UNITED STATES OF AMERICA
FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
MEDICAL DEVICES ADVISORY COMMITTEE

+ + + + +

ORTHOPEDIC AND REHABILITATION DEVICES PANEL

+ + + + +

MEETING

+ + + + +

TUESDAY,
AUGUST 31, 2004

+ + + + +

The Panel met at 8:00 a.m. in Salons A, B, C of the Hilton Washington D.C. North/Gaithersburg, 620 Perry Parkway, Gaithersburg, Maryland, Dr. Michael J. Yaszemski, Chairperson, presiding.

PRESENT:

MICHAEL J. YASZEMSKI, M.D., Ph.D. Chairperson
MAUREEN A. FINNEGAN, M.D. Voting Member
JOHN S. KIRKPATRICK, M.D. Voting Member
STEPHEN LI, Ph.D. Voting Member
SANJIV H. NAIDU, M.D., Ph.D. Voting Member
SALLY L. MAHER, Esq. Industry Representative
LEELEE DOYLE, Ph.D. Consumer Representative
FERNANDO G. DIAZ, M.D. Deputized Voting Member
JONAS ELLENBERG, Ph.D. Deputized Voting Member
CHOLL W. KIM, M.D., Ph.D. Deputized Voting Member
SALLY A. RUDICEL, M.D. Deputized Voting Member
JANET L. SCUDIERO, M.S. Executive Secretary

FDA REPRESENTATIVES:

CELIA WITTEN, Ph.D.
BARBARA D. BUCH, M.D.
JOHN P. HOLDEN, Ph.D.
RICHARD M. KOTZ, M.S.

SPONSOR REPRESENTATIVES:

GUNNAR ANDERSSON, M.D., Ph.D.
CHARLES HARTJEN, M.D.
YVONNE LYSAKOWSKI, R.N., M.S.
AUGUSTUS A. WHITE III, M.D., Ph.D.
SCOTT YERBY, Ph.D.
JAMES ZUCHERMAN, M.D.

A-G-E-N-D-A

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

8:02 a.m.

DR. YASZEMSKI: Hi, good morning everybody. Can I ask everybody to take your seats? We're going to go ahead and get started.

MS. SCUDIERO: Good morning. I'm Jan Scudiero, the executive secretary of this panel, and a reviewer in the Division of General Restorative and Neurological Devices. If you haven't already signed in at the tables at the doors, please do so. The agenda information is there, and other information about advisory panel meetings, including how to get transcripts and summaries.

Before I turn the meeting over to Dr. Yaszemski, I'm required to read two statements into the record. They are the deputization of temporary voting members for this meeting, and the conflict of interest statement.

First, the appointment to temporary voting status. Pursuant to the authority granted under the Medical Devices Advisory Committee Charter, dated October 27, 1990, and amended April 20, 1995, I

appoint the following as voting members of the Orthopedic and Rehabilitation Devices Panel for the duration of this meeting on August 31, 2004. Fernando G. Diaz, MD, PhD; Jonas Ellenberg, PhD; Choll W. Kim, MD, PhD; and Sally A. Rudicel, MD. For the record, these people are special government employees, and are consultants to this panel or another panel under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review, and have reviewed the material to be considered at this meeting.

The conflict of interest statement. The following announcement addresses conflict of interest issues associated with this meeting, and is made a part of the record to preclude even the appearance of an impropriety. To determine if any conflict existed, the agency reviewed the submitted agenda for this meeting, and all financial interests reported by the committee participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interest. However, the

agency has determined that the participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved, is in the best interest of the government.

Therefore, a waiver has been granted for Dr. Stephen Li for his interest in firms that could be affected by the panel's recommendations. Dr. Li's waiver involves consulting with several competing firms on topics that are unrelated to today's agenda. Dr. Li receives less than $10,000 for each of these consulting arrangements. We would also like to note for the record that the agency took into consideration certain matters regarding Drs. Maureen Finnegan, Choll Kim, John Kirkpatrick, and Stephen Li. Each of these panelists reported current or past interests in firms at issue, but in matters not related to today's agenda. The agency has determined therefore that they may participate fully in today's deliberations. In the event that the discussions involve any products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse himself or herself from such

involvement, and the exclusion will be noted for the record. With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial interest involvement with any firm whose products they may wish to comment upon.

There is one more tentatively scheduled meeting of this panel for this year. It's December 2 and 3. Please remember that this is tentative, and check the CDRH website for updated information. Dr. Witten, I'll give her just a moment. This is the last meeting of some of our panel members, and Dr. Witten would just like to say something briefly.

DR. WITTEN: This is the last meeting as members for Dr. Finnegan, Dr. Li, and Sally Maher. And I want to thank them for their service to FDA and their participation in this panel. We certainly rely on the outside expertise that's provided by our panel members, and we need them to carry out our mission here. I would like to present plaques to them, but unfortunately the plaques haven't come yet. So we'll

just have theoretical plaques today, and the actual plaques will come later. So thank you to those three panel members.

And I'd like to welcome Dr. Sally Rudicel and Dr. Choll Kim who will be new voting members of the panel starting September 1, and are here today as deputized voting members. Thank you.

MS. SCUDIERO: I now turn the meeting over to Dr. Yaszemski.

DR. YASZEMSKI: Thanks very much. Good morning. I'm Dr. Michael Yaszemski. I'm the chairperson of the Orthopedic and Rehabilitation Panel. I'm an orthopedic spinal surgeon and a chemical engineer. I work at Mayo Clinic in Rochester, Minnesota. At this meeting, the panel will be making a recommendation to the Food and Drug Administration on the approvability of pre-market approval application for the St. Francis Medical Technologies, Inc., Intraspinous Process Distraction System, the X STOP. The device is intended for patients aged 50 or older suffering from mild or moderate neurogenic intermittent claudication,

secondary to lumbar spinal stenosis, who have undergone a regimen of non-operative treatment. The X STOP is indicated for patients who experience relief in flexion from their symptoms of leg, buttock, or groin pain, with or without back pain.

Before we begin this meeting, I'd like to ask our distinguished panel members, who are generously giving their time to help the FDA in the matter being discussed today, and other FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and your affiliation. I'll start to my right with Dr. Kirkpatrick.

DR. KIRKPATRICK: I'm John Kirkpatrick. I'm a spine surgeon and associate professor of both orthopedics and engineering at the University of Alabama at Birmingham.

DR. NAIDU: My name is Sanjiv Naidu. I'm an orthopedic surgeon. I'm an associate professor of orthopedic surgery, and my interest is in orthopedic surgery and material science.

DR. KIM: I'm Choll Kim. I'm an assistant

professor of orthopedic surgery at the University of California - San Diego, and my specialty is in orthopedic spine surgery.

DR. DOYLE: I'm LeeLee Doyle. I'm a professor emeritus of obstetrics and gynecology, and the assistant dean for faculty development at the University of Arkansas College of Medicine. I'm a consumer rep.

MS. MAHER: Sally Maher. I'm a group director of regulatory and clinical research for Smith & Nephew Endoscopy. And I'm the industry rep.

DR. WITTEN: I'm Celia Witten. I'm the division director of reviewing division at FDA.

DR. RUDICEL: Sally Rudicel. I work at Tufts New England Medical Center. I'm an orthopedic surgeon associate professor, and my specialty is foot and ankle.

DR. FINNEGAN: Maureen Finnegan. I'm an associate professor at the University of Texas Southwestern Medical Center. And my background is trauma.

DR. ELLENBERG: Good morning. I'm Jonas

Ellenberg. My specialty is biostatistics, with a long history at the Neurology Institute at NIH. I am currently a staff member at Westat as a vice president and senior biostatistician.

DR. LI: My name is Steve Li. I'm president of Medical Device Testing Innovations in Sarasota, Florida. My areas of interest are biomaterials and biomechanics.

DR. YASZEMSKI: Thank you very much. I'd like to note for the record that the voting members here at the panel table constitute a quorum as required by 21 CFR Part 14.

You'll notice on your schedule that there is an FDA update. There is no update to present since the last meeting, and we're going to move right on now to the open public hearing. We ask at this time that all persons addressing the panel speak clearly into the microphone as the transcriptionist is dependent upon this means of providing an accurate record of this meeting.

Before Ms. Scudiero reads her statement, I'm going to say it's important for everybody to state

their name, their affiliation, and any interest they have in the product under consideration. I'll ask your forbearance at this point if you forget to do that and I remind you throughout the meeting today. Ms. Scudiero?

MS. SCUDIERO: This is the statement for the open public hearings. Both the Food and Drug Administration (FDA) and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at open public hearing sessions of advisory committee meetings, FDA believes that it is important to understand the context of any individual's presentation. For this reason, FDA encourages the open public hearing or industry speaker at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment for your travel, lodging, and 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 the issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. YASZEMSKI: Thanks Ms. Scudiero. Prior to the meeting, we received three requests to speak in the open public hearing. They'll speak in the morning open public hearing. They are Mr. William Christianson, president, Orthopedic Surgical Manufacturers Association, Ms. Merrie Miller, and Ms. Allyson Washburn. Will the first presenter, Mr. Christianson, come forward? Mr. Christianson, you're scheduled for five minutes. Good morning.

MR. CHRISTIANSON: Good morning, Dr. Yaszemski, and thank you. My name is William Christianson. I'm vice president of clinical and regulatory affairs with DePuy Spine who paid my expenses to come here today. I do not have a financial interest in the product being discussed today.

I speak here today representing the Orthopedic Surgical Manufacturers Association (OSMA). And as Dr. Yaszemski said, I am president of that organization. OSMA is a trade association with over 30 member companies. And we welcome the opportunity to provide general comments at today's orthopedic advisory panel meeting. OSMA's comments should not be taken as an endorsement of the products 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 company's views.

OSMA was formed over 45 years ago, and has worked cooperatively with the FDA, the American Academy of Orthopedic Surgeons, and the American Society for Testing of Materials, and other professional medical and standards development bodies. This collaboration has helped to ensure that orthopedic medical products are safe, of uniform high quality, and supplied in quantities sufficient to meet national needs. Association membership currently includes over 30 companies who produce over 85 percent

of all orthopedic implants intended for clinical use in the United States.

OSMA has a strong and vested interest in ensuring the ongoing availability of safe and effective medical devices. The deliberations of the panel today, and the panel's recommendation to FDA, will have a direct bearing on the availability of new products. We make these comments to remind the panel of the regulatory burden that must be met today. We urge the panel to focus its deliberations on the product's safety and effectiveness based on the data provided.

The FDA is responsible for protecting the American public from drugs, devices, food, and cosmetics that are either adulterated, or unsafe, or ineffective. However, FDA has another role, to foster innovation. The role of this panel is also very important to the analysis of the data in the manufacturer's application, and to determine the availability of new and innovative products in the U.S. marketplace. Those of you in the panel have been selected based on your expertise and training. You

also bring the view of practicing clinicians who treat patients with commercially available products.

OSMA is aware that you receive training from the FDA on the law and the regulation, and we do not intend to repeat that information today. We do, however, want to emphasize two points that may have a bearing on today's deliberations. One, a reasonable assurance of safety and effectiveness, and two, valid scientific evidence. There's a reasonable assurance that a device is safe when it can be determined that the probable benefits outweigh the probable risks. Some important caveats associated with this oversimplified statement include valid scientific evidence and proper labeling, and that the safety data may be generated in the laboratory, in animals, or in humans. There's a reasonable assurance that a device is effective when it provides a clinically significant result. Again, labeling and valid scientific evidence play an important role in this determination. The regulation and the law clearly state that the standard to be met is a reasonable assurance of safety and effectiveness. Reasonable is defined as moderate,

fair, and inexpensive.

The regulation states that well-controlled investigations shall be the principal means to generate the data used in the effectiveness determination. The following principles are cited in the regulation as being recognized by the scientific community as essentials in a well-controlled investigation: study protocol, methods of selecting subjects, method of observation and recording of results, and comparison of results with control.

The panel has an important job today. You must listen to the data presented by the sponsor, evaluate the FDA presentations, and make a recommendation about the approvability of the sponsor's application. 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 and the risks. The standard is not proof beyond the shadow of a doubt.

When considering making recommendations for further studies, remember that FDA takes these recommendations seriously, often as a consensus of the

panel as a whole. And they 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 new products that you and your colleagues use in treating patients to the market.

OSMA thanks the FDA and the panel for this 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 are available to answer questions anytime during the deliberations today.

DR. YASZEMSKI: Thank you, Mr. Christianson. Ms. Miller?

MS. MILLER: Good morning, ladies and gentlemen. I am Merrie Francis Miller. I live in Ellicott City, Maryland, and I am 73 years young. I am here to give testimony for the X STOP device implant I received in March of 2001 for a study originating from the St. Francis Medical Technologies

Incorporated of Alameda, California. Other than transportation to this meeting, and one preliminary meeting of preparation held in Baltimore, I have not received any monetary assistance from St. Francis.

Early in the fall of 2000, I began to experience pain from my lower back area and down my right leg. I say pain, but it was excruciating pain as it developed. For several years prior I had had periods of numbness in the two smallest toes of my right foot which my general practitioner doctor seemed to ignore. I also had to curtail my 3-mile walks I took four times a week because of the pain. Even Christmas shopping was shortened and almost cut out completely since I could no longer endure much walking to shop. I jokingly requested a cane as a Christmas present since I was only comfortable when bent over like the old witch in the illustrated stories of Hansel and Gretel.

In January of 2001, I saw an ad on the back page of the Baltimore Sun paper, which had questions such as `Do you have pain in your lower back going down your leg?' `Are you relieved of this pain

when sitting or lying down?' `Do you find yourself leaning on the cart when grocery shopping? If you can answer yes to these questions, you may have spinal stenosis.' I was able to answer yes to all, and to the last question, the shopping cart, I thought, ah, they've seen me.

By this time in January, I was really feeling old. I had begun to frequently take Advil to relieve the pain. My previous activities of tennis, 3-mile walks, long walks when touring new places, tending and taking care of three good size garden, taking care of a family of three in a 3-story house, grandmothering over a dozen grandchildren, and general daily normal active living, of all this I was severely limited.

I considered this ad divine providence. So I called the phone number listed, and made a consultation appointment to see Dr. Charles Hartjen at the Greater Baltimore Medical Center. I was examined, and diagnosed with spinal stenosis. After a few weeks, I received word that I was accepted for the medical study of the X STOP implant.

Near the end of March 2001, Dr. Hartjen performed the implant surgery, which lasted only one hour. It was minimally invasive. I spent an uncomfortable night in the hospital, and after receiving some physical therapy lessons, I returned home. Post-operatively, I remained on the second floor, being confined to bed when I needed it, for one week before going up and down stairs. The pain medication I received I discontinued after the third day home. I did not need it. I had discomfort around the 3-inch incision, but that was all. Six weeks later, I took a granddaughter for a 3-week tour of France.

To this day, over three years later, I am free of that pain, and I have full normal movement in any position needing a twist, a bend, or a turn of my back. I can't praise enough the work of Dr. Hartjen, nor the creative doctor who came up with this X STOP, and his name, Dr. Zucherman. I have been given not just a new life, but living proof that others with the debilitating condition of spinal stenosis might be helped with this device.

Thank you so much for allowing me to speak before you this day.

DR. YASZEMSKI: Thank you, Ms. Miller. Ms. Washburn?

MS. WASHBURN: Good morning. My name is Allyson Washburn. I am an experimental psychologist. I teach research methods, statistics, and gerontology at the Saybrook Graduate School and Research Center in San Francisco. I have no financial interest in St. Francis Medical Technologies. I have received no financial compensation other than this trip to speak with all of you this morning. And I am extremely pleased to have this opportunity to tell my story. And it in so many ways parallels the previous speaker's story. And I hope at the age of 73 I am as vital as she is.

My difficulties began when I was just 50 years old. And my first symptoms were those of some weakness in my left leg. It would collapse on me occasionally. I was starting to think maybe that I had muscular sclerosis, or something like that, and didn't say anything to anybody about it. I was too

afraid.

The first real symptoms began in the summer of 2000, and began quite suddenly, the pain in the center of my hip, radiating down my left leg. Very painful. Upon walking, became increasingly painful with walking or standing. I soon learned that the best thing for me to do would be to sit as much as possible. Certainly, curled up was the best position of all.

I had an acute episode at that time that lasted about two months. There was a lot of -- I had a lot of visits to Kaiser, a lot of diagnostic workup done. It wasn't until I had an MRI that the diagnosis was made. This took a couple of months. And when I saw the diagnosis my heart sank, because I had seen that term "spinal stenosis" in charts of the nursing home residents where I was working at the time conducting research. And I knew these patients could not be treated with regular analgesics or not even with opioids. They were not eligible for some of the studies I was conducting with pain management in dementia patients. So I was very dismayed. But soon

learned that what would help me were spinal injections. And so I became someone who sought these very painful procedures because they helped somewhat.

Although I had one particularly bad episode in the fall of 2000, where I spent the better part of two months curled up in a fetal position on my couch. I became hooked on CNN at that point. It was during the 2000 election. And I think I reached a point many similar patients reach where you ask yourself is this something I can live with for the rest of my life? And of course I decided I couldn't. But I really didn't know what I was going to do. But with this forced rest, I eventually got better. The injections didn't really help me that time. They don't work reliably. There are a lot of side effects, I was aware of that.

So I was feeling pretty desperate when I happened to meet someone at a party. We discussed similar symptoms. It was just one of those happenstances. She then saw an article about Dr. Zucherman's X STOP device in a newsletter. She thought it might help me. She hadn't gotten her

diagnosis yet. So I called Dr. Zucherman, became enrolled in the trial, but was randomized to the control group. Dr. Zucherman, though, explained that we were towards the end of the trial, that perhaps I would be able to get the device at the end of the data collection for the experimental group.

But my friend in the meantime got her diagnosis. She's 80 years old now. And I saw her a week after the procedure. She was randomized to the experimental group, and she was all dressed up and at a luncheon. This was a week after the procedure. Looked fine. She has never had pain since then. This was spring of 2001. I later saw her coming home from the gym, met her in the supermarket. I was still bent over the cart. And she was looking quite fit.

So I decided, given her experience I decided to tough it out. I would still have my injections. I consumed a lot of NSAIDs. They weren't all that effective. I think I was on Nortriptyline for awhile. But found that the injections and just limiting my activity. I walked very little in those days. I would have friends drop me off and pick me

up. I used some of the wonderful web-based services that have since gone out of business with the dot.com bust. Webvan was one of them. So I just waited very patiently, hoping that I would be eligible for the X STOP at some point, seeing what it had done for my friend.

And there were times, like I said, that the injections did not work. I was fortunate in that I was able to work at home quite a bit, although ironically I had to find a replacement for me for data collection for this pain study, because I could not walk from one nursing unit to another. I was involved in data analysis and doing some other research-related activities, but I couldn't help any further with that study.

So finally in summer of July of 2003 I got the call that I had been waiting for. I was among those in the control group for whom the device was now being offered. And it all happened very quickly. I spent just a few hours at St. Mary's where Dr. Zucherman performed the procedure. I walked out of the hospital. I was shaky, but I was fine. I spent a

week at home recuperating. I was told I wouldn't feel too great for a week, which I didn't, but it was mainly I was tired, the stress of undergoing the procedure.

The wound healed quickly without incident. Within two weeks, I was able to entertain my sister and her family visiting from out of town. We went to the new Asian art museum that I had not been able to visit because I wasn't going to museums in those days. And we did a lot of walking in San Francisco. It's a wonderful walking city, and walking has always been my exercise, walking and hiking. And so it is, again.

I also interestingly, another parallel with Merrie's story is I within two months was in Europe. We flew to London. We spent some time in the south of France, and some time in Paris. So these were three wonderful weeks. I was not restricted at all in my activity. I didn't push it. I wasn't doing any power-walking, as I called it in those days, early days of recovery, but I was walking normally. I was going to all the museums. I really had stopped thinking of myself as a pain patient, a back patient.

I had resisted that mightily all along, figuring it was a temporary thing and surely I would overcome it, although I was aware of the prognosis. I saw it in the wheelchairs in the nursing home, and I knew that that could be me, and well before my eighties or nineties, as many of the residents are at the nursing home.

So I would say that now, over one year later, I think of myself as being cured, although I do have occasional pain when I cannot lie comfortably on my right side. That's somewhat painful. That's just one of those things I'll live with. It's not a big deal. I have many other positions I can lie in comfortably. So that's really the main thing. And since pain memory is a very weird thing. Friends will ask me, well, how is your back, they're always asking me that. Less so now. But I would have these memories of the pain in my hip, mostly, that unforgettable pain. The memory is still there sometimes, I can feel it as if it's acutely bothering me. It's a pain that I won't easily forget, and I hope not to experience for real other than in a few

strong memories again.

So I would say I have a normal life. Again, mostly with some good back hygiene. My son is a physical therapist, and watches me very carefully. The X STOP devices, I actually have two of them, help my lower spine be more flexed. I also help that out myself by consciously making some adjustments, particularly when I'm sitting. And so I am back to my walks in San Francisco, and very grateful patient and recipient of this device. And again, I appreciate the opportunity to speak with all of you this morning. Thank you.

DR. YASZEMSKI: Thanks very much, Ms. Washburn. Is there anyone else who would like to address the panel at this time? Seeing none, we're going to move on to the sponsor presentation. St. Francis Medical Technologies will give their presentation on their intraspinous process distraction device. We'll have the sponsor and the FDA presentations, and then begin the panel's deliberations before lunch. After lunch, the panel will continue their deliberations on the approvability

of this pre-market application. Before the panel votes, there's going to be another open public hearing, and a time for FDA and sponsor summations. I'd like to again 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.

We'll begin now with the sponsor presentations. The first St. Francis Medical Technologies presenter is Ms. Yvonne Lysakowski, vice president of regulatory and clinical affairs. She will in turn introduce the other St. Francis Medical Technologies presenters. Ms. Lysakowski?

MS. LYSAKOWSKI: Good morning, Mr. Chairman and members of the panel. I am pleased to be here to discuss the PMA application for the X STOP device. My name is Yvonne Lysakowski, and I am vice president of clinical and regulatory affairs at St. Francis. I am a full-time employee of the sponsor.

We are here today to present the results from a multi-center IDE clinical study of the X STOP intraspinous process implant. I will begin the

presentation with a brief review of our product development history from inception to the present day.

Additional presenters are Dr. Augustus White from Harvard Medical School who will discuss the pathoanatomy and clinical presentation of lumbar spinal stenosis, along with current treatment options. Dr. White is a professor of orthopedic surgery at Harvard Medical School, and orthopedic surgeon and chief emeritus at Beth Israel Deaconess Medical Center, and has treated spine pathologies for over 30 years. Dr. White has authored over 300 abstracts, manuscripts, and books.

Dr. Scott Yerby from St. Francis Medical Technologies will discuss the design rationale for the X STOP device, and the results of our biomechanical testing.

Dr. Gunnar Andersson from Rush Medical University will discuss the rationale for our pivotal clinical study design. Dr. Andersson is the senior vice president, medical affairs, and chairman of orthopedic surgery at Rush-Presbyterian-St. Luke's Medical Center. He was president of the International

Society for the Study of the Lumbar Spine from 1989 to 1990, president of the Orthopedic Research Society, and served for over four years on the NIAMS Advisory Council. Dr. Andersson has authored over 400 publications.

Dr. Charles Hartjen from Greater Baltimore Medical Center will present the results of our pivotal clinical study. Dr. Hartjen is a board-certified orthopedic surgeon and spine specialist at Greater Baltimore Medical Center. Dr. Hartjen has been an instructor in techniques in minimally invasive spine surgery for the North American Spine Society. Dr. Andersson will then discuss the study outcomes. In addition, we have a number of other sponsor representatives in attendance.

The X STOP device has been under development since 1995. Early on, extensive preclinical testing was conducted to establish the validity of the intraspinous implant design concept. A 10-patient pilot study with 1-year follow-up was initiated with the first generation device design. And based on the results from biomechanical testing in

the pilot study, a randomized controlled multi-center clinical trial was initiated under an approved investigational device exemption application with the second generation version of the device. This study is referred to as the Phase I RCT as in the slide shown here. After a number of patients were enrolled, it became evident that a change to the device design was necessary, and enrollment of the study was halted.

Our pivotal clinical trial with the final device design used on all X STOP patients was initiated in June 2000. One hundred and ninety-one patients received treatment in this multi-center study, and were followed up through 24 months post-operatively. The results of our pivotal trial will be presented later in detail by Dr. Hartjen. St. Francis filed a PMA application with the clinical results from this study on January 6, 2004, and was granted expedited review status.

As stated earlier, the proposed indications for use of the X STOP device are as follows. The X STOP is indicated for patients aged 50 or older suffering from mild to moderate neurogenic

intermittent claudication secondary to lumbar spinal stenosis who have undergone a regimen of non-operative treatment. The X STOP is indicated for patients who experience relief in flexion from their symptoms of leg, buttock, or groin pain, with and without back pain.

I am certain that after you have reviewed our data, you will agree with us that the X STOP is safe and effective for its proposed intended use. And we hope that you will recommend approval for this device at the end of panel deliberations. Now I would like to introduce Dr. Augustus White.

DR. WHITE: Good morning, Chairman Yaszemski and distinguished panel members. My name is Augustus White, and it's my privilege to be able to describe the pathoanatomy of lumbar spinal stenosis. I have been providing consulting service to St. Francis Medical Technologies, and I do have a financial interest in the sponsor. It is a pleasure for me to be here this morning to present the clinical picture of lumbar spinal stenosis. I would add that I do this with considerable humility after having heard

from two courageous patients.

I will review the pathoanatomy of lumbar spinal stenosis and its clinical presentation. As we know, lumbar spinal stenosis often presents clinically as neurogenic intermittent claudication. This is the salient symptom of this problem. Neurogenic intermittent claudication is characterized by pain, tingling, numbness, and decreased strength in the legs which is attributed to narrowing of the lumbar spinal canal. I will also describe the natural history of stenosis, and the current treatment.

This is perhaps the most important visual presentation for orientation and understanding of this particular disease. If we look at this schematic, first looking to your left, you see a section of the lumbar spine viewed from behind. By rotating this image, we get an axial or cross-section view. Here we can see the space available in the central canal, which is a key element of the pathology of this disease. As we look at this image, we see that there is a certain amount of space that contains the dura spinal fluid and nerve rootlets. As long as there's

enough space in this particular canal, there's no compression on the nerves. But as we look at this diagram though, on the far right we see several changes to the normal anatomy that results from the process of aging, which can contribute to the loss of that space. A protruding disc can come in from the front to press on the dura, and can compress the dura from that particular side. On each side, degenerative changes to the facet joint can reduce the space available posteriolaterally. Posteriorly, the yellow ligament can compress the dura, so that all of these things contribute in varying degrees progressively to the point that enough space is lost and patients experience back and leg pain due in part also to changes in axoplasmic fluid flow, as well as venous congestion resulting in inflammation and pain.

Here we see on an MRI image the difference between a pathologic canal with lumbar spinal stenosis and a spacious normal canal. And as we've described on this schematic, we see anteriorly here coming from the front pressing on the spinal canal the nerve rootlets at this position. Here we see the facet

joints which are deformed and enlarged on each side contributing to the changes, and a trefoil type configuration which is part of the stenotic condition. And then posteriorly, the major player, the major component of the stenosis oftentimes is a yellow ligament, which is thickened and which is also folding in, folds into the canal because it loses its elasticity.

When patients walk, they extend their spines with the result being that they get their stenosis symptoms. The best description that I've heard of these, up until today perhaps, is the patient who described to me once, "Doctor, as I walk, I feel something like an electric storm going down my leg." This is a kind of poetic description, but it is a spontaneous response and description on the part of the patient. This pain obviously can be excruciating, and is characteristically associated with ambulation. Patients on their own will develop ways of ameliorating their symptoms, and quite frequently they will discover that using a cart when they are shopping allows them to flex in the lumbar spine area, as shown

in this picture, when the patient sits. And it also alleviates some of the pain from walking.

Here's another way to depict this, with demonstration of an excellent illustration from Dr. Frank Netter, showing the lumbar spine motion segment. And here is one of the exiting nerve roots which is compressed in extension. In flexion of the spine, you can see that the neural canal, the foraminal canal opens up, giving more space available for the nerve root. Here we can see radiographic correlation of this.

This is a colored, if you will, schematic of a myelogram, which shows a distinct block here in the case of lumbar spinal stenosis with extension from a lateral view. Fluid is blocked. And here we see on the AP the same blocking of the fluid. With the flexion position, however, this is ameliorated, and the space is available for the free flow of the lumbar spinal fluid. So the principle here is that with flexion there is more space available, less congestion of venous structures, and less pain.

The anatomic changes that cause lumbar

stenosis occur gradually as a natural progression of aging. The majority of patients who develop symptoms are usually stable, and symptoms will usually remain unchanged, or perhaps even slightly improved in some cases. Some patients, however, will get worse. This observation is confirmed by studies done by Johnsson and others. The natural course of lumbar spinal stenosis can be relatively benign, and the diagnosis of stenosis does not necessarily result in symptoms that are severe enough to require surgery. A large percentage of patients require only medical treatment.

This observation is confirmed by the prevalence of stenosis, which is reported in the United States to be approximately 700,000 cases per year. The number of decompression surgeries performed in the U.S. is about one-tenth of that number, as you can see. There are about 60,000 per year.

I would like to describe the current treatment alternatives that are available to stenosis patients. First of all, non-operative care is prescribed. The rationale for conservative treatment is to decrease pain and increase function. Various

types of analgesic and anti-inflammatory medications are prescribed for pain. The exercise and physical therapy can help to improve function. Conservative therapy is a continuous process, and treatment does not constitute one single application of these modalities. Epidural steroid injections may help reduce inflammation. Inflamed nerve roots may be swollen and worsen the effect of a narrow canal and foramen. These non-operative approaches are considered the standard of care for these stenosis patients with mild and moderate symptoms.

For patients with more severe symptoms, surgical intervention becomes an option. Surgery is characteristically some form of surgical decompression. That is, removing of some of the elements that are causing the narrowing of the canal. Surgery is characteristically some form of surgical decompression, often combined with a spinal fusion. But patients typically wait for some time before considering surgery. Mean symptom duration of patients' electing surgery was 4.3 years in Turner's meta-analysis.

Against the clinical and epidemiological background, a different mechanism to treat patients with stenosis was conceived. A device placed between the spinous processes to limit extension, that is the X STOP, was developed and tested by the sponsor. We know that stenosis patients have more pain with standing or extension, and we know that with flexion the space available in the canal is increased. The X STOP keeps the functional spinal unit out of full extension, and therefore limits impingement on the neural elements and the symptoms that it causes. The X STOP seems to be a straightforward mechanical solution to a well understood, straightforward biomechanical problem. The X STOP prevents the pathoanatomic positioning of the functional spinal unit which irritates the spinal nerves, and it also preserves the function of the spinal anatomy.

I would like to turn the podium over to Dr. Scott Yerby who will discuss the design rationale of the X STOP, as well as describe some of the biomechanical studies that were performed.

DR. YASZEMSKI: Thank you, Dr. White. Dr.

Yerby?

DR. YERBY: Thank you Dr. White. Good morning Mr. Chairman and members of the panel. My name is Scott Yerby. I'm a full-time employee of the sponsor as the Director of Research and Development. I'd first like to describe the design feature of the X STOP, and then I will present the results of some of the biomechanical tests we performed to characterize the function of the X STOP and its effect on the lumbar motion segment.

The X STOP, shown on the right, is a titanium alloy implant that is placed in the intraspinous space and limits extension of the implanted level. The blood tissue expander allows the implant to be inserted laterally without modifying the spinous processes. This allows the superspinous ligament to be retained. The tissue expander also has a slot to accept an adjustable wing. In addition, the X STOP has an oval spacer that is designed for optimal contact between the bone and the implant. The fixed and adjustable wings prevent lateral and anterior migration of the implant.

These figures show the X STOP in the intraspinous space from a lateral, axial, and posterior view. The lateral and axial views demonstrate that the lamina is left intact, and therefore shields the implant from the neural structures. The risk of neural injury, either during or after placement, is therefore very low. Finally, the implant is not fixed to any bony structures. Should the implant ever have to be removed, revision surgery is straightforward.

We performed a series of biomechanical tests during the development of the X STOP. Today I'm going to discuss two of these tests: the change in the dimensions of the spinal canal and neural foramen, and the change in the intervertebral kinematics following X STOP placement.

The methodology used to measure the dimension of the spinal canal and neural foramina involved eight L2 to L5 lumbar motion segments that were placed in a custom acrylic positioning frame capable of placing the specimen at 15 degrees of flexion, 15 degrees of extension, and in the neutral

position. Each specimen was placed in a 1.5 Tesla MRI Scanner in one of these three positions, with or without the X STOP placed at the L3-4 level. Axial and para-sagittal images were used to measure a number of parameters at the implanted and adjacent levels. In extension, the canal area increased by 18 percent, the canal diameter increased by 9 percent, and the subarticular diameter, which represents the lateral recess, increased by 50 percent.

We used the same method to analyze para-sagittal images to measure changes in the foraminal area. The foraminal increased by 25 percent, the foraminal width increased by 41 percent, and again, these results show that the critical dimensions are significantly increased. There were no significant differences between the mean dimensions of the intact and X STOP implanted specimens at the adjacent L2-3 and the adjacent L4-5 levels.

To measure the spinokinematics, we measured the invertebral rotations of seven L2-L5 motion segments, loaded to 7.5 Newton-meters of flexion-extension, axial rotation, and lateral

bending, with a superimposed 700 Newton axial load. The kinematic study demonstrated that flexion-extension range of motion decreased from 7.6 degrees to 3.1 degrees. This is demonstrated in the lower right. The axial rotation range of motion, shown at the top, and the lateral bending range of motion, shown at the left, however did not change significantly. At the adjacent L2-3 and L4-5 levels, there were no significant changes in the bending angles in any motion.

In conclusion, the X STOP is inserted between the spinous processes with only minimal tissue disruption. It is stable without being permanently attached to the bone, and remains shielded from sensitive neural structures. The X STOP significantly increases the dimensions of the spinal canal and neural foramen, and significantly decreases the range of motion during flexion-extension, while not affecting the range of motion during axial rotation or lateral bending. The X STOP does not significantly the adjacent levels. Clinically, the X STOP is designed to prevent the symptomatic extended position,

and by doing so increase the dimensions of the structures that cause neural compression.

Thank you. I'd now like to introduce Dr. Gunnar Andersson, who will discuss the rationale of the X STOP pivotal trial.

DR. YASZEMSKI: Thank you, Dr. Yerby. Dr. Andersson?

DR. ANDERSSON: Thank you and good morning, Mr. Chairman and panel members. My name is Gunnar Andersson. I'm the professor and chairman of Orthopedic Surgery at Rush University Medical Center.

I was not an investigator in the pivotal trial, but for five years I have been a member of a panel advising St. Francis Medical Technologies on medical matters. In that capacity I provided guidance regarding the design of the clinical trial. I do have a financial interest in the sponsor.

Today I will present some background information and discuss the design rationale of the pivotal trial. First I would like to present some data on the outcomes and risks associated with current treatment alternatives for lumbar stenosis. Dr. White

listed those for us earlier. A discussion of the risks and benefit of non-operative care, as well as the risks and benefit of decompressive surgery will help us set the stage for a discussion of the X STOP study design. Patients undergoing non-operative therapy who experience at least some improvement in their symptoms are typically considered as having a successful outcome. Usually this criteria on the success of non-operative therapy ranges from approximately 28 to 33 percent, as reported in the literature by Johnsson, Amundsen, and Atlas. These three studies are of particular interest because they report results of patients with a range of symptoms from mild to severe. They also include outcomes of surgical treatment in addition to non-operative therapy, and these outcomes form the basis for our analysis of laminectomy surgery.

While relatively infrequent, there are some risks associated with non-operative therapy. Non-steroidal anti-inflammatory medication can cause well-known secondary effects such as GI bleeding, allergies, and organ toxicity. There are a variety of

procedure related problems that have been reported as a result of epidural injections. These include dural tears, epidural hematomas, infections, and neurologic damage. But generally speaking, non-operative therapy entails very few risks. So as we assess the risks versus the benefit of non-operative therapy, it is fair to say that it offers a measurable benefit to a patient suffering from mild to moderate stenosis at low risk.

Looking again at the studies of Johnsson, Amundsen, and Atlas for results of patients undergoing decompressive surgery, we see that between 57 and 69 percent of patients experience clinical improvement in their symptoms. The most severe complications from laminectomy are listed on your left. Deyo and collaborators analyzed a large database of patient discharge information to compile the incidence of these complications. They found that 14 percent of patients experienced complications after laminectomy, and 20 percent of patients when laminectomy was combined with a fusion. So if we assess the risk compared to the benefit of laminectomy surgery, I

believe it is fair to say that the outcomes of surgery are good. The risks are not insignificant, however, and are much greater than conservative therapy. Certainly, some of the complications may have long-term sequellae, and the incident of death was reported by Deyo to be 6 in 1,000 cases. Given the generally advanced age of this patient population, usually suffering from numerous comorbid conditions, these complications are not unexpected.

Assessment of the current treatment options can be summarized in the following treatment algorithms. For patients with mild to moderate symptoms of stenosis, non-operative therapy is the standard of care. Decompressive laminectomy is generally indicated for patients with severe lumbar stenosis symptoms. What is missing in this algorithm is a treatment alternative for patients who do not achieve satisfactory relief of symptoms from non-operative therapy, but are unwilling to consider a more invasive procedure. There are many patients who are medically unfit to undergo general anesthesia, and have no alternative to non-operative care.

The population of patients with mild to moderate symptoms is the one we identified as the most appropriate for the X STOP, especially when we assess the risks of the surgical procedure to implant it. Implantation involves minimal tissue removal, and the spinal canal is not entered so the risk of neural injury is very low. The procedure itself can be performed under local anesthesia, typically in conjunction with conscious IV sedation, and it takes less than one hour. Therefore, we anticipated before the study started that the X STOP would entail a low level of risk, and the potential risks were much more comparable to a non-operative therapy than the risks associated with laminectomy. Based on this assessment, non-operative therapy was clearly the most appropriate treatment for the control group in our randomized trial.

I will now discuss the study design, primary outcome measure, and the success criteria used in the study. The pivotal trial was a prospective randomized multi-center controlled clinical trial comparing the X STOP to non-operative therapy. The

primary outcomes measure was the Zurich Claudication Questionnaire. The SF-36 was also used to assess health outcomes as a secondary measurement tool. Radiographs taken during the course of the study were sent to an independent radiologist, who made the radiographic measurements required by the study protocol.

The Zurich Claudication Questionnaire was designed and validated for neurogenic claudication. So it is very specific for those symptoms. It is divided into three distinct domains: symptom severity, physical function, and patient satisfaction. It has been shown to be reproducible, internally consistent, and very responsive. The questions are similar to what you see in the Oswestry, but they are more specific to the problem of lumbar spinal stenosis.

Here are some questions from the symptom severity domain. The questions in this section asked patients to grade the frequency and severity of their pain or discomfort experienced on a typical day within the last month. Questions relating to symptoms are specific to neurogenic intermittent claudication, and

include pain and tingling in the feet and legs, and balance disturbances.

Here are the questions from the physical function domain. The first question on this slide asks patients to grade how far they are able to walk. And this question served as a basis for the study inclusion/exclusion criteria to identify patients with severe symptoms. The remaining questions in this domain gauge how comfortably patients are able to perform some activities of daily living, such as moving around the house or doing grocery shopping.

Here we see the six questions that constitute the patient satisfaction domain. Three questions address specifically patient satisfaction with their muscle strength, balance, and ability to walk. Three questions relate to the overall satisfaction with treatment, and the amount of pain relief.

Clinically significant improvement was defined by Stucki, et al, as a function of patient satisfaction. They found that patients who met a threshold level of improvement of approximately 0.5

were satisfied. And this turned out to be true independently for both the physical function domain and the symptom severity domain. So a change of 0.5 or greater for each domain was adopted in the pivotal study as clinically significant. In the Zurich, the lower the score the better.

To be considered a success in the pivotal study, all patients had to achieve clinically significant improvement in the physical function domain and the symptom severity domain, and to be very satisfied or somewhat satisfied with their treatment. Patients could not have additional surgery for stenosis symptoms. For X STOP patients only, distraction had to be maintained, and there could be no device-related complications or dislodgement of the implant. Individual X STOP patients were required to meet seven separate criteria at 24-month follow-up to be considered a success in this study.

Last I will describe the key inclusion/exclusion criteria. Patients have to have their symptoms relieved by sitting or flexion. Patients also had to have completed at least six

months of some medical treatment. This did not mean, however, the patients had failed treatment entirely. As Dr. White mentioned, non-operative therapy is a continuous process of treatment that a patient will typically undergo for many years. Patients were excluded if they could not walk at least 50 feet or were unable to sit for at least 50 minutes.

I would like to summarize the key study design elements. First, non-operative therapy was the appropriate control for the X STOP. While I was not an investigator for the pivotal trial, I am an investigator in an ongoing NIH-funded study in which laminectomy treatment for lumbar spinal stenosis is being compared to non-operative therapy. Second, the Zurich is an excellent tool to measure results of lumbar spinal stenosis treatment because of its emphasis on functional outcomes in three domains. The greater the limitation in walking, the more severe the symptoms from neurogenic claudication. Third, the criteria for determining success in an individual in this trial was much more rigorous compared to the criteria used in the non-operative research

literature.

I would now like to turn the podium over to Dr. Hartjen who will present the study results.

DR. YASZEMSKI: Thank you very much, Dr. Andersson. Dr. Hartjen?

DR. HARTJEN: Good morning Mr. Chairman and panel members. My name is Charles Hartjen. I will be presenting the study results this morning. I do not have any financial interest in St. Francis Medical Technologies to disclose. I trust my expenses to drive here today from Baltimore will be reimbursed by the company. I'm an investigator for the X STOP pivotal study, and my center enrolled the highest number of patients in the trial.

Investigational sites and principal investigators for each site are shown here. Nine centers participated in the pivotal study, most of which were community hospitals. Of the nine principal investigators, seven are orthopedic surgeons and two are neurosurgeons.

Patients were randomized into the study using block randomization within each center. Because

we expected a relatively small number of patients to be enrolled in each center, a block size of two was selected to help ensure equal balance of treatment and control group patients. I would like to emphasize that the block size was not revealed to me or to any other investigator or study coordinators, and randomized assignments were centrally administered by the sponsor. There was a necessary delay between randomization and treatment for both groups.

There were 114 X STOP patients and 115 control patients randomized to each group. Fourteen X STOP patients and 24 control patients were randomized, but not treated. Of these, eight X STOP patients and 19 control patients voluntarily withdrew. The remainder failed to meet study entry criteria, or withdrew for health related reasons. One hundred X STOP patients and 91 control patients were enrolled and treated in the study. Four patients died in each cohort during the course of the study. In the X STOP group, two patients died from cancer, one from pneumonia, one from CHF complications following implant surgery. In the control group, causes of

death were cancer, pulmonary embolism following foot surgery, Parkinson's disease, and myocardial infarction. Six X STOP patients and 24 control patients underwent a laminectomy for stenosis during the study and were considered treatment failures. One X STOP patient fell, causing the implant to dislodge. The implant was removed, and the patient was a failure. No patients were lost to follow-up. One X STOP patient and five control patients voluntarily withdrew from the study.

Patients were placed on their right side with their legs curled up. This flexes the spine, placing the patient in the position in which they get relief of symptoms. After an incision is made, the interspinous ligament is dilated. The superspinous ligament is left intact. The X STOP is inserted from below, and the adjustable wing is attached. A key feature of the procedure is that there is minimal removal of tissue. The spinal canal is not entered, and no bone is removed from the spinous processes. The procedure is well tolerated using local anesthesia and light IV sedation.

Patients in the control group received at least one epidural injection upon entry into the study. Additional epidural injections were administered at the discretion of the investigator consistent with current treatment guidelines and following standard medical practices. Control patients also received non-steroidal anti-inflammatory medications, analgesics, and physical therapy as needed. Patients filled out the Zurich Questionnaire and SF-36 at enrollment and at each follow-up visit, and the investigators took standing plain film x-rays, and administered a physical examination. Patients were monitored at six weeks, six months, 12 months, 24 months, following the initial treatment.

Looking at the baseline data, the demographics of the two groups are quite comparable. The mean age for the patients was about 70 years old in both groups at enrollment. Approximately 60 percent of the patients in both groups experienced symptoms for more than two years. The two groups were extremely well matched at the study entry. There were no significant differences between the two groups in

any baseline variable except one. More patients in the X STOP group received epidural injections prior to study entry compared to the control group.

As expected with this elderly patient population, there were many patients with comorbid conditions. About 45 percent of the patients in each group had a history of cardiovascular disease. After cardiovascular disease, musculoskeletal disorders were the most frequent reported comorbidities. The incidence of musculoskeletal problems was more pronounced in the X STOP group at baseline.

The baseline Zurich scores are shown here. And as we see, the two groups were quite comparable. On the left are the mean baseline scores for the symptom severity domain, which were 3.14 in the X STOP group and 3.10 in the control group. Patients in the study were in the middle of the range, indicating they had moderate symptoms as a group. Mean baseline scores for physical function domain were on the right, and were 2.48 for both groups. Again, these scores are in the middle of the range. Here are the SF-36 scores at baseline. Again, the two groups were quite

comparable, and no significant differences in any of the SF-36 domains. Higher scores on the SF-36 are indicative of better function.

The X STOP operative variables are shown here. The operative time averaged just under an hour, and average blood loss was negligible at 50 cc's. Three patients had general anesthesia, 97 had local anesthesia, usually with light IV sedation. Hospital stays were less than 24 hours in 96 of 100 patients. Typically, physical therapy was initiated early in the morning after surgery, and the patient was discharged in the early afternoon. One patient, a 76-year-old female who had an ischemic coronary episode during the procedure was kept in for observation and thallium stress test. She was discharged three days later. About one-third of the X STOP patients had two-level procedures. The operative level was usually 4-5, with L3-4 being the second most common level.

Ninety-one control patients received a total of 216 epidural injections during the course of the study. All control patients received an epidural injection upon entry into the study. Twenty-two

patients received two injections, 21 patients received three injections, and several patients received four or more injections. Although not shown here, I would like to note that eight X STOP patients received epidural injections or nerve root blocks during the study, and six of these were treatment failures.

Adverse events relating specifically to the X STOP group only are listed here. There are four procedure-related adverse events. These were limited to incisional complications which resolved with treatment. There were no reports of any nerve injuries or neurologic deterioration as a result of X STOP implantation. There are three device-related adverse events. One patient fell in the early post-operative period, causing the implant to be dislodged, and it was removed. One implant was malpositioned at the time of surgery, and was later detected on x-ray examination. There's one spinous process fracture which occurred sometime between six and 12 months, in between those two follow-ups. The patient experienced on symptoms from the fracture, and had healed without sequellae.

Here we see adverse events that were determined by investigators to be related to epidural injection or the X STOP procedure. Stenosis related pain was reported as an adverse event in six X STOP patients and 26 control patients. In these cases, the pain was significant enough to trigger an unscheduled follow-up visit or require follow-up medical treatment. All six of the X STOP patients, and 24 of the 26 control patients eventually underwent a laminectomy for unresolved stenosis pain during the study period. There were no reports of complications or difficulties associated with removing the X STOP, which is what was anticipated since the implant is not adjacent to nerves or major vessels, and is not fixed to bone.

There were five reports of adverse events in the control group as a result of the epidural injections. These included two cases of increased pain that were severe enough to require hospitalization, and two complaints of paresthesias during or immediately following injection. All of the events resolved without sequellae.

Adverse events determined by the study investigators to be unrelated to treatment are shown here. There was no statistically significant differences in the incidence of these adverse events with the exception of musculoskeletal adverse events. Forty-three X STOP patients experienced these events, compared to 16 control patients.

Shown here are the results of the analysis of adverse events that we performed at the FDA's request. We examined the case histories of those events that were potentially of greatest concern, including upper and low back, lower extremity, or neurologic system. There were 47 of these adverse events in 32 X STOP patients. The majority of these events, 63 percent, were attributed to comorbid conditions. Eight percent were for excess activities, 19 percent for stenosis symptoms representing nine patients who were treatment failures. Ten patients were classified as Miscellaneous, and included peripheral neuropathy, stroke, and ataxia. Adverse events involving the upper extremity and hip were not included in this analysis, and are shown here. In

each event, the investigators determined the events were unrelated to treatment.

In summary, the musculoskeletal events we observed in the X STOP group would be expected in the elderly patient population. The patients in the X STOP group also had a higher incidence of comorbidities at baseline. What is surprising is that the incidence was relatively low in the control group. One reason may be that 26 percent of the control patients were terminated from the study after they had laminectomy. We could attribute a number of events in the X STOP patients to an increased level of activity. This unmasking effect surfaced after patients' stenosis symptoms resolved.

I now present the effectiveness results. I will present the primary outcomes for the evaluable patient population for each domain under Zurich. I will then present the results of the study, using the overall success criteria described in the protocol. Finally, I will present the outcomes measured by the SF-36, as well as improvement in frequency and severity of back and leg pain.

The population of patients who experienced clinically significant improvement in symptoms' severity at each follow-up interval is shown here. At 24-month follow-up, 58 percent of the X STOP group had significant improvement in this domain compared to 17 percent of the control group. The difference between the two groups was statistically significant at each follow-up visit. In the physical domain, the differences between the two groups was statistically significant at the follow-up visits. At 24-month follow-up, 55 percent of the X STOP patients were significantly improved versus 14 percent of the control patients. In the patient satisfaction domain, again, there was a statistical significant difference between the two groups at follow-up. At 24-month follow-up, 71 percent of the X STOP patients were satisfied, compared to 32 percent of control patients. Combining all three Zurich domains at 24-month follow-up, 47 percent of the X STOP patients met all three criteria for success, compared to five percent of the control patients.

Radiographic measurements taken at the 24-

month follow-up were compared to measurements taken at the 6-week follow-up. A number of measurements were made to monitor general changes that might have occurred to the spine as a result of implanting the X STOP. There were no significant differences at either 12 or 24 months between the X STOP group and the control group in any of these measurements. These included anterior and posterior disc height, curvature of the spine, angulation of the spine, and degree of spondylolisthesis. Distraction was maintained in 96 percent of the X STOP levels. When we combine all seven criteria for determining success in the individual patient as they apply to the X STOP patient, we can calculate the primary study endpoint. Counting patients with missing data at the 24-month follow-up as failures, 44.8 percent of the X STOP patients met all success criteria compared to 4.6 percent of the control patients.

As you heard from Dr. Andersson, in the Zurich Questionnaire, a 0.5 improvement in either symptom severity or physical function equates to a satisfied patient, and is defined as clinically

significant. But the X STOP patients on average improved much more than that threshold level. X STOP patients improved 0.99, which equates to a change of 24.8 points. At 24 months, their symptoms as a group improved from moderate to mild. X STOP patients improved 46 percent from the baseline scores. Control patients improved eight percent.

Here is the physical function score. The X STOP patients improved 0.76 on the Zurich scale, which equates to a change of 25.4 points. The control group improved 2.6 points. X STOP patients improved 52 percent over baseline.

We performed a number of subgroup analyses on success rates, three of which I will briefly describe. The patient population in the analysis includes all evaluable patients, and it excludes only those patients who died during the study. First we look at the success rate of the subgroup of patients that had one-level or two-level implantation. As you see, there is no difference in overall success rates between the two groups. There was, however, a statistically significant difference in physical

function domain of the Zurich, which patients with two-level implants had a higher success rate.

We also looked at two subgroups of X STOP patients based on symptom duration prior to study entry. We compared a subgroup of patients who had symptoms for two years or less to a subgroup of patients who had symptoms for longer than two years. There were no differences in overall success rate or in any domain of the Zurich when these two groups were compared. When we compared subgroups of clinical patients based on symptom duration, there was also no difference in the individual domain scores or overall success rates. The results of these subgroup analyses suggests that duration of symptoms does not impact outcome.

We also looked at success rates in each center. Most importantly, you will note that the X STOP success rate was consistently higher than the control group success rate at every center, even with the diversity of centers, and in both small and large centers. St. Mary's, Dr. Zucherman's site, has the highest success rate in the X STOP, and the second

highest success rate in the control group. However, even if St. Mary's is removed from the analysis, the difference between the X STOP and control groups remains highly statistically significant.

I enrolled the highest number of patients at GBMC, and you will note that the success rate at my center was 28 percent in the X STOP group. I am pleased with my result. The majority of my patients had significant improvement in symptoms and were satisfied, but did not improve enough to be a success in physical function for reasons that were unrelated to the stenosis or X STOP.

To better understand the success rates at each center, we looked at the predictors of success in the X STOP group. Patients with worse baselines for SF-36 scores correlate with a positive outcome, as well as patients who have fewer comorbidities, thus were healthier. Patients who were younger did better. Patients with lower blood loss during surgery did better. These findings are not surprising. We looked at these predictors at St. Mary's compared to other centers and found that the patients at St. Mary's

tended to be younger, had significantly fewer comorbidities, and were employed compared to the other centers. Investigators at St. Mary's conducted the original pilot study, and participated in the unwelded implant study. So their experience in screening patients may have contributed to their relatively higher success rates for both control and X STOP patients. Interestingly, the center with the lowest success rate had older patients, patients who had a high incidence of comorbidities, but were less symptomatic at baseline.

Turning our attention now to outcomes measured by SF-36. First, here are the mean baseline scores for the X STOP group which I showed you earlier. For the follow-up visits, mean scores were calculated using all available data. Here are mean scores for the 6-week, 6-month, 12-month, and 24-month visits. The SF-36 scores at 24 months was statistically significantly improved compared to the baseline in every domain except general health, mental health, and mental component summary. As the graph illustrates, the benefit of treatment was evident at

the earliest follow-up visit, and it was maintained over the course of two years.

Here are the baseline scores for the control group, which you saw earlier. And here are the scores first for the 6 weeks, 6 months, 12 months, and 24-month visits. There are sustained improvement in both the role of physical and bodily pain domains. However, this improvement was not statistically significant.

When we looked at the patients who experienced any improvement in leg pain over the baseline pain, we find a few patients in either group experienced improvement in leg pain while sitting, but 80 percent or more of X STOP patients had some improvement in leg pain while standing and walking in both frequency and severity. In the control group, the greatest improvement was seen in leg pain while walking, where 37 percent of the patients showed some improvement in frequency of leg pain, and 43 percent experienced some improvement in severity of leg pain. Outcomes for back pain mirrored results for leg pain. Significantly more X STOP patients experienced

improvement in back pain while they were standing and walking, both in frequency and severity compared to the control groups.

I would like to recap the results of our safety and effectiveness analysis. The X STOP procedure can usually be performed as a same-day procedure under local anesthesia with minimal blood loss. Patients recover rapidly. There is a minimal risk of systemic or local complications, and there is little risk of neurologic injury. Musculoskeletal adverse events were largely attributable to preexisting comorbid conditions, the prevalence of which is expected in this patient population. Revision surgery, if necessary, is straightforward. Future treatment options are not compromised. Finally, the procedure is especially suitable for patients who cannot tolerate general anesthesia.

The effectiveness of the X STOP treatment was immediate, and the superiority over control group was sustained over the follow-up period. The relative benefit of X STOP was demonstrated at all participating study centers, where X STOP success

rates were consistently greater compared to the control at every center. The magnitude of the improvement seen in the X STOP patients exceeded the threshold level defined as clinically significant. Patients improved almost double the amount defined as clinically significant. Back and leg pain symptoms improved significantly in the X STOP patients when compared to their baseline symptoms. In summary, the X STOP represents a significant breakthrough in the treatment of patients with mild to moderate symptoms of lumbar spinal stenosis. And the key findings from the pivotal trial demonstrate the device is safe and effective for use in this patient population.

I would like to turn the podium back over to Dr. Andersson for final remarks.

DR. YASZEMSKI: Thanks very much, Dr. Hartjen. Dr. Andersson?

DR. ANDERSSON: Thank you. Good morning again, Mr. Chairman and panel members. I would like to address the topic of interpreting the outcomes of this study.

To place the study results in a frame of

reference, we reviewed the published literatures and outcomes of both non-operative therapy and decompressive surgery. There is a subset of this literature reporting outcomes for patients with mild to moderate symptoms which is particularly relevant to the pivotal trial. In addition, there are studies reporting outcomes in a broader lumbar spinal stenosis population using the Zurich as well as the SF-36. Finally, we have outcomes from study patients who underwent laminectomy where we can apply the same success criteria in matched patient populations.

The observation has been made that success rates in the pivotal trial were lower than anticipated when the study was designed, and appeared to be low in comparison to results reported in the literature. It seems appropriate to first acknowledge that those criteria used in the literature to measure outcomes are different from the method used in the pivotal trial. To make a true comparison, we should apply similar standards to both. This can be done by applying the same success criteria in the pivotal trial to the clinic literature which uses the Zurich

to measure outcomes. We can also analyze the results using the criteria that are commonly applied in literature reporting results of patients with mild to moderate symptoms.

Any improvement in symptoms is typically considered a success in non-operative literature. We analyzed the pivotal trial results using the single criterion and found that 32 percent of controlled patients had some improvement in symptoms at 24 months. Thirty-two percent is comparable to outcomes reported for conservative care patients in the studies I discussed previously. This confirms that patients enrolled in the pivotal trial did not fail conservative care just because they completed six months of medical treatment. As Dr. White mentioned, stenosis patients typically experienced many years of symptoms. Six months is a relatively short period of time in the course of this disease.

We compared the improvement in symptom severity of X STOP patients to laminectomy outcomes reported by Johnsson, Amundsen, and Atlas, which I showed you earlier. In these studies, 57 to 69

percent of patients reported symptom improvement following laminectomy, where follow-up ranged from one to four years. In the pivotal trial, 58 percent of X STOP patients reported a clinically significant improvement in symptom severity. You can see the results are quite similar.

There are several published lumbar spinal stenosis studies using the Zurich. Dr. Katz and coauthors reported outcomes of a 199-patient study using individual questions from the Zurich. At our request, Dr. Katz analyzed his data using the same criteria from the pivotal trial. As you can see, the success rates are quite similar to the X STOP results. Though not shown here, mean score changes in each domain were also very similar. His patient population was more symptomatic at baseline than our patient population was. This historical comparison should not be interpreted to infer that X STOP results are comparable to outcomes from laminectomy, but it is appropriate to measure success rates of laminectomy surgery using the pivotal trial criteria if the purpose is to provide a general frame of reference.

I would like to point out that 272 patients were treated in Dr. Katz's study, and no outcomes were imputed for the 73 patients with missing data at two years. I mention this to illustrate that methods typically employed in the clinic literature to analyze data are not as stringent as those used in the pivotal trial where patients with missing data were treated as failures.

Outcomes data from 36 study patients who underwent laminectomy were also recorded. Applying the study criteria for success to this matched patient population, we get very similar outcomes as you can see here. This statistical comparison is not made for the purposes of supporting a claim of comparability to laminectomy. This does, however, indicate the true success rate from laminectomy when you apply the strict criteria used in the pivotal trial.

There are a number of studies reporting outcomes of stenosis surgery that use the SF-36 to measure success. This slide shows the mean post-operative scores of X STOP patients in the pivotal trial compared to the range of post-operative SF-36

values for patients undergoing decompressive surgery. SF-36 outcomes for the X STOP patients fell within the range of outcomes reported in the literature.

Success rates in the clinical trial appear to decline from one year to two years. And this trend was observed in both the X STOP and control groups. Similar findings have been reported in the literature where success rates tend to decline over time in laminectomy patients. This is clearly evidenced by the re-operation rates reported in these studies. As shown here, the rates of re-operation varied from 6 to 17 percent, depending on the length of follow-up, which ranged from one year to four years in these studies. This re-operation rate is quite comparable to the six percent observed in the X STOP patients.

The findings from a longitudinal study of 105 patients conducted by Johnsson and coauthors are consistent with the previous studies. This graph is reproduced from Johnsson's article, and illustrates the decline in effectiveness of operative therapy over a 5-year period. In summary, when you apply the same standards, the results of the pivotal trial for both

the control and X STOP patients are quite similar to the results reported in the literature.

With respect to achieving the primary clinical study endpoint, the statistical superiority of X STOP treatment compared to control treatment was clearly demonstrated. We anticipated a difference of 22.5 percent between the two groups at the start of the trial. Despite the lower than anticipated success rate in both the X STOP and the control groups, the difference between the groups was approximately 40 percent. This was also true for each of the Zurich domains.

I would like to end the sponsor's presentation this morning with some final remarks from the surgeon's perspective. The X STOP device can offer the surgeon a new treatment alternative for patients with lumbar spinal stenosis. Patient outcomes in the X STOP group were good, and far superior to the control group in the pivotal trial. The incidence of operative complications was low and without significant clinical sequellae. The procedure was by and large done under local anesthesia with

same-day discharge from the hospital. The advantage of having the patient out of the hospital quickly is obvious, particularly the elderly patient it certainly contributes to a low level of morbidity. The X STOP procedure does not significantly alter the functional anatomy, so it can be easily revised and replaced if necessary. From a risk-benefit perspective, the benefit clearly outweighs the risk.

The X STOP offers an immediate and quantifiable benefit to patients suffering from stenosis at low risk. I believe that the results from the pivotal trial along with the results of extensive biomechanical testing constitute valid scientific evidence, and provide reasonable assurance of the safety and effectiveness of the X STOP device. I trust the data that have been presented to you will support your recommendation for approval to the FDA today. Thank you.

DR. YASZEMSKI: Thanks very much, Dr. Andersson, and thank you to the sponsor for your thorough presentation. I'd like to ask if any panel members have a question that they'd like to ask of the

sponsor at this time. I'll note, however, that we have a long block of time devoted to asking the sponsors questions this afternoon. If there's something that needs to be asked now, please do so. Otherwise, I'd like to proceed to the FDA presentation.

Let's move on to the FDA presentation. The first FDA presenter is Dr. John Holden who is the lead reviewer for this submission. Dr. Holden?

DR. HOLDEN: Good morning. My name is John Holden. I'm a review scientist with FDA's Orthopedic Devices Branch, and I'm also the lead reviewer for the PMA application from St. Francis Medical Technologies.

FDA will provide several presentations this morning. First I will give a brief introduction and summary of the pre-clinical evaluation of the device. Dr. Barbara Buch will provide an FDA summary of the clinical study, and Mr. Richard Kotz will discuss some statistical analysis issues from FDA's perspective. Finally, we will present the questions that FDA is posing for consideration by the advisory

panel today. I would also like to point out that a large number of other FDA personnel have also made important contributions to the review of this PMA application.

As an overview, this presentation will include a very brief device description and summary of the pre-clinical testing. As the company has presented much of the data on which FDA would like to comment, my presentation will mostly highlight a few points that we wish you to consider as you address the panel questions.

From this point forward, I will simply refer to the device as the X STOP. The indications for use currently proposed by the sponsor are shown again on this slide. This statement is the same as that already presented by the sponsor.

The X STOP is manufactured from a titanium alloy that conforms to ASTM Standard F136. It consists of two components, a spacer assembly and a wing assembly. During implantation, the spacer assembly is implanted first, then the wing assembly is attached, the width is adjusted, and the locking screw

is tightened. The sizes of the device are based on the minor diameter of the oval spacer component. The sizes range from 6 to 14 millimeters in 2-millimeter increments. The system also includes an instrument set specifically for the X STOP that includes dilators, a distracter, and some insertion instruments.

Original designs of the device were used in a 10-patient pilot study, and in 22 patients who were implanted in Part One of the pivotal clinical trial. To their credit, the sponsors stopped the study when they recognized some serious device issues early on. Several design modifications were made, including a manufacturing step to laser-weld two parts of the device, a change in the taper angle of the tissue expander, and a more rounded tissue expander tip. So this new, quote, "welded" design, was used throughout the pivotal clinical study. Much of the pre-clinical testing was performed on the original unwelded version of the device, and then, following the changes leading to the welded design, additional testing was performed to validate the new design.

The pre-clinical testing included mechanical tests to characterize the X STOP and determine its ultimate strength. And as described by the sponsor, a number of biomechanical cadaver tests were also conducted to investigate the loads required to implant the X STOP, the loads experienced by the device in vivo, some spinous process failure loads, and the stability of the implanted device when it is subjected to high loads.

I will not describe all of this testing which was summarized in the review memo in your panel packs. But I will focus on just three sets of tests in particular. One set of studies examined the effect of placement location on device expulsion or dislodgement. The two other sets of tests have already been described by the sponsor. In all three cases, I will simply provide a brief summary, and a few brief comments or observations that FDA would like to highlight for the panel as it considers our questions.

A set of studies was undertaken to reproduce in vitro X STOP implant dislodgement. Human

cadaver specimens were tested at each intraspinous process level. Specimens were loaded with an axial force, and flexion-extension or axial rotation was applied. Pre and post test radiographs were taken to identify any spinous process fractures or deformations. The results showed that proper anterior placement of the X STOP is essential to preventing dislodgement of the device and/or deformation of the spinous processes. As a result, the surgical technique manual was modified during the study to emphasize that the X STOP must be placed in the concavity between the spinous processes. Also, surgeons are instructed to remove part of any hypertrophied facet if the device cannot be correctly positioned.

The measurement of spinal canal and foramen dimensions was described previously in the sponsor's presentation. Recall that eight lumbar cadaver specimens were placed in an acrylic frame for measurements in an MRI scanner. The specimens were scanned in three positions, with and without the X STOP placed at the L3-L4 level. Axial slices were

used to measure canal area, lateral recess distance, and AP canal depth. Para-sagittal slices were used to measure foramen area, foramen height, and foramen width.

This table summarizes the data presented in the PMA application. For the mean values of the dimensions in the extended position at the implanted level, the table shows that the presence of the X STOP resulted in increased dimensions for five of the seven measures. This table includes the same kind of dimension data for the implanted level, but for the specimen when it was in the flexed position. We note that in the flexed position, the presence of the X STOP actually resulted in smaller values for six of the seven dimensions, although these differences are not statistically significant. So the results of this pre-clinical study show that the X STOP limits canal narrowing at the implanted level in extension. However, FDA notes that these results are based on seven cadaver specimens, and were not confirmed by any in vivo measurements in patients.

The measurement of spinal kinematics was

also described previously by the sponsor. Recall that seven human lumbar cadaver specimens were used for the testing. With a 700 Newton compressive force, specimens were first tested intact by applying a moment in flexion or extension, axial rotation, and left and right lateral bending. The specimens were then removed from the loading frame, a spacer was placed between the L3 and L4 spinous processes, and the loading and measurement regimen was repeated, this time with the device in place.

The results showed that there was no significant difference in the mean range of motion during axial rotation or lateral bending, but that the mean flexion-extension range of motion was significantly reduced at the L3-L4 level. The ranges of motion at the adjacent levels were not significantly changed. FDA notes that these results are based on studies using seven lumbar cadaver specimens, and may not be indicative of changes seen clinically. As will be pointed out later, the ranges of segment flexion and extension were not measured in the clinical study patients.

So FDA asks the panel members to keep this pre-clinical testing in mind, especially as you consider the first three of the panel questions, which will be read in full later. Question Number 1 will ask about possible device effects on adjacent segments, and on spinal biomechanics, as reflected in the clinical data, in particular the higher incidence of other musculoskeletal events. Question Number 2 will ask about the implications of having no pre-clinical data on the effects of two-level implantation, and Question Number 3 asks the panel to comment on the fact that the clinical patients' radiographs were not taken in flexed and extended positions.

At this time, I would like to introduce Dr. Barbara Buch, who will provide FDA's clinical review summary.

DR. YASZEMSKI: Thanks very much, Dr. Holden. Dr. Buch?

DR. BUCH: Good morning members of the panel and guests. As Dr. Holden introduced me, I am clinical consultant to the Orthopedic Devices Branch

at FDA.

What I'd like to do this morning is not repeat the details of the study. I think the sponsor has done an excellent job in describing the details for you. What I would like to do is highlight some issues and raise some questions that we at FDA would like the panel to consider during the deliberation over the panel questions, as well as provide some input into the interpretation of the study outcomes.

I put these slides up just to remind you that although there have been four versions of the device, and three studies initiated to investigate this device and these versions. FDA would like you to focus your attention on the fourth version of the device which was studied in the second pivotal trial as this is the device that is intended to be marketed.

These entry criteria you have seen before. I would like to highlight the last two criteria to emphasize that these are objective means by identifying the levels of stenosis and potentially quantifying the amount of canal compromise for patients enrolled in this study. The success criteria

are also familiar to you, and are based on a patient self-assessment scale, secondary surgical intervention, device-related events, and placement retention of the device, both radiographically and clinically.

The Zurich Claudication Questionnaire is a validated scale for the determination of outcomes after surgery for the treatment of stenosis. During the validation study for these outcome measures, I'd like to point out that Stucki, et all, concluded that a 0.5 difference in the physical function scale and symptom severity scores was clinically significant when comparing the satisfied and unsatisfied patients. In the validation study, however, the studies state that while two years would be most appropriate for assessing clinical effectiveness, the point of maximal benefit was six months, and was deemed most appropriate for assessing responsiveness. This 6-month time point is a time point used to validate this scale in the population study.

The minimal clinically important difference was determined using the difference in mean

change in the symptom severity and physical function scales for patients who were somewhat satisfied and patients who were unsatisfied. The reason I point this out is the time of validation becomes important in the X STOP study, and I would like you to keep this concept in mind as the presentation continues, and as you are considering the panel questions that follow.

The next issue I want to present is the ability to interpret the long-term effectiveness. Because of rapid enrollment, there is no longer term data available for patients enrolled in this study. In many instances, trials have long enrollment periods, which allow for some longer term, that is 3-, 4-, or 5-year data. However, since this is not available in this study, further clinical assessment at later follow-up periods may be needed, especially when we look at trends in overall outcome in this trial. Again, I'd like you to keep this issue in mind when discussing the effectiveness of this device.

Now let's look at the control patients in this trial. The control patients had continuing symptoms despite conservative treatment for six

months, and the majority had symptoms for greater than two years. In the study, the control patients received additional conservative treatment, including varying numbers of epidural injections as we heard. When we look at the overall end results, 95 percent of the population in the control group failed conservative treatment, and 26 percent of the patients had symptoms that warranted a surgical decompression procedure. Based on this perspective, the question arises to us as to whether the conservative control treatment was appropriate as a comparative group to the operative treatment, given the high rate of failure in this population.

Next let's consider what potential impact the study design had on the interpretation of patient outcomes. The study protocol did not specify the criteria for progression to laminectomy or additional epidural injections. Thus the frequency and timing of repeat injections was left to the discretion of the investigator. It appears that patients were not treated the same within a group or between groups when deciding who had symptoms requiring surgical

decompression, or who required an additional injection. Some patients in the control group received only one injection, while others have received two, three, four, or more injections.

In addition, in the X STOP group, eight patients had pain injections after the implantation of the device. Although there may be a lack of consensus in the literature for a clinical trial, FDA believes that all patients should be treated equally according to a pre-described protocol to avoid any confounding factors that will confuse study outcomes. As an example, an X STOP patient with progressing pain who required serial nerve root injections did not progress to laminectomy as a result of his symptoms, while another did progress, but was not operated on until 66 days following injection failure, despite progressive neurologic deficit pain and a loss of sexual function less than two weeks after epidural injection. Overall, it is not clear if additional epidural injections in either group delayed the progression to laminectomy as the criteria for performing decompression by laminectomy was not well-defined.

As has been described, the overall safety profile shows that this is a surgical procedure that is minimally invasive, and most patients are treated as outpatients. The device-related adverse events were few in number and were relatively minor. The deaths that occurred were not considered device-related, and those that occurred related to the device were few, including spinous fracture, device migration, and local wound events that occurred only in one patient each. These safety events on the whole are unremarkable, except for a difference between the X STOP and control patients when it came to documenting musculoskeletal adverse events that were considered not device-related.

The mostly lower extremity events occurred with greater frequency in X STOP patients, and the X STOP patients experienced 3.4 times more types of these events than the control patients. The majority of these events were admittedly classified as moderate in severity, but they did trigger an additional unscheduled visit to the clinic. A percentage were attributable to excess physical activity and exercise,

but I'd like to point out that 20 percent were attributed to a return of stenosis symptoms. One possible explanation, as has been delivered by the sponsor shows that stenosis associated pain was potentially relieved and other comorbid conditions responsible for this pain were unmasked and came to the forefront. Another consideration and possible explanation is that there are potential changes in spinal dynamics and biomechanical function that occur within the limitation of extension. And these also may be responsible for pain. This investigational study does not evaluate further whether either of these or an additional explanation is the cause. This issue should be considered when evaluating the effect of this device on the biomechanical dynamics of the spine as you complete your discussion.

You've seen this chart before. Based on the low effectiveness achieved as compared to that expected in both groups, the question arises on our part whether the enrollment criteria in the patient demographics were able to discern comparable patients. In essence, was the population a homogenous

population. Additionally, did the study define the population in the continuum of lumbar spinal stenosis as has been emphasized today, as identifying the patients who would most benefit from this device, or did this population of stenosis patients all require some type of intervention surgically to decompress their stenosis at the time of entry in this study.

When we look at back and leg pain separately at 24 months, mean back and leg pain scores were significantly less frequent and less severe in the X STOP group as compared to the control group when standing or walking. Based on this secondary endpoint information, it appears that the treatment with the X STOP has the most effect on leg pain when standing and walking as compared to the relief of back pain, but not on other symptoms such as those experienced while sitting.

Even though the goal of this study was accomplished, showing a significant statistical difference between the investigation and control groups, more patients reported improvement in pain at 12 months than at 24 months. In contrast to what has

been observed in spinal fusion studies, which is also a treatment for degenerative spinal disease, in this study a percentage of patients whose symptoms improved at 6 and 12 months showed a trend of regression of pain and function symptoms towards baseline levels.

Let me explain what this chart shows. On the X axis are the three domains of the Zurich Claudication Questionnaire, and the overall success score on the questionnaire is to the far right. Each colored bar represents the percentage of patients in the X STOP treated group who were considered a success by the pre-defined criteria on each section at four different time points. The dark blue bar represents a 6-week time point. The light blue bar represents the 6-month time point. The red bar represents the 12-month time point, and the yellow bar represents the 24-month time point.

This chart shows the progression of effectiveness over time. As we start to the left, we note at 6-week time point the rate of success with patients on the ZCQ, or Zurich Claudication Questionnaire, is high, and remains somewhat

consistent to the 12-month time point, as noted in the red bars. When we compare the 12- to 24-month successes, that is the red to the yellow bars, we can see that in each domain, pain severity, function, satisfaction and overall success, there is a decrease in the number of patients with pain and function success in the X STOP group. I'd like to point out that the previous table was constructed using this data for the X STOP group, and I want you to note that the denominator changes very little for each category over time. That is, the majority of the patients in the X STOP group were included in this trend calculation. Please keep this effectiveness trend in mind when considering the panel questions that follow.

Now I'd like to touch on a slightly different perspective on the outcomes of a subgroup study which defined the number of levels that were treated by the X STOP device. The use of this device at one or two levels may have different outcomes with regard to patient populations and their post-operative results, and what the long-term impact of the device implantation on spinal mechanics may be. As has been

noted, the majority of patients in both groups had multiple coexisting variables noted on radiographs and by history. Some of these radiographic findings include a thickened ligamentum flavum, narrowed lateral recess, hypertrophied facets, and central canal narrowing by 50 percent or less. And also, up to 25 percent spondylolisthesis. In both treatment groups, there were patients with more than one level involved. In the subgroup analysis, it was noted that patients with two-level implantation had a slightly better outcome in all aspects of the effectiveness evaluation, although this was not statistically significant. More single-level patients underwent laminectomy than those with two levels implanted. Adverse event occurrence in the two-level treated patients were also less frequent than those with single levels. Again, these were not statistically significant, and the samples were small.

Cadaveric biomechanical studies, as were described by Dr. Holden, were performed by the sponsor. These showed that the dimensions of the spinal canal were larger in the X STOP implanted

levels than without the X STOP. However, I'd like to highlight that these results were observed only at the implanted level, but not at adjacent levels, and only one-level implantations were studied. Please also recall that as Dr. Hartjen explained, the surgical technique instructs surgeons to ask patients to flex the spine as much as possible to achieve maximal distraction when the device is inserted. These effects were not evaluated pre-clinically.

Given the outcome results, and the results of cadaveric biomechanical studies, our question to you is whether it's clear that it's appropriate to treat just one or two levels in cases where there are multiple level changes in the spine. Please keep this issue in mind when deliberating the answers to the panel question.

Another perspective. When we look at the number of levels that were actually decompressed at surgery, we see that not all single-level implants had single-level decompressions. For example, in the pilot study there were two failures. One patient had a two-level laminectomy at a two-level implantation