

FDA PMA P070023 Executive Summary

FzioMed, Inc.

Oxiplex®/SP Gel

July 15, 2008

FDA Executive Summary

July 15, 2008 Panel Meeting

Of

Orthopaedic and Rehabilitation Devices Panel

Introduction

This is an Executive Summary for Premarket Approval (PMA) application P070023, FzioMed's Oxiplex®/SP Gel, a gel applied during lumbar spine surgery intended to act as a physical barrier between tissues. This device has been reviewed by the Orthopedic Spinal Devices Branch of the Division of General, Restorative, and Neurological Devices at the Center for Devices and Radiological Health of the Food and Drug Administration.

The Executive Summary provides an overview of the information provided by FzioMed in P070023. The summary contains a rationale for bringing the device to panel, an identification of the applicant/manufacturer, indications for use, FDA's summary of the device description, non-clinical and preclinical testing, clinical study information, labeling, and the proposed outline of a post-approval study plan.

Rationale for Bringing Oxiplex®/SP Gel to Panel

FDA is presenting the Oxiplex®/SP Gel to panel for the deliberation of its safety and efficacy because it is a first-of-a-kind device designed to be implanted in the lower back to provide a physical separation of tissues after surgery for the purpose of reducing postoperative leg pain, back pain and neurological symptoms. The panel members will be asked to evaluate and discuss the presented data for the proposed indication and intended use, and provide their input regarding the interpretation of the results from the clinical study.

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Applicant/Manufacturer Information

Applicant/Manufacturer Name and Address:

FzioMed, Inc.

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San Luis Obispo, California 93401

USA

Indications for Use

Oxiplex®/SP Gel is indicated 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.

Contraindications

Oxiplex®/SP Gel is contraindicated for use in the presence of frank infection.

During the panel meeting, FDA will ask the Panel to comment on the appropriateness of the primary and secondary effectiveness endpoints in the study conducted for supporting the clinical utility of the proposed device in relieving pain in patients who underwent posterior lumbar laminectomy, laminotomy, or discectomy.

Device Description

Oxiplex®/SP Gel is an absorbable, clear, viscoelastic gel applied during lumbar spine surgery to provide a physical barrier between tissues. Oxiplex/SP gel is composed of sodium carboxymethylcellulose (CMC) and polyethylene oxide (PEO) in sterile water. Calcium chloride (CaCl₂) is added for stability and sodium chloride (NaCl) is added for isotonicity. Oxiplex/SP gel contains no animal or bacterial components or color additives.

-----he -----ges of different components present in Oxiplex/SP gel:

The product characteristics are identified below:

Oxiplex/SP gel is applied to the surgical area using a 3mL (maximum dose) syringe, along with a sterile applicator.

Mechanism of Action

Oxiplex/SP gel is applied to the operative site coating the neural tissue. The device remains at the site of the application for a period of time, providing a physical separation of tissues during the healing process. The material then clears from the body. It does not require a second operation for removal

Sterilization

Packaging

The primary packaging for Oxiplex/SP Gel includes a polycarbonate thermoform tray with a heat-sealed Tyvek lid. The tray is packaged in a carton (secondary packaging) with the Instructions for Use (IFU). The sealed thermoform tray containing the device is terminally sterilized with steam. The box is labeled with lot number, identification and tamper evident labels. The testing for the packaging provided was adequate.

Non-Clinical Testing

Chemical Analyses

The sponsor conducted Fourier transform infrared (FTIR) analysis on the CMC and PEO components of Oxiplex®/SP Gel and ethylene oxide (EtO) testing and aldehyde testing analyses on the Oxiplex/SP Gel.

FTIR Analysis

FTIR analyses of the CMC and PEO components of Oxiplex/SP Gel samples showed characteristic IR peaks of CMC and PEO.

EtO Testing

No EtO was detected from the Oxiplex/SP Gel samples.

Aldehyde Testing

Ald----- on the subject device was shown to contain----- of formaldehyde and ----- of acetaldehyde, respectively, which is low----- amount of form----- tissues as a result of normal metabolism.

Physical Analyses

The sponsor conducted a series of physical tests on various gel formulations t-----

During the panel meeting, FDA will ask the Panel a question on the adequacy of the chemical and physical analyses conducted by the sponsor to characterize the safety profile of this device.

Preclinical Testing
Microbiology Tests

The sponsor conducted the following tests on the Oxiplex/SP Gel: 1) rabbit pyrogen and 2) kinetic-chromogenic limulus ameocyte lysate (LAL).

Material-Mediated Rabbit Pyrogen Test

The purpose of this test was to determine the risk of pyrogenic reaction due to the material components of the Oxiplex/SP Gel. No rabbit-----d with the test article or negative control extract showed a rise in temperature of-----indicating Oxiplex/SP Gel is not pyrogenic.

LAL Test

The purpose of this test was to determine the presence of bacterial endotoxin in the Oxiplex/SP Gel. Endotoxin levels were reported to be less than 0.05EU/mL. The allowable limit of endotoxins for devices with potential contact with cerebral spinal fluid is 0.06 EU/mL. The subject device falls below this level.

Biocompatibility/Toxicity Tests

The following biocompatibility tests were conducted on Oxiplex SP/Gel and-----

Table 1. Biocompatibility/Toxicity Tests

| Test Description | Standard | ----- | ----- port |
|--|--------------------|-------|------------|
| Irritation/Intracutaneous Reactivity | ISO 10993-10:1995 | ----- | ----- |
| Maximization Sensitization Test | ISO 10993-10:1995 | ----- | ----- |
| Muscle Implant Test | ISO 10993-6:1995 | ----- | ----- |
| Genotoxicity | | | |
| AMES Test | ISO 10993-3:1992 | ----- | ----- |
| Chromosomal Aberration | ISO 10993-3:1992 | ----- | ----- |
| Cytotoxicity – MEM Elution Assay | ISO 10993-5:1993 | ----- | ----- |
| Systemic Injection Acute Toxicity | ISO 10993-11:1993 | ----- | ----- |
| 120 Day Subchronic Intraperitoneal Implant Study | ISO 10993 – 6:1994 | ----- | ----- |
| Subchronic Toxicity - 30 and 45 Day Subchronic Intramuscular Implant | ISO 10993-11 :1993 | ----- | ----- |

Oxiplex/SP passed all tests.

Clearance Studies of Dynavisc (Oxiplex) [redacted]

The sponsor conducted a clearance study to determine the clearance and excretion of ¹⁴C-labeled CMC and PEO, the polymeric components of DynaVisc (Oxiplex). Results showed that both compounds (CMC and PEO) were excreted primarily through urine. Most of the excretion occurred during the [redacted]. The radioactivity level [redacted] blood after ¹⁴C-CMC administration declined [redacted] of approximately [redacted] whereas the blood half time for the ¹⁴C-PEO was approximately [redacted]. No adverse reactions were observed in animals injected with ¹⁴C-CMC or ¹⁴C-PEO.

Miscellaneous Information

- The sponsor did not perform Chronic Toxicity test since Oxiplex/SP Gel remains in the body for less than 90 days. This is acceptable since the sponsor provide information showing that the device is not expected to remain in the body for more than 30 days.
- The sponsor conducted a Mouse Lymphoma Assay [redacted] using a different formulation of gel consisting of CMC and PEO. With this test, [redacted] evaluated the potential of a 0.9% sodium chloride for injection extract of the gel to induce a forward mutation in the TK gene of L5178Y cells. A negative response was obtained. The result was negative, and is acceptable.
- Carcinogenicity resulting from exposure to Oxiplex/SP Gel is unlikely based upon the available resorption and upon the genotoxicity testing based on International Standards Organization (ISO- 10993 -3), including AMES test and Chromosomal Abberation. The results of genotoxicity testing were negative in the potential of the device to cause mutations. .
- An Immunotoxicity Assessment of Oxiplex [redacted] which included information on safety and data on biocompatibility of CMC and PEO used either in other medical devices, or studies of CMC and PEO components. CMC presents negligible or no risk of immunotoxicity to humans, which is adequate.

Animal Performance Testing

Animal studies were conducted using various formulations of [redacted] used individually or in combination together, in rabbit animal models to determine the biocompatibility and initial efficacy of the formulations.

[Redacted area containing multiple horizontal dashed lines]

Animal Performance Studies: Studies #1-7

* The [redacted] in Oxiplex/SP gel used in the clinical trial [redacted]

For Studies #1 and #3-7, all rabbits underwent a two-level laminectomy at L4 and L5, and some also had a discectomy [redacted]. A 10x5mm defect was created on the lamina [redacted] [redacted] implanted to fill the defect [redacted]. [redacted] Control animals received sur[redacted]

Studies #5 and #6, an unfilled defect in the same animal was used as a control. The rabbits were sacrificed at various time intervals (e.g. between 19-28 days, 6 weeks after surgery). The defect sites and surrounding areas were evaluated by gross examination and/or histological analysis, which included assessing the presence and density of fibrosis, vascularity at fibrosis site, presence/absence of foreign body response, healing of bone, tethering of dura, and scoring for dural adhesions. Blinded evaluators assessed scarring.

Results for Studies 1-7 showed that all ----- and control sites were healed. See Table 2 for ----- study purpose, -----

Table 2. Animal Performance Studies #1-7

| Study #/TR# | Study Purpose | Materials Tested (% crosslinker, MW of PEO, -----) | Results |
|-------------|---|--|---|
| ----- | To test the safety and efficacy of various ----- gels and ----- in the ----- of adhesion formation in a rabbit model of perineural fibrosis. | ----- ----- ----- ----- | ----- reduced area of ----- ed to the control lesions and ----- had no effect on ----- of the fibrotic lesion. ----- yielded a lower density of fibrosis. |
| ----- | To test the efficacy of crosslinked CMC/PEO polymers in the reduction of adhesion formation in a rabbit uterine horn model of adhesion formation. | ----- ----- ----- ----- | All gels reduced adhesion formation compared to the control. ----- reduction resulting from ----- which had the highest p----- number of adhesion-free sites. Some residual material remained at the s----- -----veral animals treated with ----- ----- Gel A was completely cl ----- in 7 days. |
| ----- | To compare effectiveness of CMC/PEO polymers to ----- in rabbit mode-----al adhesions. | ----- ----- ----- ----- | ----- were more efficacious than ----- based on the percentage of ----- on free si----- d that the combination o ----- film was more effective tha ----- effect sites treated with ----- had no scar tissue at all. |
| ----- | To compare effect of three CMC/PEO formulations on | ----- ----- ----- | ----- as more efficacious than ----- and ----- at 67% of test sites t----- wit ----- were adhesion-free. The |

| Study #/TR# | Study Purpose | Materials Tested (% crosslinker, MW of PEO, -----) | Results |
|-------------|--|--|---|
| | peridural adhesions in a rabbit model. | ----- ----- ----- | significance of this difference could not be determined because 50% of the control sites were also adhesion-free. |
| ----- | To test the efficacy of various CMC/PEO ----- | ----- ----- ----- | Two (2) out of 25 control sites were adhe-----free,----- e----- of sites treated with ----- were adhesion-free. |
| ----- | peridural fibrosis To test the efficacy of various CMC/PEO polymer gels in ----- | ----- ----- ----- | The contro -- -- were -----adhesion-free, while ----- of th----- sites were a-----on-fr----- epidural adhesions. |
| ----- | perineural fibrosis To evaluate effects of applying CMC/PEO gel on dural adhesions in rabbit model and then ----- | ----- ----- ----- | The control sites were -----adhesion-free, while----- -----). |

Summary of Studies #1-7

- Gels containing ----- PEO ----- and effective in reducing post surgical adhesio----- either ----- performed equivalently.
- ----- th the ----- ad ----- hesions compared to the control group or the empty control defects. -----
- ----- l adhesion formation was less for the ----- with the ----- compared to control sites. Adhesions that formed in the presence of ----- were characterized as loose fibrosis, where ----- sions formed at the control sites were classified as moderate to severe. -----
- ----- s not interrupted with the presence of the gel/fi-----

The results show that there were fewer adhesions in the Oxiplex-treated animals than in the surgery-only controls.

Animal Performance Studies: #8-11

*These tests ----- iplex/SP gel and other ----- formulations ----- Only the Oxiplex/SP gel was used in the clinical trial.--

For Studies #8-11, all rabbits underwent a two-level laminectomy at L4 and L5. A 10x5mm defect was created on the lamina of both L4 and L5. In Studies #8 and #11, a 20-gauge and 2mm dural nick, respectively, was also created at the site. ----- were implanted to fill the defect. ----- or Study #8, the

unfilled defect in the same animal was used as a control in addition to a separate control group that received surgery only. Study #11 used control animals, which received surgery only. For Studies #9 and #10, the unfilled defect in the same animal was used as a control. The rabbits were sacrificed 28 days after surgery for all studies, except for Study #11, in which the animals were sacrificed 14-15 days post-surgery. The defect sites and surrounding areas were evaluated by gross examination and/or histological analysis, which included assessing the presence and density of fibrosis, vascularity at fibrosis site, presence/absence of foreign body response, healing of bone, scoring for dural adhesions. Blinded evaluators assessed scarring.

Results for Studies #8-11 showed that all [redacted] and control sites were healed. See Table 3 for [redacted] study purpose, [redacted] and results.

Table 3. Animal Performance Studies #8-11

| Study #/TR# | Study Purpose | Materials Tested (% crosslinker, MW of PEO, CMC:PEO, % solids) | Results |
|-------------|---|--|--|
| [redacted] | To confirm results of CMC/PEO [redacted] products and evaluate the device in a dural nick study in a rabbit model | Oxiplex/SP Gel | There was no significant difference between the device-treated or control animals in fibrosis or healing of dural nick. There was no excessive fluid at surgical site post-operatively or at sacrifice. |
| [redacted] | To compare the efficacy of [redacted] t-operative peridural or epidural adhesions in rabbit model | Oxiplex/SP Gel | All surgical sites were healed, indicating that the healing response of the treated animals was no [redacted] either the gel or [redacted] |
| [redacted] | To compare [redacted] of SP gels [redacted] post-operative peridural or epidural adhesions in a rabbit model and assess any inhibition of normal wound healing. | [redacted] | Both [redacted] and [redacted] reduced the f [redacted] between [redacted] and overlying healing tissue. There was a statistically signific [redacted] cation in adhesion scores for [redacted] gel when compared to the con [redacted] hesions (p=0.003). The effectiveness of th [redacted] [redacted] gel was not significant when compared [redacted] the control (p=0.073). |
| [redacted] | To compare effectiveness of [redacted] iplex/SP and [redacted] in rabbit laminectomy [redacted] model that includes a 2 mm dural nick | Oxiplex/SP Gel | No e [redacted] on at sites treated with [redacted] was observed. Histo [redacted] showed that the dural [redacted] ealed comparably between [redacted] gel treated and control sites, [redacted] on to the [redacted] sites, which did not show healing of dural nicks. |

** In Study 9 [redacted] some fragments of material were reported at the [redacted] sites and a leukocytic response to the material was observed. When asked to explai [redacted] aterial, the sponsor stated the residual fragmented pieces of material that were observed occurred only at lesions treated with [redacted] n, w [redacted] ear [redacted] of Oxiplex and not the subject of this PMA [redacted] rts [redacted] and [redacted] on lesions treated with only

[redacted] confirmed there was no indication that [redacted] gel remained at the site of implantation at 28 days.

Summary of Studies #8-11

- The gel- and [redacted] treated sites had lower adhesions scores compared to the control sit----- ificant difference in adhesion formation between gel-treated or [redacted] es. (Study 9/[redacted])
- Sites treated with [redacted] (Oxiplex/SP ----- e seen to have less adhesions compared to the control sites and sites treated with the oth----- (Stu----- [redacted])
- Wound healing was not impaired with the presence of the [redacted] and [redacted] gels, wh----- healing at the sites treated with Adcon-L was decre----- residual [redacted] material was observed. (Study 10/[redacted])
- Formation of epidura----- ns was significantly reduced at sites that were treated with Oxiplex/SP Gel and [redacted]----- reduction of adhesion formation between both gels was comparable. (Study 11/[redacted])

During the panel meeting, FDA will ask the Panel to discuss whether the preclinical and animal testing conducted by the sponsor is predictive of the performance of the device for its proposed indications for use and if the testing done was sufficient to characterize the device that will be marketed.

CLINICAL STUDY

The clinical data on the Oxiplex/SP Gel was collected under IDE.

Pilot Study

The sponsor conducted a pilot safety study with 35 subjects having a herniated disc at four investigational sites between March 2001 to May 2003 to assess the safety of applying Oxiplex/SP Gel (Oxiplex) during single-level spinal discectomy and to determine, through assessment of clinical response and evaluation of enhanced magnetic resonance imaging (MRI), if the extent of peridural fibrosis and related symptoms may be reduced with use of Oxiplex. Clinical response was assessed via neurological function and radiculopathy and through self-assessment questionnaires relating to pain and activities of daily living, the Oswestry Disability Questionnaire (ODI) and the Lumbar Spine Outcomes Questionnaire (LSOQ) at 30 days, 3, 6 and 12 months: MRI was used to determine the extent of epidural scar formation at 3 months.

Indication Studied:

Reduction of adhesions following lumbar surgery

Intended Use

The intended use of the Oxiplex/SP Gel (in this study) was as an adjunct to surgery during lumbar laminectomy, laminotomy, and discectomy procedures. The device was intended to inhibit the formation of peridural fibrosis and dural adhesions that might otherwise contribute to postoperative radicular pain and/or neurological dysfunction.

Study Design

The pilot study was a prospective, randomized, single-blind, clinical trial to evaluate the safety of Oxiplex when used to reduce postoperative peridural fibrosis and related symptoms following surgery for herniated lumbar disc at L4-L5 or L5-S1. Subjects were randomized to the investigational or control group intraoperatively. The investigational group received the Oxiplex gel around the dura and nerve roots, while the Control group underwent surgery for herniated disc without any additional treatment. All surgeries were performed using a posterior approach. The study was not powered to demonstrate statistically significant differences between the two groups.

There were 23 investigational and 12 control subjects in this pilot study. One control subject withdrew prior to 3 month follow-up. All subjects received clinical evaluations at baseline and postoperatively at 1 and 3 months. All subjects were to complete ODI and LSOQ preoperatively, as well as at 1, 3, 6, and 12 months postoperatively. In addition to baseline MRI, all subjects were to receive follow-up evaluations at 3 months post-op for repeat MRI of the spine, with and without contrast. Two blinded MRI readers were employed to assess for the presence and extent of fibrosis/scarring.

Endpoints

The primary endpoints of the clinical investigation evaluated the efficacy of Oxiplex in the reduction of postoperative pain and symptoms and peridural fibrosis on MRI and the safety of applying Oxiplex in lumbar disc surgery. The sponsor measured pain reduction, as well as scar score reduction on MRI. The sponsor considered a reduction in pain at any of the postoperative

evaluations in the Oxiplex group compared to the control group of at least one unit in either the ODI or LSOQ to be clinically significant.

Inclusion/Exclusion Criteria

The population studied consisted of adults scheduled to undergo a primary surgical intervention for diagnosed unilateral herniation of lumbar intervertebral disc material associated with radiculopathy.

Inclusion Criteria

- Clinical signs and symptoms indicative of lumbar or lumbosacral radiculopathy, affecting one predominant nerve root level;
 - Radiological evidence of compression of a nerve root, and/or confirmed existence of an extruded or sequestered disc fragment, at a level compatible with clinical signs and symptoms;
 - Involvement at the L4-L5 or L5-S 1 level;
 - Males or females of non-childbearing potential; or females who are not pregnant (at the time of enrollment) and who agree to avoid becoming pregnant during the 90-day follow-up period;
 - 18 to 65 years of age, inclusive;
 - Blood chemistry, urine and hematology laboratory test results within normal limits, or deemed not to be of clinical significance by the investigator and sponsor jointly.
-
- Subjects entering the study underwent a period of at least two weeks of nonoperative treatment without resolution of the problem, unless the surgeon decides the subject is experiencing intractable pain or there is substantial progression of loss of neurologic function.

Exclusion Criteria

- Previous spinal surgery at any level;
- Treatment with any epidural steroids within four (4) weeks prior to the proposed surgery;
- Treatment with any oral steroids within ten (10) days prior to the proposed surgery;
- Treatment with aspirin or other non-steroidal anti-inflammatory drugs within seven (7) days prior to the proposed surgery;
- Known history of collagen-vascular or auto-immune disease (*e.g.*, rheumatoid arthritis, systemic lupus erythematosus), bleeding abnormalities, or malignancy within 5 years (except basal cell carcinoma);
- Myelogram or lumbar puncture for any reason within 24 hours prior to the proposed surgery;
- Presence of any immunodeficiency disease, diabetes, or any systemic condition which, in the surgeon's opinion, may influence the outcome of the proposed surgery or postoperative period;

Intra operative Exclusions:

- Dural entry during surgery;
- Discovery of intraspinal tumor during surgery;
- The need to involve more than one level;

- Exploration of contralateral side;
- Epidural fat placement;
- Surgical determination that an hemostatic agent must remain at the surgery site;
- Surgical determination of the need for any other device (that would interfere with interpretation of the study results) to remain at the surgery site.

Surgical Procedure

Subjects were randomized to receive surgery plus Oxiplex/SP Gel (Oxiplex group) or to receive surgery only (Control group), with both groups having a posterior approach. The Control group was a standard surgery for herniated disc without any treatment.

Patients in the Oxiplex group had additional treatment with the device which was used to coat the dura and exiting nerve root along both its dorsal and ventral surfaces and applied to the site of the laminectomy/laminotomy to fill depth of the surgical site to the level of the ventral surface of the vertebral lamina. The gel applied to the operative site was not to exceed 5 mL.

Statistical Analysis Plan

The statistical analysis plan included an analysis of variance (ANOVA) for ODI and LSOQ and the usage of a generalized estimating equation (GEE) for the MRI scar scores. The Oswestry score is based on 10 questions scored on a scale of 0 to 5 and is treated as a percentage in order to include subjects who skip some questions. The LSOQ yields five separate scales (pain severity, functional disability, psychological distress, physical symptoms, and health care utilization). These scores were treated as continuous variables. Changes from baseline laboratory values were analyzed using the paired t-test or the Wilcoxon matched-pairs signed-ranks test. P-values less than 0.05 were treated as statistically significant.

As to the evaluation of the postoperative scar score, Magnetic resonance imaging (MRI) was used for evaluations of epidural enhancing and non-enhancing abnormalities, which are based on evaluations of four quadrants on each of five MRI slices for each subject (20 evaluations per subject). Scar assessments were graded on a scale of 0-6, where 0 = none, 1 = 0-5% abnormalities, 2 = 6-25%, 3 = 26-50%, 4 = 51-75%, 5 = 76-95%, and 6 = 96-100%. For comparisons of the two groups, each quadrant of each view was assigned a score based on the midpoint of the percentage definition of the grade given to that quadrant.

The statistical models contained factors for groups, MRI slices, quadrants and examiners.

Data were analyzed at all time points and, in addition, the "last observation carried forward" (LOCF) method was used to allow an overall analysis including subjects who did not complete the later follow-up evaluations of the pilot study.

Note – Because this was a safety/feasibility study, there was no pre-specified hypothesis on the statistical or clinical significance of the pain scores or the MRI scar scores.

Results for the Pilot Study

The rate of adverse events between the Oxiplex and Control groups is presented in Table 4. For some parameters (*e.g.* leg and back pain), there was a higher incidence of adverse events in the Oxiplex group compared to the Control group.

Table 4. Adverse Event Rates in Oxiplex and Control groups of Pilot Study

| | Oxiplex (n=23) | Control (n=12) |
|--------------------------|-------------------|-------------------|
| Leg pain | 5 (22%) | 1 (8%) |
| Back pain | 6 (26%) | 1 (8%) |
| Muscle spasm | 4 (17%) | 2 (17%) |
| Back stiffness | 3 (13%) | 2 (17%) |
| Buttock pain | 3 (13%) | 0 (0%) |
| Lower extremity pain | 5 (22%) | 1 (8%) |
| Post procedural pain | 8 (35%) | 5 (42%) |
| Incisional pain | 8 (35%) | 5 (42%) |
| Lower extremity numbness | 4 (17%) | 1 (8%) |
| Hypoaesthesia | 6 (26%) | 1 (8%) |
| Paresthesia | 3 (13%) | 0 (0%) |
| Sensory loss | 2 (9%) | 1 (8%) |
| Nausea | 8 (35%) | 2 (17%) |
| Vomiting | 4 (17%) | 1 (8%) |
| Constipation | 3 (13%) | 1 (8%) |

The results of the statistical analyses on the pilot study showed non-significant p-values when comparing the Oxiplex and Control groups in leg pain, symptoms, activity related pain index, functional disability, weakness in lower extremity, and radiculopathy score as well as MRI scar scores. Please note that it is important to recognize that this small sample size may not be adequate for the ability to determine a small clinical difference since the study was not designed or powered to detect statistically significant differences between groups.

Table 5 shows the leg pain reduction between the two groups at 30 days, 3, 6, and 12 months.

Table 5. Leg Pain (Lumbar Spine Outcomes Questionnaire (LSOQ))

| Variable | Oxiplex | | Control | | p |
|-----------------------------|---------|------|---------|------|-------|
| | N | Mean | N | Mean | |
| <i>Baseline</i> | 23 | 57.8 | 12 | 65.8 | 0.215 |
| <i>Change from Baseline</i> | | | | | |
| <i>30 Days</i> | 23 | 44.6 | 12 | 40.8 | 0.725 |
| <i>90 Days</i> | 23 | 35.8 | 11 | 43.5 | 0.526 |
| <i>6 months</i> | 22 | 40.9 | 11 | 44.2 | 0.762 |
| <i>12 months</i> | 23 | 40.7 | 11 | 46.6 | 0.532 |

p values determined using ANOVA.

Note small sample size.

LSOQ is a 100-point scale.

Table 6 shows Lumbar Spine Outcome Questionnaire scores between the two groups at 30 days, 3, 6, and 12 months.

Table 6. Symptoms (LSOQ)

| Variable | Oxiplex | | Control | | p |
|-----------------------------|---------|------|---------|------|-------|
| | N | Mean | N | Mean | |
| <i>Baseline</i> | 23 | 46.9 | 12 | 52.3 | 0.496 |
| <i>Change from Baseline</i> | | | | | |
| <i>30 Days</i> | 23 | 27.2 | 12 | 19.4 | 0.406 |

| | | | | | |
|------------------|----|------|----|------|-------|
| <i>90 Days</i> | 23 | 24.5 | 11 | 26.3 | 0.870 |
| <i>6 months</i> | 22 | 28.1 | 11 | 30.4 | 0.793 |
| <i>12 months</i> | 22 | 28.9 | 11 | 34.5 | 0.529 |

p values determined using ANOVA.

Note small sample size.

LSOQ is a 100-point scale.

Table 7 shows Activity Related Pain index between the two groups at 30 days, 3, 6, and 12 months.

Table 7. Activity Related Pain index (LSOQ)

| Variable | Oxiplex | | Control | | p |
|----------------------|---------|------|---------|------|-------|
| | N | Mean | N | Mean | |
| <i>Baseline</i> | 23 | 2.10 | 12 | 2.27 | 0.637 |
| Change from Baseline | | | | | |
| <i>30 Days</i> | 23 | 0.89 | 12 | 0.83 | 0.901 |
| <i>90 Days</i> | 23 | 0.76 | 11 | 0.99 | 0.660 |
| <i>6 months</i> | 22 | 0.92 | 10 | 0.76 | 0.692 |
| <i>12 months</i> | 23 | 0.87 | 11 | 0.92 | 0.904 |

p values determined using ANOVA.

Note small sample size.

LSOQ is a 100-point scale.

Table 8 shows Functional Disability between the two groups at 30 days, 3, 6, and 12 months.

Table 8. Functional Disability (LSOQ)

| Variable | Oxiplex | | Control | | p |
|-------------------------------|---------|------|---------|------|-------|
| | N | Mean | N | Mean | |
| <i>Baseline Score of 100?</i> | 23 | 50.7 | 12 | 51.1 | 0.966 |
| Change from Baseline | | | | | |
| <i>30 Days</i> | 23 | 12.8 | 12 | 11.2 | 0.864 |
| <i>90 Days</i> | 23 | 24.3 | 11 | 22.9 | 0.879 |
| <i>6 months</i> | 22 | 25.5 | 11 | 23.5 | 0.811 |
| <i>12 months</i> | 22 | 23.1 | 11 | 25.8 | 0.780 |

p values determined using ANOVA.

Note small sample size.

LSOQ is a 100-point scale.

Table 9 shows Weakness in Lower Extremity between the two groups at 30 days, 3, 6, and 12 months.

Table 9. Weakness in Lower Extremity (LSOQ)

| Variable | N | Oxiplex | Control | | P |
|----------------------|----|---------|---------|------|-------|
| | | Mean | N | Mean | |
| <i>Baseline</i> | 23 | 2.52 | 12 | 2.75 | 0.574 |
| Change from Baseline | | | | | |
| <i>30 Days</i> | 23 | 0.96 | 12 | 0.50 | 0.371 |

| | | | | | |
|------------------|----|------|----|------|-------|
| <i>90 Days</i> | 23 | 0.83 | 11 | 0.82 | 0.987 |
| <i>6 months</i> | 22 | 0.91 | 11 | 0.73 | 0.721 |
| <i>12 months</i> | 23 | 0.91 | 11 | 0.91 | 0.993 |

p values determined using ANOVA.

Note small sample size.

LSOQ is a 100-point scale.

Table 10 shows Radiculopathy Score ----- between the two groups at 30 days, 3, 6, and 12 months.

Table 10. Radiculopathy Score (LSOQ)

| Variable | Oxiplex | | Control | | p |
|----------------------|---------|------|---------|------|-------|
| | N | Mean | N | Mean | |
| <i>Baseline</i> | 23 | 52.7 | 12 | 59.2 | 0.271 |
| Change from Baseline | | | | | |
| <i>30 Days</i> | 23 | 36.0 | 12 | 29.9 | 0.475 |
| <i>90 Days</i> | 23 | 30.3 | 11 | 34.8 | 0.658 |
| <i>6 months</i> | 22 | 34.7 | 11 | 37.3 | 0.757 |
| <i>12 months</i> | 23 | 34.9 | 11 | 40.5 | 0.486 |

p values determined using ANOVA.

Note small sample size.

LSOQ is a 100-point scale.

Table 11 shows Oswestry Disability Index (ODI) score between the two groups at 30 days, 3, 6 and 12 months.

Table 11. Oswestry Disability Index (ODI)

| Variable | Oxiplex | | Control | | p |
|----------------------|---------|------|---------|------|-------|
| | N | Mean | N | Mean | |
| <i>Baseline</i> | 22 | 47.6 | 11 | 46.9 | 0.913 |
| Change from Baseline | | | | | |
| <i>30 Days</i> | 22 | 24.7 | 11 | 23.2 | 0.875 |
| <i>90 Days</i> | 22 | 30.9 | 10 | 31.8 | 0.921 |
| <i>6 months</i> | 21 | 32.5 | 10 | 33.2 | 0.932 |
| <i>12 months</i> | 22 | 33.1 | 10 | 30.8 | 0.786 |

p values determined using ANOVA.

Note small sample size.

There is a 100-point scale on the ODI.

Table 12 shows MRI scar score between the two groups at 3 months.

Table 12. MRI scar score analysis*

| Parameter | Statistics | Oxiplex/SP Gel | | Control | |
|-----------------------------|------------|----------------|---------|---------|---------|
| | | Reader1 | Reader2 | Reader1 | Reader2 |
| Subjects enrolled at day 90 | N | 23 | | 11 | |
| Kappa | N | 23 | 23 | 10 | 10 |
| | 0.6543(1) | 1.550 | 1.550 | 1.775 | 1.600 |
| | 0.6596(2) | 1.746 | 1.600 | 1.640 | 1.585 |

| | | | | | |
|--|----------|------------|-----------|-----------|-----------|
| | S.E. | 0.1284 | 0.1160 | 0.1536 | 0.1665 |
| | Min, Max | 0.65, 3.25 | 0.6, 2.70 | 0.70,2.25 | 0.65,2.25 |

*MRI scores were based on a scale of 0-6, where 0 = None, 1 = 0-5% abnormalities, 2 = 6-25%, 3 = 26-50%, 4 = 51-75%, 5 = 76-95%, and 6 = 96-100%.

Summary

The sponsor conducted a pilot study to determine if peridural fibrosis and related symptoms were reduced with the use of Oxiplex®/SP gel. Twenty-three (23) investigational and 12 control subjects having degenerative disc disease underwent a single-level discectomy with the investigational group receiving Oxiplex gel around the dura and nerve roots and the control subjects undergoing surgery only. All subjects received clinical evaluations during baseline and post-op visits at 1 and 3 months. All subjects completed ODI and LSOQ preoperatively, as well as at 1, 3, 6, and 12 months post-op visits. Baseline MRI and 3 month post-op MRIs were taken for most subjects in an attempt to quantify epidural scar formation and evaluate safety.

In some of the safety parameters (*e.g.* leg and back pain), there was a larger number of adverse events in the Oxiplex group than in the Control group, but with a small sample size a small difference in the adverse event rate between the two groups cannot be detected with a significant p-value because of a type II error.

In the evaluation of effectiveness, due to the small sample size, it was not possible to detect significant statistical differences between the Oxiplex and Control group with respect to the means in leg pain, symptoms, activity related pain index, functional disability, weakness in lower extremity, radiculopathy scores of LSOQ and Oswestry Disability Index at 30 days, 3, 6, and 12 months, as well as in MRI scar scores at 3 months.

Because the results from the pilot study did not raise safety concerns, FDA allowed the sponsor to initiate a new pivotal study to study the safety and efficacy of Oxiplex/SP gel in a larger population to commence.

Pivotal Study

Intended Use

Oxiplex/SP Gel is intended to be used as an adjunct to surgery during lumbar laminectomy, laminotomy, and discectomy procedures. The device is intended to improve patient outcome by reducing pain and symptoms.

Indication

Oxiplex®/SP Gel is indicated 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.

Please note this indication of the pivotal study is different from the indication studied during the pilot study since the sponsor removed inhibition of peridural fibrosis from the primary endpoint of the pivotal study.

Study Design

The sponsor conducted a prospective, multi-center, randomized, third-party blinded, parallel group study. All subjects underwent lumbar disc surgery (standard laminectomy, laminotomy, and discectomy) and were randomized 1:1 to receive surgery plus Oxiplex/SP gel (Oxiplex group) or to receive surgery only (Control group). Randomization occurred intraoperatively, immediately prior to wound closure. Subjects were not considered to be enrolled until they had met all eligibility criteria (preoperative and intraoperative) were randomized, and had received a study group assignment and subject identification number. The sponsor stated that subjects and all evaluators of data were masked to the treatment assignment. Follow-up assessments were conducted at 1, 3, and 6 months.

There were 352 subjects (177 Oxiplex and 175 Control subjects) enrolled at 29 US investigational sites between October 2002 and October 2006 in order to obtain at least 334 evaluable subjects (those who completed the 6-month postsurgical follow-up visit). The final number of evaluable subjects was 334, referred to as Completed Cases (CC).

Inclusion/Exclusion Criteria

The population studied consisted of adult males and females who were scheduled to undergo a first surgical intervention for a diagnosed unilateral herniation of lumbar intervertebral disc material associated with radiculopathy.

Inclusion Criteria

- Clinical signs and symptoms indicative of lumbar or lumbosacral radiculopathy, affecting one predominant nerve root level; Significant pain and symptoms measurable by the LSOQ;
- Radiological evidence (MRI Study or CT/myelogram) of compression of a nerve root, and/or confirmed existence of an extruded or sequestered disc fragment, at a level compatible with clinical signs and symptoms;
- Compression of a nerve root, and/or confirmed existence of an extruded or sequestered disc fragment, at the L4-L5 or L5-S1 level;
- Males, females of non-childbearing potential or females who were not pregnant; agreed not to become pregnant for at least 30 days after surgery; or who agreed to use a medically acceptable method of contraception;
- 18 to 70 years of age;
- Blood chemistry, urine and hematology laboratory test results within normal limits, or deemed not to be of clinical significance by the investigator and sponsor jointly.
- Subjects entering the Pivotal Study underwent a period of at least two weeks of non-operative treatment without resolution of pain, unless the surgeon decided the subject was experiencing intractable pain, or there was substantial progression of loss of neurological function;

Exclusion Criteria

- Previous spinal surgery or chemonucleolysis at the lumbar level;
- Treatment with any epidural steroids within 4 weeks prior to the proposed surgery; Use of steroids perioperatively and/or intraoperatively;
- Presence of scoliosis; (> 10 degrees and considered by the investigator to be clinically significant);

- Presence of foraminal stenosis;
- Known history of collagen-vascular or auto-immune disease (*e.g.*, rheumatoid arthritis, systemic lupus erythematosus), bleeding abnormalities, chronic debilitating disease, or malignancy within 5 years (except basal cell carcinoma);
- Myelogram or lumbar puncture for any reason within 24 hours prior to the proposed surgery;
- Presence of any immunodeficiency disease, uncontrolled diabetes, or any systemic condition which, in the surgeon's opinion, may influence the outcome of the proposed surgery or postoperative period;

Intraoperative Exclusions

Subjects who met any of the following criteria were not eligible for enrollment:

- Dural entry during surgery;
- Discovery of intraspinal tumor during surgery;
- The need to involve more than one level;
- Exploration of contralateral side;
- Epidural fat placement;
- Use of steroid solution
- Surgical determination that an hemostatic agent must remain at the surgery site;
- Surgical determination of the need for any other device (that would interfere with interpretation of the study results) to remain at the surgery site.

Endpoints

The primary endpoints of the clinical investigation were to evaluate the efficacy of Oxiplex in the reduction of postoperative pain and symptoms and the safety of applying Oxiplex in lumbar disc surgery.

Safety Endpoints

The *primary safety endpoint* evaluated the frequency and severity of adverse events, including surgical complications, categorized using the MedDRA coding system (Version 7.1).

The *secondary safety endpoints parameters* evaluated: 1) changes in laboratory results, physical and neurological exam and vital signs throughout the study; 2) re-operations at the lumbar level; and the 3) use of concomitant therapies.

Effectiveness Endpoints

The *primary effectiveness endpoint* was the improvement in leg pain from baseline to follow-up visits (1, 3 and 6 months), as measured by the LSOQ.

The LSOQ measures leg pain severity on a six-point rating scale for each of the six questions. The six leg pain severity responses were summed and then multiplied by 100 and divided by 30. These operations yielded a composite leg pain severity score in the range of 0 to 100, with higher scores indicating higher overall severity of experienced pain.

The *secondary effectiveness endpoints* were the improvements from baseline (follow-up visit score minus baseline score) as measured by the LSOQ, of the following:

1. back pain
2. leg weakness
3. physical symptoms
4. subject satisfaction
5. disability score
6. activities of daily living

Surgical Protocol

- Standard Midline or paramedian approach
- Remove some or all of disc from intervertebral location. Establish hemostasis and removal of hemostatic agents
- Irrigate and aspirate prior to application of Oxiplex/SP gel in treated subjects and before closure in all subjects
- Complete Surgery Worksheet for required entries to this point of the procedure. Determine that subject met criteria for randomization.
- Determine randomization assignment as to whether the subject belongs in the Treatment group or in the Control group.
- Treatment Group Only: Coat the dura and exiting nerve root along both its dorsal and ventral surfaces. Apply the gel into the site of the laminectomy/laminotomy to fill depth of the surgical site to the level of the ventral surface of the vertebral lamina. The volume delivered is not to exceed 3 mL
- Close wound in routine fashion.
- Complete the remainder of the Surgery Worksheet.

Clinical Evaluations

Each subject enrolled in the study was to be followed for 6 months after surgery to evaluate device safety and effectiveness.

Follow-up Evaluations

All subjects were to be evaluated for safety at 1 and 6 months and for effectiveness at 1, 3, and 6 months.

Postoperative clinical evaluations were to be performed at 1 month (3-6 weeks) and 6 months (22-28 weeks) by a qualified Clinical Evaluator (CE), who was blinded to the subject study group assignment. The evaluations included:

- A physical examination, including the lumbar spine and lower extremities, motor/sensory function, and an evaluation of the wound site;
- An assessment of adverse events (this was assessed at all time points);
- A review of laboratory test results for clinically significant changes (hematology and serum chemistries at 1 and 6 months; urinalysis at 1 month).

For assessment of effectiveness, subjects were to complete the LSOQ via phone (or mail) at 1, 3 and 6 months. The LSOQ, developed at Johns Hopkins University, is a self-assessment questionnaire that served as the Quality of Life instrument. Johns Hopkins University served as the masked

independent contractor that performed postoperative interviews of LSOQ via telephone or mail. The sponsor stated the interviewer and subject remained masked to the study group assignment throughout the study.

For each subject and for each follow-up evaluation period, composite measures were derived from the subjects' responses to the LSOQ: two pain severity measures (leg and back), physical symptoms, and activities of daily living. Mean scores for each composite measure were determined for the Control and Oxiplex groups at each evaluation point, including baseline.

Success/Failure

The sponsor set the success criteria of the study as an improvement of 15 points at 6 months on the 100-point LSOQ scale.

Note: FDA advised the sponsor that in order for the study to be considered a success there should exist a statistical significance, as well as a clinically meaningful difference in the chosen primary endpoint between the two treatment groups, *i.e.*, 20 point or 33% difference between the two groups in the mean LSOQ score reduction from baseline

During the panel meeting FDA will ask a question as to whether or not a 15 point improvement on the LSOQ would be meaningful clinically.

Statistical Analysis Plan

The IDE study was designed to demonstrate superiority of the Oxiplex/SP gel compared to standard surgery alone.

Safety Analyses

The sponsor proposed a descriptive presentation and univariate analysis. The sponsor planned to assess the frequencies and percentages of subjects with adverse events (treatment emergent, device-related, serious adverse events, adverse events leading to study discontinuation and those related to surgery or wound site). The frequency of various adverse events was presented by MedDRA system organ class and preferred term relationship to the device and by severity. Differences between the treatment groups for system organ class were determined using Fisher's exact test and/or the Wilcoxon rank sum test. Statistical tests were only to be conducted for those adverse events with an overall incidence greater than 5%.

Primary Effectiveness Analyses

The primary effectiveness hypothesis tested was the following:

$$H_0: \mu_t = \mu_c \text{ vs. } H_a: \mu_t \neq \mu_c$$

Where μ_t is the mean change in LSOQ leg pain from baseline to 1, 3 and 6 months post surgery in the Oxiplex group and μ_c is the mean change from baseline in the control group. The two-sided test was carried out using a multivariate Generalized Estimating Equations (GEE) model, including treatment, time, and baseline level and baseline by treatment interaction in the model. The required value of z adjusting for the interim analysis was 2.0098, corresponding to a 2-sided alpha level of 0.044.

The sponsor planned to screen all clinically relevant baseline factors for inclusion into the multivariate model after having performed the interim analysis. The list of possible covariates included but was not limited to age, weight, smoking history, surgical time, level of surgery (L4-L5 or L5-S1), surgery type (microdiscectomy or regular), baseline leg pain score, baseline back pain score, baseline lower extremity weakness score, baseline physical symptom score, baseline patient disability score, study site, and medical history variables. The sponsor also planned to study interactions with treatment.

Screening for eligibility into the final model was done by a method similar to that of Hosmer and Lemeshow (2000). A GEE model including the treatment, time, covariate, and covariate by treatment interaction was fit. If the interaction did not have a P-value less than 0.20, a second model was fit including only treatment and the covariate. If the covariate did not have a p-value less than 0.20, then it was determined to be not eligible for entry into the final model. If the number of variables and interactions exceeded 10% of the sample size, the sponsor planned to reduce the p-value for eligibility to avoid over specification of the model.

The final model was obtained by backward selection with treatment and time retained in the model starting with all covariates and covariate interactions that had screening P-values that were less than 0.20. The removal of variables from the model was done manually to assure that the largest possible set of subjects was entered into the model.

The treatment will be considered statistically significant if the treatment main effect or the treatment by time interaction is statistically significant with a 2-sided alpha of 0.044.

Secondary Effectiveness Analyses

The sponsor proposed a pre-specified closed-testing to control Type I error. With this method, the secondary effectiveness endpoints were tested sequentially in the pre-determined order, and the first secondary endpoint had to be statistically significant before the next secondary endpoint could be considered. Similar to the primary effectiveness analyses, the treatment will be considered statistically significant if the treatment effect or the treatment by time interaction is statistically significant at 0.044 level.

Interim Analysis

----- Due to having conducted the interim analysis, a two-sided alpha value of 0.044 was determined to be necessary to achieve statistical significance on the final analysis using group sequential method (alpha spending function was determined using the Hwang, Shih, and DeCani method with gamma value of -4).

Results for the Pivotal Study

The study was approved for up to 25 investigational sites and up to 394 total subjects. A total of 177 Oxiplex and 175 Control subjects underwent surgeries in the study.

Patient Demographics

The study demographics are outlined below.

Table 13. Demographics and Baseline Characteristics

| | Oxiplex (n=177) | Control (n=175) |
|------------------|--------------------|--------------------|
| | Mean | Mean |
| Age | 41.8 | 41.7 |
| Height (cm) | 173.0 | 172.5 |
| Weight (kg) | 86.0 | 83.8 |
| Gender | | |
| Male | 87 | 98 |
| Female | 90 | 77 |
| Race | | |
| Caucasian | 152 | 153 |
| African American | 9 | 4 |
| Hispanic | 8 | 11 |
| Asian | 2 | 3 |
| Other | 3 | 2 |

There were no statistically significant differences between Oxiplex and Control group in demographic characteristics at baseline.

Patient Accounting

The table below identifies patient dispositions at 6 months of the Intent-to-Treat (ITT) population. Thirteen (13) randomized subjects withdrew from the study prior to 6 month follow-up visit, for reasons that include withdrawal of informed consent, protocol violation/noncompliance, death, and lost to follow-up.

Table 14. Patient Dispositions at 6 months

| | 6 Months | |
|--|----------|---------|
| | Oxiplex | Control |
| | 177 | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |

1 Five (5) subjects had 6-month visits far beyond the 6-month visit window (> 365 days), and were excluded from the “Evaluable Population” by the sponsor.

2 At the request of FDA, the sponsor included the 5 subjects that had 6-month visit far beyond the visit window in some analyses. This population is called “Modified Complete Cases” in this summary.

Safety Results

Please note that all enrolled subjects (ITT) were included in the analysis of safety.

The Clinical Evaluator (CE) was instructed to base Adverse Event (AE) reviews on medical judgment and to assume that a subject had received the device when assessing the relationship of the device to AEs. The sponsor compared the AE rate in the investigational group to the control group. There were no statistically significant differences in the number of subjects having AEs or

serious adverse events (SAEs) between the Oxiplex and Control groups. There were no AEs leading to discontinuation of any subject from the pivotal study or discontinuation of the pivotal study.

Total Numbers of Adverse Events

A total of 163 (92.1%) Oxiplex subjects had at least one AE. Similarly, the number of subjects in the control group with any AE was 153 (87.4%). These rates were not statistically significant ($p=0.8438$ for Oxiplex vs. Control, Fisher's Exact Test).

Table 15. Analysis of AEs with Incidence ~ 5%

| Incidence occurring > 5 % | Oxiplex | % | Control | % |
|---|----------------|----------|----------------|----------|
| Subjects Randomized | N=177 | | N=175 | |
| Subjects Reporting Any Adverse Event | N=163 | | N=153 | |
| Gastrointestinal Disorders | | | | |
| Constipation | 12 | 6.8% | 6 | 3.4% |
| Nausea | 35 | 19.8% | 36 | 20.6% |
| Vomiting | 10 | 5.6% | 9 | 5.1% |
| General Disorders & Administrative Site Conditions | | | | |
| Chills | 8 | 4.5% | 8 | 4.6% |
| Pyrexia | 8 | 4.5% | 11 | 6.3% |
| Injury, Poisoning, Procedural Complications | | | | |
| Incision Site Complication | 57 | 32.2% | 69 | 39.4% |
| Procedural Pain | 56 | 31.6% | 54 | 30.9% |
| Musculoskeletal, Connective Tissue Disorders | | | | |
| Arthralgia | 12 | 6.8% | 12 | 6.9% |
| Back Pain | 44 | 24.9% | 39 | 22.3% |
| Buttock Pain | 12 | 6.8% | 13 | 7.4% |
| Intervertebral Disc Protrusion | 4 | 2.3% | 9 | 5.1% |
| Muscle Spasm | 25 | 14.1% | 31 | 17.7% |
| Muscular Weakness | 9 | 5.1% | 9 | 5.1% |
| Musculoskeletal Stiffness | 9 | 5.1% | 5 | 2.9% |
| Myalgia | 6 | 3.4% | 13 | 7.4% |
| Pain in Extremity | 26 | 14.7% | 38 | 21.7% |
| Nervous System Disorder | | | | |
| Dizziness | 10 | 5.6% | 8 | 4.6% |
| Headache | 14 | 7.9% | 12 | 6.9% |
| Hypoesthesia | 18 | 10.2% | 26 | 14.9% |
| Hyporeflexia | 9 | 5.1% | 4 | 2.3% |
| Sensory Loss | 4 | 2.3% | 8 | 4.6% |
| Psychiatric Disorders | | | | |
| Insomnia | 12 | 6.8% | 7 | 4.0% |
| Skin and Subcutaneous Tissue Disorders | | | | |
| Pruritis | 8 | 4.5% | 6 | 3.4% |

Five (5) patients in the Oxiplex group had AEs that were possibly or probably related to the device, whereas no patient in the Control group reported any AEs that were possibly or probably

| | | | |
|--------------------------------------|-------|----------|----------|
| Number of Subjects Withdrawn for AEs | N (%) | 0 (0.0%) | 0 (0.0%) |
|--------------------------------------|-------|----------|----------|

1 Subjects reporting a particular AE more than once are counted only once for that AE and at the strongest relationship to the device.

2 Subjects reporting a particular AE more than once are counted only once for that AE and at the highest severity level.

*p-value is for Oxiplex/SP Gel vs. Control and is from the Fisher's Exact test.

Note: A treatment emergent AE is defined as an AE that started post randomization, or an AE that started pre-randomization and increased in severity post randomization.

Serious Adverse Events (SAEs)

A total of 27 subjects (7.7%) were reported to have experienced an SAE, 13 SAEs (7.3%) were in the Oxiplex group and 14 (8%) in the Control group. No SAE was categorized as definitely or probably related to the device.

Table 17. Overall Incidence (%) of Serious Treatment Emergent Adverse Events by MeDRA

| | Oxiplex N (%) | Control N (%) |
|---|--------------------------|--------------------------|
| Subjects Randomized | N=177 | N=175 |
| Subjects With An SAE | N=13 | N=14 |
| Cardiac disorders | 1 (0.6%) | 1 (0.6%) |
| Gastrointestinal disorders | 1 (0.6%) | 1 (0.6%) |
| Hepatobiliary disorders | 1 (0.6%) | 0 (0.0%) |
| Infections and infestations | 5 (2.8%) | 2 (1.1%) |
| Cellulitis | 1 (0.6%) | 0 (0.0%) |
| Pneumonia | 1 (0.6%) | 0 (0.0%) |
| Wound infection | 3 (1.7%) | 2 (1.1%) |
| Injury, poisoning and procedural complications | 1 (0.6%) | 4 (2.3%) |
| Cerebrospinal fluid leakage | 0 (0.0%) | 1 (0.6%) |
| Dural tear | 0 (0.0%) | 1 (0.6%) |
| Hip fracture | 0 (0.0%) | 1 (0.6%) |
| Incision site complication | 1 (0.6%) | 0 (0.0%) |
| Nerve injury | 0 (0.0%) | 1 (0.6%) |
| Musculoskeletal and connective tissue disorders | 1 (0.6%) | 5 (2.9%) |
| Nervous system disorders | 2 (1.1%) | 1 (0.6%) |
| Headache | 1 (0.6%) | 0 (0.0%) |
| Migraine | 1 (0.6%) | 0 (0.0%) |
| Syncope | 0 (0.0%) | 1 (0.6%) |
| Psychiatric disorders | 0 (0.0%) | 1 (0.6%) |
| Respiratory, thoracic and mediastinal disorders | 2 (1.1%) | 0 (0.0%) |
| Asthma | 1 (0.6%) | 0 (0.0%) |
| Pulmonary embolism | 1 (0.6%) | 0 (0.0%) |
| Surgical and medical procedures | 1 (0.6%) | 1 (0.6%) |
| Cholecystectomy | 1 (0.6%) | 0 (0.0%) |
| Spinal fusion surgery | 0 (0.0%) | 1 (0.6%) |
| Vascular disorders | 1 (0.6%) | 0 (0.0%) |
| Deep vein thrombosis | 1 (0.6%) | 0 (0.0%) |

Note: Subjects reporting a particular adverse event more than once are counted only one for that adverse event.

Note: A treatment emergent adverse event is defined as an adverse event that started post randomization, or an adverse event that started before randomization and increased in severity post randomization. Subjects reporting a

particular adverse event more than once are counted only once for that adverse event.

Re-operations

Seven (7) subjects required a re-operation at or before the 3 month time point. Control subjects experienced higher rates of re-operations when compared to the investigational subjects (3.4% vs. 0.6%, respectively). Six (6) re-operations occurred at the same lumbar level as the initial surgery, and 1 Control subject had a re-operation at a different spinal level than the original surgery (L3-L4 vs. L4-L5).

Table 18. Subjects with a Reoperation

| Patient Number | Treatment Group | Date of 1 st Surg. | Date of Reop | Reason | Study Days | Leg Pain | Back Pain |
|----------------|-----------------|-------------------------------|--|------------------------------------|------------|----------|-----------|
| ----- | Control | 5/7/03 | 7/24/03 (78 days after initial surgery) | L4-L5 Reherniated Nucleus Pulposus | -1 | 60 | 70 |
| | | | | | 26 | 67 | 27 |
| | | | | | 82 | 80 | 80 |
| | | | | | 181 | 83 | 37 |
| ----- | Control | 8/27/04 | 11/29/04 (94 days) | L5-S1 Disc Reherniation | -1 | 60 | 17 |
| | | | | | 26 | 53 | 37 |
| | | | | | 84 | 63 | 63 |
| | | | | | 171 | 0 | 0 |
| ----- | Control | 8/4/04 | 9/2/04 (29 days) | Herniation at L4 (L3-L4 vs. L4-L5) | -6 | 80 | 83 |
| | | | | | 35 | 53 | 53 |
| | | | | | 98 | 67 | 47 |
| | | | | | 197 | 63 | 50 |
| ----- | Control | | | | -6 | 73 | 77 |

| | | | | | | |
|---------|----------|-------------------------|--|-----|----|----|
| Control | 2/18/04 | 2/20/04 (2 days) | L4-L5 Recurrent Disc Compression | 28 | 0 | 13 |
| | | | | 88 | 17 | 0 |
| | | | | 169 | 0 | 10 |
| | | | | -3 | 80 | 80 |
| Control | 10/25/04 | 2/2/05 (100 days) | L4-L5 Recurrent Disc Herniation | 94 | 73 | 87 |
| | | | | 414 | 63 | 73 |
| | | | | -2 | 73 | 73 |
| Oxiplex | 6/20/03 | 8/20/03 (61 days) | L5-S1 Recurrent Herniated Nucleus Pulposus | 25 | 47 | 37 |
| | | | | 80 | 20 | 17 |
| | | | | 171 | 0 | 33 |
| | | | | -8 | 43 | 47 |
| Oxiplex | 5/28/04 | 6/27/04 (30 days) | L4-L5 Recurrent Disc Herniation | 27 | 47 | 47 |
| | | | | 87 | 10 | 27 |

Table 19. Percentage of Subjects with a Reoperation

| | P-value* | Oxiplex N (%) | Control N (%) |
|---------------------------|----------|------------------|------------------|
| Subjects Randomized | | 177 | 175 |
| Re-operation by 3-month | 0.0665 | 1 (0.6%) | 6 (3.4%) |
| Re-operation by 6-month** | 0.0665 | 1 (0.6%) | 6 (3.4%) |

*P-value is for Oxiplex vs. Control and is from the Fisher's Exact test

**All re-operations occurred by 3 months following the primary surgery.

Other Secondary Variables

The Oxiplex and Control groups were comparable with respect to the following variables: hematology, chemistry, urinalysis, abnormal physical examination at 1-month follow-up, abnormal physical examination at 6-month follow-up and postoperative neurology examination. There appeared to be a balance in concomitant therapies received by the Oxiplex and the Control groups.

The Panel will be asked to provide their perspective on the clinical implications, of the treatment-related adverse events in the Oxiplex group as compared to the control group.

Effectiveness Results

Primary Endpoint

At FDA's request the sponsor conduct a univariate analysis that showed there was no statistically significant difference in the composite leg pain score reduction from baseline to 6 months between the two groups (p=0.59). The simple mean of leg pain between the two

groups at 6 months was 1.4 on a whole 100 scale of LSOQ score ((see Table 20 below), which could occur by chance alone. There was no statistically significant difference between the two groups and a clinically meaningful difference, as was stated in the sponsor's response, *e.g.*, a reduction of 15 points.

Table 20. Unadjusted Analyses on Leg Pain Improvement for Complete Cases at 1, 3, and 6 months for Modified CC

| Visit | Oxiplex Mean Composite Leg Pain Intensity±Std (N ¹) | Control Mean Composite Leg Pain Intensity±Std (N ¹) | Oxiplex Leg Pain Improvement from Baseline Mean±Std (N) | Control Leg Pain Improvement from Baseline Mean±Std (N) | Oxiplex Improvement – Control Improvement = Treatment Effect (95% CI) | Unadjusted P-values for Treatment Effect (T-test ²) | Unadjusted P-values for Treatment Effect (Wilcoxon Rank Sum Test ³) |
|----------------------|---|---|---|---|---|---|---|
| Baseline | 67.5±15.2 (177) | 67.7±14.1 (174) | N.A. | N.A. | N.A. | 0.90 ² | 0.96 ⁴ |
| Month 1 | 18.8±19.8 (165) | 18.5±20.8 (160) | 48.8±23.3 (165) | 48.9±23.9 (160) | -0.10 (-5.3, 5.1) | 0.97 | 0.97 |
| Month 3 | 15.7±19.0 (168) | 15.5±20.3 (162) | 51.8±22.9 (168) | 51.4±24.9 (162) | 0.44 (-4.7, 5.6) | 0.87 | 0.97 |
| Month 6 ⁵ | 15.8±20.1 (171) | 17.0±22.0 (168) | 52.0±23.7 (171) | 50.5±25.3 (168) | 1.42 (-3.8, 6.7) | 0.59 | 0.73 |

1. Number of non-missing values.
2. T-test assumes leg pain improvement is normally distributed.
3. Wilcoxon Rank Sum test does not assume leg pain improvement is normally distributed.
4. These are the p-values for baseline leg pain scores comparisons.
5. The population at Month 6 (171 Oxiplex and 168 Controls) corresponds to the “Modified Complete Cases” population in which all subjects with 6-month visit were included, even if the visits were outside the normal visit window.

The sponsor’s original primary effectiveness endpoint analyses on the ITT population screened at least 48 different covariates and their interactions with the treatment variable. (Original, Appendix D in Statistical Analysis Report (SAR)) This is analogous to conducting subgroup analyses in at least 48 different ways.

The sponsor found a subgroup of patients (with baseline back pain score ≥ 63 , 78 subjects for each of the two groups) that had nominally significant treatment effect for the composite leg pain reduction ($p=0.0123$, see Table 21 below). However, since at least 96 different subgroups were potentially analyzed (assuming 2 subgroups for each treatment-by-covariate interaction), FDA states that the probability of finding a significant treatment effect (the case of $p < 0.05$) in at least one subgroup was 99.3% (assuming independence of the 96 different subgroups).

The following is the table for the subgroup analysis for the composite leg pain.

Table 21. The subgroup analysis of Improvement in Leg Pain from Baseline at 6 Months by Treatment and Baseline Back Pain (CC) (Table 6.28 from Original SAR)

| | Leg Pain Improvement at 6 Months Mean (SD) |
|--|--|
| | |

| Treatment Group | For subjects with Baseline Back Pain Score < 63 | For subjects with Baseline Back Pain Score ≥ 63 |
|-----------------|---|---|
| Control | 48.27 (20.05) (N=63) | 52.47 (26.78) (N=78) |
| Oxiplex | 42.69 (22.77) (N=67) | 62.05 (19.91) (N=78) |
| P-value* | 0.1412 | 0.0123 |

*Two-sided t-test with adjustment for unequal variance as necessary, not adjusted for multiple comparisons.

Secondary Endpoints

The sponsor analyzed several secondary effectiveness endpoints in the Complete Cases (CC) population, which included 167 Oxiplex subjects and 167 Control subjects. FDA conducted a similar analysis on the “Modified Complete Cases” population (171 Oxiplex subjects, 168 Controls), that included all subjects who completed 6 month visits, including out-of-window visits. (See Table 22 below for these individual outcome measures). The results are similar to those obtained from the CC population.

Table 22. Mean Differences in Improvement between Control and Oxiplex Groups at 6 Months and Confidence Intervals for Effectiveness Measures (All Subjects Who Completed 6-Month Visit Including Out-of-window Visits¹)

| Measures | Difference of(Oxiplex - Control) | Control (N) | Oxiplex (N) | (95% Confidence interval) ² | Statistical significance |
|----------------------------------|----------------------------------|-------------|-------------|--|--------------------------|
| Leg Pain | 1.42 | 168 | 171 | (-3.81, 6.66) | ---- |
| Back Pain | 2.45 | 168 | 171 | (-3.19, 8.10) | ---- |
| Leg Weakness | 0.11 | 168 | 171 | (-0.08, 0.31) | ---- |
| Physical Symptoms | 3.88 | 168 | 171 | (-1.20, 8.95) | ---- |
| Patient Satisfaction | 0.11 | 168 | 171 | (-0.19, 0.41) | ---- |
| Disability Days | 1.62 | 168 | 171 | (-0.28, 3.52) | --- |
| Activities of Daily Living Index | 0.98 | 156 | 160 | (-0.68, 2.64) | --- |

1. This analysis was conducted by FDA, which showed slightly different results from the sponsor’s analysis.
2. Positive numbers indicate advantage of Oxiplex group.

In these unadjusted analyses, none of the secondary endpoints achieved statistical significance (all $p > 0.05$) and all their 95% confidence intervals included 0, indicating no statistically significant differences in means between the two groups.

The sponsor’s multivariate analyses on the secondary effectiveness endpoints screened at least 48 different covariates and their interactions with the treatment variable; this is analogous to post-hoc subgroup analyses. Since it is difficult to adjust for multiplicities in post-hoc subgroup analyses, FDA will ask the Panel questions regarding the appropriateness and interpretation of any results from such analyses.

During the panel meeting, FDA will ask the Panel for their interpretation of the effectiveness results from the sponsor’s pivotal study. The sponsor stated in the Statistical Analysis Plan that the treatment will be considered statistically significant if the treatment main effect or the treatment by time interaction is statistically significant with a 2-sided alpha of 0.044. In the PMA submission, the sponsor bases statistical significance of the primary endpoint and several

improvement.

Table 24. Results of the GEE Analysis of Improvement in Leg Pain from Baseline over Time with Pseudo-Site by Treatment Interaction (Modified CC)

| Source | Degrees of Freedom | Chi-Square | Pr > Chi Square |
|--------------------------------|--------------------|------------|-----------------|
| Model 1 | | | |
| Treatment | 1 | 0.09 | 0.7653 |
| Visit | 2 | 8.77 | 0.0125 |
| Study Site* | 18 | 36.11 | 0.0068 |
| Treatment by Site* Interaction | 18 | 30.35 | 0.0342 |
| Baseline Leg Pain LSOQ Score | 1 | 92.03 | <0.000 1 |

*Using Pseudo-Sites

During the panel meeting, FDA will ask the Panel to comment on site variability, and whether pooling data from different sites can be justified.

Labeling

Note to Panelists: The inclusion of a section on labeling in this memo should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device.

The proposed Instructions for Use and Physician Instructions are included in the panel pack for your review. Both of these include the following: 1) Description; 2) Intended Use; 3) Contraindications; 4) Precautions; 5) Storage and Handling, Instructions for Use; 6) Contents of the device; and 7) Summary of the clinical study and its results.

The sponsor did not provide patient labeling because they consider the device an adjunct to surgical treatment and believe the patient is not involved in the choice of using the Oxiplex/SP gel.

During the panel meeting, FDA will ask the Panel to discuss the need for patient labeling and the adequacy of the Physician labeling/Instructions for Use.

Post Market Study

Note to Panelists: FDA's inclusion of a section/discussion on a Post Approval study in this memo should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device. The presence of a post-approval study plan or commitment does not in any way alter the requirements for premarket approval and a recommendation from the Panel on whether to approve a device or not must be based on the premarket data. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study could be considered. The issues noted below are FDA's comments regarding a potential post-approval study should the panel find the device approvable following its discussions and deliberations of the premarket data.

The sponsor did not provide a post-approval study plan in the original PMA but has submitted a Post Approval Study (PAS) outline. The following is the outlined proposal provided as a basis for a future PAS.

Study Objective

As of May 2, 2008, the sponsor proposes to conduct a prospective, multi-center, observational study to assess whether Oxiplex®/SP Gel reduces the number of disability days at 6-month post surgery and to evaluate the device safety in subjects undergoing first-time lumbar spine surgery. The objective is to “confirm the safety and reduction in disability days in subjects who receive Oxiplex during lumbar disc surgery” in the real-world settings.

Study Design and Sample Size

The sponsor proposes a non-inferiority design to compare the number of disability days at 6 months post surgery in subjects who were treated with Oxiplex with the Oxiplex-treated subjects in the pivotal study. The sponsor calculated that [redacted] completed cases at [redacted] referred to as the “Historical control group” by the sponsor). [redacted] sponsor calculated that [redacted] post-approval subjects are needed to complete the study at 6 months post surgery with a [redacted]

of non-inferiority with [redacted] power. The sponsor proposes [redacted] ll up to [redacted] subjects at up to [redacted] clinical sites in consideration of a potential dropout rate of [redacted]

Endpoints

The proposed effectiveness endpoint is the [redacted]

[redacted]

The proposed [redacted] points include the following and will be evaluated with descriptive [redacted]

- [redacted]
- [redacted]
- [redacted]

Please refer to the Oxiplex/SP Gel Post Approval Study Summary included in the panel pack for additional details regarding the study design.

The sponsor is working interactively with the FDA on the development of the hypothesis and the justification for the study sample size for the post-approval study. The full PAS protocol has not yet been developed.

During the panel meeting, FDA will ask the Panel a series of questions about a possible Post-Approval Study. Our discussion of a PAS plan does not in any way alter the requirements for premarket approval. Please remember that recommendations from the Panel on whether or not to approve a device must be based on the premarket data.

The panel may be asked to consider the following topics applicable to Post-Approval Study Issues including but not limited to:

- *The study design*
- *The appropriateness of the proposed effectiveness end-----*
- *The adequacy of following the PAS patient cohort for [redacted]*