UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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ORTHOPEDIC AND REHABILITATIVE DEVICES PANEL

+ + +

July 15, 2008
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, MD 20877

PANEL MEMBERS:

JAY D. MABREY, M.D.
Chair, Voting Member

STUART B. GOODMAN, M.D., Ph.D.
Voting Member

PAUL C. McCORMICK, M.D., M.P.H.
Voting Member

CONNIE F. WHITTINGTON, M.S.N., R.N., O.N.C.
Consumer Representative

ELISABETH M. GEORGE
Industry Representative

BRENT A. BLUMENSTEIN, Ph.D.
Temporary Voting Member

SCOTT R. EVANS, Ph.D.
Temporary Voting Member

EDWARD N. HANLEY, M.D.
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Temporary Voting Member

RAJ D. RAO, M.D.
Temporary Voting Member

CHRISTINE N. SANG, M.D., M.P.H.
Temporary Voting Member

FDA REPRESENTATIVES:

MARK MELKERSON
Director, Division of General, Restorative, and Neurological Devices

ELIZABETH FRANK
Acting Branch Chief, Orthopedic Spine Devices Branch

RONALD P. JEAN, Ph.D.
Executive Secretary, Orthopaedic and Rehabilitation Devices Panel

FDA PRESENTERS:

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SPONSOR REPRESENTATIVES:

JOHN KRELLE
ALFRED L. RHYNE, M.D.
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RACHEL T. McGUCKIAN, J.D.
Orthopedic Surgical Manufacturers Association

PATRICK FRANSEN, M.D.

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M E E T I N G

(8:00 a.m.)

DR. MABREY: My name is Jay Mabrey. I'm the Chairperson of this Panel. I'm the Chief of Orthopedics at Baylor University Medical Center in Dallas, Texas. I specialize in total joint replacement. I have a background and fellowship training in biomechanics.

At this meeting, the Panel will make a recommendation to the Food and Drug Administration on the pre-market approval application, P-070023, for FzioMed Oxiplex/SP Gel. This device is intended to be used as a surgical adjuvant during posterior lumbar laminectomy, laminotomy, or discectomy to improve patient outcomes by reducing post-operative leg pain, back pain, and neurological symptoms.

If you haven't already done so, please sign the attendance sheets that are on the tables by the doors. If you wish to address this Panel during one of the open sessions, please provide your name to Ms. Ann Marie Williams at the registration table.

If you are presenting in any of the open public sessions today and have not previously provided an electronic copy of your presentation to FDA, please arrange to do so with Ms. Williams.

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

I would now like to ask our distinguished Panel members, who are generously giving their time to help the FDA in the matter being discussed today, and FDA staff seated at the table, to introduce themselves.

Please state your name, your area of expertise, your position, and your affiliation. And I'll start with Ms. George, to my right.

MS. GEORGE: My name is Elisabeth George. I'm the Vice President of Quality, Regulatory, Sustainability, and Product Security at Philips Healthcare.

MS. WHITTINGTON: My name is Connie Whittington. I'm the Vice President for Patient Care Services and Chief Nursing Officer at Piedmont Hospital in Atlanta. I have over 32 years experience in surgical intraoperative and postoperative care of the orthopedic patient, including spine and total joint.

DR. BLUMENSTEIN: I'm Brent Blumenstein.

I'm a biostatistician in private practice.

DR. SANG: I'm Christine Sang. I am an anesthesiologist and pain specialist at the Brigham Women's Hospital at Harvard Medical School in Boston, and I direct the Translational Pain Research Program at the Brigham.

DR. EVANS: Scott Evans, Department of Biostatistics, Harvard University.

DR. McCORMICK: Good morning. I'm Paul McCormick. I'm a professor of clinical neurosurgery at Columbia University, College of Physicians and Surgeons, in New York. I direct a spine surgery program up at Columbia. I also have a Master's in clinical outcomes and effectiveness.

DR. RAO: I'm Raj Rao. I'm an orthopedic surgeon specializing in spine surgery, professor of orthopedic surgery at the Medical College of Wisconsin, and I also run the spine surgery program.

DR. GOODMAN: Stuart Goodman. I'm a professor of orthopedic surgery at Stanford University and a member of the bioengineering and biomechanical engineering programs. My specialty is total joint replacement and adult reconstruction, and my research is in the area of orthopedic biomaterials and tissue engineering.

DR. HORLOCKER: I'm Terese Horlocker. I'm a professor of anesthesiology at Mayo Clinic, Rochester. I'm an anesthesiologist there and work in orthopedics.

DR. HANLEY: Edward Hanley. I'm a spine surgeon, Chair of the Department of Orthopedic Surgery at Carolina's Medical Center in Charlotte.

MR. MELKERSON: I'm Mark Melkerson. I'm the Division Director for the Division of General, Restorative, and Neurological Devices.

DR. MABREY: And thank you all for being here and giving so much of your time.

Now, Dr. Jean, if you would, introduce yourself and make your introductory remarks.

DR. JEAN: Good morning. First, I would like to make a few general announcements related to today's activities. Transcripts of today's meeting will be available from Free State Court Reporting. Their telephone number is (410) 974-0947. Information on purchasing videos of today's meeting can be found on the table outside of the meeting room.

Let me take the time to introduce our FDA press contact, Ms. Peper Long. Will you please stand?

I would like to remind everyone that members of the public and the press are not permitted in the Panel area at any time during the meeting, including breaks. If you are a reporter and wish to speak to FDA officials, please wait until after the Panel meeting has ended.

Finally, as a courtesy to those around you, please silence your electronic devices if you haven't already done so.

I will now read into the record three Agency statements prepared for this meeting, two appointment of temporary voting member statements, and the Conflict of Interest statement.

Pursuant to the authority granted under the Medical Devices Advisory Committee charter, dated October 27th, 1990, and as amended, August 18th, 2006, I appoint Dr. Terese Horlocker and Dr. Christine Sang as temporary voting members on the Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee for the duration of the meeting on July 15th, 2008.

For the record, Drs. Horlocker and Sang are consultants to the Anesthetic and Life Support Drugs Advisory Committee of the Center for Drug Evaluation and Research. They are special government employees

who have undergone the customary Conflict of Interest review and have reviewed the material to be considered at this meeting. Signed by Dr. Randy Lutter, Deputy Commissioner for Policy of the FDA, on June 24th, 2008.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter, dated October 27th, 1990, and amended August 18th, 2006, I appoint the following as voting members of the Orthopaedic and Rehabilitation Devices Panel for the duration of this meeting on July 15th, 2008: Dr. Blumenstein, Dr. Evans, Dr. Hanley, and Dr. Rao.

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. Signed by Dr. Dan Schultz, Director of the Center for Devices and Radiological Health, on June 19th, 2008.

Now, I'll read the FDA Conflict of Interest Disclosure Statement.

The Food and Drug Administration is convening today's meeting of the Orthopedic and

Rehabilitation Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants of the Panel are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with federal ethics and conflict of interest law is covered by, but not limited to, those found at 18 U.S.C., Section 208 and Section 712 of the federal Food, Drug and Cosmetic Act, are being provided to participants in today's meeting and to the public. FDA has determined that members and consultants of this Panel are in compliance with federal ethics and conflict of interest laws.

Under 18 U.S.C., Section 208, Congress has authorized FDA to grant waivers to special government employees who have potential financial conflicts of interest when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress

has authorized FDA to grant waivers to special government employees and regular government employees with potential financial conflicts of interest.

Related to the discussions of today's meetings, members and consultants of this Panel who are special government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C., Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves the discussion of a pre-market approval application for the Oxiplex/SP Gel, sponsored by FzioMed. This device is intended to be used as a surgical adjuvant during posterior lumbar laminectomy, laminotomy, or discectomy to improve patient outcomes by reducing postoperative leg pain, back pain, and neurological symptoms. This is a particular matters meeting during which specific matters related to the PMA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the Panel members

and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208 and Section 712 of the FD&C Act.

A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Ms. Elisabeth George is serving as the Industry representative acting on behalf of all related industry and is employed by Philips Medical Systems.

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

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

I'll now turn the meeting back over to Dr. Mabrey.

DR. MABREY: There will be a brief presentation before the main agenda topic.

Ms. Elizabeth Frank will give us an orthopedics update since the July 17, 2007, panel meeting. But before Ms. Frank's presentation, Mr. Melkerson has a brief announcement.

MR. MELKERSON: Thank you, Chair. Ms. Connie Whittington, our consumer representative, and Ms. Pam Adams, our Panel industry rep, have been serving us quite well and will be rotating off of the Panel soon. Ms. Adams couldn't be in attendance today, but Ms. Elisabeth George has graciously agreed to act as industry rep today.

Both Ms. Whittington and Ms. Adams have been serving the Panel with distinction over the past few years. I'd like to take a moment to recognize their service, and, Ms. Whittington, I have a plaque for you to present from the FDA in recognition of your distinguished service, and I think I can speak for both the Panel, the FDA, and the public, saying, thank you very much.

(Applause.)

DR. MABREY: Thank you, Mr. Melkerson. And, again, thank you, Ms. Whittington, and our thanks to Ms. Adams as well.

Ms. Frank, you may now proceed with your FDA update presentation.

DR. MABREY: You should have gotten a Mac.

(Laughter.)

MS. FRANK: Okay. Thank you for your patience. Good morning. My name is Elizabeth Frank, and I am the Acting Branch Chief of the Orthopedic Spine Devices Branch. This morning, I am going to give you an FDA update on what the Agency has been up to since our last Panel meeting of July 2007.

First, I will discuss the upcoming Panel meetings, approvals since the July 2007 Panel meeting, recent guidance documents that have been published, new FDA initiatives, including the CDRH Matrix, as well as staffing updates.

The August 2008 Orthopedics Advisory Panel has been cancelled. There are still tentative dates for October and December. Please watch the FR notice for more details.

Two PMAs have been approved since the July 2007 Panel meeting. These include the Zimmer NexGen Mobile Bearing Knee and the Synthes Spine ProDisc-C Total Disc Replacement.

We've published several orthopedic-specific guidance documents, including one on articular cartilage, non-clinical testing for femoral stem prostheses and total artificial discs.

The Agency has published quite a few general guidance documents that apply to all of us. These include the Interactive Review Guidance, which outlines how the Agency and Industry should interact during pre-market review submissions. We've also published documents on medical device tracking, anti-microbials, PMA application time clocks, expedited review.

The Office of Compliance and Bioresearch Monitoring has published guidances on manufacturing and inspections. The Office of Surveillance and Biometrics has published a guidance on handling post-approval studies. The Office of Science and Engineering Laboratories has published a guidance on consensus standards recognition.

There are several new initiatives underway at the Agency. Many of these relate to the FDAAA legislation that was passed last fall. This renewed the Medical Device User Fees. It implemented quite a bit regarding pediatric medical devices, unique device identifiers, and clinical trial certification.

This spring, the Commissioner announced the Sentinel Initiative, which is a national integrated electronic system for monitoring medical product safety. It will pose a targeted query of electronic

health records, patient registry data, insurance claims data, and other large healthcare information databases in order to improve patient safety. We are also working on IT modernization.

One of the other new initiatives specific to the Center for Devices is the Matrix Structure. We have six offices within the Center for Devices, and we have now implemented a horizontal structure. The column on the left outlines the nine product-specific networks, as well as the four diagonal cross-cutting areas, which include science and regulatory and special interests.

The purpose of the Matrix is to create a culture of collaboration for information-sharing and informed decision-making that provides timely risk identification, risk analysis, and public health responses to issues. Network leaders were hired for each network to plan, manage, and direct total product life-cycle activities for the network. Each office has then identified a liaison to assist the network leaders in identifying important cost-cutting issues. The Matrix was officially open for business yesterday.

In specifics to orthopedics, Dan McGunagle (ph.) has been identified as the network leader.

Each office has identified a liaison that will be the contact point for Dan in identifying important issues. We've had several orthopedic staffing changes since last summer. These include adding quite a few members to both the Orthopedic Spine and Joint Devices Branches. We have had one departure.

As always, we need you. We are looking for new members for our advisory panel or full or part-time employment with the Agency. Thank you very much for your time.

DR. MABREY: Thank you, Ms. Frank. We'll now proceed to the open public hearing portion of the meeting.

Prior to the meeting, two people requested to speak in the open public hearing, one in the morning and one in the afternoon. We ask that you speak clearly into the microphone to allow the transcriptionist to provide an accurate record of this meeting. Please state your name and the nature of any financial interest you may have in this or another medical device company.

Dr. Jean will now read the Open Public Hearing Statement.

DR. JEAN: Both the Food and Drug Administration and the public believe in a

transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of any individual's presentation. For this reason, FDA encourages you, 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 know, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. MABREY: The first open public hearing presenter is Dr. Reginald Davis.

DR. DAVIS: Good morning, and thank you. My name is Reginald Davis. I'm a neurosurgeon in private practice in the greater Baltimore region. I

have no financial interests in FzioMed. I am not a consultant. I have no consulting agreements or arrangements, and other than reimbursement for travel here today, I have no financial involvements whatsoever. This is truly a report from the front lines.

By way of background, I, as do most neurosurgeons and spinal surgeons, perform many lumbar decompressive laminotomies and discectomy procedures. These are very successful operations for the most part with thousands of patients being treated annually. It is a universal procedure for all spine surgeons. However, a significant number of these patients, even those with successful outcomes, do report residual pain, sometimes significant enough to be a clinical problem and even require additional surgery.

There are many factors involved with this phenomenon. Acute factors include the toxicity of the disc material itself and inflammatory mediators precipitated by the act of surgery and the trauma therein. Chronic factors include adhesions and epidural fibroses. A potential ideal solution to this problem would be a barrier to these factors.

Many methods have been employed to mitigate

against these factors: copious irrigation, epidural steroids, even fat grafts and minimally invasive surgery. I myself utilize copious irrigation following a minimally invasive procedure, and then I marinate the fat graft and steroids in the hope to try and mitigate against this phenomenon. Any reduction in pain would be significant and welcome, and the patient's ability to perceive any less pain represents in my mind a clinically significant improvement. There exists a universally recognized yet unmet need in this arena.

An ideal design would be a mechanical barrier to protect the nerve roots. Of course, it must be safe. It should be inert. Ideally, it would be absorbable. The safety would have to be demonstrated with Class 1 data in a clinical trial. And significant reduction or improvement of residual back pain, leg pain, and neurological symptoms, again, demonstrated in Class 1 clinical trial, would be imperative for acceptance and widespread use.

A recent electronic poster presentation at Spine Week in Geneva suggested that Oxiplex may meet these criteria. In this very large cohort of prospective patients in a multi-center randomized trial, third-party blinded, it was demonstrated that

patients receiving Oxiplex in conjunction with their surgeries had reduction in residual back pain and leg pain and neurological symptoms.

On this basis, I draw the following conclusions. Oxiplex is an intuitive and logical solution to an unmet clinical need, which does have significance in treatment for my patients. Oxiplex is demonstrated safe and efficacious in reduction of residual back pain and leg pain and decompressive lumbar laminotomy and discectomy. I personally therefore would welcome the availability of Oxiplex for use as a mechanical barrier in lumbar decompressive procedures and in the armamentarium and treatment of my patients.

I thank you for your time and attention.

DR. MABREY: Thank you, Dr. Davis. Is there anyone else who would like to speak at this time? Yes?

MS. McGUCKIAN: Good morning. My name is Rachel McGuckian, and I'm here today representing the Orthopedic Surgical Manufacturers Association, OSMA. OSMA is a trade association with over 30 member companies, and we welcome this opportunity to provide general comments at this panel meeting. Our comments should not be taken as an endorsement of the products

being discussed. We ask instead that our comments be considered and that these comments -- let you know that these comments represent the careful compilation of the member companies' views.

We were formed over 45 years ago, and we've worked cooperatively with the FDA, the American Academy of Orthopedic Surgeons, the American Society for Testing and Materials, and other professional medical societies and standard development bodies. This collaboration has helped to ensure that orthopedic medical products are safe, of uniform, high quality, and supplied sufficient to meet national needs.

Association membership currently includes over 30 companies who produce 85 percent of all orthopedic implants intended for clinical use in the U.S. We have a strong and vested interest in ensuring the ongoing availability of safe and effective medical devices.

Now, the FDA, of course, is responsible for protecting the American public from drugs, devices, food, and cosmetics that are either adulterated or unsafe or ineffective. However, the FDA has another role, to foster innovation.

The Orthopedic Devices Branch is fortunate

to have available a staff of qualified reviewers, including a board-certified orthopedic surgeon, to evaluate the types of applications brought before this Panel. The role of the Panel is also important to the analysis of data in the manufacturer's application and to determine the availability of new and innovative products in the U.S. marketplace.

Those of you on the Panel have been selected based on your expertise and training, and you bring the view of practicing clinicians who treat patients with commercially available products.

OSMA is aware that you have received training from FDA on the law and regulation. We don't intend to repeat that information, but we did want to emphasize two points that may have a bearing on today's deliberations, the first being reasonable assurance of safety and effectiveness and the second, valid scientific evidence.

To the first point, there is 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 safety data may be generated in the laboratory in

animals or in humans. There is reasonable assurance that a device is effective when it provides a clinically significant result. The regulation and law clearly state that the standard to be met is reasonable assurance, which is defined as moderate, fair, and inexpensive.

As to point two, valid scientific evidence, 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: a study protocol, method of selecting subjects, method of observation, and reporting of results, as well as a comparison of results with a control.

The Panel, of course, has an important job today to listen to the data presented by the Sponsor, evaluate 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, but please keep in mind that the standard is a reasonable assurance balancing the benefits with the risk. The regulatory

standard is not proof beyond a shadow of a doubt. Please be thoughtful in weighing the evidence and remember that the standard is a reasonable assurance of safety and effectiveness and that there is a legally broad range of valid scientific evidence to support the determination.

OSMA thanks the FDA and the Panel for the opportunity to speak briefly to you today. Our association trusts that its comments are taken in the spirit offered, which is to help the 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 throughout the deliberations today. Thank you.

DR. MABREY: Thank you. Is there anyone else who'd like to speak during the open public forum? Not seeing any hands, I would ask the FzioMed sponsor to begin their presentation.

We will now proceed to the sponsor presentation for the FzioMed Oxiplex/SP Gel. I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel. The Sponsor will

introduce the speakers. You have 75 minutes.

MR. KRELLE: Good morning, and thank you for the opportunity to present to you today. I am John Krelle, the president and CEO of FzioMed, the Oxiplex study sponsor. I am an employee of the sponsor, who is covering my expenses for attending this meeting, and I hold financial interests in the company.

Joining me today are employees and consultants of the company, each of whom will make their own introductions as we proceed through this presentation to Panel.

We have the pleasure to present to you the results of over 11 years of research and clinical study.

The device that is the subject of today's meeting is Oxiplex intraoperative gel. Oxiplex is a clear, viscoelastic gel used to coat and protect neural tissues. Oxiplex is provided in a three mL syringe together with a flexible applicator for use in applying the gel. The device is ready-to-use. No mixing or assembly is required other than the attachment of the applicator to the syringe. The syringe and applicator are packaged together and terminally sterilized by steam. The device is for

single use only.

Oxiplex is comprised of sodium carboxymethylcellulose, or CMC, and polyethylene oxide, PEO, and sterile water for injection. Both are well-characterized polymers used extensively in implantable medical devices and pharmaceuticals. Oxiplex is bioabsorbable. The gel is non-pyrogenic and contains no animal or bacterial components.

The proposed indication for use is as a surgical adjuvant during posterior lumbar spine surgery to improve patient outcomes by reducing postoperative leg pain, back pain, and neurological symptoms. This indication is a first of a kind.

Our first priority is to demonstrate the safety of Oxiplex. The effectiveness of Oxiplex study was to reduce residual pain and symptoms that often remain after lumbar disc surgery. Now, what do I mean by residual pain?

As described in the literature and shown in this graph, patients typically experience substantial pain relief following lumbar surgery. Unfortunately, in many patients, residual pain can persist for months or years after surgery and continue to be a reason for patient dissatisfaction, physical and medical therapy, and even re-operation. This study

was designed to assess if Oxiplex could improve outcomes for these patients by reducing their residual pain.

This debilitating condition has been designated by the FDA as an unmet clinical need. This unmet need is the reason for our study.

Now, the nature of residual pain is a complex situation with multiple co-morbidities and factors that complicate its clinical presentation and measurement. Because of this complex situation, the approved analytical method in this study was a multivariate analysis. This is an accepted and commonly used approach for analyses of pain related to lumbar disc disorders. Multivariate analysis is therefore the most appropriate method for this study, was pre-specified in the statistical analysis plan, and unconditionally approved by the FDA.

This was a successful study. Across all effectiveness measures, all patients treated with Oxiplex had greater improvement than controls, demonstrating consistent clinical benefit from the use of Oxiplex. Multivariate analysis allowed identification of an important patient subgroup, which comprised the majority of subjects in the Oxiplex study. Those are patients with severe back

pain at baseline.

You will hear a lot about this large subgroup throughout our presentation. This is a challenging group of patients often dissatisfied with their outcome and for whom Oxiplex was particularly effective in improving their outcomes. The target for success in this superiority study was a 33 percent difference in pain reduction between group, which was met in this subgroup.

Here is a snapshot of how Oxiplex reduced residual pain in the subgroup of patients with severe baseline back pain, just one of the positive outcome measures from this study.

As you can see, at the 6-month study end, the Oxiplex-treated patients benefited from an additional 35 percent reduction in residual leg pain, the primary effectiveness variable, compared to controls. Additionally, there was a 28 percent reduction in residual back pain, the secondary effectiveness variable, in Oxiplex subjects compared to controls. Both of these reductions in residual pain were statistically significant.

Outside of the United States, Oxiplex is currently approved for sale in 49 countries, including countries in the European Union, Asia, and

Australia, and, more recently, in Canada, using the same data package and method of analysis that you will see in this U.S. PMA. In fact, Oxiplex is approved for sale in more countries than Starbuck's is sold in.

Since introduction in 2002, over 100,000 -- let me say that again -- 100,000 spine procedures have been performed using Oxiplex. We distribute Oxiplex primarily through Medtronic and DePuy Spine. Six years of international surveillance through these companies has already demonstrated product safety.

I would now like to turn the podium over to Dr. Al Rhyne, who will expand further on this unmet clinical need.

DR. RHYNE: Good morning. I am Dr. Al Rhyne, an orthopedic surgeon in practice in Charlotte at the Ortho Carolina Spine Center. I am not an employee of FzioMed. I participated as a clinical investor in the Oxiplex pivotal study. I am a paid consultant for the sponsor who is covering my expenses for attending the meeting, and I have a financial interest in the company.

Many studies have shown that lumbar discectomy is generally a successful procedure with the majority of the patients having significant

improvement and satisfaction with their outcomes. Success rates reported ranging from 60 to 90 percent. Nonetheless, this leaves a substantial number of patients, up to 40 percent in some reports, who experience residual or recurrent pain and symptoms following surgery with re-operation rates ranging from 5 to 20 percent.

These patients pose a considerable challenge to both surgeons and society, with increasing demands for medication and diagnosis, the need for additional treatment, additional cost to the overburdened healthcare system, and a loss of productivity. For a surgeon such as myself, having performed over 2,000 discectomies in my career, these patients can pose a substantial challenge to my practice. These are the patients most likely to benefit from Oxiplex.

The nature of residual leg and back pain and surgery is complex. Pain and symptoms are multi-factorial because there are numerous possible etiologies, such as incomplete decompression, irritation of the colliquina (ph.), recurrent herniation, nerve entrapment, inflammation, to name a few. In addition, pain and symptoms are multi-dimensional because each patient may present with

unique combinations of clinical symptoms.

Further confounding each case, there are numerous clinical factors that contribute to outcome, many of which are shown in the next slide. This is an example of the many co-morbidities or clinically relevant co-variants that were shown to be imported in the SPORT study recently published in JAMA. As is clearly evident, clinical pain from herniated disc herniation is complex and multi-factorial.

The literature identifies two categories of pain mechanisms associated with lumbar spine conditions. First, there are mechanical mechanisms. For example, physical compression of nerve roots, such as incomplete decompression, recurrent herniation, stenosis, or instability. Of course, this is only a partial list of the possible mechanical disorders responsible for leg pain.

Second, there are biological and biochemical mechanisms for nerve pain, including fibrin, cytokines, and pro-inflammatory mediators.

It is widely recognized that there is a cascade of biochemical events that are the components of surgical environment and normal healing process. These are the results of a variety of irritants that come into contact with the nerve root during and

after disc surgery and can sensitize neural tissue and lead to the inflammation and to the potential of adhesion formation.

Oxiplex was developed to act as a temporary mechanical barrier cutting the nerve root to provide physical separation of tissue and thereby reducing exposure to the irritants that may eventually lead to residual post-surgical pain and neurological symptoms and which often lead to re-operation.

Today, there is no FDA surgical adjuvant indicated for the reduction of pain in symptoms following lumbar spine surgery. Nonetheless, surgeons attempt to protect the nerve root for this purpose include padding the epidural space with fat grafts or using products not designed for this indication and/or being used off-label, such as sealants and dural regeneration sheets.

I would like to demonstrate the application and benefits of Oxiplex gel following the removal of disc -- desiccation of retraction lead to nerve root trauma, edema, and cellular injury. The epidural space fills with fibrin and cytokines, inflammatory mediators, such as TNF Alpha, which may lead to pain and adhesive formation.

Oxiplex is easy to assemble and can be

applied in direct visualization to the surgical site. The gel is easily applied. Because of its unique adherent properties, it remains around neural elements and provides a protective mechanical barrier.

Next is an intraoperative video of the gel application. First, let me provide some orientation. To the left is the patient's head. To the right, the thecal sac, and then the exiting nerve route, the shoulder of the exiting nerve root, the axle of the exiting nerve root, and the suction is being used as a retractor.

You can see that the nerve root will be elevated and that the place where the discectomy was performed, the gel is applied under the thecal sac, under the nerve root, and subsequently, it's applied to the lateral surface side and in posterior, or behind, the column.

Since the gel can be applied in just a few seconds, it does not prolong the surgical intervention. Post-application, it provides a barrier to the cascade of events that follows.

What would benefit my patients is a product that can be applied easily and rapidly directly to the nerve root, and to provide a safe mechanical

barrier that separates and protects epidural tissues. This would reduce surgical pain and neurological sequelae. I believe that you will see in this presentation that Oxiplex fulfills this important clinical need. I'll now turn the podium over to Dr. Gere diZerega.

DR. DiZEREGA: Thank you, Dr. Rhyne. I am Dr. Gere diZerega, Medical Director of FzioMed. I am not an employee of FzioMed. I am a paid consultant for the Sponsor, who is covering my expenses for attending this meeting, and I have financial interests in the company.

A large battery of pre-clinical tests were conducted to fulfill the appropriate ISO and USP standards. Biocompatibility was confirmed by these tests. Testing, including in vitro, acute, subacute, and chronic evaluations of the device, Oxiplex passed all of these tests.

One of the FDA's questions to Panel today is regard to carcinogenic toxicity and immunotoxicity. Carcinogenic toxicity studies were not performed for three reasons. One, none of the Oxiplex components have been shown to be carcinogenic. Oxiplex is cleared within 30 days in animal studies and Oxiplex is a single-use product.

Immunotoxicity studies of delayed hypersensitivity and chronic inflammation were performed as part of the battery of tests described in the previous slide. There was no evidence of an immunologic response or immune suppression in any of the acute or chronic toxicity studies. In addition, Oxiplex has been used in routine spinal surgery in over 100,000 cases without a device-related adverse event.

Specialized safety studies were also conducted. One study involved creation of an injury to the dura after laminotomy. We then euthanize the animals at a time when healing was not complete to enable the evaluation of delay or acceleration of healing of the dural injury. This study showed that Oxiplex does not affect normal healing of the dura or bone and does not elicit an inflammatory response. This was particularly important because dural nicks are a well-known complication of spine surgery.

This is a histological representation of the results of that study. On the left-hand portion of the slide, histology from the control animals and the right, histology from the Oxiplex-treated animals. The laminotomies were performed in this area. The dural adhesion, in the case of the

control, is here, and you can see the dural membrane attaching to the adhesion. I'll describe this in a bit more detail.

In the controls, as you can see, the laminotomy site is partially healed. The dural membrane is involved in the dural adhesion to the laminotomy site. In contrast, when Oxiplex was used at the time of surgery to coat the dura, the dural membrane is separated from the laminotomy site, as you can see here, a nice intervening space, a free dura and free spinal cord.

This is a summary of the histological observations of dural healing and inflammation. The study groups are listed in the left-most column. The ends represent the number of histological sites. The total number of animals in each group is six. As you can see, at the control sites, the injury to the dura was healed in 73 percent of sections, with partial or no healing in the remaining sections.

Oxiplex did not delay healing, with 91 percent of the sites fully healed at 14 days. Importantly, no inflammatory response was observed in controls in Oxiplex-treated sites. This study demonstrates that Oxiplex does not inhibit dural healing and is not associated with inflammation.

In summary, pre-clinical safety studies demonstrated that Oxiplex was biocompatible and non-inflammatory. Oxiplex allowed normal healing to occur. It did not inhibit dural healing, did not inhibit normal bone repair, and did not inhibit normal wound healing. These results show that Oxiplex was safe in the pre-clinical setting.

Now, I would like to review with you the results from our feasibility study. The objective of the clinical feasibility study was to evaluate safety and symptoms following single-level lumbar disc surgery.

The feasibility study was a prospective, randomized, single-blinded study conducted at four sites. The study was not powered to assess efficacy. Thirty-five subjects were enrolled in a 2 to 1 ratio. Twenty-three received surgery plus Oxiplex and twelve underwent surgery alone.

The measures in a feasibility study were a clinical evaluation performed in the surgeon's office, laboratory tests, and an MRI at 3 months for safety evaluation. Effectiveness was assessed by two quality-of-life instruments, the Oswestry Disability Questionnaire and the Lumbar Spine Outcomes Questionnaire.

The Lumbar Spine Outcomes Questionnaire, referred throughout today's presentation as the LSOQ, is a quality-of-life instrument developed and validated by a team of blue ribbon spine surgeons in response to an NIH request. This team was led by Professor Donlin Long, who was, at that time, chief of neurosurgery at the Johns Hopkins School of Medicine.

The LSOQ contains 56 questions which are directly answered by the study subject. The large validation studies were conducted through 24 months. The LSOQ measure of clinical significance is patient satisfaction. An important feature of the LSOQ is its ability to quantify outcomes on seven different clinical measures of importance to lumbar spine disorders, including leg pain, back pain, patient satisfaction, and disability days, which are effectiveness endpoints in the pivotal study.

Let's look at how the improvement in leg pain came out in this feasibility study. The top graph shows the results of leg pain improvement using the LSOQ. The bottom graph shows improvements in ODI. The results were determined at one, three, six, and twelve months. Results for the Oxiplex subjects are shown in blue; the controls in orange.

There are three points I would like to make with this slide. The first, Oxiplex subjects with severe pain at baseline had greater improvement than controls. The results at 6 months were similar to those at twelve, as you can see the differences here.

The LSOQ is more specific than the ODI in that it allows discrimination of individual variables such as leg pain. I'll show the safety results in a moment, but, first, let me show you how the LSOQ works. What does a change in LSOQ score, that is, the numerical score, mean from a clinical perspective, which is the view of the patient? This slide reproduces the actual questions in the LSOQ case report form that are used to calculate a subject's leg pain score. The terms patients use to describe their pain are listed from left to right, with one being no pain and six, excruciating. The answers are calculated to produce the leg pain scores.

Now, let's review some results. This set of questions yields a score of 77. This is the baseline or pre-op score of a typical subject in the feasibility study. Note: the subjects' responses to achieve this score included three instances of excruciating, one of horrible, and two of

discomforting.

Now, let's see how the subjects' answers changed after surgery. Here is a score of 23, which is a typical subject's score 6 months following surgery. Look at the shift. There are no longer any answers of excruciating or horrible. Now, there are three of discomforting, one mild, and two, no pain. As you can see, the subjects' perception of leg pain has changed dramatically.

To summarize the feasibility study results, there are no adverse events attributed to Oxiplex. There were no abnormal laboratory values, no abnormal findings on MRI, and no abnormal physical findings. Pain reduction was comparable at six and twelve months.

In conclusions, because the results from the pilot study did not raise safety concerns, FDA allowed the Sponsor to initiate a new pivotal study to determine safety and efficacy of Oxiplex in a larger population.

I will now turn the podium over to Dr. Ron Ehmsen to describe that study for you.

DR. EHMSEN: Thanks, Gere. I'm Ron Ehmsen, Vice President of Clinical and Regulatory Affairs for FzioMed. I'm an employee of the company, who is

sponsoring my participation in this meeting and covering the expenses, and I hold financial interest in the company.

Our pivotal study was designed as a superiority study to determine the safety of Oxiplex and the effectiveness of Oxiplex beyond that of surgery alone. To achieve these objectives, we measured clinical outcomes, such as pain, symptoms, disability days, and overall patient satisfaction.

The primary safety variable was measured by the occurrence of adverse events, including surgical complications. Secondary safety variables included physical and neurological exams, re-operations, and concomitant therapies.

The primary effectiveness variable was the improvement in leg pain from baseline to post-surgical follow-ups at one, three, and 6 months. The secondary effectiveness variables were back pain, leg weakness, physical symptoms, patient satisfaction, disability days, and activities of daily living. These were also measured from baseline to follow-up visits at 1, 3, or 6 months.

All patients underwent single-level disc surgery at either the L4 or L5 or L5-S1 level. Patients were randomized intraoperatively to receive

either surgery alone or surgery plus Oxiplex treatment. This was a multi-center study involving 29 sites. No more than 24 sites were active at any time.

This slide shows noteworthy inclusion criteria. All subjects were undergoing their first disc surgery for unilateral herniation of lumber intervertebral disc associated with radiculopathy. Subjects ranged from 18 to 70 years of age.

Subjects were excluded if they had previous spine surgery at the lumbar level. In addition, no subject was to receive steroids within four weeks of surgery or during the procedure itself. No subject was party to a workmen's compensation claim or personal injury action.

Intraoperative exclusion included incidental dural entry, the need for multi-level involvement or contralateral exploration, and epidural fat placement.

This table shows all of the preoperative screening that took place in order to ensure that subjects satisfied every entry criteria and to establish baseline values.

Clinical effectiveness was defined by LSOQ score, physical examination, and neurological

assessment. LSOQ scores were measured at baseline, one, three, and 6 months post-op. Physical and neurological exams were carried out at baseline, one, and 6 months.

352 subjects were enrolled in the study, and these are known as the intent to treat, or ITT population. Randomization was well-balanced, with 177 subjects in the Oxiplex group and 175 in the control group. The evaluable population included 339 subjects who completed the end-of-study LSOQ any time after 6 months. 286 subjects completed the end-of-study LSOQ within the protocol-defined window. We refer to these as the completed cases, or CC population. These subjects all had endpoints within the protocol window. All populations were analyzed.

Following FzioMed's presentation, FDA will present. It is critical that you understand that what FDA calls the CC population is not our CC population. FDA's CC population is based on 334 subjects. This population is comprised of the per-protocol CC population of 286 subjects, in other words, ours, plus 48 additional subjects who completed the end-of-study LSOQ out of protocol, some as far out as 52 weeks following surgery.

Attributing values collected beyond 28

weeks to a 6-month value is prone to error, as shown in the quotation below. After decompression surgery, pain outcomes should be measured within a maximum of 6 months after surgery. Longer follow-ups may introduce error that influence patients' ratings of outcome, especially if based on self-ratings of current pain, disability, or quality of life.

This slide displays the demographic characteristics at baseline. Each characteristic is listed in the far left-hand column, and the next two columns list the mean values for both Oxiplex and control groups. The P-values at the far right confirm that the groups were well-balanced.

This slide shows procedural characteristics. The far left column lists each characteristic followed by values for Oxiplex, control, and the P-values in the right-hand column. Again, the groups were well-balanced.

Here are the baseline neurological examinations, which demonstrate that there was good balance between the Oxiplex and control groups. The complete table is part of your Panel pack.

Randomization occurred at the end of surgery after hemostasis had been achieved and when the surgeon was ready to close the operative site.

All subjects, clinical evaluators, and LSOQ interviewers were blinded to randomization assignment throughout the study and therefore maintaining the study blind. Randomization codes were provided only to the pivotal trial statistician after the trial was completed and the database had been locked.

Overall, this was a balanced, well-controlled clinical study.

I'll now turn the podium over to Dr. Paul Arnold.

DR. ARNOLD: Good morning. I am Dr. Paul Arnold, Professor of Neurosurgery at the University of Kansas Medical Center in Kansas City. I participated as a clinical investigator in the Oxiplex Pivotal Study. I am not an employee of FzioMed. In connection with attending this meeting, I am receiving consulting fees, and the Sponsor is covering my expenses. I have no financial interests in the company.

Before we talk about the safety results in the United States Pivotal Study, it's important to note the established safety of Oxiplex in routine clinical practice. Oxiplex is in its sixth year of real-world experience. It has been used in more than 100,000 spine procedures outside of the United

States.

The Sponsor has an active safety surveillance program conducted together with DePuy and Medtronic. The monitoring program includes capture and analysis of feedback, field training, audits, and regular communications with surgeons using Oxiplex on a routine basis. Importantly, throughout these six years, there have been no reported adverse events attributed to Oxiplex.

Independent clinical trials reported in both peer review publications and in presentations at major medical meetings further support the strong safety profile of Oxiplex. With the exception of the feasibility studies reported by Kim, et al., none of these studies in this list were requested, financed, or managed by the Sponsor. When combined, this cohort of more than 1,300 patients provides real-world confirmation of the safety and efficacy of Oxiplex.

Assessment of clinical safety in this pivotal study was based on adverse events, laboratory tests, concomitant therapies, and physical and neurological examinations.

The primary safety variable was the occurrence of adverse events, including surgical

complications, as summarized in this table. All enrolled subjects, the intent-to-treat population, were included in the analysis of Oxiplex's safety. No subjects were withdrawn from the study due to an adverse event, and no events occurred that led to the discontinuation of the study. There were no adverse events that were considered to be definitely related to the device.

I would like to call your attention to the seven adverse events in five Oxiplex patients that were considered to be possibly or probably related to the device. These will be the subject of one of FDA's questions to Panel today.

These events are detailed in this table. The far-left column gives the relation to the device with a definite, probable, or possible. The columns across the top detail intensity, site, subject, onset, and duration. The last two columns give the P-value and noteworthy information. Note that there were no adverse events definitely related to the advice.

For both probable and possible, there were no statistical significance associated with these events. Please note that the three events that were noted as probably related to the device occurred in

the same subject on the day of surgery. As you can see, they are typical events that occur during routine post-operative recovery from back surgery and anesthesia. All of these events resolved spontaneously.

In addition, please note that the four events that were regarded as possibly related to the device occurred between four weeks and four months following surgery. Two of these events were likely to have been associated with other factors. Specifically, difficulty with urination could have been related to the subject's prostatitis. The delayed wound healing in subject E08 could have been caused by a retained suture which required removal.

Low back pain is not uncommon following lumbar disc surgery, and this event occurred at five weeks after surgery and resolved spontaneously. Common condition requiring re-operation following lumbar disc surgery is recurrent herniated nucleus pulposus, or HNP.

We thought you might be interested in the overall distribution of disc-related disorders in the study, including HNPs. As you can see, the number of disc-related disorders in the control group outnumbered those in the Oxiplex group. Please note

that some of the HNPs in the control group could have progressed to re-operation.

This table detailed here and continued on the next slide lists all of the adverse events occurring in at least five percent of all subjects. The type of adverse event is listed in the left column followed to the right by the number and percent of Oxiplex and control subjects reporting that adverse event. On this slide, the adverse events are well-balanced between the groups.

Here is the second half of the same table. Note the differences in some neurological symptoms that were found, including myalgias, lower extremity pain, and hypoesthesias. In each of these, the adverse event occurred less frequently in Oxiplex than in the control group.

Although CSF leaks did not meet the 5 percent cutoff for this table, I'd like to point out that there were no post-operative CSF leaks in the Oxiplex group throughout this study compared to two in the control group.

This table shows abnormal physical exams at one month following surgery. Note musculoskeletal exams, which include pain, decreased range of motion, muscle spasms, or decreased motor strength. The

difference in musculoskeletal favoring Oxiplex approached statistical significance at this time point. This trend continued at 6 months.

This table shows abnormal physical exams at 6 months. Again, the difference in musculoskeletal favoring Oxiplex approached statistical significance.

During the course of this study, a difference in the incidents of re-operations was observed. A total of seven subjects required re-operation, all of them 3 months following the surgery. Of these seven, only one subject was an Oxiplex patient, and the other six were surgery-only controls.

This difference approached statistical significance. In my practice, this difference would be clinically significant.

Note that a 0.6 percent incidence of re-operations in the Oxiplex group is far lower than reported in the literature for a study of this size.

In summary, related to the primary safety variables, there were no significant differences in adverse events between the Oxiplex and control groups. There were no adverse events that led to discontinuation of any subject or discontinuation of the study. There were nor significant differences in

serious adverse events between Oxiplex and the control groups, and there were no serious adverse events related to Oxiplex.

Related to the secondary safety variables, there were no significant differences in laboratory values or vital signs between the Oxiplex and control groups. There was good balance between concomitant therapies received by both groups. However, there were fewer neurological complications in the Oxiplex group compared to the control group. There were fewer musculoskeletal abnormalities in the Oxiplex group compared to the control group. There were no post-operative CSF leaks in Oxiplex subjects compared to two in the control group, and there were fewer re-operations in the Oxiplex group compared to the controls, one versus six.

In conclusion, across all measures, there were no safety issues in Oxiplex subjects and Oxiplex provided additional safety benefits versus surgery alone. The safety results from this pivotal study combined with over 100,000 procedures performed outside the United States demonstrate reasonable assurance that Oxiplex is safe for its intended use.

I will now turn the podium over to Dr. Richard Chiacchierini.

DR. CHIACCHIERINI: Good morning, distinguished Panel members. I am Dr. Richard Chiacchierini, president of R.P. Chiacchierini and Associates. I conducted the statistical analysis on the clinical data derived from this pivotal study. The Sponsor is covering my expenses for attending this meeting today, and I receive fees for my consulting services. I am not an employee of the company, and I hold no financial interest.

The primary hypothesis to be tested was that considering co-morbidities, Oxiplex-treated subjects would have a greater improvement in leg pain from baseline than control subjects. Data was collected at baseline, one, three, and 6 months. The primary analysis was a multivariate longitudinal analysis using generalized estimating equations, GEE, as approved by the FDA.

The initial limited list of possible covariates offered by the Sponsor was augmented by FDA to include all clinically relevant baseline variables. This resulted in 48 covariates and 96 main effects and covariates -- main effects and interactions, many of which were correlated.

The large number of possible terms in the model necessitated a thorough screening process to

eliminate covariates with little or no correlation or interaction with the endpoint. Screening potential covariates by the method of Hosmer and Lemeshow provides protection against model-overspecification. This means that the final model in this study provided estimates that are reliable.

In this slide, there is a summary of the baseline LSOQ values. Dr. Ehmsen gave you the other baseline variables for the other -- for the medical history and demographics. Note in this table that the Oxiplex and control groups are balanced. Of special note, I would like to add that the correlation between baseline back pain and baseline leg pain was .55.

You will see two analyses presented today. First, the planned multivariate analysis, which is the method approved by the FDA to assess effectiveness in this study and is the focus of FzioMed's presentation.

Second, you will see a post-hoc univariate analysis performed on a different population that is the focus of FDA's presentation and is similar to the data given here for the ITT population.

Neither univariate analysis is appropriate because it does not take into account the multiple

baseline co-morbidities that relate to pain following lumbar disc surgery. Pain related to disc herniation is complex and multifactorial, as we have heard from Dr. Rhyne, and therefore multivariate analysis is the clinically relevant approach.

In this slide we have the key analytical steps specified in the statistical analysis plan. After imputation for missing values and univariate screening, the primary multivariate analysis was performed on the ITT population. Surviving screening with a cutoff value of .15 were eight main effects and eleven interactions with treatment. Six of these were from the baseline LSOQ covariates.

Including the interactions in the competition for the final model required adding 11 main effects for those covariates. The parsimonious multivariate model obtained by pre-specified manual backward elimination in which the term with the highest P-value is removed at each step, consistent with the hierarchal modeling principles, provides identified several treatment interactions.

In a widely used basic statistics text by Fisher and van Belle, treatment interactions should be further analyzed to identify clinically important subgroups and interactions. The interaction analysis

of subgroups provides valid protection against the post-hoc charge in such analyses.

Categorical interactions have self-defined subgroups. Quantitative interactions were interpreted by regression analysis by treatment group. Subgroups were then formed overall and at specific time points, and, finally, a sensitivity analysis was performed to demonstrate the robustness of the cutoff.

This table presents the results of the multivariate GEE analysis in the ITT population for the primary effectiveness variable, leg pain. The variables that remained in the final model are listed in the left-hand column, with the P-values in the far right. Five main effects and six interactions with treatment with their main effects were significant in the final parsimonious model. We would be happy to answer questions about the main effects, but the remainder of our presentation will be devoted to the interactions.

The six treatment by covariate interaction that remain in the final model are further detailed on the next slide, but before we go there, the subject of one of FDA's questions to the Panel today will be about a site-by-treatment interaction.

Overall, there were differences in the improvement in leg pain between sites, as is seen by the statistically significant study site main effect. However, there was no site-by-treatment interaction. In fact, the site-by-treatment interaction term did not even survive screening. It had a P-value of 0.64 and our cutoff was 0.15.

This means that, overall, differences between Oxiplex and control subjects were independent of differences between sites and therefore do not impact on the interpretation of the study results.

A variable that is an interaction with treatment means that the clinical response to Oxiplex is dependent on the value or level of that variable. The clinical response to Oxiplex relative to control was found to interact with, in other words, depend on six variables, five categorical and one quantitative.

In four of the five categorical interactions for the majority of patients, those with normal histories, Oxiplex subject had a greater response than controls. And for the minority, those with abnormal histories, control subjects had the greater improvement. The only exception to this was for the left L5, in which the patients with normal history favored neither Oxiplex or control, but the

abnormal patients favored Oxiplex. The small number of subjects with abnormal histories, and many of these interact in many of these variables, covariates, make these interactions difficult to interpret.

The quantitative variable, baseline back pain, requires a more extensive analysis for interpretation. The substantial evidence of effectiveness is provided by this significant interaction between treatment and baseline back pain, with a P-value of 0.0113. To provide a context for the clinical interpretation, a regression analysis of the change in leg pain by baseline back pain for each treatment group was performed. This analysis does not involve any subgrouping and is intended to compare the rates of improvement in leg pain as a function of baseline back pain.

This table shows the regression analysis which was computed for all subjects averaged over all visits in the top section. The P-values reported here and elsewhere in the analyses investigating interactions are used to indicate a trend towards statistical significance and should not be interpreted literally because these comparisons were not pre-specified.

There is a strong statistically significant relationship between the improvement in leg pain and baseline back pain noted by the very small P-values for the slope, but this change was significantly greater in the Oxiplex group, with a P-value of 0.0206.

The slope tells us that the amount of leg pain improvement in the Oxiplex group is nearly twice that of the control group for each unit increase in baseline back pain.

The analysis at the 6-month visit for the ITT and CC population had a similar result. However, the amount of leg pain improvement from Oxiplex patients is nearly three times that of the control group. This demonstrates that for all subjects across all visits, as well as at 6 months, the greater the baseline back pain, the greater the improvement in leg pain of Oxiplex patients relative to the control.

Another way of presenting this interaction is to plot the improvement of leg pain against levels of back pain. A separation of the study population into two subgroups was done at the median baseline back pain value of 63 and is shown here. It should be noted that due to the extensive number of ties at

63, the actual cut of the data was about 45 percent lower than 63 and 55 percent with values of 63 or more. We refer to those with baseline back pain at or above 63 as having severe back pain and those with back pain less than 63 as having less severe back pain.

The Sponsor felt it was important to evaluate the robustness of using the median of 63 with statistical analysis. Therefore, a sensitivity analysis was performed and this is shown on the next slide.

This table represents the results of that sensitivity analysis. Baseline back pain scores are on the left-hand column, and the respective P-value is in the far right. That is, the cutoff would be in the left-hand column.

To see how robust the median score of 63 would be to statistical significance, we started at 63 and then dropped the value by one point to determine whether or not statistical significance was maintained. Note that a baseline back pain score of 58 still yields a statistically significant result with a P-value below .05, and this represents approximately 62 percent of the population above 58. This shows that selecting the median value of 63 as

the point of distinction is robust in demonstrating the superiority of Oxiplex versus control.

This slide shows the improvement in leg pain at each visit, one, three, and 6 months, for the Oxiplex patients, shown by the blue line, and for the control subjects, shown by the orange line, subgrouped by baseline back pain. Subjects with severe pain are shown in the top graph and those with less severe pain are shown in the bottom graph. In the less severe subgroup, although the controls had slightly better responses at each time point, the results were very similar across both groups with no statistical significance.

Now, let's consider the top graph. In subjects with severe baseline back pain, Oxiplex provided a greater mean improvement at all time points. Furthermore, this difference of improvement increased over time and approaches statistical significance at 6 months.

Now, let us look at the improvement in leg pain over time in the CC population. In the top graph, we've reproduced the severe back pain results for the ITT population. In the bottom graph are the results for the completed cases population. Again, the increase in leg pain improvement over Oxiplex

subjects increased over time and is statistically significant at 6 months. As you can see, the result of the ITT population are confirmed in the CC population. You will see more clinical detail on the CC population later in our presentation.

Now, let us move to our secondary endpoints. The change in back pain from baseline to 6 months was analyzed in exactly the same way as leg pain. Screening resulted in 9 main effects and 12 interactions, and, of course, we have to include the 12 main effects for these interactions.

This slide shows the final model with interactions and main effects that resulted from the multivariate analysis. There were 4 main effects and 3 interactions with main effects that remain statistically significant in the final model. As was done with leg pain, we will focus on the interactions, which are further detailed on the next slide.

For back pain, the treatment effect was found to interact with three variables. Two categorical interactions were found that were similar to those identified for leg pain with similar interpretations. Again, for the quantitative variable, baseline back pain, more extensive analysis

is needed.

The evidence for effectiveness, for back pain improvement, is provided by the significant interaction between treatment and baseline back pain with a P-value of 0.0007.

To begin to find a clinical interpretation of this interaction, a regression analysis was done as was done with leg pain, and the results were consistent with the leg pain model. There is a statistically significant relationship between baseline back pain and the improvement in back pain, which is significantly greater than the Oxiplex group.

Again, the improvement in back pain was plotted against levels of baseline back pain, separating the group at a median pain score of 63. A prominent treatment effect of Oxiplex in reducing back pain was found in subjects with severe back pain at baseline. Once again, a sensitivity analysis was performed. It demonstrated that a baseline back pain score of 54, representing 70 percent to the right of that number, yields a statistic-significant value below .05.

These data once again show that selecting the median value of 63 as a point of distinction is

conservative.

In this slide, we see the improvement of back pain over time as was done with leg. The subgroup with less severe back pain is shown in the top -- with severe back pain is shown in the top and less severe in the bottom.

In the subgroup with less severe back pain, the results are very similar, and there is no statistically significant difference at any time point. In the top graph, in the subgroup with severe baseline back pain, the majority of subjects, as was true with leg pain, Oxiplex subjects had greater back pain improvement at all time points, and, again, the difference in improvement increased over time.

This difference in improvement in back pain at three and 6 months had nominal significant P-values at .03 and .019.

In summary, I would like to leave you with four key points. First, the multivariate analysis was the approved method and the most appropriate to analyze this clinically complex data, identifying an interaction that provided clinically important subgroup. Second, we defined and analyzed clinically important subgroup of subjects, those with severe back pain at baseline, which was the majority of the

study population. In subjects with severe baseline back pain, Oxiplex provided a substantial and significant improvement in both leg and back pain. Third, the subgroup results in the ITT population were confirmed with the CC population. And, finally, Oxiplex patients have twice the rate of improvement in leg pain as controls for each unit of increase in baseline back pain.

I will now turn the podium over to Dr. Scott Blumenthal, who will present the clinical relevance of these results.

DR. BLUMENTHAL: Good morning. My name is Scott Blumenthal, and I'm an orthopedic spinal surgeon at the Texas Back Institute in Plano, Texas. I participated as an investigator in the Oxiplex pivotal study. I'm not an employee of FzioMed. I am a paid consultant for the Sponsor, who is covering my expenses for attending this meeting, and I have financial interests in the company. By means of additional disclosure, I have had the honor of presenting to this Panel previously, and I can provide reasonable assurance that it doesn't get any less intimidating.

The presentation by Dr. Chiacchierini has set the stage statistically for what I believe is the

real benefit of Oxiplex, the benefit to the patient. What you will see throughout this presentation are consistent clinical benefits provided by Oxiplex, benefits which are amplified in the challenging group with severe baseline back pain.

As well as improvement in both leg and back pain, we saw fewer disability days and enhanced patient satisfaction, which is the most important factor to my patients. Patient satisfaction is also the principal measure of LSOQ effectiveness.

This graph shows the leg pain improvement in the CC population with severe back pain. Before I go into detail, let me orient you to the chart. The *y*-axis represents the change in leg pain from baseline, referred to here as leg pain improvement. The blue bar on the left is the Oxiplex-treated group at 6 months. The orange bar on the right are the controls. The white box gives the percentage difference in improvement between the groups and the P-value for the difference is at the top of the graph.

The subject of one of FDA's questions to Panel today is to consider if this 9.6 point change, with a P-value of .0.0123 is clinically significant. To see an additional reduction in leg pain at 6

months of 18.3 percent compared to controls, in my opinion, is clinically meaningful evidence that Oxiplex is providing additional benefit to the patient. This difference is also statistically significant.

This chart provides even better insight into the treatment effect. The two bars on the left show mean leg pain scores for Oxiplex and control at baseline, before surgery. Note that there is good balance between groups at baseline.

The two bars on the right show the residual leg pain at 6 months. This can result in the need for additional therapies. Surgery alone results in a large reduction in pain; in this case, nearly 70 percent.

The benefit of Oxiplex is shown in the additional 35 percent reduction in that pain. Patients treated with Oxiplex enjoyed a clear advantage compared to surgery alone. A difference of this magnitude is statistically significant.

I will illustrate this using samples of patients' LSOQ case report forms from the study.

Here is the baseline score for two patients in the study, one control and one Oxiplex-treated patient, each of whom started out with a leg pain

score of 83 before surgery. Both of these patients had severe back pain at baseline, which were the majority of patients in the Oxiplex study.

Here, again, are the six questions that are used to calculate a patient's leg pain score. There are two notations of excruciating, three of horrible, and one of distressing. These patients are clearly debilitated by their pain.

Let's fast-forward to the surgery-only control patient at 6 months following surgery. As expected, surgical intervention provided significant pain reduction. However, the control patient still has some substantial residual leg pain at 6 months, as seen by two descriptors of discomforting, three of mild, and only one of no pain, resulting in a score of 23.

So what does it mean to the patient when his score is reduced by an additional 10 points? Let's take a look. Here is the case report form for the Oxiplex-treated patient at 6 months. Oxiplex reduced the patient's leg pain to an even lower score of 13. There are no longer any references to discomforting leg pain, as in the control patient on the previous slide. The Oxiplex-treated patient responds with only four references of mild and two of

no pain at all.

This illustration demonstrates a clinically significant reduction in leg pain for the Oxiplex patient, a score of 13, compared to the control patient's score of 23. This shows what a 10-point reduction really means to the patient.

Let's move on to the results of the secondary endpoints. The first secondary endpoint was the improvement in back pain between Oxiplex and controls. Here are the results in the CC study population at 6 months in patients with severe baseline back pain.

Oxiplex patients experienced 19.7 percent greater improvement in back pain compared to controls. That's 19.7 percent less pain for a patient who started out at a severe level and was treated with Oxiplex versus a patient undergoing surgery without Oxiplex.

And here is the effect of Oxiplex in terms of reduction of residual back pain at 6 months. The baseline scores before surgery are on the left, well-balanced with no statistical difference. After surgery, shown in the bars on the right side of the graph, control patients show good improvement, but Oxiplex, again, amplifies the treatment effect and

reduces residual back pain by an additional 28 percent.

This statistically significant difference corresponds to a clinical significant outcome.

This figure summarizes the additional improvements that Oxiplex provides patients at 6 months compared to surgery alone, shown in both leg pain and back pain displayed together. Having performed spine surgery for over 20 years, I can tell you that my patients would welcome this additional benefit, especially those in the challenging group with both leg pain and severe back pain.

This chart demonstrates a clinically significant benefit in the majority of patients in this trail, those with severe back pain with baseline. Oxiplex provides the greatest relief to those patients who need it the most.

This chart shows the disability days results. The vertical axis shows the reduction in disability days from no reduction at the base to greater reduction at the top. Disability days are days when a patient is completely disabled by his or her back pain condition measured during the 30-day period prior to surgery and again at 6 months. In this case, disability days are measured in a CC

population. As you can see, there were two fewer disability days in the Oxiplex group compared to controls. This difference was statistically significant.

Now, for patient satisfaction, a common measure of success, and the LSOQ measure of clinical success. This graph is laid out a little differently. The vertical axis represents patient satisfaction ranging from extremely satisfied at the bottom to extremely dissatisfied at the top. In other words, the lower the score, the better the outcome.

In this study, when asked the question, if your lower back condition were to remain the same as it is now, how satisfied would you be, patients treated with Oxiplex had 22.7 percent greater satisfaction in their outcome at 6 months than control patients. This result was statistically significant. This is an important clinical result that reflects the bottom line for the patient, overall satisfaction with his or her treatment.

Here are the results of all clinical effectiveness measures in the study displayed by odds ratio in a forest plot format. The 7 primary and secondary measures are shown on the vertical axis.

The horizontal axis shows the mean difference in improvement between Oxiplex and controls. The average values are shown by these circles, and the confidence intervals by the lines.

Any circles to the right of zero show that Oxiplex patients did better than controls. Any circles to the left would mean the controls did better. As you can see, all circles are to the right. This demonstrates that across all effectiveness measures, all patients treated with Oxiplex had greater average differences in improvement than controls, demonstrating consistent clinical benefit from the use of Oxiplex.

A subject of one of FDA's questions to Panel today is whether this could have happened by chance alone. Including all 7 measures in this graph, the P-value for O'Brien's Test is P = 0.049. This confirms the consistent clinical benefit of Oxiplex.

Let's take a look at the same plot, but this time for patients with severe back pain before surgery, which were the majority of patients in the study. Again, all of the clinical measures are displayed on the vertical axis, and the mean difference in improvement are on the horizontal axis.

All circles are to the right of zero, indicating Oxiplex patients did better than the controls across all measures. However, the results are even more compelling in these patients with severe baseline back pain.

The advantage of Oxiplex over controls is both clinically and statistically significant for both leg pain and for back pain. We know this because the confidence intervals are also to the right of zero. The same is true for physical symptoms, patient satisfaction, and for disability days, with clinically and statistically significant differences for the Oxiplex patients.

Okay. You've seen a lot of data. Now, let's summarize all of the evidence that supports Oxiplex effectiveness.

First, the evidence that Oxiplex provides a greater reduction in baseline, leg, and back pain at 6 months. This is the subject of one of FDA's questions to Panel today. The question is about this subgroup: patients with severe baseline back pain who experience the most prominent treatment effect with Oxiplex.

FDA uses this group and the P-value of 0.012 as its example to ask the following: Did this

significant treatment effect in this subgroup happen by chance, and does it affect the interpretation of effectiveness?

Let's review all of the evidence. In the left-hand box, for both leg and back pain, in both the ITT and CC populations, Oxiplex patients with severe back pain experienced statistically significant improvements in their pain at 6 months following surgery. The box on the right shows the magnitude of treatment effect. Again, for both leg and back pain, in both the ITT and CC populations, Oxiplex patients with severe back pain experienced clinically significant improvement in their pain.

Another principal study objective was the reduction of residual pain. The data in this slide is organized in the same manner as the preceding slide for the same subgroup that benefited the most from Oxiplex and demonstrates the reduction of residual pain.

As before in the left-hand box, Oxiplex patients with severe back pain experienced statistically significant improvements in both their leg and back pain at 6 months following surgery, leg pain in the CC population, and back pain in both the ITT and CC.

The box on the right shows the magnitude of treatment effect. Again, for both leg and back pain, in both the ITT and CC populations, Oxiplex patients with severe back pain experienced clinically significant improvements in their pain. The relative reductions in residual pain provided by Oxiplex ranged from 25 to 35 percent compared to controls.

Finally, you'll remember that there were differences in important safety measures that favored Oxiplex. We believe that these outcomes are so important in lumbar disc surgery that they should be considered in the overall effectiveness of Oxiplex.

They are reduced re-operations, .6 percent versus 3.4 percent. The rate of revisions in this study was actually lower than that reported in the literature. In addition, there were reduced neurological symptoms, reduced musculoskeletal abnormalities, and increased patient satisfaction, and fewer disability days, all in favor of Oxiplex. They all confirm that Oxiplex provides additional patient benefits compared to surgery alone.

I'd like to turn the podium over to John Krelle for the summary.

MR. KRELLE: Thank you, Dr. Blumenthal. I'd like to take just a few more moments to summarize

everything that you've heard this morning. The results of the study demonstrate that Oxiplex is safe across all measures in all patients. There were no significant differences in adverse events or serious adverse events between Oxiplex and controls. There were no serious adverse events related to Oxiplex.

There were fewer neurological complications and fewer musculoskeletal abnormalities in Oxiplex patients compared to controls. There were no CSF leaks in Oxiplex patients and fewer re-operations in the Oxiplex group compared to controls, 1 versus 6.

The strong safety profile in the study is supported by six years of real-world experience, including over 100,000 procedures to date with no report device-related adverse events.

The data from this study shows reasonable assurance of Oxiplex effectiveness in an important subgroup of patients, those patients who present with severe back pain at baseline, which, in our study, was the majority of patients. They experienced significantly greater improvement in leg pain, greater improvement in back pain, and greater overall satisfaction compared to patients who underwent surgery without Oxiplex.

And the data from the study showed

reasonable assurance of Oxiplex effectiveness across all patients regardless of baseline back pain in several important clinical measures. Fewer disability days, fewer neurological symptoms, fewer musculoskeletal abnormalities and an important reduction in the rate of re-operation.

The primary endpoint was the improvement in leg pain from baseline to follow-up visits at one, three, 6 months. The target P-value was 0.044. Let's look at the reduction in leg pain at 6 months. For the ITT population in the subgroup with severe back pain at baseline, the majority of patients in the study, the P-value was 0.0507. Please note that an additional 0.1 on the 100-point LSOQ scale in either treat or control would have resulted in a less than .05 P-value. For the CC population, the P-value was 0.0123.

The secondary endpoint, improvement in back pain from baseline to follow-up visits at one, three, 6 months. Let's look at the reduction in back pain at 6 months here. For the ITT population in the subgroup with severe back pain, the P-value was 0.0193. For the CC population, the P-value, 0.0127.

The FDA advised the Sponsor that the target for study success should be a 33 percent difference

in pain reduction between treat and control groups. With the primary endpoint of leg pain, across all patients at all levels of baseline back pain, differences were in favor of Oxiplex at 6 months. In the CC population, Oxiplex achieved almost a 35 percent reduction in leg pain in patients with severe back pain. For the secondary endpoint of back pain, again, across all patients and all levels of baseline pain, differences were in favor of Oxiplex. In the CC group, Oxiplex achieved a 28 percent reduction in back pain in this subgroup. The results of the CC population were consistent with and confirmed the results of the ITT population.

There is reasonable assurance that Oxiplex is safe based upon valid scientific evidence and that the probable benefits to health outweigh any probable risks. There is reasonable assurance that Oxiplex is effective in a significant portion of the target population and that the use of Oxiplex for its intended use provides clinically significant results.

I'd like to thank you for the opportunity today to present Oxiplex and the results of this 11 years of clinical study. There is no approved surgical adjuvant indicated for the reduction of pain and neurological symptoms following lumbar disc

surgery, and we ask for your recommendation to approve the Sponsor's PMA, which we believe fulfills this unmet clinical need. This concludes the Sponsor's presentation. Thank you.

DR. MABREY: I'd like to thank the Sponsor's representatives for their presentations.

At this point, I would ask the Panel if they have any brief -- and I will emphasize the word brief -- clarifying questions for the Sponsor. Please remember that the Panel will be asking the Sponsor questions during the Panel deliberations later this morning and in the afternoon.

Are there any brief questions for clarification at this time? Yes, Dr. Blumenstein?

DR. BLUMENSTEIN: I would like considerable more detail on how the sample size was computed, and, specifically the role of this effect size of 33 percent, which I'm thoroughly confused about. I'd like more detail on the analysis plan, the very specific analysis plan matching the sample size computations. I don't know that that can be answered now or something that can be provided to us subsequently.

DR. MABREY: I think we'll allow the Sponsor to answer that at a later time.

MR. KRELLE: Yes, I think we would like to do that. Thank you.

DR. BLUMENSTEIN: All right. And then I had one question that might be answerable now, and that is, on the re-operations, was the individual participating in the decision for re-operations blinded as to the treatment group?

MR. KRELLE: A simple answer to that question is, yes, they were blinded to the treatment group.

DR. MABREY: Thank you. Dr. McCormick?

DR. McCORMICK: I have a question. On the analysis of the severe back pain patients, I notice on Page 40, under Statistical Analysis, it shows that there were 92 patients with baseline scores above 63 in the Oxiplex group and 101 in the control group, but on the histograms given, say, one -- they're given on multiple pages -- but this on Page 36, the *n* is listed as only 78 in each group, so I'm curious as to the discrepancy between those two numbers. There's a difference of about 40 patients.

MR. KRELLE: Yes, we'd like the opportunity to check that and get back to you this afternoon if that's okay.

DR. McCORMICK: Okay. Thank you.

MR. KRELLE: Thank you.

DR. MABREY: Thank you. Any other Panel members? Yes, Dr. Evans?

DR. EVANS: Let me just ask to comment on the biological reasoning about why this would work with people who have high back pain but perhaps not low back pain? So biological justification for --

MR. KRELLE: Thank you. We'd like to go into a little more detail with that in the afternoon session, if we may.

DR. EVANS: Thanks.

DR. MABREY: Dr. Sang?

DR. SANG: I have a very basic question, actually. How were the surgeons blinded to the treatment? Did they administer a control gel or a solution from the syringe and was it controlled for temperature?

MR. KRELLE: I'll bring Dr. Ehmsen back to answer that question right now.

DR. EHMSEN: The surgeons could not be blinded to the treatment because they actually administered the Oxiplex during surgery.

DR. SANG: So the surgeons were not blinded? Who performed the physical examinations during the follow-ups?

DR. EHMSEN: All physical examinations during the follow-up periods were conducted by what was referred to in the protocol as a clinical evaluator, or CE. Those CEs were medically trained personnel who were not part of the surgical team and were completely blinded to the treatment throughout the study.

DR. SANG: I'm sorry to keep asking these questions. Was there a single blinded reader of the MRIs or were there different blinded readers based on the sites, at each site?

MR. KRELLE: Yeah, the MRIs were actually a part of the pilot study and not the pivotal study, and that was a safety -- designed for safety only.

DR. SANG: I see.

MR. KRELLE: So there were no MRIs in the pivotal study.

DR. SANG: So, then, in the pilot study, were there multiple readers or one single reader?

MR. KRELLE: Dr. diZerega will answer that question.

DR. DiZEREGA: Thank you for your question, Dr. Sang. In the feasibility study, there were two readers. They read them independently, and they were blinded to treatment assignment.

DR. SANG: Thank you. I'm sorry to elaborate on one small -- on my first question, actually. So what was the temperature of the gel when it was applied?

MR. KRELLE: The temperature has a temperature range which should be stored at room temperature. So it's not refrigerated. It's at normal room temperature, and that's how it's stored and delivered.

DR. SANG: So it's cooler than the body temperature?

MR. KRELLE: Yes.

DR. MABREY: Anyone else with a brief question?

(No response.)

DR. MABREY: All right. It's 9:50. I'd like to take a 10-minute break and reconvene at 10:00, please, and we'll have the FDA presentations at that time.

MR. MELKERSON: Dr. Mabrey? Dr. Mabrey. Just a quick announcement.

DR. MABREY: Yes.

MR. MELKERSON: The slide presentation from the Sponsor is now available outside for those people in the audience.

DR. MABREY: Thank you.

(Off the record at 9:50 a.m.)

(On the record at 10:00 a.m.)

DR. MABREY: -- take their seats. If we could close the outer doors, please?

The FDA will now give their presentation on this issue. Ms. Jose, you have one hour.

MS. JOSE: Okay. Good morning. My name is Jismi Jose, and I'm a reviewer in the Orthopedic Spine Devices Branch in the Office of Device Evaluation. I would like to thank the Panel members for taking time out of their busy schedules to be here for the FDA.

I will present the non-clinical and pre-clinical studies. Dr. Lee will present the clinical study design. Jack Zhou will present the statistical analysis, and Dr. Chen will discuss a potential post-approval study.

I'd like to acknowledge the hard work of all the members of our review team, who are from various offices within the center.

Today, FDA will be reporting the data and analyses from FzioMed's PMA for the Oxiplex/SP gel. Here is an overview of what we will be presenting.

First, we will introduce the device and

provide a summary of the non-clinical and pre-clinical studies. Then, we will provide an overview of the clinical study and statistical analysis, followed by a review of a post-approval study plan.

The FDA questions for the Panel are scheduled for this afternoon.

Before I continue, I'd like to talk about why FDA has convened this Panel of experts. We are looking for your input on this first-of-a-kind device designed to act as a physical separation of tissues after lumbar surgery for the reduction of postoperative pain and symptoms. Input is needed from the Panel on the clinical significance of the proposed device and on the results from the Sponsor's clinical study.

Oxiplex/SP gel is proposed to be used as a surgical adjuvant during posterior lumbar laminectomy, laminotomy, or discectomy to improve patient outcomes by reducing postoperative leg pain, back pain, and neurological symptoms. Later today, we will be asking the Panel a question on the appropriateness of these indications for this product.

Oxiplex/SP gel is an absorbable clear, viscoelastic gel applied during lumbar spine surgery

to provide a physical separation of tissues. The gel is composed of sodium carboxymethylcellulose and polyethylene oxide and sterile water. Calcium chloride is added for stability while sodium chloride is added for isotonicity. The gel contains no animal or bacterial components or color additives. It is applied to the surgical area using a syringe and sterile applicator and three milliliters is the maximum dose.

Following lumbar surgery after hemostasis is achieved and immediately prior to wound closure, Oxiplex is applied to the operative site, coating the neural tissue and filling the duct of the laminectomy or laminotomy site. It is designed to clear from the body within 30 days and does not require a second operation for removal.

Now, I'll give a brief summary of the non-clinical and pre-clinical studies. The Sponsor conducted the following chemical and physical analyses. The chemical analyses were conducted to confirm the components of the Oxiplex gel and to test for ethylene oxide and aldehydes. Physical tests were performed on various gel formulations to determine the appropriate specifications of the final Oxiplex/SP gel.

The Sponsor conducted microbiology and biocompatibility tests, as well as animal studies. The biocompatibility tests were performed according to ISO 10993. Please note, in lieu of performing tests for chronic toxicity, carcinogenicity, and immunotoxicity, the Sponsor provided a rationale and literature search. The Sponsor explained that due to the length of time, Oxiplex remains in the body, based upon their pre-clinical animal studies and literature search, and the use of CMC and PEO and other medical device applications, additional testing is not necessary. The animal studies will be reviewed in the following slides.

As presented by the Sponsor, rabbit animal studies were conducted using various formulations of CMC and PEO gels and films used individually or in combination together to determine the biocompatibility and initial efficacy of the formulations and reducing adhesion formation.

As you take into consideration the results of the animal studies, particularly consider the different formulations and compositions used, the location of implantation sites, and the sacrifice times.

Later today, we will be asking the Panel to

comment on the adequacy of the non-clinical and pre-clinical studies, including whether the animal studies are predictive of the performance of the device for its proposed indications.

Now, Dr. Lee will give you an overview of the clinical study.

DR. MABREY: Just remind the Panel members, the FDA slides are in your gray folder that was handed out this morning.

DR. LEE: Good morning, Panel members. My name is Kevin Lee, and I am the clinical reviewer for this PMA.

Today, I will be discussing the clinical studies conducted for the Oxiplex PMA.

The Sponsor first conducted a pilot study followed by a pivotal study.

The pilot study was conducted to determine if peridural fibrosis and related symptoms were reduced with the use of Oxiplex/SP gel. At four investigational sites, 35 subjects were enrolled into the Oxiplex and the control groups. All subjects received the clinical evaluations and completed the Oswestry Disability Index and Lumbar Spine Outcomes Questionnaire pre-operativity and post-operativity. Scar formation was assessed using baseline and 3-

month post-op MRIs.

The indications studied in this pilot study was the reduction of adhesions following lumbar surgery. Please note that these indications and intended use vary from that proposed in the PMA and the pivotal study.

Before we discuss the pilot study results, note that the small sample size used in the pilot study may not be adequate to determine a small clinical difference since the study was not designed or powered to detect statistically significant differences between the two groups.

As to the adverse events, there was a higher instance of adverse event in the Oxiplex group compared to the control group. For example, there was a higher instance of leg and back pain in the Oxiplex group.

The results of the statistically analyses on the pilot study showed non-significant P-values at all time points, one, three, six, and twelve months in leg pain symptoms, activity-related pain index, functional disability, weakness in lower extremity, radiculopathy, and ODI scores.

The MRI Scar Score analysis at 3 months showed that the scar scores were similar between the

Oxiplex and the control groups.

After the pilot study, the Sponsor initiated a new pivotal study to study the safety and the efficacy of Oxiplex/SP gel in a larger population.

The indications studied for the Oxiplex gel in the pivotal study and proposed in this PMA differ from the indication studied during pilot study since the Sponsor removed inhibition of peridural fibrosis from primary endpoint of the pivotal study.

During the pivotal study, all subjects underwent lumbar disc surgery and were randomized 1 to 1 to receive surgery plus Oxiplex/SP gel or to receive surgery only. In the same manner as the pilot study, the Oxiplex group received the gel along the dura and on the operating site and the control group received surgery only.

Follow-up assessment was conducted at one, three, and 6 months.

There were 352 subjects enrolled consisting of 177 Oxiplex and 175 control subjects at 29 U.S. sites.

There were 334 evaluable subjects who completed the 6-month post-surgical follow-up visit. The evaluable subjects are referred to as completed

cases population as defined by the Sponsor in the PMA. This population will be referred to as PMA completed cases throughout the presentation. The PMA completed cases included those subjects who completed the 6-month LSOQ regardless of a specific window of time except for five subjects who were evaluated significantly outside of their window. The Sponsor's CC population refers to 280 subjects who completed the 6-month LSOQ within the 22 to 28 week window.

The primary safety endpoint evaluated the frequency and severity of adverse events categorized using the MedDRA coding system.

The secondary safety endpoint evaluated changes in laboratory results, physical and neurological and vital signs, re-operations at the lumbar level, and the use of concomitant therapies.

The safety endpoint did not change throughout the study.

The primary effectiveness endpoint was the improvement of leg pain from baseline to follow-up visit, one, three, and 6 months, as measures by LSOQ. The LSOQ measures leg pain severity on a 6-point rating scale for each of the six questions. The composite leg pain severity score ranged from 0 to 100, with higher scores indicating higher overall

severity of experienced pain.

Prior to the FzioMed clinical study, the LSOQ has not been used in clinical studies initiated to collect data for a PMA. The LSOQ was validated through two multicenter studies by the creators of the questionnaire.

The secondary effectiveness endpoint was the improvement from baseline through 6-months, as measured by LSOQ, of the following endpoints whose order was pre-specified for sequential closed testing.

The statistical analysis plan changed throughout the study. Originally in the IDE, the Sponsor proposed a longitudinal analysis of improvement in composite leg pain using generalized estimating equation, including treatment, time, baseline-level, and baseline-by-treatment interaction in the statistical model.

After the interim analysis and prior to PMA submission, the Sponsor proposed to revise the protocol to analyze the primary endpoint using one-tailed t-test. FDA asked the Sponsor to include all clinically relevant covariate such as baseline pain score and site, using the original analysis plan. The Sponsor also stated that they would additionally

perform a descriptive presentation and multivariate test of primary hypothesis for leg pain using a GEE model.

The statistical overview presentation will discuss changes in statistical analysis in more detail.

For the primary effectiveness, the Sponsor set success criteria of the pivotal study as an improvement of 15 points in composite leg pain score from baseline at 6 months on the 100-point LSOQ scale when measured using longitudinal data analysis.

The FDA advised the Sponsor that in order for study to be considered a success, there should be a statistical significance, as well as a clinical meaningful difference in the chosen primary endpoint between the two treatment groups; that is, a 20-point or 33 percent difference between the two groups in the mean LSOQ score reduction from baseline.

The Sponsor has described the inclusion and exclusion criteria. The Sponsor also previously presented the surgical protocol.

Each subject enrolled in the study was to be followed for 6 months after surgery to evaluate device safety and effectiveness. All subjects were to be evaluated for safety at one and 6 months and

for effectiveness at one, three, and 6 months by masked clinical evaluator.

Safety evaluation included a physical exam, assessment of adverse events, and lab tests.

For assessment of effectiveness, subjects were to complete the LSOQ at one, three, and 6 months. The Sponsor stated the interviewer and subjects remained masked to the study group assignment throughout the study.

Now, that clinical study design has been reviewed, we will move onto the results. There were no statistically significant differences between Oxiplex and control groups in demographic characteristics at baseline.

When assessing adverse events, the clinical evaluator was instructed to base adverse event reviews on medical judgment and to assume that subjects had received the device when assessing the relationship of the device to adverse events. The adverse event for incidence greater than or equal to 5 percent showed that both the Oxiplex and the control groups were comparable to each other. The adverse events were comparable in both groups.

As to the treatment emergent adverse events, five patients in the Oxiplex group had

adverse events that were possibly or probably related to the device, whereas no patient in the control group reported any adverse events that were possibly or probably related to the device. The three probable adverse events occurred in one subject while the possible adverse events occurred in four different subjects.

A total of 27 subjects experienced a serious treatment emergent adverse event; 13 serious adverse events occurred in the Oxiplex group, and some of these include cellulites, wound infection, and incision site complication; 14 serious adverse events occurred in the control group, and some of those that were identified include wound infection, cerebral spinal fluid leakage, and dural tear. No serious adverse event was categorized as definitely or probably related to the device.

Seven subjects required re-operation at or before 3-month time point. Control subjects experienced higher rate of re-operations when compared to the investigational subjects.

For other secondary safety variables, Oxiplex and control groups were comparable with respect to lab findings, abnormal physical examination at one and 6-month follow-up and

postoperative neurology examination. There was a balance in concomitant therapies received by Oxiplex and control groups.

I will now summarize the effectiveness results. The analysis of primary endpoint, as originally specified in the IDE, included treatment, visit, site, and baseline LSOQ score in the GEE model. Based on this original model, the FDA analysis shows that the overall difference of the least square means between the two groups is 0.1 on a 100-point scale with a P-value of 0.96.

In order to see the simple mean difference in pain reduction between the two groups from Sponsor's analysis, FDA conducted an unadjusted analysis on the composite leg pain score improvement from baseline through 6 months. This calculation showed that treatment group effective between the two groups at 6 months was 0.9 on a 100-point scale. Details of these results will be covered in the statistical overview section of this presentation. There will be a Panel question on the clinical significance of the mean difference between the two groups.

As to the secondary effectiveness endpoint, this table presents the mean differences in

improvement between the control and Oxiplex group at 6 months, including confidence intervals for effectiveness measures. None of the secondary effectiveness endpoint achieved a statistically significant difference and their 95 confidence intervals included zero, indicating no statistically significant differences in means between the two groups.

Before I conclude the clinical study presentation, I will discuss the outside U.S. experience. The Oxiplex/SP gel has been marketed outside of the U.S. for several years. It received a CE mark in July 2001. There were six post-market reports related to issues with the device. The Sponsor concluded that these reports were not attributable to the use of device.

The Sponsor also conducted a prospective subject-blinded clinical study in China from October 2006 to April 2007. This study included six subjects randomized 2 to 1 at two sites. The Sponsor reported that data collection and efficacy analysis is ongoing and no results have yet been provided to the FDA.

Now, Jack Zhou will discuss the statistical analysis and results.

MR. ZHOU: Thanks, Kevin. Good morning

Panel members. My name is Jack Zhou. I'm the statistical reviewer for this PMA. I will give a statistical overview of the pivotal study. As Dr. Lee already talked about the device safety, I will focus on the effectiveness of the device.

This is the outline of my presentation. First, I will talk about a couple issues regarding the pivotal study design, sample size, and key changes in the statistical analysis plan. Then I will describe the subject dispositions and populations used in the analysis. I will briefly compare the demographics and baseline characteristics of the Oxiplex and control subjects. Then I will talk about -- sorry. Then I will talk about the primary effectiveness endpoints in detail, especially the analyses of the overall treatment effect, the exploratory subgroup analyses, and the issue of site variability. I will also talk about the secondary effectiveness endpoints. Finally, I will conclude with a summary.

The sample size estimation was based on a mean comparison of two independently normally distributed variables with one interim analysis. Originally, 192 subjects per group were estimated, with one interim analysis at 33 percent of the data.