REDACTED 061808

July 15, 2008

FzioMed, Inc

Premarket Approval Application P070023

"Randomized, Third-Party Blinded, Multicenter, Clinical Trial to Determine the Safety and Effectiveness of Oxiplex®/SP Gel for the Reduction of Pain and Symptoms Following Lumbar Disc Surgery"

Orthopaedic and Rehabilitation Devices Advisory Panel

SPONSOR'S PANEL PACK
EXECUTIVE SUMMARY

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1. Synopsis

This Sponsor's Executive Summary describes the results of FzioMed Inc.'s pivotal clinical study entitled, "Randomized, Third-Party Blinded, Multicenter, Clinical Trial to Determine the Safety and Effectiveness of Oxiplex/SP Gel for the Reduction of Pain and Symptoms Following Lumbar Disc Surgery." The study was conducted entirely in the United States and no foreign data were used.

Oxiplex/SP Gel ("Oxiplex") is an absorbable, clear, viscoelastic gel that is applied during lumbar spine surgery, immediately prior to closure. It is composed of synthetic materials and does not contain any animal or bacterial by-products. Oxiplex is easily placed around exposed tissues (e.g., nerve root and dura) and remains at the site of application for a period of time, providing a protective environment and physical separation of tissues during the healing process. Oxiplex clears from the body and is not metabolized; it does not require a second operation for removal.

The condition that Oxiplex is intended to address (residual pain and symptoms following lumbar surgery), which represents a debilitating condition that is not adequately treated by an existing therapy. Because no legally marketed alternative device is currently available to meet this unmet medical need, the FDA granted expedited review of this PMA for Oxiplex.

The biocompatibility of Oxiplex has been established through ISO10993 testing. Preclinical animal studies have demonstrated that Oxiplex is non-inflammatory and does not inhibit normal healing of bone and dura.

Oxiplex was first marketed outside the U.S. in 2002 and is now approved in 49 countries, including the European Union, Canada and Australia. Worldwide surveillance of over 100,000 units that have been commercially distributed by Medtronic and DePuy Spine has resulted in no reports of adverse events attributable to the device.

This study was a superiority study. All subjects underwent lumbar disc surgery at the L4/L5-L5/S1 level. Subjects were randomized to one of two treatment groups:

1. The Oxiplex group received surgery plus Oxiplex
2. The Control group received surgery only

Randomization (1:1) occurred intraoperatively, immediately prior to wound closure.

Each subject enrolled in the study was followed for 6 months after surgery to evaluate device safety and effectiveness (see Appendix A). The Lumbar Spine Outcomes Questionnaire (LSOQ), developed at Johns Hopkins University School of Medicine, was used as the validated quality of life instrument (see Appendix B).

There were 352 subjects (referred to as the "Intent-to-Treat," or ITT population) enrolled at 29 investigational sites (see Table 1.1) between October 2002 and October 2006. The number of subjects who completed the 6-month LSOQ was 334 (referred to as "Completed Cases," or CC).

Johns Hopkins University (the independent contractor that performed postoperative LSOQ interviews), the subjects, and the Clinical Evaluators (the medically trained professionals who completed the postoperative clinical evaluations) were not informed of study group assignments. These parties remained blinded throughout the study.

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Pain in spine surgery patients is complex, with multifactorial conditions that cannot be adequately characterized by univariate methods or simple models. Therefore, the Sponsor performed a multivariate analysis that was pre-specified and approved by the FDA to assess effectiveness. The interpretation of statistically significant interactions with covariates is important to provide an accurate assessment of the effect of the treatment as modified by baseline covariates. FDA required that all clinically relevant variables be investigated.

Primary and secondary objectives of this Pivotal Study were:

Primary Objectives	1. To evaluate the safety of using Oxiplex in lumbar disc surgery. 2. To evaluate the efficacy of Oxiplex in the reduction of postoperative pain and symptoms beyond that achieved by surgery alone.
Secondary Objective	To evaluate pain, symptoms, disability, patient satisfaction, and quality of life measures relevant to the postsurgical condition of subjects undergoing lumbar surgery.

Primary and secondary safety variables were:

Primary Safety Variable	The occurrence of adverse events, including surgical complications, categorized using the MedDRA coding system (Version 7.1).
Secondary Safety Variables	1. To evaluate the changes in laboratory results, physical and neurological examinations and vital signs throughout the study. 2. To evaluate reoperations at the lumbar level. 3. To evaluate the use of concomitant therapies.

Primary and secondary effectiveness variables were:

Primary Effectiveness Variable	Improvement in Leg Pain from baseline to follow-up visits (1, 3 and 6 months), as measured by the LSOQ.
Secondary Effectiveness Variables	Improvement from baseline as measured by the LSOQ in: 1. Back pain 2. Leg weakness 3. Physical symptoms 4. Patient satisfaction (the LSOQ measure of clinical effectiveness) 5. Disability days 6. Activities of daily living.

1.1. Summary of Safety Results

The primary and secondary safety variables were:

Primary Safety Variable	The occurrence of adverse events, including surgical complications, categorized using the MedDRA coding system (Version 7.1).
Secondary Safety Variables	1. To evaluate the changes in laboratory results, physical and neurological examinations and vital signs throughout the study. 2. To evaluate reoperations at the lumbar level. 3. To evaluate the use of concomitant therapies.

- Safety was assessed in all randomized subjects who were enrolled in this study (ITT population, N=352). Oxiplex was safe and did not expose patients undergoing lumbar surgery to additional risk.
- One (1) reoperation occurred in the Oxiplex group, while six (6) reoperations occurred in the Control group (P=0.0665). Five of the six subjects in the Control group who underwent reoperations had severe back pain at baseline. No Oxiplex subjects who had severe back pain at baseline had a reoperation.
- There were no significant differences in the number of subjects having adverse events (AEs) or serious adverse events (SAEs) between the Oxiplex and Control groups.
- There were no AEs leading to discontinuation of the Pivotal Study or discontinuation of any subject from the Pivotal Study.
- There were no significant differences between the Oxiplex group and the Control group with respect to laboratory values (hematology, chemistry and urinalysis) and vital signs.
- Physical examinations at 1-month follow-up and at 6-month follow-up revealed clinical differences in favor of Oxiplex.
- Postoperative neurological examinations revealed that muscle spasms, pain in extremities and hypoaesthesia were reported less frequently in the Oxiplex subjects.
- There was comparability between concomitant therapies received by the Oxiplex group and the Control group.

The results of this Pivotal Study provided reasonable assurance that Oxiplex is safe for its intended use.

1.2. Summary of Effectiveness Results

1.2.1. Effectiveness Overview

The primary and secondary effectiveness variables were:

Primary Effectiveness Variable	Improvement in Leg Pain from baseline to follow-up visits (1, 3 and 6 months), as measured by the LSOQ.
Secondary Effectiveness Variables	Improvement from baseline as measured by the LSOQ in: 1.Back pain 2.Leg weakness 3.Physical symptoms 4.Patient satisfaction (the LSOQ measure of clinical effectiveness) 5.Disability days 6.Activities of daily living.

- All subjects were treated surgically and generally showed substantial improvement following surgery.
- Pain in spine surgery patients is complex with multifactorial conditions that can not be adequately characterized by univariate methods or simple models. Therefore, multivariate analysis was approved to assess effectiveness.
- A tabulation of unadjusted means showed an improvement in leg pain that favored Oxiplex but was not amenable to statistical testing by univariate methods. Multivariate analysis allowed for multiple clinical conditions to be included in tests of statistical significance.
- Across all 7 primary and secondary effectiveness measures, Oxiplex subjects had greater mean differences in improvement than Control subjects, demonstrating consistent clinical benefit from the use of Oxiplex.
- The most prominent gains in improvement for Oxiplex subjects were demonstrated at the 6-month follow-up visit in patients who enrolled with severe back pain before surgery (LSOQ score ≥63 at baseline).
- The improvements afforded by Oxiplex (at 6 months in subjects with severe baseline back pain) were statistically significant in both primary and secondary effectiveness variables (leg and back pain), in ITT and CC populations, as confirmed by regression and sensitivity analyses.
- The study yielded 7 sets of clinical and statistical evidence demonstrating that Oxiplex subjects had significant improvements in outcomes compared to surgery-only Control subjects:
    1. Reduced leg pain
    2. Reduced back pain
    3. Enhanced patient satisfaction

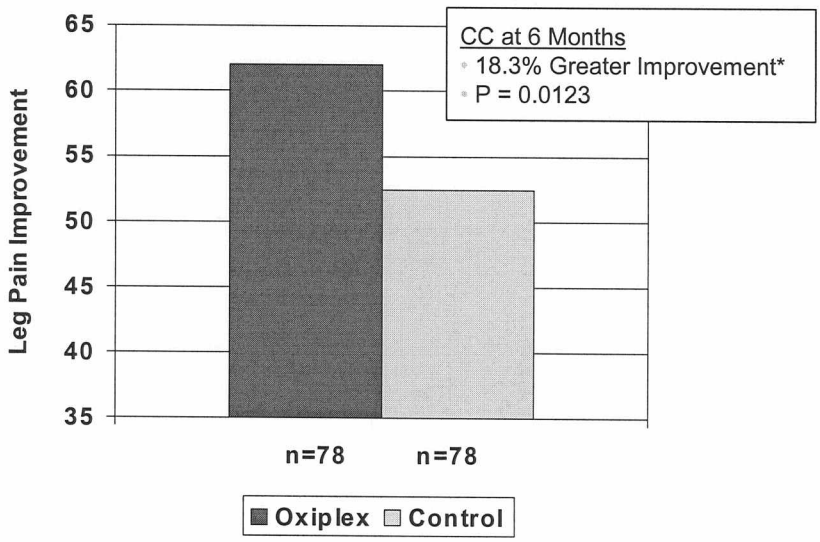
4. Fewer neurological abnormalities (pain in extremity and hypoaesthesia)
5. Fewer musculoskeletal abnormalities
6. Fewer disability days
7. Fewer reoperations

1.2.2. Effectiveness Results

- **Leg Pain:**

  Oxiplex subjects with severe back pain in the CC population experienced 18.3% greater improvement in leg pain at 6 months relative to Control subjects (P=0.0123). The most prominent gain in improvement in the ITT population was also at the 6-month visit (13.6%, P=0.0507).

Figure 1.1. Improvement in Leg Pain from Baseline at 6 Months in Subjects with Severe Baseline Back Pain (≥63) (CC)

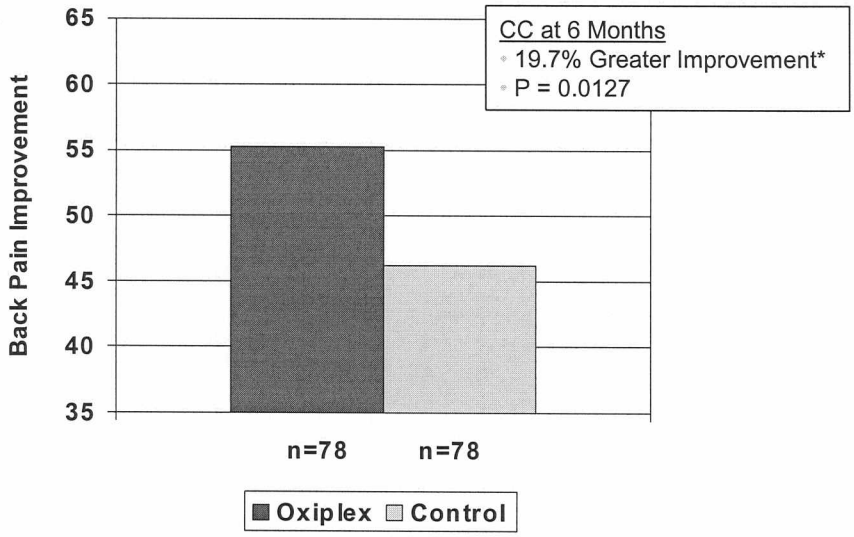


*Simple mean difference between treatment groups.

- **Back Pain:**

  Oxiplex subjects with severe back pain in the CC population experienced 19.7% greater improvement in back pain at 6 months relative to Control subjects (P=0.0127). The most prominent gain in improvement in the ITT population was also at the 6-month visit (17.1%, P=0.0193).

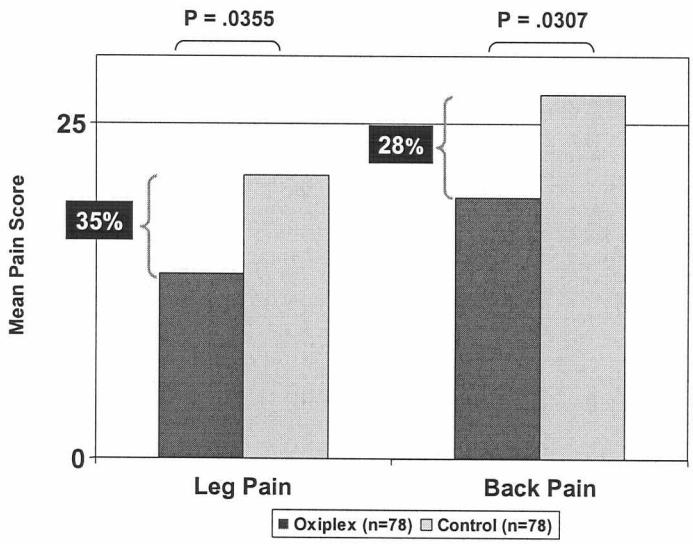
Figure 1.2. Improvement in Back Pain from Baseline at 6 Months in Subjects with Severe Baseline Back Pain (≥63) (CC)



*Simple mean difference between treatment groups.

As shown in Figure 1.3, these findings represent clinically significant additional measurable reductions in leg pain and back pain provided by Oxiplex in a challenging group of patients (those with severe baseline back pain) versus surgery alone.

Figure 1.3 Additional Reduction* in Leg and Back Pain at 6 Months in Subjects with Severe Baseline Back Pain (≥63) (CC)

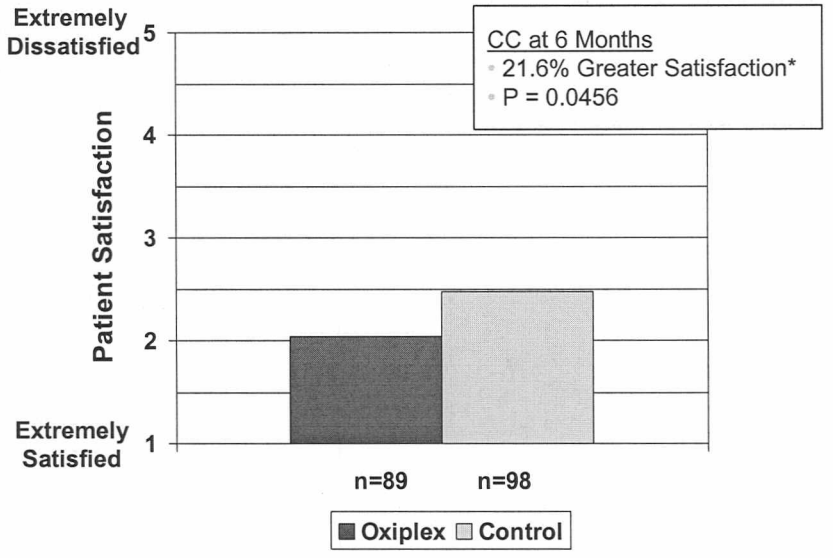


*Simple mean difference between treatment groups

- **Patient Satisfaction:**

  Patient satisfaction is the LSOQ measure of clinical significance. Oxiplex subjects having severe back pain at baseline experienced 21.6% relative greater satisfaction at 6 months compared to Control subjects (P=0.0456).

Figure 1.4. Satisfaction at 6 Months by Treatment in Subjects with Severe Baseline Back Pain (≥63) (CC)



*Simple mean difference between treatment groups.

- **Reoperations (ITT):**

  There were fewer reoperations in Oxiplex subjects (n=1, 0.6%) compared to Control subjects (n=6, 3.4%), a clinically significant improvement in patients with severe back pain at baseline.

- **Postoperative Neurological Abnormalities (ITT):**

  Clinically significant improvements for Oxiplex subjects were also observed regarding postoperative neurological abnormalities. Oxiplex subjects had fewer findings of pain in extremity compared to Control subjects, especially at the 6-month study endpoint (Oxiplex group, n=26, 15%; Control group, n=38, 22%). Oxiplex subjects also had fewer findings of hypoaesthesia compared to Control subjects, especially at the 6-month study endpoint (Oxiplex group, n=18, 10%; Control group, n=26; 15%).

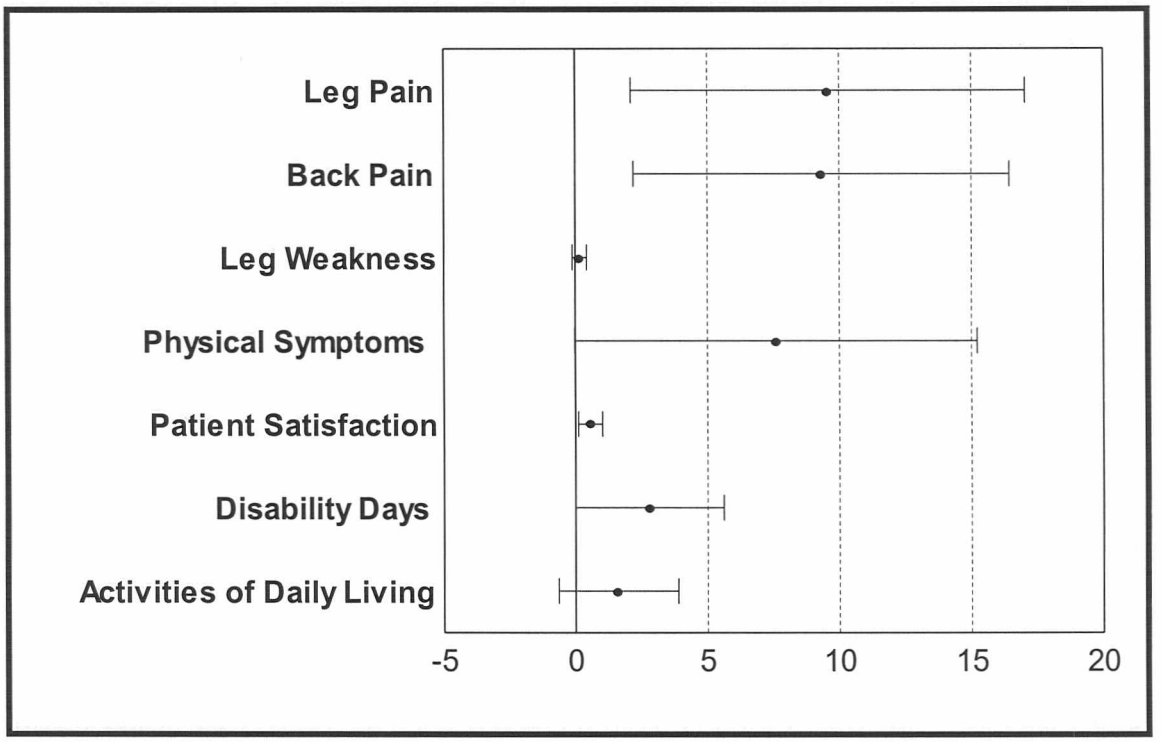
- **Disability Days:**

  Disability days are defined as days when the subjects are completely disabled by their lower back conditions. Oxiplex subjects had fewer disability days than Control subjects (P=0.0497) at study end.

- **All Variables:**

  Across all effectiveness measures, the mean improvement was higher for Oxiplex subjects than for Control subjects demonstrating that Oxiplex was consistently effective at reducing pain and symptoms (P=0.049). This is shown in Figure 1.5.

Figure 1.5. Mean Differences in Improvement between Oxiplex and Control Groups at 6 Months and Confidence Intervals for Effectiveness Measures for Subjects with Severe Baseline Back Pain (≥63) (CC)



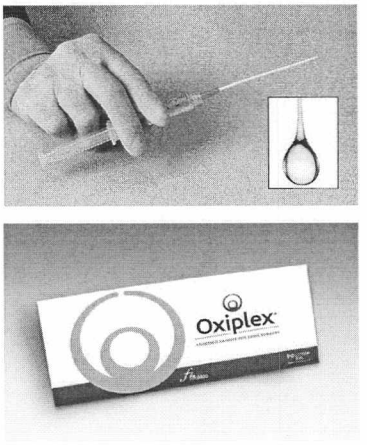
The lower confidence limit excludes zero for leg pain, back pain and satisfaction for completed cases at 6 months with severe baseline back pain. Therefore, the mean improvements in those measures in the Oxiplex group were statistically significant.

The results of this Pivotal Study provided reasonable assurance that Oxiplex is effective for its intended use.

2. Product Description

Oxiplex is an absorbable, clear, viscoelastic gel that is comprised of sodium carboxymethylcellulose (CMC) and polyethylene oxide (PEO) in sterile water for injection. Calcium chloride ($CaCl_2$) is added for stability and sodium chloride (NaCl) is added for isotonicity. Oxiplex is non-pyrogenic and contains no animal or bacterial components. No color additives are used in the device.

Oxiplex is provided sterile in a 3 mL syringe, together with a sterile, flexible applicator for application during surgery. These components are packaged together in a thermoform tray, sealed with a Tyvek® lid, and terminally sterilized by steam. Oxiplex is for single use only.



Oxiplex Intraoperative Gel for Spine

Oxiplex is applied during lumbar spine surgery. Following the primary surgical procedure, after hemostasis is achieved and immediately prior to wound closure, Oxiplex is applied to the operative site surrounding the dura and the nerve root and coating the neural tissue. Oxiplex is easily placed around exposed tissues (e.g., nerve root and dura) to fill the surgical site to the ventral surface of the vertebral lamina and coat the neural tissues. After application, the surgical procedure is concluded according to the surgeon's standard technique. The device remains at the site of application for a period of time, providing a protective environment and physical separation of tissues during the healing process. Oxiplex is cleared by the body (excreted, not metabolized) and does not require a second operation for removal.

As shown in this Pivotal Study, Oxiplex is intended to coat and protect neural tissues and thereby significantly reduce nerve root-related postoperative pain and related symptoms following lumbar disc surgery.

Preclinical studies have demonstrated that Oxiplex is biocompatible, non-inflammatory, and does not inhibit normal healing of neural tissues, dura or bone.

The device was CE marked in the European Union in 2001 and was first marketed outside the U.S. in 2002. Oxiplex is now approved in 49 countries, including Canada and Australia. Over 100,000 units have been commercially distributed to date. A number of independent studies have been conducted and presented/published at international medical congresses (Agarwal, Spine Week 2008; Agarwal, ISSLS 2007; Assietti, CNS 2006; De Meeus, BSNS 2004; Fransen, ASIR 2008; Fransen AANS 2007; Fransen, EANS 2006; Guizzardi, CNS 2006; Simons, CNS 2004; Zuki, MOA 2006).

3. Clinical Presentation and Unmet Clinical Need

3.1 Spine Surgery Success and Failure

Studies have shown that lumbar spine surgery is generally a successful procedure, with a majority of patients having significant improvement (reduction in pain) and satisfaction with the outcome. Success rates ranging from 60% to 80% have been reported (Abramovitz et al, 1991; Asch et al, 2002; Atlas et al, 1996; Chatterjee et al, 1995; Findlay et al, 1998; Gatchel et al, 2004; Hutchinson et al, 2000; Klekamp et al, 1998; Mannion and Elfering, 2006; NASS 2006; Weinstein et al, 2006). Nonetheless, this leaves a substantial number of patients (up to 40%) who experience residual or recurrent pain and symptoms following surgery with reoperation rates ranging from 5% to 20% (Abramovitz et al, 1991; Follett et al, 1993; Fritsch et al, 1996; North et al, 1991; Gatchel et al, 2004; Malter et al, 1998). 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 an over-burdened healthcare system and loss of productivity.

3.2 Complexity of Pain and Symptoms After Lumbar Surgery

The nature of back pain and leg pain in spine surgery patients is complex. Pain and symptoms are both multifactorial because there are numerous possible etiologies (e.g., incomplete decompression, irritation of the cauda equina, spinal stenosis, recurrent herniation, nerve entrapment, inflammation and instability) and multidimensional because such patients may present with some combination of issues. Further confounding each case are the numerous clinical factors that contribute to outcome, including demographics, location and severity of pain, prior therapies, psychological condition and surgical history (Follett et al, 1993; Gatchel et al, 2004; Slipman et al 2002; Weinstein et al, 2006).

The literature identifies two categories of pain mechanisms at the tissue level: mechanical deformation of the nerve roots (physical compression), and biologic or biochemical irritation of nerve roots (Burke et al, 2002; Olmarker et al, 2004; Manchikanti et al, 2000 and 2001; McCarron et al, 1987).

It is widely recognized that there is a cascade of biochemical events that contribute to the pain experience. These are the result of a variety of irritants that come in contact with the nerve root during and after disc surgery that can sensitize neural tissue to postoperative pain and neurological symptoms (Aoki et al, 2002; Burke, 2001; Manchikanti et al, 2001, McCarron et al, 1987; NASS, 2006; Olmarker et al, 2004).

For example, surgical dissection and retraction cause nerve root trauma and cellular injury, neural tissues are exposed to blood and disc material (nucleus pulposus) and the epidural space fills with fibrin, cytokines and pro-inflammatory mediators. These lead to significant nerve root irritation, inflammation and the potential for adhesion formation each of which, in turn, can trigger additional inflammation, trauma, compression or tethering. In addition to irritants, there is also mechanical deformation of nerve tissue.

In light of these complex clinical issues, the Sponsor designed this Pivotal Study to determine, in a balanced group of lumbar spine surgery candidates, if (1) protecting the nerve root and neural tissues with Oxiplex immediately following surgery provided patients with a greater improvement in postoperative pain and neurological symptoms

compared to patients undergoing surgery only and, if so, (2) identify patient groups who might be afforded the greatest benefit from Oxiplex treatment.

3.3 Proposed Indication for Use

Oxiplex is indicated for use 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.

3.4 Unmet Need

FDA has determined that reduction of postsurgical pain following lumbar disc surgery remains an unmet medical need. Because there are no legally marketed devices available for this indication in the United States, FDA granted expedited review status to the Premarket Approval application (PMA) for Oxiplex.

4. Clinical Study Rationale

Postsurgical pain including the multidimensional aspects of lumbar spine patients, and variety of contributing clinical factors necessitated that the Pivotal Study evaluate the relationship of several different variables on patient outcomes. It was pre-determined that multivariate, longitudinal analysis was most appropriate for this purpose and that the Lumbar Spine Outcomes Questionnaire (LSOQ) was the most relevant instrument.

4.1 Lumbar Spine Outcomes Questionnaire (LSOQ)

The LSOQ is a multi-item, quality of life questionnaire designed to assess complex factors that are considered clinically relevant in evaluating treatment outcomes specific to lumbar pain. The instrument provides for the collection of information that is specific to pain and other disabilities associated with the lumbar spine.

The LSOQ was developed by a multicenter group of neurosurgeons and orthopedic surgeons in response to a request for applications by NIH. Donlin Long, M.D., Chief of Neurosurgery, Johns Hopkins School of Medicine, served as the committee chairman. The LSOQ was validated as part of a multicenter, prospective, longitudinal study of subjects referred to a tertiary care neurological or orthopedic surgeon for evaluation and treatment of persistent lower back (lumbar) pain with and without leg pain (BenDebba et al. 2000, 2007).

The LSOQ yields separate composite scores for leg pain severity, back pain severity, physical symptoms and activities of daily living from subjects' responses at designated time points (baseline, 1, 3, and 6 months). In addition, the LSOQ measures clinical significance (patient satisfaction), disability days and pain medication for lower back condition. The LSOQ may be administered via telephone, by mail or in the clinic setting.

The Sponsor elected to use the LSOQ for assessment of the effectiveness of Oxiplex in this Pivotal Study to measure multiple clinical outcomes after site-specific surgical therapy in patients undergoing laminectomy, laminotomy or treatment of herniated disks, and FDA agreed to allow the use of this validated QOL instrument. Examples of the baseline and postoperative LSOQs are attached in Appendix B. Further discussion of the scoring procedure for the LSOQ and the derivation of composite scores is found in Section 11.3 of this document.

4.2 Multivariate Analysis

Contemporary studies of pain following removal of a herniated disc often use multivariate analysis to take into account the overall clinical condition. Multivariate analysis allows for multiple variables to be evaluated across groups, and for the exploration of interactions and patterns of differences. Attempts to characterize any pain component by univariate methods (i.e., by examining only one independent variable) or simple models would not adequately describe the changes in pain from baseline. The inappropriate use of univariate analyses for such a complex clinical condition resulted in a primary focus on multivariate analyses. Therefore, it was prespecified in the Sponsor's FDA-approved Statistical Report and Analysis Plan that a prospective, multivariate, longitudinal analysis would be used to analyze the data from this study.

5. Pivotal Study Variables

5.1 Primary Safety Variable

The primary safety variables were the occurrence of adverse events (AEs), including surgical complications, categorized using the Medical Dictionary for Regulatory Activities coding system ("MedDRA", Version 7.1)

5.2 Secondary Safety Variables

- Changes in laboratory results, physical and neurological exams and vital signs throughout the study
- Reoperation at the same lumbar level
- Differences in concomitant therapies

5.3 Primary Effectiveness Variable

The primary effectiveness variable in this Pivotal Study was the improvement in leg pain from baseline to follow-up visits (1, 3 and 6 months), as assessed by the LSOQ.

5.4 Secondary Effectiveness Variables

Secondary effectiveness variables were the improvements from baseline (follow-up visit LSOQ score minus baseline LSOQ score) in:

- Back pain
- Leg weakness
- Physical symptoms
- Patient satisfaction (the LSOQ measure of clinical effectiveness)
- Disability days
- Activities of daily living

6. Preclinical Studies

6.1 Chemical and Physical Characterization

Oxiplex components were verified through testing and/or manufacturer's certification to meet USP requirements. Each lot of sodium carboxymethylcellulose (CMC) and polyethylene oxide (PEO) was verified for identity using Fourier Transform Infra Red (FTIR) analysis.

In addition to chemical characterization of the product components, ethylene oxide, aldehyde and endotoxin testing and physical characterization of Oxiplex were conducted, including bioadhesiveness testing (viscometry, coatability).

6.2 Biocompatibility

The Sponsor performed preclinical biocompatibility tests on Oxiplex in accordance with ISO 10993-1, Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing. Table 6.1 summarizes the results.

Table 6.1. Biocompatibility & Toxicity Testing

Test		Standard	Result
Sensitization	Maximization Sensitization	ISO 10993-10:1995	Pass
Irritation	Intracutaneous Reactivity	ISO 10993-10:1995	Pass
Implantation	Muscular Implant Test	ISO 10993-6:1995	Pass
Cytotoxicity	MEM Elution Assay	ISO 10993-5:1993	Pass
Systemic Toxicity	System Injection	ISO 10993-11:1993	Pass
	Subchronic Toxicity	ISO 10993-11:1993	Pass
	Chronic Toxicity	ISO 10993-6:1994	Pass
Genotoxicity	AMES Test	ISO 10993-3:1992	Pass
	Chromosomal Aberration	ISO 10993-3:1992	Pass
Microbiology	Material Mediated Rabbit Pyrogen	USP 23 <151>: 1995	Pass
	Kinetic-Chromogenic Limulus Assay (LAL)	USP <85>current edition	Pass @ ≤0.06 EU/mL (CSF exposure)
	Hemolysis	ISO 10993-4: 2002	Pass

6.3 Preclinical Performance

The Sponsor completed multiple animal studies for the purpose of evaluating the safety, biocompatibility, and performance of Oxiplex. The preclinical studies demonstrated that Oxiplex is safe and effective when used in the laminectomy/laminotomy site and covering the dura. Test animals that received Oxiplex treatment typically had normal histological evaluation of the epidural space including normal bone healing. In contrast, most of the surgery-only controls showed histological abnormalities, including fibrosis and adhesions (Rodgers et al, 2003). Additional studies were performed to evaluate the effect of Oxiplex on dural repair. Dural incisions that were covered with Oxiplex showed normal dural healing by both gross and histological exam.

6.4 Preclinical Studies Conclusion

Preclinical laboratory testing (per applicable standards) has shown that Oxiplex is biocompatible, non-toxic, and performs as expected in preclinical animal models.

6.5 Sterilization and Packaging

Oxiplex is terminally sterilized by steam. The sterilization cycle was validated per ANSI/AAMI/ISO 11134 to meet a minimum sterility assurance level (SAL) of 10^{-6}. Validation of the sterile barrier system for Oxiplex was performed per ISO 11607. Package integrity, seal strength, and shipping tests all passed.

7 Feasibility Study

A feasibility clinical study entitled, "Randomized Single-Blind, Multicenter Pilot Clinical Trial to Determine the Safety of Oxiplex/SP Gel for the Reduction of Postoperative Peridural Fibrosis and Related Symptoms Following Lumbar Disc Surgery," (Feasibility Study) was initiated in January 2001. The primary objective was to evaluate the safety of applying Oxiplex during single-level spinal laminectomy, laminotomy, and discectomy, performed to eliminate or reduce symptoms associated with acute or subacute unilateral herniation of a lumbar intervertebral disc, in subjects undergoing their first surgeries for such conditions.

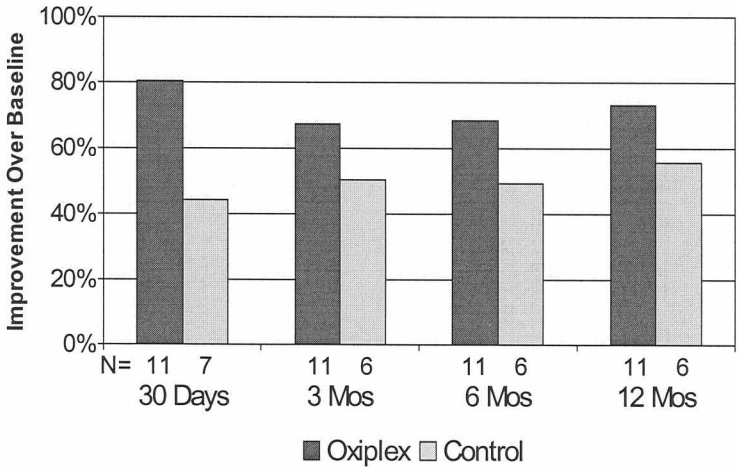
The Feasibility Study was designed as a 3-month safety study with quality-of-life (QOL) assessments at 1, 3, 6 and 12 months using the LSOQ and the Oswestry Disability Index (ODI). Thirty-five (35) subjects were enrolled at four (4) investigational sites; 23 were treated with Oxiplex and 12 received surgery only. The 3-month safety evaluation final report was submitted in March 2002, the QOL assessments were completed in October 2002 and the database was locked in May 2003. A final report was filed with the FDA in November 2003.

The results of the Feasibility Study have been published by Kim et al (2003, 2004) and demonstrated that Oxiplex was safe postoperatively at 3 months. Also, the study confirmed the similarity between the ODI and LSOQ results and showed that the LSOQ scores were similar at 6 and 12 months (see Figure 7.1). When subjects entered the Feasibility Study with severe pain and leg weakness, the subsequent responses to treatment with Oxiplex were greater than in subjects having lower baseline pain (i.e., the greater the disability entering the Feasibility Study, the greater the subject benefit derived from Oxiplex).

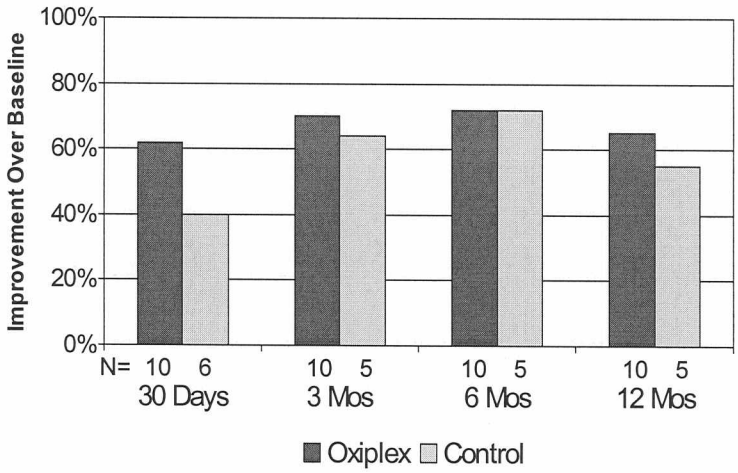
The Feasibility Study was not powered to demonstrate statistical significance in any efficacy measure.

Figure 7.1. Comparison of LSOQ Leg Pain and ODI Scores in Oxiplex Feasibility Study

LSOQ Leg Pain



ODI Global Score



8 Pivotal Study

The FDA approved an IDE supplement to initiate a Pivotal Study using the LSOQ with 6-month endpoints analyzed by multivariate techniques.

8.1 Study Design

- The study was a randomized, third-party blinded, multicenter clinical trial to evaluate the safety and efficacy of Oxiplex used to reduce postoperative pain and related symptoms following surgery for herniated lumbar disc at L4-L5 or L5-S1.
- Subjects underwent presurgical eligibility evaluations, including an examination by a neurosurgeon or orthopedic spine surgeon.
- At the time of surgery, certain unanticipated intraoperative findings or events, as defined in the study protocol, could disqualify a subject from randomization.
- Preoperatively, and at scheduled postoperative intervals at 1, 3 and 6 months following surgery, subjects completed the LSOQ self-assessment questionnaire.
- All subjects received surgery and were randomized in a 1:1 ratio to either receive surgery only (Control group) or to also be treated with Oxiplex (Oxiplex group).
- Randomization occurred when hemostasis had been achieved and the surgeon was ready to close the operative site.
- Subjects, independent contractors and evaluators were blinded to the treatment group assignments.
- All subjects were evaluated for safety at 1 month and 6 months following surgery through clinical assessments, including physical examination, lower extremity neurologic function, wound inspection and laboratory tests.
- All subjects were evaluated for effectiveness at 1 month, 3 months and 6 months following surgery by completing the LSOQ.
- Qualified Clinical Evaluators (CE) performed postoperative examinations. The CEs were medically trained professionals who were blinded to the subjects' study group assignments (not a part of the treatment team and, therefore, not present at the time of intraoperative randomization).
- Independent contractors blinded to the study group assignments contacted subjects to complete the postoperative LSOQs.
- One interim analysis was planned when approximately 75% of the subjects had completed the 6-month LSOQ.

8.1.1 Noteworthy Inclusion Criteria

- Adults 18 to 70 years of age scheduled to undergo first surgical intervention for diagnosed unilateral herniation of lumbar intervertebral disc material associated with radiculopathy
- 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
- 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

8.1.2 Noteworthy Exclusion Criteria

- Previous spinal surgery or chemonucleolysis at the lumbar level
- Treatment with any epidural steroids within four (4) weeks prior to the proposed surgery
- Use of steroids perioperatively and/or intraoperatively
- Presence of scoliosis; (> 10degrees and considered by the investigator to be clinically significant)
- Presence of foramenal stenosis
- Myelogram or lumbar puncture for any reason within 24 hours prior to the proposed surgery
- Subject of a current or anticipated worker's compensation claim for any reason and/or party to a current or anticipated personal injury litigation for any reason
- Special Intraoperative Exclusions
  - Dural entry during surgery
  - Required spinal fusion
  - Multilevel herniation or the need to involve more than one level
  - Exploration of contralateral side
  - Epidural fat placement
  - Surgical determination that a hemostatic agent must remain at the surgery site

8.1.3 [redacted]

[redacted]

8.1.4 [redacted]

[redacted]

[redacted]

- [redacted]

8.1.5 Maintaining the Study Blind

[redacted]

- The study was third-party blinded, in which all subjects and evaluators of data were not informed of the randomization assignment during the course of the study.
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

8.1.6 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.1.7 Study Duration

The duration of the study was approximately five years. The first subject was enrolled in October 2002. The final subject was enrolled in October 2006 and completed the 6-month follow-up visit in March 2007.

8.1.8 Subject Population

8.1.8.1 Demographics and Baseline Characteristics

The results of the analysis of demographic variables are summarized in Table 8.1. There were no statistically significant differences between the Oxiplex and Control groups in demographic characteristics at baseline. The groups were well balanced.

Table 8.1. Demographic Variables

Characteristic	Oxiplex	Control	P-value*
Continuous Covariate:	**Mean (SD) N**	**Mean (SD) N**	
Age (yrs)	41.81 (10.53) 177	41.71 (10.66) 175	0.9278
Height (m)	1.73 (0.10) 177	1.72 (0.10) 175	0.6286
Weight (kg)	85.30 (19.10) 177	83.13 (20.43) 174	0.2574
BMI	28.45 (5.84) 177	27.75 (5.55) 174	0.4300
Pulse	74.21 (9.84) 175	75.48 (10.63) 168	0.2563
Blood Pressure			
Systolic	125.88 (16.86) 176	124.60 (15.82) 169	0.4585
Diastolic	78.53 (10.75) 176	77.76 (9.70) 169	0.3053
Respiration	16.61 (2.45) 167	16.51 (2.73) 167	0.9007
Categorical Measures:	**n/N (%)**	**n/N (%)**	**P-value****
Gender (Male)	87/177 (49.15)	98/175 (56.00)	0.2025
Race			
Caucasian	152/177 (85.88)	153/175 (87.43)	1.0000
Other	25/177 (14.12)	22/175 (12.57)	

*Two-sided two sample Wilcoxon Rank Sum Test.
**Two-sided Fisher's Exact Test.

8.1.8.2 Medical History

The results of the analyses of medical history variables are summarized in Table 8.2. Overall, the two groups were balanced for the measures of medical history.

Table 8.2. Medical History Variables

Characteristic	Oxiplex		Control		P-value*
	n/N (%)	Not Assessed	n/N (%)	Not Assessed	
Ears, Eyes, Nose and Throat	40/174 (22.99)	3	37/175 (21.14)	0	0.7002
Dermatologic	27/168 (16.07)	9	18/170 (10.59)	5	0.1518
Cardiovascular	59/176 (33.52)	1	59/175 (33.71)	0	1.0000
Pulmonary	34/176 (19.32)	1	33/175 (18.86)	0	1.0000
Gastrointestinal	60/175 (34.29)	2	55/174 (31.61)	1	0.7062
Musculoskeletal	127/177 (71.75)	0	128/175 (73.14)	0	0.8119
Genitourinary	42/165 (25.45)	12	37/164 (22.56)	11	0.6060
Renal	11/165 (6.67)	12	8/166 (4.82)	9	0.4899
Hematologic/Immunologic	14/166 (8.43)	11	14/168 (8.33)	7	1.0000
Psychosocial	93/173 (53.76)	4	79/174 (45.40)	1	0.1332
Neurologic	111/176 (63.07)	1	113/175 (64.57)	0	0.8244
Endocrine/Metabolic	33/165 (20.00)	12	34/169 (20.12)	6	1.0000
Surgical/Trauma (≤10 yrs)	102/177 (57.63)	0	89/173 (51.45)	2	0.2831
Psychological	46/172 (26.74)	5	43/172 (25.00)	3	0.8056
Allergies	71/176 (40.34)	1	68/175 (38.86)	0	0.8274

*Two-sided Fisher's Exact Test of assessed subjects only.

8.1.8.3 Procedural Comparability

There were no significant differences in the procedural characteristics between the Oxiplex and Control groups, as shown in Table 8.3.

Table 8.3. Procedural Characteristics

Characteristic	Oxiplex		Control		P-value*
	n/N (%)	Missing	n/N (%)	Missing	
Operative Level:					
L4-L5	83/175 (47.43)	2	81/173 (46.82)	1	0.9149
L5-S1	92/175 (52.57)		92/173 (53.18)		
Operative Site:					
Left	104/177 (58.76)	0	102/174 (58.62)	0	1.0000
Right	72/177 (40.68)		72/174 (41.38)		
Right/Left	1/177 (0.56)		0/174 (0.00)		
Macro/Micro Surgery:					
Macro Surgery	86/177 (48.59)	0	87/174 (50.00)	0	0.8312
Micro Surgery	91/177 (51.41)		87/174 (50.00)		
Prolonged Surgery Yes	2/177 (1.13)	0	6/174 (3.45)	0	0.1716
Anesthesia:					
General	173/177 (97.74)	0	171/174 (98.28)	0	1.0000
Spinal	3/177 (1.69)		3/174 (1.72)		
Other	1/177 (0.56)		0/174 (0.00)		
Hemostatic Agent Use:					
Yes	113/177 (63.84)	0	115/174 (66.09)	0	0.7372
Removed	112/112 (100.00)	1	112/115 (97.39)		0.2468
Continuous Variables	**Mean (SD) N Median(Min, Max)**	**Missing**	**Mean (SD) N Median(Min, Max)**	**Missing**	**P-value****
Surgical Time (min)	69.93 (27.73) 177 66.0 (28.0, 180.0)	0	71.87 (32.40) 174 63.0 (22.0, 195)	0	0.8813
Estimated Blood Loss (ml)	66.91 (68.12) 173 50.0 (0.0, 400.0)	4	75.85 (191.9) 174 50.0 (0.0, 2500.0)	0	0.8490

*Two-sided Fisher's Exact Test.
**Two-sided two sample Wilcoxon Rank Sum Test.

8.1.8.4 Baseline Neurology Examination

The results of the analyses of baseline neurological examinations are summarized in Table 8.4.

Table 8.4. Baseline Neurological Examination

Characteristic	Oxiplex n/N (%)	Oxiplex Not Assessed	Control n/N (%)	Control Not Assessed	P-value*
Clinical Presentation:					
Pain Radiating to or Past the Knee with Neurological Signs	143/176 (81.25)	1	137/175 (78.29)	1	0.5990
Pain Radiating Past the Knee with w/o Neurological Signs	29/176 (16.48)		31/175 (17.71)		
Pain Radiating to the Knee w/o Neurological Signs	4/176 (2.27)		7/175 (4.00)		
Deep Tendon Reflexes:					
Right Patella Present	164/176 (93.18)	1	164/175 (93.71)	1	1.0000
Right Achilles Present	143/176 (81.25)	1	139/175 (79.43)	1	0.6889
Left Patella Present	161/176 (91.48)	1	157/174 (90.23)	1	0.7143
Left Achilles Present	136/176 (77.27)	1	124/174 (71.26)	1	0.2220
Sensory Examination:					
L4 Right Reduced	5/176 (2.84)	1	7/175 (4.00)	1	0.5737
L4 Left Reduced	13/177 (7.34)	0	15/174 (8.62)	0	0.6974
L5 Right Reduced	22/177 (12.43)	0	35/175 (20.00)	0	0.0605
L5 Left Reduced	51/177 (28.81)	0	37/175 (21.14)	0	0.1106
S1 Right Reduced	26/177 (14.69)	0	33/175 (18.86)	0	0.3200
S1 Left Reduced	42/177 (23.73)	0	35/174 (20.11)	0	0.4408
Straight Leg Raise:					
Negative	38/177 (21.47)	0	45/175 (25.71)	0	0.5987
Positive Bilateral	15/177 (8.47)		16/175 (9.14)		
Positive Unilateral	124/177 (70.06)		114/175 (65.14)		
Gait:					
Foot Drop	12/177 (6.78)	0	16/175 (9.14)	0	0.1473
Limp	81/177 (45.76)		69/175 (39.43)		
Normal	74/177 (41.81)		77/175 (44.00)		
Other	10/177 (5.65)		8/175 (4.57)		
Waddling	0/177 (0.00)		5/175 (2.86)		
Motor Examination:					
Right Iliopsoas Abnormal	3/177 (1.69)	0	6/175 (3.43)	0	0.3353
Left Iliopsoas Abnormal	8/177 (4.52)	0	11/175 (6.29)	0	0.4895
Right Quadriceps Abnormal	5/177 (2.82)	0	7/175 (4.00)	0	0.5727
Left Quadriceps Abnormal	6/177 (3.39)	0	15/175 (8.57)	0	0.0447
Right Ant. Tibialis Abnormal	18/177 (10.17)	0	21/175 (12.00)	0	0.6140
Left Ant. Tibialis Abnormal	29/177 (16.38)	0	23/174 (13.22)	1	0.4538
Rt Gastrocnemius Abnormal	24/177 (13.56)	0	14/175 (8.00)	0	0.1215
Lt Gastrocnemius Abnormal	31/177 (17.51)	0	36/174 (20.69)	1	0.4980
Rt Ext.Hal. Longus Abnormal	21/177 (11.86)	0	30/175 (17.14)	0	0.1750
Lt Ext.Hal. Longus Abnormal	50/177 (28.25)	0	40/174 (22.99)	1	0.2733
Bladder Function Unsatis.	16/176 (9.09)	1	17/174 (9.77)	1	0.8567
Sexual Function Unsatisfactory	16/174 (9.20)	3	18/169 (10.65)	6	0.7193

*Two-sided Fisher's Exact Test of assessed subjects only.

9 Clinical Safety

9.1 Primary Safety Analyses

The primary safety variable was the *occurrence of adverse events* (AEs), including surgical complications as summarized in Table 9.1. All enrolled subjects (i.e., ITT population) were included in the analysis of device safety. No subjects were withdrawn from the study due to an AE, and no events occurred that led to study discontinuation.

Table 9.1. Treatment Emergent Adverse Events Summary

		Oxiplex	Control	Total Subjects
Subjects Randomized	N	177	175	352
Subjects with any AE(s)	N (%)	163 (92.1%)	153 (87.4%)	316 (89.8%)
Total Number of Reported AEs	N	685	738	1423
Total Number of Unique AEs	N	119	122	241
Number of AEs by Relationship to Device[1]	N	621	657	1278
None	N (%)	454 (73.1%)	529 (80.5%)	983 (76.9%)
Unlikely	N (%)	160 (25.8%)	128 (19.5%)	288 (22.5%)
Possible	N (%)	4 (0.6%)	0 (0.0%)	4 (0.3%)
Probable	N (%)	3 (0.5%)	0 (0.0%)	3 (0.2%)
Definite	N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number of AEs by Severity[2]	N	621	657	1278
Mild	N (%)	323 (52.0%)	335 (51.0%)	658 (51.5%)
Moderate	N (%)	232 (37.4%)	252 (38.4%)	484 (37.9%)
Severe	N (%)	64 (10.3%)	63 (9.6%)	127 (9.9%)
Life threatening	N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Fatal	N (%)	0 (0.0%)	1 (0.1%)	1 (0.1%)
Unknown	N (%)	2 (0.3%)	6 (0.9%)	8 (0.6%)
Subjects with any SAE	N (%)	13 (7.3%)	14 (8.0%)	27 (7.7%)
	P-value*	0.8438		
Total Number of Serious AEs	N	19	16	35
Total Number of Unique Serious AEs	N	15	11	26
Number of Subjects Withdrawn for AEs	N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

[1,2] Notes: 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. Subjects reporting a particular AE more than once are counted only once for that AE and at the strongest relationship to the device and at the highest severity level.

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

9.1.1 Adverse Events (AEs) Related to the Device

Table 9.2 indicates the numbers of AEs by relationship to the investigational device. The seven (7) events noted were experienced in five (5) subjects.

Table 9.2. Summary of AEs by Relation to Device (ITT)

Relationship	Intensity	Site	Subject	Postop Onset	Duration	P-Value	Comment
Definite – None			[redacted]			N/A	None.
Probable						1.0000*	
Nausea	Mild	[redacted]	[redacted]	Day of Surgery	Day of Surgery		Spontaneous Resolution
Dizziness	Mild	[redacted]	[redacted]	Day of Surgery	Day of Surgery		Spontaneous Resolution
Back Pain	Mild	[redacted]	[redacted]	Day of Surgery	1 week		Spontaneous Resolution
Possible						0.1229**	
Difficulty with Urinating	Moderate	[redacted]	[redacted]	6 Weeks	Ongoing		Prostatitis
Low Back Pain	Severe	[redacted]	[redacted]	5 Weeks	8 Weeks		Spontaneous Resolution
Recurrent HNP	Severe	[redacted]	[redacted]	4 Months	Ongoing		Conservative Treatment
Delayed Wound Healing	Mild	[redacted]	[redacted]	4 Weeks	7 Weeks		Retained Suture Removed

*Two-sided P-value is for 0/174 versus 1/177 using Fisher's Exact Test
**Two-sided P-value is for 0/174 versus 4/177 using Fisher's Exact Test

No AEs were coded by the investigators as being definitely related to the device.

One investigator [redacted] reported one subject who developed three (3) AEs in the perioperative period that were coded as "probable," all of which spontaneously resolved (2: day of surgery; 1: within one week of surgery). These AEs (nausea, dizziness and back pain) commonly occur as a result of lumbar surgery and may not be attributable to the device.

Four AEs were reported in four separate subjects as possibly related to the device:

- Difficult with Urinating. Prostatitis can cause difficulty in urinating. It is uncertain whether there is any medical relationship between the device and the prostititis reported as occurring 6 weeks after surgery.
- Low Back Pain. This is a common occurrence following lumbar surgery and may not be attributable to the device. The P=0.1229 indicates that it is not statistically significant.
- Recurrent HNP. It is difficult to ascertain whether this event was attributable to the device; treatment was conservative and P=0.1229.
- Delayed Wound Healing. This event could have been due to the retained suture that was reported. It is uncertain whether there is any medical relationship between the device and the delayed wound healing under these circumstances.

[redacted]

Table 9.3 lists AEs that occurred at least once in ≥5 % of the subject population.

Table 9.3. Incidence of AEs Occurring ≥5 %

	Oxiplex	%	Control	%	Total Subjects	%
Subjects randomized	N=177		N=175		N=352	
Subjects reporting any AEs	n=163		n=153		n=316	
System Organ Class Preferred Term						
Gastrointestinal Disorders						
Constipation	12	6.8%	6	3.4%	18	5.1%
Nausea	35	19.8%	36	20.6%	71	20.2%
Vomiting	10	5.6%	9	5.1%	19	5.4%
General Disorders & Administrative Site Conditions						
Chills	8	4.5%	8	4.6%	16	4.5%
Pyrexia	8	4.5%	11	6.3%	19	5.4%
Injury, Poisoning, Procedural Complications						
Incision Site Complication	57	32.2%	69	39.4%	126	35.8%
Procedural Pain	56	31.6%	54	30.9%	110	31.3%
Musculoskeletal, Connective Tissue Disorders						
Arthralgia	12	6.8%	12	6.9%	24	6.8%
Back Pain	44	24.9%	39	22.3%	83	23.6%
Buttock Pain	12	6.8%	13	7.4%	25	7.1%
Intervertebral Disc Protrusion	4	2.3%	9	5.1%	13	3.7%
Muscle Spasm	25	14.1%	31	17.7%	56	15.9%
Muscular Weakness	9	5.1%	9	5.1%	18	5.1%
Musculoskeletal Stiffness	9	5.1%	5	2.9%	14	4.0%
Myalgia	6	3.4%	13	7.4%	19	5.4%
Pain in Extremity	26	14.7%	38	21.7%	64	18.2%
Nervous System Disorder						
Dizziness	10	5.6%	8	4.6%	18	5.1%
Headache	14	7.9%	12	6.9%	26	7.4%
Hypoaesthesia	18	10.2%	26	14.9%	44	12.5%
Hyporeflexia	9	5.1%	4	2.3%	13	3.7%
Sensory Loss	4	2.3%	8	4.6%	12	3.4%
Psychiatric Disorders						
Insomnia	12	6.8%	7	4.0%	19	5.4%
Skin and Subcutaneous Tissue Disorders						
Pruritis	8	4.5%	6	3.4%	14	4.0%

9.1.2 Analysis of AEs With Incidence ≥5% (ITT)

Clinically relevant differences noted in this population of subjects were:

Intervertebral Disc Protrusion	Oxiplex group, 2% Control group, 5%
Muscle Spasm	Oxiplex group, 14% Control group, 18%
Myalgia	Oxiplex group, 3% Control group, 7%
Pain in Extremity	Oxiplex group, 15% Control group, 22%
Hypoaesthesia	Oxiplex group, 10% Control group, 15%

In every case, the incidence of these AEs was higher in the Control group.

9.1.3 Serious Adverse Events (SAEs)

No unanticipated SAEs were considered by the investigators to be device related. All SAEs, regardless of relation to the device, were reviewed and tracked throughout the course of the study. [redacted]

9.1.3.1 [redacted]

9.1.3.2 [redacted]

9.2 Secondary Safety Analyses

Secondary safety variables were the changes in laboratory results, physical and neurological exams and vital signs throughout the study, reoperation at the same lumbar level, and comparisons of concomitant therapies. There were no significant changes from baseline values in hematology, chemistry, urinalysis results and vital signs between the Oxiplex and Control groups.

9.2.2 Reoperations (ITT)

During the course of the study, a clinically significant difference in the incidence of reoperations was observed. Seven (7) subjects required a reoperation within 3-months following the initial surgery. Of the seven, only one (1) subject (0.6%) was treated with Oxiplex and six (6) (3.4%) subjects were from the Control group.

Five of the six subjects in the Control group who underwent reoperations had severe baseline back pain. No Oxiplex subjects who had severe back pain at baseline had a reoperation.

Table 9.4 summarizes data for reoperations.

Table 9.4. Percentage of Subjects with a Reoperation 0-6 months

	P-value*	Oxiplex N (%)	Control N (%)	Total Subjects N (%)
Subjects Randomized	0.1902	177	175	352
Re-operation 0-3-months	0.0665	1 (0.6%)	6 (3.4%)	7 (2.0%)
Re-operation 3-6 months**	N/A	0	0	0

*P-value is for Oxiplex vs. Control and is by the Fisher's Exact Test
**All reoperations occurred by 3 months following the primary surgery.

Table C.4 in Appendix C lists details regarding reoperations, including reasons, dates and LSOQ outcome measures for each subject having a reoperation.

9.2.3 Physical Examinations (ITT)

Physical examinations performed for the study were the routine standard of care examinations performed at the site, with the exception of the neurological exams. Other abnormal neurological exam results (those not related to the lower spine) were noted on case report forms. Neurological physical exam abnormalities (non-lower spine) included headache, hand tremors, seizure disorder, and cervical spondylosis. Abnormal physical exams are tabulated in Tables 9.5 and 9.6 at 1 month and 6 months following surgery, respectively.

Table 9.5. Abnormal Physical Examination at 1 Month

Body System	P-value*	Oxiplex N (%)	Control N (%)	Total Subjects N (%)
Subjects Randomized	N/A	177	175	352
Subjects with Physical Ex	N/A	173	169	342
General Appearance	1.0000	10 (5.8%)	9 (5.3%)	19 (5.6%)
Ears, Eyes, Nose, Throat	0.1956	5 (2.9%)	10 (5.9%)	15 (4.4%)
Head, Neck, Thyroid	0.6820	2 (1.2%)	3 (1.8%)	5 (1.5%)
Lungs	1.0000	2 (1.2%)	2 (1.2%)	4 (1.2%)
Heart/Cardiovascular	0.1180	1 (0.6%)	5 (3.0%)	6 (1.8%)
Lymph Nodes	0.4942	0 (0.0%)	1 (0.6%)	1 (0.3%)
Abdomen	1.0000	5 (2.9%)	4 (2.4%)	9 (2.6%)
Musculoskeletal	0.0728	26 (15.0%)	39 (23.1%)	65 (19.0%)
Neurological (non-lower spine)	0.2669	36 (20.8%)	27 (16.0%)	63 (18.4%)
Skin	0.4910	12 (6.9%)	8 (4.7%)	20 (5.8%)
Other	N/A	0 (0.0%)	0 (0.0%)	0 (0.0%)

*P-value is for Oxiplex vs. Control at 1 month and is from Fisher's Exact Test

Table 9.6. Abnormal Physical Examination at 6 Months

Body System	P-value*	Oxiplex N (%)	Control N (%)	Total Subjects N (%)
Subjects Randomized	N/A	177	175	352
Subjects with Physical Ex	N/A	140	144	284
General Appearance	1.0000	7 (5.0%)	7 (4.9%)	14 (4.9%)
Ears, Eyes, Nose, Throat	0.4419	6 (4.3%)	10 (6.9%)	16 (5.6%)
Head, Neck, Thyroid	1.0000	2 (1.4%)	3 (2.1%)	5 (1.8%)
Lungs	0.4983	0 (0.0%)	2 (1.4%)	2 (0.7%)
Heart/Cardiovascular	0.2140	1 (0.7%)	5 (3.5%)	6 (2.1%)
Lymph Nodes	1.0000	0 (0.0%)	1 (0.7%)	1 (0.4%)
Abdomen	0.5366	6 (4.3%)	4 (2.8%)	10 (3.5%)
Musculoskeletal	0.0769	22 (15.7%)	35 (24.3%)	57 (20.1%)
Neurological (non lower spine)	0.3623	44 (31.4%)	38 (26.4%)	82 (28.9%)
Skin	0.4834	11 (7.9%)	8 (5.6%)	19 (6.7%)
Other	N/A	0 (0.0%)	0 (0.0%)	0 (0.0%)

*P-value is for Oxiplex vs. Control at 6 months by Fisher's Exact Test

Neurological physical exam abnormalities (non-lower spine) included headache, hand tremors, seizure disorder, and cervical spondylosis.

Abnormalities noted in the musculoskeletal examination included pain on palpation at L4-L5 or L5-S1, leg edema, pedal edema, joint swelling, tenderness to palpation at lumbar paraspinals, paraspinous muscle spasms, tight spine muscles, plantar fasciitis, loss of leg motor strength, tendonitis, hamstring tightness, decreased range of motion or loss of motion-lumbar spine, guarded movements, divot in quadriceps muscle, surgical scars related to prior knee surgery, knee amputation, metacarpal fracture and neck/shoulder stiffness/weakness.

9.2.4 Concomitant Therapies

There were no significant differences between Oxiplex and Control groups in concomitant therapies.

9.2.5 Safety Summary and Conclusions

- In general, subjects did well following their surgical procedures throughout the 6-month study interval.
- Reoperations: A clinically significant difference in the incidence of reoperations was observed. Seven (7) subjects required a reoperation at or before the 3-month time point. Of the seven, one (1) subject (0.6%) was treated with Oxiplex and six (6) subjects (3.4%) were from the Control group. This difference between groups approached statistical significance (P=0.0665). Five of the six subjects in the Control group who underwent reoperations had severe baseline back pain. No Oxiplex subjects who had severe back pain at baseline had a reoperation.
- Throughout all of these analyses, subjects in the Oxiplex group had fewer findings of neurological abnormalities compared to the subjects in the Control group, especially at the 6-month study endpoint.
- There were no significant differences in the number of subjects having AEs or SAEs between the Oxiplex and Control groups.
- No AEs were reported that led to study discontinuation; the study continued to completion.
- No subjects were discontinued due to AEs.
- Oxiplex treatment was not associated with abnormal laboratory results or clinical examinations.
- Wound Healing: There were no wound healing abnormalities or CSF leaks in the Oxiplex group. Fewer subjects in the Oxiplex group had wound healing abnormalities than subjects in the Control group.
- CSF Leaks: No subjects in the Oxiplex group had a CSF leak or dural tear; whereas one subject in the Control group had a CSF leak and one subject in the Control group reported a dural tear.
- Tissue Repair: Oxiplex had no deleterious effect on tissue repair following lower lumbar surgery for the treatment of disc herniation.
- Concomitant Therapies: There were no significant differences between concomitant therapies received by the Oxiplex and Control groups.

The results of this Pivotal Study provided reasonable assurance that Oxiplex is safe for its intended use.

10 Clinical Effectiveness

The study yielded 7 sets of clinical and statistical evidence demonstrating that Oxiplex subjects had significant improvements in outcomes compared to surgery-only Control subjects:

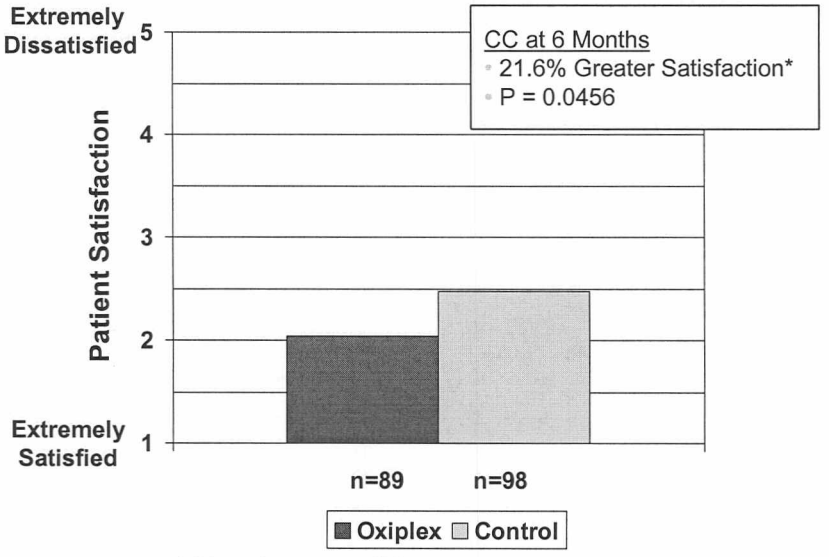
1. Reduced leg pain
2. Reduced back pain
3. Enhanced patient satisfaction
4. Fewer neurological abnormalities (pain in extremity and hypoaesthesia)
5. Fewer musculoskeletal abnormalities
6. Fewer disability days
7. Fewer reoperations

The following demonstrate clinically meaningful benefits experienced by Oxiplex-treated subjects.

10.1 Patient Satisfaction: The LSOQ Measure of Clinical Significance

Patient satisfaction was the LSOQ measure of clinical significance and is a common measure of a patient's perception of clinically important change (i.e., clinical significance) (Mannion and Elfering, 2006). In this study, there was a 21.6% greater level of satisfaction (P=0.0456) in the Oxiplex group compared to the Control group for subjects with severe back pain at baseline. (The median baseline LSOQ back pain score was 63. Subjects having baseline back pain scores greater than or equal to 63 were defined as having severe back pain.) The difference in satisfaction between the Oxiplex and Control groups in these subjects was both statistically and clinically significant. Figure 10.1 below shows this result.

Figure 10.1. Satisfaction at 6 Months by Treatment and Baseline Back Pain for Subjects with Severe Baseline Back Pain (≥63) (CC)



*Simple mean difference between treatment groups.

Note that patient satisfaction was a single question on the LSOQ and had a response ranging from 1 to 5, with 1 being extremely satisfied and 5 being extremely dissatisfied. Therefore, in Figure 10.1, a lower score indicates greater satisfaction.

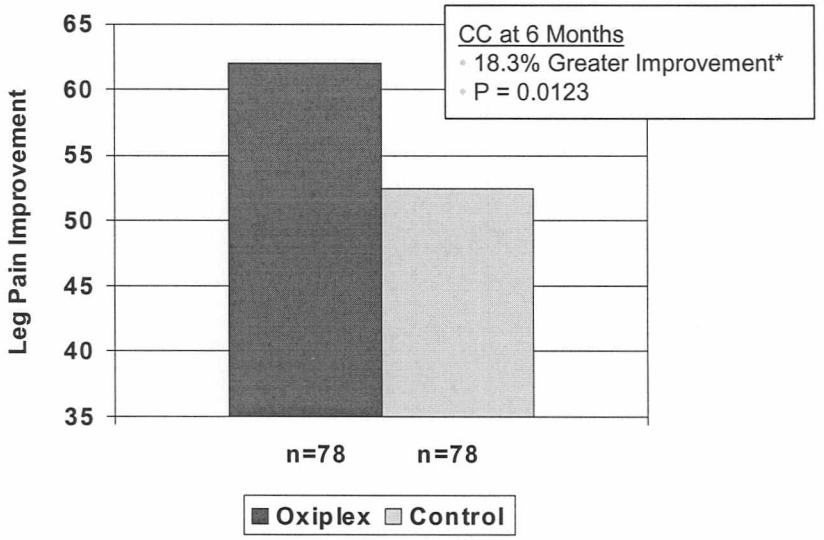
10.2 Reoperations (ITT)

Although reoperation rate may be considered to be a safety variable, it is also an indicator of clinical effectiveness. Clinically significant differences were observed regarding reoperation rates for subjects in the Oxiplex group compared to subjects in the Control group across all subjects. Seven (7) subjects required a reoperation for pain during the course of the study. Of the seven, six (6) subjects (3.4%) were from the Control group while only one (0.6%) was from the Oxiplex group. Five of the six subjects in the Control group who underwent reoperations had severe baseline back pain. No Oxiplex subjects who had severe back pain at baseline had a reoperation.

10.3 Leg Pain

Subjects with severe back pain at baseline demonstrated greater improvement in leg pain in the Oxiplex-treated group compared to the Controls at 6 months (P=0.0123). These subjects experienced a clinically significant benefit of 18.3% improvement in leg pain relative to Control subjects. This is shown in Figure 10.2 below.

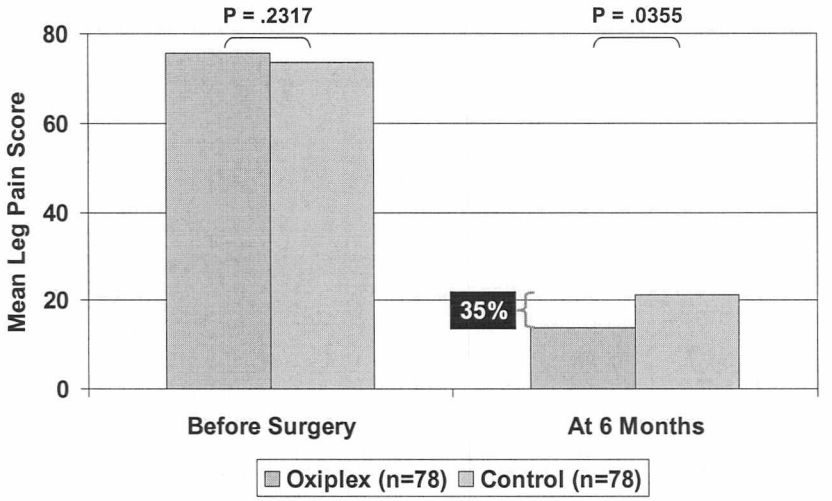
Figure 10.2. Improvement in Leg Pain from Baseline at 6 Months in Subjects with Severe Baseline Back Pain (≥63) (CC)



*Simple mean difference between treatment groups.

Figure 10.3 shows the residual leg pain that remained at 6 months in subjects having severe back pain at baseline. The incremental benefit provided by Oxiplex over surgery alone was 35%.

Figure 10.3. Additional Reduction in Leg Pain Provided by Oxiplex in Subjects with Severe Baseline Back Pain (≥63) (CC)

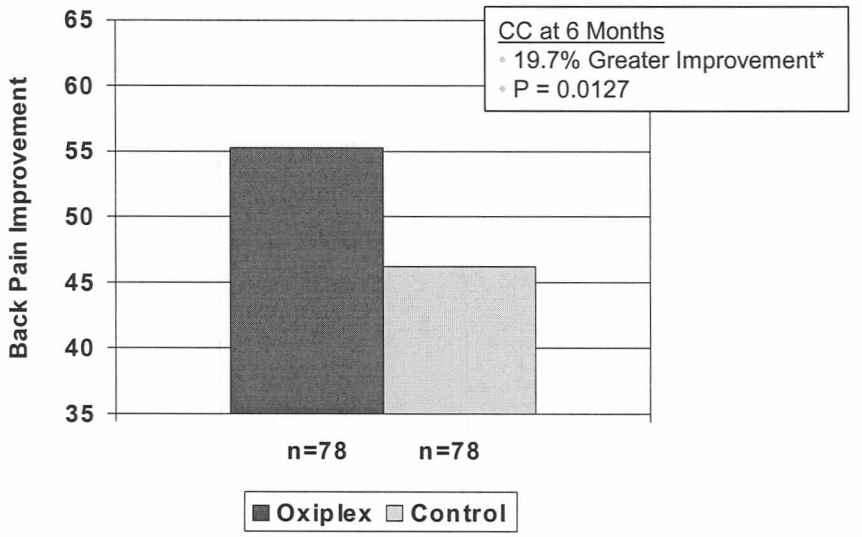


*Simple mean difference between treatment groups.

10.4 Back Pain

Subjects with severe back pain at baseline demonstrated greater improvement in back pain in the Oxiplex group compared to the Controls at 6 months (P=0.0127). Those subjects experienced a clinically significant improvement (19.7%) in back pain scores at 6 months relative to Control subjects. This is shown in Figure 10.4 below.

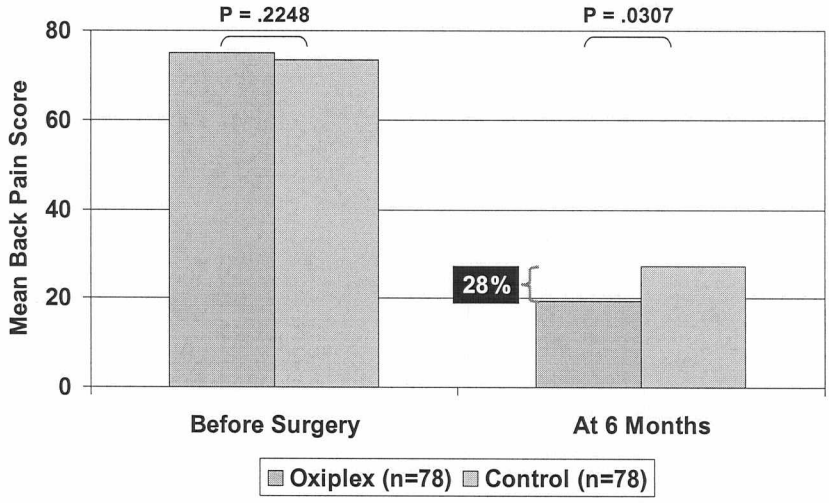
Figure 10.4. Improvement in Back Pain from Baseline at 6 Months in Subjects with Severe Baseline Back Pain (≥63) (CC)



*Simple mean difference between treatment groups.

Figure 10.5 shows the residual back pain that remained at 6 months in subjects having severe back pain at baseline. The incremental benefit provided by Oxiplex over surgery alone was 28%.

Figure 10.5. Additional Reduction* in Back Pain Provided by Oxiplex in Subjects with Severe Baseline Back Pain (≥63) (CC)



*Simple mean difference between treatment groups.

10.5 Postoperative Neurological Abnormalities (ITT)

Clinically significant differences were observed regarding postoperative neurological abnormalities for subjects in the Oxiplex group compared to subjects in the Control group. Subjects in the Oxiplex group had fewer findings of pain in extremity compared to subjects in the Control group, especially at the 6-month study endpoint (Oxiplex group, n=26, 15%; Control group, n=38, 22%).

Additional clinically significant differences were observed regarding postoperative neurological abnormalities for subjects in the Oxiplex group compared to subjects in the Control group. The Oxiplex group had fewer findings of hypoaesthesia compared to the Control group, especially at the 6-month study endpoint (Oxiplex group, n=18, 10%; Control group, n=26; 15%).

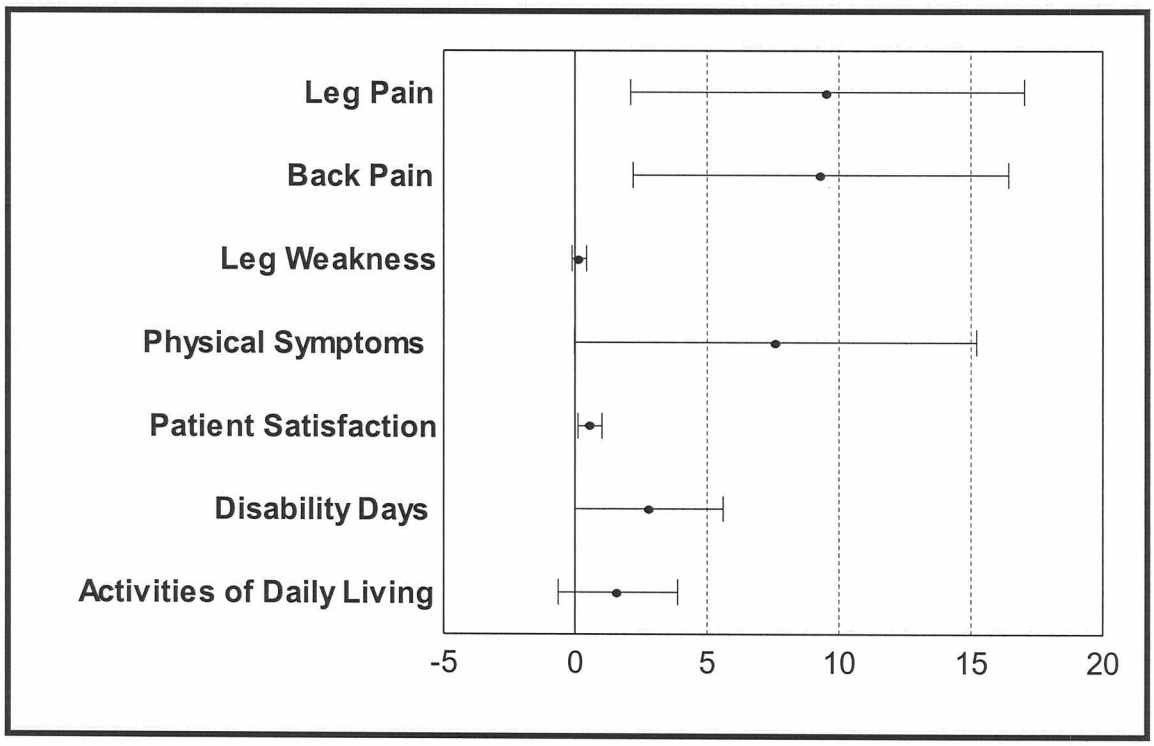
10.6 Disability Days (ITT)

Oxiplex subjects had fewer disability days than the Control group (2 fewer days, as measured over the last 30 days prior to the 6-month visit, P=0.0497, difference in means). Disability days are defined as days when the subjects are completely disabled by their lower back conditions (i.e., days when the subjects remain immobile and inactive all or most of the time, e.g., in bed).

10.7 All Effectiveness Endpoints

Across all effectiveness measures, the mean improvement was higher for Oxiplex subjects than for Control subjects demonstrating that Oxiplex was consistently effective at reducing pain and symptoms (P=0.049). This is shown in Figure 10.6.

Figure 10.6. Mean Differences in Improvement between Oxiplex and Control Groups at 6 Months and Confidence Intervals for Effectiveness Measures for Subjects with Severe Baseline Back Pain (≥63) (CC)



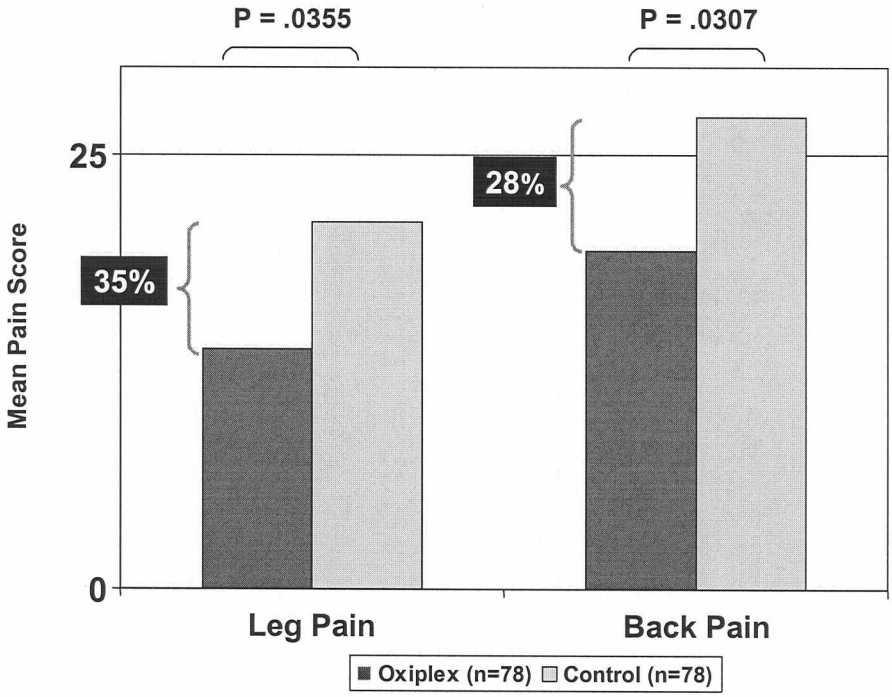
The lower confidence limit excludes zero for leg pain, back pain and satisfaction for completed cases at 6 months with severe baseline back pain. Therefore, the mean improvements in those measures in the Oxiplex group were statistically significant.

10.8 Summary

In summary, each of these measures demonstrated that subjects in the Oxiplex group showed clinically significant improvements in outcomes compared to Control subjects: enhanced patient satisfaction, reduced leg pain (absolute reduction, percentage reduction), reduced back pain (absolute reduction, percentage reduction), fewer reoperations and fewer neurological abnormalities (pain in extremity, hypoaesthesia).

As shown in Figure 10.7 below, Oxiplex subjects experienced a clinically significant additional reduction in leg pain and back pain at 6 months compared to Control subjects.

Figure 10.7. Additional Reduction* in Leg and Back Pain at 6 Months in Subjects with Severe Baseline Back Pain (≥63) (CC)



*Simple mean difference between treatment groups.

11 Statistical Analysis

The methods used to analyze the clinical data were prespecified in the Sponsor's Statistical Report and Analysis Plan that was approved by the FDA. [redacted]

11.1 Primary Effectiveness

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

11.2 Scoring Procedure for the LSOQ

For each subject and for each follow-up evaluation period (1, 3 and 6 months), separate composite scores were derived from the subjects' responses to the LSOQ. Composite scores for leg pain and back pain severity were calculated as follows. Severity of pain was assessed on a six-point adjective rating scale (none, mild, discomforting, distressing, horrible, or excruciating). Subjects used this scale to rate separately the severity of lower back pain and leg pain (1) when it hurt the most, (2) when it hurt the least, (3) on average, (4) at end of an active day, (5) upon awakening, and (6) at this moment. Subjects' responses were first converted to numerical values ranging from 1 (no pain) to 6 (excruciating), generating six low back pain severity responses and six leg pain severity responses for each subject at each evaluation. To obtain the composite pain severity scores, the six lower back pain severity responses and the six leg pain severity responses were separately summed and the resulting sums were then multiplied by 100 and divided by 30, yielding separate composite low back pain and leg pain scores in the range of 0 to 100, with higher scores indicating higher overall severity of experienced pain.

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11.4 Primary Effectiveness Analyses

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11.4.3 Primary Effectiveness Analysis (ITT)

The complexity of measuring pain is illustrated in the multivariate GEE analysis of the primary effectiveness variable, improvement in leg pain, presented in Table 11.3 for the ITT subject population. Univariate screening resulted in eight (8) main effects and 11 interactions (including six (6) treatment-by-baseline interactions) with P-values less than 0.15. All clinically relevant covariates were screened.

Table 11.3. Results of the GEE Analysis of Improvement in Leg Pain from Baseline over Time (ITT)

Source	Degrees of Freedom	Chi-Square	Pr > Chi Square
Treatment	1	11.52	0.0007
Visit	2	32.09	<0.0001
Baseline Leg Pain LSOQ Score	1	76.85	<0.0001
Baseline Back Pain LSOQ Score	1	0.67	0.4144
Baseline Back Pain by Treatment Interaction	1	6.42	0.0113
Baseline Function LSOQ Score	1	11.03	0.0009
Study Site	18	31.12	0.0279
History of Pulmonary Abnormality	1	0.21	0.0309
History of GI Abnormality	1	0.01	0.6463
GI Abnormality by Treatment Interaction	1	7.71	0.0055
History of Hematologic/Immunologic Abnormality	1	4.47	0.0344
L5 Right	1	0.78	0.3775
L5 Right by Treatment Interaction	1	6.74	0.0094
L4 Left	1	0.10	0.7546
L4 Left by Treatment Interaction	1	5.10	0.0240
L5 Left	1	11.08	0.0009
L5 Left by Treatment Interaction	1	4.86	0.0274
Sexual Function	1	3.80	0.0511
Sexual Function by Treatment Interaction	1	5.96	0.0147

Note that the P-values for several interaction terms between Oxiplex and other covariates (such as baseline back pain) fell below the interim analysis-adjusted P-value of 0.044. The data for the six (6) variables were further analyzed to characterize the by-treatment-interactions: Baseline Back Pain, Baseline GI Abnormality, Baseline L5 Right (L5RT) Abnormality, Baseline L4 Left (L4LT) Abnormality, Baseline L5 Left (L5LT) Abnormality, and Baseline Sexual Function (Table 11.4). While such analysis may be considered post hoc, Fisher and van Belle (1993) indicate that there is valid protection in such analyses based on a pre-specified global interaction. Note that there is no statistically significant site-by-treatment interaction.

Table 11.4. Number of Subjects with Interaction by Treatment – Leg Pain (ITT)

Baseline Finding Categorical (Normal vs. Abnormal)	Group	Normal	Abnormal	Interaction P-Value
GI History	Oxiplex (n) Control (n)	117 119	60 55	0.0055
Neuro Exam L5 Right	Oxiplex (n) Control (n)	155 140	22 35	0.0094
Neuro Exam L4 Left	Oxiplex (n) Control (n)	164 159	13 15	0.0240
Neuro Exam L5 Left	Oxiplex (n) Control (n)	126 137	51 37	0.0274
Sexual Function	Oxiplex (n) Control (n)	161 156	16 18	0.0147
Continuous (0-100)				
Baseline Back Pain	Oxiplex (n) Control (n)	177 174		0.0113

Interactions were found with five medical history variables. Oxiplex subjects with normal sensory exams had less leg pain (70-93% of subjects) than Control subjects; Control subjects with abnormal sensory exams did better than Oxiplex subjects (7-30% of subjects) depending on the variable. The only covariate that contained all of the subjects and was clinically interpretable was the baseline back pain score.

In order to investigate the significant interaction between treatment and baseline back pain score (P=0.0113), a regression analysis of the change in leg pain by baseline back pain for each treatment was performed.

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11.4.3.3 Primary Effectiveness Supportive Analysis: Completed Cases (CC) with Visit Time as a Continuous Covariate

To determine whether the ITT results were consistent with data from the CC population, a supportive analysis was performed. The number of patients in this analysis accounts for patients with late visits, so an analysis strategy was developed to use visit time as a continuous covariate. This resulted in 348 subjects of the 351 in the study remaining in the analysis. (Note that 286 subjects are included in this analysis that had the 6-month endpoint in-window, representing 81.5% of all enrolled subjects.)

The final model for the analysis in which time was considered a continuous covariate is presented in Table 11.8. Ten (10) subjects were not used in this analysis because of missing data on at least one of the covariates in the final model.

Table 11.8. Results of the GEE Analysis of Improvement in Leg Pain from Baseline over Time (CC Analysis with Visit Time as a Continuous Covariate)

Source	Degrees of Freedom	Chi-Square	Pr > Chi Square
Treatment	1	17.18	<0.0001
Baseline Leg Pain LSOQ Score	1	80.59	<0.0001
Baseline Back Pain LSOQ Score	1	0.67	0.3116
Baseline Back Pain by Treatment Interaction	1	6.42	0.0267
Baseline Function LSOQ Score	1	11.20	0.0008
Study Site	18	30.69	0.0313
CPT (Macro or Micro)	1	5.17	0.0229
History of Pulmonary Abnormality	1	6.32	0.0119
Pulmonary Abnormality by Treatment Interaction	1	6.71	0.0096
L5RT (Neurosensory Exam)	1	0.82	0.3647
L5RT by Treatment Interaction	1	8.78	0.0030
L4LT (Neurosensory Exam)	1	0.01	0.9346
L4LT by Treatment Interaction	1	7.26	0.0071
L5LT (Neurosensory Exam)	1	7.49	0.0062
Sexual Function (Subject assessment)	1	5.35	0.0207
Sexual Function by Treatment Interaction	1	4.51	0.0338

The model was consistent with the ITT model presented previously. The interactions indicated a non-uniformity of response to treatment across the levels of the covariate involved in the interaction. Note that the treatment interactions with baseline back pain, L4LT, and sexual function abnormality are also in this model. The back pain, L4LT and sexual function interactions are the same as for the ITT population.

Note that the P-values for several interaction terms between Oxiplex and other covariates (such as baseline back pain) fell below the interim analysis-adjusted P-value of 0.044. The data for the five (5) variables were further analyzed to chracterize the by-treatment-interactions: Baseline Back Pain, Baseline L5 Right (L5RT) Abnormality, Baseline L4 Left (L4LT) Abnormality, Baseline Pulmonary Abnormality and Baseline Sexual Function (Table 11.9). While such exploration

may be considered post hoc, Fisher and van Belle (1993) indicate that there is valid protection in such analyses based on a pre-specified global interaction. Note that there is no statistically significant site-by-treatment interaction.

11.5 Secondary Effectiveness Analyses

The secondary effectiveness outcomes were the improvements from baseline (follow-up visit LSOQ score minus baseline LSOQ score) in back pain, leg weakness, physical symptoms, subject satisfaction, disability score and activities of daily living.

The secondary effectiveness variables were evaluated in the same way as the primary variable with the same alternative hypothesis being evaluated (i.e., for a given endpoint, the treated group will have a greater mean change from baseline than the control group). Type I error for the secondary endpoints was controlled by using a hierarchical closed form test procedure with the secondary variables being tested in the order that was prespecified in the Sponsor's approved Statistical Report and Analysis Plan. This procedure required a testing of each variable in sequence as long as the previous hypothesis was rejected. After the first non-rejection of a null hypothesis, the testing of the remaining variables was exploratory. Testing in this manner preserved the experimental error rate at the prescribed nominal level ($P \leq 0.044$ [2-sided]).

The analyses of the secondary effectiveness endpoints were performed on both the ITT subject population over all visit times and the CC populations with visit time as a quantitative covariate for back pain, leg weakness, and symptom score. For satisfaction, disability days, and activities of daily living, only the CC population with time as a quantitative covariate was used as the analysis population.

11.5.1 GEE Analysis of First Secondary Effectiveness Variable: Improvement from Baseline in Back Pain

The analysis of the improvement in back pain over time was done by the GEE method and the final model is presented for the ITT population in Table 11.10.

Table 11.10. Results of the GEE Analysis of Improvement in Back Pain from Baseline Over Time (ITT)

Source	Degrees of Freedom	Chi-Square	Pr > Chi Square
Treatment	1	16.65	<0.0001
Study Visit (Time)	2	13.59	0.0011
Back Pain LSOQ Score	1	65.67	<0.0001
Back Pain by Treatment Interaction	1	11.37	0.0007
Function LSOQ Score	1	9.88	0.0017
CPT (Macro or Micro)	1	8.59	0.0034
History of a GI Abnormality	1	0.33	0.5633
GI Abnormality by Treatment Interaction	1	11.49	0.0007
Straight Leg Raise (Neuro Exam)	2	10.27	0.0059
Sexual Function (Subject Assessment)	1	0.01	0.9159
Sexual Function by Treatment Interaction	1	6.34	0.0118

The interactions with the categorical baseline covariates of GI abnormality and sexual function abnormality were similar to those for leg pain. Normal GI patients comprised over 65% of all subjects and subjects with normal sexual function comprised over 90% of all patients. Among subjects with either condition, Oxiplex subjects showed a greater improvement in back pain than the Control subjects. Among subjects with abnormal GI or abnormal sexual function histories, Control subjects showed greater improvements.

Note that the P-values for several interaction terms between Oxiplex and other covariates (such as baseline back pain) fell below the interim analysis-adjusted P-value of 0.044. The data for the three (3) variables were further analyzed to characterize the by-treatment-interactions: Baseline Back Pain, Baseline GI Abnormality, and Baseline Sexual Function [redacted]. While such analysis may be considered post hoc, Fisher and van Belle (1993) indicate that there is valid protection in such analyses based on a pre-specified global interaction. Note that there is no statistically significant site-by-treatment interaction.

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11.5.2 Supportive Analysis: Improvement in Back Pain from Baseline over Time

A supportive analysis, carried out using the CC population with visit time as a quantitative covariate, is presented in Table 11.12. Only 1 subject was deleted from this analysis due to missing data on at least one covariate included in the final model.

Table 11.12. Results of the GEE Analysis of Improvement in Back Pain from Baseline over Time (CC with Visit Time as a Continuous Covariate)

Source	Degrees of Freedom	Chi-Square	Pr > Chi-Square
Treatment	1	7.38	0.0066
Study Day (Time)	1	5.00	0.0253
Back Pain LSOQ Score	1	75.64	<0.0001
Back Pain by Treatment Interaction	1	5.63	0.0177
Function LSOQ Score	1	9.35	0.0022
CPT (Macro or Micro)	1	14.12	0.0002
History of a Neurologic Abnormality	1	0.11	0.7381
Neurological Abnormality by Treatment Interaction	1	7.15	0.0075
S1Right (Neurosensory Exam)	1	0.53	0.4670
S1Right by Treatment Interaction	1	6.24	0.0125
Straight Leg Raise (Neuro Exam)	1	10.83	0.0045

This analysis confirms the interaction between treatment and baseline back pain but introduces two different interactions between treatment and baseline neurological abnormality and baseline abnormality on the right of S1. Similar to the analysis of L4LT and sexual function, the S1RT interaction indicates that in subjects with normal function (about 83% of all patients), Oxiplex subjects have greater improvement and in subjects with abnormal function (about 17%), Control subjects had greater improvement. In subjects with normal neurological history (about 35% of all patients) Oxiplex subjects had greater improvement than Controls and in abnormal subjects (about 65%) the improvement was about the same in both groups.

Note that the P-values for several interaction terms between Oxiplex and other covariates (such as baseline back pain) fell below the interim analysis-adjusted P-value of 0.044. The data for the three (3) variables were further analyzed to characterize the by-treatment-interactions: Baseline Back Pain, Baseline Neurologic Abnormality and Baseline Sexual Function [redacted]. While such analysis may be considered post hoc, Fisher and van Belle (1993) indicate that there is valid protection in such analyses based on a pre-specified global interaction. Note that there is no statistically significant site-by-treatment interaction.

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11.5.2.2 Secondary Effectiveness Variable: Improvement from Baseline in Lower Extremity (Leg) Weakness

While there were two treatment-by-covariate interactions with P-values below 0.044 in this analysis, they were not considered to support significance because the relationships were either based on small sample size or were clinically uninterpretable. Therefore, under the hierarchical method specified in the SAP, analyses of secondary endpoints from this point on were considered exploratory.

11.5.3 Exploratory Analysis of Patient Satisfaction

The SAP specified that exploratory analyses could be carried out. Satisfaction was a single question on the LSOQ and had a response ranging from 1 to 5, with 1 being extremely satisfied and 5 being extremely dissatisfied. The analysis in the CC population with visit time as a continuous covariate is presented in Table 11.15. Note that BenDebba et al (2000, 2007) indicated in their validation analysis of the LSOQ that a statistically significant difference in patient satisfaction is the measure of a clinically significant difference.

Table 11.15. Results of the GEE Analysis of Patient Satisfaction Score (CC with Visit Time as a Continuous Covariate)

Source	Degrees of Freedom	Chi-Square	Pr > Chi Square
Treatment	1	0.55	0.4603
Study Day (Time)	1	29.21	<0.0001
Back Pain LSOQ score	1	0.60	0.4400
Back Pain by Treatment Interaction	1	5.47	0.0194
History of Dermatologic Abnormality	1	0.24	0.6275
Dermatologic Abnormality by Treatment Interaction	1	6.49	0.0108
History of Pulmonary Abnormality	1	0.36	0.5461
Pulmonary Abnormality by Treatment Interaction	1	5.59	0.0180
History or a Renal Abnormality	1	0.29	0.5897
Renal Abnormality by Treatment Interaction	1	4.83	0.0279
History of Surgery/Trauma ≤10 Years	1	8.89	0.0029
Sexual Function (Subject assessment)	1	4.00	0.0456
R. Iliopsoas (Neuromotor Exam)	1	3.60	0.0579
R. Iliopsoas by Treatment Interaction	1	3.94	0.0472

Baseline dermatologic abnormality, pulmonary abnormality, and renal abnormality exhibited an interaction with treatment with normal Oxiplex subjects having better satisfaction (lower is better) than Controls and among abnormal Control subjects have better satisfaction than Oxiplex treated patients. The secondary effectiveness endpoint of satisfaction showed a statistically significant interaction between treatment and baseline back pain (P=0.0194) consistent with the results for the change in leg pain and the change in back pain.

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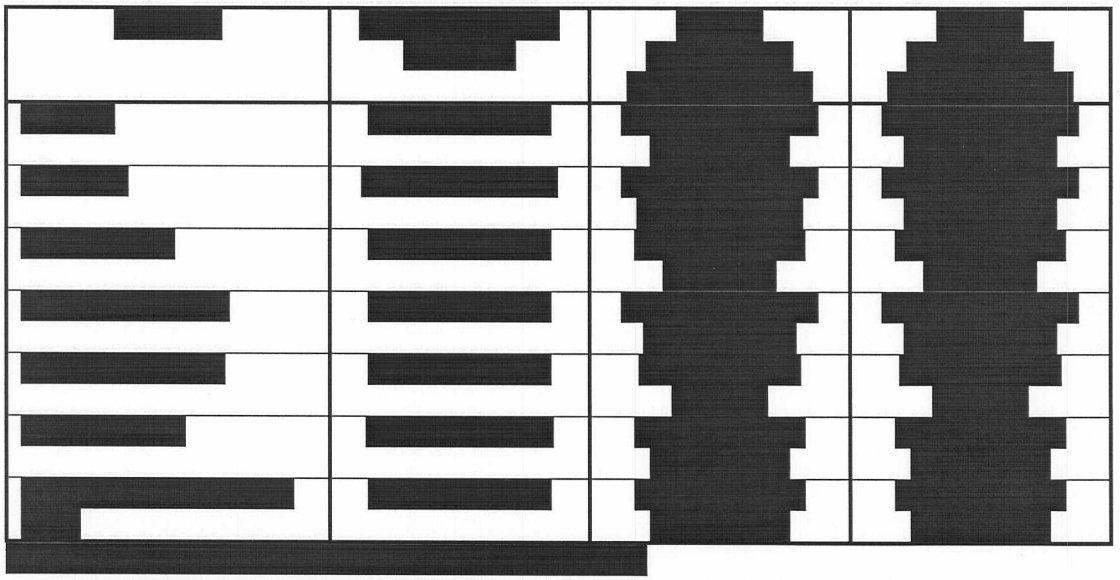

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