Food and Drug Administration
Orthopaedic and Rehabilitation Devices Panel
March 31, 2009

OP-1 Putty
for Posterolateral Lumbar Spinal Fusion in Adult Patients with Degenerative Spondylolisthesis

Stryker
Biotech
CC-1
Introduction and Overview

Julie Krop, M.D.
Vice President, Clinical and Regulatory Affairs
Stryker Biotech
Presentation Agenda

Introduction and Overview of Product

Overview of Degenerative Spondylolisthesis and Unmet Medical Need

Preclinical Overview

Pivotal Trial Data

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Presentation Agenda

Radiologic Issues

Lee D. Katz, M.D.
Professor
Head of Musculoskeletal Radiology
Yale University Medical School

Relevance of the Antibody Response

Huub Schellekens, M.D., Ph.D.
Professor of Pharmaceutical Biotechnology
Department of Pharmaceutical Sciences
Utrecht University

Statistical Overview

Eugene Poggio, Ph.D.
President
Chief Biostatistician
Biostatistical Consulting, Inc.

Context for Understanding Data in a Clinical Setting

David Wong, M.D., FRCSC
Director
Advanced Center for Spinal Microsurgery
Presbyterian St. Luke’s Medical Center, Denver
Past President, North American Spine Society
External Experts Available to Committee

Victor DeGruttola, Ph.D.
Acting Head of Biostatistics Department
Harvard School of Public Health

Michael G. Fehlings, M.D., Ph.D., FRCSC
Professor of Neurosurgery
Chairman of Neuroscience, Krembil Endowed Chair
University of Toronto

Jonathan Grauer, M.D.
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Co-Director, Orthopedic Spine Service
Yale University Medical School

Lee-Jen Wei, Ph.D.
Professor, Biostatistics
Scientific Director of the Program of Quantitative Science in Pharmaceutical Industry
Harvard School of Public Health
OP-1 Putty: Proposed Indication

For use in posterolateral lumbar spinal fusion in adult patients with Grade I or Grade II degenerative spondylolisthesis who have failed at least 6 months of conservative therapy.
Why Product Needed:

1. Degenerative spondylolisthesis is a common problem:
   - Strong evidence for use of decompression and fusion surgery in these patients*

2. Iliac crest bone graft standard of care but has significant drawbacks including:
   - Increased pain and morbidity due to bone graft harvest
   - Sub-optimal bone graft material in certain patients
     - Osteoporosis
     - Diabetes
     - Poor vascularity

3. No approved alternative for these patients

Device Description and HDE Approval

- OP-1 Putty: 3.5 mg rhBMP-7 (OP-1) + 1 gram Type 1 Bone Collagen + 230 mg Carboxymethylcellulose (CMC)
- Putty-like consistency

HDE Approved Indication (2004)

“Alternative to autograft in compromised patients requiring revision posterolateral lumbar spinal fusion, for whom autologous bone and bone marrow harvest are not feasible or are not expected to promote fusion.”
OP-1 Putty is Safe

- Extensive preclinical studies conducted
- Identical product approved in the U.S. under a Humanitarian Device Exemption (HDE)
  - 15,000 patients treated with OP-1 Putty in the U.S.
- Additional 25,000 patients treated with the drug product world-wide since 2001
- No specific safety trends observed
OP-1 Putty is Effective

- 24 month follow-up: Clinically comparable to iliac crest autograft on 6/7 endpoints
- 36+ month follow-up extension study: Clinically comparable on all 7 endpoints using more sensitive CT scan
- All other clinically relevant endpoints (SF-36, VAS) also clinically comparable
Rigorous Composite Endpoint

- Overall Success required “success” on all 7 endpoints:

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>“Success” Criterion</th>
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<td>• ≤ 3 mm of translational movement</td>
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Unmet Medical Need

- OP-1 Putty eliminates need for autograft harvest
  - Avoids autograft harvest site pain and other potential complications associated with autograft harvest
  - Decreased operative time/ anesthesia exposure
  - Decreased intra-operative blood loss
Overview of Degenerative Spondylolisthesis and Unmet Medical Need

Jeff Fischgrund, M.D.
Principle Investigator
Editor-in-Chief, J Am Acad of Ortho Surg
Spine Surgeon, Beaumont Hospital

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Overview

1. Degenerative spondylolisthesis is an important clinical problem
   - Natural history is well understood
   - Treatment with decompression and fusion strongly supported by level 1 clinical trial evidence*

2. Current gold standard therapy, fusion with iliac crest autograft, can be problematic in many patients

3. Alternative therapy needed

Degenerative Spondylolisthesis

- Degenerative changes
- Elderly
- Associated with stenosis
- Back, leg pain
- Diminished quality of life
  - Difficulty walking
  - Loss of independence

Grade I Slip
Spondylolisthesis Grading System

- % Slip
  - Grade I < 25%
  - Grade II 25-50%

% SLIP = \( \frac{a}{A} \times 100 \)
Treatment

• First line - conservative
  • Meds
  • Physical therapy
  • Epidural steroids
• Surgery
  • Decompression
  • Fusion-autograft
# SPORT Study

## Population: Degenerative Spondylolisthesis with Stenosis

Outcomes at 24 months (changes from baseline)

<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>Conservative Therapy</th>
<th>Treatment Effect of Surgery (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ODI</strong></td>
<td>-24.2</td>
<td>-7.5</td>
<td>-16.7 (-19.5 to -13.9)</td>
</tr>
<tr>
<td><strong>Physical function: SF-36</strong></td>
<td>26.6</td>
<td>8.3</td>
<td>18.3 (14.6 to 21.9)</td>
</tr>
<tr>
<td><strong>Bodily pain: SF-36</strong></td>
<td>29.9</td>
<td>11.7</td>
<td>18.1 (14.5 to 21.7)</td>
</tr>
</tbody>
</table>

Treatment Options

- Decompression alone (no fusion)
  - Poor results
  - Recurrent leg pain
  - Continued back pain
  - Progressive instability
Post-Laminectomy Instability

Decompression → No Fusion → Fusion
Decompression Alone

• Decompression only
  • Clinical outcome:
    • Excellent-Good 44%
    • Listhesis 5.3→7.9 mm

• Decompression + fusion
  • Clinical outcome:
    • Excellent-Good 96%
    • Listhesis 4.8→5.3 mm

Patients treated with decompression alone have poor outcomes

Goal of Fusion Surgery

- Create a bony union across involved vertebrae resulting in:
  - Stability
  - Good long term outcome
Iliac Crest Autograft

- “Gold standard”
- Additional surgery
  - Time
  - Pain
  - Complications
Bone Graft Harvesting
Major Complications Due to Iliac Crest Bone Harvest

- Study evaluated 414 patients
  - 6% major complications
    - Donor defect herniations
    - Vascular injuries
    - Nerve injuries
    - Deep infections
    - Deep hematomas
    - Iliac wing fractures

- 10% minor complications

<table>
<thead>
<tr>
<th>Author</th>
<th>n (% )</th>
<th>n (% )</th>
<th>n (% )</th>
<th>n (% )</th>
<th>n (% )</th>
<th>n (% )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frymoyer (n = 96)</td>
<td>35 (37)</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>35 (37)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Fernyhough (n = 151)</td>
<td>44 (29)</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>5 (3)</td>
<td></td>
</tr>
<tr>
<td>Younger (n = 243)</td>
<td>71 (29)</td>
<td>21 (9)</td>
<td>50 (21)</td>
<td>6 (3)</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Banwart (n = 195)</td>
<td>88 (45)</td>
<td>3 (2)</td>
<td>20 (10)</td>
<td>*</td>
<td>53 (27)</td>
<td>*</td>
</tr>
<tr>
<td>Summers (n = 82)</td>
<td>40 (49)</td>
<td>*</td>
<td>*</td>
<td>40 (49)</td>
<td>*</td>
<td>25 (32)</td>
</tr>
<tr>
<td>Goulet (n = 87)</td>
<td>33 (38)</td>
<td>*</td>
<td>*</td>
<td>33 (38)</td>
<td>16 (18)</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Mirovsky (n = 48)</td>
<td>9 (19)</td>
<td>*</td>
<td>*</td>
<td>9 (19)</td>
<td>9 (19)</td>
<td></td>
</tr>
<tr>
<td>Schnee (n = 184)</td>
<td>13 (7)</td>
<td>5 (3)</td>
<td>8 (4)</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

**Overall Complications** 8 studies 333 (31)

**Major Acute** 3 studies 29 (5)

**Minor Acute** 3 studies 78 (13)

**Pain > 6 months** 3 studies 79 (19)

**Pain > 24 months** 4 studies 113 (27)

**Severe Pain** 4 studies 53 (11)
Unmet Need-Autograft Alternative

- Infuse (Rh-BMP2)
- Anterior fusion approval
- LT cage
Unmet Need for Autograft Alternative

- Posterolateral fusion
- Most common procedure
- Iliac crest harvest
Unmet Need for Autograft Alternative

- No approved BMP
- Surgeons looking for approved alternatives
- Decrease patient morbidity
Preclinical Overview

Dean Falb, Ph.D.
Vice President Research and Development
Stryker Biotech
Preclinical Overview

- OP-1 Basic Biology
- Efficacy Studies/Dose Selection
- Toxicology Studies
- Immunogenicity Studies
- Summary
Bone Morphogenetic Proteins

- First described by Marshall Urist in 1965
- Involved in fracture healing cascade
- >20 BMPs identified
OP-1 induces a molecular cascade resulting in new bone formation.
OP-1 Putty

Carrier Selection
Carrier Selection

Bone formation requires matrix + BMP combination
Manufacturing Process

OP-1 protein and the collagen matrix are combined during manufacturing.
OP-1 Manufacturing Process
Sterilization Effects

Sterilized OP-1 induces osteoblast differentiation
OP-1 Putty
Consistency of Manufacturing

Biological Activity of $\gamma$-Irradiated OP-1 Lots Manufactured 1999-2005
OP-1 Manufacturing Process

BMP-7

Type-1 Collagen

Sterilize

Bioactivity

Validated Release Assay

Acceptable Activity Range

 Released OP-1 meets validated activity specifications.
Changes induced by sterilization are characterized and controlled.
OP-1 Putty

OP-1 Efficacy/Dose Selection
### Efficacy
**Multiple Models, Species and Collaborators; Adverse Environments**

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Species</th>
<th>Model</th>
<th>Fusion Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cunningham</td>
<td>Baboon</td>
<td>Instrumented PLF</td>
<td>100%</td>
</tr>
<tr>
<td>Diwan</td>
<td>Rat</td>
<td>Osteoporotic PLF</td>
<td>100%</td>
</tr>
<tr>
<td>Grauer</td>
<td>Rabbit</td>
<td>Nicotine PLF</td>
<td>82%</td>
</tr>
<tr>
<td>Jenis</td>
<td>Sheep</td>
<td>PLF</td>
<td>100%</td>
</tr>
<tr>
<td>Cunningham</td>
<td>Dog</td>
<td>PLF</td>
<td>77%</td>
</tr>
</tbody>
</table>
Efficacy – Dose Selection
Rat Bone Nodule Dose Curve

Reconstituted OP-1 Putty

Quantification of Bone Mineral Content by PIXI

Threshold concentration of OP-1 in matrix required to initiate bone formation cascade

Efficacy – Dose Selection
African Green Monkey Dose Response

- Critical-size tibial defect (African green monkey)
- Complete healing at 20 weeks

Efficacy – Dose Selection
Baboon PLF Fusion Data

Clinical Concentration

Percent Animals Fused

- Autograft
- Carrier alone
- 0.33 mg/cc
- 1.0 mg/cc
- 2.0 mg/cc
- 4.0 mg/cc

12 weeks
16 weeks

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Efficacy – Dose Selection
Baboon PLF Bone Volume Data (CT)

- Autograft
- 1 mg/cc OP-1
- 4 mg/cc OP-1

Total Fusion Volume at 4 Months

OP-1 Putty Treatment (mg/cc)

0 0.33 1.0 2.0 4.0 Autograft

Volume mm³

Excessive Bone

Efficacy
Baboon PLF Histology Data

57% of bone density in autograft is residual graft particles


Efficacy
Different Mechanisms of Bone Formation

Autograft Group

OP-1 Putty Group

Bone Volume by CT

Surgically implanted Autograft

New Bone Formation

Percent Bone Present

Surgery

Time Post Surgery (Months)

100%

57%

43%

100%

Percent Bone Present

Surgery

Time Post Surgery (Months)

Bone Volume by CT

New Bone Formation

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Efficacy/Dose Selection Summary

- Clinical dose chosen above the threshold for bone formation
  - Dose based on rat, rabbit, dog and primate studies
  - Clinical dose (1 mg/cc) consistently above threshold in multiple models
  - Basis for selection consistent with other BMP filings
- Spine fusion efficacy shown in multiple species and models
- Autograft is radiopaque and apparent CT volume includes unincorporated graft
- OP-1 is radiolucent and all bone volume seen on CT is de novo bone
OP-1 Putty

OP-1 Safety Studies
Pharmacokinetics: IV Study

Serum Clearance Following a Single IV Dose of BMP-7

- Blood levels never exceed more than 3% of the implanted dose
- OP-1 serum half-life less than 1 Hour

T1/2 elimination:
M: 0.3 h for monkey
R: 0.8 h for rat
# Toxicology
Systemic, Implantation and Physiologic Safety

<table>
<thead>
<tr>
<th>Study</th>
<th>Species</th>
<th>Duration</th>
<th>Fold Human Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic intravenous</td>
<td>Mouse Rat Monkey</td>
<td>Acute (1 injection) Subacute (up to 28 days)</td>
<td>20 - 70X</td>
</tr>
<tr>
<td>Implantation</td>
<td>Rat Hamster</td>
<td>14 days-13 weeks</td>
<td>3.5 - 69X</td>
</tr>
<tr>
<td>Physiologic safety</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS CV Respiratory</td>
<td>Rat Rat, Dog Dog</td>
<td>Acute single dose</td>
<td>30 - 35X</td>
</tr>
</tbody>
</table>

No significant observations at high multiples of clinical dose
## Toxicology

### Developmental Toxicology Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Formulation</th>
<th>Safety Margin</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat intravenous</td>
<td>OP-1 protein in acetate buffer</td>
<td>35X for 12 days</td>
<td>No Observations</td>
</tr>
<tr>
<td>Rat intravenous</td>
<td>OP-1 in 5% lactose</td>
<td>4X for 12 days</td>
<td>No Observations</td>
</tr>
<tr>
<td>Rabbit intravenous</td>
<td>OP-1 in 5% lactose</td>
<td>4x for 13 days</td>
<td>No Observations</td>
</tr>
</tbody>
</table>

No developmental abnormalities observed
OP-1 Putty

OP-1 Immunogenicity Studies
Immunogenicity Assays

- Binding antibodies detected by ELISA
- Neutralizing status evaluated by cell-based assays
- Assays were developed based on FDA recommendations and were validated to meet FDA guidelines
- Positives identified using a statistically-based cut point defined to allow for a 5% false positive rate

Reported immunogenicity results are accurate
OP-1 initiates a cascade which perpetuates itself to form bone
Immunogenicity and Efficacy: Baboon PLF Study

OP-1 Antibodies in Baboon PLF

OP-1 Putty 1 mg/cc

Baboon with high baseline OP-1 antibodies fuses successfully
Pre-existing Anti-BMP Antibodies


**Significant numbers of healthy individuals have spontaneous anti-BMP antibody titers**
Developmental Toxicology
Effect of OP-1 Immunization

- Female rabbits immunized with OP-1 prior to mating and then boosted 3 times
- Very high anti-OP-1 titers seen in mothers and F1’s
- Study A completed at term
- Study B completed after F1 generation is 28 days old

Female rabbits intentionally immunized with OP-1 to study effects on offspring
Developmental Toxicology
Effect of OP-1 Immunization

- All rabbits (dams and fetuses) developed strong immunoreactivity to OP-1 (IgG and IgM)
- No effects on female fertility or fetal mortality
- No effect on body weight, food consumption, ovarian or uterine parameters
- Limited effects noted - within normal range for historical controls
- Kidney histology normal in kits
OP-1 Immunogenicity
Preclinical Efficacy and Safety

• Efficacy
  • Efficacy seen in all models regardless of antibody response

• Safety
  • No immune-related safety observations
  • Normal development occurs in the presence of antibodies

• Spontaneous BMP antibodies seen in 5-10% of healthy individuals
Summary

- Dose selection based on multiple preclinical studies
- Systemic toxicology studies show no adverse effects
- Local toxicology studies show no significant observations
- Safety pharmacology studies show no effects
- Developmental toxicology studies show no significant abnormalities
- Developmental immunization studies show no significant abnormalities
Pivotal Trial Data

Julie Krop, M.D.
Vice President, Clinical and Regulatory Affairs
Stryker Biotech
Overview

Non-inferiority study comparing OP-1 Putty to autograft

1. All clinically relevant outcomes in study were comparable between OP-1 Putty and autograft

2. Radiographic success rates using well accepted criteria were comparable between OP-1 Putty and autograft

3. Safety outcomes were reassuring and comparable between OP-1 Putty and autograft

4. OP-1 Putty patients had high rates of neurologic success that were at least as good, if not better than, autograft
   - Important because we know other BMP’s have been associated with neural complications
Study Design

• Pivotal study designed in 1999 – Input from FDA
  • Uninstrumented fusion still commonly performed
  • Plain x-rays still standard of care

• Objective: Isolate effect of OP-1 without potential confounding effect of instrumentation
  • Most challenging model to induce fusion
  • Based on historical control data there is only a 45% overall success rate with autograft alone¹

• Preclinical and case series data support efficacy in instrumented fusion²
  • Instrumentation enhances stability
  • Instrumentation likely to lead to higher rates of fusion (83% instrumented vs. 45% uninstrumented)¹

Study Design

- Randomized, controlled, pivotal trial
  - 25 centers, U.S. + Canada
  - Treatment group: OP-1 Putty at a dose of 1 unit per side for a total of 2 units
  - Control group: Autograft
  - Uninstrumented study
  - Non-inferiority design

- Patient Population
  - Degenerative lumbar spondylolisthesis, Grade I-II that have failed 6 months of conservative therapy
  - Symptomatic spinal stenosis
  - All patients underwent decompressive laminectomy

- Primary Endpoint: Overall Success
  - 208 patients treated with OP-1 Putty
  - 87 patients treated with autograft

Designed as a 2:1 randomization
Key Entry Criteria

- Skeletally mature male or female less than 85 years of age
- Not of child-bearing potential (must be post-menopausal or have undergone hysterectomy)
- No prior exposure to ANY bone morphogenetic protein
- No active spinal or systematic infection and no active malignancy
- Diagnosis of Grade I or Grade II degenerative lumbar spondylolisthesis with spinal stenosis and radiculopathy
- Candidate for decompression and spinal fusion with the use of autograft from the iliac crest
- Require only one level of lumbar fusion (L-3 to S-1)
- No history of previous fusion attempts to the affected spinal level
- Non-responsive to at least 6 months of non-operative treatment prior to study enrollment
- Preoperative Oswestry Disability Index of 30-100
- ≤ 20 degrees of angular movement and ≤ 50% translation
Primary Endpoint at 24 Months

Overall Success required “success” on all 7 endpoints:

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Key Additional Endpoints

- Individual components of Overall Success
- SF-36 - validated measure of quality of life
- Visual Analog Scale (VAS) pain assessment
- Operative time, blood loss
- Donor site pain (autograft only)
### Selected Demographic and Baseline Characteristics - Pivotal Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Statistic</th>
<th>OP-1 Putty</th>
<th>Autograft</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean</td>
<td>68</td>
<td>69</td>
<td>0.129</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td>0.501</td>
</tr>
<tr>
<td>Male</td>
<td>%</td>
<td>34.3</td>
<td>30.2</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>%</td>
<td>65.7</td>
<td>69.8</td>
<td></td>
</tr>
<tr>
<td>Level fused</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L3-L4</td>
<td>%</td>
<td>10.1</td>
<td>11.6</td>
<td>0.760</td>
</tr>
<tr>
<td>L4-L5</td>
<td>%</td>
<td>86.0</td>
<td>86.0</td>
<td></td>
</tr>
<tr>
<td>L5-S1</td>
<td>%</td>
<td>3.9</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Oswestry Disability Index</td>
<td>Mean</td>
<td>48.8</td>
<td>48.8</td>
<td>0.998</td>
</tr>
<tr>
<td>Angulation (degrees)</td>
<td>Mean</td>
<td>3.9</td>
<td>4.7</td>
<td>0.086</td>
</tr>
<tr>
<td>Translational movement (mm)</td>
<td>Mean</td>
<td>1.7</td>
<td>1.6</td>
<td>0.802</td>
</tr>
<tr>
<td>Diagnosis of degenerative lumbar spondylolisthesis with spinal stenosis</td>
<td>%</td>
<td>100.0</td>
<td>100.0</td>
<td>0.443</td>
</tr>
<tr>
<td>Grade 1</td>
<td>%</td>
<td>93.2</td>
<td>91.9</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>%</td>
<td>3.9</td>
<td>2.3</td>
<td></td>
</tr>
</tbody>
</table>

No difference in any baseline characteristics
Components of Overall Success at 24 Months

Difference in Success Rates at 24 Months for Components of Modified Overall Success, mITT 95% Confidence Intervals

- Neurologic Success
- No Retreatment
- No Treatment Related SAEs
- ODI
- Angulation Success
- Translation Success
- Presence of Bone
- Average

* 90% confidence interval
Missing or non-evaluable data are excluded

CC-70
24 Month Results

Question: Why were all endpoints comparable except presence of bone?

- CT scans originally read for inter-transverse bone formation only were carefully re-evaluated
  - Scans collected at 9 months only and were not part of the original primary endpoint
  - Bone formation was present but was more medial than anticipated
  - Medial location of the bone formation led to underestimation of presence of bone at 24 months - readers instructed to look only for inter-transverse process fusion on x-ray
  - Plain x-rays provide poor visualization of medial bone
    - Vertebrae themselves may block the visualization of medial bone
Medial Conformity

Figure 1
Initial placement of OP-1 Putty

Figure 2
Upon release of muscle retraction, OP-1 Putty conforms to medial, bony anatomy
24 Month Plain Radiograph vs. 9 Month CT Scan

AP X-ray

No visible bone on plain radiograph

Coronal Multiplanar Reformatted Image

Significant bone formation medially
Extension Study

- Designed extension study to correct for insensitivity of plain films and assess the efficacy of OP-1 Putty compared to autograft using a more sensitive imaging modality
  - 36+ month CT scans
  - Mean follow-up = 4.4 years
- Also collected:
  - 36+ month assessments of angulation, translation and all clinical endpoints
- Protocol and statistical analysis plan finalized prior to data collection and analysis
Disposition of Patients in Pivotal and Extension Studies

Randomized and Treated in Pivotal Study N=295

OP-1 Putty N=208
- 7 (3%) Died During Pivotal Study
- 18 (9%) Retreatment Failure During Pivotal Study
- 4 (2%) Deaths After Completion of Pivotal Study

Autograft N=87
- 4 (5%) Died During Pivotal Study
- 8 (9%) Retreatment Failure During Pivotal Study
- 1 (1%) Deaths After Completion of Pivotal Study

Total Eligible for Extension Study N=252*
- 179
- 35 (20%) Not Enrolled in Extension Study (refusals, unable to locate)

Total Enrolled in Extension Study N=202
- 144

Not Enrolled in Extension Study N=73
- 15 (20%)

Extension study enrollment 202/252 = 80.2%

* Excludes 1 patient with no post-baseline visit
## Comparison of Key Clinical Parameters for Eligible and Enrolled Patients in 36+ Month Follow-Up Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Statistic</th>
<th>OP-1 Putty</th>
<th>Autograft</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Eligible</td>
<td>Enrolled</td>
</tr>
<tr>
<td>Age</td>
<td>Mean</td>
<td>67.6</td>
<td>66.8</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>%</td>
<td>35.0</td>
<td>34.7</td>
</tr>
<tr>
<td>Female</td>
<td>%</td>
<td>65.0</td>
<td>65.3</td>
</tr>
<tr>
<td>Degree of Angular Motion (degrees) - Baseline</td>
<td>Mean</td>
<td>4.0</td>
<td>4.1</td>
</tr>
<tr>
<td>Translational Movement (mm) - Baseline</td>
<td>Mean</td>
<td>1.7</td>
<td>1.8</td>
</tr>
<tr>
<td>ODI - Baseline</td>
<td>Mean</td>
<td>48.5</td>
<td>48.2</td>
</tr>
<tr>
<td>Overall success at 24 months</td>
<td>%</td>
<td>42.9</td>
<td>43.8</td>
</tr>
</tbody>
</table>
Primary Endpoint at 36+ Months

- Primary endpoint is the same as original endpoint except radiographic assessment uses CT scan
  - Needed to address insensitivity of plain films at evaluating medial bone formation
- 36+ month time point also used to assess retreatment rate - most significant clinical endpoint
Overall Success Using 36+ Month Radiographic Data

Non-Inferiority Endpoint Achieved

<table>
<thead>
<tr>
<th>Overall Success</th>
<th>OP-1 Putty</th>
<th>Autograft</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>47.2</td>
<td>46.8</td>
</tr>
</tbody>
</table>

p = .025

11.6% upper bound of difference
Components of Overall Success, (36+ Month Radiographic Data) mITT

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OP-1 Putty</th>
<th>Autograft</th>
<th>P-Value Superiority&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical and Safety Parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Oswestry Disability Index (24 Months)</td>
<td>74.5%</td>
<td>75.7%</td>
<td>0.839</td>
</tr>
<tr>
<td>• Absence of Retreatment (36+ Months)</td>
<td>87.0%</td>
<td>83.3%</td>
<td>0.529</td>
</tr>
<tr>
<td>• Absence of Serious Treatment-related AEs (24 Months)</td>
<td>85.6%</td>
<td>84.7%</td>
<td>0.863</td>
</tr>
<tr>
<td>• Neurological Success (24 Months)</td>
<td>92.1%</td>
<td>84.1%</td>
<td>0.057</td>
</tr>
<tr>
<td><strong>Components of Overall Radiographic Success at 36+ Months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Angular motion ≤ 5 degrees at 36+ Months&lt;sup&gt;2&lt;/sup&gt;</td>
<td>69.3%</td>
<td>68.4%</td>
<td>1.000</td>
</tr>
<tr>
<td>• Translational movement ≤ 3 mm at 36+ Months&lt;sup&gt;2&lt;/sup&gt;</td>
<td>75.7%</td>
<td>75.4%</td>
<td>1.000</td>
</tr>
<tr>
<td>• Presence of Bone by 36+ month CT Scan&lt;sup&gt;2&lt;/sup&gt;</td>
<td>74.8%</td>
<td>77.4%</td>
<td>0.852</td>
</tr>
</tbody>
</table>

Remarkable consistency across all components of the primary endpoint

---

<sup>1</sup> P-value is based on Fisher’s exact test

<sup>2</sup> Missing or non-evaluable data are excluded
Radiographic and Clinical Outcomes at 36+ Months

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OP-1 Putty</th>
<th>Autograft</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical and Safety Parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Oswestry Disability Success (36+ months)</td>
<td>68.6%</td>
<td>77.3%</td>
<td>0.201(^1)</td>
</tr>
<tr>
<td>• Absence of retreatment (36+ months)</td>
<td>87.0%</td>
<td>83.3%</td>
<td>0.529(^1)</td>
</tr>
<tr>
<td>• Absence of serious treatment related adverse events (36+ months)</td>
<td>79.5%</td>
<td>73.5%</td>
<td>0.387(^1)</td>
</tr>
<tr>
<td>• Neurological Success (36+ Months)</td>
<td>84.4%</td>
<td>80.0%</td>
<td>0.540(^1)</td>
</tr>
<tr>
<td><strong>Radiographic Parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Angulation</td>
<td>69.3%</td>
<td>68.4%</td>
<td>1.000</td>
</tr>
<tr>
<td>• Translation</td>
<td>75.7%</td>
<td>75.4%</td>
<td>1.000</td>
</tr>
<tr>
<td>• Presence of bone</td>
<td>74.8%</td>
<td>77.4%</td>
<td>0.852</td>
</tr>
</tbody>
</table>

**Overall success using 36+ month data for all parameters not statistically different between treatment groups**

\(^1\) P-value is based on Fisher’s exact test
Retreatment Failure Over Time

* Includes patients not shown whose retreatment occurred after 1200 days (4 OP-1; 1 autograft)
Insensitivity of Plain Films in Pivotal Study

• Insensitivity of plain films further supported by analysis of all OP-1 patients who did not have presence of bone by plain film at 24 months, and of those patients:
  • 71% exhibited presence of bone by CT scan at 36+ months
    • 81.5% of those patients had medial bone formation
### Key Additional Endpoints

#### Visual Analog Scale for Right, Lower Extremity at 24, and 36+ Months

<table>
<thead>
<tr>
<th>Visit</th>
<th>Statistic</th>
<th>OP-1 Putty Change from Baseline</th>
<th>Autograft Change from Baseline</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 Month</td>
<td>Mean</td>
<td>-3.1</td>
<td>-2.9</td>
<td>0.681</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>36+ Month</td>
<td>Mean</td>
<td>-3.2</td>
<td>-2.6</td>
<td>0.301</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

#### SF-36 Physical Function Score

<table>
<thead>
<tr>
<th>Visit</th>
<th>Statistic</th>
<th>OP-1 Putty Change from Baseline</th>
<th>Autograft Change from Baseline</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 Months</td>
<td>Mean</td>
<td>11.8</td>
<td>11.3</td>
<td>0.636</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>36+ Months</td>
<td>Mean</td>
<td>11.4</td>
<td>9.7</td>
<td>0.206</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>
Intraoperative Clinical Benefits

• Mean operative times shorter for OP-1 Putty
  • 144 minutes (OP-1 Putty) vs. 164 minutes (autograft) - p=0.006

• Mean estimated blood loss was lower for OP-1 Putty
  • 309 cc (OP-1 Putty) vs. 471 cc (autograft): p=0.0004

Shorter operative times and reduced blood loss are important clinical benefits
## Donor Site Pain in Autograft Subjects

<table>
<thead>
<tr>
<th>Visit</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>55.6%</td>
<td>23.6%</td>
<td>20.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td>24 months</td>
<td>54.5%</td>
<td>29.1%</td>
<td>14.5%</td>
<td>1.8%</td>
</tr>
<tr>
<td>36+ months</td>
<td>65.4%</td>
<td>17.3%</td>
<td>17.3%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

Pain associated with autograft is common and of substantial duration
Autograft Harvest Related Adverse Events

- Serious adverse events:
  - Intraoperative hemorrhage
  - Anemia – 2 days postoperatively

- Adverse events:
  - Donor site complications: 9.2%
    - 2 donor site infections
    - 3 excessive donor site pain
    - 3 donor site pain
Safety Summary

- OP-1 Putty marketed under Humanitarian Device Exemption
  - Alternative to autograft in compromised patients requiring revision posterolateral fusion for whom autologous bone or bone marrow harvest are not feasible or are not expected to promote fusion
- Over 15,000 patients treated in U.S. under HDE approval since 2004
  - No trends in serious adverse events have been seen
  - Average of 0.28 adverse events reported per 100 units of OP-1 Putty sold in U.S.
- Additional 25,000 patients treated with OP-1 product world-wide
  - OP-1 Implant in U.S., Osigraft in Europe, Canada and Australia

Pivotal trial safety profile consistent with post-marketing data
Pivotal Study Safety Summary

- Safety of OP-1 Putty treatment in PLF is similar to that of autograft treatment with respect to the proportion of patients experiencing:
  - Treatment-emergent adverse events
  - Treatment-related adverse events
  - Serious adverse events
  - Neurologic complications
  - Neoplasms
  - Deaths
<table>
<thead>
<tr>
<th>System Organ Class Preferred Term</th>
<th>Percent of Patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OP-1 Putty (n=208)</td>
<td>Autograft (n=87)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>3.4%</td>
<td>6.9%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>0.5%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Arthritis</td>
<td>0.5%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Back pain</td>
<td>0.5%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Lumbar spinal stenosis</td>
<td>1.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Musculoskeletal stiffness</td>
<td>0.0%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>0.5%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Spinal column stenosis</td>
<td>0.5%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Radiculopathy</td>
<td>1.4%</td>
<td>3.5%</td>
</tr>
</tbody>
</table>
Deaths – Pivotal and Extension Studies

• 16 patients died during study participation
  • 11 (5.3%) in OP-1 Putty group \( p=1.000 \)
  • 5 (5.8%) in the autograft group
• No significant trends observed in cause of death by treatment group
Malignancy/Carcinogenicity – Pivotal and Extension Studies

• No malignancies had causal relationship to OP-1 Putty or autograft
  • 24 patients had adverse events associated with malignancy
  • 8 (3.8%) in the OP-1 Putty group, and 6 (6.9%) in the autograft group: \( p = 0.2413 \)
Heterotopic Bone

- Heterotopic bone was defined as any bone seen outside the intended area of fusion
- 24 patients with radiographic evidence of heterotopic bone
  - No incisional bone formation
  - No bone formation in the canal
  - All had extension of bone towards the adjacent levels
- 3 adverse events related to heterotopic bone
  - None required intervention
The immune response to OP-1 is transient. Mean titers back to baseline by 24 months.
Incidence of Neutralizing Antibodies

No neutralizing antibodies detected by 24 months
Assessment of Immunogenicity Impact on Safety and Efficacy

• Impact on efficacy
  • Overall Success
  • Components of Overall Success
    • Radiographic success
    • ODI success
    • Absence of retreatment
    • Neurological success

• Impact on safety
  • Adverse events and serious adverse events
# No Impact of Neutralizing Antibodies

<table>
<thead>
<tr>
<th></th>
<th>Neutralizing Antibody Positive</th>
<th>Neutralizing Antibody Negative</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Success</td>
<td>36.4%</td>
<td>38.2%</td>
<td>0.86</td>
</tr>
<tr>
<td>Radiographic success</td>
<td>52.5%</td>
<td>57.0%</td>
<td>0.71</td>
</tr>
<tr>
<td>ODI success</td>
<td>68.0%</td>
<td>73.2%</td>
<td>0.47</td>
</tr>
<tr>
<td>Absence of retreatment</td>
<td>88.7%</td>
<td>90.3%</td>
<td>0.79</td>
</tr>
<tr>
<td>Neurologic success</td>
<td>88.0%</td>
<td>89.4%</td>
<td>0.79</td>
</tr>
<tr>
<td>Absence of treatment-related SAEs</td>
<td>77.4%</td>
<td>87.0%</td>
<td>0.12</td>
</tr>
</tbody>
</table>

No impact of neutralizing antibodies on efficacy of any of the clinical subcomponents of Overall Success
## Adverse Events by Neutralizing Antibody Status

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Neutralizing Status</th>
<th>% of Patients</th>
<th>Total No. with Adverse Events</th>
<th>Total No. with Serious Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>OP-1 Putty</td>
<td>Positive</td>
<td>35.8</td>
<td></td>
<td>11.3</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>39.6</td>
<td></td>
<td>12.3</td>
</tr>
</tbody>
</table>
Immunogenicity - Safety

• Antibodies to OP-1 Putty do not pose safety risk to patients
  • 5-10% of patients have antibodies against OP-1 Putty prior to exposure
  • More than 40,000 patients on a worldwide basis treated with either OP-1 Putty or OP-1 Implant
    • No safety signals related to immunogenicity have emerged
  • Pivotal trial patients evaluated for adverse events related to immunogenicity
    • No difference in adverse event profile seen between patients with neutralizing antibodies and those without
    • Serum creatinine showed no differences from baseline
Summary

Difference in Success Rates by Components of Overall Success, mITT
95% Confidence Intervals

1) Neurologic
2) No Retreatment
3) No Treatment-Related
4) ODI
5) Angulation Success
6) Translation Success
7) Presence of Bone

Average*

Favors Autograft ← -10 0 10 30 50 Favors OP-1

* 90% confidence interval
Missing or non-evaluable data are excluded

CC-99
Conclusion

- OP-1 Putty is safe and avoids the morbidity associated with autograft bone harvest
  - Safety profile reinforced by data from 36+ month extension study and extensive post-marketing data
- OP-1 Putty achieved clinical success on all key clinical parameters
  - Persists through 36+ months which is a clinically more rigorous time point
Radiologic Issues

Lee D. Katz, M.D.
Professor
Head of Musculoskeletal Radiology
Yale University Medical School
Radiographic Success Definition

- Angulation $\leq 5^\circ$
- Translation $\leq 3$ mm

Measures of stability

- Presence of bone – marker of OP-1 activity
- Definition is strongly supported by 2005 consensus guidelines

Radiographic Success Measures

Guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine.
Part 4: radiographic assessment of fusion

1. The assessment of fusion status by static plain radiography is only accurate in approximately two thirds of patients treated with lumbar fusion and is not recommended to assess fusion status following lumbar spinal fusion.

2. Lateral flexion and extension radiography is recommended to determine the presence of lumbar fusion postoperatively. The lack of motion between vertebrae, in the absence of rigid instrumentation, is highly suggestive of successful fusion.
Components of Overall Success at 24 Months

Difference in Success Rates at 24 Months for Components of Modified Overall Success, mITT
95% Confidence Intervals

- Neurologic Success
- No Retreatment
- No Treatment Related SAEs
- ODI
- Angulation Success
- Translation Success
- Presence of Bone
- Average

* 90% confidence interval
Missing or non-evaluable data are excluded

Favors Autograft ← Favors OP-1

CC-104
Main Radiologic Questions

• Why were plain films insensitive in the evaluation of the original endpoint?

• Why was the 9 month CT time point not optimal?

• Why gather additional data?
Question 1: Why Were Plain Films Insensitive in the Evaluation of the Original Endpoint?

1. OP-1 produced bone formation more medial than anticipated
   - Readers were focused on visualizing traditional lateral inter-transverse process fusion
2. Plain film technique may interfere with visualization of medial bone formation
   - Plain films detect an average of densities from front to back in 2 dimensions
   - Medial structures difficult to visualize as vertebrae themselves may block visualization
Question 2: Why Were the 9 Month CT Scan Results Inconclusive?

• 9 months CT for presence of bone
  • OP-1 Putty: 80%
  • Autograft: 100%

• 36+ month CT for presence of bone
  • OP-1 Putty: 75%
  • Autograft: 77%
Question 2: Why Were the 9 Month CT Scan Results Inconclusive?

- 9 months is not an adequate time point to compare bone formation between OP-1 and autograft:
  - Autograft (iliac bone) is detectable immediately after surgery
  - Residual autograft is likely to be present at 9 months, and thus there is bias in favor of autograft
  - This is confirmed by the fact that there is only 77% of autograft patients with presence of bone by CT at 36+ months compared to 100% at 9 months
Efficacy
Baboon PLF Histology Data

57% of bone density in autograft is residual graft particles


CC-109
Postoperative AP X-ray

OP-1 Putty

Autograft

CC-110
Question 3: Why Gather Additional Data?

- Performed to correct for the inability to measure the presence of bone, which was our primary endpoint.
- CT scanning is the gold standard in evaluating bony vertebral body anatomy as well as new bone formation:
  - CT allows detailed cross sectional view of structures lateral, medial and posterior to the vertebral bodies.
  - CT data stack can undergo multiplanar reformatted imaging.

Therefore, the study endpoint used CT scans, rather than plain films, to allow for more accurate detection of new bone formation, especially medial.
24 Month Plain Radiograph vs. 36+ Month CT Scan

AP X-ray

No visible bone on plain radiograph

MPR of CT

Significant bone formation medially
Axial CT slice (prospective) as well as a coronal multiplanar reformatted image demonstrating solid fusion mass in a patient receiving OP-1 Putty. Note the medial positioning of the fusion mass (solid white arrows).
Anterior and posterior views of a 3D reconstruction of a spine where OP-1 Putty has been placed between L4/5. Note the medial position of the graft material (white arrows).
## Radiographic and Clinical Outcomes at 36+ Months

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OP-1 Putty</th>
<th>Autograft</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical and Safety Parameters</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Oswestry Disability Success (36+ Months)</td>
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<td>73.5%</td>
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<td>80.0%</td>
<td>0.540</td>
</tr>
<tr>
<td><strong>Radiographic Parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angulation</td>
<td>69.3%</td>
<td>68.4%</td>
<td>1.000</td>
</tr>
<tr>
<td>Translation</td>
<td>75.7%</td>
<td>75.4%</td>
<td>1.000</td>
</tr>
<tr>
<td>Presence of Bone</td>
<td>74.8%</td>
<td>77.4%</td>
<td>0.852</td>
</tr>
</tbody>
</table>

*Remarkable consistency across all components at 36+ months*

*P-value is based on Fisher's exact test*
Conclusion

- CT scans allow for a more appropriate comparison between treatment groups
- From a radiologist’s perspective, the key endpoints for determination of successful fusion are stability by angulation and translation as described by Resnick et al, coupled with good clinical outcomes
- 36+ month radiographic assessment is comparable to what results would have been at 24 months had CT scans been obtained
  - 9 and 36+ month CT scan results comparable for OP-1 Putty
  - Autograft rates appear to decrease but likely due to artificially high rate at 9 months
The Antibody Response

Huub Schellekens, M.D., Ph.D.
Professor of Pharmaceutical Biotechnology
Department of Pharmaceutical Sciences
Utrecht University
Overview

- Incidence and clinical consequence of immunogenicity
- Neutralizing antibody results for the trial
- Potential causes of OP-1 immunogenicity
- Impact of OP-1 immunogenicity
- Overall risk assessment

No observed impact of OP-1 immunogenicity on the clinical efficacy and safety of the OP-1 Putty product
Most Therapeutic Proteins are Immunogenic

- Every recombinant protein but one (GCSF) induces antibodies
- Incidence differs from low to very frequent
- Clinical consequences of antibodies to human proteins only seen after prolonged chronic treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Incidence of Anti-Drug Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>44%</td>
</tr>
<tr>
<td>rHu-GH</td>
<td>3%-16%</td>
</tr>
<tr>
<td>GRH</td>
<td>20%</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>35%</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>95%</td>
</tr>
<tr>
<td>Lenercept</td>
<td>88%</td>
</tr>
<tr>
<td>OKT3</td>
<td>86%</td>
</tr>
<tr>
<td>Remicade</td>
<td>61%</td>
</tr>
<tr>
<td>Rituximab</td>
<td>up to 11%</td>
</tr>
<tr>
<td>Rabtiva</td>
<td>6.3%</td>
</tr>
<tr>
<td>rHu IL-2</td>
<td>66 – 74%</td>
</tr>
<tr>
<td>rHu-IL-11</td>
<td>1%</td>
</tr>
<tr>
<td>Avonex</td>
<td>10%</td>
</tr>
<tr>
<td>EPO</td>
<td>&lt; 1:10,000</td>
</tr>
</tbody>
</table>

Incidence Not Predictive of Safety

• Examples:
  • EPO induces antibodies in very few patients but clinical consequences are severe
  • Cerezyme, Calcitonin, Insulin, Remicade induce responses in majority of patients with no clinical consequences

No correlation between high incidence and clinical consequence

Question 1

Is the reported neutralizing antibody data accurate?
ROS Neutralizing Antibody Assay

- Stryker worked with FDA to develop an improved version of ROS neutralizing assay
- New version used in the pivotal study
- As requested by FDA, ROS assay cut point is statistically-based and reports a 5% false positive rate
- ROS assay validated according to FDA guidance document for bioanalytical methods

<table>
<thead>
<tr>
<th>Validation Parameter</th>
<th>Stryker Results</th>
<th>FDA Guidance*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inter-Assay Precision</td>
<td>% CV = 13</td>
<td>&lt; 15%</td>
</tr>
<tr>
<td>Intra-Assay Precision</td>
<td>% CV &lt; 7</td>
<td>&lt; 15%</td>
</tr>
<tr>
<td>Standard Curve</td>
<td>9 points</td>
<td>≥ 6 points</td>
</tr>
<tr>
<td>Accuracy</td>
<td>% CV &lt; 13</td>
<td>&lt; 15%</td>
</tr>
<tr>
<td>Stability</td>
<td>5 Freeze-thaws</td>
<td>≥ 3 Freeze-thaws</td>
</tr>
<tr>
<td>Specificity</td>
<td>% CV = 24.6</td>
<td>No specified range</td>
</tr>
</tbody>
</table>

Question 2

What is the cause of the observed immunogenicity of the product?
Immunogenicity is Multifactorial

- Patient related risk factors:
  - Age, genetics, disease
  - Concomitant treatments
  - Duration of treatment
  - Route of administration
  - Previous exposure to similar proteins

- Product related risk factors
  - Protein structure (aggregation, glycosylation, oxidation, deamidation…)
  - Formulation
  - Excipients and impurities

Immunogenicity is Multifactorial

• Stryker has evaluated potential causes for OP-1 immunogenicity:
  • Product irradiation
  • Protein aggregation
  • Protein dose
  • Route of administration

Non-Irradiated OP-1 Putty is Immunogenic in Primates

Human and primate OP-1 amino acid sequences are identical. Non-irradiated OP-1 induces antibody production in primates.
The Route of Administration is an Important Contributing Factor to OP-1 Immunogenicity

### Immunogenicity with Non-Irradiated OP-1

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Species</th>
<th>Immunogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterolateral Fusion</td>
<td>Rabbit</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Baboon</td>
<td>Yes</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Rabbit</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Rat</td>
<td>Yes</td>
</tr>
<tr>
<td>Intra-Articular</td>
<td>Monkey</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Dog</td>
<td>Yes</td>
</tr>
<tr>
<td>Intervertebral Disc</td>
<td>Rabbit</td>
<td>No</td>
</tr>
<tr>
<td>Intravenous</td>
<td>Monkey</td>
<td>No</td>
</tr>
</tbody>
</table>

**Route of administration plays an important role in OP-1 immunogenicity**
Cause of OP-1 Immunogenicity: Summary

• Immunogenicity is multifactorial
• Non-irradiated OP-1 immunogenic in preclinical studies
• Route of administration and dose appear to be relevant
• Mechanism is breaking tolerance
  • Direct interaction with B cells
  • No memory – minimal concern for retreatment
Question 3

What is the potential effect of anti-OP-1 antibodies during development?
Developmental Concern: Overview

- OP-1 is a single use product
- Neutralizing antibodies are transient in patients, decline rapidly after 3 months and are gone by 24 months
- No preclinical evidence of immunogenicity effects on development
- Labeling requires female patients to avoid pregnancy for 1 year (this will be incorporated into physician training)
Immunogenicity Risk Assessment: Efficacy

- No effect on clinical efficacy
  - No effect of immunogenicity on efficacy in preclinical models
  - Efficacy independent of neutralizing antibody status in pivotal trial patients
Immunogenicity Risk Assessment: Safety

- No effect on clinical safety
  - 5-10% of healthy individuals have spontaneous BMP antibodies
  - Neutralizing antibodies are transient and diminish rapidly after 3 months
  - No memory
  - No trends in immune-related adverse events reported in pivotal trial
- 40,000 patients treated with OP-1
  - 15,000 with OP-1 Putty

- Precautionary product labeling
  - Single administration/contraindicated for repeat use
  - Female patients to avoid pregnancy for 1 year

Conclusion: Reasonable assurance of safety
Statistical Overview

Eugene Poggio, Ph.D.
President
Chief Biostatistician
Biostatistical Consulting Inc.
Chronology

Pivotal Study
- Protocol
- FDA meeting
- Statistical Analysis Plan (SAP) finalized
- Database lock

Extension Study
- Protocol
- Statistical Analysis Plan (SAP) finalized
- Database lock

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Pivotal Study

Non-Inferiority Design

• Intended to demonstrate that OP-1 is not more than a certain amount (Δ) worse than autograft on primary endpoint, Overall Success Rate:

\[
\text{Autograft rate minus OP-1 rate} \leq \Delta
\]
Pivotal Study

Design

- Randomized, multi-center, open label trial
- Blinded radiographic assessments
- Non-inferiority design
  - Protocol: 10% fixed margin
  - Original SAP: Variable margin
- 25 centers
- 24 month follow-up (minimum)
Pivotal Study

Design: Composite Primary Endpoint

Clinical components
- ODI
- Neurologic success
- No retreatment
- No treatment related SAEs

Radiographic components
- Angulation
- Translation
- Presence of bone
Pivotal Study

Design: Analysis

• Analysis population for efficacy
  • Protocol: Intent-to-treat (ITT) and Per Protocol (PP)
  • Original SAP: Modified intent-to-treat (mITT)

• Method of handling missing values
  • Protocol: Last observation carried forward (LOCF)
  • Original SAP: Multiple imputation
Pivotal Study

Results at 24 Months

- Estimated Overall Success rates:
  - OP-1: 38.7%
  - Autograft: 49.4%

- $p = 0.33$ (based on variable margin)
Difference in Success Rates at 24 Months, mITT
95% Confidence Intervals

- Neurologic Success
- No Retreatment
- No Treatment Related SAEs
- ODI
- Angulation Success
- Translation Success
- Presence of Bone
- Average*

*90% Confidence Interval
Missing or non-evaluable data are excluded
Extension Study

Design

- Intent: to use same primary endpoint as original study, but to use CT scan to measure presence of bone
- Same patients
- 24 month results used for clinical components except retreatment
- Patients brought back for CT scan as soon as possible (mean = 4.4 years)
Approximately 80% of eligible patients participated.

Conducted extensive analyses to examine evidence of potential bias.

Compared those eligible for, and those participating in, the extension study within each treatment group:
- Demographic and baseline characteristics
- Results on primary endpoint of original study

Found no evidence of systematic differences.
Extension Study

Results

- Estimated success rates:
  - OP-1: 47.2%
  - Autograft: 46.8%
- Estimated rate difference (OP-1 minus autograft): 0.4%
- Based on 95% confidence bounds for difference, OP-1 is:
  - At most 11.6% worse than autograft
  - At best 12% better than autograft
- \( p=0.025 \) (based on variable margin)
Extension Study

Differences in Component Success Rates

95% Confidence Intervals

- Neurologic Success
- No Retreatment
- No Treatment-Related SAEs
- ODI
- Angulation Success
- Translation Success
- Presence of Bone
- Average

Favors Autograft ← Lower confidence bound of average is -6.1% → Favors OP-1

*90% Confidence Interval
Missing or non-evaluable data are excluded
Sensitivity Analyses

Sensitivity Analysis of Extension Study
Difference in Success Rates (%)  
90% Confidence Intervals

- Primary analysis
- No imputation
- Missing imputed as failure
- Missing imputed as success
- Per Protocol, non-imputed
- 24 mo, except bone, non-imp
- Clinical only, non-imputed
- Radiographic only, stratified

Favors Autograft → Favors OP-1

24 month clinical, 36+ month radiographic, and mITT population unless otherwise noted; imputation as noted

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Summary (1)

• In original study, analysis of primary endpoint did not demonstrate non-inferiority

• It is evident, however, that detection of bone by plain film in that study was biased in favor of lateral bone and hence in favor of autograft

• Extension study using CT scans to detect bone was conducted to rectify this issue

• Results combining clinical results from original study and radiographic results from extension study are thought to be less biased and more meaningful due to use of CT scans
• These results are robust and consistent

• Two treatments have virtually identical estimated Overall Success rates

• Based on Overall Success, OP-1 is, to a statistical certainty:
  • At most 11.6% worse than autograft
  • At best 12% better than autograft

• Two treatments are similar regardless of method of handling missing data, analysis population, and even variations on primary endpoint
Summary (3)

• Two treatments are also very similar across each of 7 components of Overall Success

• Based on component average success rate, OP-1 is, to a statistical certainty:
  • At most 6% worse than autograft
  • At best 9% better than autograft

• We believe the totality of evidence supports non-inferiority of OP-1 as compared to autograft
Context for Understanding Data in a Clinical Setting

David Wong, M.D., FRCSC
Director
Advanced Center for Spinal Microsurgery
Presbyterian St. Luke's Medical Center, Denver
Past President, North American Spine Society
Key Points – Clinical Impact of OP-1 for Posterolateral Lumbar Fusion

What are important outcomes for clinicians and patients?

• Does it work?
• Does it improve quality of life?
• Is it safe?
Publication

The Safety and Efficacy of OP-1 (rhBMP-7) as a Replacement for Iliac Crest Autograft in Posterolateral Lumbar Arthrodesis
A Long-term (>4 Years) Pivotal Study

Oral Presentations

- AAOS, February 25, 2009, Spine Section
  8:06am-8:12am 032-Safety and Efficacy of OP-1(rh-BMP-7) as a Replacement for Iliac Crest Autograft

- NASS, October 16, 2008
  7:37am-7:42am 64- Safety and Efficacy of OP-1(rh-BMP-7) as a Replacement for Iliac Crest Autograft: A long-Term (>4 year) Pivotal Study
Key Points – Clinical Impact of OP-1 for Posterolateral Lumbar Fusion

**Fulfills Unmet Clinical Need**

- No other approved product for this indication
- Avoids iliac crest bone graft harvest
  - Less OR time
  - Reduced blood loss
  - Eliminates chronic pain
- Aging patient population – need alternative
Autograft Harvest Related Adverse Events – Pivotal Study

- Serious adverse events:
  - Intraoperative hemorrhage
  - Anemia – 2 days postoperatively

- Adverse events:
  - Donor site complications: 9.2%
    - 2 donor site infections
    - 3 excessive donor site pain
    - 3 donor site pain
Pivotal Trial Outcome

Composite Endpoint

- Measures of Stability
  - Angulation
  - Translation
- Bone Formation
  - De novo for OP-1 Putty
  - NO bone graft to start
- Radiographic success criteria strongly supported by consensus guidelines
- Clinical Endpoints
  - ODI, re-operation rate, neurologic success, absence of treatment-related SAEs
  - Maintained to 4.4 yr average follow-up
    - Range 3.5 – 5.5 yrs

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Retreatment Failure Over Time

- Includes patients not shown whose retreatment occurred after 1200 days (4 OP-1; 1 autograft)
Components of Overall Success
36+ Month Follow-Up with CT Scans

Difference in Success Rates by Components of Modified Overall Success, mITT
95% Confidence Intervals

- Neurologic Success
- No Retreatment
- No Treatment-Related SAEs
- ODI
- Angulation Success
- Translation Success
- Presence of Bone
- Average*

Favors Autograft ← [-50, -30, -10, 0, 10, 30, 50] Favor OP-1

* 90% confidence interval
  Missing or non-evaluable data are excluded
Key Points – Clinical Impact of OP-1 for Posterolateral Lumbar Fusion

Excellent Safety Profile

- 36+ month extension study follow-up

- Humanitarian Device Exemption (HDE) Approval
  - Post marketing data from approximately 15,000 cases
Key Points – Clinical Impact of OP-1 for Posterolateral Lumbar Fusion

What are important outcomes for clinicians and patients?

- Does it work?

- Does it improve quality of life?

- Is it safe?
Food and Drug Administration
Orthopaedic and Rehabilitation Devices Panel
March 31, 2009

OP-1 Putty
for Posterolateral Lumbar Spinal Fusion in Adult Patients with Degenerative Spondylolisthesis