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

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Introduction and Overview

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

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Presentation Agenda

Introduction and Overview of Product	**Julie Krop, M.D.** Vice President, Clinical and Regulatory Affairs Stryker Biotech
Overview of Degenerative Spondylolisthesis and Unmet Medical Need	**Jeff Fischgrund, M.D.** Prinicipal Investigator Editor-in-Chief, J Am Acad of Ortho Surg Spine Surgeon, Beaumont Hospital
Preclinical Overview	**Dean Falb, Ph.D.** Vice President, Research & Development Stryker Biotech
Pivotal Trial Data	**Julie Krop, M.D.** Vice President, Clinical and Regulatory Affairs Stryker Biotech

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.
Associate Professor
Orthopedic Surgery
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

* Weinstein JN, Lurie JD, Tosteson TD, et al. Surgical Versus Nonsurgical Treatment for Lumbar Degenerative Spondylolisthesis. *N Engl J. Med* 2007; 356: 2257-70.

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:

Endpoint	"Success" Criterion
Clinical Success	
1) Oswestry Disability Index	• ≥ 20% improvement
2) Neurologic	• No clinically relevant decreases in neurologic function
3) Treatment-related SAEs	• No serious adverse events related to treatment
4) Retreatments	• No retreatments intended to induce fusion
Radiological Success	**Assessed by blinded reviewers**
5) Angulation	• ≤ 5° of angular movement } Measures of stability
6) Translation	• ≤ 3 mm of translational movement } Measures of stability
7) Presence of bone	• Presence of bone – marker of OP-1 activity

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.
Prinicipal 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

* Weinstein JN, Lurie JD, Tosteson TD, et al. Surgical Versus Nonsurgical Treatment for Lumbar Degenerative Spondylolisthesis. *N Engl J. Med* 2007; 356: 2257-70.

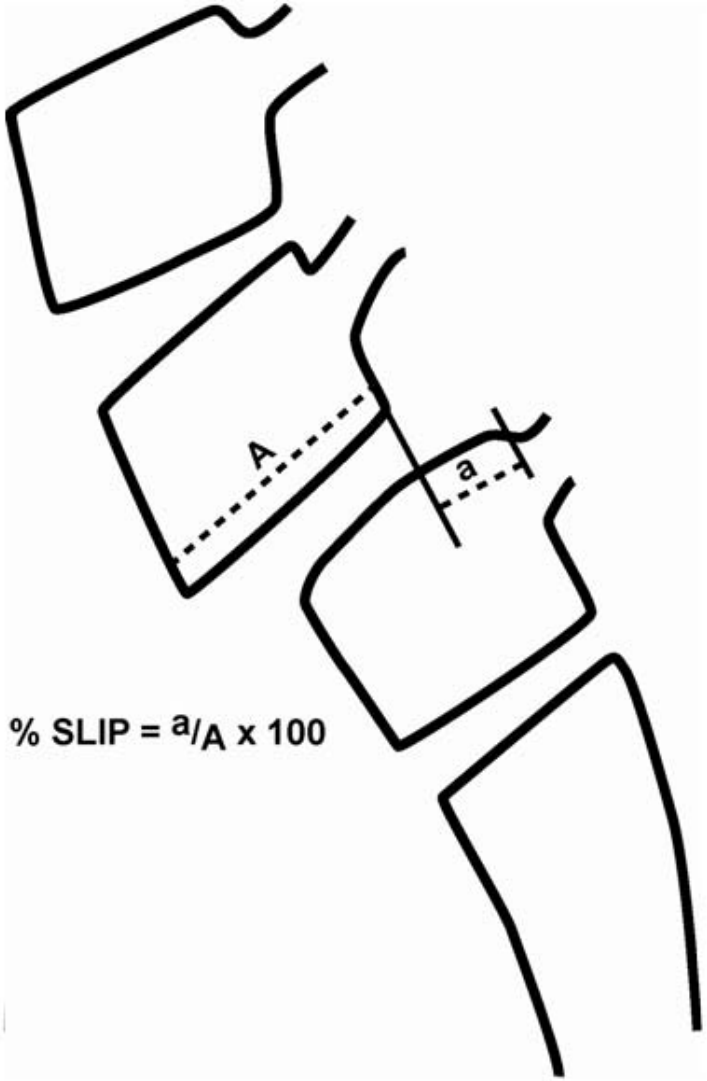
Degenerative Spondylolisthesis

- 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%



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)

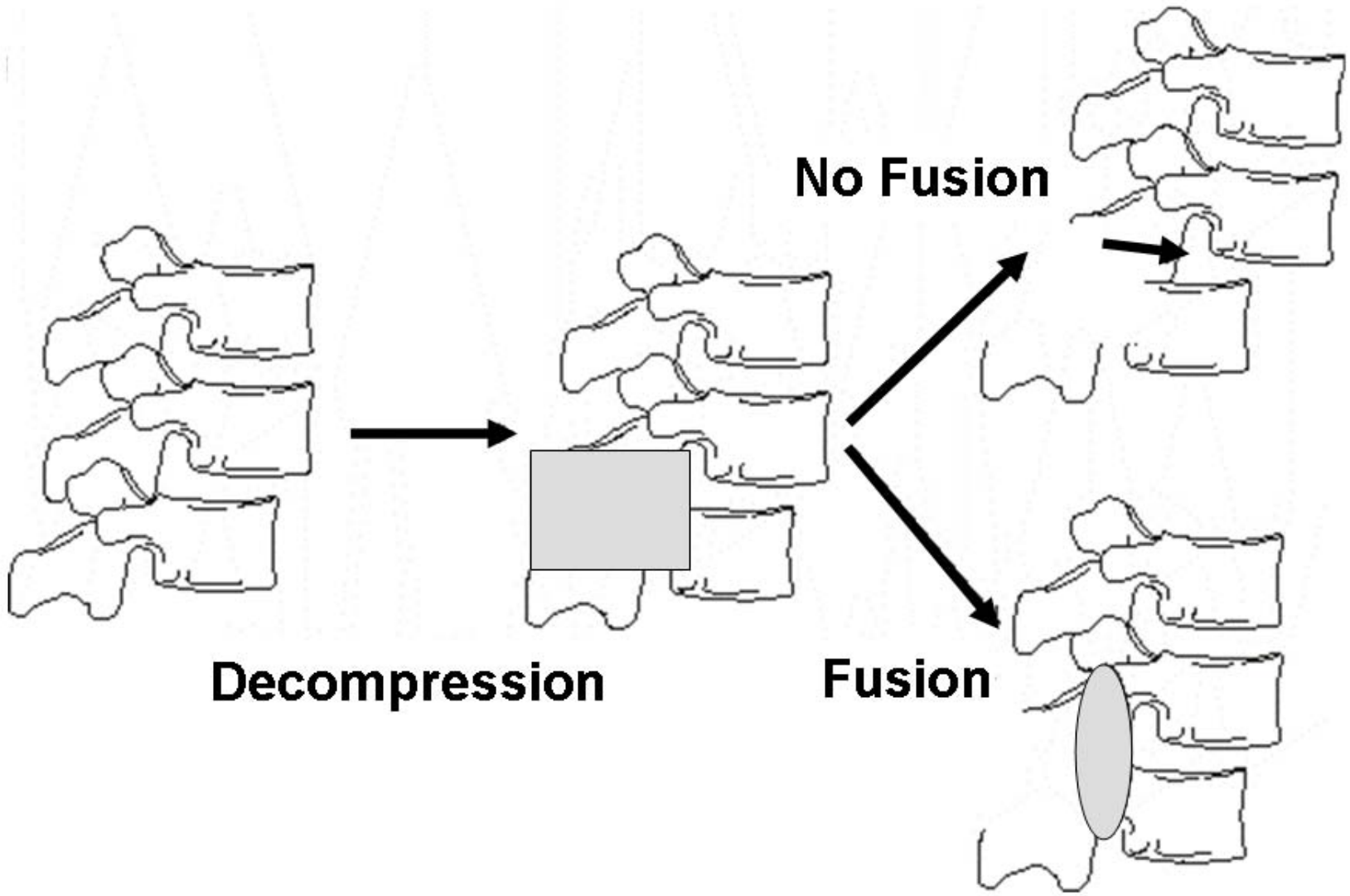
	Surgery	Conservative Therapy	Treatment Effect of Surgery (95% CI)
ODI	-24.2	-7.5	-16.7 (-19.5 to -13.9)
Physical function: SF-36	26.6	8.3	18.3 (14.6 to 21.9)
Bodily pain: SF-36	29.9	11.7	18.1 (14.5 to 21.7)

Weinstein JN, Lurie JD, Tosteson TD, et al. Surgical Versus Nonsurgical Treatment for Lumbar Degenerative Spondylolisthesis. *N Engl J. Med* 2007; 356: 2257-70.

Treatment Options

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

Post-Laminectomy Instability



Decompression Alone

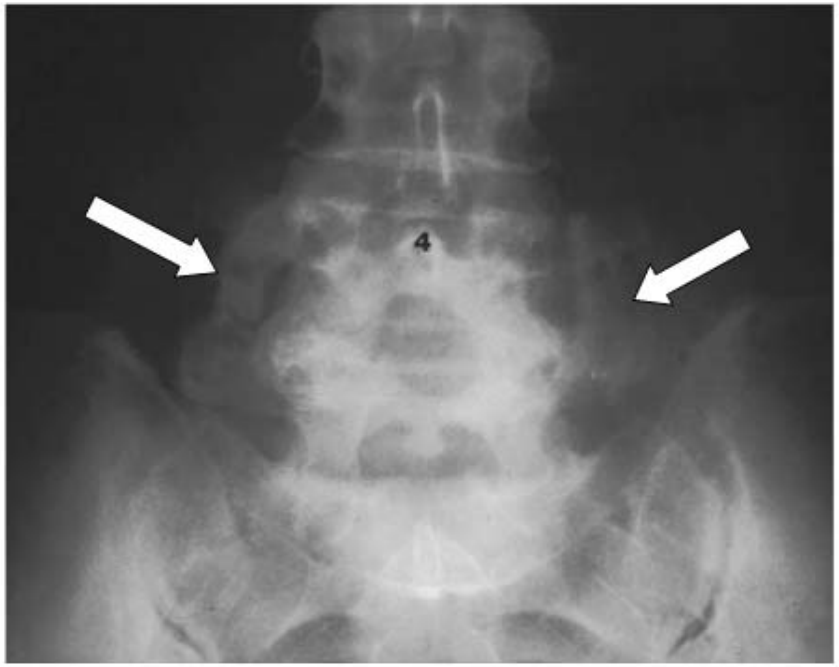
- Decompression only
  - Clinical outcome:
    - Excellent-Good 44%
    - Listhesis 5.3→7.9 mm
- Decompression + fusion
  - Clinical outcome:
    - Excellent-Good 96%
    - Listhesis 4.8→5.3 mm

Patients treated with decompression alone have poor outcomes

Herkowitz, Kurz, *JBJS* 1992.

Goal of Fusion Surgery

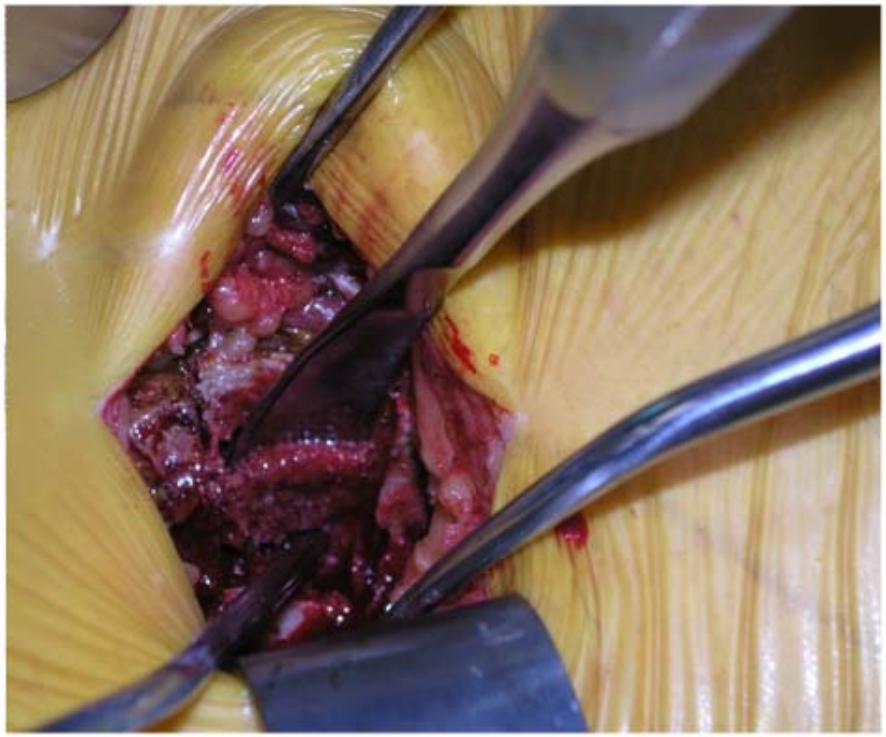
- Create a bony union across involved vertebrae resulting in:
  - Stability
  - Good long term outcome

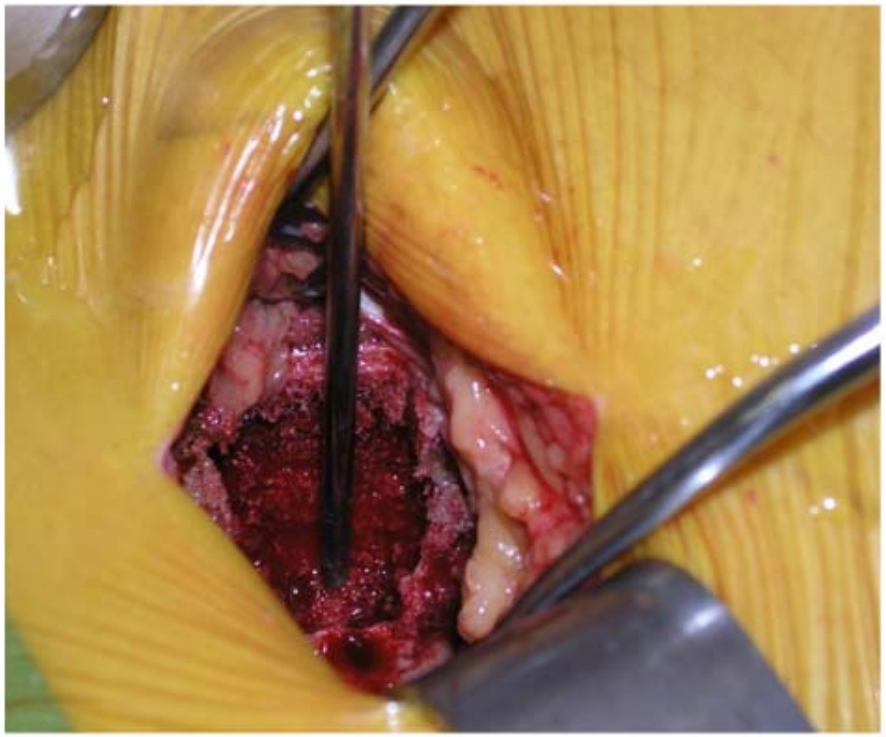


Iliac Crest Autograft

- "Gold standard"
- Additional surgery
  - Time
  - Pain
  - Complications

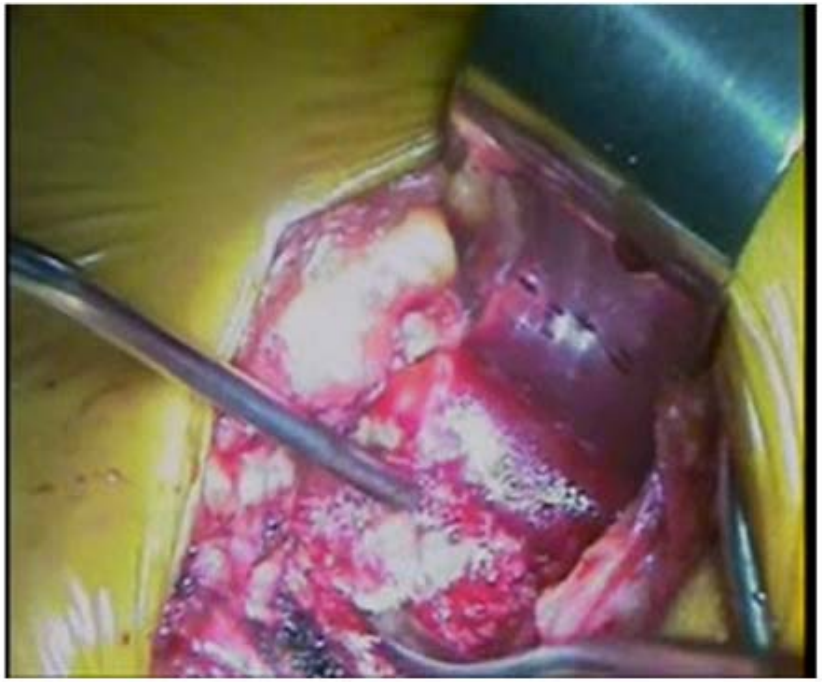
Bone Graft Harvesting





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



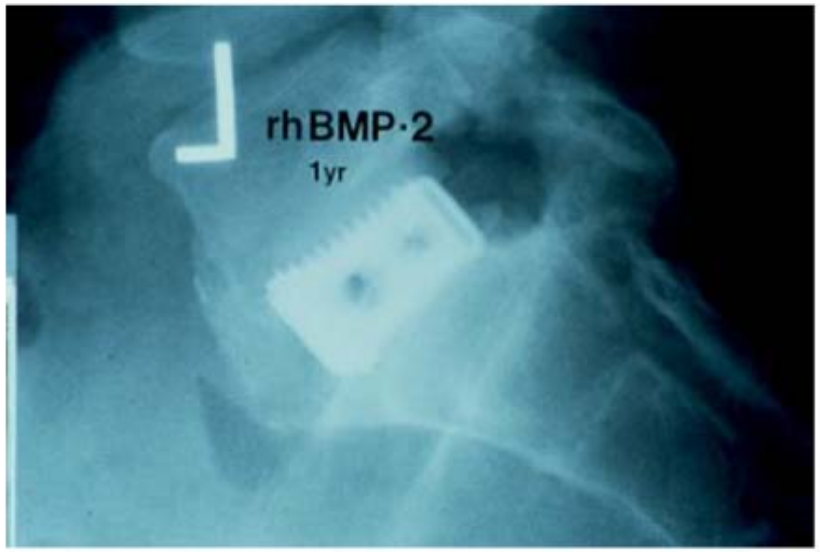
Arrington, *CORR*, 1995.

Bone Graft Harvest Complication: A Meta-Analysis of the Literature

	Author	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	Frymoyer (n = 96)	35 (37)	*	*	*	35 (37)	6 (6)
	Fernyhough (n = 151)	44 (29)	*	*	*	*	5 (3)
	Younger (n = 243)	71 (29)	21 (9)	50 (21)	6 (3)	*	*
	Banwart (n = 195)	88 (45)	3 (2)	20 (10)	*	53 (27)	*
	Summers (n = 82)	40 (49)	*	*	40 (49)	*	26 (32)
	Goulet (n = 87)	33 (38)	*	*	33 (38)	16 (18)	7 (9)
	Mirovsky (n = 48)	9 (19)	*	*	*	9 (19)	9 (19)
	Schnee (n = 184)	13 (7)	5 (3)	8 (4)	*	*	*
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

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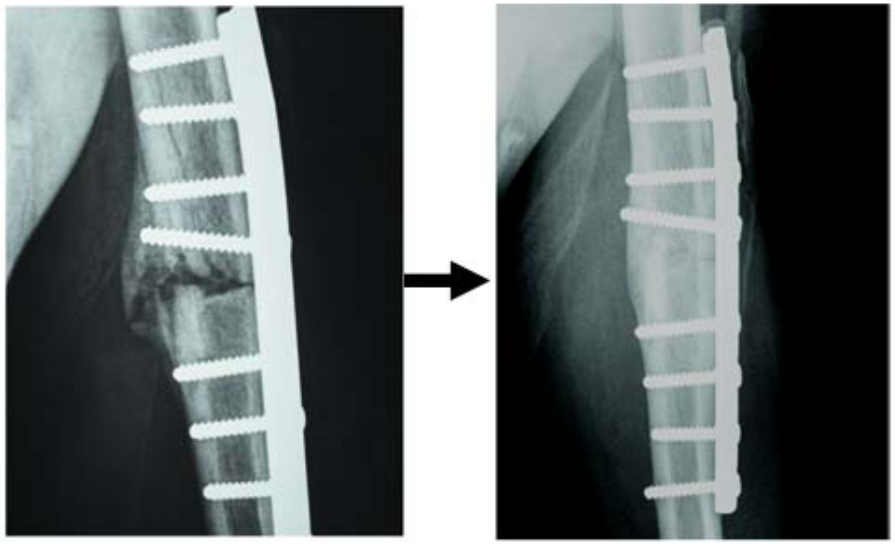
Preclinical Overview

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

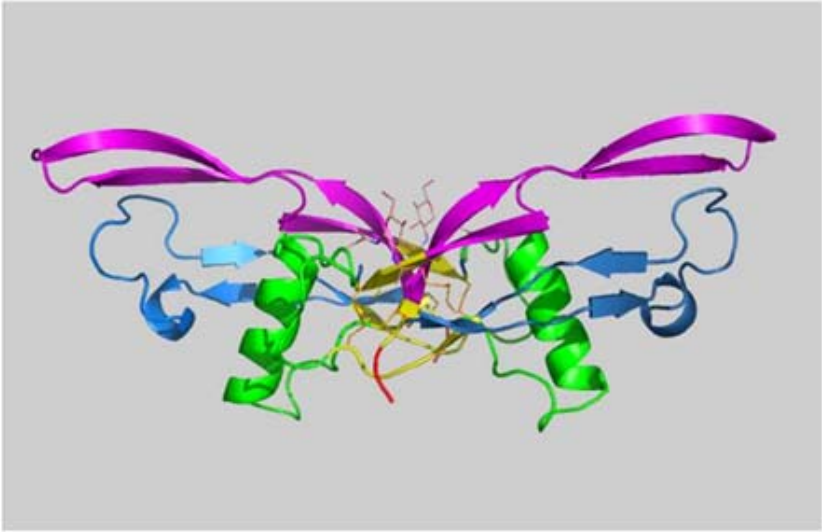
Bone Morphogenetic Proteins

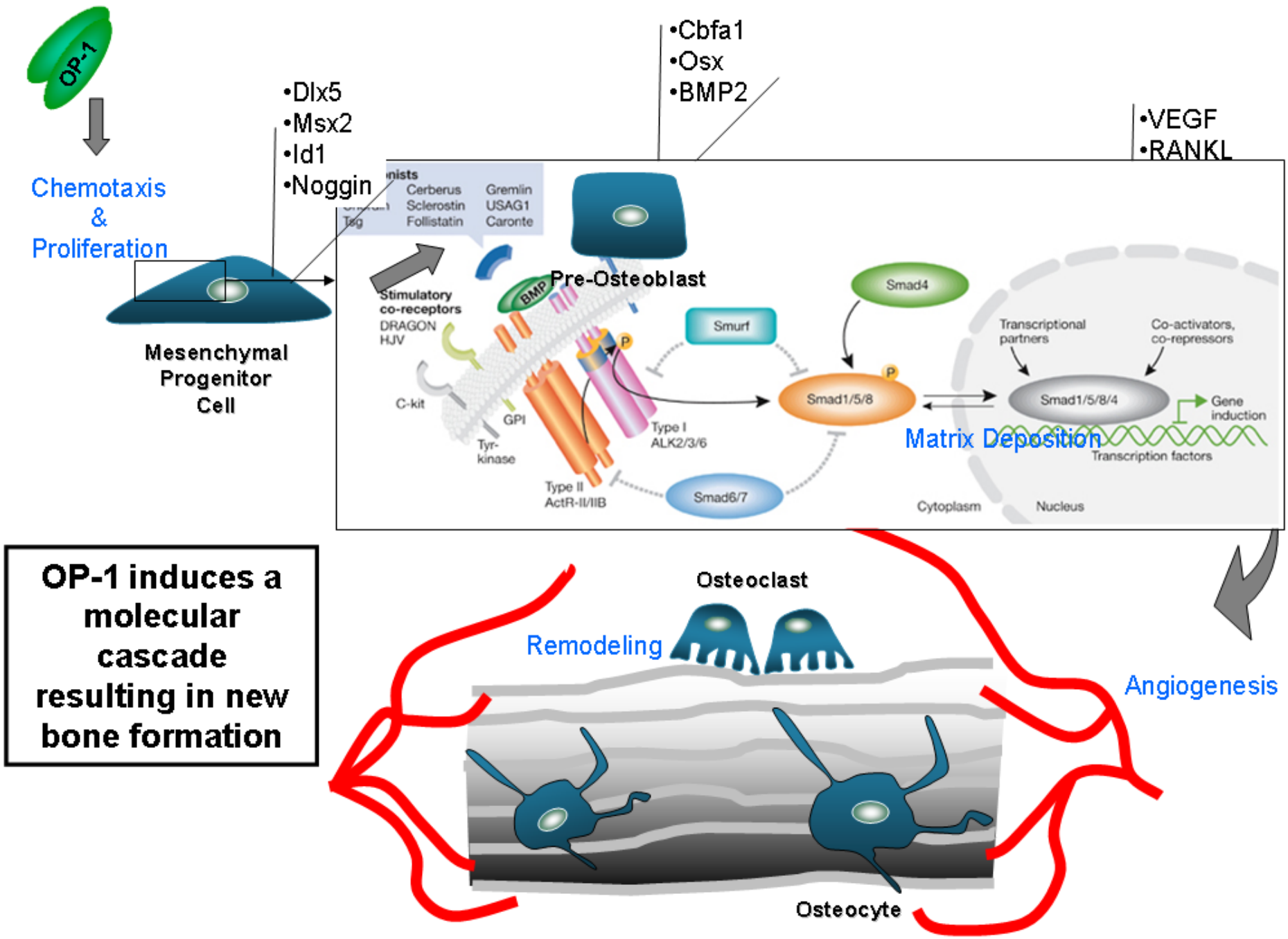
- First described by Marshall Urist in 1965
- Involved in fracture healing cascade
- >20 BMPs identified

Normal Fracture Healing



OP-1 (BMP-7) Crystal Structure





OP-1 induces a molecular cascade resulting in new bone formation

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Carrier Selection

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Carrier Selection

Proc. Natl. Acad. Sci. USA
Vol. 78, No. 12, pp. 7599–7603, December 1981
Cell Biology

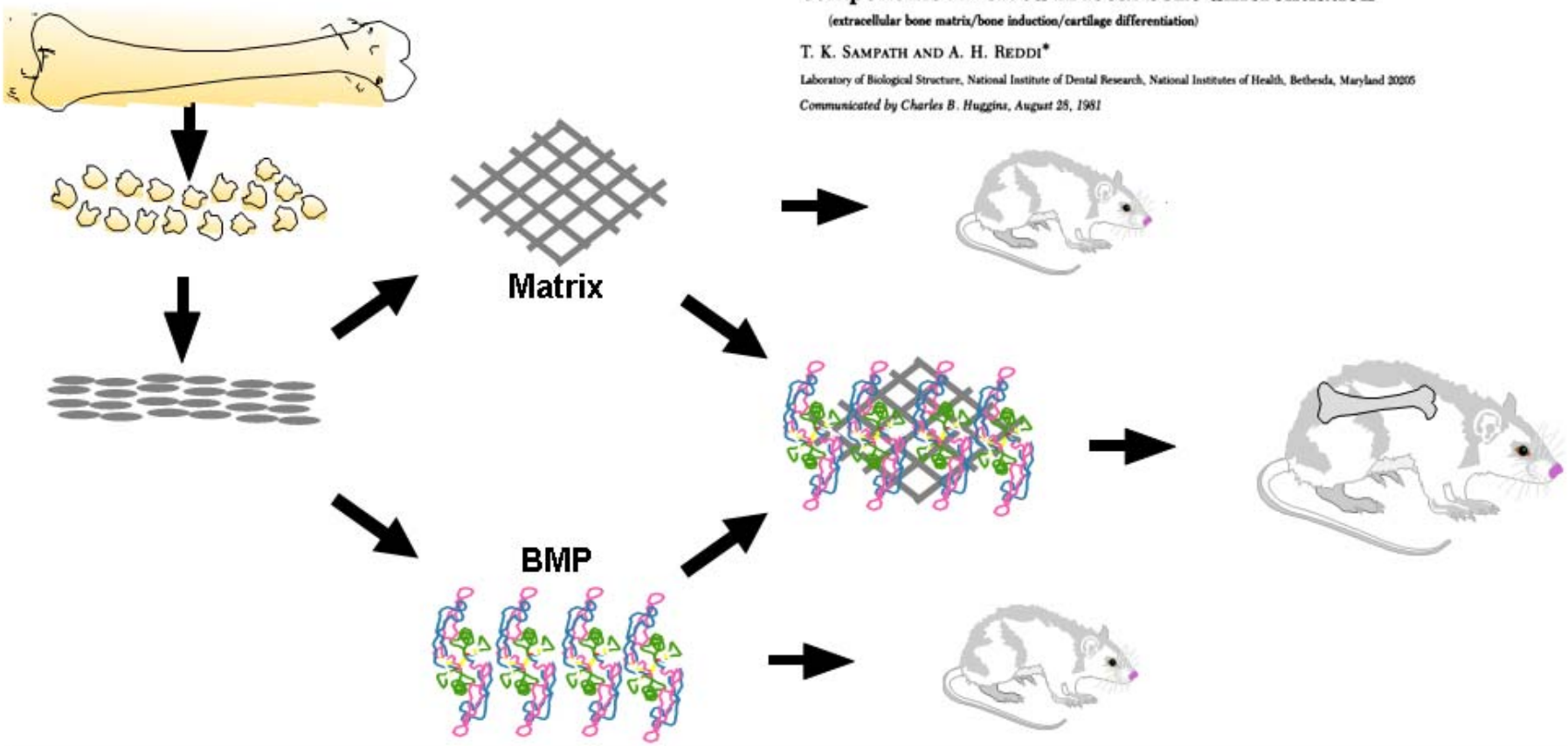
Dissociative extraction and reconstitution of extracellular matrix components involved in local bone differentiation

(extracellular bone matrix/bone induction/cartilage differentiation)

T. K. SAMPATH AND A. H. REDDI*

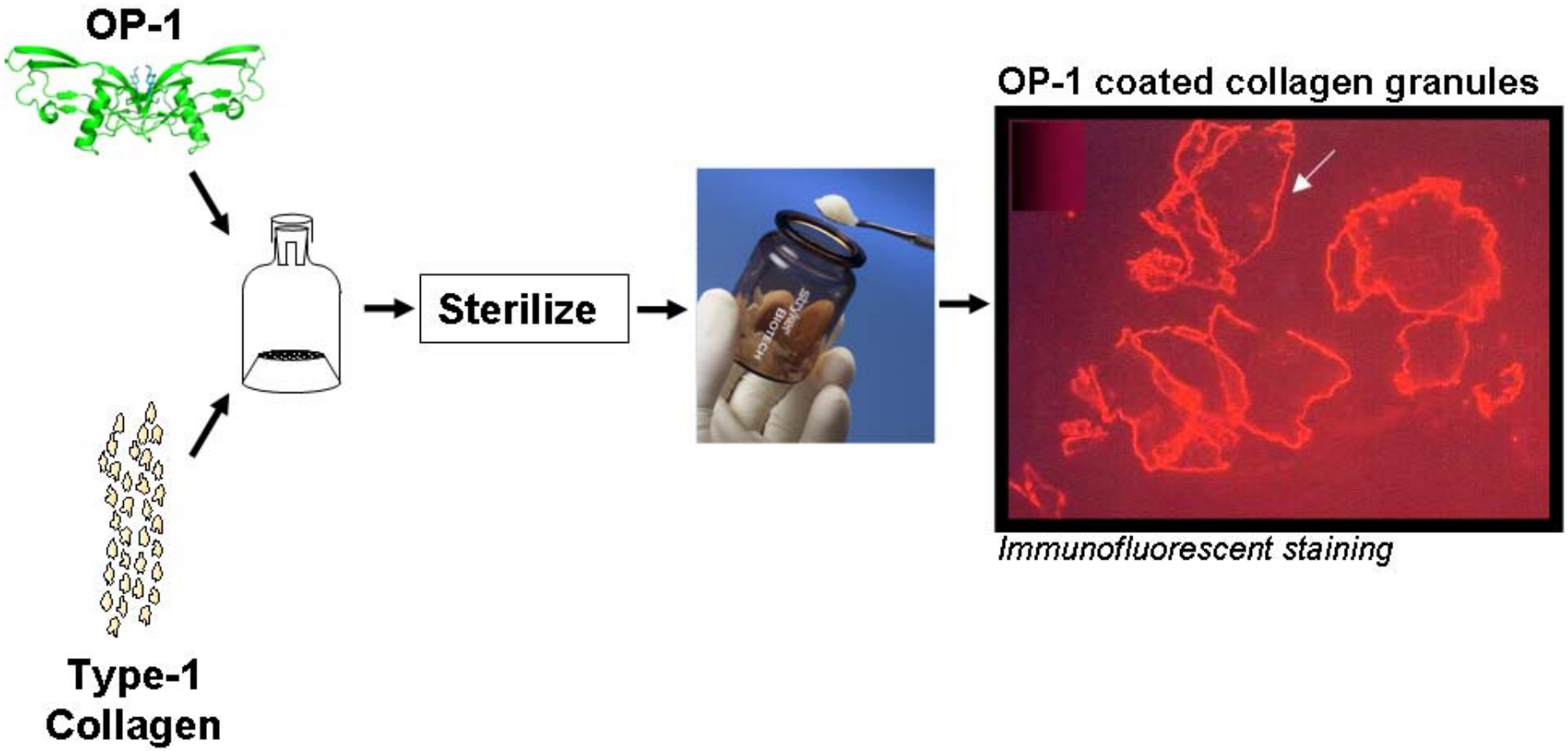
Laboratory of Biological Structure, National Institute of Dental Research, National Institutes of Health, Bethesda, Maryland 20205

Communicated by Charles B. Huggins, August 28, 1981



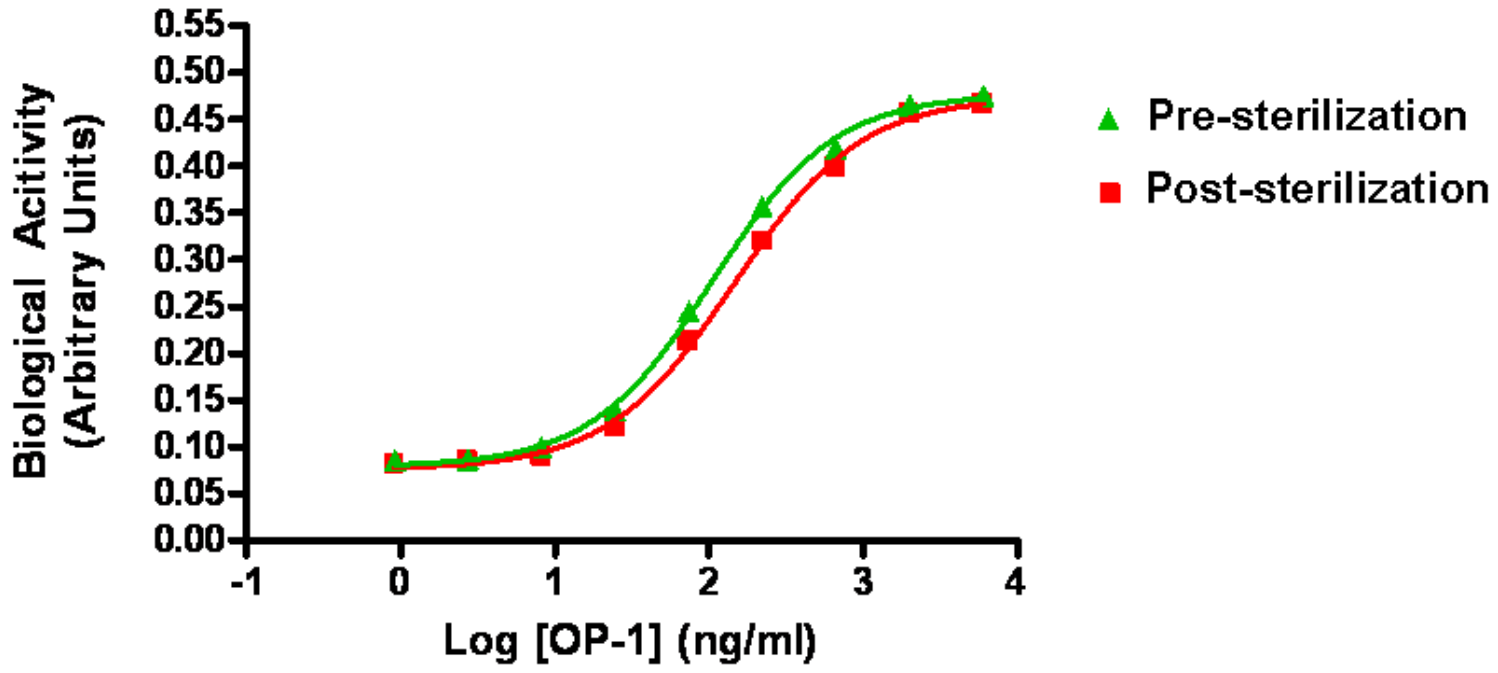
Bone formation requires matrix + BMP combination

Manufacturing Process



OP-1 protein and the collagen matrix are combined during manufacturing

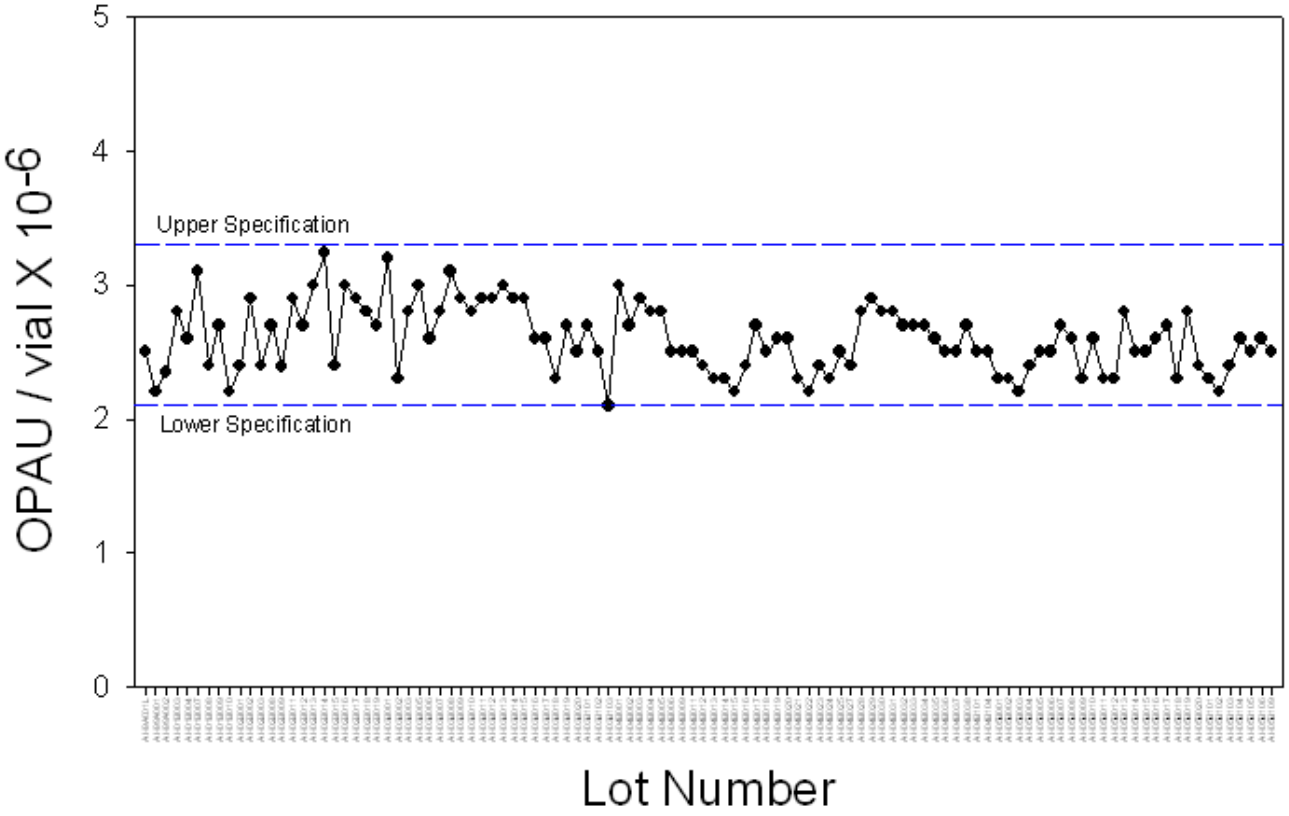
OP-1 Manufacturing Process
Sterilization Effects



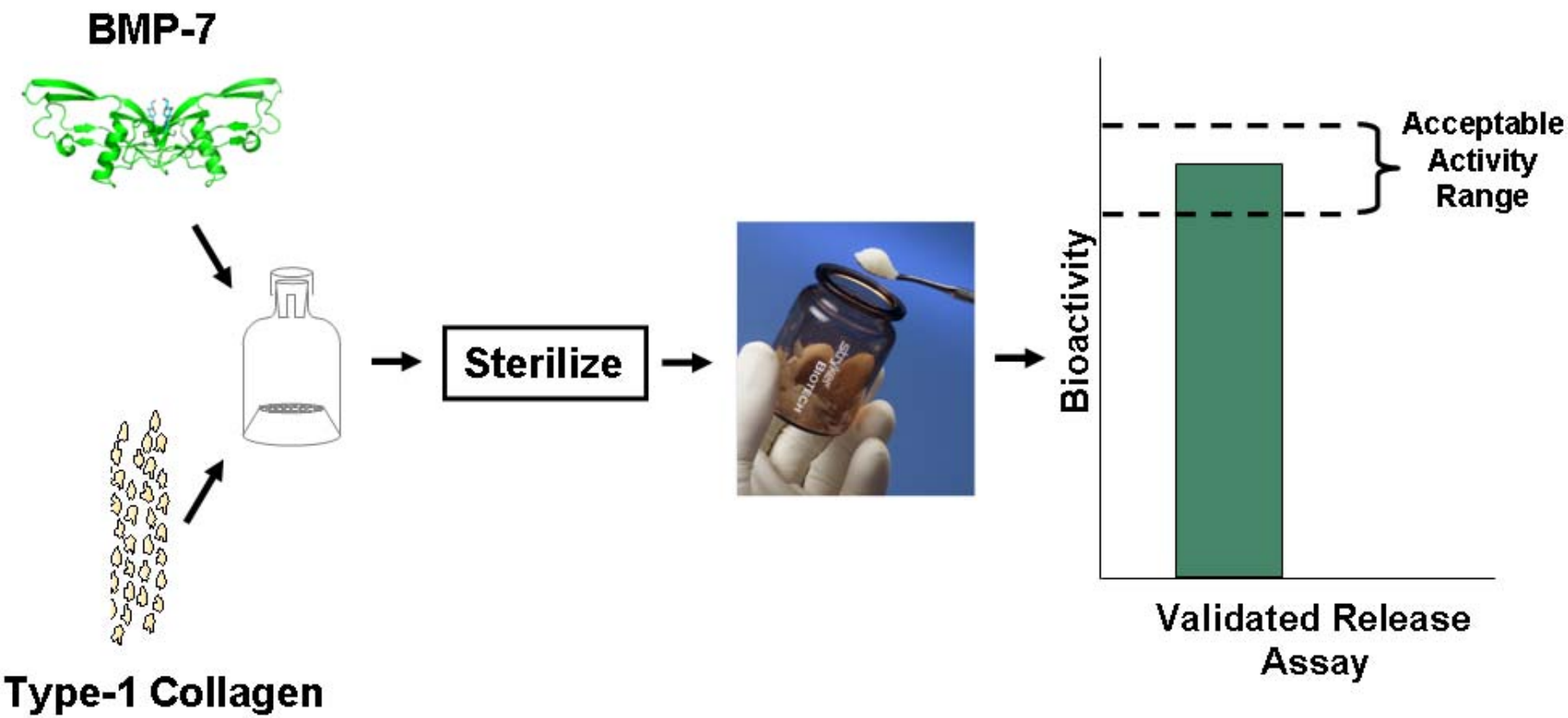
Sterilized OP-1 induces osteoblast differentiation

OP-1 Putty
Consistency of Manufacturing

Biological Activity of γ-Irradiated OP-1 Lots Manufactured 1999-2005



OP-1 Manufacturing Process



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

OP-1 Putty

OP-1 Efficacy/Dose Selection

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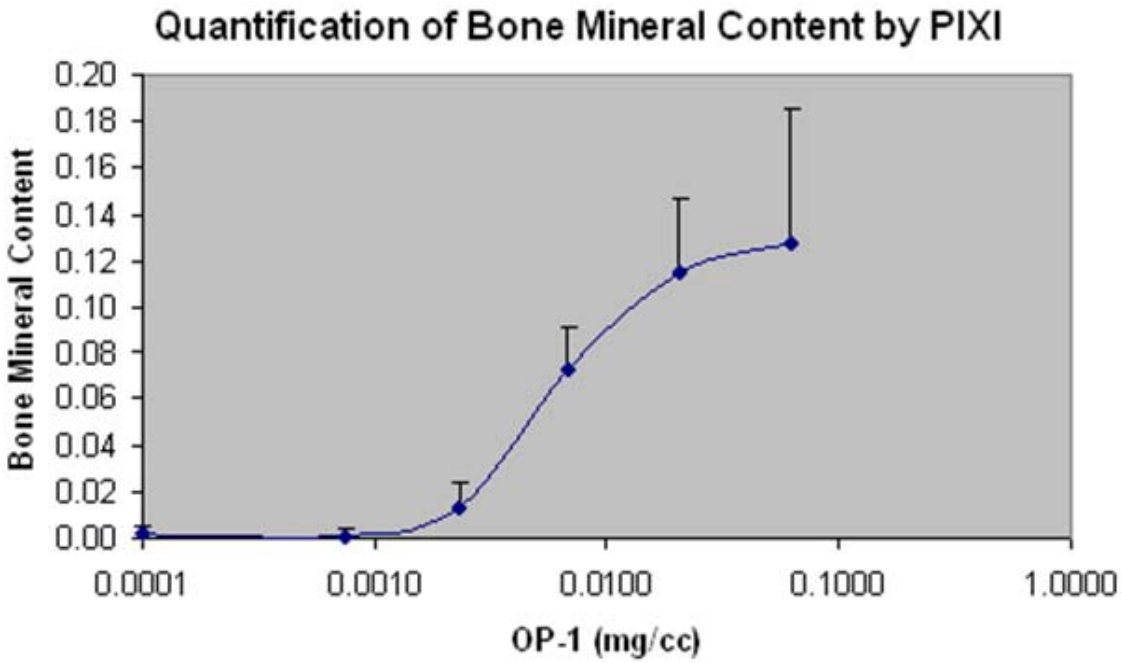
Efficacy
Multiple Models, Species and Collaborators; Adverse Environments

Investigator	Species	Model	Fusion Rate	
			OP-1	Autograft
Cunningham	Baboon	Instrumented PLF	100%	100%
Diwan	Rat	Osteoporotic PLF	100%	
Grauer	Rabbit	Nicotine PLF	82%	42%
Jenis	Sheep	PLF	100%	
Cunningham	Dog	PLF	77%	50%

Efficacy – Dose Selection
Rat Bone Nodule Dose Curve

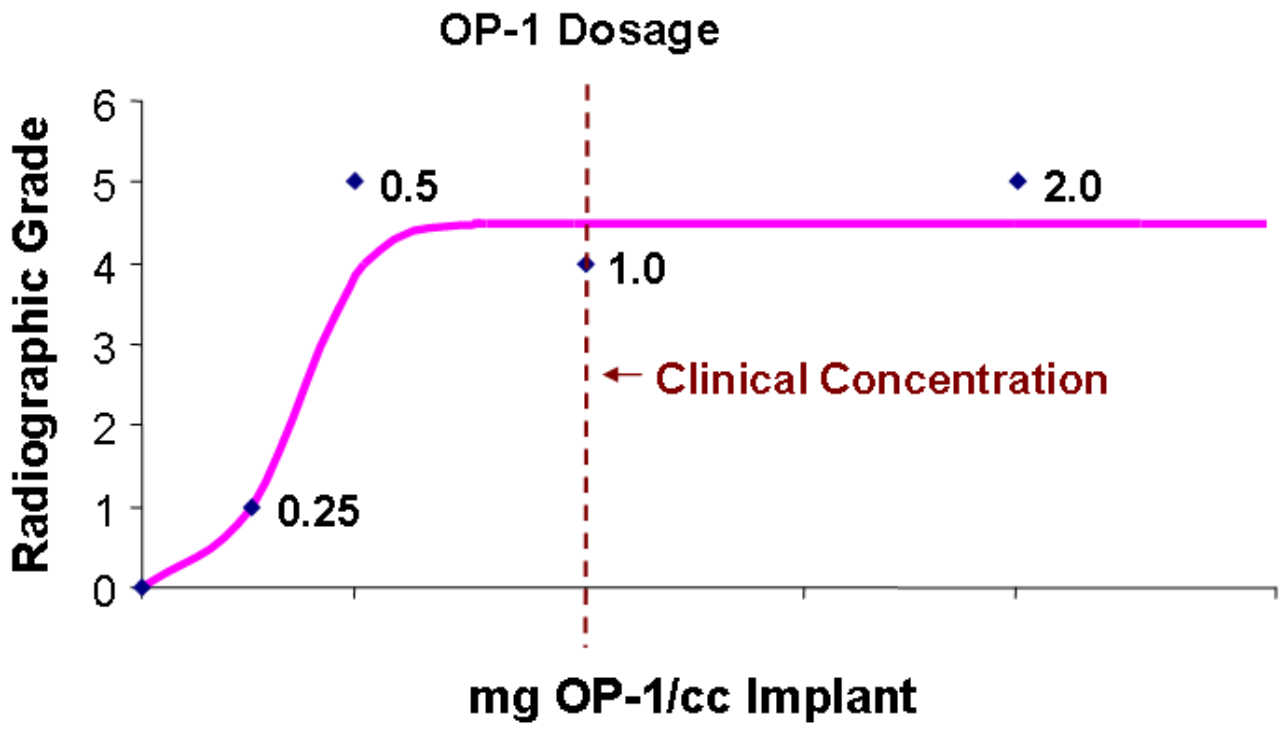
Reconstituted OP-1 Putty



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

Jenis, L.G et al. (2009, February). Poster P390, presented at the annual meeting of the American Academy of Orthopaedic Surgeons, Las Vegas, NV.

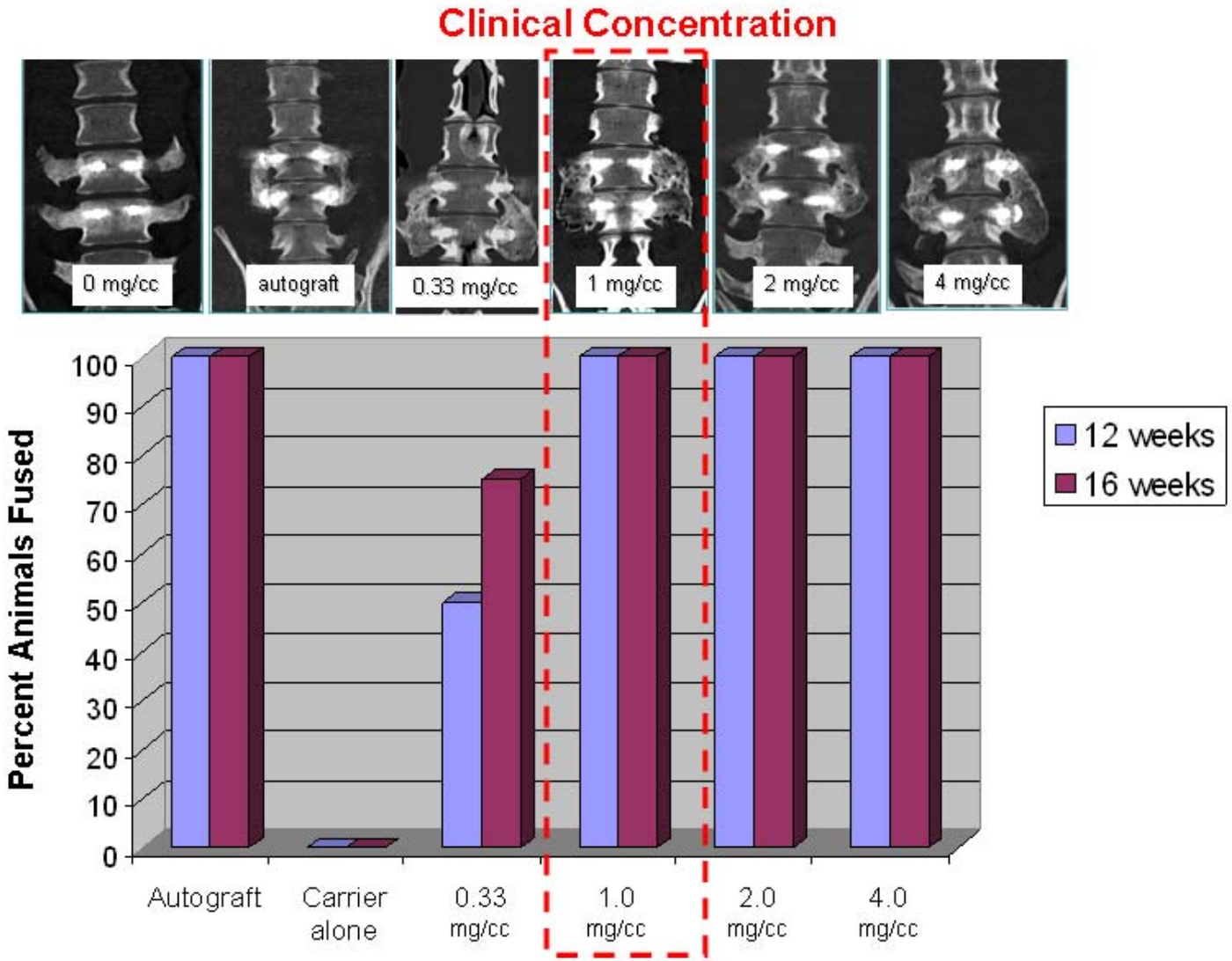
Efficacy – Dose Selection
African Green Monkey Dose Response



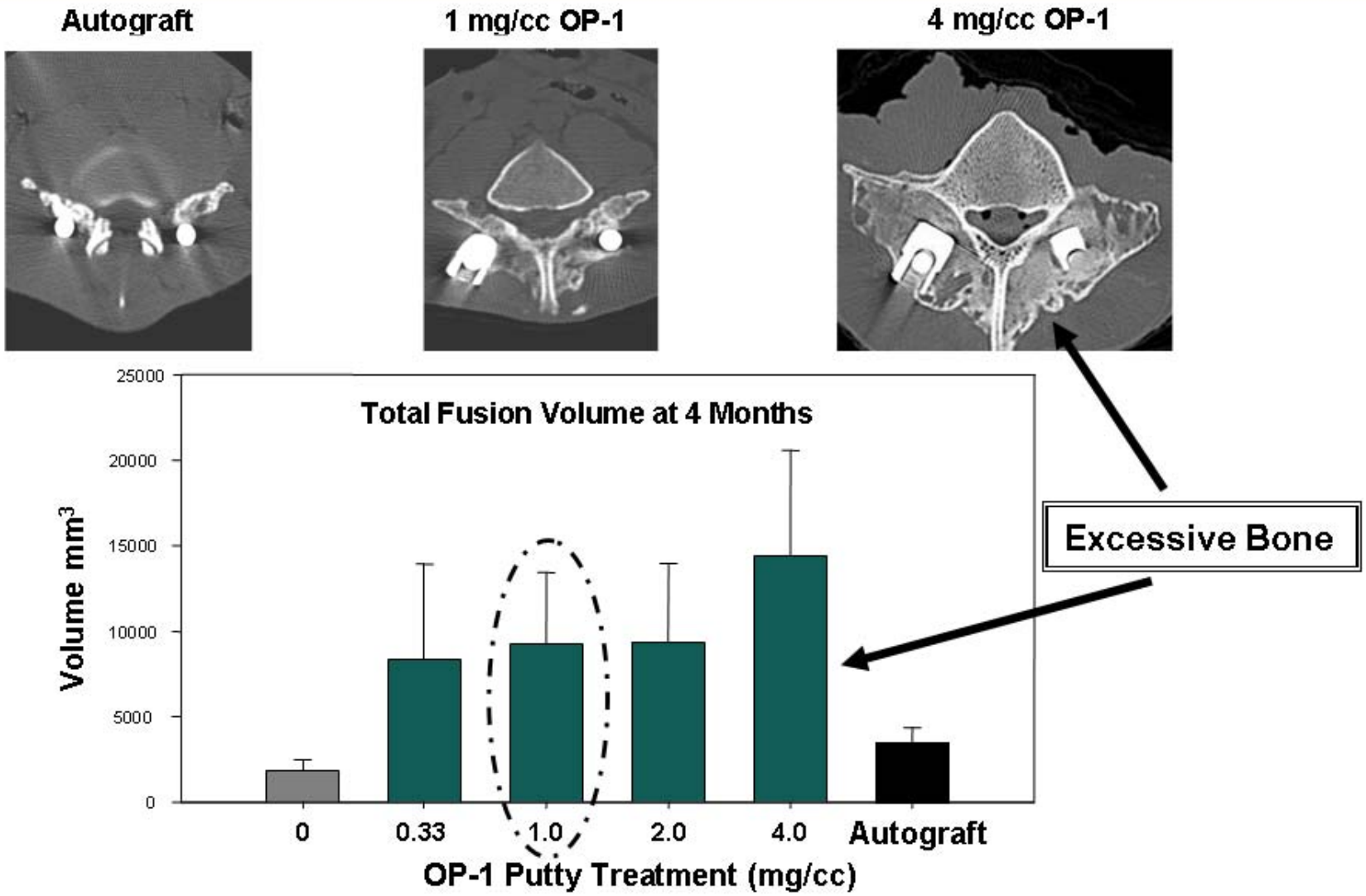
- Critical-size tibial defect (African green monkey)
- Complete healing at 20 weeks

Cook SD et al. 1995 *J. Bone Joint Surg. Am.* 77:734-750.

Efficacy – Dose Selection
Baboon PLF Fusion Data

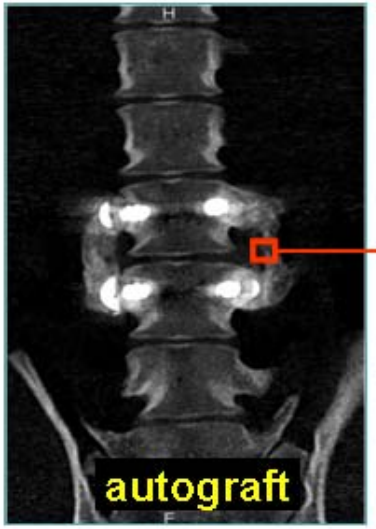


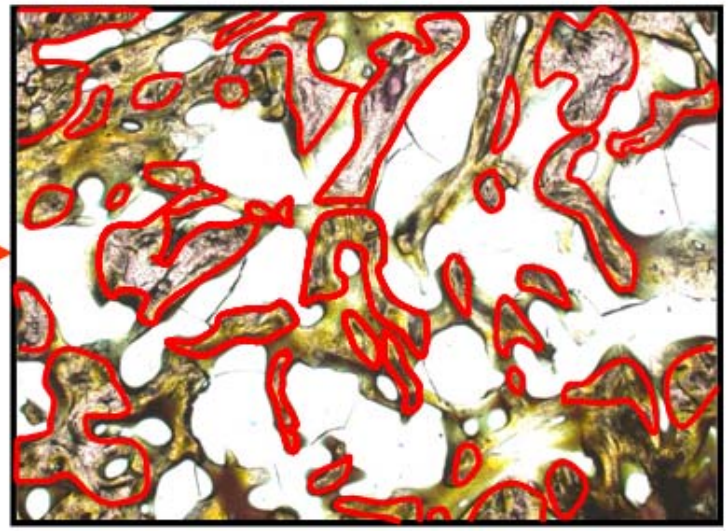
Efficacy – Dose Selection
Baboon PLF Bone Volume Data (CT)

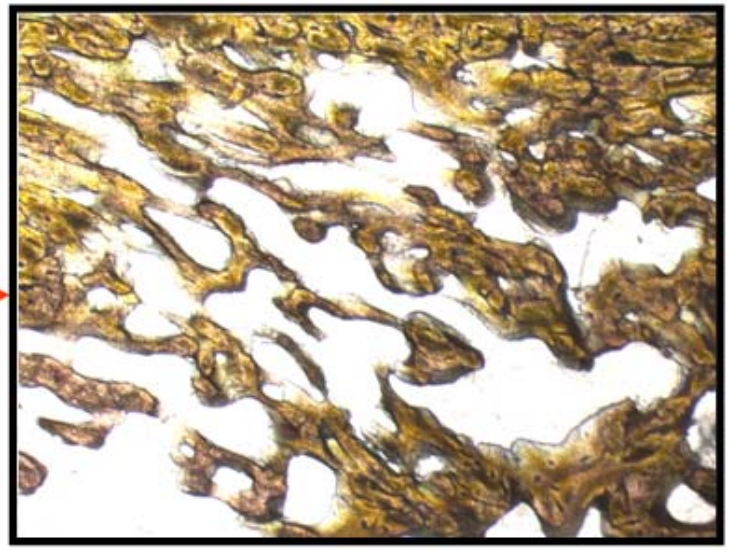


Jenis et al. Proceedings of the NASS 23rd Annual Meeting / *The Spine Journal* 8 (2008) 1S–191S.

Efficacy
Baboon PLF Histology Data







CT

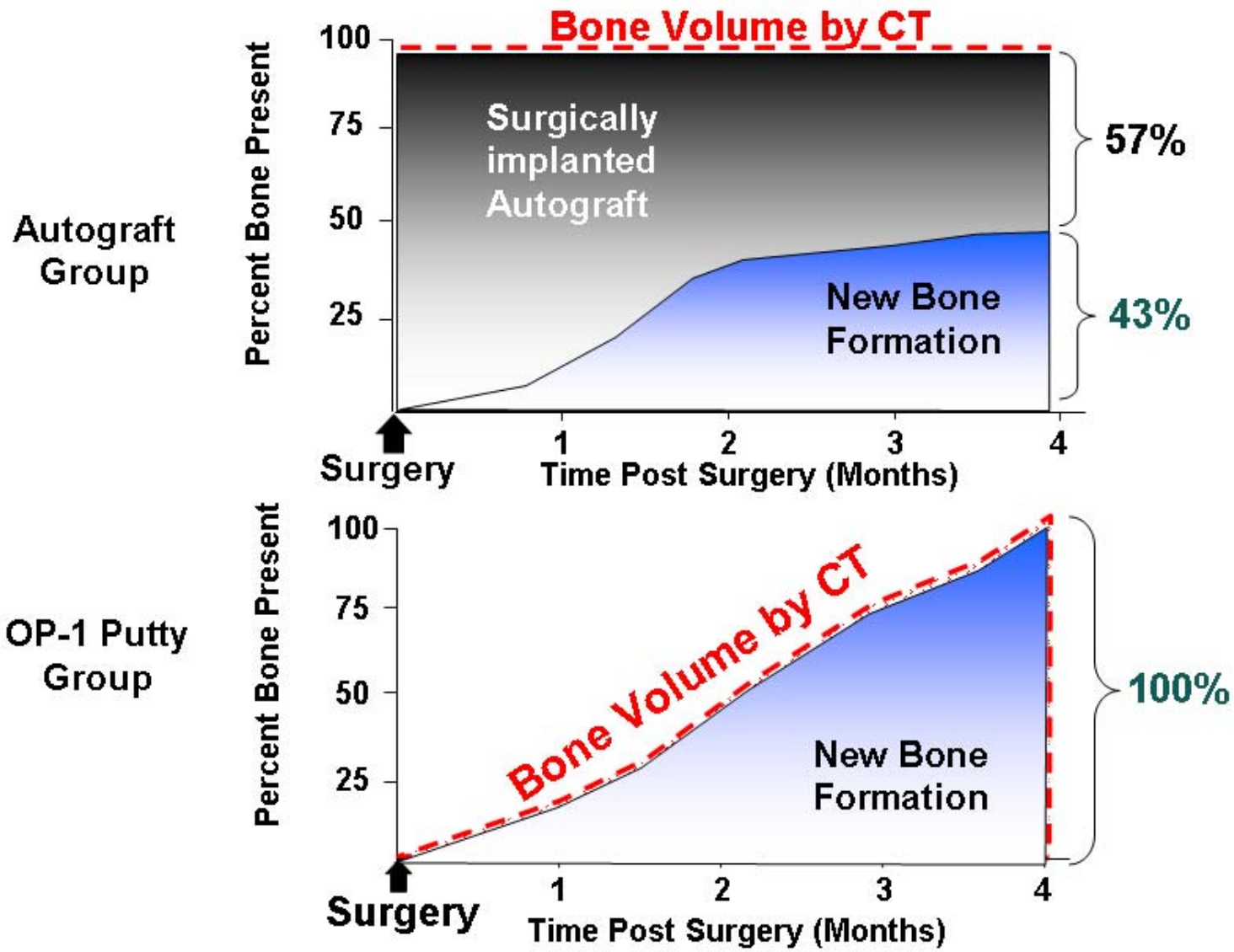
Goldner's Trichrome Staining

57% of bone density in autograft is residual graft particles

Jenis et al. Proceedings of the NASS 23rd Annual Meeting / The Spine Journal 8 (2008) 1S–191S.

Van Loon et al. *J Bone Joint Surg [Br]* 2000;82-B:436-44.

Efficacy
Different Mechanisms of Bone Formation



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

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OP-1 Safety Studies

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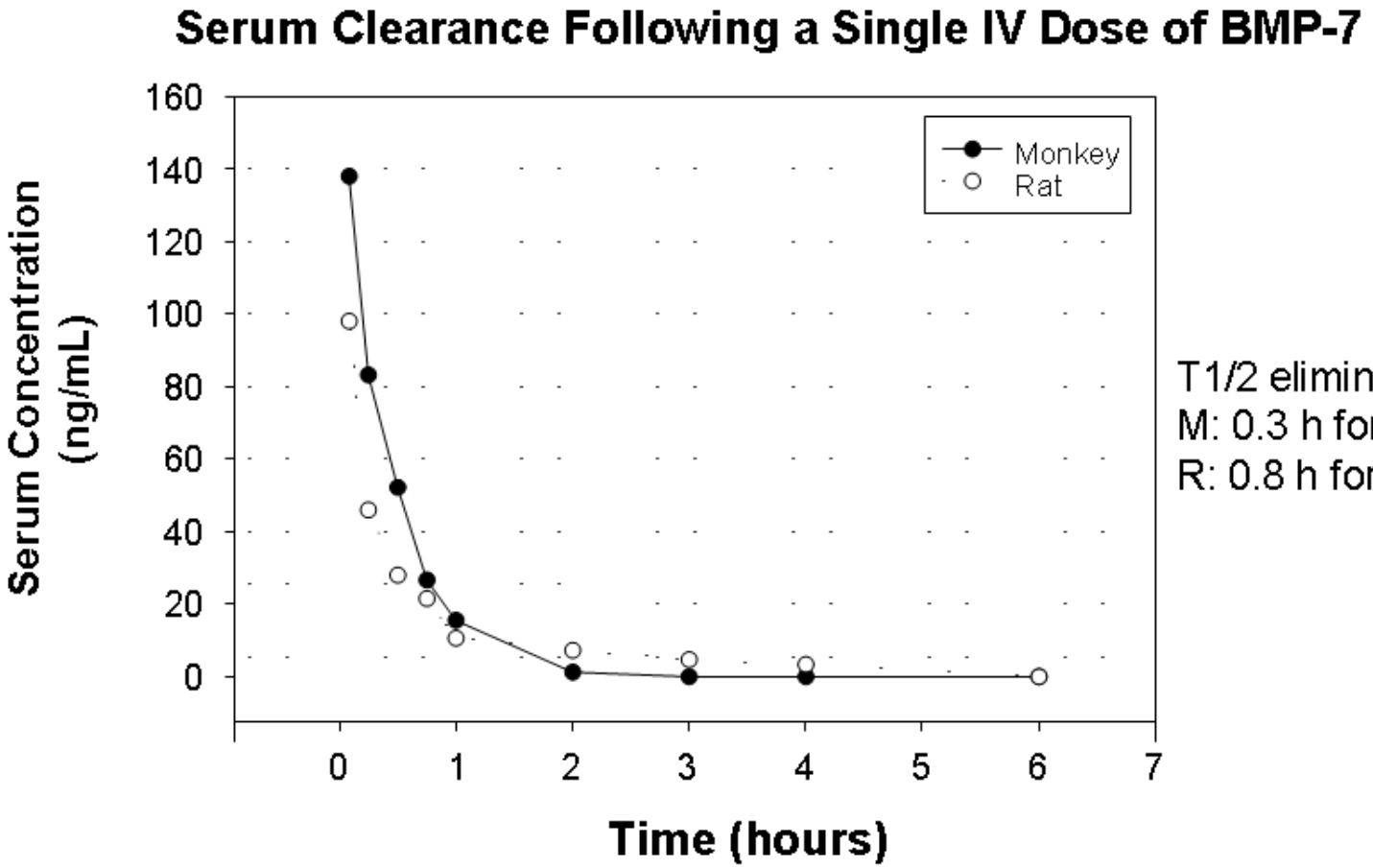
Pharmacokinetics: IV Study



T1/2 elimination:
M: 0.3 h for monkey
R: 0.8 h for rat

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

Toxicology
Systemic, Implantation and Physiologic Safety

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

No significant observations at high multiples of clinical dose

Toxicology
Developmental Toxicology Studies

Study	Formulation	Safety Margin	Outcome
Rat intravenous	OP-1 protein in acetate buffer	35X for 12 days	No Observations
Rat intravenous	OP-1 in 5% lactose	4X for 12 days	No Observations
Rabbit intravenous	OP-1 in 5% lactose	4x for 13 days	No Observations

No developmental abnormalities observed

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OP-1 Immunogenicity Studies

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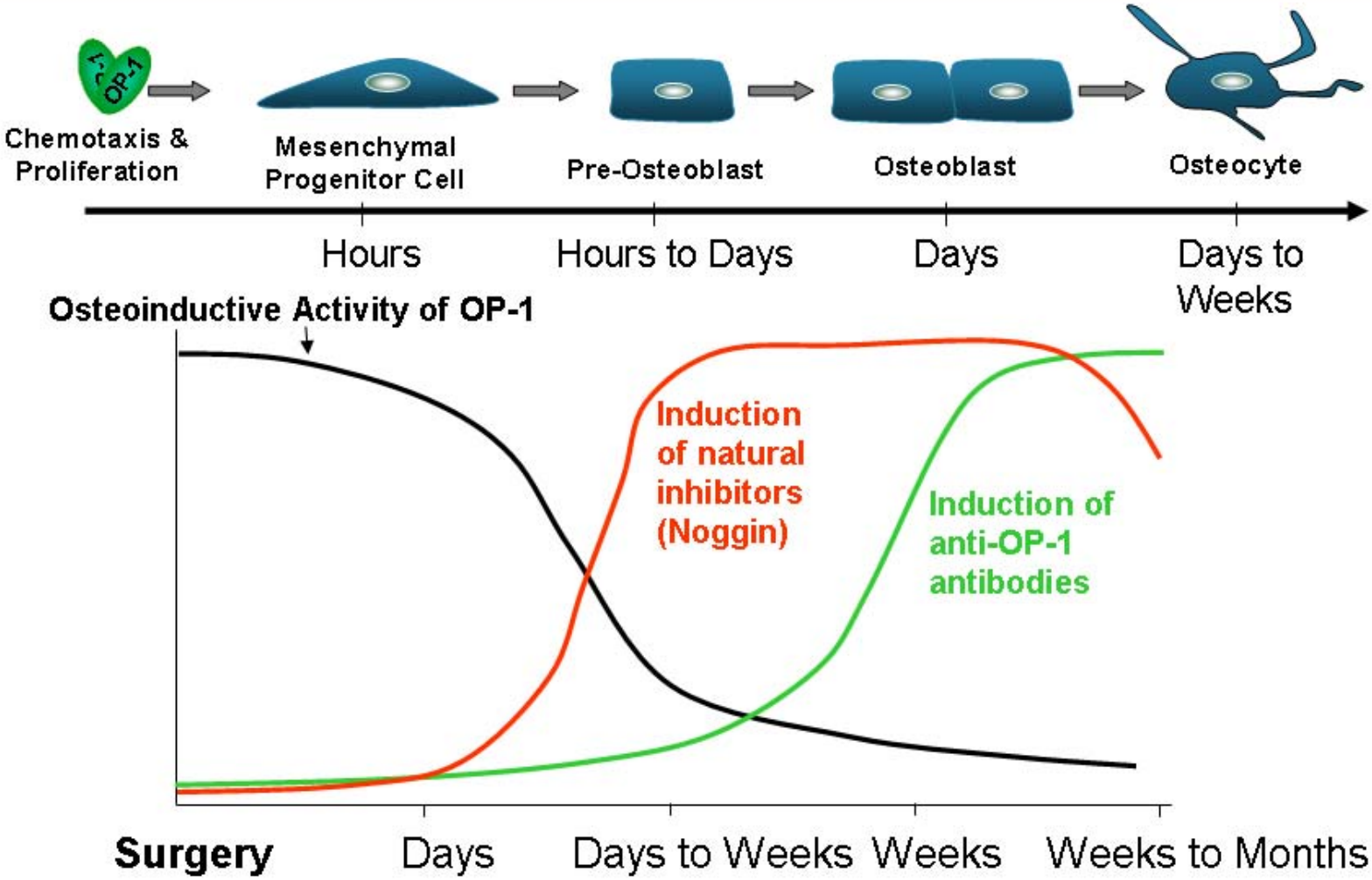
Immunogenicity Assays

- 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

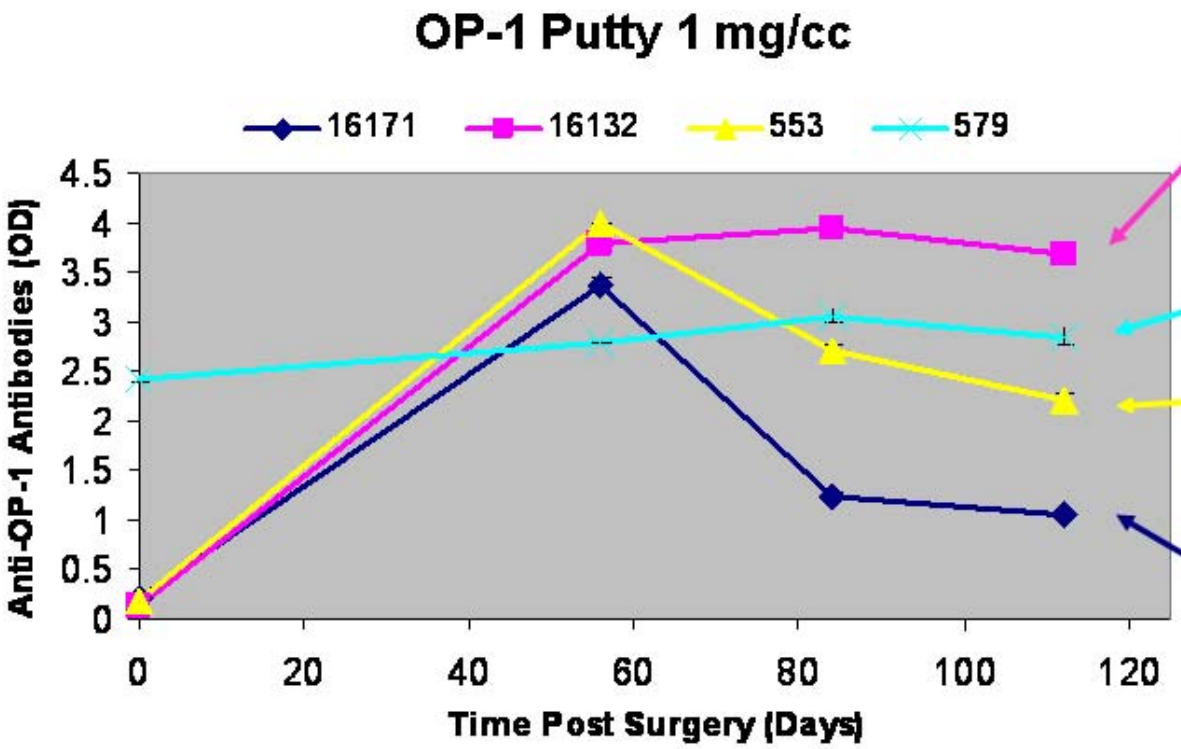
Immunogenicity and Efficacy: Osteoblast Differentiation Cascade

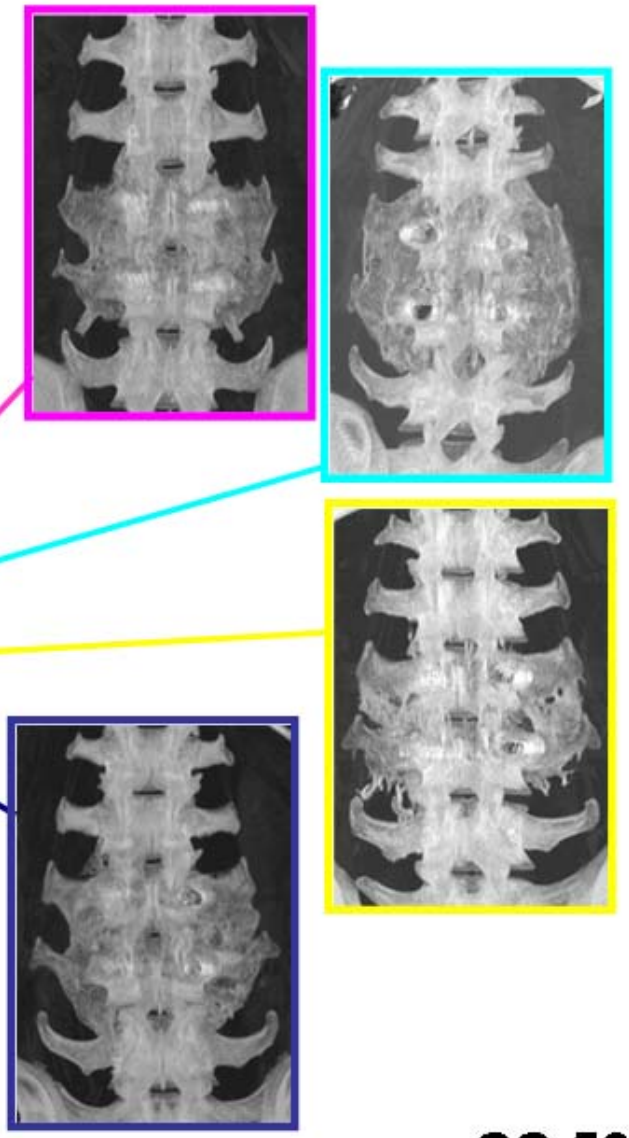


OP-1 initiates a cascade which perpetuates itself to form bone

Immunogenicity and Efficacy: Baboon PLF Study

OP-1 Antibodies in Baboon PLF



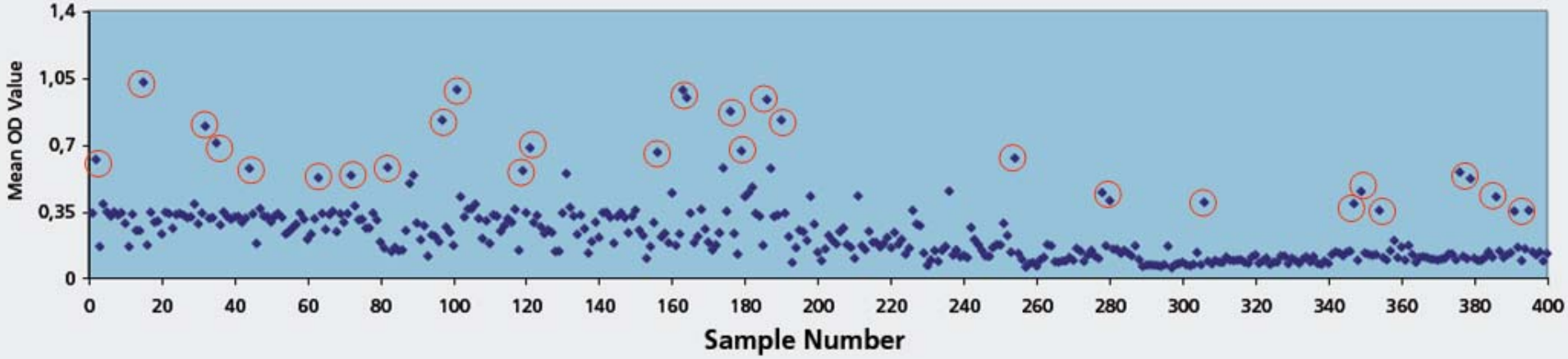


Baboon with high baseline OP-1 antibodies fuses successfully

Pre-existing Anti-BMP Antibodies

	BMP-2	BMP-7
screened	410	400
initally positive	36	44
confirmed by competition	24	31
% of true positives	5,90%	7,75%

Anti-BMP-7 Antibody ELISA results



Sauerborn et al. International BMP Conference. Lake Tahoe. CA. 2008.

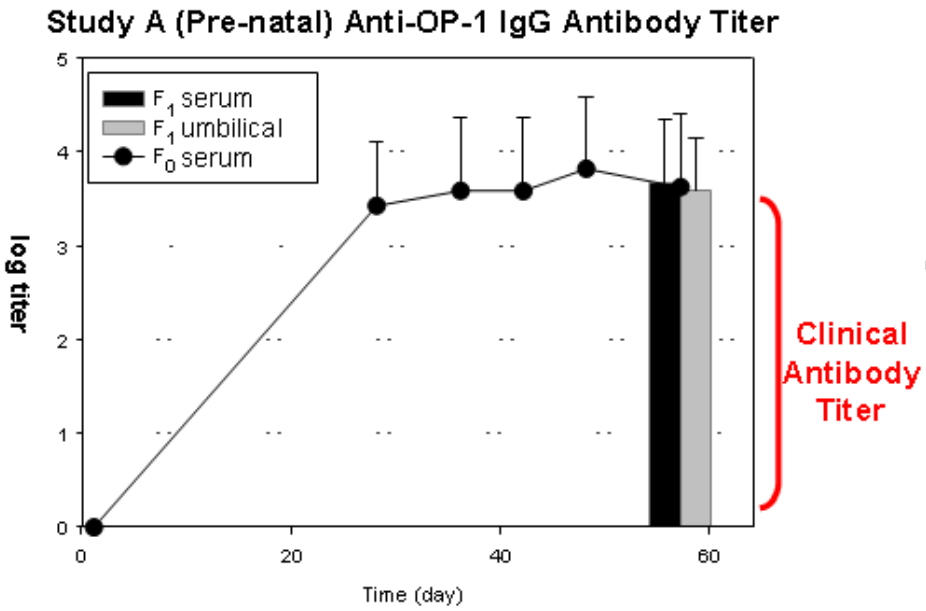
Significant numbers of healthy individuals have spontaneous anti-BMP antibody titers

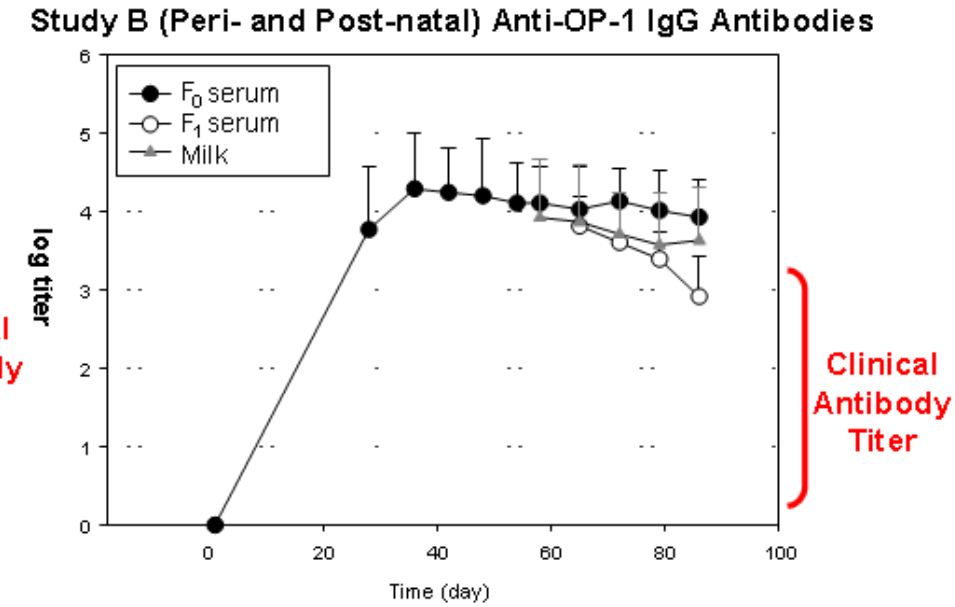
Developmental Toxicology
Effect of OP-1 Immunization

- 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

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 alone[1]
- Preclinical and case series data support efficacy in instrumented fusion[2]
  - Instrumentation enhances stability
  - Instrumentation likely to lead to higher rates of fusion (83% instrumented vs. 45% uninstrumented)[1]

1. Fischgrund et al, *SPINE* 1997.
2. Fehlings et al, *J Neurosurg Spine* 2007.

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:

Endpoint	"Success" Criterion
Clinical Success	
1) Oswestry Disability Index	• ≥ 20% improvement
2) Neurologic	• No clinically relevant neurologic changes
3) Treatment-related SAEs	• No serious adverse events related to treatment
4) Retreatments	• No retreatments intended to induce fusion
Radiological Success	**Using plain films – assessed by blinded reviewers**
5) Angulation	• ≤ 5° of angular movement } Measures of stability
6) Translation	• ≤ 3 mm of translational movement } Measures of stability
7) Presence of bone	• Presence of bone – a marker of OP-1 activity

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)

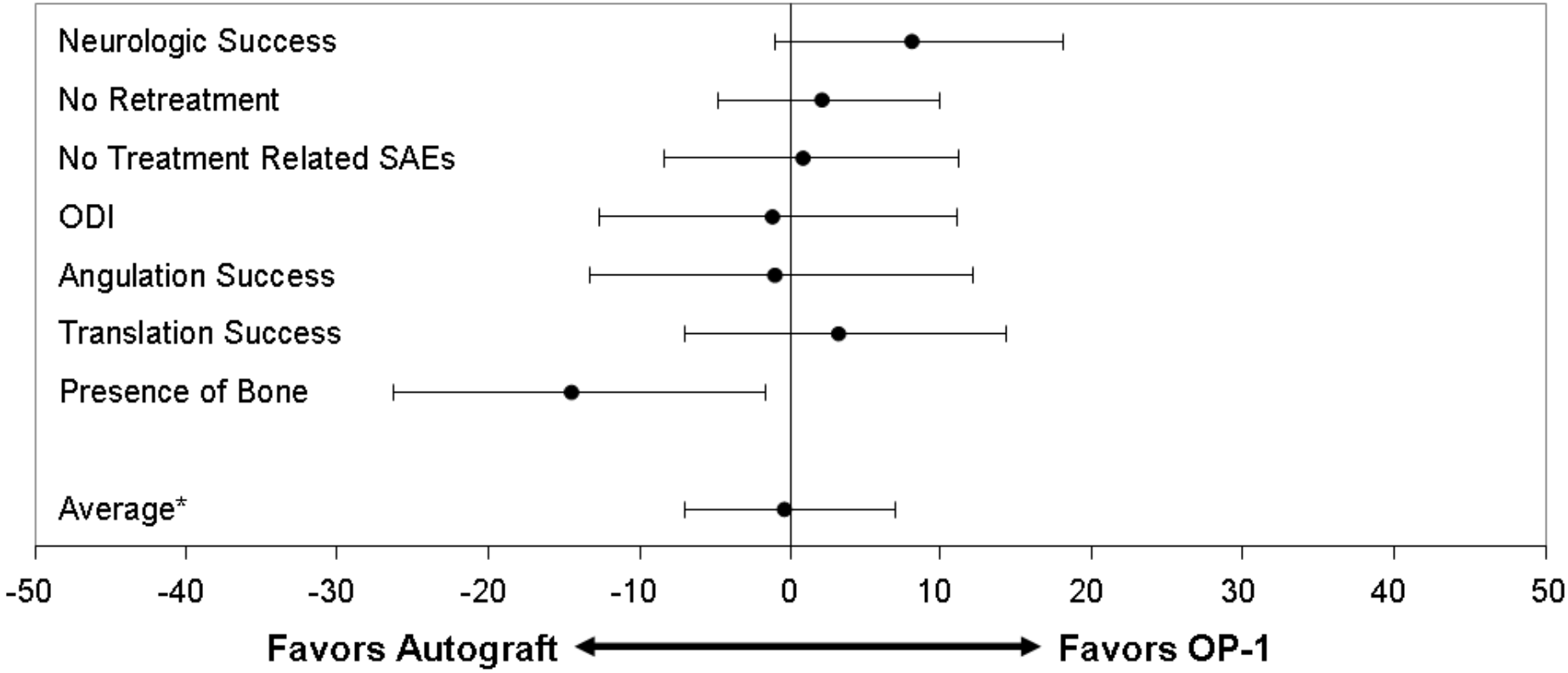
Selected Demographic and Baseline Characteristics - Pivotal Study

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

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



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

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

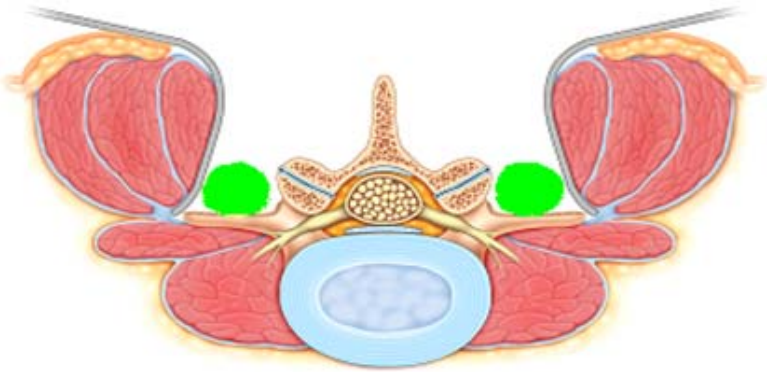
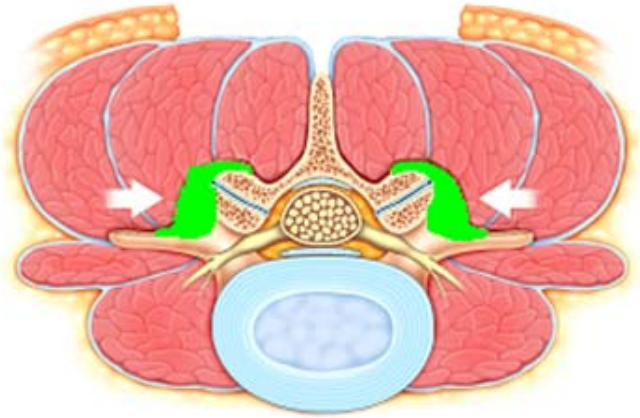


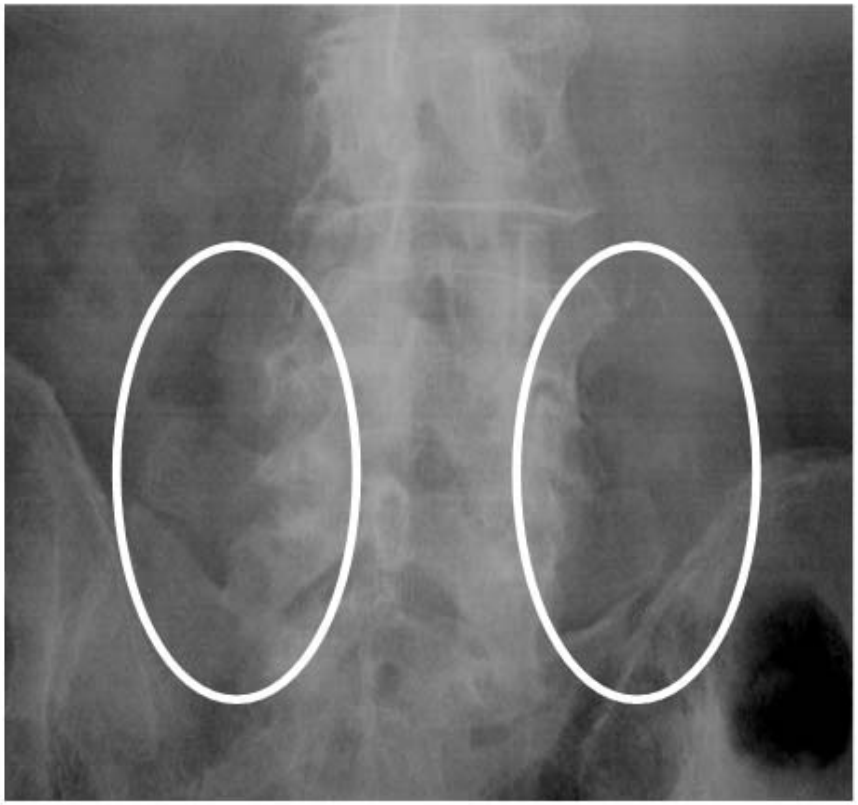
Figure 2

Upon release of muscle
retraction, OP-1 Putty conforms
to medial, bony anatomy



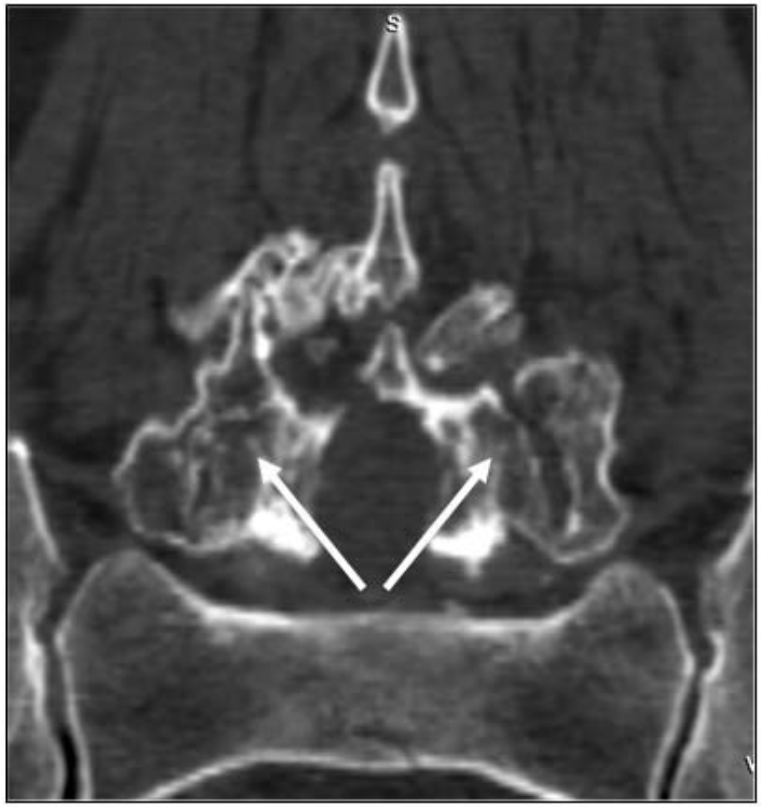
24 Month Plain Radiograph vs. 9 Month CT Scan

AP X-ray



No visible bone on plain radiograph

Coronal Multiplanar Reformatted Image

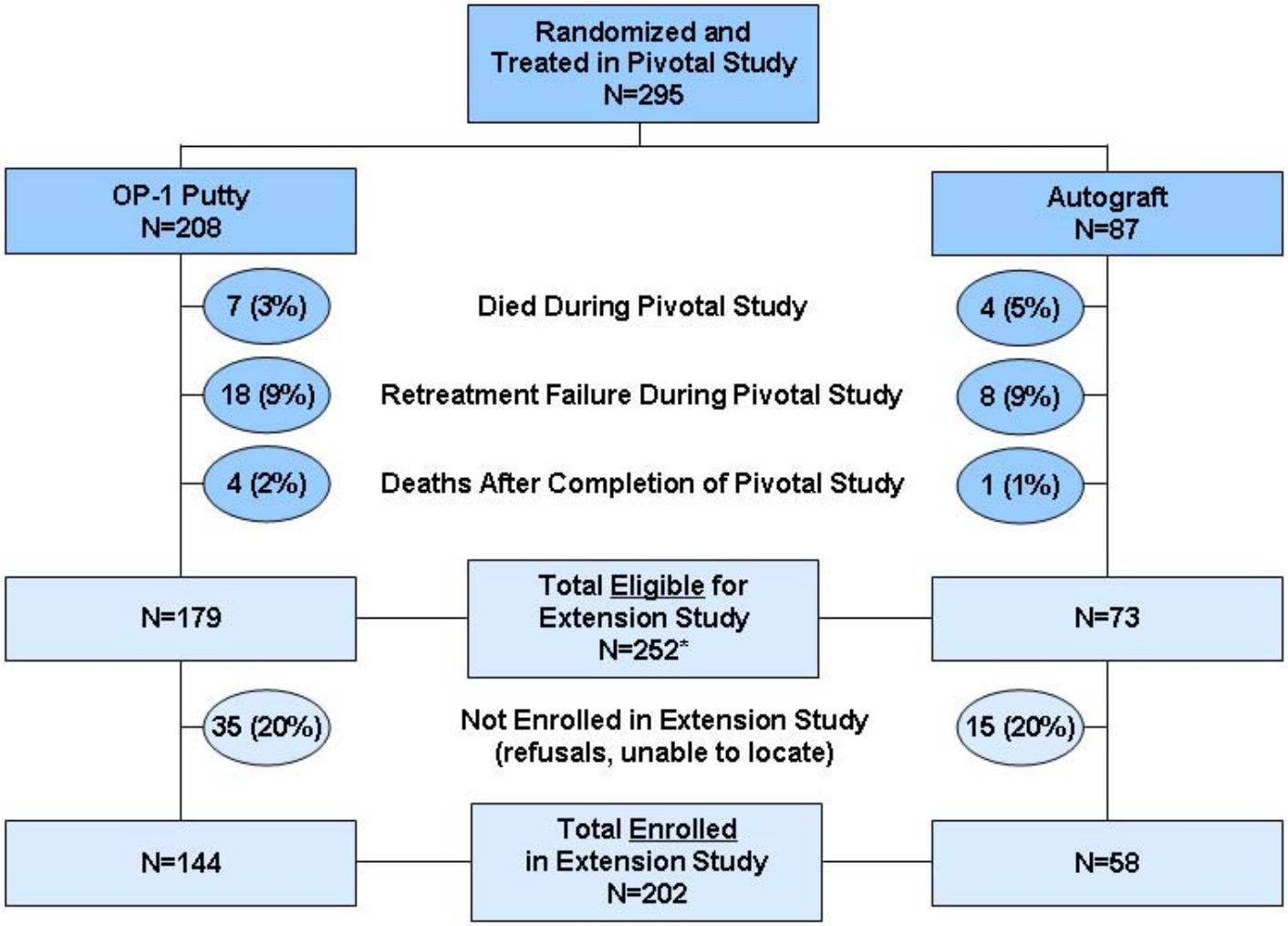


Significant bone formation medially

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



* Excludes 1 patient with no post-baseline visit

Extension study enrollment 202/252 = 80.2%

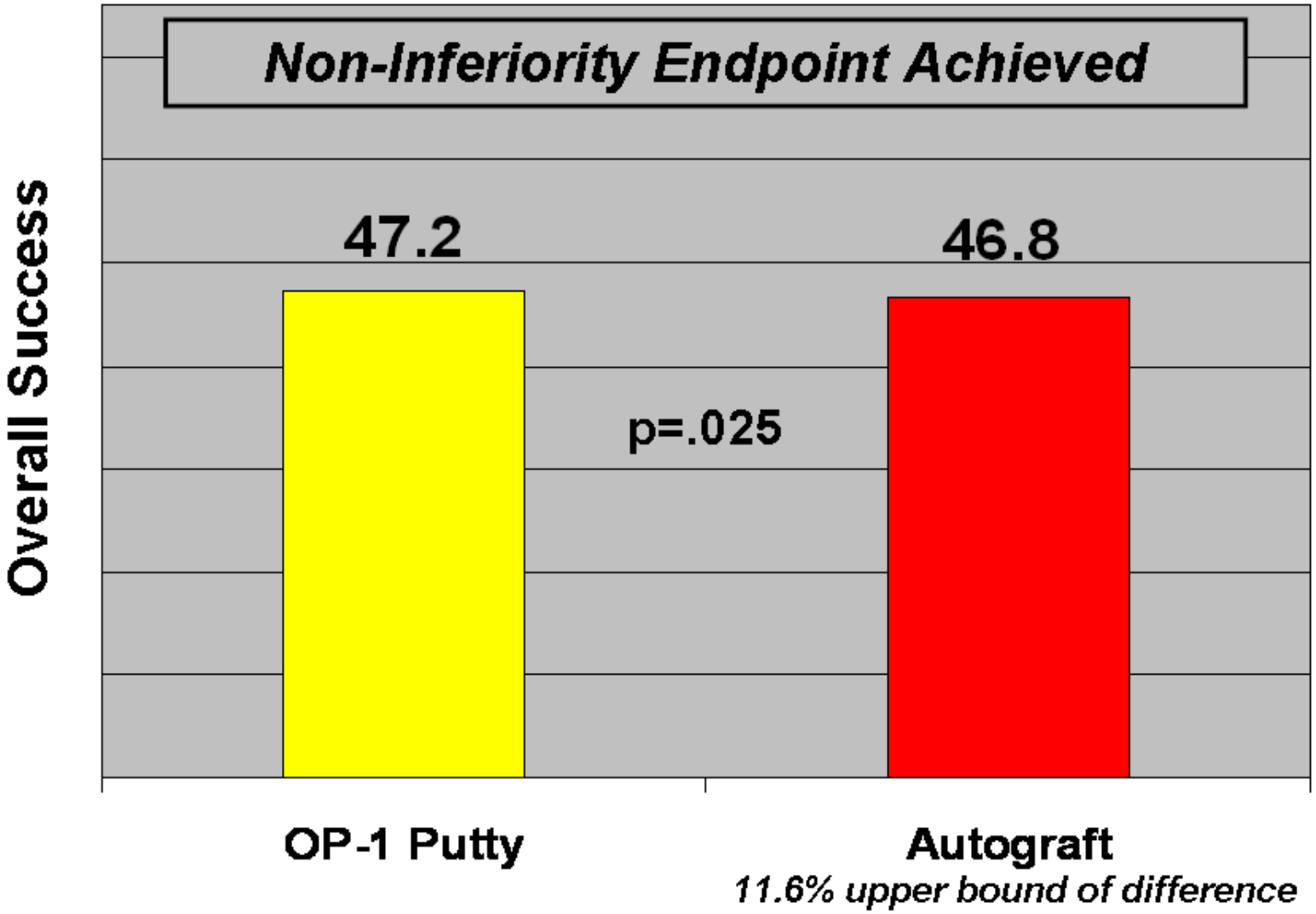
Comparison of Key Clinical Parameters for Eligible and Enrolled Patients in 36+ Month Follow-Up Study

Parameter	Statistic	OP-1 Putty		Autograft	
		Eligible	Enrolled	Eligible	Enrolled
Age	Mean	67.6	66.8	69.3	68.7
Gender					
Male	%	35.0	34.7	25.7	27.6
Female	%	65.0	65.3	74.3	72.4
Degree of Angular Motion (degrees) - Baseline	Mean	4.0	4.1	4.7	4.3
Translational Movement (mm) - Baseline	Mean	1.7	1.8	1.6	1.5
ODI - Baseline	Mean	48.5	48.2	50.1	50.7
Overall success at 24 months	%	42.9	43.8	57.6	60.0

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



Components of Overall Success, (36+ Month Radiographic Data) mITT

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

Remarkable consistency across all components of the primary endpoint

[1] P-value is based on Fisher's exact test
[2] Missing or non-evaluable data are excluded

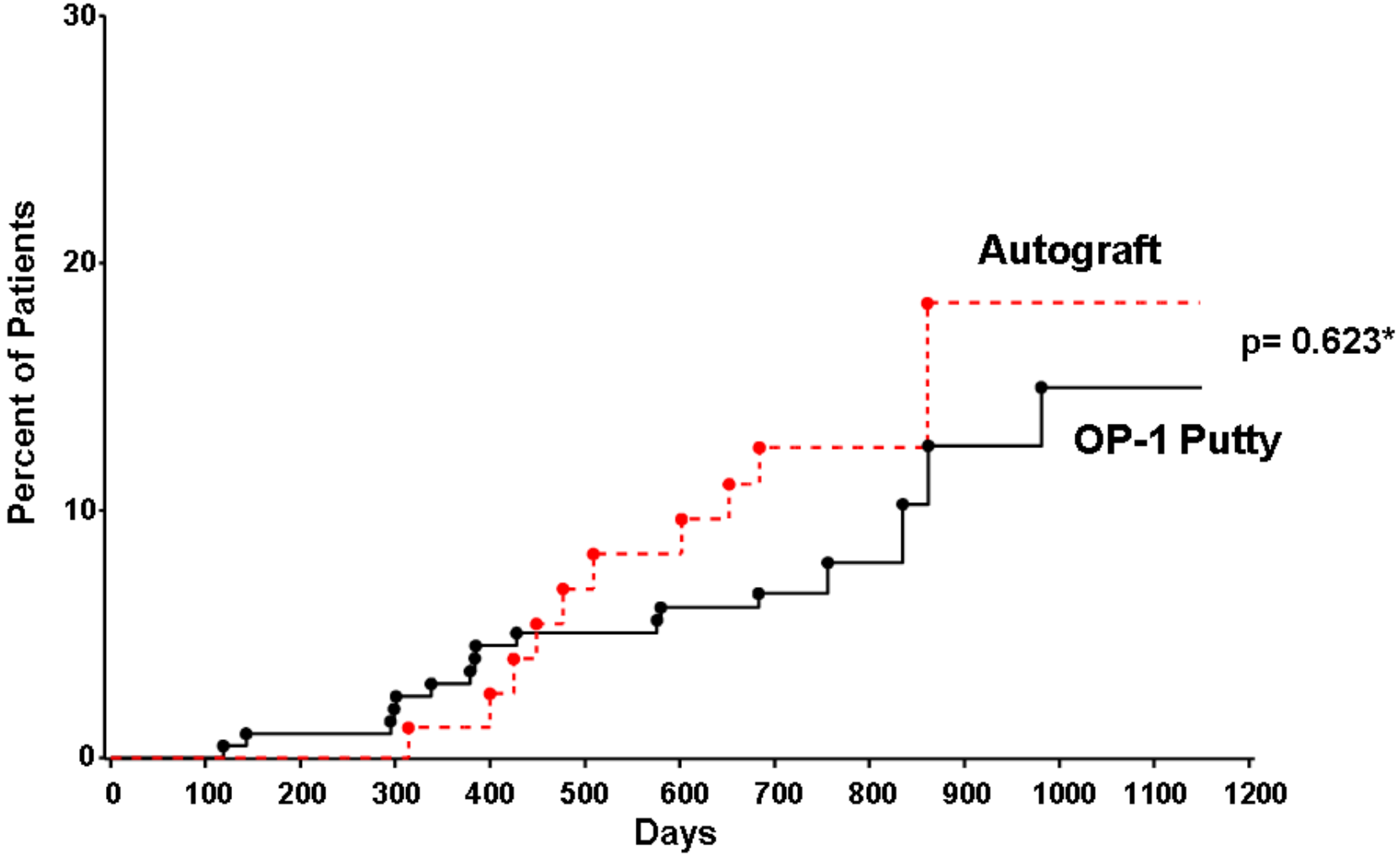
Radiographic and Clinical Outcomes at 36+ Months

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

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

Visit	Statistic	OP-1 Putty Change from Baseline	Autograft Change from Baseline	P-Value
24 Month	Mean	-3.1	-2.9	0.681
	p-value	<0.001	<0.001	
36+ Month	Mean	-3.2	-2.6	0.301
	p-value	<0.001	<0.001	

SF-36 Physical Function Score

Visit	Statistic	OP-1 Putty Change from Baseline	Autograft Change from Baseline	P-Value
24 Months	Mean	11.8	11.3	0.636
	p-value	<0.001	<0.001	
36+ Months	Mean	11.4	9.7	0.206
	p-value	<0.001	<0.001	

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

Visit	Autograft			
	None	Mild	Moderate	Severe
12 months	55.6%	23.6%	20.8%	0.0%
24 months	54.5%	29.1%	14.5%	1.8%
36+ months	65.4%	17.3%	17.3%	0.0%

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

Musculoskeletal Serious Adverse Events

System Organ Class Preferred Term	Percent of Patients		P-Value
	OP-1 Putty (n=208)	Autograft (n=87)	
Musculoskeletal and connective tissue disorders	3.4%	6.9%	0.214
Arthralgia	0.5%	1.1%	
Arthritis	0.5%	1.1%	
Back pain	0.5%	3.4%	
Lumbar spinal stenosis	1.0%	0.0%	
Musculoskeletal stiffness	0.0%	1.1%	
Scoliosis	0.5%	0.0%	
Spinal column stenosis	0.5%	0.0%	
Radiculopathy	1.4%	3.5%	

Deaths – Pivotal and Extension Studies

- 16 patients died during study participation
  - 11 (5.3%) in OP-1 Putty group
  - 5 (5.8%) in the autograft group

  p=1.000
- No significant trends observed in cause of death by treatment group

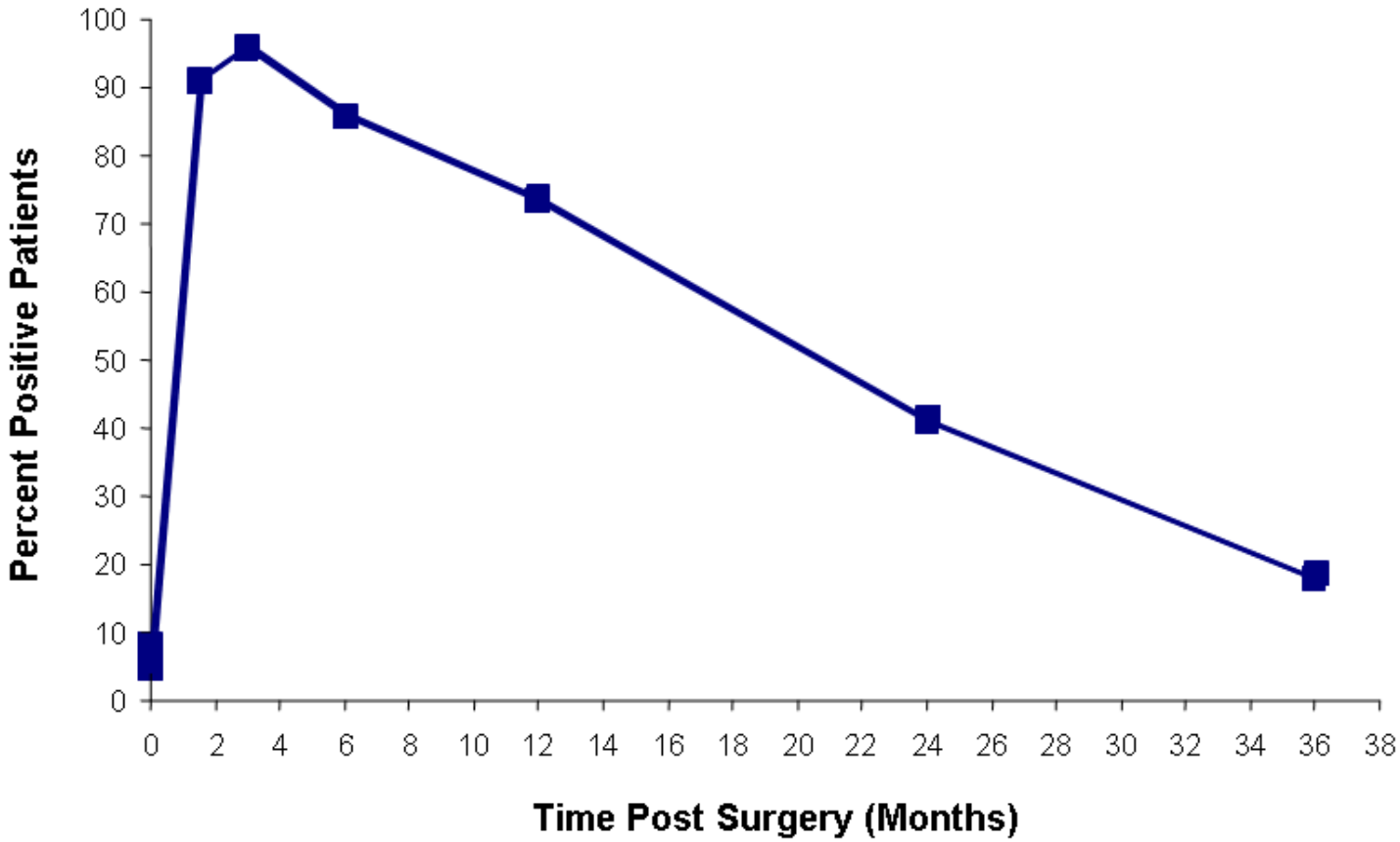
Malignancy/Carcinogenicity – Pivotal and Extension Studies

- 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

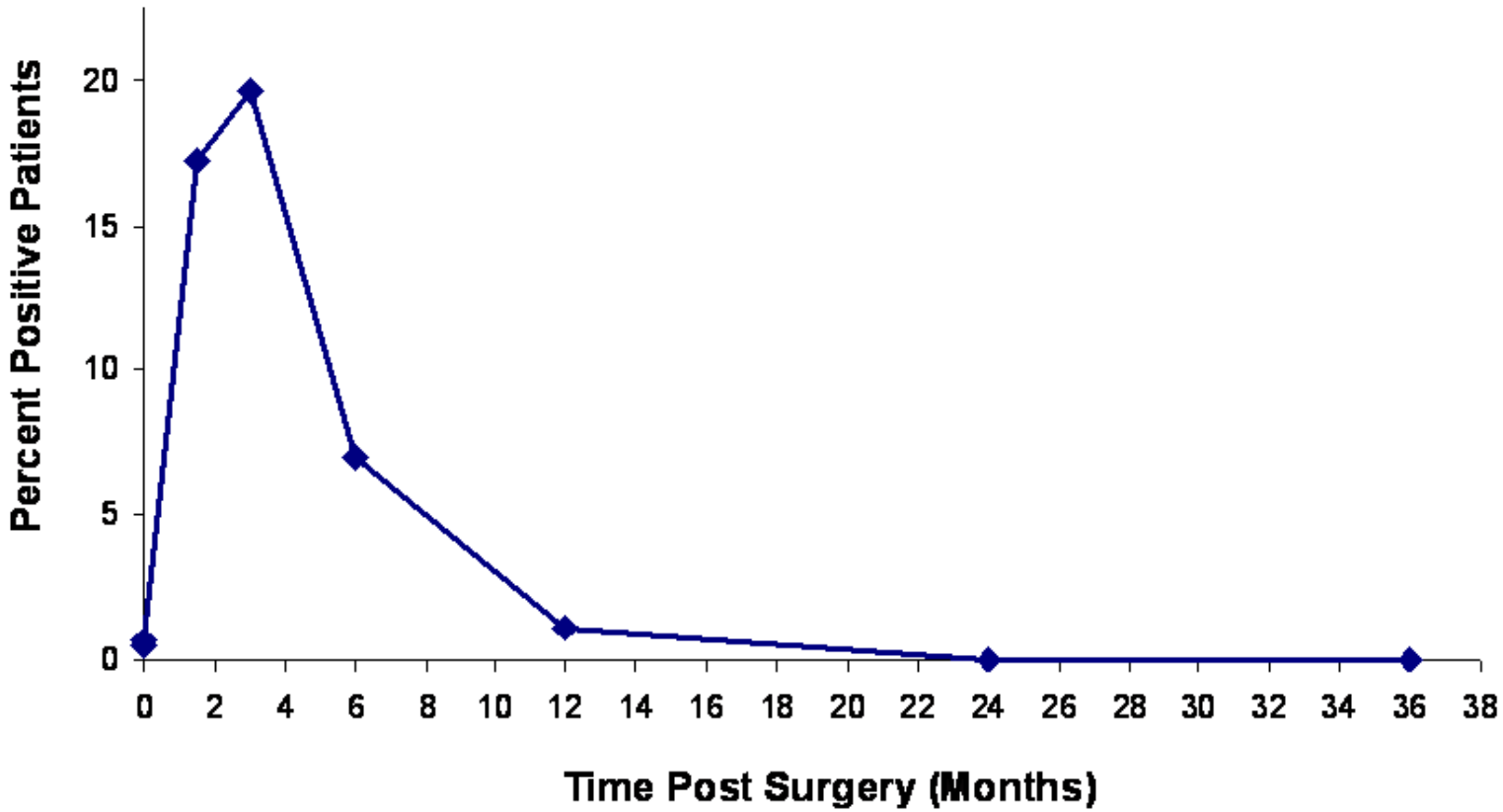
- Heterotopic bone was defined as any bone seen outside the intended area of fusion
- 24 patients with radiographic evidence of heterotopic bone
  - No incisional bone formation
  - No bone formation in the canal
  - All had extension of bone towards the adjacent levels
- 3 adverse events related to heterotopic bone
  - None required intervention

Incidence of Antibodies to OP-1 Putty



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

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

No impact of neutralizing antibodies on efficacy of any of the clinical subcomponents of Overall Success

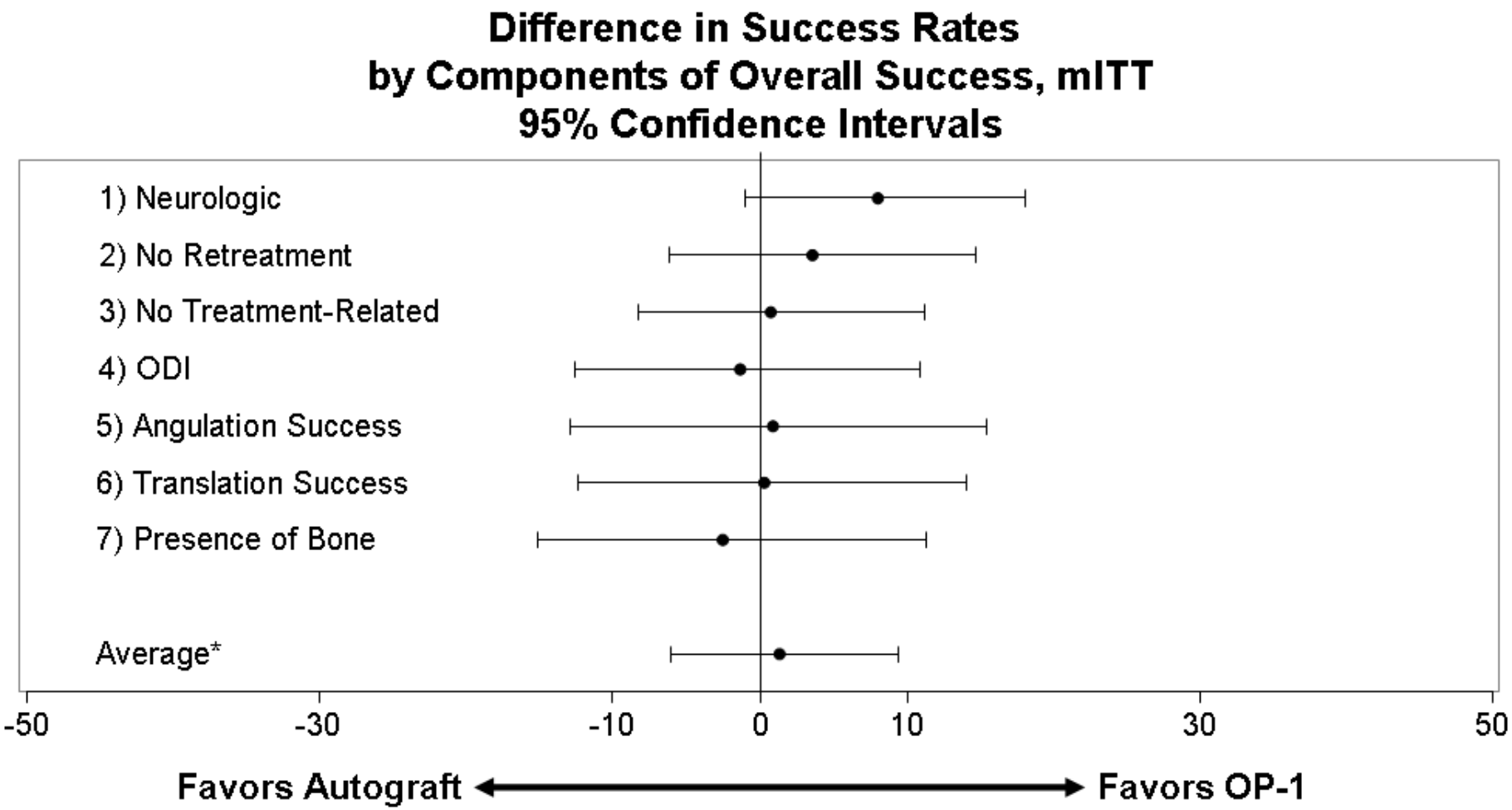
Adverse Events by Neutralizing Antibody Status

Treatment	Neutralizing Status	% of Patients	
		Total No. with Adverse Events	Total No. with Serious Adverse Events
OP-1 Putty	Positive	35.8	11.3
	Negative	39.6	12.3

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



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

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

stryker®
Biotech

CC-101

Radiographic Success Definition

- Angulation ≤ 5°
- Translation ≤ 3 mm

} Measures of stability

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

1. D. Resnick et al. Journal of Neurosurgery, Spine 2:653-657, 2005.

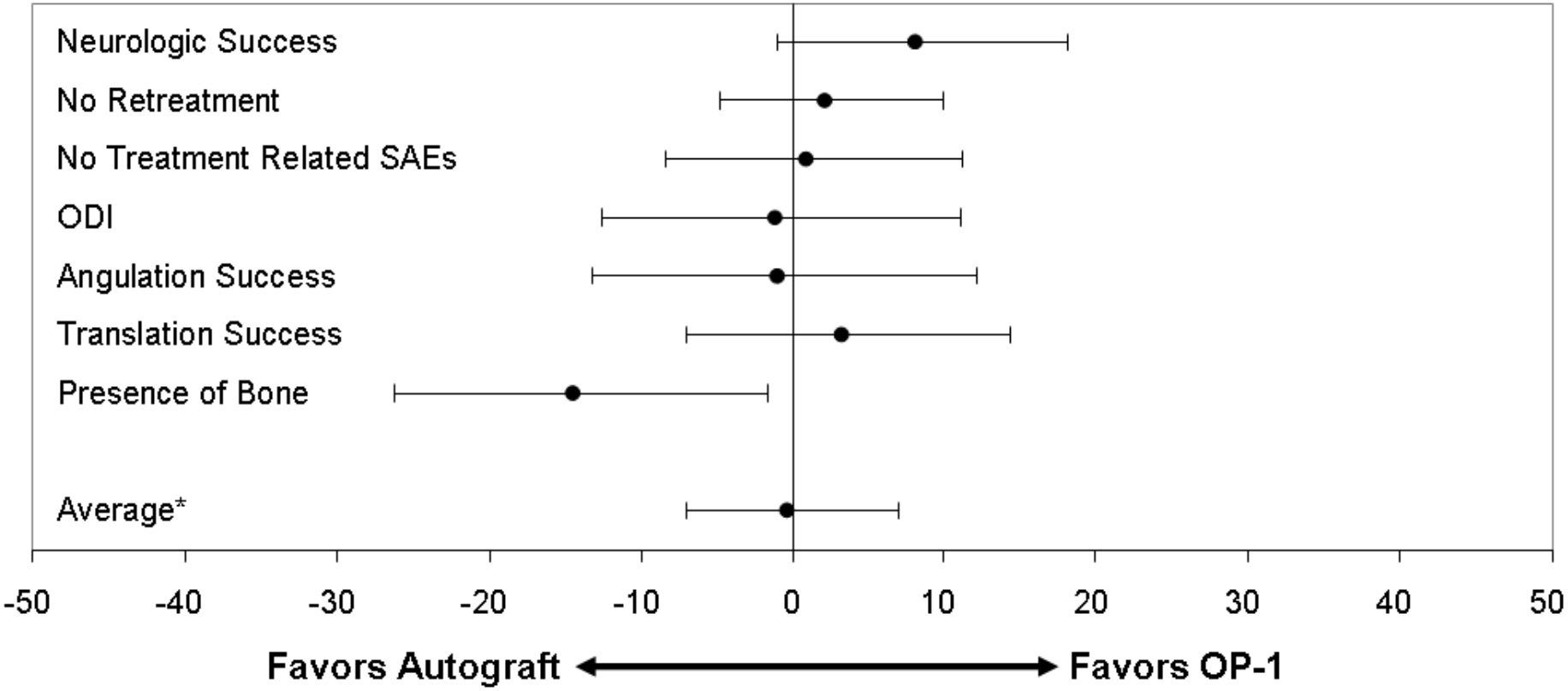
Radiographic Success Measures

Guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 4: radiographic assessment of fusion
D. Resnick et al. *Journal of Neurosurgery, Spine* 2:653-657, 2005

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



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

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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

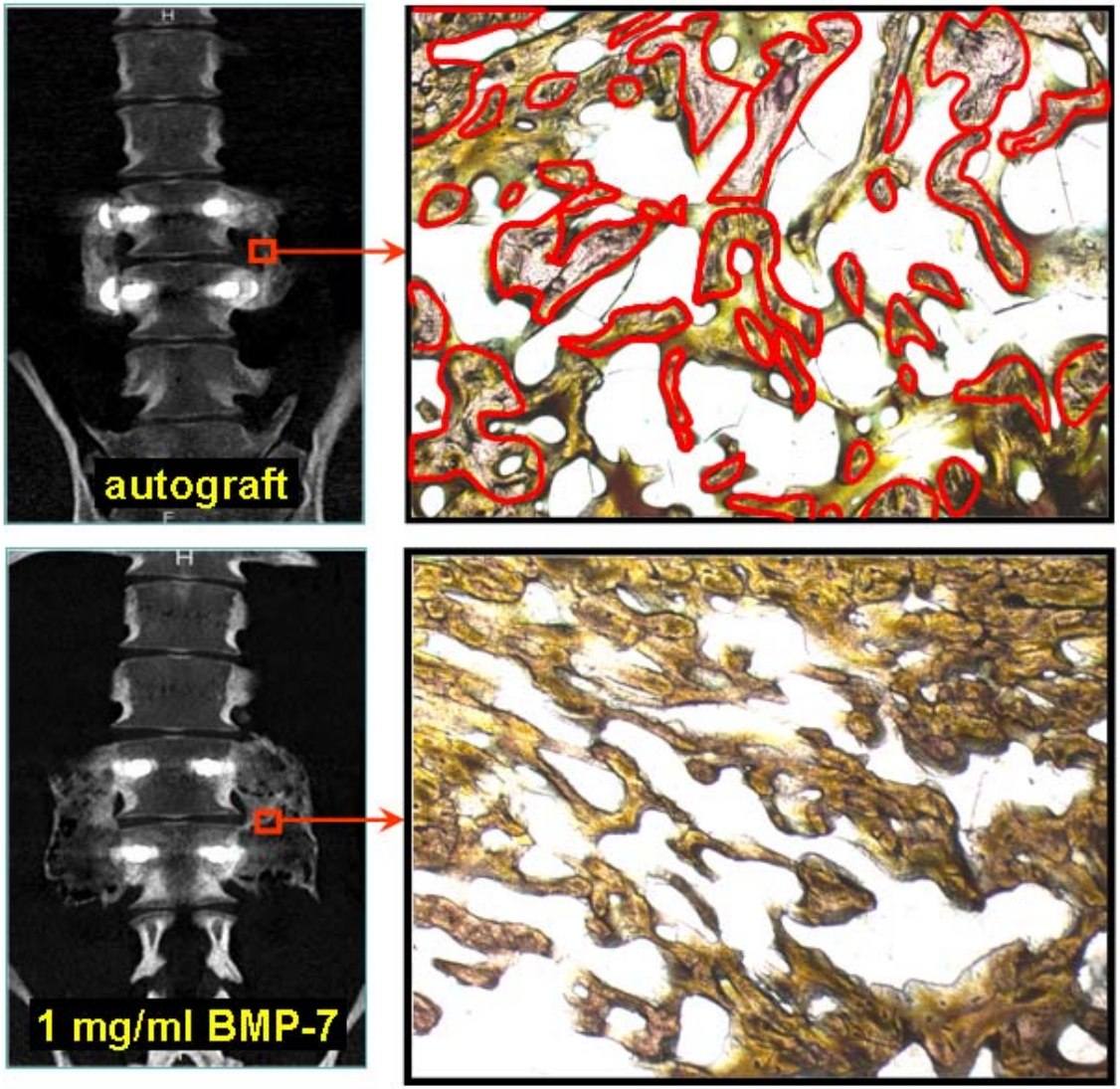
Question 2: Why Were the 9 Month CT Scan Results Inconclusive?

- 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

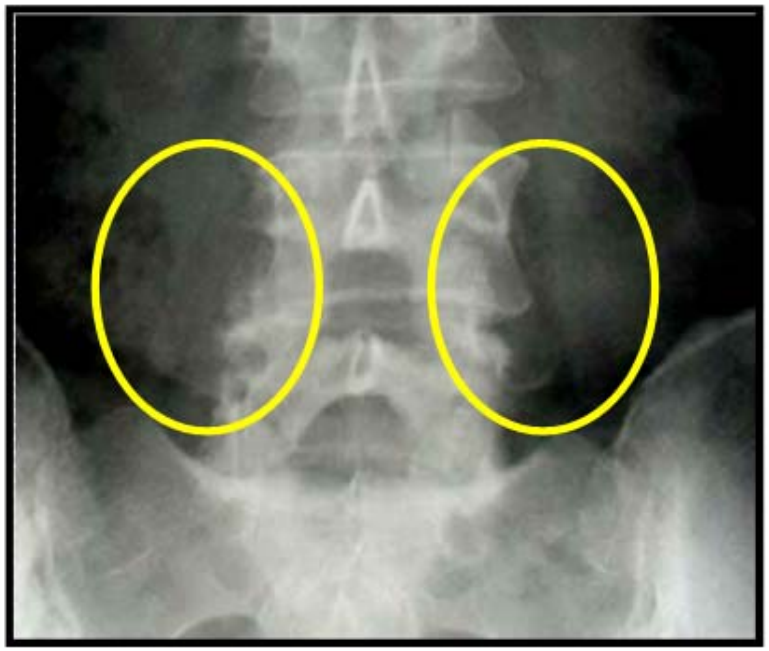


57% of bone density in autograft is residual graft particles

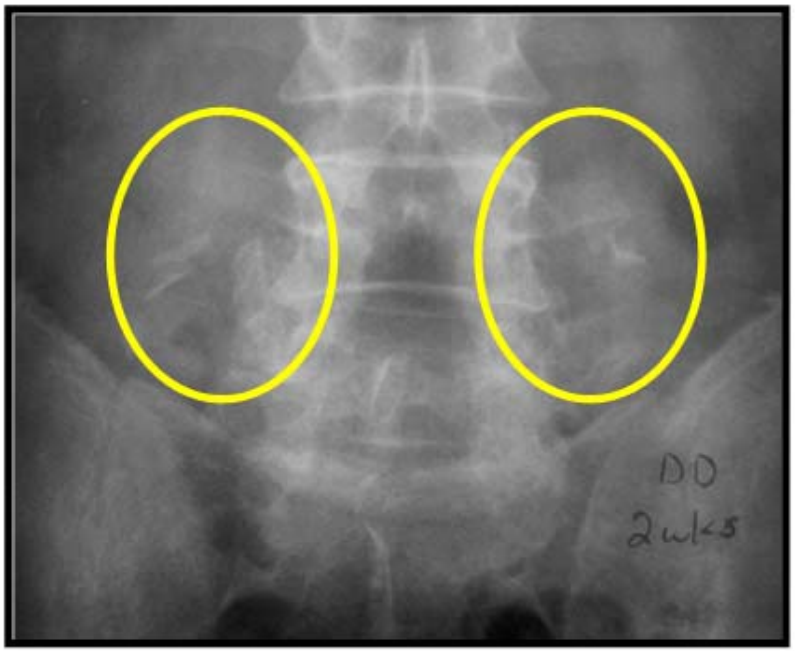
Jenis et al. Proceedings of the NASS 23rd Annual Meeting / *The Spine Journal* 8 (2008) 1S–191S.

van Loon et al. *J Bone Joint Surg [Br]* 2000;82-B:436-44.

Postoperative AP X-ray



OP-1 Putty



Autograft

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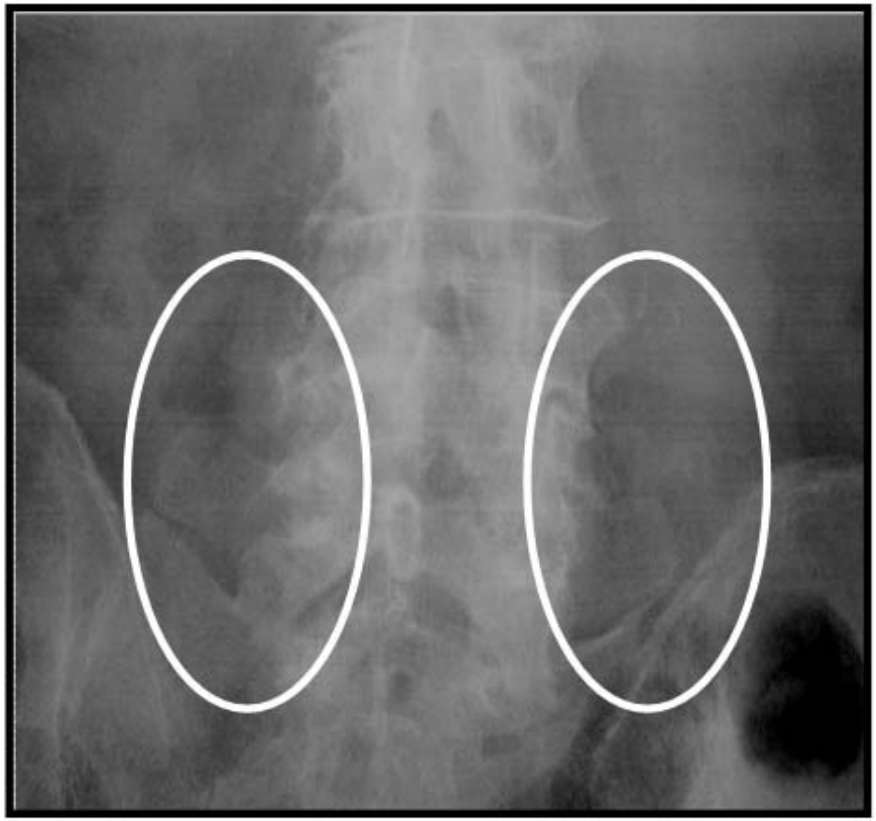
Question 3: Why Gather Additional Data?

- 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.

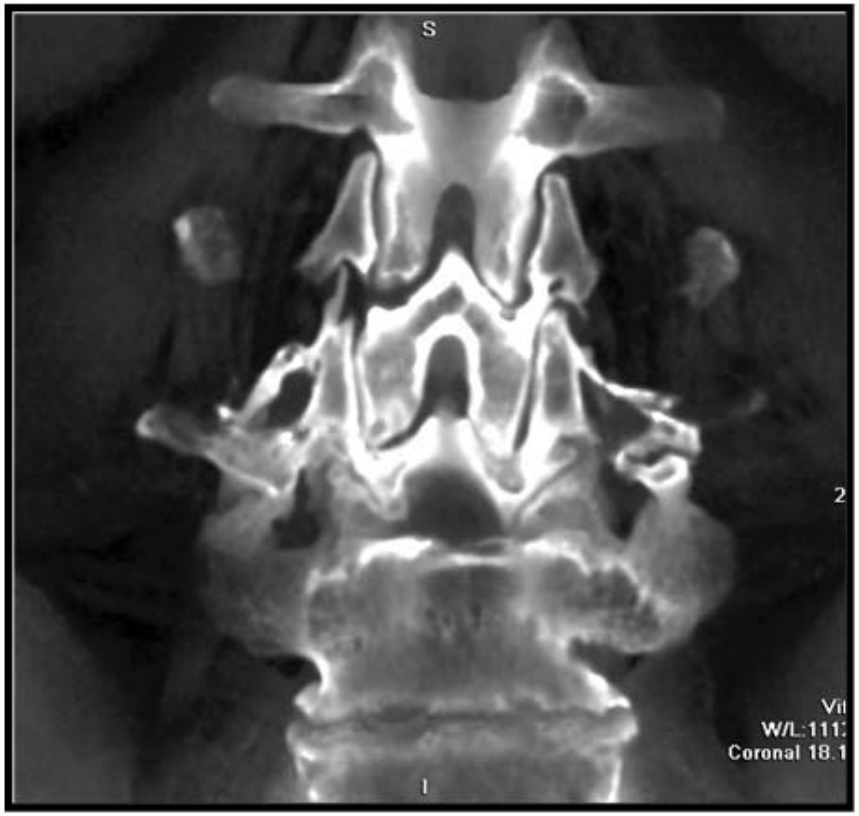
24 Month Plain Radiograph vs. 36+ Month CT Scan

AP X-ray



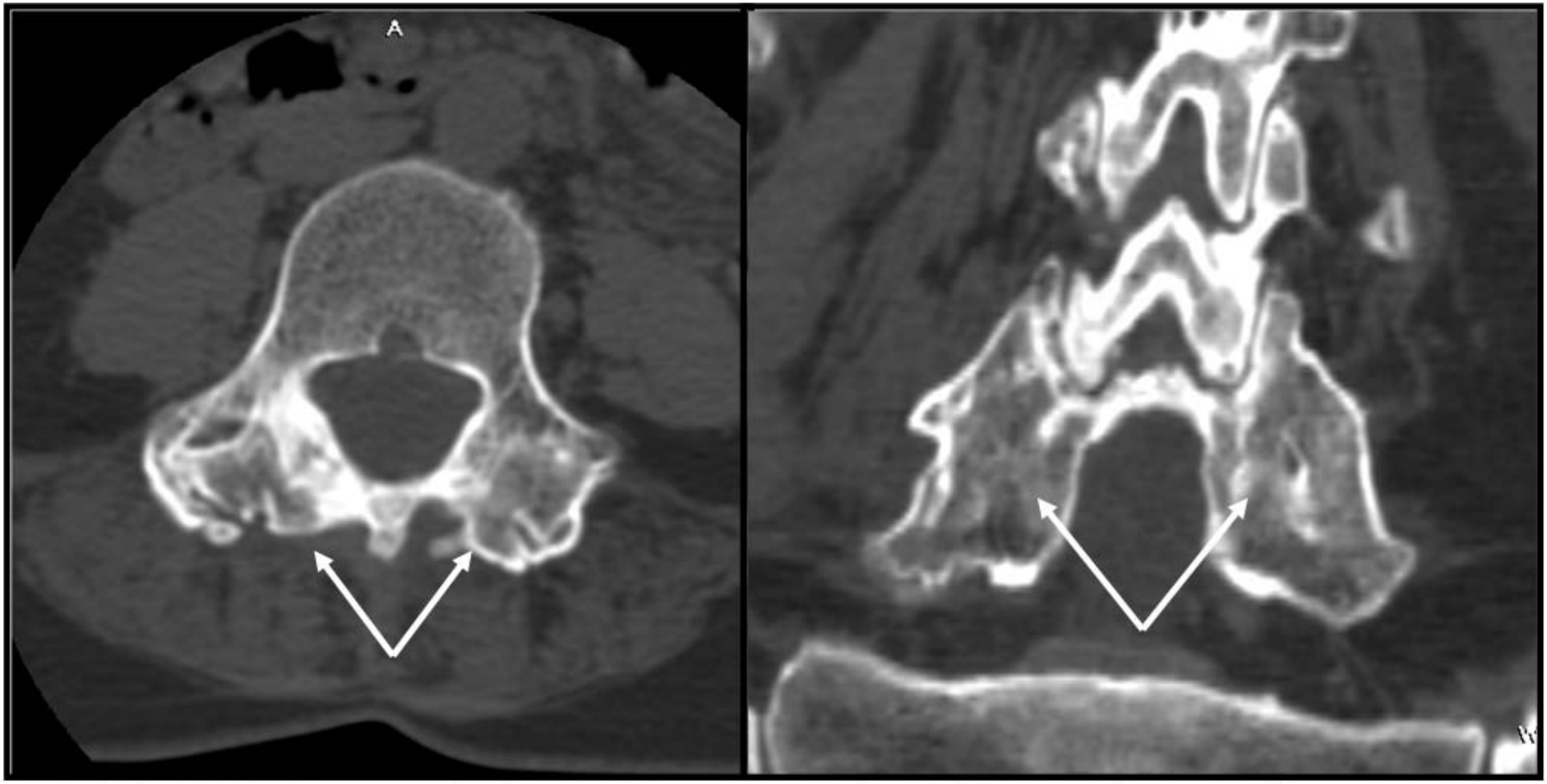
No visible bone on plain radiograph

MPR of CT



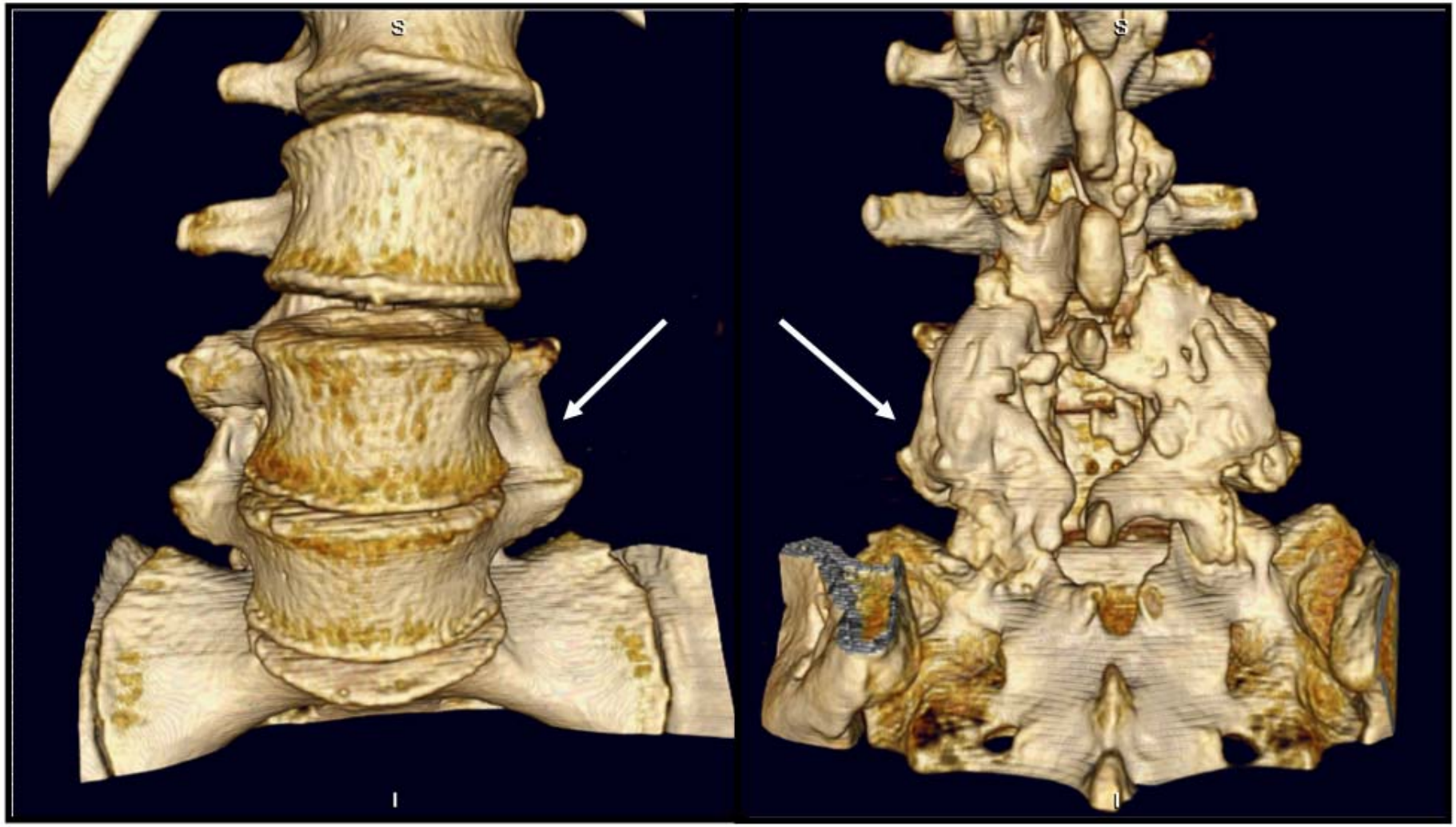
Significant bone formation medially

CC-112



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).

CC-113



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).

CC-114

Radiographic and Clinical Outcomes at 36+ Months

Outcome	OP-1 Putty	Autograft	P-Value*
Clinical and Safety Parameters			
Oswestry Disability Success (36+ Months)	68.6%	77.3%	0.201
Absence of Retreatment (36+ Months)	87.0%	83.3%	0.529
Absence of Serious Treatment Related Adverse Events (36+ Months)	79.5%	73.5%	0.387
Neurological Success (36+ Months)	84.4%	80.0%	0.540
Radiographic Parameters			
Angulation	69.3%	68.4%	1.000
Translation	75.7%	75.4%	1.000
Presence of Bone	74.8%	77.4%	0.852

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

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CC-117

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

Drug	Incidence of Anti-Drug Antibodies
• Insulin	44%
• rHu-GH	3%-16%
• GRH	20%
• Factor VIII	35%
• GM-CSF	95%
• Lenercept	88%
• OKT3	86%
• Remicade	61%
• Rituximab	up to 11%
• Rabtiva	6.3%
• rHu IL-2	66 – 74%
• rHu-IL-11	1%
• Avonex	10%
• EPO	< 1:10,000

Schellekens, *Clin. Ther.* V24, 2002, p1720-40.

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

Schellekens, *Clin. Ther.* V24, 2002, p1720-40.

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

Validation Parameter	Stryker Results	FDA Guidance*
Inter-Assay Precision	% CV = 13	< 15%
Intra-Assay Precision	% CV < 7	< 15%
Standard Curve	9 points	≥ 6 points
Accuracy	% CV < 13	< 15%
Stability	5 Freeze-thaws	≥ 3 Freeze-thaws
Specificity	% CV = 24.6	No specified range

* FDA Guidance for Industry. *Bioanalytical Method Validation*. May 2001.

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

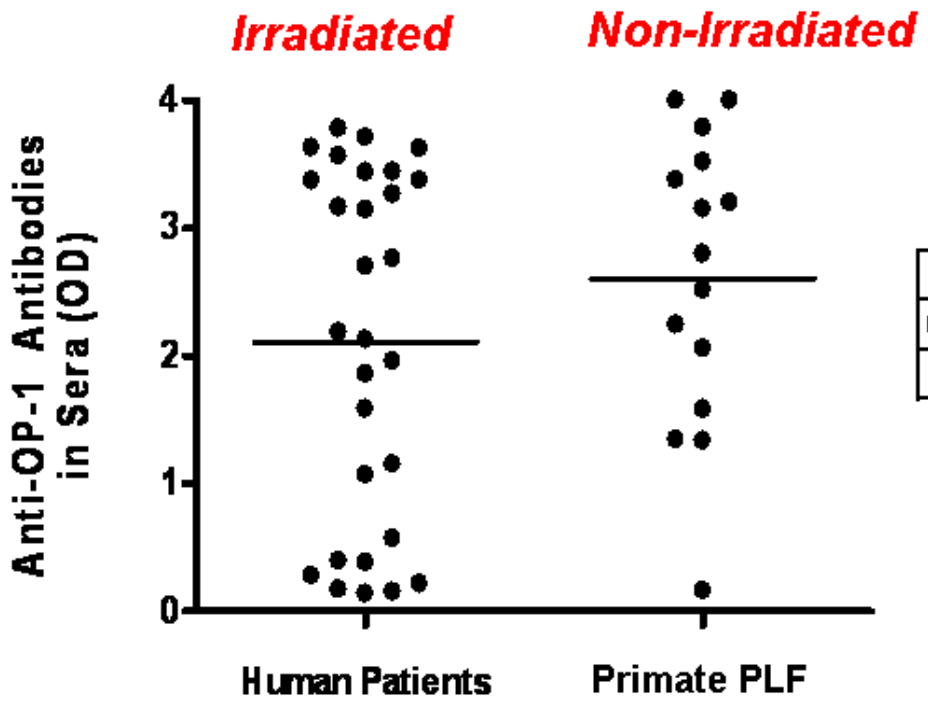
Adapted from: The Guideline On Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins. *EMEA. CHMP*. 2007.

Immunogenicity is Multifactorial

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

Adapted from: The Guideline On Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins. *EMEA. CHMP*. 2007.

Non-Irradiated OP-1 Putty is Immunogenic in Primates



OP-1 Sequence Homology

	Human	Chimp	Rhesus
Chimp	100		
Rhesus	100	100	

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

Route of Administration	Species	Immunogenicity
Posterolateral Fusion	Rabbit	Yes
	Baboon	Yes
Subcutaneous	Rabbit	Yes
	Rat	Yes
Intra-Articular	Monkey	Yes
	Dog	Yes
Intervertebral Disc	Rabbit	No
Intravenous	Monkey	No

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.

stryker®
Biotech

CC-133

Chronology

Pivotal Study

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

Extension Study

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

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

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

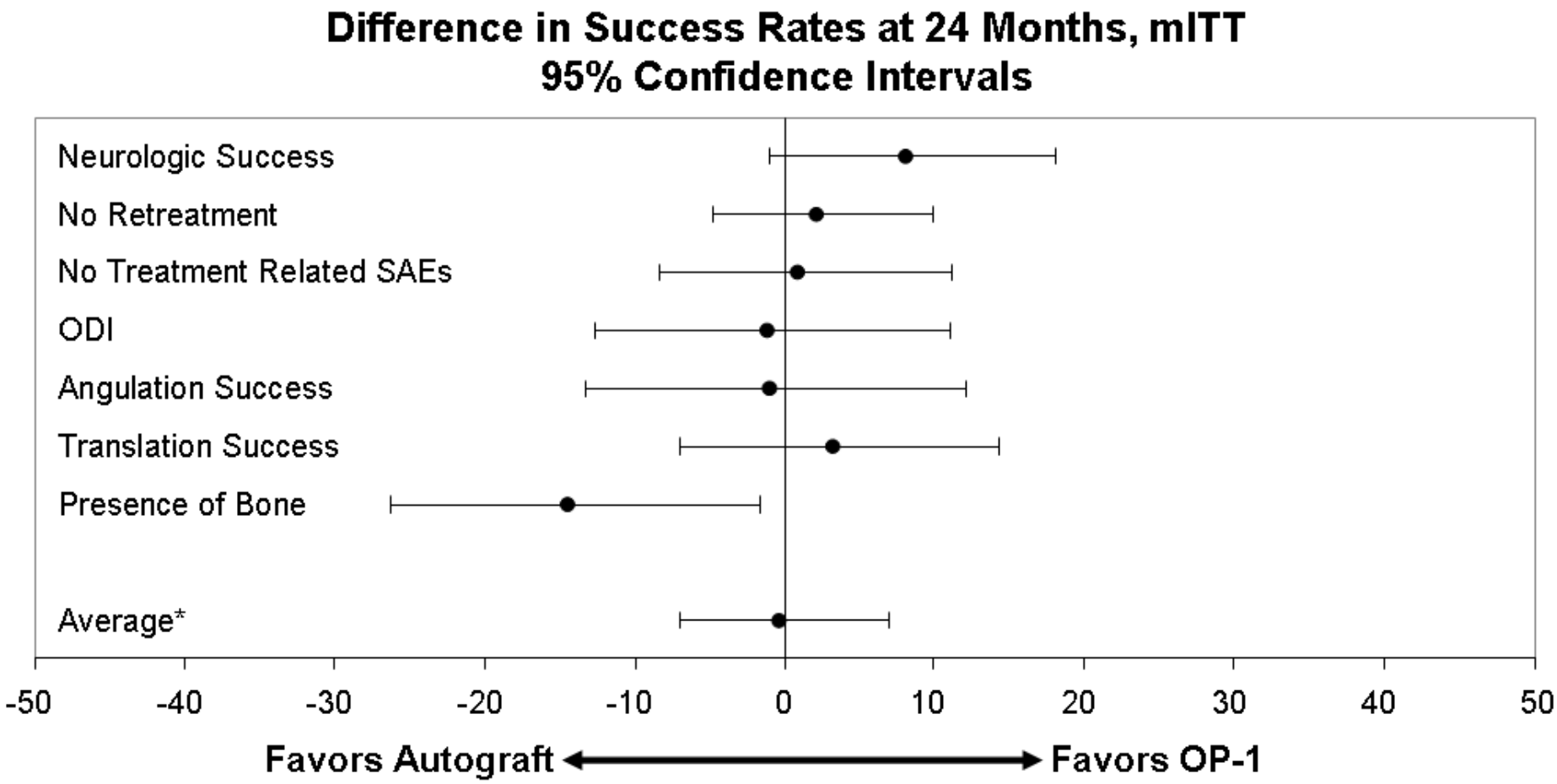
Pivotal Study

Results at 24 Months

- Estimated Overall Success rates:
  - OP-1: 38.7%
  - Autograft: 49.4%
- p = 0.33 (based on variable margin)

Pivotal Study

Components of Overall Success at 24 Months



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

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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)

Comparability

- Approximately 80% of eligible patients participated
- Conducted extensive analyses to examine evidence of potential bias
- Compared those eligible for, and those participating in, extension study within each treatment group
  - Demographic and baseline characteristics
  - Results on primary endpoint of original study
- Found no evidence of systematic differences

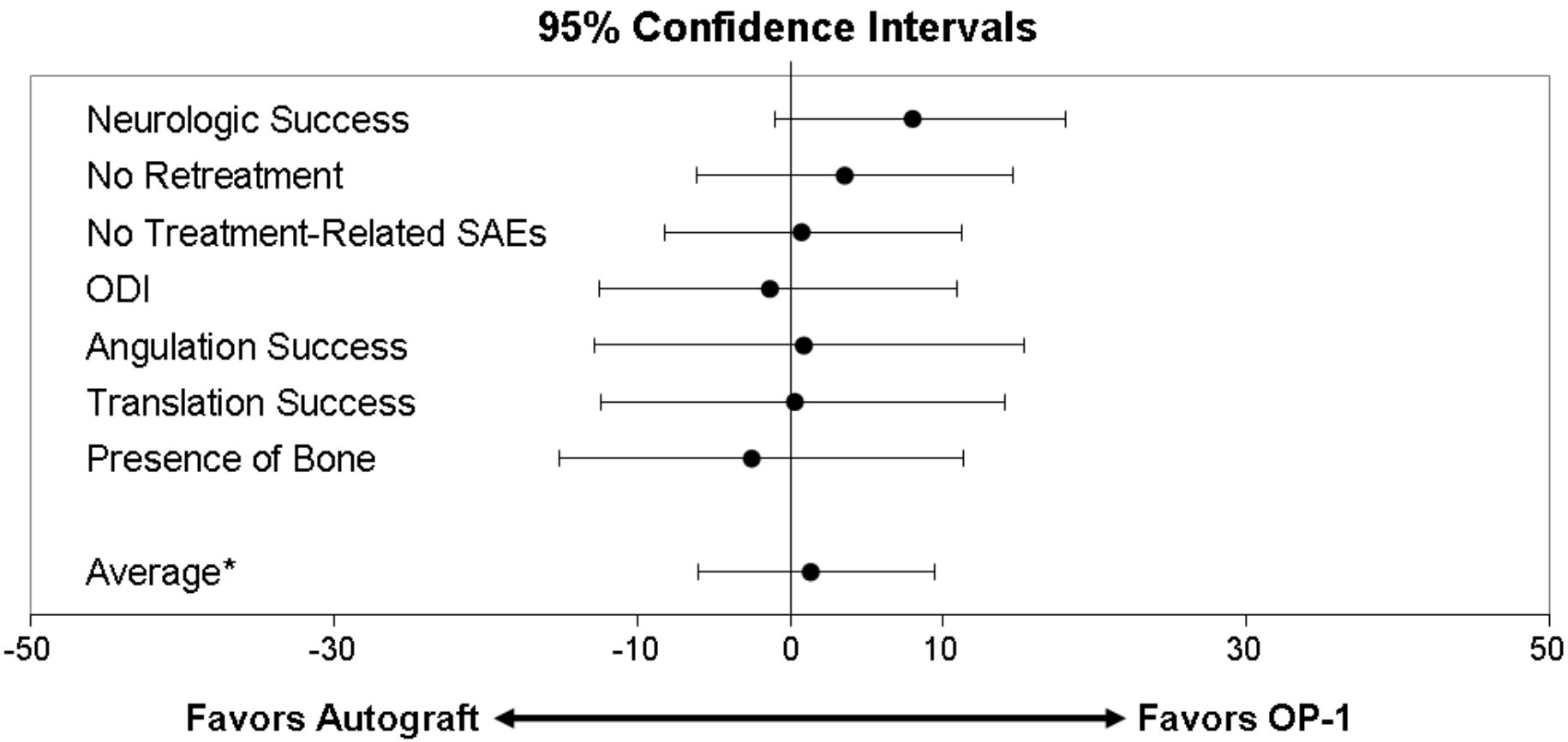
Extension Study

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

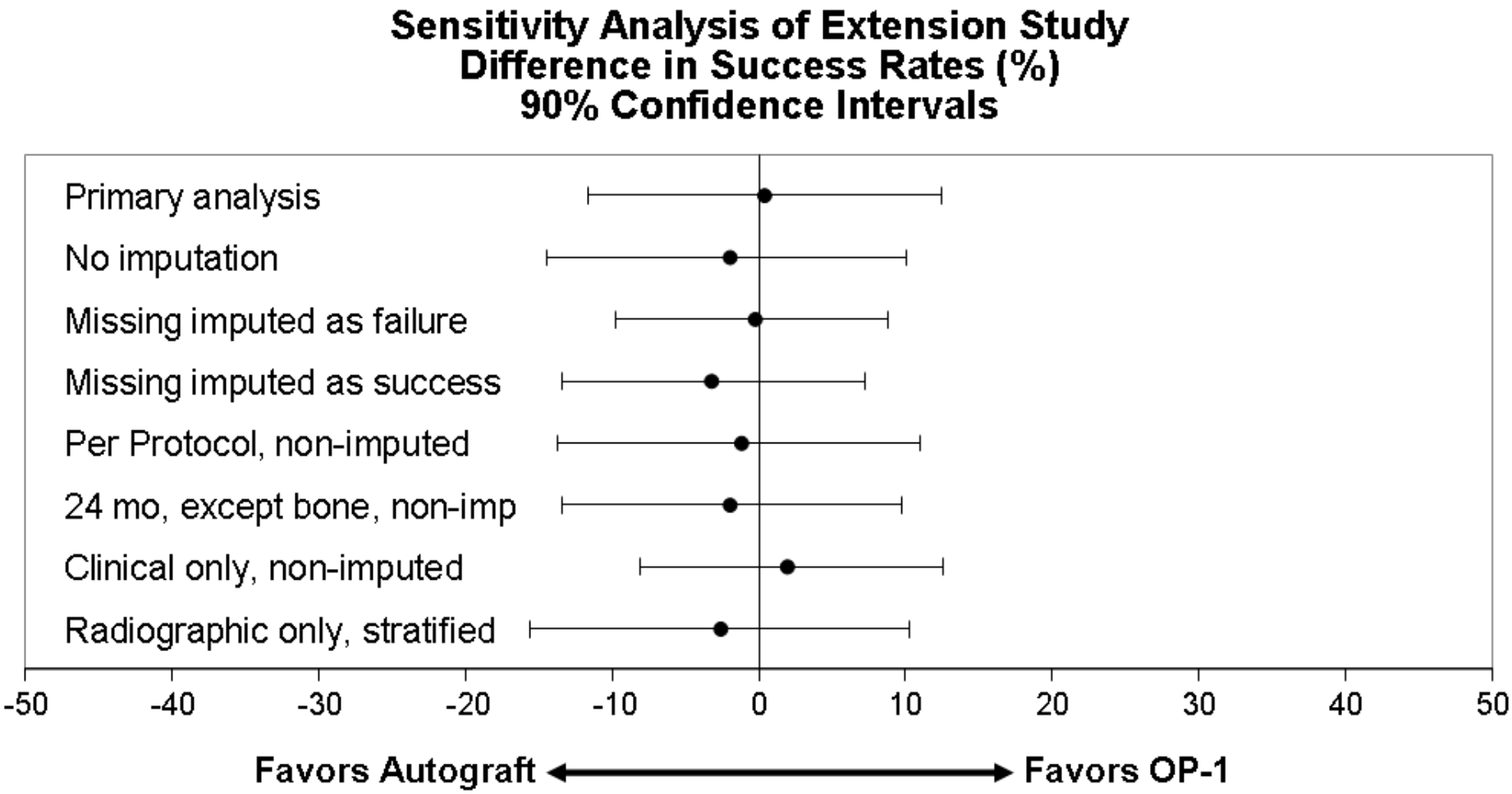
Differences in Component Success Rates



Lower confidence bound of average is -6.1%

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

Sensitivity Analyses



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

Summary (2)

- 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

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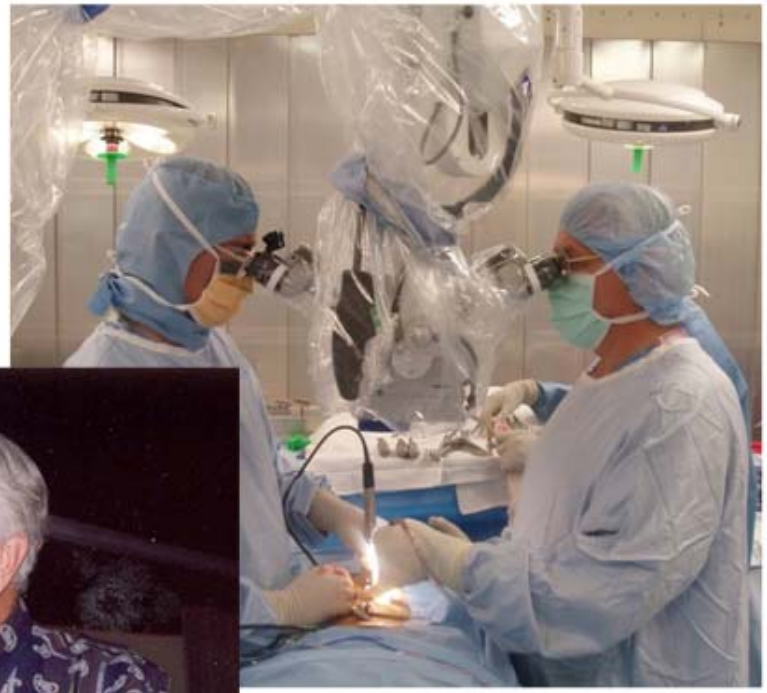
Key Points – Clinical Impact of OP-1 for Posterolateral Lumbar Fusion

What are important outcomes for clinicians and patients?

- Does it work?
- Does it improve quality of life?
- Is it safe?



Peer Reviewed

Publication

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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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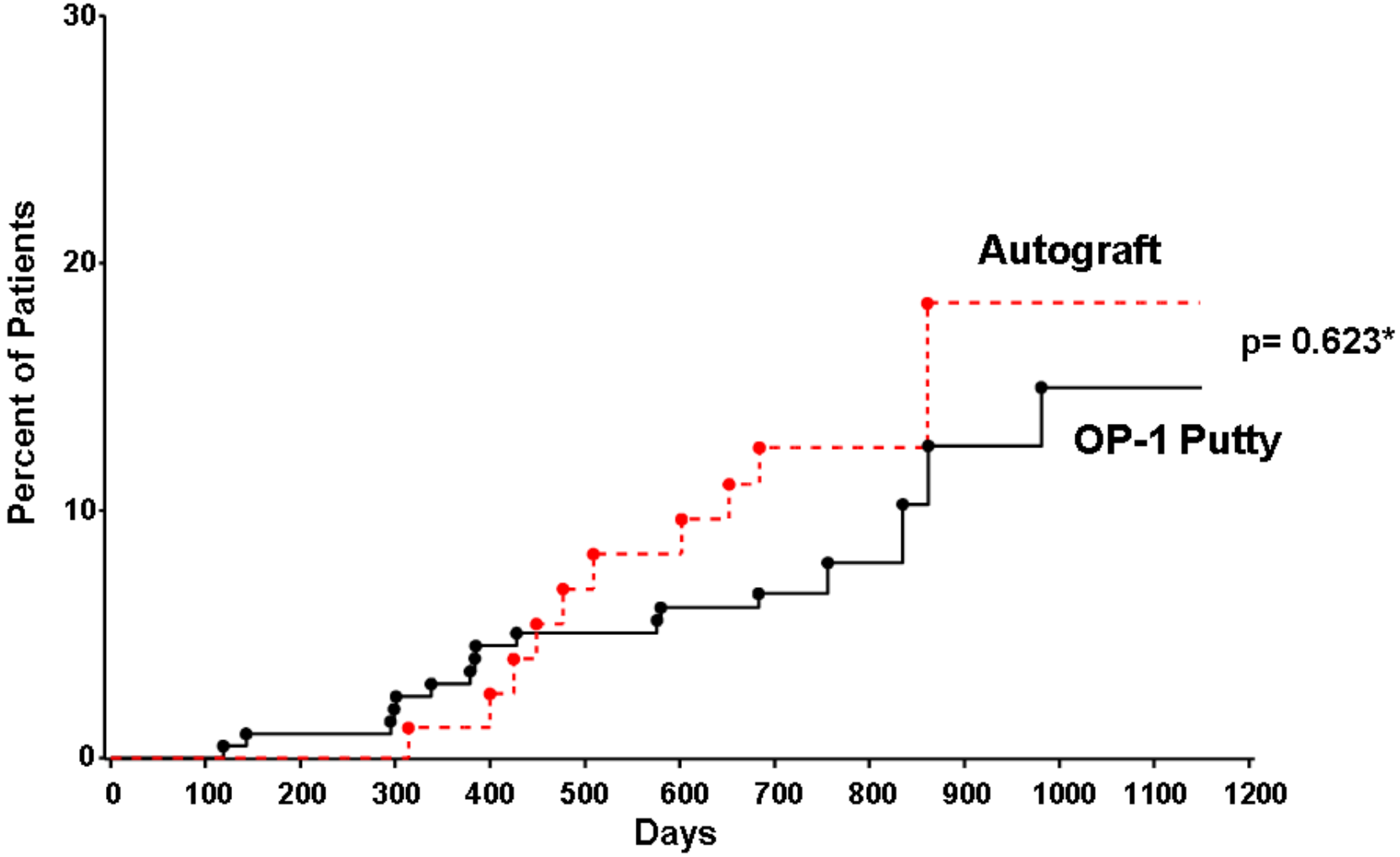
Retreatment Failure Over Time



* Includes patients not shown whose retreatment occurred after 1200 days (4 OP-1; 1 autograft)

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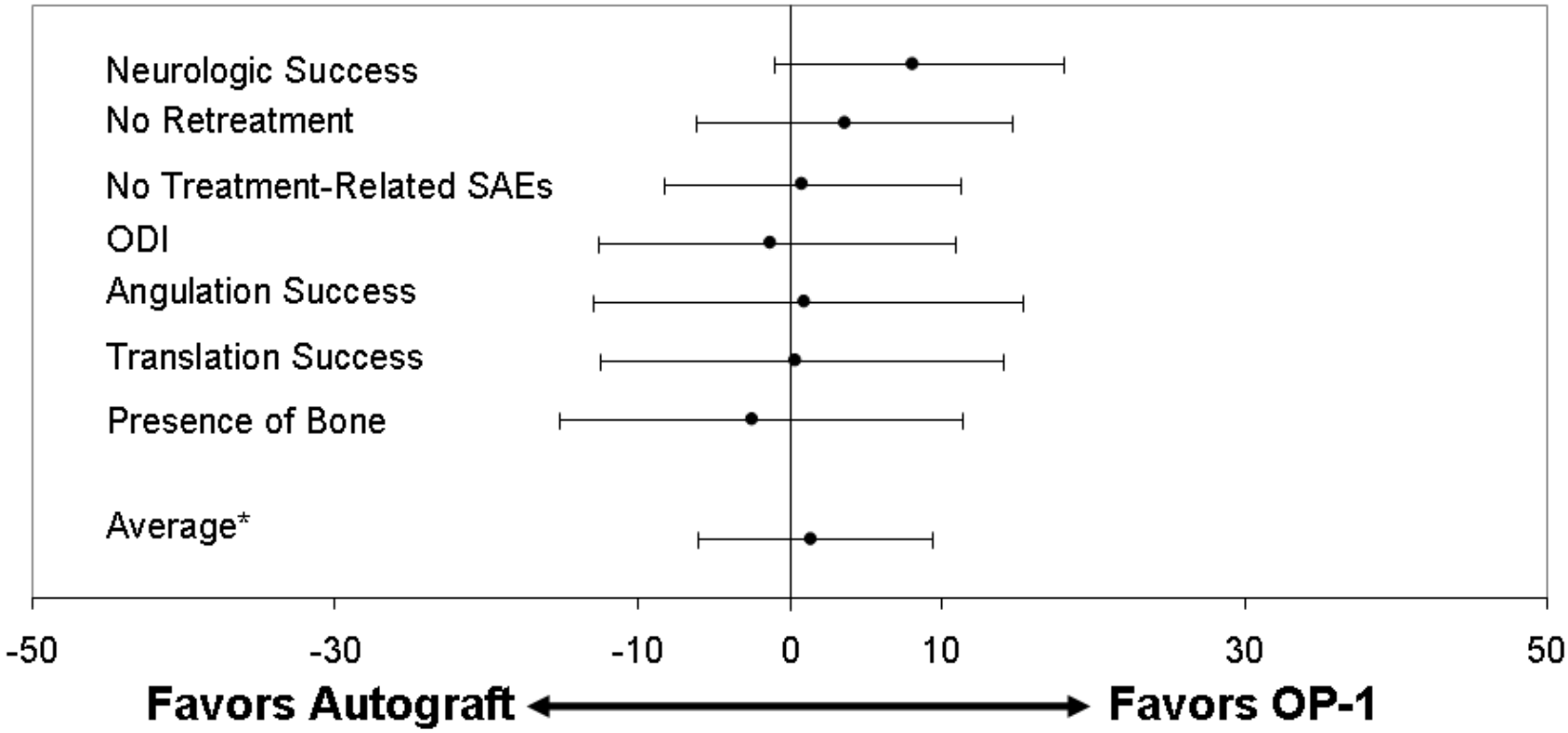
Components of Overall Success
36+ Month Follow-Up with CT Scans

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

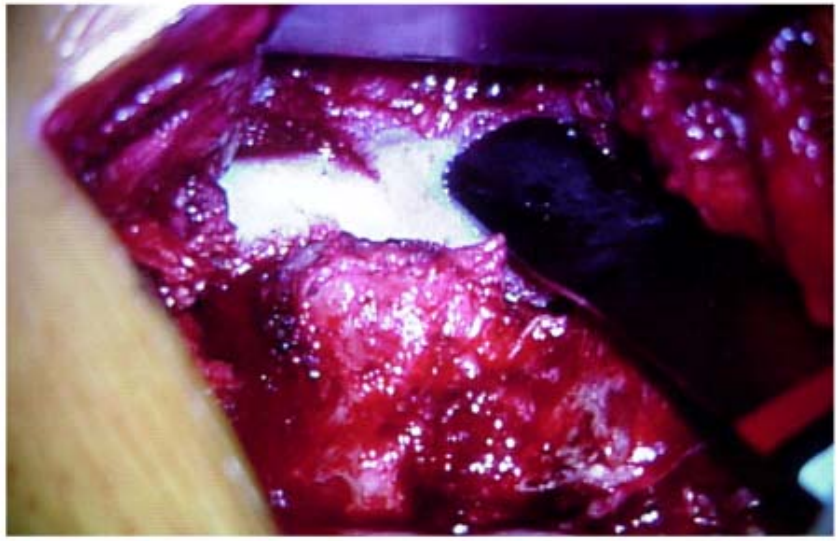


* 90% confidence interval
Missing or non-evaluable data are excluded

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

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- 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

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