR. RAO: No, I think that may be distracting it a little bit. They've got pain.

DR. BERRY: All right, say it again.

DR. RAO: No. They are saying they have pain, and I accept that. They're saying they continue to have pain at 6 months. Now, at 6 months, they know they can switch to the operative arm. And there's this rash of patients that switch from the nonoperative to the operative right at the 6-month mark. So is it possible that this just somehow creates a less than ideal statistical environment for the entire study?

Your point was, for the first 6 months, everything was perfect. The statistical design was perfect. And maybe it was. But then, overall, do we get good enough data to evaluate the product well?

DR. BERRY: So, first of all, it's not a rash at 6 months. There -- you qualify at 6 months, and it's always the 6-month value that's carried over because there are no visits scheduled between 6 and 12. So there is a accumulation over that period of time. So what

happens then is you get the surgery. And as you saw from my graph, you do better. And so when you get to Month 12, you do better.

And so in some of the analyses that we did, we used the actual ODI, and we forgot about -- we didn't do this LOCF. We didn't do this, you know, negative association with crossing over. And so you got the benefit -- in the control arm, you got the benefit of that value. And my own view is, especially when you compared it to those who didn't cross over, that you did better if you crossed over, and you contributed to a higher success rate in the control arm, and the data, I think, suggests that.

DR. RAO: Thank you, Dr. Berry.

Dr. Yang and then Dr. Topoleski, and then Dr. Graf and Mr. O'Brien, Dr. Finnegan. A lot of people.

(Laughter.)

DR. RAO: Dr. Yang first.

DR. LYNDA YANG: So, yeah. So, like Dr. Cheng, I'm looking at this from a clinician, and I'm reading these package insert and labeling. And already, you know, in the indications line, it talks about, you know, for moderate low back pain, not for, you know, DDD or something else. That's already a problem.

But even worse is in the contraindications, it actually says, symptoms attributed to more than one lumbar level. Now, even looking at the examples that were presented this morning, after 10 years of -- for more than 10 years of practice, I don't know how to attribute low back pain to one lumbar level, especially when given without a radicular component or electrodiagnostics or something. So how do you know? I mean, how do you

know what lumbar level are we targeting here?

DR. RAO: So the question really is, in a patient with multi-level degenerative changes, without translation at any one level, without marked stenosis at any one level, how do you identify the level you're going to treat with this device? If we could get a quick answer, please, because we've got three or four questions, and we've got 9 minutes.

DR. SIMPSON: Sure. Okay, Dr. Bailey's going to address that.

DR. BAILEY: I would agree, it's a challenge. We treat our patients who come in our office with back pain. We try to identify their primary pathology. We try to diagnose them through imaging studies, clinical examination, to provide the best treatment possible.

Those patients with multi-level disease, I don't take them to multi-level fusion. Those patients with multi-level abnormalities of stenosis, I try to treat the primary pathology that matches their radiculopathy. Low back pain is far more challenging in terms of that diagnosis.

We look at MRI scans. We look at patients. We use provocative discography if we have a question. And the symptomatic multi-level degenerative disc disease patients, at least through our clinical acumen, were never included in the study.

If we look at the long-term data through this process, 5.5% of patients received additional surgical care at adjacent levels. So looking at our 5-year data, we have been fairly accurate in identifying the single symptomatic level. That actually is better than my fusion rates.

DR. RAO: Thank you.

Dr. Topoleski.

DR. TOPOLESKI: Well, just let me ask you, Dr. Rao. I'd like to ask some questions about the mechanics of the device, and the thread of the questioning is a little bit different now.

DR. RAO: If we can get it -- wait, no.

DR. TOPOLESKI: Shall I wait until after the break and let the --

DR. RAO: No. Actually, this is the time to ask --

DR. TOPOLESKI: This is the time? Okay.

DR. RAO: -- just a quick response, please. A quick question and a quick response.

DR. TOPOLESKI: So in the Sponsor's presentation -- and I agree with Mr. VanLandingham, it's a very simple and elegant device. But oftentimes the response to the erosion was it's not inflammatory erosion, it's just a response to Wolff's law. And I would probably make the argument that any orthopedic device, and anything connected to the bone, if it's not aseptic failure or if it's not related to osteolysis, any loosening is a response to Wolff's law. And you can Wolff's law yourself to having no process there.

So I'd like to see, you know, perhaps a little more maybe effort in explaining what's going on with the mechanics. And if you look back at the mechanical testing -- and I realize this was agreed to in 2006, something like that. I can accept that those were good standards and good place to start. But a couple of comments that I have is that all of the conditions and loading were probably based on healthy spinal biomechanics, and seeing your patient population, there's going to be a huge range of mechanics going on there and maybe more severe tests are necessary.

The tethers are actually kind of acting like ligaments. And their tightness or laxity is

going to be important in the mechanics as time goes on. And so tensile creep of this, of the PET, I would think, would be a very important set of data to have and to understand. I would think Medtronic would want to know that. What's going to happen to this material as it's pulled and stretched over time?

And, finally, in tension fatigue -- and I noticed that there's a lot of good data on artificial aging, but one of the classic failure initiation mechanisms in a woven fabric is fraying. And I think Dr. Gilbert pointed out earlier, and Dr. Rao, that there was evidence of fraying. And so the artificial aging addresses the polymer itself but not the structure. And perhaps maybe it would be appropriate in a post-approval study or going down the line to do some more extensive and more defined testing on the integrity of the device.

DR. SIMPSON: Okay. Sure. Dr. Bailey can address this.

DR. BAILEY: Partially, I believe.

I understand the question around the tethers. I would indicate, from a clinical basis, the tethers have very little to do with the mechanism or function of this device. I would indicate that the tethers are placed to position the device, to secure it in position as scar tissue develops and the device becomes truly embedded in the area. I don't think, on the long term, a tether secures that device in its position.

The shape and form of the device is inherently positioned. But I think if those tethers even broke at 6 months, it would have no clinical effect. I can't prove that aspect, but from a biomechanical aspect, just from a logical spine issue, I don't think it has any long-term issue.

DR. TOPOLESKI: Well, that's -- and that's a good point, but there was nothing to

indicate that that was how the device worked, that the tethers were to be embedded or surrounded by soft tissue. And I did have a question, what would happen if a tether broke. So those are things that maybe could be put into official documentation or something.

DR. BAILEY: From an in vivo standpoint, I think, shortly after scarring and healing, they have no clinical benefit.

DR. RAO: We have two --

DR. BAILEY: Or detriment.

DR. RAO: Thank you.

We have two quick questions, and then we'll move on to the question session. And there will be some time for discussion during the question section, but we have Dr. Golish and Dr. Finnegan.

DR. SIMPSON: Can we also address the portion of that question about the erosion, too, from a radiological standpoint? Is it okay?

DR. RAO: Say that again.

DR. ROBERTSON: Bioengineering.

DR. SIMPSON: Bioengineering standpoint, sure. Yes. Is that okay?

DR. RAO: I'm sorry. Say that again.

DR. SIMPSON: I don't think we completely answered all aspects of that question.

DR. RAO: If you have a quick question we can -- quick response, we can go ahead.

DR. ROBERTSON: I'm Doug Robertson. I'm a radiologist and bioengineer from Emory University and Georgia Tech. Quickly, I agree with you. Wolff's law, by itself, can be catastrophic. Wolff's law and inflammatory reactions are different option. If we're thinking

of total joints, right, and you've got calcar resorption with a total hip, that's more Wolff's law. The osteolysis is in the inflammatory reaction, right?

What we're seeing here, radiographically, is a finding of contour change, but you need a secondary finding. The secondary finding is you maintain the cortex or the bone mineral density adjacent to that edge, with an erosion or an inflammatory reaction contour change, but you lose bone density, the cortex either goes, and that's how we differentiate. And you mentioned it today, were they healing? Well, this is remodeling. It's not an inflammatory reaction where it's either an active lesion or an inactive lesion.

But with regards to the -- we're not seeing osteolysis. We're not seeing inflammatory reaction. We're seeing contour change. And I don't -- it's not catastrophic. Wolff's law can be catastrophic, right. You've got that gray zone where you maintain bone, and then if you -- too much, it goes away, too little, same -- you've got the same -- too much, you break it, too little, it goes away. We're in that gray zone of remodeling, and it seems stable up to 60 months.

So it's -- I truly think it is Wolff's law with no -- at least, as far as we can tell from the histology and what we see radiographically with the findings, it's compatible to what we'd be calling remodeling changes for, you know, decades now.

DR. RAO: Thank you.

Dr. Golish.

DR. GOLISH: I defer, in the interest of time.

DR. RAO: Dr. Finnegan.

DR. FINNEGAN: Two quick points. One is, there were more smokers in the control

group than there were in the DIAM group, and I'm wondering if smoking cessation or smoking education was part of the program. And the second one was, to follow up with the radiologist, was there any consideration to limited slice CT with 3-D reconstruction to actually figure out exactly what was going on with these lesions?

DR. SIMPSON: The answer to your first question is, I don't believe that that was a part of this. And Dr. Harry Genant is going to address the second part of your question.

DR. GENANT: Good afternoon. I'm Harry Genant. I'm a Professor Emeritus of Radiology, Orthopedic Surgery, and Medicine at the University of California, San Francisco.

So -- repeat the question, please.

(Laughter.)

DR. FINNEGAN: The question was, was there any consideration given to limited slice CT with 3-D reconstruction to --

DR. GENANT: Yes.

DR. FINNEGAN: -- actually get a good feel for these.

DR. GENANT: Yes. With regard to the use of a CT, we recognize that there have been some publications that have indicated a CT is more sensitive than conventional radiography in detecting either erosive process or spinous process fractures. However, we must be mindful that with this device, this is largely radiolucent. And so conventional radiography, in fact, is pretty sensitive and reasonable at visualizing the spinous process and to be able to determine aspects of bone remodeling and/or the fracture, particularly these being near the tip of the spinous process and posterior to the interface with the device.

DR. RAO: Thank you, Dr. Genant.

Mr. O'Brien, we are 1 minute past our schedule, but you can either continue taking care of the American public's good health, or you can reduce the amount of time you have for a break. What would you like to do?

(Laughter.)

MR. O'BRIEN: Being who I am, in interest of everybody else, I'll wait.

DR. RAO: No. Please go ahead. I was just joking. Go ahead --

MR. O'BRIEN: No, no.

DR. RAO: -- ask your question. We'll just shorten the break a little bit.

MR. O'BRIEN: I was just looking at the patient brochure, and I just have two items with that, and one other question for Dr. Berry, comment.

In the patient brochure, the one item that's exclusionary is BMI. But I don't remember, is BMI included as an inclusion or exclusion criteria within either arms of the study?

DR. SIMPSON: There as an exclusion criterion, or there was some kind of maximum rate. Actually, I don't have that document in front of me right now, but I --

MR. O'BRIEN: There was --

UNIDENTIFIED SPEAKER: It was 40.

DR. SIMPSON: Forty.

MR. O'BRIEN: Okay. So it was in the study?

DR. SIMPSON: Yes.

MR. O'BRIEN: And in both arms of the study?

DR. SIMPSON: Yes.

MR. O'BRIEN: Okay. The second thing is, is that there is a question, a frequently asked question regarding how long it will last. And the answer to that highlights the 80-year lab. I would suggest that, you know, as has been pointed out by Dr. Kitchel and others here, clearly there's no evidence to show that this is curative in any nature or that it's going to stop the nature of degenerative disc disease. And there's no evidence to show that long term, fought within humans, it's going to be -- it addresses this a little bit, but as we saw the one testimony from Mr. VanLandingham, he made a 40-year decision. I'm not quite sure he was informed to say that this really is a 40-year decision, and he should know that.

DR. SIMPSON: And as you know, the patient labeling is part of the ongoing negotiation with FDA, and so that point -- point well taken.

MR. O'BRIEN: The last question with Mr. Berry -- Dr. Berry, sorry, regarding bias. On a non-blinded study, patients were coming in with ODI of 49 indicated on there. Anecdotally, clearly yes, patients will put misinformation on outcome instruments, absolutely, to either get medication or to get a treatment they want or to be validated. We saw in the evidence and the data -- and I don't know what -- we don't have no detail, that 10% of the investigative group has psychological disorders.

I don't know what the nature of that is, but clearly from a patient perspective, yes, you will see that, to do that. So I think that has to be understood, that that bias does have a strength there. It is important to understand.

DR. SIMPSON: I do want to point out that although -- yes. Dr. Berry can speak, but I want to say very quickly that there were also many non-patient reported outcomes included in the study that are handled by independent reviewers, too. Dr. Berry can add to this.

DR. BERRY: I agree. I don't have anything to add.

MR. O'BRIEN: Okay. Thanks.

DR. RAO: Well, thank you. We will take a 10-minute break. We will be back here in the room at 3:15 and start sharply at 3:15.

(Off the record at 3:05 p.m.)

(On the record at 3:14 p.m.)

DR. RAO: At this time, let us focus our discussion on the FDA discussions. Panel members, copies of the questions are in your folders. I would ask that each Panel member identify himself or herself each time he or she speaks, to facilitate transcription.

Mr. O'Neill, please show the first question.

MR. O'NEILL: Please refer to Section 1.2 in the FDA Executive Summary for background information related to the FDA questions.

Study Population. Based upon the observations described regarding the study population in Section 1.2 of the FDA Executive Summary, please address the following questions:

a. Please comment on the adequacy of the study population in this IDE clinical trial to support the proposed indications for use.
b. Please comment on the impact of the observations (for example, heterogeneity, ODI severity) described in Section 1.2 in interpreting the results of this IDE clinical trial in the context of the DIAM investigational device and its proposed target population.

DR. RAO: Do you have a slide with the questions? Yeah.

MR. O'NEILL: c. Please comment specifically on the heterogeneity of the study

population and whether the clinical data provided in support of the PMA are poolable for the purpose of evaluating the safety and effectiveness of the DIAM Spinal Stabilization System for the proposed indications for use. Please comment regarding whether the clinical data requires stratification and analysis according to specific types of spinal pathology (i.e., disc herniation, spinal stenosis, facet degeneration, degenerative spondylolisthesis, low back pain associated with degenerative changes limited to the anatomic components of the intervertebral disc) in order to permit a clinically meaningful interpretation of the results of this clinical trial. If you believe that stratification of the study data according to clinical subgroups is necessary, which specific subgroups are recommended, and how should these subgroups be defined?

DR. RAO: Thank you, Mr. O'Neill.

I think we will now go around the table and get responses from each of the Panel members. Let's do Question 1a first.

Based upon the observations described regarding the study population, please address the following questions. Please comment on the adequacy of the study population in this clinical trial to support the proposed indications for use.

Dr. Trier.

DR. TRIER: My understanding -- this is Dr. Trier.

My understanding of the study population is that it is representative of the population of patients that individual practitioners would see in their practice. As called out in the indications, it is for moderate low back pain secondary to DDD. Based on the evidence that was presented by both the Sponsor and also by FDA, they did look at various

subgroups in the population and presented those results. And the results, as presented by FDA and the Sponsor, were relatively consistent across those groups. So I would say that it is reflective of the practice that you would see.

DR. RAO: Ms. Harmon.

MS. HARMON: Monica Harmon.

I would also agree with Dr. Trier that the study population that has been presented today, as the information was presented, does look like patients that you would see. I do, however, have a concern that wasn't addressed, and that's in terms of the makeup of the population, that being that when you look at the demographics, it is overwhelmingly male, overwhelmingly white.

And so my concern is, who was really offered the treatment? Was it just these patients, or were others offered as well, or were just clinically excluded? Thank you.

DR. RAO: Mr. O'Brien.

MR. O'BRIEN: First, I do want to address that. I absolutely appreciate what Medtronic, the Sponsor and what the device industry does, and express an incredible need for innovation and a support of innovation and understand the gap that has been identified.

Relative to the question of (a) and perhaps with (b), I am left not with the opinion that we've really identified the targeted population that could benefit from this. I think there's too much confounding issues and bias and etc. So I don't think we've really -- I think there's a real need. I think the device may be good. But when I look at this study, I don't walk away with the sense that we've really got to the targeted person and compared that and satisfied with the risk-benefits versus other options that are there, either over-treating

or under-treating -- well, under-treating.

DR. RAO: Thank you.

Dr. Yang.

DR. LYNDA YANG: Lynda Yang.

Like Mr. O'Brien, I think that taking on back pain is really commendable. However, like Dr. Gilbert, I feel like I'm swimming, and I really don't think, given what we saw today and the volume of questions and the lack of answers, that the study population was in any way adequate to support these proposed indications.

DR. RAO: Thank you, Dr. Yang.

Dr. Topoleski.

DR. TOPOLESKI: Tim Topoleski.

I don't have much to add. I need to defer to my colleagues on this. But given that there's a lot of confusion in the room, I have to agree that I'm not --

DR. RAO: Dr. Smith.

DR. SMITH: Harvey Smith.

I think a problem is that the primary target audience for the device is axial or back pain patients, but in the study population is heterogeneous with a significant number of people with buttock and leg pain, which also confounded the treatment effects. And based on that, I don't think it's an adequate study population.

DR. RAO: Dr. Finnegan.

DR. FINNEGAN: Maureen Finnegan.

I do not think there's adequate study population based on the pure bottom line,

which was 93 patients that didn't fall out in the DIAM group and a smaller number even in the controls. And I don't think that's an adequate number for a study.

DR. RAO: Thank you, Dr. Finnegan.

Dr. Gilbert.

DR. GILBERT: Jeremy Gilbert.

I think what I learned today is that the beautiful mathematical discipline of statistics, when it meets the world of a clinical study, does not -- the Venn diagram does not overlap. It just seems like when you try to bring the pure statistical assessment to real people with real conditions, and a device that's attempting to address those conditions, it's an extraordinarily difficult thing to do.

And so I'm left here trying to decide whether the bias and the heterogeneity of the population group was so significant to render the differences that were presented to be more chance than not.

And so I'm having difficulty reconciling that. I believe there is some beneficial effect of this device based on the ODI scores that were presented. I guess what I would -- in my very simple -- I'm a statistical amateur, I think. And so the way I would think about this is, I have two groups that have a mean. They have a variation about the mean. You're trying to see if they're far enough away, based on the spread of the variation, to say they are different and that one is better than the other.

And then the heterogeneity, it seems to me, spreads the variation. And then the bias perhaps shifts the means and maybe changes the spread. And in all of that, I'm still trying to decide if there's a real difference or not that demonstrates safety and

effectiveness.

And I came into this meeting thinking that even with all of those biases and all of that heterogeneity, there is some benefit that was borne out in this study. But with the uncertainty that's been raised, I am now in an uncertain place.

DR. RAO: Thank you. Thank you, Dr. Gilbert. We're talking just about Question 1a.

Dr. Evans, what do you think of the adequacy of the study population to support the proposed indications?

DR. EVANS: Yeah. I don't have any specific comments on the population.

DR. RAO: Dr. Blumenstein.

DR. BLUMENSTEIN: Well, I -- not being a clinician that sees these patients, or a clinician at all, for that matter, I'm sensitive to the idea that maybe the intent of the type of patients coming into the trial were not realized in the trial. And, in fact, a more serious or more advanced patient was actually enrolled than was envisioned.

I don't know that. There seem to be words to that effect. I'm particularly concerned about the influence of the promise of a drop-in or crossover, whatever you want to call it, on the way the control arm patients behaved, knowing that eventually they would be able to get the "good stuff" and how that might have influenced the outcome of the study.

So those two elements together give me pause as to whether the study is informative with respect to the intent of the treatment or the gap, as it was referred to before.

DR. RAO: Thank you.

In case anyone doesn't know, I think that Commander Anderson mentioned it

earlier. The Section 1.2 of the FDA Executive Summary is in your folder. I believe it's on the right-hand side of your folder, in case anyone would like to refer to it.

Dr. Golish.

DR. GOLISH: I can be empathetic with the Sponsor in that attempting to adopt FDA's DDD definition 4.1, they are left with the opportunity and the challenge to acknowledge that we're talking about anterior, middle column, posterior degenerative stenotic pathology and really the whole thing. And this has bedeviled us so many times. It has confused the 2010 AMPLIFY Panel, the 2015 Superion Panel. All the way back to 2005, the panels could not arrive on a definition. We essentially reinvented that definition just last year within the context of a specific PMA. And it continues to be problematic.

So, that said, I would say that it's hard to understand how the design rationale of this device captures all of those different subsets that we talk about, clinically. Though they may be overlapping in a pathoanatomic cascade, clinically we attempted to find anterior discogenic type phenotypes, posterior facetogenic type phenotypes, stenotic neural compressive and with or without instability type phenotypes. And without differentiating those three things, trichotomizing them, previously the whole thing at the end, having to look at it with post hoc rea, I find scientifically unsatisfying.

DR. RAO: Dr. Graf.

DR. GRAF: Carl Graf.

Yeah, I think that was nicely said, because this is a big problem that does exist in clinical studies but is very difficult to define. In fact, the FDA's definition of degenerative disc diseases as presented today is different, in fact, than Medtronic's definition.

So, you know, we're taking multiple diagnoses and trying to lump them together, and it's very difficult to do. And I can appreciate it from both sides. You know, does the study population -- it's a difficult question to answer because we can't even agree upon a definition of what we're attempting to answer.

DR. RAO: Thank you, Dr. Graf.

Dr. Cheng.

DR. CHENG: So I would agree, the answer's no. It's too broadly defined right now, and I think it's -- if the FDA and expert panel couldn't do it in 2005, and it's broadly defined as in the slides we were given today, I think it's going to be very, very difficult for the surgeon and the community to choose the correct patient.

DR. RAO: Dr. Auerbach?

DR. ESKAY-AUERBACH: I would agree with everything that's been said before. And I would agree, no. I particularly have difficulty with the multi-level degenerative disc disease in terms of being able to isolate a single level as the symptomatic level.

DR. RAO: Mr. Melkerson, with regards to Question 1a, I believe the Panel generally feels that the heterogeneity of the study population, in terms of the lumbar disc and facet joint and motion segment pathology, leads us to state that the study population in this trial does not allow us to support the proposed indications for use.

In addition, there was some question that the way the study was designed, it was difficult to say whether the results resulted purely from chance.

In addition, there was a suggestion that there should be greater gender and racial diversity within the study population to allow extrapolation to the greater population.

Is that adequate?

MR. MELKERSON: Yes, thank you.

DR. RAO: I think Question 1b is somewhat similar and somewhat overlaps. But we'll go around it in a different way.

And Marj -- Dr. Auerbach, could you comment on your response for Question 1b?

DR. ESKAY-AUERBACH: Well, I think there were four topics, at least, identified, including heterogeneity, ODI severity, post-treatment surgical interventions, and a screening algorithm. I think many of those are confounding factors, particularly the post-treatment surgical interventions. So they -- I do think that plays a role or does have an impact on the study.

DR. RAO: Thank you, Dr. Auerbach.

Dr. Cheng.

DR. CHENG: I don't have anything additional to add.

DR. RAO: Dr. Graf.

DR. GRAF: You know, again, it's just difficult to interpret the results, given that we're starting out with a single diagnosis which contains multiple subset diagnoses within that.

DR. RAO: Dr. Golish.

DR. GOLISH: Nothing to add.

DR. RAO: Dr. Blumenstein.

DR. BLUMENSTEIN: Nothing at this moment.

DR. RAO: Dr. Evans.

(No response.)

DR. RAO: Dr. Gilbert.

DR. GILBERT: Nothing to add.

DR. RAO: Dr. Finnegan.

DR. FINNEGAN: So the only thing that I had to add was that it seemed to me that perhaps the ODI severity would suggest that this study, in fact, shows that it's a good adjunct to treating the more severe disease, but it certainly doesn't look like it's a primary.

DR. RAO: Thank you, Dr. Finnegan.

Dr. Smith.

DR. SMITH: I don't have anything to add.

DR. RAO: Dr. Topoleski, nothing. Dr. Yang, nothing. Mr. O'Brien.

MR. O'BRIEN: I would just say, I'm not sure about adjunct versus primary. I think there -- in fact, there are -- I believe there are patients, I think the DIAM would be very effective and is effective for them. But as I said, my concern is I couldn't tell from the study who that is.

DR. RAO: Thank you.

Ms. Harmon.

MS. HARMON: The only thing that I do have to add is that we should -- well, the Sponsor should probably think about another study and adding more information.

DR. RAO: Thank you, Ms. Harmon.

Dr. Trier.

DR. TRIER: One comment that I think needs to be said at this point is that the clinical study obviously had its issues. There are various biases or observations that have been

made. But I think when you look at the analysis across the various subgroups, and when the bias has been taken into account, there is still at least a seeming treatment effect that we need to at least consider.

DR. RAO: Thank you, Dr. Trier.

Mr. Melkerson, with regards to Question 1b, the Panel generally seems to feel that the observations described in Section 1.2 of the FDA Executive Summary, including heterogeneity, ODI severity, do impact our ability to interpret the results of this IDE clinical trial.

Is that adequate?

MR. MELKERSON: Yes. Thank you.

DR. RAO: With regards to Question 1c, Dr. Finnegan, I'll start with you this time. Let's just go through the question real quickly, so there's no rush to answer.

Specifically, on the heterogeneity of the study population and whether the clinical data in this PMA are poolable for evaluating the safety and effectiveness of the Stabilization System for the proposed indications, would you prefer stratification and analysis according to different types of pathology in order to allow a more clinically meaningful result? If you prefer, if you believe that stratification is important, which specific subgroups do you recommend?

DR. FINNEGAN: Which one?

DR. RAO: Dr. Finnegan, yes.

DR. FINNEGAN: Okay. So I actually do think that stratification would help everybody. And what I would do is the true single-level disease. And then I would leave it

up to the spinal surgeons to do the other ones, but I would think that spinal stenosis and spondylolisthesis are sort of in a class by themselves. But I do think stratification would help.

DR. RAO: Dr. Gilbert.

DR. GILBERT: Jeremy Gilbert.

So, again, I revert back to my knowledge of statistics. And when you have a heterogeneous study population, it brings in inherent variability into the group, making it more difficult to show a difference, yet a difference was still shown. And so I'm not entirely sure that it's inappropriate to pool these, based on that concept. And I will defer to my clinical colleagues as to if you need to stratify or not.

DR. RAO: Dr. Evans.

DR. EVANS: Well, when you're deciding whether you should pool data across subgroups and so forth, you can take two approaches. You can either assume it's okay until there's evidence to the contrary, or assume it's not okay until there's evidence to the contrary.

Unfortunately, in order to get enough evidence to answer either one of those question usually requires external data, and enough data to answer that question, which I don't think you'd have enough -- given the number of factors here and the number of different ways that it could be broken up, and the concern of the clinical colleagues about the clinical heterogeneity, you're not going to get enough information from the study itself to determine that.

So I think that the data that would indicate whether it's okay to pool or not is going

to have to come externally.

DR. RAO: Dr. Smith, if you could in your answer also talk briefly about what the pools could be potentially.

DR. SMITH: Harvey Smith.

I concur with the comments that have been made to date, in terms of I think it is too heterogeneous and would benefit from being subdivided. In terms of groups, I think it's important to differentiate mechanical low back pain, like true, what is classically called true discogenic disc disease from individuals that have a neurogenic component of buttock and leg pain. Because as we've seen some from many other -- such as the SPORT trial, individuals can have neurogenic buttock and leg pain and associated back pain, and the back pain will improve when the neurogenic leg pain gets better if you do something that, intentionally or not, causes an indirect decompression of the neural elements.

And so I think we have to differentiate the pathologies from true mechanical low back pain versus neurogenic symptoms. And I recognize that, at times, that's hard to do, but perhaps if an individual we can't truly delineate which is the primary symptom, then they may not be the best individual for a trial to try to assess the efficacy of the device.

DR. RAO: Thank you, Dr. Smith.

Dr. Topoleski.

DR. TOPOLESKI: Tim Topoleski.

I don't have much to add, although I agree with Dr. Trier that it's quite interesting that regardless of the patient's background, they seemed to have had an improvement, which indicates to me that now we have an interesting hypothesis. But in listening to my

colleagues, we don't quite have the study to prove that hypothesis.

DR. RAO: Dr. Yang.

DR. LYNDA YANG: Lynda Yang.

Given that the indication is for the treatment of moderate low back pain, etc., I agree with Dr. Smith. I still think it's important to have the back pain only, and back pain plus leg pain, however difficult it may be to define.

DR. RAO: Thank you.

Mr. O'Brien.

MR. O'BRIEN: I don't have a statistics background, so I can't really address poolability from a statistics perspective.

DR. RAO: It didn't stop Dr. Blumenstein from doing that.

(Laughter.)

MR. O'BRIEN: I do think it would help to stratify. I don't think that's the most important point. I think the next thing we get into is. And I would just look at the colleagues around this table, the experts, as to what the group should be.

DR. RAO: Ms. Harmon.

MS. HARMON: I also believe that it would be important to stratify. As my colleagues, nonclinical and clinical, have already stated, there are a lot of questions with the information that has been provided today. And probably stratifying will give us more questions, but I think we'll have a better sense of where we need to go with this device.

DR. RAO: Thank you.

Dr. Trier.

DR. TRIER: I have nothing to add.

DR. RAO: Dr. Blumenstein.

DR. BLUMENSTEIN: Unfortunately, the trial size is too feeble to be able to see anything but a really distinct evidence of heterogeneity. I can't comment, clinically, whether it's important, other than to mention that I still -- I've had from the beginning, still have concern about long-term effects beyond a year and whether or not there might be differences in the subgroups with respect to long term.

DR. RAO: Dr. Golish.

DR. GOLISH: You know, I think that both the Sponsor and FDA have presented post hoc subset analyses with these common-sense categories, which are, in fact, the appropriate ones. And though they look different through those two different lenses, those are the subsets to consider clinically.

DR. RAO: Dr. Graf.

DR. GRAF: So would it be nice if these could be pooled? Yes. Is that possible in real life? I don't know because oftentimes these diagnoses do come together. So while it would be nice to have a study, that valid discogram at one level, does this device show that it's efficacious? Sure. But is that possible? I don't know. I don't know if that's possible.

DR. RAO: Dr. Cheng.

DR. CHENG: I think I would try and -- so I wouldn't pool it together. But if I were to suggest a way of doing it, I would isolate it to single-level disease that you can confirm with some type of concordance, whether it's discogram or other means. I would delete the people with -- or I would state it has to be people with a non-sequestered disc herniation,

since those are excluded. People can't have a central stenosis and no listhesis.

So if you isolate it to those people and then stratify it by those with leg pain and those with just back pain or both, I think that -- excuse me, leg pain and back pain versus just back pain, I think that would be helpful.

DR. RAO: Thank you.

Dr. Auerbach.

DR. ESKAY-AUERBACH: Marjorie Eskay-Auerbach.

I have nothing to add.

DR. RAO: Thank you.

Just a clarification. Dr. Golish, you talked about stratification, and you said groups. I just wasn't clear which groups you meant. You meant the groups that Dr. Smith and Yang talked about, which is like a clinical subdivision? Or did you mean the pathologic groups as listed in -- based on the pathology?

DR. GOLISH: My feeling is that both Dr. Yang and Smith's clinical comments are consistent with the subgroups listed in (c), which are relatively consistent with the subgroups that both --

DR. RAO: Okay.

DR. GOLISH: -- the Sponsor and FDA answered.

DR. RAO: Thank you.

Mr. Melkerson, with regards to Question 1c, the Panel generally feels that the clinical data would be better if it was stratified, and the stratification could be done in different ways, including clinical presentations into predominantly back pain or

predominantly leg pain. Or it could be stratified in terms of the pathology involved, such as described in the slide, including disc herniation, spondylolisthesis, spinal stenosis, or facet arthrosis. Is that adequate?

MR. MELKERSON: I believe that'll help, yes.

DR. RAO: Thank you.

And go to Question 2, please.

MR. O'NEILL: Nonoperative -- Question 2, Nonoperative Control Group and Nonoperative Therapies. Based on the observations related to the study control and nonoperative therapies described in Section 1.2 of the FDA Executive Summary, please comment on the adequacy of the nonoperative control group in this IDE clinical trial as a comparator.

DR. RAO: Thank you, Mr. O'Neill.

Dr. Auerbach, could we start with you this time? What do you feel about the adequacy of the control group as a comparator?

DR. ESKAY-AUERBACH: I think that the combination of nonoperative therapies and the duration of nonoperative therapies was very varied, which is a concern. I also was concerned about the fact that the nonoperative treatments were really personalized by the investigator, so it would depend on their orientation or their bias with respect to nonoperative treatment.

There are evidence-based guidelines that recommend when an epidural injection should be done. It's not clear that that was addressed, so I have concerns about the nonoperative therapies.

DR. RAO: Dr. Trier.

DR. TRIER: Yes. Dr. Trier.

The conservative treatment as a nonoperative or the control group, I believe, was really, at least from my perspective, would be the only choice. And thinking about it from a practitioner's standpoint and from a patient standpoint, a sham surgery, to me, is not acceptable, and I would find it very difficult to get through an ethics committee. So in the reality of doing clinical trials, you know, in practice, I think that may have been the only possible control group.

DR. RAO: Thank you.

Ms. Harmon.

MS. HARMON: I'm not sure about the adequacy of the nonoperative control group. The numbers, to me, are markedly smaller than -- I don't know, the other group. So I can't really make a comparison of the two.

DR. RAO: Thank you.

Dr. Cheng.

DR. CHENG: So I do think it's inadequate in terms of the control groups. First, I already mentioned, I appreciate the difficulties of the placebo control group, but if you really want the answer of the question, unfortunately you have to adjust for that somehow.

The second reason is, I do think the crossover group does create some problems in terms of the results reporting. I think there was a -- I know the Sponsor disagreed that there was no rash, but the curve clearly shows that after 6 months there were quite a few patients that decided to cross over, and then it plateaued afterwards. So I think there was

this built up sense of people who wanted to transfer and have the surgical treatment. I think that affects the results.

DR. RAO: Thank you, Dr. Cheng.

Mr. O'Brien.

MR. O'BRIEN: I think the nonoperative arm of the study was the weakest part of the study. I think the combination of the question as to whether or not -- who was a nonoperative, an appropriate nonoperative person within the control arm in the first place.

Secondly is that I would wish that sponsors, whoever they are, would put the same amount of attention and time and discipline in both arms. We saw a lot of laxity and lack of specificity and evidence-based methods used on that particular arm versus the other. And I think if we're going to have a good study, we have to have discipline on both sides of that regarding it. So I -- and the crossover indicates a lot to me as well. So I think, looking at the whole thing, I think that's the weakest part of the study.

DR. RAO: Thank you, Mr. O'Brien.

Dr. Graf.

DR. GRAF: I agree with what's been said. I come back to the point that, again, there are multiple diagnoses here. And it would be difficult to therefore standardize some sort of treatment, because if you're starting with a different diagnosis, you obviously can't standardize that treatment for everybody. But as a whole, I don't think that there was adequate nonoperative treatment in that control group.

DR. RAO: Thank you, Dr. Graf.

Dr. Yang.

DR. LYNDA YANG: Lynda Yang.

So for all the problems that have been discussed, I do not think that the nonoperative was a good comparator.

DR. RAO: Thank you.

Dr. Topoleski.

DR. TOPOLESKI: I have nothing to add and agree with what's been said.

DR. RAO: Thank you.

Dr. Smith.

DR. SMITH: I concur with what's been said. I don't think it was adequate, and I don't have anything further to add.

DR. RAO: Thank you.

Dr. Golish.

DR. GOLISH: I think the heterogeneous group of what we could call usual care in the nonoperative group was the Sponsor's attempt to provide the patients some degree of ethical choice in their care as they attempt to retain them in a control arm, get them some relief as they can, and not have them drop out or cross over.

And though it would, in principle, be appealing to have that nonoperative care much more regimented, I don't think that's very consistent with FDA's least burdensome approach. And I think this was probably the best the Sponsor could ethically do.

DR. RAO: Thank you.

Dr. Blumenstein.

DR. BLUMENSTEIN: So the structure of the control group makes a certain amount of

sense to compare to the DIAM device. However, the way the study was designed, there would be two possible choices. It could be a comparison of early versus delayed DIAM use, but that would have required the 12-month data from those that crossed over to be compared to the data for those that were treated initially. And I'm not sure -- and of course, that would not provide patients with data about the -- a choice of using the device or not.

What they chose to do instead was to use the 6-month data for those that crossed over, which introduces problems because then you don't have the outcome of a year to compare. And, of course, it may be difficult to delay any kind of a non -- an invasive intervention for as much as a year.

If they had chosen to allow the patient to go to another, a standard of care, invasive choice, and then evaluate a year, that might have been something better to give the patients the data to be able to make a choice between immediate DIAM or delayed alternative invasive standard of care.

So there's a lot of variations on this. I think the study that was, as designed, with the possibility of the crossover influencing the way in which the outcome is assessed in the control group makes the study very, very difficult to interpret.

DR. RAO: Thank you, Dr. Blumenstein.

Dr. Finnegan.

DR. FINNEGAN: So my comment is that, with a background in clinical research at a county hospital Level I trauma, it is possible to do a good controlled group. You just have to be really on top of it. And that -- this was my biggest disappointment with this is, this -- I

think this is really poorly designed.

DR. RAO: Thank you, Dr. Finnegan.

Dr. Gilbert.

DR. GILBERT: I agree with pretty much everything that was said. The only additional comment I would make is that I think somebody earlier referred to the control group as, as good as no treatment at all, and that there was really no benefit observed in the control treatment. And so I guess I'm just not sure it's the best group.

DR. RAO: Thank you.

Dr. Evans.

DR. EVANS: Nothing.

DR. RAO: Nothing to add. Thank you.

Mr. Melkerson, with regards to Question 2, the Panel generally feels that the control arm in this trial did not serve its purpose as a valid comparator for several reasons, including the variability of care provided, the personalization of the care, and the lack of following established guidelines in some circumstances, the smaller numbers of patients in the control arm, the high number of crossover patients. And the Panel felt that, in general, there was a little lack of rigor in the way the control arm was treated.

Is that adequate?

MR. MELKERSON: Yes, that is. Thank you.

DR. RAO: Thank you.

Question 3, please.

MR. O'NEILL: Question 3, Study Endpoint and Time for Assessment. Please

comment on the adequacy of the primary effectiveness endpoint and evaluation time point of overall success at 12 months, considering the factors described relating to the study endpoint and time point for assessment in Section 1.2 of the FDA Executive Summary.

DR. RAO: Thank you, Mr. O'Neill.

Dr. Blumenstein.

DR. BLUMENSTEIN: Well, I feel like the primary endpoint was designed to mitigate the observations of a change in this ODI, with -- by penalizing it according to the bad things.

But then the way in which the bad things were entered into it through attribution and difference between the arms in the way things were attributed and so forth made it very, very difficult to interpret and may have worked against the control arm, and therefore I think it was an unfortunate choice.

DR. RAO: Thank you. I'd just like to point out that this question has two sections. One is the actual endpoint, and two is the evaluation time point. I think you addressed both of them, Dr. Blumenstein, but I just wanted to kind of point that out.

DR. BLUMENSTEIN: I can comment further on the evaluation endpoint.

DR. RAO: Yeah.

DR. BLUMENSTEIN: I think it seems awfully short to me because of the fact that you're doing an implant of some foreign body that has degenerative possibilities.

DR. RAO: Thank you.

Dr. Evans.

DR. EVANS: In statistics, we have a saying. There are lies, damn lies, and orthopedics.

(Laughter.)

DR. EVANS: You guys may have heard a different version.

(Laughter.)

DR. EVANS: But --

DR. RAO: Actually, we flip it around in orthopedics. We say there's research, there's lies, and then there's statistics.

(Laughter.)

DR. RAO: But I'll let you continue with your answer. Thank you.

DR. EVANS: Unfortunately, I -- perhaps at the top of my list of concerns with this particular study was the definition of the endpoint. I thought there was a fundamental flaw in the definition in the sense that there was sort of differing definitions of what was meant by success in the different arms, which to me when you go to make between-arm comparisons in success rates, you don't know what you have. And given that, of course, a primary endpoint is very fundamental to the design and conduct and analysis and interpretation of a study, that this is a, you know, a real concern.

So I had -- you know, I was -- I think, fundamentally, you cannot create different definitions for different treatment groups. You have to -- some ways you have to evaluate them via the same standard. And, of course, different treatments have different benefits and harms associated with them, but you don't get to select which ones you, on an arm-specific basis, which ones you include and which ones you don't.

DR. RAO: Thank you, Dr. Evans.

Dr. Gilbert.

DR. GILBERT: So I think the Sponsor did present beyond the 12 months for many of the measures that we use to assess, and that gave some hope that this longer term performance would be adequate. But in terms of the specifics for endpoint and time point, I defer to my colleagues.

DR. RAO: Thank you, Dr. Gilbert.

Dr. Finnegan.

DR. FINNEGAN: I think 12 months is too short.

DR. RAO: Dr. Smith.

DR. SMITH: I concur. I think 12 months is too short for an endpoint, in terms of time point. In terms of the primary effectiveness endpoint, I actually didn't object to that. I thought maintenance of the ODI over time was acceptable for measuring the effectiveness. I just had concerns about the duration of the endpoint at 12 months, from a safety perspective.

DR. RAO: Thank you.

Dr. Golish.

DR. GOLISH: With respect to the endpoint defined as a composite endpoint meaning, you know, the logical and of individual binary endpoints, each in their own domain, I applaud the Sponsor for that. Keep in mind, we've had panels in which we had a single clinical or radiographic endpoint that was not composite. I think that's adequate.

The subset of that, which is the continued unclarity about which definition of device- or treatment-related adverse event in the different arms, that continues to be concerning. The duration of final follow-up at 12 months is inadequate. If you go back for every spinal

PMA that's come before FDA in the 21st century, both before this Panel and not, and look at the final follow-up, I think this is inconsistent with that.

DR. RAO: Thank you, Dr. Golish.

Dr. Topoleski.

DR. TOPOLESKI: Thank you. I agree with the other panelists that it's probably not adequate. However, I commend the Sponsor for continuing to follow the patients and present data far beyond the 12th month endpoint.

DR. RAO: Thank you.

Dr. Graf.

DR. GRAF: I agree with what has been said and have nothing else to add.

DR. RAO: Dr. Yang.

DR. LYNDA YANG: Given the problems with the SAE definition in the context of primary endpoint and also comparing apples and oranges, I don't think it's adequate as an endpoint.

And then also with regard to the time point, 12 months is too short, given the precedents set for other devices that are out 2 to 5 years.

DR. RAO: Thank you.

Dr. Cheng.

DR. CHENG: So I think the primary endpoint is adequate. I have to admit, I didn't quite understand Dr. Evans' point of how they were different between the two arms. But failing to understand, I think they're adequate in terms of the primary endpoint.

The timing, or the time point, I think it's okay for the evaluation of pain. But for

safety, I think it's not long enough. We're looking at implants and inflammatory-related changes with implants that occur, you know, for most implants it's upwards of 10 years. And that's a long time, but certainly 1 year is too short for that.

DR. RAO: Thank you.

Mr. O'Brien.

MR. O'BRIEN: Twelve months, to me, is adequate for patient satisfaction, someone who's in intense pain and comes out of that pain and can function. But I'm not quite sure it addresses the longer-term issue that you're trying to address with safety and efficacy of the device.

DR. RAO: Thank you.

Dr. Auerbach.

DR. ESKAY-AUERBACH: The only concern I have about the primary endpoint is the crossover group, because actually they don't have 12 months of follow-up. So I would say I'm not sure that the primary endpoint is adequate, and I would agree that 12 months is too short a period for an implanted device.

DR. RAO: Ms. Harmon.

MS. HARMON: I would also agree that what we have here is not adequate. I do, however, appreciate that we had the opportunity to hear from a actual patient. And I think that's the true measure of success. So I would like to see some kind of -- see some way of streamlining this process a bit more so we can see more successes like the patient we heard from today.

DR. RAO: Thank you.

Dr. Trier.

DR. TRIER: Yeah, Dr. Trier.

While the primary endpoint was set at 12 months, the Sponsor did clearly demonstrate out to -- I think several of the graphs were out to 36 months, a demonstrated continued treatment effect, both based on success and also the various components of that criteria for success, and that it was consistent. I mean, you know, basically it flatlined out to 36 months' follow-up.

So the question about 12 months being adequate, you know, I think that's something to be negotiated or described, but they clearly showed data that went out to 36 months, demonstrating the primary effectiveness and the endpoints to that time point.

DR. RAO: Thank you.

Mr. Melkerson, with regards to Question 3, the Panel generally believes that the study endpoints were generally acceptable, with the exception and concern that some of the definitions of the adverse events could have been refined to make them clearer.

In terms of the time point, I think there is general consensus that 12 months is too short. It may be adequate to assess patient pain relief and patient satisfaction but was inadequate to assess safety of the device that was implanted. And in some cases, the concern was that the duration was even shorter, like in the crossover group.

Is that adequate?

MR. MELKERSON: I believe I heard 2 to 5 years, 10 years. Is it the Panel's opinion that when saying consistent with other PMAs, are they saying 24 months at minimum, or do they have a suggestion?

DR. RAO: I don't think -- there was some talk of 2 to 5 years from some. But I think, in general, rather than go around, I mean, I would propose that it's a minimum of 2 years, and then I'll just ask for a show of hands, or if anyone objects to that, then I think we can go for that.

Does anyone have any thoughts if I say a minimum of 2 years? Yeah, go ahead.

DR. CHENG: Well, maybe an alternative way is just make it consistent with other PMAs for other products of a similar nature than an implant, and the rest is handled through the postmarket study or post-approval study.

DR. RAO: Dr. Golish.

DR. GOLISH: Twenty-four months with the opportunity for postmarket surveillance.

DR. RAO: Twenty-four months with an opportunity for postmarket surveillance.

Dr. Gilbert.

DR. GILBERT: I would agree with that. And in particular, some of the long-term concerns about implant degradation and adverse events, it may be really difficult to run a study out long enough to see where those events might arise. And so you have to call it somewhere, and I think 2 years is a good place to do so, but to follow them after introduction into the market.

DR. RAO: So seeing no further comments, I think, Mr. Melkerson, with regards to your supplemental question, I think the answer would be 2 -- at a minimum of 24 months with potential for further follow-up.

Is that adequate?

MR. MELKERSON: Yes. Thank you.

DR. RAO: Thank you.

Question 4, please.

MR. O'NEILL: Colin O'Neill.

Question 4, Role of the DIAM as a Primary Therapy versus Adjunctive Therapy with Direct Spinal Decompression.

The Sponsor provided a summary of soft tissue, for example, ligamentum flavum and/or bone resection described in the operative reports related to the implantation of the DIAM investigational device. Please refer to Section 1.2 of the FDA Executive Summary. These reported observations suggest that indirect and/or direct spinal decompression was performed in conjunction with the implantation of the DIAM investigational device in a number of cases within this clinical trial.

Please comment on the significance and effect of the soft tissue and/or bone resections performed at the time of implantation of the DIAM device, both in terms of understanding if this technology should be considered a primary treatment or an adjunctive treatment with direct spinal decompression, and in terms of interpreting the safety and effectiveness results, and investigational device treatment effect, in this IDE clinical trial.

DR. RAO: That's a complex question with multiple subparts, you know, multiple subparts. But why don't we take a stab at it, Dr. Trier? I start with the easy ones. For you, I start with the easy ones.

DR. TRIER: I have to -- yeah, I've noticed. Yeah, I have.

The comment, I guess, in a general comment, with regards to this question, I'm not a practitioner, I'm not a surgeon. And, you know, I'm going to defer to clinicians with regards

to primary versus adjunct.

I think there is a difference, at least in my mind, there is this, a difference in the definition of whether or not there was a direct spinal decompression. And, you know, not being a practitioner and not having seen all of the various comments that the FDA commented on, you know, in terms of the operative notes and so forth, I'm not sure that I'm in a position to be able to respond.

DR. RAO: Thank you.

Ms. Harmon.

MS. HARMON: I'm not sure we were given enough information to answer this question. When we looked at the study, it was only patients in the U.S. And, of course, there was some mention in the packet that we were given before this Panel that talked about global and what other countries, how they used this procedure in their patients. And some actually had used it as adjunct.

But I'm not sure that you can compare populations globally with populations in the U.S. I guess that's another study. But, you know, that's what I would want to see. So I don't know if I can adequately answer that question.

DR. RAO: Thank you.

Mr. O'Brien.

MR. O'BRIEN: I would echo that, in terms of my thought as I went through it, is I'd love to see what the 140,000 cases already used, are actually using it for, because my sense in going through and listening to and reading this study and looking at the issue of heterogeneity in the population and in the study, etc., my sense is that in some cases it's

used primary, in some cases it's used adjunctive.

And I could see a tool like this being important enough to be applied by clinicians in a number of different cases. But as to whether or not what I would see based on this study, I don't think we have enough evidence to say.

DR. RAO: Thank you.

Dr. Yang.

DR. LYNDA YANG: So, first of all, I don't know how you're defining spinal decompression here. I guess I'd start with that.

Second of all, I don't generally offer spinal decompression for back pain alone patients. It usually is for, you know, leg pain. So because of those two problems, I don't think I can comment on the adjunct part.

DR. RAO: Thank you.

Dr. Topoleski.

DR. TOPOLESKI: I agree and echo my colleagues. I don't think we've defined the terms. And I don't believe there were data presented to compare any quantitative measures of safety and effectiveness for any of the soft tissue resections versus no soft tissue resections, or the same for the investigational device treatment. So I don't think there's enough data to answer this question.

DR. RAO: Thank you.

Dr. Smith.

DR. SMITH: I believe the answer to the question lies in the heterogeneity of the patient population and what disease we're treating. We saw an excerpt from an op report

earlier in which the surgeon appears to have done a lateral recessed decompression and possibly a foraminotomy.

So, in that particular case, the device was an adjunct because they're primarily treating neural element compression, whereas in someone with mechanical low back pain and no neurologic symptoms, the device might be the primary treatment effect. And so I think, to answer this question, it would be predicated upon a more homogenous patient population.

DR. RAO: Thank you.

Dr. Finnegan.

DR. FINNEGAN: Maureen Finnegan.

So I'm going to do a little bit of out-of-the-box. It seemed to me, if the ODIs were fairly high, then you could, in fact, say you have enough data to suggest this could be an adjunctive therapy. I think that the fact that they were nowhere near their 20 to 40 ODI patient group would suggest they don't have enough data for a primary.

DR. RAO: Thank you.

Dr. Gilbert.

DR. GILBERT: I have a hard time with this one. I think I would say yes.

(Laughter.)

DR. GILBERT: Yes, there is an effect of the soft tissue and/or bone resections performed at the time of implantation of the DIAM device. And yes, both in terms of understanding the technology and the primary treatment or adjunctive treatment effects. So I think the answer is yes.

DR. RAO: Dr. Evans. No comments.

Dr. Blumenstein.

DR. BLUMENSTEIN: No comment.

DR. RAO: Thank you.

Dr. Golish.

DR. GOLISH: The trial wasn't designed to study adjunctive therapy with decompression. For those op notes where it appears too much was done to be consistent with the non-decompressive technique guide, those can be treated as exclusion and inclusion enrollment failures and analyzed with the usual techniques and sensitivity analyses associated with that.

DR. RAO: Dr. Graf.

DR. GRAF: Carl Graf.

So to try and break down the question, you know, is there a significance of soft tissue decompression? Yes. Now, was that the intended purpose? No. I think that what is intended is that there's a portion of bone that's being removed to allow the seating of the device, which is, you know, far from a lumbar laminectomy.

The second portion, you know, this device is intended as a primary device, not as an adjunct treatment. But does it cause direct spinal decompression? It does, as has been shown by the initial gap of increased disc height. But is that maintained? You know, no, it's not.

Going on down further in the question, you know, would it be considered safe? In my opinion, it is safe. But the last part of that question, is it effective, I mean, that's the

real question we're arguing here.

DR. RAO: Thank you.

Dr. Cheng.

DR. CHENG: I feel comfortable with the DIAM being the primary therapy. If the operative notes that were presented to us, and comments, are representative of the other tissue resections you're talking about, those seem to me to be mostly surgeons' attempts to get it to fit right. And if it's -- and the external surface of the lamina, that's probably not going to have any effect on the central canal, the ligamentum. You might say it a little bit differently. I didn't see many comments about the ligamentum being removed, though. So I thought it was okay as a primary therapy.

DR. RAO: Thank you.

Dr. Auerbach.

DR. ESKAY-AUERBACH: I actually agree with Dr. Cheng and found the same thing.

DR. RAO: Thank you.

Mr. Melkerson, with respect to Question Number 4, I think the Panel generally feels that in this study, the DIAM device was generally used as a primary therapy versus and adjunctive therapy. The degree of associated surgical procedures that were listed did not appear to be significant.

It's possible that there was some indirect decompression with the expansion of the interspinous space. But in the absence of any further information, the Panel is having a hard time commenting on whether this should be used as a primary device or an adjunctive device. And the heterogeneity of the study population further precludes an adequate

response to this question.

Is that adequate?

MR. MELKERSON: That's sufficient. That's sufficient.

DR. RAO: Thank you.

Question Number 5, please.

MR. O'NEILL: Question Number 5, Radiographic Outcomes. The Sponsor provided the results and analyses of radiographic outcomes related to spinous process erosions, spinous process fractures, and sagittal plane angular motion and translational motion. Considering the observations described on radiographic outcomes in Section 1.2 of the FDA Executive Summary, please address the following:

a. Please comment on the clinical significance of the reported spinous process erosions for a device that relies upon the spinous processes to exert its treatment effect, as well as on the adequacy of the outcome analysis performed by the Sponsor to assess the significance of the observed spinous process erosions.
b. Please comment on the clinical significance of the reported spinous process fractures for a device that relies on the spinous processes to exert its treatment effect, as well as on radiographic plan to detect and identify the incidence of these fractures.
c. Please comment on the clinical significance of these results, given the proposed intended use of the DIAM investigational device to provide stability during flexion and extension motions, as well as to stabilize yet preserve motion.

DR. RAO: Thank you, Mr. O'Neill. Let's take this question in three parts. I think -- or maybe we could take it together. The first part is about the clinical significance of the

spinous process erosions and whether they will have an effect on the treatment and whether the Sponsor carried out enough of an analysis to assess the significance of the erosions.

The second part is on the clinical significance of the fractures as well as on the Sponsor's efforts on identifying these fractures.

And the third part is whether these erosions and fractures could have an effect on the device's ability to provide stability in flexion-extension and somewhat stabilize the motion segment.

Dr. Auerbach, why don't we start with you this time?

DR. ESKAY-AUERBACH: Okay. So with respect to the erosions, I guess my concern would be why are they occurring? And I think we don't have enough information to understand that. I think it would help understand the mechanics of the device a little bit better and explain the effectiveness perhaps. And the bigger question would be, longer term, does it result in migration or dislodging of the device? So I think we need more information about the erosions.

The spinous process fractures, clinically, in my experience, they're not significant. And the way they're described here, they tend to be at the tip of the spinous process. I'm not sure why they happen, but in terms of clinical significance, I wouldn't treat it differently -- I mean, they really don't get any specific treatment. You wait for it to heal. There was some comment about displacement of those spinous process fractures, but again, if they're far enough away from the device, I'm not sure that that matters.

And with respect to flexion and extension, I think the erosion probably plays a role in

understanding that. But it was my understanding of the data that overall flexion-extension didn't change. It reverted back to what the pre-procedure level was. So, again, I think there we are missing some information about how the actual mechanics of the device work or play out.

DR. RAO: Thank you.

Dr. Cheng.

DR. CHENG: I think the analysis is, as was pointed out to us earlier, would have been better if a CT was used, as opposed to plain radiographs, as the CT's more sensitive to detecting changes.

Part (b), I don't think we can comment. There was really no analysis of the relationship between spinous process fractures and the outcome. I did see that four fractures had occurred in the control group, and you might wonder how that might occur. But then I thought maybe that's due to them going to the crossover group. So that was the only part I saw about relating the fracture to the outcome.

And then Part (c), the clinical significance with respect to the flexion-extension motions, I didn't -- unless I missed it, I didn't see any analysis of, to the extent that the motion was maintained at 1 year, even at 60 months in some of the patients who were followed that long. So I don't think I can comment on whether or not that is preserved and how that affects the outcome.

DR. RAO: Thank you.

Dr. Graf.

DR. GRAF: So I would agree. Specifically, though, for Part (a), in my opinion, the

spinous process erosions have minimal clinical significance.

In reference to the portion, Part (b), again, how many were actually caught? Because these were determined by plain radiographs, and again, some of them could have been missed. There was no CT study that was done.

As far as (c), I think that's how this device is providing its or trying to achieve its results as by providing some stability or limitation in flexion-extension and initial distraction. And if you look again back to the initial distraction compared to how that drops off, I think that's comparable to the results of how patients initially did well with this and then those results just seemed to taper off.

DR. RAO: Thank you.

Dr. Golish.

DR. GOLISH: Yeah. All three of the FDA-approved interspinous process devices that are non-fusion devices, and this fourth device proposed, have somewhat different labels, but all of them have had issues with spinous processes, be they fractures or erosions.

I think what is sort of uniquely interesting about this one is that the process, so far as we know, is ongoing, based on the long-term radiographic follow-up. But in the early phase, up to 12 months, it doesn't appear to be terribly pernicious. But having that reassurance at 24-month final follow-up, I think, would do much in contradistinction to other devices where the fractures seem to have plateaued, stabilized, and not had a big clinical impact. That's what we'd be look for at a longer time point.

DR. RAO: Thank you.

Dr. Blumenstein.

DR. BLUMENSTEIN: No comment.

DR. RAO: Dr. Evans.

DR. EVANS: I defer to the clinical colleagues.

DR. RAO: Gilbert.

DR. GILBERT: One comment I would make -- Jeremy Gilbert.

One comment I would make that I was a little disconcerted about was to hear that in the animal, the sheep study, there was no evidence of inflammatory response, and yet in the explant analysis we did -- in the human, we did see inflammatory responses occur. And so using the animal study for some measure of the implant's biocompatibility in the sheep model may not be appropriate.

And so I do -- I guess I am concerned about the potential for inflammation at the point of contact between the implant and the bone, leading to some long-term, beyond the 12 months that we have looked at, effects, in fact, maybe beyond the 24. And that's why I think a postmarket surveillance is going to be important in this device.

In terms of the fractures, Dr. Golish has described this pretty well. You know, we do see the tips fracture in many of these spinous devices, but there are also cases -- and I would suspect in this device as well, where the fracture does occur at the point of contact of the device to the spinous process. It just biomechanically makes sense that that would occur. And if that is the case, there may be an unassessed potential for dislodgment or displacement as a result of that fracture. And so I would be concerned about that.

And then I will defer to my clinical colleagues for the third part.

DR. RAO: Thank you, Dr. Gilbert.

Dr. Finnegan.

DR. FINNEGAN: Maureen Finnegan.

So I agree with Dr. Auerbach on the significance of the spinous process erosions. I think that needs to be much better defined and followed more closely. I also agree that the fractures are probably not that significant. And I didn't actually see enough data to give me a good feeling about the stability.

DR. RAO: Thank you.

Dr. Smith.

DR. SMITH: I echo some of the prior comments. Given one of the animal models did show some histologic changes that were concerning, there's also been the question raised about the presence of possible wear debris. And in the setting of a device that may have wear debris and may be causing a foreign body reaction, I think the spinous process erosions are something that are of potential clinical significance. And so that's the answer to Part (a).

For Part (b), the reported spinous process fractures, I agree with what others have stated, that in this setting, they're probably clinically relatively insignificant, with a caveat that I believe the mean age of the population in the study was in the mid-40s. And so presumably osteoporosis wasn't significant. But if this device is going to be implanted into individuals that are older, which most of the DDD patients are, then it could be a much larger problem than it was in this investigational cohort.

And for Part (c), the clinical significance of the results, given the proposed intended use, I think it's not enough information to say. It's a little bit -- again, part of the

heterogeneity, it's not really entirely clear how the device is achieving -- clearly there's an effect that's going on in the outcomes, but from a mechanistic perspective, I don't think we fully understand how the device is achieving that effect with the data that we have.

DR. RAO: Thank you.

Dr. Topoleski.

DR. TOPOLESKI: Tim Topoleski.

I would just add to what Dr. Gilbert has already said and what my colleagues have already said. I don't necessarily know whether there's clinical significance in the sense of enhanced pain from the erosion, but it is changing the geometry of the spine. And that's likely related to the materials and/or the placement of the device, and that may just require further study and further follow-up.

And the same with the spinous process fractures. As Dr. Gilbert said, it depends on where the fracture is. If it's happening right at the point of contact, then that's going to change the whole ball game, and it may not be effective.

And as for Part (c), looking at some of the stability during flexion and extension, I think it was mentioned that that's changed throughout the course of the study. And that could very well be related to the spinous process erosions, where you don't have the same geometry or the same material responses you had in the beginning, and therefore you do get a change in the flexion and extension motions. So I just think it has to be followed up a lot longer.

DR. RAO: Thank you.

Dr. Yang.

DR. LYNDA YANG: With regard to (a) and (b), I don't think there was enough data presented to really understand the erosions or the fractures, and certainly I don't think I can attribute entirely the treatment effect to the integrity of the spinous process or its erosions. So for those two, I just, you know, I don't know enough to be able to comment.

For (c), you know, for providing stability, etc., I think CT imaging is critical, and I also think that definition of the facet joint and the dimensions of the neural foramen should be looked at as well during flexion-extension.

DR. RAO: Thank you.

Mr. O'Brien.

MR. O'BRIEN: I have nothing to add.

DR. RAO: Thank you.

Ms. Harmon.

MS. HARMON: Monica Harmon.

In terms of the clinical significance, I will defer to my clinical colleagues. I do, though, want to point out -- and I think some of this was answered by some of the comments earlier, but why do we see these patients have these types of erosions and fractures, and is it that this population is predisposed to these type of fractures? And is it because of the actual procedure, or is it because it was so much degeneration in the first place, of the joints, that is, this is kind of like collateral damage?

The other piece is, we heard about supportive therapies in terms of physical therapy, but I'm not quite sure if they, in this study, they thought about nutritional therapy as well, to kind of build up those areas. So that would be my only comments.

DR. RAO: Thank you.

Dr. Trier.

DR. TRIER: I have nothing to add.

DR. RAO: Thank you.

Mr. Melkerson, with regards to Question 5, as far as the erosions go, I think there is some concern that these erosions may mean something that we don't fully understand at this point and that longer follow-up may give us some more information. There is some concern raised about some of the histological findings, and there's a feeling that this might indicate that there's some inflammation going on at the point of contact.

With respect to the spinous process fractures, there is -- generally, the Panel feels that spinous process fractures tend to be relatively minor issues in the patient with -- in the spectrum of spinal disorders but that it would be nice to have more information on the incidence of spinous process fractures and to try and determine whether the geometry of placement or of the device is contributing to the incidence of spinous process fractures in some way, because there is some concern that these fractures may eventually, with time, result in a greater degree of dislodgment than was seen with the period of follow-up.

With respect to stability provided by the device, generally there's consensus that there wasn't enough data available to provide an adequate answer or response to that question.

Is that adequate?

MR. MELKERSON: That's sufficient. Thank you.

DR. RAO: Thank you.

Question Number 6, please.

MR. O'NEILL: Before proceeding to Question 6, I'd like to provide a quick reminder. The discussion of a post-approval study prior to FDA determination of product approvability should not be interpreted to mean that the FDA is suggesting that the product is safe and effective. The plan to conduct a post-approval study does not decrease the threshold of evidence required by FDA for product approval. The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness and an appropriate risk-benefit balance.

And there's two slides of this question. Post-Approval Study. Based on concerns with the premarket study design, including a heterogeneous patient population, and in view of concerns regarding confounding variables related to treatment non-uniformity in both the DIAM and crossover groups, the Agency has concerns that the Sponsor's proposed continued enrollment (extended follow-up of the DIAM and crossover groups) of the IDE study may not be adequate. Should the Panel determine that the premarket data reach the threshold for providing a reasonable assurance of safety and effectiveness, the Agency requests that the Panel discuss the following:

a. Please discuss your assessment of the adequacy of the Sponsor's proposed continued enrollment post-approval study.
b. Does the Panel believe a new enrollment post-approval study is necessary? If yes:
    - Please discuss the appropriate patient population or patient populations (for example, specific spinal pathology subgroups) for a new enrollment post-approval study;

- Please discuss the appropriate control group or groups for the target population for a new enrollment post-approval study if you believe that the control group or groups is necessary;

c. Based on the incidence of adverse events and radiographic findings (for example, spinous process erosions and spinous process fractures) beyond the 12-month time point in the premarket study, and based on the concern for potentially diminished effectiveness long term, please discuss the appropriate duration of follow-up for the post-approval study for assessment of the continued long term safety and effectiveness;

d. Please discuss what the Panel proposes as an appropriate post-approval study design (for example, two-arm observation cohort study, randomized controlled trial, etc.); and

e. Please discuss if there are additional postmarket concerns that can be addressed if the device is approved.

DR. RAO: Thank you, Mr. O'Neill. Could you go back to the Slide 1? Thank you. Let's do (a) and (b) first, and then switch to (c), (d), and (e). Let's just go around the table, starting with Dr. Trier.

DR. TRIER: Yeah. Dr. Trier.

By the Sponsor's presentation today, there has been this proposal put forth to FDA about their post-approval study if this device were to be approved. But based on their comments today and in their presentation that they are interested in negotiating with FDA the post-approval requirements, with regards to (b), I think, you know, doing a new

enrollment study would probably help to address some of the questions that have been raised here today about the study design. And that could be included as part of the discussion and the negotiations with FDA.

With regards to the appropriate patient population, I would like to defer to the clinicians in the group, identifying the patient population they believe is the most appropriate for the device. And then again, the same thing is true about the appropriate control group.

DR. RAO: Thank you, Dr. Trier.

Ms. Harmon.

MS. HARMON: At this time I have nothing more to add.

DR. RAO: Okay. Thank you.

Mr. O'Brien?

MR. O'BRIEN: I do think there should be a new enrollment for the PAS that's there. As to the -- relative to the design and the approach, I would -- I have nothing to add to that.

DR. RAO: Thank you.

Dr. Yang.

DR. LYNDA YANG: I think there should be a new enrollment for the PAS. And then as far as the subgroups, that's the --

DR. RAO: I'm sorry. Could you repeat that again, please?

DR. LYNDA YANG: I'm sorry?

DR. RAO: What did you say? What was your first sentence? You think new enrollment?

DR. LYNDA YANG: I think there needs to be new enrollment. Yeah.

DR. RAO: New enrollment, okay. Thank you.

DR. LYNDA YANG: And as far as the subgroups, that was what we discussed in Question 1.

DR. RAO: Yeah.

DR. LYNDA YANG: And then the -- yes, I do believe a control group is necessary, Question 1 again.

DR. RAO: Thank you.

Dr. Topoleski.

DR. TOPOLESKI: I'm going to defer to my colleagues on this one.

DR. RAO: Thank you.

Dr. Smith.

DR. SMITH: Yes, I do think that a new enrollment is necessary. In terms of the appropriate patient population, I think, for the proposed indication of mechanical low back pain, it should be single-level degenerative disease and without buttock or leg pain. And though I recognize that that may be a hard population to find, anecdotally, I think all of us clinically see those patients frequently. There are plenty of single-level DDD patients out there that don't have buttock and leg pain that could be enrolled in such a study.

DR. RAO: Thank you.

Dr. Finnegan.

DR. FINNEGAN: Maureen Finnegan.

I also agree there should be a new enrollment. Interestingly enough, I'm not actually

sure they need a control group anymore. I think maybe they just need new enrollment of the experimental patients, but --

DR. RAO: Okay. Thank you.

Dr. Gilbert.

DR. GILBERT: I have nothing to add.

DR. RAO: Dr. Evans.

DR. EVANS: I think a new enrollment study is needed. I also think you need a control group for context. This trial estimated 40% control group response rate, and they saw 15. I don't know how you're going to interpret anything without context. And given that sort of variation, I think it should be randomized. I don't know how you're going to sort that up.

There's also been a lot of talk about heterogeneity of effects. The only way you're going to get heterogeneity or assess heterogeneity of effects is assess those effects in these various subgroups that are being talked about. And in order to do that, you're going to need to get control group information on those subgroups.

DR. RAO: Thank you.

Dr. Blumenstein.

DR. BLUMENSTEIN: I concur. And I would add that the goal should be, in the end, to be able to provide the patient with data on the choices that they could make.

DR. RAO: Thank you.

Dr. Golish.

DR. GOLISH: Nothing to add.

DR. RAO: Dr. Graf.

DR. GRAF: I agree that there needs to be new enrollment. The follow-up to that, when -- in my mind there's really, we're trying to answer questions of multiple different pathologies with one device, including, you know, we're trying to answer, is this indicated for degenerative disc disease? Well, I mean, although it could be debated, one would, you know, have to say that there has to be some initial diagnosis that there is symptomatic degenerative disc disease at that level. I mean, as a discogram, you could debate if that's, you know, valid or -- but it's the only way that we have possible to do that.

Or is this -- are we treating facet arthrosis here? Well, could it be that a patient's receiving this and having medial branch blocks who have good relief, could be a candidate for something like this? It's just a very different question to answer because we're trying to take a shotgun approach with one device treating multiple different pathologies.

DR. RAO: Thank you.

Dr. Cheng.

DR. CHENG: So I agree that a new enrollment PAS is necessary. As far as the control group, I think it's defined by the target population. I made comments earlier about that, pertaining to Question Number 1.

I would say, though, that I'm rather impressed that you were actually able to do a randomized study of surgery versus no surgery. I didn't actually think that was even possible. And probably that's the reason why you had the crossover because you had to tell patients they have the option to have the treatment if they want later on. But I think it's very hard to get randomization or have a patient randomized to two possible treatments

that they see as being unequal, and clearly surgery versus no surgery is unequal.

DR. RAO: Thank you.

Dr. Auerbach.

DR. ESKAY-AUERBACH: I do agree that there should be a new trial. I also agree with Dr. Yang and Dr. Smith and would add one other thing, which again would be that there should just be single-level disease in the new group as opposed to multi-level degenerative disc disease.

DR. RAO: Thank you.

Mr. Melkerson, with regards to Question 6a and b, with regard to Question 6a, I think it's fair to say, although -- I think it's fair to say that the Panel generally felt that the Sponsor's proposed continued enrollment PAS was not adequate.

With regards to Question 6b, the Panel does generally feel that a new enrollment PAS would be appropriate, would be necessary. And how this new enrollment PAS is designed could vary but could be divided either on the basis of clinical syndromes of back versus back and leg pain versus leg pain alone, or it could be divided by specific pathology in the motion segment, including single-level versus multiple-level involvement. And the control group would likely mirror what was being proposed for the investigational group at that time.

Is that adequate?

MR. MELKERSON: I have a couple of qualifying of qualifying questions. With regards to what questions are you trying to answer in a new enrollment study, for the Part (b), and Part (a), even though the proposed is not adequate, does it address the issue of -- I thought

I heard long-term erosions. What's the impact of those types of things? Typically, a continuation study, as proposed by the Sponsor, is the way to get that longer-term data. And for a new study, what is the question that we're trying to address in that new study?

DR. RAO: Sure. I think the longer-term follow-up of the current patients, currently enrolled patients, would provide some useful information in terms of what happens at the level of the erosion, what happens to the fractures. Do the fractures and/or the erosions result in device dislodgment? What is the clinical outcome of these patients over a longer period of follow-up? And are there any other unforeseen events that occur with the long-term follow-up?

I think the Panel was generally trying to assess the efficacy/safety -- efficacy issues of the device and to address that based on the heterogeneity. I think the Panel feels that a new, more stratified enrollment study might be more beneficial.

Would everyone agree with that, or --

DR. BLUMENSTEIN: I would just add that I think the control should not be a crossover, should not contain a crossover. And I think that if it doesn't, and for example, it includes an invasive standard of care, that the amount of data that would come out from the long-term follow-up of that study would be very valuable.

DR. RAO: Thank you.

So I think, just -- I think, to reiterate the continued follow-up of the current study patients would provide useful information in terms of safety; to provide useful in terms of efficacy, a new enrollment PAS would probably be likely.

Is that adequate?

MR. MELKERSON: Just one follow-up to that. You're talking about long-term efficacy or short-term efficacy?

DR. RAO: I think the new enrollment, I think there was consensus on an earlier question, that a 24-month follow-up with a new enrollment PAS would be adequate.

Is that adequate?

MR. MELKERSON: Thank you. That actually may bleed into the next question, so --

DR. RAO: Okay. Is that adequate?

MR. MELKERSON: That's adequate. Thanks.

DR. RAO: Thank you.

Let's go to the next slide, please. Actually, let's go back to 6(c) now. There you go. We haven't answered these. Thank you.

Based on the incidence of adverse events and radiographic findings beyond the 12-month time point, and based on the concern for diminished effectiveness, please discuss the appropriate duration of follow-up for a PAS.

I think we've responded to that already, Mr. Melkerson. Would that be adequate, a 24-month follow-up period?

MR. MELKERSON: That's fine. Thank you.

DR. RAO: Question (d) is what does the Panel propose as an appropriate PAS study design? And I think we've answered that to some degree. In terms of the statistical design, a two-arm randomized control trial. I'm going to defer to Dr. Blumenstein, Evans, Gilbert, Topoleski to provide some feedback and input into this, and then the rest of the panel can comment.

Dr. Blumenstein.

DR. BLUMENSTEIN: Well, I've been thinking about it a bit, and it's always dangerous to put forth your first idea. But I think a study design similar to what we already saw but with a standard of care invasive option, and looking at the difference between the time to a durable response would be helpful, to know the kind of outcome that you would get if you were to do something like that. And then, of course, have other endpoints that would look at the duration of response in a more descriptive way. That's just off the top of my head.

DR. RAO: Dr. Evans.

DR. EVANS: I think you need to do randomized trials given the heterogeneity of effects that we've seen or are concerned about. There's been a lot of discussion about potential heterogeneity of effects, and so if you get something in a single arm design or an observational design, what does it mean?

And as I mentioned, you know, this trial assumed that they would see 40% response rate in control; they saw 15. So given that sort of heterogeneity, how do you put the result of a single arm trial into context? What do you compare it to?

And as time goes by, you know, sort of standard medical practice and that sort of thing is going to hopefully improve, and those numbers change over time. So you need context.

DR. RAO: Thank you. Dr. Gilbert.

DR. GILBERT: So -- Jeremy Gilbert.

This is a post-approval study, so presumably we've already agreed that it is a safe and effective device to move to this post-approval study. And so the design of the

experiment to deal with long-term performance isn't focused on, necessarily, effectiveness and safety, since we've already agreed that it is safe and effective.

So I would say that a study of this -- a post-approval study should focus on long-term safety effects. And the one thing I would add, and maybe this is Part (e), is that some systematic, well-described explant analysis and feedback into the overall performance of the device is needed to track what happens to these patients long term. What happens to the device, and what happens to the bone adjacent to the contact zone of the device?

DR. FINNEGAN: So I mainly agree with -- Maureen Finnegan.

I mainly agree with Dr. Gilbert. The only thing that I would suggest is there does need to be stratification of the patient group so that we do pull out low back pain versus some of the other problems.

DR. SMITH: I concur with the prior comments, with the exception that if it's already been approved from a safety and effectiveness standpoint, then a two or even multi-arm observational cohort study may be adequate for the purposes of a PAS study and also may help to mitigate some of the issues with the crossover.

DR. RAO: Thank you.

Dr. Topoleski.

DR. TOPOLESKI: Tim Topoleski.

I have nothing to add on (d), but on (e), as I've already said, I think there are additional materials or long-term effects of materials that could be addressed by the Sponsor. One of the Sponsor's presenters mentioned that they believed that the device would function adequately if the tethers broke. They could possibly do some studies to

show what the biomechanical effects of that would be, or other potential failure modes, for example, iatrogenically induced fraying of the polyester or of the PET on insertion. How would that affect the fatigue life? So there may be some other material studies that could be done.

DR. RAO: Thank you. Any other comments on Question 6(d)? 6(d)?

(No response.)

DR. RAO: I think, Mr. Melkerson, the Panel generally feels that the response to this question, to some degree, will depend on what stage we're designing the PAS study. If we're designing it after this device was approved, then maybe a two-arm observational cohort study would be okay. If we're designing it proactively before the device was approved, then maybe it could be a continuation of a randomized control trial. I think --

Is that adequate for now?

MR. MELKERSON: Typically, post-approval studies are after we've made the decision. That's why we put the reminder. So in terms of your comments, that's why I was trying to ascertain what was the question you were trying to answer by the post-approval study, because that helps define what control groups are necessary or not.

DR. RAO: I think we've discussed this to some degree in some of the earlier questions. The questions we would be, in terms of efficacy, I don't think -- maybe I shouldn't speak out of turn right now, but in terms of safety, it would be good to have long-term data on some of the issues that were noticed already. I think that we've discussed already. In terms of efficacy, I'll let people comment on that.

Mr. O'Brien.

MR. O'BRIEN: I would just like to say that I'm not quite sure I understand your question asking us what -- I don't think the basic question has been answered yet, so it's difficult to say what's next afterwards, because I don't think we've addressed the basic question, is DIAM better than a nonoperative option or a microsection option or a fusion? I don't think we've adequately answered that question yet. So it's tough for me to say.

MR. MELKERSON: That makes -- this is why we've tried to put the reminder in here. Typically we wait for the vote and then -- but these discussions will go into, at what point in time we've made the determination of safety and effectiveness, what is it that you're trying to answer with a post-approval study? Is it based on findings in the premarket data? Is it long-term safety and effectiveness? What is the question? It's pre-supposing that you've found it safe and effective.

I know it's hard to answer that question before you've voted and made your determinations, but that's why we keep reminding people that this is the post-approval study, and typically post-approval studies are either to address findings that you've seen in the data, or with the typical orthopedic problem of, you really don't know until you get out to 5 or 10 years. And then it's physically infeasible to be doing studies at that long to make a cut, are they sufficient to go to market.

So we're always kind of balancing how long, how much for an implant, and then ultimately, do we have a 40-year solution, as was brought up earlier.

DR. RAO: I think I'll take a stab at that, Mr. Melkerson. I think, presupposing that we found or find this device safe and effective, the post-approval study should, will have two components. For the safety side, we have to see that there's no additional adverse effects

that occur with time. And the currently observed adverse effects need to be followed with time to see if they have any further consequences.

Presupposing that we found the device safe and effective, on the effectiveness side, we'll have to see if the effectiveness of the device continues to maintain itself over time, or if the effectiveness drops off with time or if it develops other side effects or consequences, where additional treatments may be necessary, more so than in the control arm.

Is that adequate?

MR. MELKERSON: That's adequate. Thank you.

DR. RAO: Thank you.

6e, please discuss if there are any additional postmarket concerns that should be addressed if the device is approved. Additional postmarket concerns, anyone? If the device is approved, if there is any additional --

DR. GILBERT: I've already articulated my concerns. Do you want me to --

DR. RAO: Yeah. Sure, go ahead. Yeah.

DR. GILBERT: So, again, just to -- I think I said it for (d), but I'll say it for (e) again, that explant analysis should be part of a follow-on safety study.

DR. RAO: Thank you.

I think -- is that adequate, Mr. Melkerson?

MR. MELKERSON: Yes. Thank you.

DR. RAO: Thank you.

Mr. O'Neill.

MR. O'NEILL: Panel voting questions. The proposed target population for the DIAM

Spinal Stabilization System consists of patients with moderate low back pain secondary to single --

DR. RAO: Are we supposed to go with the voting questions now, or is there supposed to be a summation right now?

MR. O'NEILL: Oh, yeah.

DR. RAO: A summation? Yeah. Let's just go with the FDA summations first, please. Is it FDA first? FDA summation first?

MR. O'NEILL: Colin O'Neill.

We have no further comment.

DR. RAO: Sorry?

MR. O'NEILL: FDA has no further comment.

DR. RAO: Okay, no further.

Does the Sponsor have a summation speech?

DR. SIMPSON: Hi. Kathryn Simpson.

I'd like to thank the Panel for their time and thoughtful conversations today. Through our presentation, our responses to questions, and our previous interactions with FDA, we've tried to address many of these issues. We wish we had more time today to allow us the opportunity to address all of the panel-specific questions, especially with regards to long-term safety. However, following this meeting, we look forward to continuing to work with FDA collaboratively on these issues.

I'd like to make a few final points on the specific issues. There seems to be little disagreement that there's an unmet need for this primary low back pain population in terms

of treatment options.

There's numerous real world concerns with the study design, as has been discussed today. We have attempted to replicate clinical practice in the design of the study and the nonoperative control, and we have attempted to follow an established definition of DDD in defining the patient population.

I'd like to emphasize that all patients in the primary dataset have at least 24 months of follow-up, and many have much more data beyond 24 months. We believe we've demonstrated a consistent and sustained effect of the device, and there is a high level of patient satisfaction with the treatment.

Thank you again for your time and attention.

DR. RAO: Thank you very much.

Before we proceed to the panel vote, I would like to ask our non-voting members -- Ms. Harmon, our Consumer Representative; Dr. Trier, our Industry Representative; and Mr. O'Brien, our Patient Representative -- if they have any additional comments.

Ms. Harmon.

MS. HARMON: No additional comments.

DR. RAO: Thank you, Ms. Harmon.

Dr. Trier, any comments?

DR. TRIER: Yeah, a final comment. You know, clinical studies in the real world are very difficult to do. And it's very rare to find the perfect study. And while this study may have discussion points, and this study may have lacked definition in some ways, I think the statement made by the Sponsor in their last comments is the fact that they do have data

out to 24 months, and that through all of that, there was a significant effect as a treatment effect for that device.

DR. RAO: Thank you, Dr. Trier.

Mr. O'Brien.

MR. O'BRIEN: I'd like to reiterate my appreciation for innovation, and the importance of what's being done and what's being presented, and the fact that 90% of our population is expected to be a potential recipient for something like this.

To me, the problem exists with the design or the heterogeneity. I don't think we can tell, really answer the question that we want to answer. I don't think there's any doubt that there are successful, satisfied patients. But if we start applying that to all the population, I don't think we've answered that question adequately to say, how is that to be applied, and is there options, and how do we properly inform the patient to let them make the decisions that they think they have to make?

DR. RAO: Thank you, Mr. O'Brien.

Yes?

DR. CHENG: Are we able to make any comments with regards to the indications label?

DR. RAO: I'll defer to Mr. Melkerson.

MR. MELKERSON: In regards to our panel questions, it'll actually identify your reasonings and what could or could not be a path forward, depending on how you vote. So you'll have a chance to do that, in why you voted the way you voted. Because the submission, as is, is the indication which we have to vote on the relative safety and

effectiveness. It's not a negotiation. It's what is proposed, and does the data support it.

DR. CHENG: So we're not able to amend that at all?

MR. MELKERSON: In your vote or your comments on why you voted -- in other words, the indication for use is what is being discussed today. If there's a chance, a potential path forward, if you don't agree with the indications, that you can bring up in your vote or your comment regarding your vote.

DR. RAO: Thank you, Dr. Cheng and Mr. Melkerson.

We are now -- yeah, Dr. Blumenstein.

DR. BLUMENSTEIN: I'm wondering if the sensitivity analysis I requested was computed.

DR. RAO: Dr. Blumenstein is wondering -- I think we're done with our presentations now, right. Are we allowed to ask for the sensitivity analysis at this time?

MR. MELKERSON: It was asked for so --

DR. RAO: Okay.

MR. MELKERSON: It's up to you.

DR. RAO: It's up to me. So do you have the sensitivity --

(Laughter.)

DR. RAO: If you have the sensitivity analysis, if Dr. Blumenstein could get a quick 2-minute overview of the issue.

DR. BERRY: So the idea of the sensitivity analysis, Dr. Blumenstein, was to impute the adverse, the serious adverse effects of any type as a failure. Is that what you were suggesting?

DR. BLUMENSTEIN: Correct.

DR. BERRY: So what it comes down to is that the -- as you saw from the table, the serious adverse effects in the treatment group were like 85%, actually 82.5%. And so the overall success rate for the DIAM is 17.5%. In the control group, it's something like 11 -- it is, 11%.

So but the analysis -- you know, the analysis is not reasonable, from my perspective, because it attributes any kind of adverse effect, like, you know, a knee surgery, or any kind of a thing that happens in the course of daily living, to the two groups. So they both have huge adverse effects.

If you did the opposite way, if you said, let's get rid of all SAEs and just ask the question, what happens in the end, that analysis you've seen, because that analysis is the ODI success analysis, which as you know, was highly positive for the treatment.

DR. BLUMENSTEIN: Yes, and I appreciate that. But I was just wondering what the impact of a -- in a randomized trial, where the serious AEs could occur, things like knee replacement, with equal probability between the arms assumedly.

DR. BERRY: So it certainly makes sense to do treatment-related AEs, but not any AE.

DR. BLUMENSTEIN: Well, I don't -- I mean, a knee replacement I don't think would be a treatment-related AE, would it -- SAE? It would be just an SAE.

DR. BERRY: Yeah. Well, so I thought that's what you wanted.

DR. BLUMENSTEIN: Okay.

DR. RAO: Thank you very much, Dr. Berry.

And thank you, Dr. Blumenstein.

We're now ready to vote on the Panel's recommendation to the FDA for the DIAM Spinal Stabilization System. The Panel is expected to respond to three questions relating to the safety, effectiveness, and benefit versus risk. Commander Anderson will now read three definitions to assist in the voting process. Commander Anderson will also read the proposed indications for use statement for this device.

Commander Anderson.

CDR ANDERSON: Thank you.

The Medical Device Amendment to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allow the Food and Drug Administration to obtain a recommendation from an expert Advisory Panel on designated medical device premarket applications that are filed with the Agency. The PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

The definitions of safety, effectiveness, and valid scientific evidence are as follows:

Safety as defined in 21 C.F.R. Section 860.7(d)(1) - There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risk.

Effectiveness as defined in 21 C.F.R. Section 860.7(e)(1) - There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its

intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

Valid Scientific Evidence as defined in 21 C.F.R. Section 860.1(c)(2) is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of safety and effectiveness of the device under its conditions of use. Isolated case reports, random experience, reports lacking significant details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness. The valid scientific evidence used to determine the effectiveness of a device shall consist principally of well-controlled investigations, as defined in paragraph (f) of this section, unless the Commissioner authorizes reliance upon other valid scientific evidence which the Commissioner has determined is sufficient evidence from which to determine the effectiveness of a device, even in the absence of well-controlled investigations.

The Sponsor has proposed the following indications for use: The DIAM Spinal Stabilization System is indicated for skeletally mature patients that have moderate low back pain, with or without radicular pain, with current episode lasting less than 1 year in duration, secondary to lumbar degenerative disc disease, at a single symptomatic level from L2-L5.

Panel member, please use the buttons on your microphone to place your vote of yes, no, or abstain to the following three questions. I will read the voting questions.

Voting Question 1 reads as follows: Is there a reasonable assurance that the DIAM Spinal Stabilization System is safe for use in patients who meet the criteria specified in the proposed indications for use described above?

(Panel vote.)

DR. RAO: I didn't vote.

CDR ANDERSON: I think it's somebody else. Okay.

(Pause.)

CDR ANDERSON: Okay. Thank you.

Voting Question 2 reads as follows: Is there a reasonable assurance that the DIAM Spinal Stabilization System is effective for use in patients who meet the criteria specified in the proposed indications for use described above?

Please vote now. Okay, wait one second. Okay, yes, no, abstain.

(Panel vote.)

CDR ANDERSON: Okay. Thank you.

Okay. Voting -- the third and final voting question reads as follows: Do the benefits of the DIAM Spinal Stabilization System outweigh the risks when used in patients who meet the criteria specified in the proposed indications for use described above?

Please vote now, yes, no, abstain.

(Panel vote.)

CDR ANDERSON: Okay. The votes have been captured. I will now read the votes into the record.

On Question 1, the Panel voted 4 yes, 0 abstain, 7 no that the data shows reasonable

assurance that the DIAM Spinal Stabilization System is safe for use in patients who meet the criteria specified in the proposed indications. Okay.

On Question 2, the Panel voted 2 yes, 1 abstain, 8 no that there is reasonable assurance that the DIAM Spinal Stabilization System is effective for use in patients who meet the criteria specified in the proposed indications.

On Question 3, the Panel voted 0 yes, 4 abstain, 7 noes that the benefits of the DIAM Spinal Stabilization System outweigh the risks for use in patients who meet the criteria specified in the proposed indications.

The three voting questions are now complete.

DR. RAO: Thank you very much, Commander Anderson.

I will now ask the Panel members to discuss their votes. I would like to go around the table and have each Panel member state how they voted on each question so it can be entered into the public record. Please also discuss the reasoning for your vote. If you answered no to any question, please state whether changes to labeling, restrictions on use, or other controls would make a difference to your answer.

Let me start with Dr. Auerbach.

DR. ESKAY-AUERBACH: I voted yes with respect to reasonable assurance for safety. I didn't see any issues there. With respect to whether or not the device was effective, I think we spent most of the afternoon discussing that. And so for many of the reasons that we discussed earlier, I voted no. And I abstained with respect to benefits because I couldn't answer Question 2 with a yes.

DR. RAO: Thank you, Dr. Auerbach. Is there anything in the labeling, restrictions, or

other controls that would make a difference to your answer?

DR. ESKAY-AUERBACH: I think that the discussion that we had earlier with respect to better defining the indications would address that.

DR. RAO: Thank you very much.

Dr. Cheng.

DR. CHENG: I voted yes to the safety. I voted to abstain from the latter two questions. The reasons are, I believe the indications are too broad. And I would have wanted to see the indications changed. What kind of change? I'll just read to you what I wrote down in my own text.

The indications would be that the DIAM Spinal Stabilization System is indicated for skeletally mature patients that have moderate low back pain, with or without radicular pain, with current episode lasting less than 1 year in duration, secondary to lumbar degenerative disc disease, attributable to a single level from L2 to L5. So that's one change.

Then degenerative disc disease is confirmed radiologically with one or more of the following factors:

1) Patients must have greater than 2 mm of decreased disc height, compared to the adjacent level;
2) Scarring or thickening of the ligamentum flavum, annulus fibrosis, or facet joint capsule; or
3) A non-sequestered herniated nucleus pulposus.

The DIAM device is implanted via a posterior approach.

So there were two other changes that you'll note I made as well.

DR. RAO: Thank you very much, Dr. Cheng.

Dr. Graf.

DR. GRAF: Carl Graf.

As far as the first question, I voted yes, that it was indeed safe.

Second and third questions, I voted both no, for the reasons as I discussed. Just in general, I think that the labeling again, as was mentioned, is too broad. The indications include too many diagnoses. And, you know, while it sounds like a great idea, I think the indications for this are just way too broad.

DR. RAO: Thank you very much, Dr. Graf.

Dr. Golish.

DR. GOLISH: I want to congratulate the Sponsor and FDA on doing an elephantine amount of work on an important problem. We here on the Panel recognize that we get to come in and look at this difficult work at a late hour, the goal not to second-guess all the difficulties that go into it but instead to participate in the public debate.

I voted yes, yes, abstain. The rationale was that although I feel the trial is positive in its current form and incarnation, it has a number of problems with it that could be cleaned up in a future trial.

DR. RAO: Thank you.

Dr. Blumenstein.

DR. BLUMENSTEIN: I voted no, no, no, because I'm a statistician.

(Laughter.)

DR. BLUMENSTEIN: No. I voted no because I think there are serious issues with the

information that we got from the trial. I don't -- I think the endpoint, as I pointed out, the primary endpoint was mixed up and flawed with respect to its applicability to both arms. The proper emphasis on the intent-to-treat analysis was not done, leaving doubts as to whether, how much biases resulted from not doing the intent-to-treat analysis.

The existence of crossover messed up the ability to ascertain whether the trial was really giving us a positive signal or not and also influenced the behavior of the patients randomized to the control arm in ways that's unknown and can't be assessed.

The population seemed to be more serious and therefore influencing attitudes and what might happen in the control arm.

And that's it.

DR. RAO: Thank you, Dr. Blumenstein.

Dr. Evans.

DR. EVANS: I voted no on all three questions, primarily for the same reasons, and general concern about the design and conduct aspects of the study that, you know, jeopardized some of the integrity of the study, which made me come down on the wrong side of reasonable assurance. Revisions to labeling would not change my evaluation.

DR. RAO: Thank you.

Dr. Gilbert.

DR. GILBERT: Jeremy Gilbert.

I voted no, no, and abstain. The principal reason I voted no on both safety and effectiveness is I couldn't get over the valid scientific evidence bar. I think the device is safe. I think it is effective. But I don't think they demonstrated that with valid scientific

evidence. And so I voted no for the two cases, and then I abstained for the last vote because I can't determine it without having that valid scientific evidence.

DR. RAO: Thank you, Dr. Gilbert.

Dr. Finnegan.

DR. FINNEGAN: Maureen Finnegan.

I voted no on the safety because I am concerned about the spinous process erosions.

I voted yes on the effectiveness because I think it does do something. I just have no idea what it does, and I actually don't think there are too many people in the room that have any idea what it does.

And I voted no on the third question because of the safety concerns and the lack of understanding of the effectiveness.

DR. RAO: Thank you.

Dr. Smith.

DR. SMITH: Harvey Smith.

On Question 1, I voted no, primarily due to concerns there was an animal -- I believe it was the rabbit model, did show some histologic concerns that there may be a foreign body reaction. There was fairly pronounced spinous process resorption at early time points. And while it's certainly possible that that's due to bony remodeling, we didn't have any additional data. The people who made the -- we didn't have any additional evidence of that that was the only cause, and I thought it was something that was glossed over. And given prior history of wear debris and issues with resorption, also given the fact that the device's stability is predicated upon the bony structures that were resorbing, I just felt there

was insufficient data to say it was safe, based on primarily that concern.

For Question 2, I voted no, predominantly -- clearly, the device clearly has an effect. But through the -- we spent the afternoon discussing the limitations of the study, both with respect to the heterogeneity of the inclusion criteria, and also there's raised concerns about the statistical analysis. And based on that, I voted no for Question 2 just because the -- although it clearly has an effect, from a statistical, scientific standpoint, the data wasn't -- didn't demonstrate it.

And then the same reasons, Question 3, I also voted no, due to the fact that from Question 1 there's -- I have clear concerns about potential risks that are being glossed over. And in the benefits, we don't have a rigorous statistical understanding due to the issues with the study design.

DR. RAO: Thank you, Dr. Smith.

Dr. Topoleski.

DR. TOPOLESKI: I voted no, no, and no, primarily for the same reasons Dr. Gilbert expounded on. I don't believe that -- I believe they show the device as not unsafe to this point, but I haven't seen the evidence. I'd like to see more long-term evidence to show that it is safe in an active sense. The same with effectiveness, and the same with the risk-benefit study.

DR. RAO: Thank you.

Dr. Yang.

DR. LYNDA YANG: Based on the data that we were given in the package, and also what we saw today, I had to vote no for all three questions. But the clinician in me would

like to think that it's probably safe, given the, you know, construct and what I know clinically. And there probably is an effect. I just don't know for whom.

DR. RAO: Thank you.

I would like to thank everyone now, including Commander Anderson, Mr. Melkerson, the FDA, all the FDA analysts and FDA presenters who did an outstanding job. I'd like to particularly thank the Sponsors for doing an outstanding job with collection of the data, presenting the data to us today, being on time and being very helpful.

Dr. Melkerson, do -- Mr. Melkerson, do you have any final remarks?

MR. MELKERSON: I just want to echo my thanks to the Panel for dealing with a tough set of questions and a tough issue that we're going to be facing in the future with other panels with study design issues. I also want to thank the Sponsor and the review teams for trying to interact as best we can to present the information from each perspective and have the discussions today. So thank you very much.

DR. RAO: Thank you, Mr. Melkerson. And thank you again to all the Panel members who participated in very respectful and intellectual discussions on this topic and reviewed all the evidence very carefully.

I now pronounce the February 19th, 2016 meeting of the Orthopaedic and Rehabilitation Devices Panel adjourned.

(Whereupon, at 5:20 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

ORTHOPAEDIC AND REHABILITATION DEVICES PANEL

February 19, 2016

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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TIMOTHY J. ATKINSON, JR.

Official Reporter