P070023
Oxiplex®/SP Gel
Fziomed, Inc.

FDA Presenters:

Jismi Jose
Kyung (Kevin) Lee, MD
Jie (Jack) Zhou
Jiping Chen, MD, PhD, MPH

Orthopaedic and Rehabilitation Devices Panel
Meeting

July 15, 2008
PMA Review Team

- Jismi Jose – Lead Review
- Kevin Lee, MD – Clinical Review
- Jack Zhou – Statistical Review
- Sambasiva Arepalli, PhD – Non-Clinical Review
- Jiping Chen, MD, PhD, MPH – Post-Approval Study
- Isatu Bah – BIMO Review
- Jodi Anderson, Emil Wang, Eric Horowitz – Manufacturing Review
- Mary Ann Wollerton – Patient Labeling
FDA Presentation

- Introduction
- Summary of Non-Clinical/Pre-Clinical Studies
- Clinical Study
- Statistical Overview
- Post-Approval Study
- Panel Questions
Rationale for Bringing to Panel

• First-of-a-kind device
• Clinical significance of device
• Interpretation of clinical study results
Proposed Indications for Use

Oxiplex®/SP Gel is intended to be used as a surgical adjuvant during posterior lumbar laminectomy, laminotomy, or discectomy to improve patient outcomes by reducing postoperative leg pain, back pain and neurological symptoms.

(Panell Question #1)
Device Description

• Absorbable, clear, viscoelastic gel
• Physical separation of tissues
• Sodium carboxymethylcellulose (CMC) and polyethylene oxide (PEO) in sterile water
• CaCl₂ for stability and NaCl for isotonicity
• No animal/bacterial components or color additives
• Single-use sterile kit containing 3mL syringe and applicator
Mechanism of Action

- Applied to operative site coating neural tissue and filling laminectomy/laminotomy site
- Intended to provide physical separation of tissues during healing process
- Designed to clear from body
- Does not require removal operation
FDA Presentation

- Introduction
- Summary of Non-Clinical/Pre-Clinical Studies
- Clinical Study
- Statistical Overview
- Post-Approval Study
- Panel Questions
Non-Clinical Studies

Chemical Analyses
- FTIR Analysis
- EtO Testing
- Aldehyde Testing

Physical Analyses
- Contact Angle Measurement
- Viscometry
- Coatability Testing
- SEC-MALS Testing
- Gel Swelling Test
Pre-Clinical Studies

• Microbiology Tests
  – Rabbit Pyrogen Test
  – LAL Test

• Biocompatibility Tests
  – ISO 10993
  – Literature search

• Animal Studies
Animal Studies

• 2-level rabbit laminectomies at L4 and L5*
  – Purpose: to study effect of device on epidural, dural, or perineural adhesion formation
  – Implanted material: different Oxiplex gel and/or film formulations consisting of CMC and PEO**
  – Sacrifice: various time intervals (e.g. btw 19-28 days, 6 wks after surgery)

• Results
  – Fewer adhesions in Oxiplex-treated animals

*Some test animals also underwent a discectomy
**Exact formulation used in Oxiplex/SP Gel was not used in these studies
Animal Studies

• Rabbit laparotomy and uterine horns abraded
  – Purpose: to study efficacy of device in reducing adhesions in uterine horn
  – Implanted materials: different Oxiplex gel formulations consisting of CMC and PEO**
  – Sacrifice: 7 days post-surgery

• Results
  – Adhesion formation reduced at gel-treated sites

**Exact formulation used in Oxiplex/SP Gel was not used in this study
Animal Studies

- **2-level rabbit laminectomies at L4 and L5 + dural nicks**
  - Purpose: to study efficacy of device in reducing epidural adhesions & effect of device on dural nick
  - Implanted material: Oxiplex/SP Gel or different gel and/or film formulations consisting of CMC and PEO
  - Sacrifice: 28 days or 14-15 days post-surgery

- **Results**
  - Wound healing, including healing of dural nicks, not impaired
  - Fewer adhesions in Oxiplex-treated animals
  - No remanent Oxiplex/SP gel at 28 days

*(Panel Question #2)*
FDA Presentation

• Introduction
• Summary of Non-Clinical/Pre-Clinical Studies
• Clinical Study
• Statistical Overview
• Post-Approval Study
• Panel Questions
Pilot Study Design

• # of sites: 4
• # of subjects in Oxiplex group: 23
• # of subjects in Control group: 12
• Post-Operative
  – Clinical evaluations: 1 and 3 mos
  – ODI and LSOQ evaluations: 1, 3, 6 and 12 mos
  – MRI: 3 mos
Indications/Intended Use for Pilot Study

• Indication
  – Reduction of adhesions following lumbar surgery.

• Intended Use
  – 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.
Pilot Study Results

- Study not powered to demonstrate statistically significant differences between two groups
- Higher incidence of adverse events (AEs) in Oxiplex group compared to Control group

<table>
<thead>
<tr>
<th>Condition</th>
<th>Oxiplex (n=23)</th>
<th>Control (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leg pain</td>
<td>5 (22%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>6 (26%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>4 (17%)</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Back stiffness</td>
<td>3 (13%)</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Buttock pain</td>
<td>3 (13%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Lower extremity pain</td>
<td>5 (22%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Post procedural pain</td>
<td>8 (35%)</td>
<td>5 (42%)</td>
</tr>
<tr>
<td>Incisional pain</td>
<td>8 (35%)</td>
<td>5 (42%)</td>
</tr>
<tr>
<td>Lower extremity numbness</td>
<td>4 (17%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td>6 (26%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>3 (13%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Sensory loss</td>
<td>2 (9%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (35%)</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (17%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>3 (13%)</td>
<td>1 (8%)</td>
</tr>
</tbody>
</table>

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### Pilot Study Results at 12 Months

<table>
<thead>
<tr>
<th>Variable</th>
<th>Oxiplex</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>N</td>
<td>Mean</td>
</tr>
<tr>
<td><strong>Change from Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg Pain (LSOQ)</td>
<td>23</td>
<td>40.7</td>
</tr>
<tr>
<td>Symptoms (LSOQ)</td>
<td>22</td>
<td>28.9</td>
</tr>
<tr>
<td>Activity Related Pain Index (LSOQ)</td>
<td>23</td>
<td>0.87</td>
</tr>
<tr>
<td>Functional Disability (LSOQ)</td>
<td>22</td>
<td>23.1</td>
</tr>
<tr>
<td>Weakness in lower Extremity (LSOQ)</td>
<td>23</td>
<td>0.91</td>
</tr>
<tr>
<td>Radiculopathy Score (LSOQ)</td>
<td>23</td>
<td>34.9</td>
</tr>
<tr>
<td>Oswestry Disability Index (ODI)</td>
<td>23</td>
<td>33.1</td>
</tr>
</tbody>
</table>

P values determined using ANOVA
Note small sample size
LSOQ is a 100 point scale.
MRI Scar Score Analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Oxiplex</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reader1</td>
<td>Reader2</td>
</tr>
<tr>
<td>Subjects enrolled at day 90</td>
<td>N</td>
<td>23</td>
</tr>
<tr>
<td>Kappa</td>
<td>N</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>1.550</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>1.746</td>
</tr>
<tr>
<td></td>
<td>S.E.</td>
<td>1.284</td>
</tr>
<tr>
<td></td>
<td>Min, Max</td>
<td>0.65, 3.25</td>
</tr>
</tbody>
</table>

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%.
Indications for Use in Pivotal Study*

Oxiplex®/SP Gel is intended to be used as a surgical adjuvant during posterior lumbar laminectomy, laminotomy, or discectomy to improve patient outcomes by reducing postoperative leg pain, back pain and neurological symptoms.

*Differs from pilot study indications; same as proposed in PMA
Pivotal Study Design

• Prospective, multi-center, randomized, third-party blinded, parallel group study
• Subjects underwent lumbar disc surgery (standard laminectomy, laminotomy, and discectomy)
• Subjects randomized 1:1 intraoperatively, immediately prior to wound closure
  – Oxiplex group: surgery + Oxiplex/SP Gel
  – Control group: surgery
• Subjects and evaluators masked to treatment assignment
• Follow-up assessments conducted at 1, 3, and 6 mos
Pivotal Study Design, Continued

• Study approved for up to 25 sites investigational sites and up to 394 total subjects.
• # of US sites: 29
  – no foreign sites
• Intent-to-Treat (ITT): 352 subjects
  – # of subjects in Oxiplex group: 177
  – # of subjects Control group: 175
• Completed Cases (CC): 334 subjects who completed 6 mos post-surgical follow-up visit
Safety Endpoints

Primary Safety Endpoint
• Evaluation of frequency and severity of AEs, including surgical complications, categorized using MedDRA coding system (Version 7.1)

Secondary Safety Endpoints
• Changes in laboratory results, physical and neurological exam and vital signs throughout the study;
• Re-operations at lumbar level; and
• Use of concomitant therapies.
Effectiveness Endpoints

• Primary Effectiveness Endpoint
  – Improvement in composite leg pain from baseline to follow-up visits (1, 3 and 6 months), as measured by LSOQ

• LSOQ
  – Measures leg pain severity on 6-pt rating scale for each of the 6 questions
  – Calculated composite leg pain severity score ranges from 0 to 100
    • Higher scores indicate higher overall severity of pain
  – Validated through two multicenter studies
Effectiveness Endpoints, Continued

- Secondary Effectiveness Endpoints:
  - Improvements from baseline (follow-up visit score minus baseline score) as measured by LSOQ, through 6 months, in the following order for sequential closed testing:
    1. back pain
    2. leg weakness
    3. physical symptoms
    4. subject satisfaction
    5. disability score
    6. activities of daily living
Changes in Statistical Analysis Plan

• IDE
  – Sponsor proposed a longitudinal analysis of improvement in composite leg pain using GEE, including treatment, time, and baseline level and baseline by treatment interaction in the model.
  – Sponsor provided null and alternative hypotheses:
    • $H_0: \mu_t = \mu_c$ vs. $H_a: \mu_t \neq \mu_c$
Changes in Statistical Analysis Plan, Continued

• Sponsor proposed to analyze primary endpoint with one-tailed t-test after interim analysis. FDA asked sponsor to include all clinically relevant covariates, such as baseline pain score and site, using original analysis plan.

• The sponsor also stated that they would perform a descriptive presentation and multivariate test of the primary hypothesis for leg pain using a GEE model.
Study Success/Failure

• For the primary effectiveness endpoint, the sponsor set the success criteria of the Pivotal Study as an improvement of 15 points in composite leg pain score from baseline at 6 months on 100-pt LSOQ scale.

• FDA Advisory: In order for study to be considered a success, there should be a statistical significance, as well as a clinically meaningful difference in chosen primary endpoint between two treatment groups, i.e., 20 point or 33% difference between two groups in mean LSOQ score reduction from baseline.
Inclusion/Exclusion Criteria

• Adult males and females scheduled to undergo first surgical intervention for a diagnosed unilateral herniation of lumbar intervertebral disc material associated with radiculopathy.

• Subjects entering Pivotal Study underwent period of at least 2 weeks of non-operative treatment without resolution of pain, unless surgeon decided subject was experiencing intractable pain, or there was substantial progression of loss of neurological function.
Inclusion Criteria

- Clinical signs and symptoms indicative of lumbar or lumbosacral radiculopathy, affecting one predominant nerve root level; Significant pain and symptoms measurable by 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 L4-L5 or L5-S1 level;
- Males, females of non-childbearing potential or females who were not pregnant (at time of enrollment) and agreed not to become pregnant for at least 30 days after surgery;
- Sexually active females of childbearing potential who agreed to use a medically acceptable method of contraception;
- 18 to 70 years of age;
Inclusion Criteria, Continued

• Laboratory test results within normal limits for following parameters:
  – Hematology;
  – Urinalysis;
  – Chemistry Panel
Exclusion Criteria

• Previous spinal surgery or chemonucleolysis at lumbar level;
• Treatment with any epidural steroids within 4 weeks prior to proposed surgery; Use of steroids perioperatively and/or intraoperatively;
• Presence of scoliosis; (> 10 degrees and considered by 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);
Exclusion Criteria, Continued

- Myelogram or lumbar puncture for any reason within 24 hours prior to proposed surgery;
- Presence of any immunodeficiency disease, uncontrolled diabetes, or any systemic condition which, in surgeon's opinion, may influence the outcome of proposed surgery or postoperative period;
- History of analgesic abuse/addiction;
- 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;
- Participation in any other clinical study involving an investigational device or drug within the 30 days immediately preceding enrollment in Oxiplex/SP Gel Pivotal Study;
- Any known condition or circumstance, which would prevent completion of Pivotal Study or interfere with interpretation of Pivotal Study results.
Intraoperative Exclusions

• Subjects who met any of following criteria were not eligible for enrollment:
  – Dural entry during surgery;
  – Discovery of intraspinal tumor during surgery;
  – Required spinal fusion;
  – Multilevel herniation or the need to involve more than one level.
Surgical Protocol

• Standard posterior 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;
• Determine randomization assignment (Treatment group vs. Control group);
Surgical Protocol, Continued

- **Treatment Group Only:** Coat dura and exiting nerve root along both its dorsal and ventral surfaces. Apply gel into site of laminectomy/laminotomy to fill depth of surgical site to level of ventral surface of vertebral lamina. Volume delivered is not to exceed 3 mL.
- Gel implanted at L4-L5 or L5-S1.
- Close wound in routine fashion.
Clinical Evaluations

• Postoperative clinical evaluations performed at 1 mos (3-6 weeks) and 6 mos (22-28 weeks) by masked Clinical Evaluator (CE). Evaluations included:
  – Physical examination, including lumbar spine and lower extremities, motor/sensory function, and evaluation of wound site;
  – Assessment of AEs (assessed at all time points);
  – Review of laboratory test results for clinically significant changes (hematology and serum chemistries at 1 and 6 months; urinalysis at 1 month).
Clinical Evaluations, Continued

• For assessment of effectiveness, subjects completed LSOQ via phone (or mail) at 1, 3 and 6 mos
  – LSOQ: self-assessment questionnaire that served as Quality of Life instrument

• Interviewer and subject remained masked to study group assignment throughout study
## Patient Demographics

<table>
<thead>
<tr>
<th>Race</th>
<th>Oxiplex (n=177)</th>
<th>Control (n=175)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>Mean</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>41.8</td>
<td>41.7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173.0</td>
<td>172.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>86.0</td>
<td>83.8</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>87</td>
<td>98</td>
</tr>
<tr>
<td>Female</td>
<td>90</td>
<td>77</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>152</td>
<td>153</td>
</tr>
<tr>
<td>African American</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Hispanic</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Asian</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>
# Safety Results

## Analysis of AEs with Incidence ≥ 5%

### Incidence occurring > 5 %

<table>
<thead>
<tr>
<th>Condition</th>
<th>Oxiplex %</th>
<th>Control %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects Randomized</td>
<td>N=177</td>
<td>N=175</td>
</tr>
<tr>
<td>Subjects Reporting Any ADE</td>
<td>N=163</td>
<td>N=153</td>
</tr>
</tbody>
</table>

### Gastrointestinal Disorders

<table>
<thead>
<tr>
<th>Condition</th>
<th>Oxiplex</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Nausea</td>
<td>35</td>
<td>36</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
<td>9</td>
</tr>
</tbody>
</table>

### General Disorders & Administrative Site Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Oxiplex</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chills</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>8</td>
<td>11</td>
</tr>
</tbody>
</table>

### Injury, Poisoning, Procedural Complications

<table>
<thead>
<tr>
<th>Condition</th>
<th>Oxiplex</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incision Site Complication</td>
<td>57</td>
<td>69</td>
</tr>
<tr>
<td>Procedural Pain</td>
<td>56</td>
<td>54</td>
</tr>
</tbody>
</table>

### Musculoskeletal, Connective Tissue Disorders

<table>
<thead>
<tr>
<th>Condition</th>
<th>Oxiplex</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Back Pain</td>
<td>44</td>
<td>39</td>
</tr>
<tr>
<td>Buttock Pain</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Intervertebral Disc Protrusion</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Muscle Spasm</td>
<td>25</td>
<td>31</td>
</tr>
<tr>
<td>Muscular Weakness</td>
<td>9</td>
<td>9</td>
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<tr>
<td>Musculoskeletal Stiffness</td>
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<td>5</td>
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<tr>
<td>Myalgia</td>
<td>6</td>
<td>13</td>
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<tr>
<td>Pain in Extremity</td>
<td>26</td>
<td>38</td>
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</tbody>
</table>

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## Analysis of AEs with Incidence $\geq$ 5%, Continued

<table>
<thead>
<tr>
<th>Incidence occurring $&gt;5%$</th>
<th>Oxiplex %</th>
<th>Control %</th>
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</thead>
<tbody>
<tr>
<td>Subjects Randomized</td>
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<td>N=175</td>
</tr>
<tr>
<td>Subjects Reporting Any Adverse Event</td>
<td>N=163</td>
<td>N=153</td>
</tr>
</tbody>
</table>

### Nervous System Disorder

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Oxiplex</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>10 5.6%</td>
<td>8 4.6%</td>
</tr>
<tr>
<td>Headache</td>
<td>14 7.9%</td>
<td>12 6.9%</td>
</tr>
<tr>
<td>Hypoasthesia</td>
<td>18 10.2%</td>
<td>26 14.9%</td>
</tr>
<tr>
<td>Hyporeflexia</td>
<td>9 5.1%</td>
<td>4 2.3%</td>
</tr>
<tr>
<td>Sensory Loss</td>
<td>4 2.3%</td>
<td>8 4.6%</td>
</tr>
</tbody>
</table>

### Psychiatric Disorders

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Oxiplex</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>12 6.8%</td>
<td>7 4.0%</td>
</tr>
</tbody>
</table>

### Skin and Subcutaneous Tissue Disorders

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Oxiplex</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>8 4.5%</td>
<td>6 3.4%</td>
</tr>
</tbody>
</table>
# Treatment-Emergent AEs

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Intensity</th>
<th>Subject</th>
<th>Postop Onset</th>
<th>Duration</th>
<th>Treatment Group</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definite — None</strong></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
<td></td>
<td>None.</td>
</tr>
<tr>
<td><strong>Probable</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>Mild</td>
<td>*</td>
<td>Day of Surgery</td>
<td>Day of Surgery</td>
<td>Oxiplex</td>
<td>Spontaneous Resolution</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Mild</td>
<td>*</td>
<td>Day of Surgery</td>
<td>Day of Surgery</td>
<td>Oxiplex</td>
<td>Spontaneous Resolution</td>
</tr>
<tr>
<td>Back Pain</td>
<td>Mild</td>
<td>*</td>
<td>Day of Surgery</td>
<td>1 week</td>
<td>Oxiplex</td>
<td>Spontaneous Resolution</td>
</tr>
<tr>
<td><strong>Possible</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficult with Urinating</td>
<td>Moderate</td>
<td>**</td>
<td>6 Weeks</td>
<td>Ongoing</td>
<td>Oxiplex</td>
<td>Prostatitis</td>
</tr>
<tr>
<td>Low Back Pain</td>
<td>Severe</td>
<td>**</td>
<td>5 Weeks</td>
<td>8 Weeks</td>
<td>Oxiplex</td>
<td>Spontaneous Resolution</td>
</tr>
<tr>
<td>Recurrent HNP</td>
<td>Severe</td>
<td>**</td>
<td>4 Months</td>
<td>Ongoing</td>
<td>Oxiplex</td>
<td>Conservative Treatment</td>
</tr>
<tr>
<td>Delayed Wound Healing</td>
<td>Mild</td>
<td>**</td>
<td>4 Weeks</td>
<td>7 Weeks</td>
<td>Oxiplex</td>
<td>Retained Suture Removed</td>
</tr>
</tbody>
</table>

* Same Subject
** 4 Different Subjects

43 of 96
Serious Adverse Events (SAEs)

- 27 subjects (7.7%) experienced SAE
  - 13 SAEs (7.3%) in Oxiplex group
    - e.g. cellulitis, wound infection, incision site complication, headache, migraine, deep vein thrombosis
  - 14 SAEs (8%) in Control group
    - e.g. wound infection, CSF leakage, dural tear, hip fracture, nerve injury, spinal fusion surgery
- No SAE was categorized as definitely or probably related to device.
## Re-operations

<table>
<thead>
<tr>
<th></th>
<th>P-value*</th>
<th>Oxiplex N (%)</th>
<th>Control N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects Randomized</td>
<td></td>
<td>177</td>
<td>175</td>
</tr>
<tr>
<td>Re-operation by 3-month</td>
<td>0.0665</td>
<td>1 (0.6%)</td>
<td>6 (3.4%)</td>
</tr>
<tr>
<td>Re-operation by 6-month**</td>
<td>0.0665</td>
<td>1 (0.6%)</td>
<td>6 (3.4%)</td>
</tr>
</tbody>
</table>

*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 Safety Variables

• Oxiplex and Control groups comparable with respect to following variables:
  – Hematology
  – Chemistry
  – Urinalysis
  – Abnormal physical examination at 1-mos follow-up
  – Abnormal physical examination at 6-mos follow-up and post-operative neurology examination

• Balance in concomitant therapies received by Oxiplex and Control groups.
Effectiveness Results: Primary Endpoint

- FDA conducted an analysis of the primary effectiveness endpoint based on the original IDE model that showed that the difference of least squares means between the two groups was 0.1 on a 100-pt scale ($p=0.96$).
### FDA Unadjusted Analyses on Leg Pain Improvement for CC

<table>
<thead>
<tr>
<th>Visit</th>
<th>Oxiplex Leg Pain Improvement from Baseline Mean±Std (N&lt;sup&gt;1&lt;/sup&gt;)</th>
<th>Control Leg Pain Improvement from Baseline Mean±Std (N&lt;sup&gt;1&lt;/sup&gt;)</th>
<th>Oxiplex Improvement – Control Improvement = Treatment Effect (95% CI)</th>
<th>Unadjusted P-values for Treatment Effect (T-test)&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Unadjusted P-values for Treatment Effect (Wilcoxon Rank Sum Test)&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>67.5±15.2 (177)</td>
<td>67.7±14.1 (174)</td>
<td></td>
<td>0.90&lt;sup&gt;4&lt;/sup&gt;</td>
<td>0.96&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Month 1</td>
<td>48.8±23.3 (165)</td>
<td>48.9±23.9 (160)</td>
<td>-0.1 (-5.3, 5.1)</td>
<td>0.97</td>
<td>0.97</td>
</tr>
<tr>
<td>Month 3</td>
<td>51.8±22.9 (168)</td>
<td>51.4±24.9 (162)</td>
<td>0.4 (-4.7, 5.6)</td>
<td>0.87</td>
<td>0.97</td>
</tr>
<tr>
<td>Month 6</td>
<td>51.7±23.8 (167)</td>
<td>50.7±25.3 (167)</td>
<td>0.9 (-4.4, 6.2)</td>
<td>0.74</td>
<td>0.88</td>
</tr>
</tbody>
</table>

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.
### FDA Analysis of Endpoints (6-month PMA CC)

<table>
<thead>
<tr>
<th>Measures</th>
<th>Difference Of (Oxiplex-Control)</th>
<th>Control (N)</th>
<th>Oxiplex (N)</th>
<th>(95% Confidence interval)</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leg Pain</td>
<td>0.91</td>
<td>167</td>
<td>167</td>
<td>(-4.38, 6.20)</td>
<td>No</td>
</tr>
<tr>
<td>Back Pain</td>
<td>2.32</td>
<td>167</td>
<td>167</td>
<td>(-3.37, 8.01)</td>
<td>No</td>
</tr>
<tr>
<td>Leg Weakness</td>
<td>0.10</td>
<td>167</td>
<td>167</td>
<td>(-0.10, 0.29)</td>
<td>No</td>
</tr>
<tr>
<td>Physical Symptoms</td>
<td>3.40</td>
<td>167</td>
<td>167</td>
<td>(-1.68, 8.48)</td>
<td>No</td>
</tr>
<tr>
<td>Patient Satisfaction</td>
<td>0.08</td>
<td>167</td>
<td>167</td>
<td>(-0.22, 0.38)</td>
<td>No</td>
</tr>
<tr>
<td>Disability Days</td>
<td>1.47</td>
<td>167</td>
<td>167</td>
<td>(-0.44, 3.38)</td>
<td>No</td>
</tr>
<tr>
<td>Activities of Daily Living Index</td>
<td>0.92</td>
<td>156</td>
<td>156</td>
<td>(-0.76, 2.59)</td>
<td>No</td>
</tr>
</tbody>
</table>

- This analysis was conducted by FDA, which showed slightly different results from the sponsor’s analysis in the in-window population.
- Positive numbers indicate advantage of Oxiplex group.
- Completed Cases (PMA CC): 334 subjects who completed 6 mos post-surgical follow-up visit
OUS Experience

• CE Mark received in July 2001
• 6 post-market reports related to issues with device
  – Sponsor concluded reports were not attributable to use of device
• Prospective, subject blinded clinical study in China
  – October 2006-April 2007
  – 60 subjects, randomized 2:1 (Oxiplex: Control), 2 sites
  – Data collection and efficacy analysis ongoing
FDA Presentation

• Introduction
• Summary of Non-Clinical/Pre-Clinical Studies
• Clinical Study
• Statistical Overview
• Post-Approval Study
• Panel Questions
P070023
Statistical Overview

Jie (Jack) Zhou
General and Surgical Devices Branch
Division of Biostatistics
Office of Surveillance and Biometrics

Orthopaedic and Rehabilitation Devices Panel Meeting
July 15, 2008
Outline

• Pivotal Study Design
  – Sample Size
  – History of Key Changes in Statistical Analysis Plan

• Subject Dispositions and Populations

• Comparability of Oxiplex and Control Subjects

• Analyses on Primary Effectiveness Endpoint
  – Overall Treatment Effect
  – Exploratory Subgroup Analyses
  – Site Variability

• Analyses on Secondary Effectiveness Endpoints

• Summary
Sample Size

• Sample Size Estimation:
  – Two Independent Normal Means with One Interim Analysis, $\delta=10$, $\sigma=32$, 15% loss of f/p
  – Originally 192 per Group, Interim Analysis Proposed at 33.3% Data
  – May 05 Changed the Interim Analysis to 75% Data, Sample Size to 394 for 334 Evaluable
  – Alpha Value 0.044 for Final Analysis

• Actual Enrolled:
  – 177 Oxiplex, 175 Controls for 352 Enrolled and 334 Evaluable at 6 months
Timeline of Key Changes in the Planned Statistical Analyses on the Primary Endpoint

- May 02 Protocol w/ Statistical Methods Conditionally Approved
  - Initial GEE model for the primary endpoint would contain treatment, time, baseline level and baseline level by treatment interaction term
  - Interaction term removed if not significant
- Aug 02 Enrollment Began
- Apr 06 Interim Analysis
- Dec 06 Revised Statistical Analysis Plan Submitted
  - All clinically relevant baseline factors would be screened
  - Interactions with treatment would be studied
- Aug 07 PMA Submission
Subject Dispositions at 6 Months and Subject Populations

<table>
<thead>
<tr>
<th></th>
<th>Oxiplex</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled (ITT&lt;sup&gt;1&lt;/sup&gt;)</td>
<td>177</td>
<td>175</td>
</tr>
<tr>
<td>Died</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Withdrawn/Terminated</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Lost to Follow-up</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Far beyond visit Window&lt;sup&gt;2&lt;/sup&gt;</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>“Completed Cases” (PMA CC)</td>
<td>167</td>
<td>167</td>
</tr>
<tr>
<td>6-month In-window Population</td>
<td>145</td>
<td>141</td>
</tr>
</tbody>
</table>

1. One control subject was unblinded and excluded from the ITT population by the Sponsor.
2. Five subjects had 6-month visit far beyond the visit window (> 365 days), and were excluded from the “Complete Cases” by the sponsor.
## Comparability of Oxiplex Subjects and Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Control (N=175)</th>
<th>Oxiplex (N=177)</th>
<th>P-value$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>41.7 (10.7)</td>
<td>41.8 (10.5)</td>
<td>0.93</td>
</tr>
<tr>
<td>Gender (Male)</td>
<td>98 (56.0%)</td>
<td>87 (49.2%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>27.8 (5.6)</td>
<td>28.4 (5.8)</td>
<td>0.25</td>
</tr>
<tr>
<td>Baseline Leg Pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>67.7 (14.1)</td>
<td>67.5 (15.2)</td>
<td>0.90</td>
</tr>
<tr>
<td>Baseline Back Pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>59.4 (21.8)</td>
<td>59.2 (20.9)</td>
<td>0.90</td>
</tr>
</tbody>
</table>

1. One control patient had missing baseline leg pain and back pain scores and was unblinded following surgery.
2. Not adjusted for multiplicity. T-test for continuous variables, Fisher’s exact test for categorical variables.
Primary Effectiveness Endpoint

- Improvement in Leg Pain Measured by LSOQ at 1, 3 and 6 months post surgery
- Converted to 0-100 Scale
- Analyzed with GEE model
- In ITT (primary) and CC (supportive) population
  - Overall Treatment Effect
  - Exploratory Subgroup Analyses
  - Site Variability
Model (Covariate) Selection

• Why Statistical Models?
  – To adjust for possible covariate imbalance between arms

• Model Selection Methods
  – Pre-specified covariates
  – Automated covariate selection by software (with pre-specified rules)
  – Combination of pre-specified covariates and automated selection

• (Pre-specified) Treatment-by-covariate Interactions Added Last
Sponsor’s Model Selection Process

• Unusual
• Screens Treatment-by-covariate Interactions Early
• Manual Backward Selection Process
  – Difficult to Replicate
  – Prone to Biases
• Complex Model
• Difficult to Interpret
The Sponsor’s GEE Model (PMA CC)

• Ten Covariates
  – Site, baseline leg pain, back pain, functional score, cpt, pulmonary abnormality, three neurosensory exam results, sexual function

• Five Treatment-by-covariate Two-way Interactions
  – Treatment by baseline back pain, pulmonary abnormality, two neurosensory exam results, sexual function

• Overall Treatment Effect Difficult to Characterize
  – P-value for main treatment effect should not be used when interaction present

(Panel Question #4)
Hypothetical Example: Treatment-by-gender Interaction

Overall Trt Effect
No Interaction

Overall Trt Effect
Quantitative Interaction

No Overall Trt Effect
Qualitative Interaction

A
B
C

62 of 96
Treatment-by-covariate Interactions

- Allows different treatment effect for different subgroups
- Usually first step towards subgroup analyses
- Exploratory if not pre-specified
- Model more complex
- Overall treatment effect difficult to characterize
FDA’s GEE Models for Primary Effectiveness Endpoint

- Model 1 – Derived from Sponsor’s Model (PMA CC) without the Interaction Terms
- Model 2 – IDE Model with Treatment, Visit and Baseline Leg Pain (Treatment-by-baseline Leg Pain Not Significant)
FDA’s Results from Primary Endpoint Models (PMA CC Population)

<table>
<thead>
<tr>
<th></th>
<th>Adjusted Overall Trt Effect(^1)</th>
<th>95% Confidence Interval</th>
<th>P-value for Overall Trt Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>1.8</td>
<td>(-1.5, 5.1)</td>
<td>0.29</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.1</td>
<td>(-3.6, 3.8)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

1. Difference in leg pain reduction at 1, 3 or 6 months on 0-100 scale
## Primary Effectiveness Endpoint – FDA Unadjusted Analysis (PMA CC Population)

<table>
<thead>
<tr>
<th>Visit</th>
<th>Leg Pain Improvement from Baseline Mean±Std (N&lt;sup&gt;1&lt;/sup&gt;)</th>
<th>Oxiplex Improvement – Control Improvement = Treatment Effect (95% CI)</th>
<th>P-values for Treatment Effect&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oxiplex</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>Month 1</td>
<td>48.8±23.3 (165)</td>
<td>48.9±23.9 (160)</td>
<td>-0.1 (-5.3, 5.1)</td>
</tr>
<tr>
<td>Month 3</td>
<td>51.8±22.9 (168)</td>
<td>51.4±24.9 (162)</td>
<td>0.4 (-4.7, 5.6)</td>
</tr>
<tr>
<td>Month 6</td>
<td>51.7±23.8 (167)</td>
<td>50.7±25.3 (167)</td>
<td>0.9 (-4.4, 6.2)</td>
</tr>
</tbody>
</table>

1. Number of non-missing values
2. From t-test, not adjusted for multiplicity
Treatment-by-covariate Interactions
Screened by Sponsor

- Trt-by-age
- Trt-by-weight
- Trt-by-BMI
- Trt-by-baseline leg pain
- Trt-by-baseline back pain
- Trt-by-baseline function pain
- Trt-by-baseline symptom score
- Trt-by-gender
- Trt-by-site
- Trt-by-surgical time
- Trt-by-cpt
- Trt-by-operation level
- Trt-by-leg weakness
- Trt-by-history of eye, ENT abnormality
- Trt-by-history of dermatological abnormality
- Trt-by-history of cardiovascular abnormality
- Trt-by-history of pulmonary abnormality
- Trt-by-history of gastrointestinal abnormality
- Trt-by-history of musculoskeletal abnormality
- Trt-by-history of genitourinary abnormality
- Trt-by-history of renal abnormality
- Trt-by-history of hematologic/immunologic abnormality
- Trt-by-history of psychosocial abnormality
- Trt-by-history of neurological abnormality
- Trt-by-history of endocrine/metabolic abnormality
- Trt-by-history of surgical/Trauma (<=10 years)
- Trt-by-history of psychological abnormality
- Trt-by-history of allergies
- Trt-by-clinical presentation
- Trt-by-L4rt (neurosensor exam)
- Trt-by-L5rt (neurosensor exam)
- Trt-by-s1rt (neurosensor exam)
- Trt-by-l4lt (neurosensor exam)
- Trt-by-l5lt (neurosensor exam)
- Trt-by-s1lt (neurosensor exam)
- Trt-by-slrl
- Trt-by-gait
- Trt-by-sexual function
- Trt-by-RILIO (Right Iliopsoas Neuromotor Exam)
- Trt-by-RQUAD (Right Quadriceps Neuromotor Exam)
- Trt-by-RANT (Right Anterior Tibialis Neuromotor Exam)
- Trt-by-RGAST (Right Gastronemius Neuromotor Exam)
- Trt-by-REXT (Right Extensor Hallucis Longus Neuromotor Exam)
- Trt-by-LILIO (Left Quadriceps Neuromotor Exam)
- Trt-by-LQUAD (Left Quadriceps Neuromotor Exam)
- Trt-by-LANT (Left Anterior Tibialis Neuromotor Exam)
- Trt-by-LGAST (Left Gastronemius Neuromotor Exam)
- Trt-by-LEXT (Left Extensor Hallucis Longus Neuromotor Exam)
### FDA Exploratory Subgroup Analysis (PMA CC Population)  

<table>
<thead>
<tr>
<th>Baseline Back Pain</th>
<th>Visit</th>
<th>Leg Pain Improvement from Baseline Mean (N^2)</th>
<th>Treatment Effect (95% CI)</th>
<th>P-values for Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Oxiplex</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>&lt; 63</td>
<td>Month 1</td>
<td>40.9 (78)</td>
<td>42.4 (70)</td>
<td>-1.5 (-8.4, 5.3)</td>
</tr>
<tr>
<td></td>
<td>Month 3</td>
<td>42.7 (82)</td>
<td>44.2 (71)</td>
<td>-1.5 (-8.4, 5.5)</td>
</tr>
<tr>
<td></td>
<td>Month 6</td>
<td>43.1 (79)</td>
<td>47.2 (70)</td>
<td>-4.1 (-11.1, 2.9)</td>
</tr>
<tr>
<td>&gt;= 63</td>
<td>Month 1</td>
<td>55.9 (87)</td>
<td>53.9 (90)</td>
<td>2.0 (-5.2, 9.1)</td>
</tr>
<tr>
<td></td>
<td>Month 3</td>
<td>60.5 (86)</td>
<td>57.0 (91)</td>
<td>3.5 (-3.5, 10.5)</td>
</tr>
<tr>
<td></td>
<td>Month 6</td>
<td>59.3 (88)</td>
<td>53.3 (97)</td>
<td>6.0 (-1.4, 13.4)</td>
</tr>
</tbody>
</table>

1. This Analysis was conducted by FDA for the PMA CC population, which may show different results from the sponsor’s analysis in the in-window population  
2. Number of non-missing values  
3. From t-test, not adjusted for multiplicity  

(Panel Question #6)
Site Variability

- Tested by Treatment-by-site Interaction
- FDA Model 1
  - Remove All Five Interaction Terms from Sponsor’s GEE Model
  - Add Trt-by-site Interaction
  - P-value = 0.030 for Trt-by-site Interaction
- FDA Model 2
  - Add Site and Trt-by-site Interaction to IDE Model
  - P-value = 0.010 for Trt-by-site Interaction
- Site Variability Existed
Site Variability

Difference in 6-month Leg Pain Improvement between Oxiplex and Control by Site

1. Positive treatment effect indicates advantage of Oxiplex Group
Secondary Effectiveness Endpoints

• Hierarchical Closed Testing Procedure
• Proposal Conditionally Approved in 12/06
• Sequential Testing of Back Pain, Lower Extremity Weakness, Physical Symptoms, Patient Satisfaction, Disability Days and Activities of Daily Living
FDA’s Understanding of a Hierarchical Closed Testing Procedure

- **Primary Endpoint Significant?**
  - Yes: Stop and claim significance of the primary endpoint
  - No: 1st Secondary Significant?
    - Yes: Stop and claim significance of the primary and 1st secondary endpoint
    - No: 2nd Secondary Significant?
      - Yes: Keep Testing 3rd, 4th… Secondary Endpoints Until One Becomes Not Significant
      - No: Stop. No significance can be claimed

- **1st Secondary Significant?**
  - Yes: Stop and claim significance of the primary endpoint
  - No: 2nd Secondary Significant?
    - Yes: Stop and claim significance of the primary and 1st secondary endpoint
    - No: Stop. No significance can be claimed

- Keep Testing 3rd, 4th… Secondary Endpoints Until One Becomes Not Significant
FDA’s Assessment of Secondary Effectiveness Endpoint Analyses

- According to hierarchical closed testing procedure, these analyses should not have been performed
- Similar to primary effectiveness endpoint analyses
- Unusual model selection processes
- Complex GEE Models with multiple treatment-by-covariate interactions
- Difficult to characterize overall treatment effects of secondary endpoints
- Subsequent exploratory subgroup analyses
FDA Unadjusted Analysis – All Effectiveness Endpoints at 6-month (PMA CC Population)

Treatment Effect *

* Difference between Oxiplex and Control. Positive treatment effect indicates advantage of Oxiplex
Summary

• Primary Effectiveness Endpoint (PMA CC)
  – Overall treatment effect was not significant based on FDA’s analysis
  – Subgroup analyses were exploratory
  – Site variability may exist

• Secondary Effectiveness Endpoints (PMA CC)
  – None significant at 6 months based on FDA’s analysis
FDA Presentation

• Introduction
• Summary of Non-Clinical/Pre-Clinical Studies
• Clinical Study
• Statistical Overview
• Post-Approval Study
• Panel Questions
P070023

Oxiplex/SP Gel

Post-Approval Study (PAS)

Jiping Chen, MD, PhD, MPH
Epidemiology Branch
Division of Postmarket Surveillance
Office of Surveillance and Biometrics

Orthopaedic and Rehabilitation Devices Panel Meeting
July 15, 2008
Outline

• General principles
• Rationale for postmarket questions
• Proposed Post-Approval Study (PAS) outline
• Assessment of the PAS outline
• PAS issues for panel discussion
Reminder

• The discussion of a Post-Approval Study (PAS) prior to a formal recommendation on the approvability of this PMA should not be interpreted to mean FDA is suggesting the Panel find the device approvable.

• The plan to conduct a PAS does not decrease the threshold of evidence required to find the device approvable.

• The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness in order for the device to be found approvable.
General Principles for Post-Approval Studies

• Objective is to evaluate device performance and potential device-related problems in a broader population over an extended period of time after premarket establishment of reasonable evidence of device safety and effectiveness.

• Post-approval studies **should not** be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness.
Need for Post-Approval Studies

• Gather postmarket information
  ▪ Longer-term performance
  ▪ Real world community performance
  ▪ Effectiveness of training programs
  ▪ Sub-group performance
  ▪ Rare adverse events

• Account for Panel recommendations
Important Postmarket Questions

- What will the real world performance of the device be in the more general population of patients and providers?

- What is the long-term safety and effectiveness of the device postmarket?
### Overview of Sponsor’s PAS Outline

<table>
<thead>
<tr>
<th>Study Objective</th>
<th>To confirm the safety and reduction in disability days in subjects who receive Oxiplex during first-time lumbar disc surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design</td>
<td>Prospective, multi-center cohort, non-inferiority design with historical controls</td>
</tr>
</tbody>
</table>
| Population and Sample Size | Oxiplex PAS Group: subjects who will be treated with Oxiplex in the PAS (N = 210)  
                          Historical Controls: Oxiplex-treated subjects in the pivotal study who completed 6-month follow-up (N = 145) |
| Follow-up           | 6-month postoperative office visit                                                                                       |
## Overview of Sponsor’s PAS Outline (Cont’d)

<table>
<thead>
<tr>
<th>Effectiveness Endpoint</th>
<th>Reduction in <strong>disability days</strong> that occur over the last 30 days of the 6-month period after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothesis</td>
<td>the mean reduction in disability days for the last 30 days of the 6- month period in subjects who will receive Oxiplex is no worse than Oxiplex-treated subjects in the pivotal study (reduction in disability days) by a margin of 2.5 days (~33%).</td>
</tr>
<tr>
<td>Safety Endpoints</td>
<td>Descriptive analysis (AEs by type and overall with rates and 95% CIs):</td>
</tr>
<tr>
<td></td>
<td>▪ Procedure- and device-related AEs</td>
</tr>
<tr>
<td></td>
<td>▪ Number of re-operations; and</td>
</tr>
<tr>
<td></td>
<td>▪ Musculoskeletal and lower extremity neurological function</td>
</tr>
</tbody>
</table>
Sponsor’s PAS Outline

**FDA Assessment**

**Study Design**

- Non-inferiority design with historical controls
  - Patient comparability: PAS Oxiplex-treated group vs. Oxiplex-treated subjects in the pivotal study

- Non-inferiority margin ($\delta$) for the primary endpoint
  - The appropriateness of the margin (2.5 days = ~ 33% of the pivotal study reduction)
  - Lack of clinical justification
  - “3.5 times lower than the standard deviations“ not clear
  - The same standard deviation not applicable to both groups
Effectiveness Endpoint

The reduction in disability days that occurs over the last 30 days of the 6-month period after surgery

- Lack of justification for not using mean changes from baseline in leg pain as the primary endpoint
- Testing the statistical significance of the difference in the secondary effectiveness endpoints when the difference in the primary endpoint is not significant
Sponsor’s PAS Outline

**FDA Assessment (cont’d)**

**Safety Endpoints**

Procedure- and device-related AEs ONLY

- An underestimation of AEs
Duration of follow-up

Subjected will be followed for 6 months post surgery

- Literature: AEs (e.g. Intervertebral disc protrusion) may occur with scars within 12 month after surgery
- Postmarket: An AE report analysis with other CMC-based adhesion barrier indicated ~ 8% AEs occurred beyond 6 months
Sponsor’s PAS Outline

FDA Assessment (cont’d)

Study sample size

• N=355 [210 PAS Oxiplex subjects (156 evaluable subjects), 145 pivotal Oxiplex subjects]
• 25% drop-off rate
  • Mean 7.67 reduction in disability days in pivotal Oxiplex subjects, PAS subjects have similar value (0 in difference)
  • Non-inferiority margin of 2.5 days
  • One-sided test at alpha 0.05
  • 145 pivotal Oxiplex subjects

• Sample size = 154 for PAS Oxiplex subjects
• Develop a better plan to minimize loss to follow-up
• Lack of measures to be taken if the number of subjects falls below 355 during follow-up
PAS Issues for Panel Discussion

1. Study Objective/Question

**Planned:** To confirm device safety, and reduction in disability days, in subjects who receive Oxiplex during first-time lumbar disc surgery

**Issue:**

- Appropriateness of the objective/question to be studied in a PAS to address device long-term safety/effectiveness
PAS Issues for Panel Discussion

2. Study Design

Planned: Non-inferiority design to compare the reduction in disability days in PAS Oxiplex-treated patients vs. the Oxiplex-treated patients in the pivotal study

Issue:
• Appropriateness of the study design to address device long-term safety/effectiveness
• Appropriateness of the non-inferiority margin (2.5 days)
3. Control Selection

**Planned:** Oxiplex-treated PAS population vs. Oxiplex-treated subjects in pivotal study (historical controls)

**Issue:**

- Appropriateness of the study population to address device safety/effectiveness postmarket
PAS Issues for Panel Discussion

4. Effectiveness Endpoint

**Planned:** The reduction in disability days that occur over the last 30 days of the 6-month period after surgery

**Issue:**
- Appropriateness of the endpoint to address device long-term effectiveness
5. **Duration of Follow-up**

**Planned:** 6 months of follow-up

**Issue:**
- Optimal duration of follow-up to address device safety/effectiveness postmarket
Reminder

• The discussion of a Post-Approval Study (PAS) prior to a formal recommendation on the approvability of this PMA should not be interpreted to mean FDA is suggesting the Panel find the device approvable.

• The plan to conduct a PAS does not decrease the threshold of evidence required to find the device approvable.

• The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness in order for the device to be found approvable.
Questions?