

1. TITLE PAGE

Title:	A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 [®] Putty in Uninstrumented Posterolateral Fusions
Investigational Device:	OP-1 Putty
Indication:	To be used as a replacement for autograft for an uninstrumented posterolateral fusion of the lumbar spine for patients with degenerative spondylolisthesis (Grade 1 or 2) with spinal stenosis.
Methods:	Controlled, prospective, randomized, multicenter, pivotal clinical trial
Sponsor Name and Address:	Stryker Biotech 35 South Street Hopkinton, MA 01748
Protocol Identification:	S01-01US
Development Phase:	Pivotal Study
Study Initiation Date:	(first patient treated) 4 December 2001
Study Completion Date:	(last patient examination) 14 November 2005
Principal Investigators:	Jeffrey Fischgrund MD William Beaumont Hospital, Royal Oak, MI Tushar Ch. Patel MD Commonwealth Orthopaedics and Rehabilitation, P.C., Fairfax, VA
Compliance Statement:	This study was conducted in accordance with standards of Good Clinical Practice, as defined by the International Conference on Harmonization, the Food and Drug Administration, and all applicable federal and local regulations.
Company Sponsor/Representative	Julie Krop, MD Vice President Clinical Development and Medical Affairs
Date of Report:	7 June 2006
Confidential Information:	The information contained within this report is confidential and may not be used, divulged, published, or otherwise disclosed without the prior written consent of Stryker Biotech.

SIGNATURE PAGE

STUDY TITLE: A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

STUDY NUMBER: S01-01US

I have read this report and confirm that to the best of my knowledge it accurately describes the results of the study.

Approved by:

Julie Krop, MD
Vice President Clinical Development and Medical Affairs
Stryker Biotech, LLC

Date

Katherine B. Giovino
Director, Clinical Operations
Stryker Biotech, LLC

Date

Eugene C. Poggio PhD
President/Chief Operating Officer and Chief Biostatistician
ClinQuest, Inc.

Date

Bonnie S. Bielefeld MS
Director and Principal Biostatistician
Biostatistics and Epidemiology
Abt Associates Clinical Trials

Date

Rong Lin MD, MPH
Biostatistics and Epidemiology
Abt Associates Clinical Trials

Date

2. SYNOPSIS

Name of Sponsor/Company: Stryker Biotech	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: OP-1® Putty		
Name of Active Ingredient: Human recombinant Osteogenic Protein-1 (OP-1)		
Title of Study: A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions		
Investigator: See complete investigator list in Section 16.1.4.		
Study Centers: Patients were enrolled from 25 institutions in the United States and Canada. See complete list of study centers in Section 16.1.4.		
Publication (reference): Not applicable		
Study Period: Duration of this study was 4 years. First patient treated: 4 December 2001 Last patient examination: 14 November 2005		
Phase of Development : Pivotal Study		
Objectives: The objectives of this pivotal study as stated in the protocol were to demonstrate the safety and efficacy of OP-1 Putty as a replacement for autograft as measured by: <ul style="list-style-type: none"> • Safety: By comparison of the complications^a and neurological status between the OP-1 Putty group and the control autograft group. • Efficacy: By comparison of overall fusion success considering radiographic evidence along with pain/function outcomes between the OP-1 Putty group and the control autograft group. 		

^a Complications were defined as any AE.

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<p>The objectives as restated and clarified in the SAP were the following:</p> <p>The objectives of this pivotal study were to demonstrate the safety and efficacy of OP-1 Putty as a replacement for autograft in patients undergoing posterolateral spinal fusion as measured by:</p> <ul style="list-style-type: none"> • Safety: By comparison of the complications (adverse events) and neurological status between the OP-1 Putty group and the control autograft group. • Efficacy: By comparison of overall patient success considering radiographic evidence along with pain/function outcomes, absence of retreatment, absence of serious treatment-related AEs, and neurological outcomes between the OP-1 Putty group and the control autograft group. 		
<p>Methodology: This was a controlled, open-label, blinded radiographic assessment, randomized, prospective, multicenter, multinational pivotal study in which patients with single level (L3-S1) degenerative lumbar spondylolisthesis (Grade 1 or 2) with spinal stenosis underwent decompression and spinal fusion. After signing the informed consent form, and prior to the surgical procedure, patients were randomized to treatment in a 2:1 ratio to either OP-1 Putty or a control arm, in which autogenous bone graft from the iliac crest (autograft) was used.</p> <p>The duration of the study was to be approximately 3 years from the commencement of patient enrollment. Patient enrollment was expected to take 1 year. All patients were to be followed for at least 2 years after surgery, and annually thereafter, until the last patient achieved 2 years of follow-up.</p>		
<p>Number of Patients (planned and analyzed): A total of 312 patients was planned. A total of 336 patients was actually enrolled and randomized, and 295 were treated: 208 received OP-1 Putty and 87 received autograft. The remaining 41 patients withdrew prior to study treatment.</p>		
<p>Diagnosis and Main Criteria for Inclusion: Patients diagnosed with degenerative lumbar spondylolisthesis (Grade 1 or 2) with spinal stenosis and requiring decompression and spinal fusion treatment.</p>		

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<p>Name of Active Ingredient: Human recombinant Osteogenic Protein-1 (OP-1)</p>		
<p>Test Product: OP-1 Putty.</p> <p>OP-1 Putty is composed of recombinant human osteogenic protein (rhOP-1), Type I bovine bone collagen matrix, and a putty additive of carboxymethylcellulose (CMC) sodium, an anionic cellulose derivative, which yields a product with putty-like consistency. Two product units of OP-1 Putty were provided, each consisting of 2 components:</p> <ul style="list-style-type: none"> • A large vial containing a sterile dry powder consisting of 3.5 mg of human recombinant osteogenic protein-1 (OP-1) in 1 gm of collagen matrix • A small vial containing the putty additive consisting of a sterile dry powder composed of 230 mg CMC <p>Dose and Mode of Administration</p> <p>For the OP-1 Putty arm, 1 product unit was used on each side of the spine at the level of fusion, i.e., 2 product units per patient.</p>		

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Duration of Treatment: The treatment took place only once, at the time of surgery.																																																																	
Reference Therapy, Dose and Mode of Administration: Lumbar spinal fusion with the use of autogenous bone graft from the iliac crest (autograft).																																																																	

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Name of Active Ingredient: Human recombinant Osteogenic Protein-1 (OP-1)		
<p>Criteria for Evaluation:</p> <p><u>Efficacy:</u></p> <p><i>Primary Efficacy Endpoint:</i> overall success rate at 24 months in the OP-1 Putty and the autograft groups using a multiple imputation technique.</p> <p>Overall success was a composite measure with the following components:</p> <ul style="list-style-type: none"> • Improvement of at least 20% in the ODI from baseline • Absence of retreatment • Absence of treatment-emergent serious adverse events (SAEs) • Absence of a decrease in neurological status (assessing muscle strength, reflexes, sensory and straight leg raise), unless attributable to a concurrent medical condition or to the surgical procedure by a blinded Independent Neurological Reviewer. • Radiographic demonstration of spinal fusion, which was also a composite measure comprising all of the following: <ul style="list-style-type: none"> ○ Presence of bone formation ○ Angulation of $\leq 5^\circ$ on flexion/extension radiographs of the affected level ○ Translational movement of ≤ 3 mm on flexion/extension radiographs of the affected level <p><i>Secondary Efficacy Endpoints:</i></p> <ul style="list-style-type: none"> • Overall success at 12, 24, and 36 months without imputation of missing data • Components of overall success: success based on Oswestry Disability Index, absence of serious treatment related adverse events, absence of retreatment to promote fusion, neurologic success, and overall radiographic success at 12, 24, and 36 months without imputation of missing data • Overall radiographic success at 24 months with missing data imputed <p><u>Safety:</u> Adverse events, clinical laboratory evaluations, and neurological status</p>		

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Statistical Methods: Continuous variables were summarized using descriptive statistics (mean, median, standard deviation, minimum, maximum). Categorical variables were summarized using frequencies and percentages. Inferential tests were performed at the 5% level of significance.

The primary efficacy endpoint was the 24-month overall success rate for the (modified) intent-to-treat population with missing data imputed using a multiple imputation technique. The percentage of successes (and standard error) was based on estimates of the treatment effect adjusted for covariates in logistic regression and on variance estimates obtained from multiple imputations. Secondary efficacy endpoints included overall success at 12, 24, and 36 months without imputation of missing data; the components of overall success (success based upon Oswestry Disability Index, success based upon absence of serious treatment related adverse events, success based upon absence of retreatment to promote fusion, neurologic success, and overall radiographic success) at 12, 24, and 36 months without imputation of missing data; and overall radiographic success at 24 months with missing data imputed. Success rates were also tabulated for the per protocol population to aid in interpretation of the primary efficacy analysis.

The null hypothesis was that the difference in success rates between the autograft treatment group and the OP-1 Putty treatment group were comparable. For both imputed overall success and imputed overall radiographic success at 24 months, a one-sided two-sample asymptotic test for non-inferiority was used to test for non-inferiority in the angular scale with a variable non-inferiority margin ranging up to approximately 14%. For the other secondary efficacy endpoints, the equivalence limit for the test of non-inferiority was 0.10, and was not based upon an angular transformation. If non-inferiority was demonstrated, Fisher's exact test would be used to test superiority.

For both the primary and secondary efficacy analyses, the 95% upper confidence bound was generated corresponding to the difference in success rates (autograft minus OP-1 Putty) in the two treatment groups.

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For adverse events, each SOC and each preferred term reported by \geq of 5% of patients in either treatment arm were tested for treatment differences using Fisher's exact test. For laboratory values differences over time within and between treatment groups were tested using t-tests for continuous variables, and Stuart-Maxwell or McNemar's tests for shifts in status within treatment. For neurological status Chi-square or Fisher's exact test was used to test the difference between treatments groups at each visit and McNemar's test to test the shifts in status within treatment group.

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Summary – Conclusions:

Efficacy:

This study demonstrated the following results at 24 months:

- Overall Success: OP-1 Putty treatment was not demonstrated to be non-inferior to autograft ($P=0.331$). The estimated success rates were 38.7% for OP-1 Putty and 49.4% for autograft.
- Oswestry Disability Index (ODI) success: the treatment groups were similar (80.4% for OP-1 Putty, and 85.5% for autograft). While statistical testing of non-inferiority did not show that OP-1 Putty was non-inferior to autograft with respect to ODI ($P=0.178$), neither did statistical testing of superiority indicate that autograft was superior to OP-1 Putty ($P=0.376$).
- Absence of retreatment: OP-1 Putty was statistically non-inferior to autograft at 24 months (92.3% for OP-1 Putty and 88.6% for autograft, $P=0.001$).
- Absence of serious treatment-related AEs: OP-1 Putty was statistically non-inferior to autograft (88.7% for OP-1 Putty and 91.4% for autograft, $P=0.038$).
- Neurological success: OP-1 Putty was statistically non-inferior to autograft (100% for OP-1 Putty, and 93.9% for autograft, $P<0.001$).
- Radiographic success: OP-1 Putty patients had a statistically significantly lower rate of overall radiographic success than autograft patients (52.4% for OP-1 Putty and 74.6% for autograft, $P=0.003$). *Post hoc* analyses revealed:
 - Presence of bone on plain film: presence of bone on plain film was statistically significantly lower in the OP-1 Putty patients compared to autograft (61.7% for OP-1 Putty and 83.1% for autograft, $P<0.001$).
 - Translational movement success: OP-1 Putty was non-inferior to autograft (93.6% for OP-1 Putty and 96.3% for autograft, $P=0.004$).
 - Angulation success: OP-1 Putty was similar to autograft (76.6% for OP-1 Putty and 79.3% for autograft). While statistical testing of non-inferiority did not show that OP-1 Putty was non-inferior to autograft with respect to angulation success ($P=0.087$), neither did statistical testing of superiority indicate that autograft was superior to OP-1 Putty ($P=0.629$).

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<p>○ Presence of bone on CT at 9 months: OP-1 Putty was clinically similar to autograft (84.9% for OP-1 Putty and 98.6% for autograft). Statistical testing of non-inferiority did not show that OP-1 Putty was non-inferior to autograft with respect to presence of bone by CT ($P=0.929$).</p> <ul style="list-style-type: none"> ● Additional patient outcome measures of SF-36 and VAS pain scales suggest early and durable improvements for patients in both groups. In addition, the avoidance of a second surgical procedure resulted in decreased operative time, decreased blood loss, and absence of donor site pain, all of which are clinical benefits of OP-1 Putty versus autograft. ● In a <i>post hoc</i> analysis, OP-1 Putty was statistically non-inferior to autograft with regard to overall clinical success, a composite parameter consisting of ODI success, absence of retreatment, absence of serious treatment-related AEs, and neurological success (71.2% in the OP-1 Putty group, and 69.0% in the autograft group, $P=0.029$). <p>Efficacy of OP-1 Putty is further demonstrated by consistency of success rates, and similarity between groups, in all clinically-relevant outcomes.</p>		
<p><u>Safety:</u></p> <p>The safety of OP-1 Putty treatment in posterolateral fusion (PLF) is similar to that of autograft treatment with respect to the proportion of patients experiencing:</p> <ul style="list-style-type: none"> ● Treatment-emergent AEs ● Severe AEs ● Treatment-related AEs ● Unanticipated AEs ● SAEs ● Serious and unanticipated AEs ● Treatment-related SAEs ● Neoplasm ● Death 		

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Table 1: Treatment-Emergent Adverse Events (Safety Population)

Parameter	OP-1 Putty (N=208)		Autograft (N=87)	
	Number (%) of Patients with Events	95% CI	Number (%) of Patients with Events	95% CI
Any Adverse Event	201 (96.6)	(93.2, 98.6)	82 (94.3)	(87.1, 98.1)
Severe Adverse Event	43 (20.7)	(15.4, 26.8)	17 (19.5)	(11.8, 29.4)
Treatment-related Adverse Event	54 (26.0)	(20.1, 32.5)	23 (26.4)	(17.6, 37.0)
Unanticipated Adverse Event	6 (2.9)	(1.1, 6.2)	0 (0.0)	(0.0, 4.2)
Serious Adverse Event	104 (50.0)	(43.0, 57.0)	43 (49.4)	(38.5, 60.4)
Serious and Unanticipated Adverse Event	5 (2.4)	(0.8, 5.5)	0 (0.0)	(0.0, 4.2)
Treatment-related Serious Adverse Event	25 (12.0)	(7.9, 17.2)	6 (6.9)	(2.6, 14.4)
Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps)	12 (5.8)	(3.0, 9.9)	8 (9.2)	(4.1, 17.3)
Death	7 (3.4)	(1.4, 6.8)	4 (4.6)	(1.3, 11.4)

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<ul style="list-style-type: none"> • No clinically significant changes in clinical laboratory parameters have been associated with OP-1 Putty treatment. • There does not appear to be any association of antibody status and the development of potentially immunologically-related AEs or SAEs of any kind. • The presence of neutralizing antibodies is not statistically correlated with clinical success outcomes. • The risk of post-operative AEs related to the lumbar spine is clinically equivalent for OP-1 Putty and autograft treatments. • There was a higher reported rate of AEs in the cardiac and infections and infestations SOCs in the OP-1 Putty treated groups, and in the autograft group higher reported rate of AEs in blood and lymphatic system disorders and injury, poisoning and procedural complications SOCs. • Future clinical use of OP-1 Putty should carefully assess patients for infection risks pre-operatively and for cardiac and infectious events post-operatively. • Although respiratory and gastrointestinal SOC categories were identified (statistical significance at $P=0.2$) as having a higher rate of AEs in the OP-1 Putty group compared to autograft, there were no clinically relevant patterns of AEs that emerged in these areas. • OP-1 Putty treatment is generally safe and well-tolerated in the PLF population. 		

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<p>Conclusion:</p> <p>OP-1 Putty treatment was highly effective, showing:</p> <ul style="list-style-type: none"> • Pharmacologic success as judged by osteoinduction; • Clinical success as shown by improvements in ODI and success in other clinical outcome measures; • Radiographic success, as shown by success on both dynamic and static outcomes; and • Durability of success, demonstrated through follow-up periods as long as 3 years. <p>Additionally, OP-1 Putty is generally comparable to autograft treatment with respect to all of the following parameters:</p> <ul style="list-style-type: none"> • The proportion of patients experiencing treatment-emergent AEs, severe AEs, treatment-related AEs, SAEs, treatment-related SAEs, neoplasms, or death; • The occurrence of clinically important laboratory abnormalities; • The occurrence of local adverse events involving the lumbar spine; • The occurrence of immunologically-related adverse events or clinical outcomes, despite the occurrence of neutralizing anti-OP-1 antibodies in 25.6% of treated patients. <p>Given its favorable profile with respect to clinically relevant efficacy and safety outcomes, OP-1 Putty offers an attractive alternative to the use of autograft in patients undergoing lumbar posterolateral spinal fusion.</p>		
<p>Date of the Report: 7 June 2006</p>		

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4. ABBREVIATIONS AND DEFINITIONS OF TERMS

AACT	Abt Associates Clinical Trials
ALT	Alanine Aminotransferase
AP	Anteroposterior
AST	Aspartate Aminotransferase
BMP	Bone Morphogenetic Proteins
BUN	Blood urea nitrogen
CMC	Carboxymethylcellulose
CO ₂	Carbon Dioxide
CRA	Clinical Research Associate
CRF	Case Report Form
CT	Computerized Tomography
ELISA	Enzyme-Linked Immunosorbent Assay
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IDE	Investigational Device Exemption
IRB	Institutional Review Board
ITT	Intent-to-Treat
MCHC	Mean Corpuscular Hemoglobin Concentration
MCS	Mental Component Score
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
mITT	Modified Intent-to-treat
MRI	Magnetic Resonance Imaging.
Nab	Neutralizing antibody
ODI	Oswestry Disability Index
OP-1	Osteogenic Protein-1
PCS	Physical Component Score
PI	Principal Investigator
PLF	Posterolateral fusion
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software (SAS Institute Inc., Cary, NC)
SD	Standard Deviation
SGPT	Serum Glutamic Pyruvic Transaminase
SGOT	Serum Glutamic Oxalacetic Transaminase
SLR	Straight Leg Raises
SOC	System Organ Class

5. ETHICS

5.1 INSTITUTIONAL REVIEW BOARD (IRB)

The protocol and informed consent documents were approved by the sites' IRBs.

The protocol is provided in Appendix 16.1.1. Information on the IRBs, with the names of the committee chairs, is provided in Appendix 16.1.3.

5.2 ETHICAL CONDUCT OF THE STUDY

This study was conducted with adherence to the principles of Good Clinical Practice (GCP), as required by the US Code of Federal Regulations (21 CFR parts 50, 54, 56, and 812); the International Conference on Harmonization Guidelines, effective 17 January 1997; and in accordance with the ethical principles contained in the Declaration of Helsinki.

5.3 PATIENT INFORMATION AND CONSENT

All patients in this study were informed in accordance with GCP and local regulatory authority requirements concerning the pertinent details and purpose of the study, potential risks, and treatment options. A signed Patient Informed Consent was to be obtained by the Investigator, or designee, prior to study participation.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

6.1 INVESTIGATORS

This study was sponsored by Stryker Biotech and was conducted at 25 centers. The Principal Investigator at each center assumed ultimate responsibility for the conduct of the trial at that center. The institutional affiliations and qualifications of the study investigators are provided in Section 16.1.4.

6.2 STUDY CONDUCT

Stryker Biotech was responsible for the overall conduct of this study. The signature of the Sponsor's medical monitor is provided in Section 16.1.5.

Study monitors employed by Caravaty & Kramer, Inc. (805 La Mesa Dr., Portola Valley CA 94028-7420) were assigned to monitor the progress of the study, assure site compliance with GCP and appropriate federal regulations, and ensure that accurate data were collected.

Clinical laboratory evaluations were performed by Quest Diagnostics Clinical Trials Lab (Van Nuys CA). Serum samples for immunological testing were stored at Quest Diagnostics and then shipped to Stryker Biotech for testing.

Patient radiographs (plain films and CT scans) were sent to Stryker Biotech and initially reviewed for quality parameters by a consultant radiologist. Upon acceptance of films based on quality parameters the films were reviewed by 2 primary musculoskeletal radiologists at Washington Hospital Center (Washington, DC). A third musculoskeletal radiologist at Henry Ford Hospital (Detroit, MI) was used to evaluate plain films as the secondary reviewer when the 2 primary reviewers were not in agreement. There was no adjudication of discrepant CT evaluations. The qualifications of the study radiologists are provided in Section 16.1.4.

Final determination of overall neurological status was performed by an orthopedic spine surgeon from the Boston Spine Group at The New England Baptist Hospital (Boston, MA), based on neurological exams performed by the Investigator. This individual was not involved in the conduct of the study. The qualifications of orthopedic spine surgeon is provided in Section 16.1.4.

Data entry, data cleaning, and statistical analyses were performed by Abt Associates Clinical Trials (AACT) (Lexington, MA).

Medical writing was performed by MedWrite, Inc., Westford, MA.

7. INTRODUCTION

This study was designed to evaluate the safety and efficacy of OP-1[®] Putty as a replacement for autograft in posterolateral fusion of the lumbar spine in patients with degenerative spondylolisthesis with spinal stenosis.

It has been estimated that up to 70% of the adult population suffers from some form of low back (lumbar sacral) pain,¹ which is usually attributed to a degenerative disease process within the vertebral spine. Spondylolisthesis, a condition characterized by the slippage of one vertebral segment on the one below in the presence of an intact neural arch,² is one of the diagnoses attributed to the degenerative disc disease process. If patient pain, neurological deficits, and instability do not respond to conservative management, decompression and lumbar spinal fusion are the most common surgical treatments of choice for degenerative spondylolisthesis.³

Spinal fusion is a surgically created bony union across the involved vertebrae.

Approximately 70,000 posterolateral lumbar spinal fusions are performed annually in the US.⁴ The use of bone graft to stimulate new bone growth is a standard surgical technique in spinal fusion, both with and without instrumentation. Bone graft stimulates new bone formation and acts as a matrix or scaffold into or over which new bone can grow.

Currently, autologous bone (autograft) is considered the most successful bone grafting material and is preferred over allograft bone.^{5,6,7,8} The most common site for harvesting autograft material is the iliac crest.⁹ However, this procedure increases operative time, blood loss, and the morbidity associated with spinal fusion.¹⁰

In recent years, there has been a focus on Bone Morphogenetic Proteins (BMPs) as bone graft material.¹¹ Osteogenetic Protein-1 (OP-1) is one such BMP. Implants containing OP-1 and collagen matrix have been shown to be osteoinductive and osteoconductive, to speed the rate of bone healing^{12,13,14,15,16} and to improve the performance of autograft in animals. Implants containing OP-1 and collagen matrix have also been shown to promote stable spinal fusions significantly faster than autograft.^{17,18} Safety and efficacy of other BMPs in spinal applications have also been reported in animal models.^{10,19,20,21,22}

It was postulated that the use of OP-1 Putty would prove beneficial in the treatment of patients requiring decompression and lumbar spinal fusion while also eliminating the pain and morbidity associated with harvesting autograft bone from the iliac crest. For the purposes of this study, the disease process was restricted to Grade 1 and 2 degenerative spondylolisthesis with stenosis affecting one level of the lumbar spine (L3 to S1).

8. STUDY OBJECTIVES

The objectives as stated in the protocol were the following:

The objectives of this pivotal study were to demonstrate the safety and efficacy of OP-1 Putty as a replacement for autograft as measured by:

- Safety: By comparison of the complications^b and neurological status between the OP-1 Putty group and the control autograft group.
- Efficacy: By comparison of overall fusion success considering radiographic evidence along with pain/function outcomes between the OP-1 Putty group and the control autograft group.

The objectives as re-stated and clarified in the SAP were the following:

The objectives of this pivotal study were to demonstrate the safety and efficacy of OP-1 Putty as a replacement for autograft in patients undergoing posterolateral spinal fusion as measured by:

- Safety: By comparison of the complications (AEs) and neurological status between the OP-1 Putty group and the control autograft group.
- Efficacy: By comparison of overall patient success considering radiographic evidence along with pain/function outcomes, absence of retreatment, absence of serious treatment-related AEs, and neurological outcomes between the OP-1 Putty group and the control autograft group.

^b Complications were defined as any AE.

9. INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN

This was a controlled, open-label, blinded radiographic assessment, randomized, prospective, multicenter, multinational pivotal study in which patients with single level (L3-S1) degenerative lumbar spondylolisthesis (Grade 1 or 2) with spinal stenosis underwent decompression and spinal fusion. After signing the informed consent form, and prior to the surgical procedure, patients were randomized to treatment in a 2:1 ratio to either OP-1 Putty or a control arm using autogenous bone graft from the iliac crest (autograft). A total of 312 patients was planned.

This study was a one-sided, non-inferiority trial comparing the overall success between the OP-1 Putty group and the control autograft group. It was anticipated that the overall success rate in the OP-1 Putty group would be comparable to the success rate in the autograft group.

The duration of the study was to be approximately 3 years from the commencement of patient enrollment. Patient enrollment was expected to take 1 year. All patients were to be followed for at least 2 years after surgery, and annually thereafter, until the last patient achieved 2 years of follow-up.

9.2 DESCRIPTION AND DISCUSSION OF THE DESIGN AND CHOICE OF CONTROL

The objective of the study was to establish OP-1 Putty as a safe and effective alternative to autograft for uninstrumented posterolateral fusion of the lumbar spine. A product with similar effectiveness, but that avoids the pain and morbidity associated with iliac crest bone harvest, is clinically desirable. Therefore, the trial was designed to demonstrate the comparability of the overall success rate in the OP-1 Putty treatment group to the autograft treatment group.

The control group consisted of patients who received autograft. This was considered appropriate, as autograft was the current standard of care for spinal fusion.

9.3 SELECTION OF STUDY POPULATION

Patients diagnosed with degenerative lumbar spondylolisthesis with spinal stenosis qualifying for decompression and fusion of one spinal level (L3-S1) with the use of autograft were recruited through the medical institutions of participating investigators. All patients had undergone non-operative treatment for at least 6 months prior to study enrollment.

9.3.1 Inclusion Criteria

Patients were included in the study only if they met all of the following criteria:

1. The patient or legal guardian was willing and able to understand, sign and date the study specific Patient Informed Consent, which was approved by the Institutional Review Board.
2. The patient was a skeletally mature male or female less than 85 years of age.
3. The patient had a diagnosis of degenerative lumbar spondylolisthesis of Grade 1 or 2 with spinal stenosis demonstrated by medical history, physical examination, and radiographic imaging. Radiographic diagnosis was performed showing a cross sectional image using a CT scan or MRI demonstrating an intact pars interarticularis with evidence of central or lateral recess stenosis accompanied by an anterolisthesis on upright lateral radiographs. The patient had leg and/or back pain and the manifestation of one or more of the following phenomena:
 - radiculopathy
 - sensory deficit
 - motor weakness
 - reflex changes
 - disc herniation
 - neurogenic claudication
 - instability (defined as > 0% and < 50% translation of the vertebrae and/or > 10 degrees and < 20 degrees angular motion) measured on flexion/extension radiographs
 - osteophyte formation or hypertrophy of the facet joint
4. The patient was a candidate for decompression and spinal fusion with the use of autograft from the iliac crest.
5. The patient required one level lumbar fusion (L-3 to S-1).
6. The patient agreed to participate in post-operative clinical and radiographic evaluations and required rehabilitation regimen.
7. The patient had no history of previous fusion attempt(s) to the affected spinal level.
8. The patient was non-responsive to at least 6 months of non-operative treatment prior to study enrollment.
9. The patient had a preoperative Oswestry Disability Index (ODI) of 30-100.

9.3.2 Exclusion Criteria

Patients were excluded from the study if they met any of the following reasons:

1. The patient had non-degenerative spondylolisthesis of any grade at the affected level.
2. The patient had degenerative spondylolisthesis of Grade 3 or 4.
3. The patient had active spinal and/or systemic infection.
4. The patient had a systemic disease or condition, which affected his/her ability to participate in the study requirements or the ability to evaluate the efficacy of the investigational product (i.e., active malignancy, neuropathy).
5. The patient was a prisoner, a transient, or had been treated for alcohol and/or drug abuse in an inpatient substance abuse program within 6 months prior to proposed study enrollment.
6. The patient had participated in clinical trials evaluating investigational devices, pharmaceuticals, or biologics within 3 months of enrollment in the study.
7. The patient was a woman able to bear children, e.g., not post-menopausal, had not had a hysterectomy, etc.
8. The patient was morbidly obese (defined as weight =60% over the recommended ideal weight as described in the 1996 Metropolitan Height and Weight Tables for Men and Women).
9. The patient had a known sensitivity to any component of OP-1 Putty.
10. The patient was known to require at the time of treatment, additional surgery to the lumbar spinal region within the next 6 months.
11. The patient had spinal instability measured on flexion/extension radiographs of = 50% translation of the vertebrae or = 20 degrees of angular motion.
12. The patient used tobacco or nicotine or was prescribed steroids such as cortisone.

9.3.3 Removal of Patients from Therapy or Assessment

Patients were able to withdraw from the study at any time, if they chose to.

If an intraoperative decision was made to perform something other than what was intended for study enrollment, the patient was considered a withdrawal. If a randomized patient was withdrawn prior to treatment, the next patient was assigned the next randomly determined treatment as per the study randomization plan.

9.4 TREATMENTS

9.4.1 Treatments Administered

All patients received posterior decompression with concomitant posterolateral intertransverse process arthrodesis. Multiple-level decompression was permitted, however, only 1 level could be fused. The product under investigation or autogenous bone graft from the iliac crest was implanted using standard surgical procedures for lumbar spinal fusion. All participating investigators and co-investigators received instruction on appropriate use of the investigational product. Any question concerning the surgical aspects of use of the investigational product was answered by the Principal Investigator (PI), T. Patel, MD, Commonwealth Orthopaedics & Rehabilitation, P.C., Virginia and/or Co-PI, J. Fischgrund, MD, William Beaumont Hospital, Royal Oak, Michigan in conjunction with Stryker Biotech.

Prophylactic antibiotic treatment, pre- and post-operatively, was recommended. The following standard post-operative rehabilitation schedule was used by all investigators: Walking was encouraged on the first post-operative day, progressive walking (10-to-20 minutes twice daily) was started during the first 4 to 6 weeks postoperatively, exercises on a stationary bicycle or in water were begun at 6 to 8 weeks, and exercises for gentle flexion of the spine and strengthening of the abdominal muscles were started at 8-to-12 weeks. Exercise was monitored through physical therapy or individualized through a therapist. Use of a corset or brace for 3 months was required.

9.4.2 Identity of Investigational Product

The Investigational product evaluated in this study was OP-1 Putty. OP-1 Putty is composed of recombinant human Osteogenic Protein-1 (rhOP-1), Type I bovine bone collagen matrix and a putty additive of carboxymethylcellulose (CMC) sodium, an anionic cellulose derivative, which yields a product with putty-like consistency. Two product units of OP-1 Putty were provided, each consisting of 2 components::

- A large vial containing a sterile dry powder consisting of 3.5 mg of human recombinant Osteogenic Protein-1 (OP-1) in 1 gm of collagen matrix
- A small vial containing the putty additive consisting of a sterile dry powder composed of 230 mg CMC.

For the OP-1 Putty arm, 1 product unit was used on each side of the spine at the level of fusion, i.e., 2 product units per patient.

9.4.3 Method of Assigning Treatment

This was a controlled, randomized, prospective, multicenter, multinational pivotal study. All patients enrolled in this study received surgical procedures for the purpose of decompression and spinal fusion utilizing either OP-1 Putty (treatment group) or autograft (control group). Assignment of treatment was randomized. Randomization occurred after signing of the informed consent form and prior to the surgical procedure.

The randomization scheme was produced in SAS using the PLAN procedure and was stratified by investigational site. The randomization scheme was maintained at Stryker Biotech. The Investigator or designee contacted Stryker Biotech by phone to receive the randomization assignment. Patients were notified prior to surgery of the treatment group to which they had been randomized. There were patients who withdrew consent for study participation after learning of their randomized treatment. The randomization scheme was at the ratio of 2:1 (OP-1 Putty : autograft). The study was to be terminated upon treatment of 208 OP-1 Putty patients or a maximum of 312 patients total. The randomization schema is presented in Section 16.1.6.

9.4.4 Selection of Doses in the Study

Nonclinical studies have been conducted to determine the optimal ratio of the osteoinductive and osteoconductive components of OP-1 Putty for human use. The dose was determined from a series of OP-1 dose-ranging studies in rabbits, dogs, and primates. These investigations used critical-sized, long-bone defects of a sufficient size such that healing would not occur without bone or a synthetic osteoinductive implant.

Bone healing in species such as dogs and primates is believed to approximate healing observed in humans. Dogs and humans show distinct similarities in bone structure, and in appositional bone formation rates (ABFR, 1.0 - 1.5 µg/day in humans and 1.5 - 2.0 µg/day in dogs). However, the capacity of a mammalian species for bone repair and regeneration varies inversely with its position on the phylogenetic tree. For this reason studies were also conducted in a non-human primate.

Figure 1 presents data from a non-human primate study, in which the association between radiographic grade and escalating doses of OP-1 Implant was assessed.²³ Based on this study, a dose of 3.5 mg OP-1/gram collagen was chosen because it is on the plateau of the dose curve. Similar data were obtained with the dog model.

The contribution of the collagen component in bone formation was determined using a rat subcutaneous bone formation assay. Implants were made with a constant amount of OP-1 and increasing amounts of collagen. Twelve days following implantation, bone formation was determined by implant weight and confirmed by calcium content and histological evaluation.

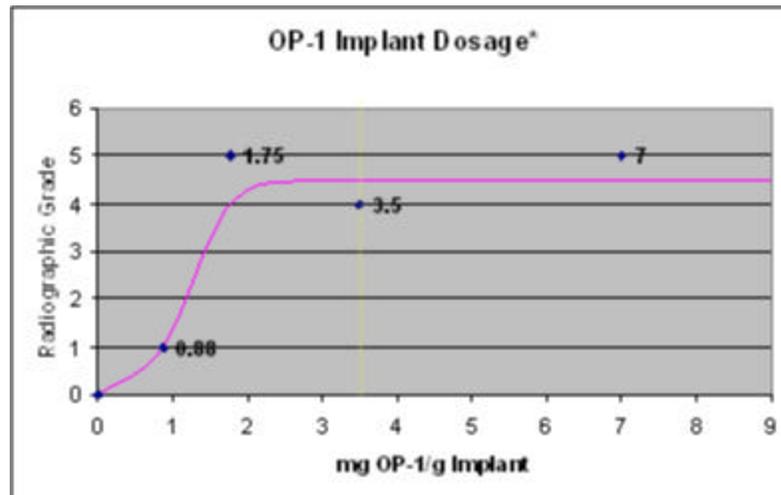


Figure 1. OP-1 Dose Curve in Primates

9.4.5 Timing of Treatment for Each Patient

OP-1 Putty or autograft was implanted at the time of the surgical procedure.

9.4.6 Blinding

The control treatment involved harvesting autograft material from the iliac crest; therefore, the treating physicians and patients were not blinded to the treatment assignment. To minimize bias, the radiographic outcomes were evaluated by reviewers who were blinded to the treatment.

9.4.7 Prior and Concurrent Therapy

All patients underwent non-operative treatment for at least 6 months prior to study enrollment. Current medication use was recorded preoperatively and at the 6-week and 3, 6, 9, 12, 24, and 36 month follow-up visits.

9.4.8 Treatment Compliance

Patients received treatment for decompression and lumbar spinal fusion under the care of the study investigator, in an in-patient hospital setting, according to the randomization scheme.

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 Efficacy and Safety Measurements Assessed and Study Schedule

Efficacy was measured by calculating the 12-, 24-, and 36-month overall success rates in the OP-1 Putty and the autograft groups. The following assessments were used for the patient success criteria:

- Radiographic demonstration of spinal fusion: Presence of bridging (on AP or lateral radiographs) between transverse processes of 2 vertebral bodies, and angulation of $\leq 5^\circ$ * and translational movement of ≤ 2 mm* demonstrated on flexion/extension radiographs of the affected level.^{20,21}
- ODI improvement of at least 20% from the pre-treatment visit.
- No revisions, removals or supplemental fixations. All reoperations that were intended to promote fusion at the treated level were considered failures. Reoperations that were not intended to promote fusion, such as drain removal were not considered failures. Revision, removals, supplemental fixations and reoperations were defined (definitions based on the Guidance Document for Preparation of IDEs for Spinal Systems, January 13, 2000) as follows:
 - A revision was a procedure that adjusted or in any way modified or removes *part* of the original implant configuration, with or without replacement of a component. A revision may also have included adjusting the position of the original configuration.
 - A removal was a procedure where *all* of the original system configuration was removed with or without replacement.
 - A reoperation was any surgical procedure at the involved level(s) that did not remove, modify or add any components to the system.
 - A supplemental fixation was a procedure in which additional instrumentation not under study in the protocol was implanted (e.g., supplemental placement of a rod/screw system or a plate/screw system).
- Any patient who experienced a revision, removal, supplemental fixation, or reoperation intended to promote fusion at the treated level was to be considered a failure, regardless of the timing of the procedure.
- Absence of a serious device-related adverse event during the course of the study.

* Rounded to the nearest integer.

- No unresolved neurological deficits at the final examination that were not present prior to study treatment, unless the deficit was due to a concurrent medical condition. Unresolved neurological deficits due to a concurrent medical condition were not to be considered failures.
- No decreases in neurological status at the final examination from the preoperative evaluation, unless the decrease was due to a concurrent medical condition. Decreases in neurological status due to a concurrent medical condition were not to be considered failures.

Failure to achieve each of the above constitutes an individual patient failure.

Safety was assessed principally by AEs, clinical laboratory evaluations (including immunologic evaluations), and neurological status. The terms “complication” (used in the protocol) and “concurrent medical event” (used in the CRFs) were herein considered synonymous with the term “adverse event.”

The following additional information was also collected for each patient:

- Visual Analog Scale Results for Pain Assessment
- Donor Site Pain (autograft patients only)
- Medication Use
- Hospitalization Data
- General Health Survey (SF-36)

Patients had the following scheduled visits: preoperative, hospitalization (surgical procedure), postoperative (within 72 hours of operative), 6 weeks (± 14 days), 3 months (± 14 days), 6 months (± 30 days), 9 months (± 30 days), 1 year (± 60 days), 2 years (± 60 days), and annually thereafter until the last patient achieved the 2-year follow-up (± 60 days).

Efficacy and safety assessments are shown in Table 2.

Table 2: Schedule of Assessments

Study Evaluations	Pre-operative	Operative ¹	6 Weeks	3 Months	6 Months	9 Months	12 Months	24 Months	Annual ⁴
Inclusion/Exclusion Criteria	X								
Informed Consent	X								
Randomization	X								
Demographics and Baseline Characteristics	X								
Medical History	X								
ODI	X		X	X	X	X	X	X	X
Visual Analog Scale	X		X	X	X	X	X	X	X
SF-36 Health Survey	X		X	X	X	X	X	X	X
Physical Exam	X		X	X	X	X	X	X	X
Laboratory Evaluation ²	X	X	X	X	X		X	X	
Radiographic Evaluation	X		X	X	X		X	X	X
Surgical Intervention		X							
CT Evaluation						X			
Disposition								X	
Current Medication	X		X	X	X	X	X	X	X
Concurrent Medical Events ³		X	X	X	X	X	X	X	X

¹ Operative includes hospitalization (surgical procedure) and within 72 hours of postoperative.

² Immunological, hematology and biochemistry; no immunological assessment beyond the 24 months.

³ Concurrent Medical Events were assessed at each post-treatment visit.

⁴ Annual examinations represent those collected at 36 months.

9.5.2 Appropriateness of Measurements

The assessments performed were appropriate toward meeting the study objectives, and were consistent with the recommendations in the Guidance Document for Preparation of IDEs for Spinal Systems (Jan 2000).

9.5.3 Primary Efficacy Variable

The primary efficacy variable was the overall success rate at 24 months in the OP-1 Putty and the autograft groups.

9.6 DATA QUALITY ASSURANCE

Stryker Biotech, as the Sponsor, was responsible for the conduct of this study.

9.6.1 Site Training

Prior to the initiation of the study, a representative of the sponsor conducted an orientation in order to train the Investigator and/or the Investigator's designee in the protocol as well as appropriate use and completion of all patient Case Report Forms (CRFs) utilized in the study. All communications with the site, concerning this training, were documented by the sponsor or delegate and maintained as part of the sponsor's study files.

9.6.2 Data Monitoring

All submitted CRFs were reviewed by trained, experienced clinical monitors for completeness, accuracy, and any evidence of unforeseen patient risk. Any issue concerning incomplete or discrepant data was resolved by documented clarification/correction communication with the site. Accuracy of submitted data was verified during monitoring site visits.

9.6.3 Data Management

Data entry, data cleaning, and statistical analyses were performed by AACT, a contract research organization located in Lexington, MA. AACT followed applicable quality control procedures regarding the database, statistical analysis plan (SAP), analyses, and report writing.

9.7 PROTOCOL-SPECIFIED STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

9.7.1 Statistical and Analytical Plans

The statistical analyses described here reflect those in the clinical protocol. A description of the changes to statistical analyses as specified in the SAP of 29 December 2005 may be found in Section 16.1.9. The SAP for the study is provided in Section 16.1.9. All summary tables and listings were produced and all statistical analyses were performed using the SAS® statistical software system.

Continuous variables were summarized using descriptive statistics, specifically the mean, median, standard deviation, minimum, and maximum. Categorical variables were summarized using frequencies and percentages.

Inferential tests were performed at the 5% level of significance. All *P* Values were rounded to 3 decimal places. If a rounded *P* Value was 0.000 (i.e., *P* Value < 0.0005), then this was presented as a *P* Value of <0.001.

All data entered into the database were displayed in data listings.

9.7.1.1 Hypothesis Testing

For comparison of the OP-1 Putty group to the autograft group regarding non-inferiority, the null hypothesis was that the difference between the proportion of comprehensive success in the autograft treatment group and the OP-1 Putty treatment group was greater than 10% ($P_A - P_O > 10\%$). This hypothesis was to be tested calculating the difference between the proportion of success in the 2 treatment groups ($P_A - P_O$), the associated standard error $\{[P_A(1-P_A)/N_A + (P_O(1-P_O)/N_O)]^{1/2}\}$ and the upper 95% confidence limit (1.64 times the standard error). If the null hypothesis of non-inferiority is rejected by a corresponding *t* test at level 0.05, then a *P* Value associated with a test of superiority was to be performed.

Each success criteria may also have been evaluated individually for non-inferiority.

9.7.1.2 Populations for Statistical Analyses

Two populations were defined for efficacy analyses:

- *Per Protocol Population*: The per protocol population included all patients who did not violate the inclusion/exclusion criteria, had an ODI assessment at 24 months, had evaluable 24 month radiographic results and had an evaluable neurological assessment.
- *Intent-to-Treat (ITT) Population*: The ITT population included all treated patients.

9.7.1.3 Demographic and Baseline Characteristics

Selected baseline characteristics were to be compared between the treatment groups to ensure that the groups are comparable. These characteristics were to include age, gender, preoperative ODI, level fused, degree of angular motion, and translational movement.

Statistical significant ($p \leq 0.05$) differences in baseline characteristics between treatment groups were to be addressed in the analysis by use of an appropriate adjustment method or by stratification of study results. Both the unadjusted and adjusted or stratified results were to be presented in the study report.

Baseline characteristics were also to be presented by investigational site to evaluate the poolability of data across sites.

9.7.1.4 Analysis of Efficacy

9.7.1.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint was the 24-month overall success rate. This analysis was to be the basis for the test of non-inferiority. A patient was considered an “overall success” if he or she met all 6 of the following criteria.

1. Radiographic demonstration of spinal fusion (radiographic success) defined as meeting all three of the following conditions:

- Presence of bridging bone (on AP or lateral radiographs), and
- Angulation of $\leq 5^\circ$, and
- Translational movement of ≤ 2 mm

For each assessment of radiographic success, if the 2 radiologists were in disagreement on the determination of overall radiographic success, a third independent, masked radiologist was to evaluate those radiographs in question. The third radiologist was to conduct an evaluation of all success parameters for discrepant radiographs and record the evaluation on the postoperative radiographic evaluation form (Form 12). The determination of overall radiographic success made by the third radiologist was to be the deciding evaluation for fusion success of the patient.

2. ODI improvement of at least 20% from the pre-treatment visit. The improvement was measured by the change in the percent disability from pre-treatment. The percent disability was calculated as the sum of all non-missing individual scores divided by the number of non-missing scores multiplied by 5, and then multiplied by 100.
3. No revisions, removals, or supplemental fixations. All reoperations that were intended to promote fusion at the treated level were considered failures. Reoperations that were not intended to promote fusion, such as drain removal, were not considered failures. Revision, removals, supplemental fixations, and reoperations were defined (based on the Guidance Document for Preparation of IDEs for Spinal Systems, January 13, 2000) as follows:
 - a) A revision is a procedure that adjusted or, in any way, modified or removed part of the original implant configuration, with or without replacement of a component. A revision also includes adjusting the position of the original configuration.
 - b) A removal is a procedure in which all of the original system configuration is removed with or without replacement.

- c) A reoperation is any surgical procedure at the involved level(s) that does not remove, modify, or add any components to the system.
- d) A supplemental fixation is a procedure in which additional instrumentation not under study in the protocol is implanted (e.g., supplemental placement of a rod/screw system or a plate/screw system).

The term retreatment is used to refer to a revision, removal, supplemental fixation, or reoperation intended to promote fusion at the treated level. Any patient who experienced a retreatment was considered a failure, regardless of the timing of the procedure.

- 4. The absence of serious device-related AEs during the course of the study.
- 5. No unresolved neurological deficits at the final examination that were not present prior to study treatment, unless the deficit was due to a concurrent medical condition. Unresolved neurological deficits due to a concurrent medical condition were not considered failures. Neurological status was to be measured using all 4 neurological parameters: muscle strength, reflexes, straight leg raises, and sensory/dermatomal distribution.
- 6. No decreases in neurological status at the final examination from the preoperative evaluation, unless the decrease is due to a concurrent medical condition. Decreases in neurological status due to a concurrent medical condition were not considered failures.

Any patients who did not meet all of the success criteria were to be classified as failures for the 24 months study analysis. An analysis of successful patients at 6 and 12 months compared to 24 months was to be performed.

Missing data during the 24-month follow-up interval were to be considered as missing. Patients with missing data were to be initially classified using the last value carried forward approach. A sensitivity analysis was then to be performed to examine the stability of the conclusions to alternative classification methods (i.e. patients with missing data considered as treatment failures). The distribution of patients in each treatment group with missing data was to be examined in order to assess the impact of missing data on the intent-to-treat results. Patients missing a clinical or radiographic assessment at 24 months were to be excluded from the per protocol analysis.

9.7.1.4.2 Efficacy Analysis at 3 Months, 6 Months, 9 Months, 12 Months, 24 Months

The overall success rate and the 6 individual success criteria were to be reported as a time-course distribution based on data available at 3 months, 6 months, 12 months, and

24 months. At 9 months, the ODI improvement and rate of operation designed to promote fusion of the treated level was to be reported. These data were only to be based on the data available at each time point.

CT evaluation reported at 9 months was also to be assessed based upon available data, but was not to be included as a criteria for patient success; these data were to be collected solely as additional information and was not a study endpoint. Success based on the CT scans was to be defined as the presence of bridging at the right and left side of the operated level. The presence of bridging was to be evaluated as:

- No presence of bone
- Bone is present with no bridging
- Bone is present with bridging
- Solid bridging
- Not evaluable

A patient was to be deemed a success on the CT evaluation if bone is present with bridging, and/or solid bridging is apparent at the right and left side of the operated level. A patient was to be deemed a failure if there was no evidence of bone, or bone was present without bridging.

The radiologists were also to assess the CT scans for pseudarthrosis.

For the ITT analyses, patients who were considered as no longer participating in the study at the 24 month follow-up visit or who had missing data during the 24 months follow-up interval were to be considered as missing. For patients included in the ITT analyses, missing data was to be classified using the LOCF approach. For the per protocol analyses, patients who are included were classified based on the definition of individual patient success/failure.

9.7.1.5 Safety Analysis

The safety of OP-1 Putty was to be evaluated by documenting the number of anticipated and unanticipated complications/AEs that occurred within the study population. This frequency was to be compared to the frequency of events in the control population. The percentage of any serious product related events were also to be reported. In addition, unresolved neurological deficits, unrelated to a concurrent medical condition, that were not present prior to study treatment as well as decrease in neurological status from the preoperative evaluation were to be reported.

9.7.1.5.1 Adverse Events

All AEs occurring during the study were to be reported in adverse event tables. The tables were to report both the number and percent of patients with events and were to be stratified by treatment group.

Tables to be generated were to include the incidence of events, the intensity of AEs (severity), type of event, incidence of AEs over time, and the investigator's assessment of the relationship to study treatment. Additional tables were to be generated for events classified as either unanticipated AEs or serious AEs.

Confidence intervals were to be calculated around the overall incidence of AEs by treatment group.

9.7.1.5.2 Clinical Laboratory Evaluations

Blood was drawn pre-operatively (baseline), post-operatively, and at the 6-week and 3-, 6-, 12-, and 24-month follow-up visits. Serum was utilized for immunological testing. Whole blood was analyzed for hematology and biochemistry; the following parameters were evaluated:

- **Hematology:** Hematocrit, hemoglobin, neutrophils, basophils abs., eosinophils abs., lymphocytes abs., MCHC, MCV, monocytes abs., neutrophils abs., platelet count, red cell count, white cell count
- **Biochemistry:** Albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), creatinine, CO₂ content, chloride, glucose, potassium, sodium, uric acid, bilirubin (total), protein, urea nitrogen

Descriptive statistics were presented for actual value and change from baseline to the post-baseline time points for hematology and biochemistry parameters by treatment. The percent of patients with abnormal values were to be evaluated using statistical methods (Chi-square or Fisher's Exact Test), as appropriate, where an abnormal laboratory value was to be defined as a value that is >10% outside of the normal range. Shift tables were used to examine shifts in status (low, normal, high) from baseline to the post-baseline time points for hematology and biochemistry parameters.

If 2 or more laboratory evaluations were performed within the visit window, the most abnormal evaluation was to be used for the statistical evaluation.

9.7.1.5.3 Neurological Status

The neurological status of each patient was reported at baseline and at each follow-up visit. Tables were to report the percent of patients in each treatment group who

experienced abnormalities in muscle strength, reflexes, straight leg raises, and sensory evaluation.

Muscle strength evaluation was to consist of rating muscle groups associated with hip, knee, ankle and toe. Each group was to be evaluated for both the right and left side of the body. Scaling was to range from 0 (absent-total paralysis) to 5 points (normal). A cumulative score was to be evaluated from the sum of the scores from all muscle groups.

9.7.1.6 Additional Assessments

The following additional information was also to be reported for each patient:

- Visual Analog Scale Results for Pain Assessment
- Donor Site Pain (autograft patients only)
- Medication Use
- Hospitalization Data
- General Health Survey (SF-36)

9.7.2 Determination of Sample Size

The number of treated patients in this trial was based on hypothesized overall success rates of 53% for the OP-1 Putty group as compared to 47% for the autograft group. The maximum allowable difference between the treatment groups that could be used to conclude that OP-1 Putty was not inferior to autograft was set in the protocol at 10%. Using a 2:1 treatment to control group randomization assignment, an alpha level of 0.05 and power of 80%, 270 treated patients (180 OP-1 Putty and 90 autograft) were determined to be needed for this study. Assuming that approximately 15% of treated patients would not be evaluable at 24 months due to a number of reasons (lost-to-follow-up, withdrawn from study, visit outside of the established visit window), it was assumed that 42 additional patients would need to be treated during the study. This assumption increased the required number of treated patients to 312.

9.8 CHANGE FROM THE PROTOCOL AND PLANNED ANALYSES

9.8.1 Changes in the Conduct of the Study

9.8.1.1 Protocol Modifications

The first patient was treated under Protocol Version 2.1 (dated 10/31/01). Table 3 is a summary of the protocol modifications:

Table 3: Protocol Modifications

US Protocol Version (Date)	Equivalent Canadian Protocol Version (Date)	Summary of Changes
2.2 (2/01/02)	NA	Deletion of the unnecessary pregnancy test Increase in the number of US sites from 15 to 20 Proposed change in evaluation of neurological status
2.3 (4/26/02)	1.0 (12/12/01)	Proposed change in evaluation of neurological status not accepted by FDA, revert to previous version
3.0 (7/25/02)	2.0 (7/31/02)	Increase the upper age limit from 81 to 85
FDA approval September 10, 2002	NA	Increase in number of US sites from 20 to 25
3.2 (1/6/04)	3.2 (1/6/04)	Additional blood draw at 24 months for immunologic evaluation

9.8.1.2 Changes to Overall Success—Overall Radiographic Success Criterion

As a result of the Pre-PMA meeting and with the FDA's agreement that presence of bone, rather than bridging bone was an appropriate endpoint for evaluating the osteoinductive potential of OP-1 Putty all AP plain films were re-read for the presence of bone by the independent radiologists. The same radiologists who performed the initial radiographic evaluations were utilized for this new assessment. The procedure for this radiographic evaluation is provided in Appendix 16.1.10. Additionally the translational movement success threshold was modified from protocol-defined ≤ 2 mm to ≤ 3 mm, for consistency with the FDA's Guidance on IDEs for Spinal Systems (Jan 2000).

9.8.1.3 Changes to Overall Success—Overall Neurological Success Criterion

At baseline and at each post-operative visit the Investigator assess the patient's neurological status with regard to muscle strength, sensory function, reflex function and straight leg raises. The protocol defined 2 neurological success criteria but did not provide any additional direction as to how the 4 neurological parameters were to be

utilized in determining “neurological deficits” and “decreases in neurological status.” Prior to database lock, the Sponsor consulted with an experienced orthopedic spine surgeon, who was not otherwise involved in the conduct of the study, to establish a clinically relevant method for determining overall neurological status. This resulted in the combination of the 2 protocol defined criteria into a single criterion. This method was documented in a training module and is provided, along with the curriculum vitae of the consultant orthopedic spine surgeon, in Sections 16.1.10 and 16.1.4, respectively.

In the patient population under investigation in this clinical study it is generally acknowledged that reflexes are often unreliable and affected by the patient’s age, sensory evaluations are subjective in nature, and straight leg raises, which primarily provoke a sciatic nerve response, are not clinically relevant for patients with degenerative spondylolisthesis. Muscle strength tests are frequently used in orthopedic practice, utilize a widely used 0-5 scale and are considered the most clinically relevant indicator of neurological damage. For these clinical reasons, the overall neurological success criteria presented in the SAP utilizes all 4 neurological parameters, however it is most sensitive to changes in the muscle strength parameter.

In addition to assessing if the neurological deficit/decreased neurological status was related to a concurrent medical condition, as specified in the original protocol defined analyses, the blinded Independent Neurological Reviewer was asked to determine if the failures were attributable to the surgical procedure. A known risk of decompression and posterolateral fusion is neurological deficit. This risk is the same in both treatment groups and the intent of the neurological success criteria is to assess the impact of either OP-1 Putty or autograft to effect a change in the patient’s baseline neurological status. Therefore if the blinded Independent Neurological Reviewer assessed the decrease in neurological function as attributable to the surgical procedure that patient was considered a neurological success.

Overall Neurological Success was defined in the SAP as:

The patient was considered an overall neurological success in the absence of a decrease in neurological status, unless attributable to a concurrent medical condition or to the surgical procedure, defined as follows:

- A patient was considered to have a decrease in neurological status and was considered an overall neurological FAILURE if either of the following conditions were met:
 - i. Muscle Strength: decrease of at least 2 or more grades in =1 of the 24 muscle groups that were assessed parameters;
 - ii. At least 2 of the following 3 changes occurred:
 - Reflexes: Change of =1 of the 4 reflex assessments from normal (1) to absent (3);

- Sensory: Change of =1 of the 8 sensory assessments from normal (2) to absent (0);
- Change in straight leg raise pain from negative to positive.
- For patients who were failures as defined above, the Neurological Patient Profile and Safety Patient Profile was reviewed by a blinded Independent Neurological Reviewer to determine if the neurological status failure was attributed to
 - i. a concurrent medical condition;
 - ii. surgical procedure (decompression and posterolateral fusion)
 - iii. study treatment (OP-1 Putty or autologous bone graft)
 - iv. unable to determine based on the available information

Patients were considered an Overall Neurological SUCCESS if any of the following conditions were satisfied:

- i. Not an overall neurological FAILURE
- ii. FAILURE in overall neurological status but attributed to a concurrent medical condition, as assessed by Independent Neurological Reviewer
- iii. FAILURE in overall neurological status but attributed to the surgical procedure, as assessed by independent Neurological Reviewer

9.8.1.4 Determination of Serious Adverse Events

As this study was conducted under Investigational Device Exemption (IDE) regulations, the Concurrent Medical Event (AE) CRF did not explicitly capture whether an AE met the criteria for seriousness as defined in CFR 312.32. During monitoring visits, study monitors were supplied with AE listings and asked to document any events that could be categorized as serious AEs based on the information available at the monitoring visit.

At the conclusion of the study, all AE underwent medical review to determine if any AE met the criteria for serious adverse event (SAE), defined as “any adverse experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.” Adverse events that were determined by the medical reviewer to meet the definition for serious were identified and provided to AACT for inclusion in the study database.

9.8.2 Changes in Planned Analyses

The clinical protocol included an abbreviated statistical methods section. On October 18, 2005, prior to database lock, a Pre-PMA Meeting was held to discuss the proposed

Statistical Analysis plan. As a result of that meeting Stryker Biotech submitted the Statistical Analysis Plan (SAP) for the study. This plan included the revisions to the definition of Overall Success (changes to radiographic success and overall neurological success), definition of the efficacy populations for analysis, modification to the fixed non-inferiority margin as well as other minor clarifications and changes. Table 4 presents changes to the planned analysis.

Per FDA's request, all original analyses defined in the protocol were performed in addition to the analyses planned in the SAP. The original protocol analyses are described in the Addendum to the SAP. All statistical tables are provided in Appendix 14. The tables defined by the SAP are identified as x.x or Ax.x, where the "A" series tables indicate Addendum to the SAP. All *post hoc* tables are identified with a "B" prefix (i.e., Bx.x).

In an effort to illuminate the results of the SAP and original protocol analyses, *post hoc* statistical tables were generate and included in the report. Table 5 describes these *post hoc* analyses. *Post hoc* tables are identified with a "B" prefix and are provided in Section 14.3.

9.8.2.1 Changes to Fixed Non-Inferiority Margin

A major change from the protocol that was included in the SAP was a modification to the fixed non-inferiority margin for overall success and overall radiographic success at 24 months. The non-inferiority margin in the protocol was specified at 10%. In the SAP, the non-inferiority margin was modified to be variable, ranging up to approximately 14% depending upon the success rate in the control group, to take into account differences in variability in the underlying parameters. The non-inferiority margins for all other variables remained at 10%. A full description of the statistical methodology and rationale for this modification are provided in Section 16.1.9.

9.8.2.2 Changes to Efficacy Populations for Analysis

The efficacy populations for analysis were conducted on a modified intent-to-treat population which includes all treated patients with at least one post-treatment follow-up visit. The protocol analyses were performed on the intent-to-treat population. Both efficacy analyses will also be performed on a per protocol population.

9.8.2.3 Changes to Imputation Methodology

For the overall success and overall radiographic success endpoints at 24 months imputation was changed from LOCF to multiple imputations. A full description of the imputation methodology and rationale for this modification are provided in Section 16.1.9.

Table 4: Changes in Planned Analyses of Overall Success

Item	Protocol Description	Changes from Protocol		Tables Affected
Populations				
Definition of Intent-to-Treat Population	All treated patients	SAP Addendum	As per protocol	All "A" tables based upon ITT population
		SAP	The definition of the ITT population was modified to include all patients who are randomized and have at least one post-treatment visit. Note: within the CSR this population is referred to as "mITT" in order to differentiate it from the ITT population used for the SAP Addendum analyses.	T1.1, T2.2, plus all tables based upon mITT population
Definition of Per Protocol Population	All patients who did not violate the inclusion/exclusion criteria, had an Oswestry assessment at 24 months, had an evaluable 24 month radiographic result, and had a neurological assessment	SAP Addendum	As per protocol	All "A" tables based upon per protocol population
		SAP	Defined as all patients who did not violate the inclusion/exclusion criteria and who had at least 1 post-treatment visit.	T1.1, T2.3, plus all tables based upon per protocol population
Definition of Safety Population	Not specified	SAP Addendum	N/A	-
		SAP	All patients who were treated using either OP-1 Putty or autograft.	T1.1, T1.2, T1.2.1, plus all tables based upon safety population
Definition of Enrolled Population	Not specified	SAP Addendum	N/A	-
		SAP	All patients who were enrolled in the study. Clarified within the report to include all patients who were enrolled and randomized in the study.	T1.1

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Item	Protocol Description	Changes from Protocol		Tables Affected
Populations (Continued from previous page)				
ODI	No statistical analyses of post-baseline values specified	SAP Addendum	None	-
		SAP	Two-sample t-test used to test difference in change from baseline between treatment groups. One-sample t-test used to test mean change within each treatment group	T5.11, T5.11.1
	Analysis of components of overall success (missing data non-imputed) to be performed at 3, 6, 12, and 24 months	SAP Addendum	Analysis at 3, 6, 12, 24, 36 months with missing data at 6, 12, and 24 months imputed using LOCF approach	A3.2, A3.2.1
		SAP	As per SAP Addendum with the addition of test for difference between treatment groups (chi-square or Fisher's exact test). Missing data not imputed	T5.2, T5.2.1
Absence of Retreatment	Analysis of components of overall success (missing data non-imputed) to be performed at 3, 6, 12, and 24 months	SAP Addendum	Analysis at 3, 6, 12, 24, 36 months with missing data at 6, 12, and 24 months imputed using LOCF approach	A3.3, A3.3.1
		SAP	As per SAP Addendum with the addition of test for difference between treatment groups (chi-square or Fisher's exact test). Missing data not imputed	T5.3, T5.3.1
Absence of Serious Treatment-related Adverse Event	Analysis of components of overall success (missing data non-imputed) to be performed at 3, 6, 12, and 24 months	SAP Addendum	Analysis at 3, 6, 12, 24, 36 months with missing data at 6, 12, and 24 months imputed using LOCF approach	A3.4, A3.4.1
		SAP	As per SAP Addendum with the addition of test for difference between treatment groups (chi-square or Fisher's exact test). Missing data not imputed	T5.4, T5.4.1

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Item	Protocol Description	Changes from Protocol		Tables Affected
Populations <i>(Continued from previous page)</i>				
Overall Neurological Success Rates	Criteria for neurological success not defined in detail in the protocol.	SAP Addendum	Defined as indicated in section 9.8.1.3	A3.5, A3.5.1 As component of overall success (A1.1, A1.2, A1.3, A2.1, A2.2)
		SAP	As per SAP Addendum	T5.5, T5.5.1 As component of overall success (T3.2, T3.2.2, T3.2.2.1, T3.2.2.2, T3.2.A, T3.3, T4.1, T4.2)
Overall Neurological Success Rates	Analysis of components of overall success (missing data non-imputed) to be performed at 3, 6, 12, and 24 months	SAP Addendum	Analysis at 3, 6, 12, 24, 36 months with missing data at 6, 12, and 24 months imputed using LOCF approach	A3.5, A3.5.1
		SAP	As per SAP Addendum with the addition of test for difference between treatment groups (chi-square of Fisher's exact test). Missing data not imputed	T5.5, T5.5.1
Radiographic				
Translational movement	Translational movement of ≤ 2 mm considered success.	SAP Addendum	None	As component of radiographic success (A3.1, A.3.1.1) As component of overall success (A1.1, A1.2, A1.3, A2.1, A2.2)
		SAP	Translational movement to be ≤ 3 mm.	As component of radiographic success (T5.1, T5.1.A, T5.1.1) As component of overall success (T3.2, T3.2.2, T3.3, T4.1, T4.2)
	Handling of different values/different reviewers not specified	SAP Addendum	If third reviewer evaluated radiographs, use values from third reviewer. If only two reviewers, use average of two values.	As component of radiographic success (A3.1, A.3.1.1) As component of overall success (A1.1, A1.2, A1.3, A2.1, A2.2)

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Item	Protocol Description	Changes from Protocol	Tables Affected	
Radiographic (Continued from previous page)				
Translational movement (cont'd)		SAP	As per SAP Addendum	T5.10, T5.10.1, T5.10.2 As component of radiographic success (T.5.1,T.5.1A,T5.1.1) As component of overall success (3.1, 3.1.1, 3.2, 3.2.2, 3.3, 4.1, 4.2)
	No statistical analyses of post-baseline values specified	SAP Addendum	None	-
		SAP	Two-sample t-test used to test difference in change from baseline between treatment groups. One-sample t-test used to test mean change within each treatment group	T5.10, T5.10.1
Angular Motion	Handling of different values/different reviewers not specified	SAP Addendum	If third reviewer evaluated radiographs, use values from third reviewer. If only two reviewers, use average of two values.	As component of radiographic success (A3.1, A.3.1.1) As component of overall success (A1.1, A1.2, A1.3, A2.1, A2.2)
		SAP	As per SAP Addendum	T5.9, T5.9.1, T5.9.2 As component of radiographic success (T.5.1,T.5.1A,T5.1.1) As component of overall success (3.1, 3.1.1, 3.2, 3.2.2, 3.3, 4.1, 4.2)
	No statistical analyses of post-baseline values specified	SAP Addendum	None	-

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Item	Protocol Description	Changes from Protocol		Tables Affected
Radiographic (Continued from previous page)				
Angular Motion (<i>cont'd</i>)		SAP	Two-sample t-test used to test difference in change from baseline between treatment groups. One-sample t-test used to test mean change within each treatment group	T5.9, T5.9.1
Presence of Bone/bridging bone	Presence of bridging (on AP or lateral radiographs) between transverse processes of two vertebral bodies	SAP Addendum	As per protocol	As a component of overall success (A1.1, A1.2, A1.3, A2.1, A2.2) As a component of radiographic success (A3.1, A3.1.1)
		SAP	Presence of bone as defined on AP radiograph	As component of radiographic success (T.5.1, T.5.1A, T5.1.1) As component of overall success (3.1, 3.1.1, 3.2, 3.2.2, 3.3, 4.1, 4.2)
Overall Radiographic Success	Success defined as presence of bridging bone (on AP or lateral radiographs), angulation ($\leq 5^\circ$), and translational movement (≤ 2 mm).	SAP Addendum	As per protocol	A3.1, A3.1.1
		SAP	Success defined as of presence of bone (on AP radiograph), angulation ($\leq 5^\circ$), and translational movement (≤ 3 mm).	T5.1, T5.1.A, T5.1.1 Also, as component of overall success (T3.2, T3.2.2, T3.2.2.1, T3.2.2.2, T3.2.A, T3.3, T4.1, T4.2)
	Imputing data specified for 24 month visit only (using LOCF method).	SAP Addendum	Missing data imputed using LOCF for 6, 12 and 24 months.	A3.1, A3.1.1

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Item	Protocol Description	Changes from Protocol		Tables Affected
Radiographic (Continued from previous page)				
Overall Radiographic Success (<i>cont'd</i>)		SAP	Missing data at 24 mos imputed using multiple imputation technique.	T5.1
			A 2nd analysis was conducted in which missing values at 12, 24, and 36 mos were not imputed.	T5.1.A
	Equivalence limit for non-inferiority of 0.10	SAP Addendum	none	T3.2, T5.1
		SAP	Equivalence limit at 24 mos (imputed) based on angular score with non-inferiority margin of 0.14 radians	
Overall Success				
Overall Success	See sec. 9.7.1.4.1 for full definition. Criteria 4,5,6: 4: absence of serious device-related AEs during course of study. 5: no unresolved neurological deficits at final exam that were not present prior to treatment, unless deficit due to concurrent medical condition. Unresolved neurological deficits due to concurrent medical condition not to be considered failures 6: no decreases in neurological status at final exam from preop evaluation, unless decrease is due to concurrent medical condition. Decreases in neurological status due to concurrent medical condition not to be considered failures.	SAP Addendum	Uses protocol definition, with exception of changing wording of criteria #4 from absence of serious device-related adverse events during the course of the study to absence of serious treatment related adverse events during the course of the study, and combining criteria #5 and #6 into one neurological endpoint.	A1.1, A1.2, A1.3, A2.1, A2.2

Item	Protocol Description	Changes from Protocol	Tables Affected
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Overall Success (Continued from previous page)

		SAP	Modifications per SAP Addendum, with additional changes noted below: Overall radiographic success: defined as presence of bone (on AP radiograph), angulation ($\leq 5^\circ$), and translational movement (≤ 3 mm).	T3.1, T3.1.1, T3.2, T3.2.2, T3.3, T4.1, T4.2
	Equivalence limit for non-inferiority of 0.10	SAP Addendum	none	
		SAP	Equivalence limit at 24 mos (imputed) based on angular score with non-inferiority margin of 0.14 radians	
	For ITT analysis of patient success, patients missing data at 24 months will be classified using the LOCF approach.	SAP Addendum	For ITT analyses, missing data imputed using LOCF for 6, 12, and 24 months.	A1.1, A1.2
			For analyses by gender and age group, missing data were not imputed.	A1.3, A2.2
			For analyses of per protocol population, missing data were not imputed	A2.1
		SAP	Missing data at 24 mos imputed using multiple imputation technique described in section 9.8.2.3	T3.1, T3.1.1, T3.2
		SAP	Overall success rate at 12, 24, and 36 mos computed with missing data not imputed (mITT and per protocol populations).	T3.2.2, T4.1
		SAP	For analyses by gender and age group at 24 months, missing data were not imputed	T3.3, T4.2

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Item	Protocol Description	Changes from Protocol		Tables Affected
Overall Success (Continued from previous page)				
	An analysis of successful patients at 6 and 12 months compared to 24 months will be performed	SAP Addendum	This analysis was not performed.	
		SAP	This analysis was not performed.	
Secondary and Additional Endpoints				
CT scan:	Presence of bridging at right and left side of operated level: two primary reviewers	SAP Addendum	N/A	-
		SAP	Classified as bridging by both reviewers if both reviewers evaluated. If one review could not evaluate the presence of bridging bone will be based on the other reviewer's result.	T5.6, T5.6.1
	No statistical analysis specified	SAP Addendum	N/A	
		SAP	Fisher's exact test on proportion of successes	T5.6, 5.6.1
Pseudarthrosis	Presence of pseudarthrosis based on 9 Month CT scan	SAP Addendum	N/A	
		SAP	CT scans to be assessed for both pseudarthrosis and fusion. Fusion was not assessed.	T5.7, T5.7.1
Visual Analog Scale for Pain Assessment	No statistical analyses specified	SAP Addendum	N/A	
		SAP	Two-sample t-test used to test difference in change from baseline between treatment groups. One-sample t-test used to test mean change within each treatment group	T10

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Item	Protocol Description	Changes from Protocol		Tables Affected
Secondary and Additional Endpoints (Continued from previous page)				
SF-36	No statistical analyses specified	SAP Addendum	N/A	-
		SAP	Wilcoxon rank-sum to test the difference in change from baseline between treatment groups. Wilcoxon signed-rank test to test the mean change from baseline within treatment groups.	T14.1 through T14.9
Safety				
Adverse Events	Confidence intervals will be calculated around the overall incidence of adverse events by treatment group.	SAP Addendum	N/A	
		SAP	Confidence intervals calculated per protocol. Additional statistical testing indicated below: For each SOC, Fisher's exact test was used to test for differences (at the P=0.2 level) between treatment groups. Fisher's exact test was used to test for treatment differences (at the P=0.2 level) among preferred terms reported by ≥5% of patients in either treatment arm.	T6.2

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Item	Protocol Description	Changes from Protocol		Tables Affected
Safety (Continued from previous page)				
Normal/Abnormal Laboratory Status	Abnormal defined as >10% outside normal range; normal defined as ≤10% normal range. Chi-square or Fisher's exact test used to test percent of patients with abnormal values.	SAP Addendum	N/A	
		SAP	Low defined as below the lower normal range. Normal defined as within the normal range High defined as above the normal range As specified in protocol with the addition of Stuart-Maxwell test or McNemar's test to test the shifts in status within treatment	T8.2, 8.4
	No statistical analyses specified for descriptive statistics.	SAP Addendum	N/A	
		SAP	Two-sample t-test used to test difference in change from baseline between treatment groups. One-sample t-test used to test mean change within each treatment group	T8.1, 8.3
Neurological Status	The tables will report the percent of patients in each treatment group who experience abnormalities in muscle strength, reflexes, straight leg raises, and sensory evaluation. No statistical analysis specified	SAP Addendum	N/A	
		SAP	As specified in the protocol with the addition of statistical analysis specified below: Chi-square or Fisher's exact test, as appropriate, to test the difference between treatment groups at each specified visit. McNemar's test to test the shifts in status within treatment group.	T9.1, 9.2, 9.3, 9.4

Item	Protocol Description	Changes from Protocol		Tables Affected
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Safety (Continued from previous page)

Neurological Status (<i>cont'd</i>)	For muscle group, scaling was to range from 0 (absent-total paralysis) to 5 points (normal). A cumulative score was to be evaluated from the sum of the scores from all muscle groups.	SAP Addendum	N/A	
		SAP	Overall cumulative muscle score was not evaluated	
Immunology	Analyses not specified	SAP Addendum	N/A	
		SAP	Tabulation of patients with positive ELISA and with antibody status at each visit Descriptive statistics for titer results at each visit Patient profiles for patients with neutralizing antibodies Success by neutralizing antibody status TEAE, SAE, and immunologically -related TEAE and SAE, at patient level, by neutralizing antibody status	

Table 5: Post Hoc Statistical Tables Description

Item	Protocol Description	Changes from Protocol	Tables
Translational movement	No analysis of success rates specified	Calculated using mean scores from all reviewers, for each patient at each visit Missing data imputed using LOCF approach for 6, 12, and 24 months. Missing data not imputed for 3 or 36 months. 95% confidence bound calculated for difference between success rates in 2 treatment groups. Two-sample <i>t</i> test for non-inferiority with non-inferiority margin of 0.10. Based on mITT population Chi-square or Fisher's exact test, as appropriate, to test difference between treatment groups	B1.1
		Analysis of success by baseline status by post-treatment time point McNemar's test of significance for shift from baseline Fisher's exact test of the difference between groups at post-treatment time points	B5.10
Angular Motion	No analysis of success rates specified	Calculated using mean scores from all reviewers, for each patient at each visit Missing data imputed using LOCF approach for 6, 12, and 24 months. Missing data not imputed for 3 or 36 months. 95% confidence bound calculated for difference between success rates in 2 treatment groups. Two-sample <i>t</i> test for non-inferiority with non-inferiority margin of 0.10. Based on mITT population Chi-square or Fisher's exact test, as appropriate, to test difference between treatment groups	B1.2
		Analysis of success by baseline status by post-treatment time point McNemar's test of significance for shift from baseline Fisher's exact test of the difference between groups at post-treatment time points	B5.9
Presence of Bone on Plain Film	No analysis of success rates specified	Calculated proportion of reviewers indicating presence of bone for each patient Missing data imputed using LOCF approach for 6, 12, and 24 months. Missing data not imputed for 3 or 36 months. 95% confidence bound calculated for difference between success rates in 2 treatment groups. Two-sample <i>t</i> test for non-inferiority with non-inferiority margin of 0.10. Based on mITT population Chi-square or Fisher's exact test, as appropriate, to test difference between treatment groups	B1.3

(Continued on next page)

Item	Protocol Description	Changes from Protocol	Tables
<i>(Continued from previous page)</i>			
Presence of Bone on CT	<p>No analysis of presence of bone</p> <p>No analysis of success rates specified</p>	<p>Presence of bone defined as “bone is present, although no bridging” or “bone is present with bridging” or “solid bridging” on either side.</p> <p>Calculated as proportion of reviewers indicating presence of bone for each patient</p> <p>Missing data imputed using LOCF approach for 6, 12, and 24 months. Missing data not imputed for 3 or 36 months.</p> <p>95% confidence bound calculated for difference between success rates in 2 treatment groups.</p> <p>Two-sample <i>t</i> test for non-inferiority with non-inferiority margin of 0.10.</p> <p>Based on mITT population</p> <p>Chi-square or Fisher’s exact test, as appropriate, to test difference between treatment groups</p>	B1.4
Overall clinical success	Not specified in protocol	<p>Composite based on the following parameters:</p> <ul style="list-style-type: none"> • ODI improvement of at least 20% • Neurological success • Absence of retreatment intended to promote fusion • Absence of serious treatment-related AEs <p>Missing values not imputed.</p> <p>Two-sample <i>t</i> test for non-inferiority with non-inferiority margin of 0.10</p>	B3.2.1
Success rate based on degree of angular motion	Not specified in protocol	<p>Chi-square or Fisher’s exact test, as appropriate, to test the difference between treatment groups at each specified visit.</p> <p>McNemar's test to test the shifts in status within treatment group.</p>	B5.9
Success rate based on degree of translational movement	Not specified in protocol	<p>Chi-square or Fisher’s exact test, as appropriate, to test the difference between treatment groups at each specified visit.</p> <p>McNemar's test to test the shifts in status within treatment group.</p>	B5.10
Association of presence of neutralizing antibodies with radiographic components	Not specified in protocol	<p>Run on Safety Population</p> <p>Association between Nab at any point in time compared to:</p> <p>Translational Movement success</p> <p>Angulation success</p> <p>Presence of Bone by Plain Film</p> <p>Presence of Bone on CT</p>	B15.4.3

10. STUDY PATIENTS

10.1 PATIENT DISPOSITION

Figure 2 presents disposition for patients enrolled in this study, and Table 6 presents patient disposition up to and including 24 months, and Table 7 presents reasons for withdrawal. Patients were enrolled in the study after signing informed consent and completion of the baseline eligibility criteria. Randomization occurred after enrollment.

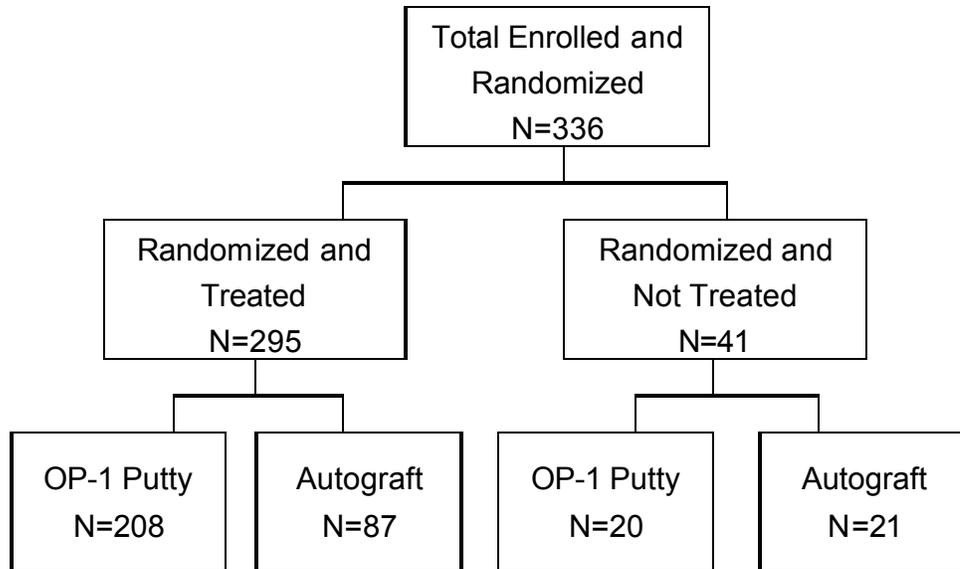
Of 336 enrolled and randomized patients, 41 patients did not receive treatment and so are not included in analyses. Of the 41 patients, 20 were randomized to receive OP-1 Putty and 21 were randomized to autograft. There were 11 (4.8%) OP-1 Putty patients and 8 (7.5%) Autograft patients who voluntarily withdrew prior to surgery citing reconsiderations regarding surgery, or the treatment group to which they have been randomized, or for other reasons. The remaining 9 OP-1 Putty patients and 13 autograft patients did not receive treatment due to failure to meet inclusion/exclusion criteria (concurrent medical condition, low ODI), or an intra-operative decision to perform a procedure other than decompression and single level uninstrumented fusion, or because of lack of insurance coverage for surgery. There does not appear to be a clear reason to account for the higher rate of autograft patients who were randomized but did not receive treatment. The reasons for withdrawal prior to or during treatment are provided in Listing 16. The remaining 295 were randomized to a treatment group: 208 received OP-1 Putty and 87 received an autograft.

Table 6 presents patient accounting up to and including 24 month follow-up. At the 24 month visit the follow-up rate was 87% in the OP-1 Putty group and 76% in the autograft group.

All patients were required to be followed for annual visits until the last treated patient completed 24 month follow-up. The last patient in the study was seen for the 24 months of follow-up visit on 14 November 2005. At this point, 37 OP-1 Putty and 14 autograft patients had been evaluated at 36 months.

A total of 11 patients died over the course of the study: 3.4% in the OP-1 Putty group, and 4.6% in the autograft group. There was 1 death in each group after the 24 month visit which is not represented in Table 6.

Figure 2: Patient Disposition



Source: Tables 14.1-1.1 and 14.1-1.2

Table 6: Patient Accounting through 24 Months

	Operative ^a	6 Weeks	3 Months	6 Months	9 Months	12 Months	24 Months
OP-1 Putty							
Theoretical	208	208	208	208	208	208	208
Deaths (cumulative)	0	1	1	3	4	4	6
Failures (cumulative)	1	1	1	3	6	10	15
Expected	207	206	206	202	198	194	187
Actual ^b	193	189	179	188	169	171	162
Actual ^c	208	206	201	200	193	198	193
% Follow-up ^d	93	92	87	93	85	88	87
Autograft							
Theoretical	87	87	87	87	87	87	87
Deaths (cumulative)	0	0	0	0	0	1	3
Failures (cumulative)	0	0	0	0	0	3	8
Expected	87	87	87	87	87	83	76
Actual ^b	77	77	73	74	71	70	58
Actual ^c	87	86	83	80	81	79	67
% Follow-up ^d	89	89	84	85	82	84	76

Source: Statistical Table 1.12.1 in Section 14.

(a) Occurring on or prior to the day of surgery.

(b) Patients with all films taken, complete data for physical examination, and Oswestry Disability Index for each point, evaluated per protocol in the window time frame.

(c) Patients with any follow-up data reviewed or evaluated by investigator ("all evaluated" accounting) for the nominal visit, which may include patients who are "Failures", and patients who have visit out of the window time frame.

(d) Patients who are "Expected", having all films taken, complete data for physical examination, and Oswestry Disability Index for each point, evaluated per protocol, in the window time frame.

Table 7: Reasons for Withdrawal

	Operative^a (<28 Days)	6 Weeks (28-77 Days)	3 Months (78-152 Days)	6 Months (153- 305 Days)	12 Months (306- 670 Days)	24 Months (671- 1035 Days)
OP-Putty						
Deaths during time interval	1	0	2	2	1	0
Withdrawals during time interval						
Voluntary Subject Withdrawal	0	0	0	1	2	0
Subject Illness/Concurrent Medical Condition	0	1	0	0	1	0
Lost to Follow-up	0	0	1	0	2	0
Subject Withdrawn by Investigator	1	0	0	0	0	0
Autograft						
Deaths during time interval	0	0	0	1	2	0
Withdrawals during time interval						
Voluntary Subject Withdrawal	1	1	0	1	3	0
Subject Illness/Concurrent Medical Condition	0	0	0	0	2	0
Lost to Follow-up	0	0	0	1	3	0
Subject Withdrawn by Investigator	0	1	1	0	1	0
Revision, Removal, Reoperation to Promote Fusion, or Supplemental Fixation before 24 Months	0	0	0	0	1	0
Missing	0	0	0	0	1	0

(a) Occurring on or prior to the day of surgery.

10.2 PROTOCOL DEVIATIONS

Several protocol deviations occurred during the course of the study, most of which were minor and had no impact on safety or efficacy outcomes. The following were protocol deviations which may have affected the clinical outcomes:

Inclusion/Exclusion Violations: (these 4 patients are excluded from the Per Protocol analyses):

- 1503 (OP-1 Putty): did not meet Inclusion Criterion #9. This patient's pre-operative ODI score was 29.
- 4401 (autograft): did not meet Inclusion Criteria #9. This patient's pre-operative ODI score was 24.
- 4803 (OP-1 Putty): did not meet Inclusion Criteria #9. This patient's pre-operative ODI score was 20.
- 5004 (OP-1 Putty): did not meet Inclusion Criteria #3. This patient did not have an intact par interarticularis at baseline.

Surgical Technique Violations:

- 2512 (autograft): the iliac crest donor site was back filled after harvest with bone taken from the laminectomy.
- 2513 (autograft): the iliac crest donor site was back filled after harvest with bone taken from the laminectomy.
- 2519 (autograft) the iliac crest donor site was back filled after harvest with a bone void filler.
- 5009 (OP-1 Putty): surgery was performed using a minimally invasive surgical technique.

Rehabilitation Violations: A total of 26 patients (12 OP-1 Putty and 14 autograft) did not wear a brace or other back support against the investigator's instructions.

- Patients in the OP-1 Putty group: 1114, 1129, 1506, 1707, 1801, 2303, 2504, 4002, 4414, 4803, 5004, 5202
- Patients in the autograft group: 1108, 1119, 1124, 1314, 2302, 3001, 3006, 3009, 3105, 4005, 4304, 4501, 5007, 5201

11. EFFICACY EVALUATION

11.1 DATA SETS ANALYZED

Table 8 presents populations used for SAP analysis, and Table 9 presents populations by time point. Populations were defined in SAP the following way:

- *All Enrolled*: all enrolled and randomized patients. No analyses were performed on this population.
- *Safety*: all randomized patients who received study treatment (either OP-1 Putty or autograft)
- *Modified intent-to-treat (mITT)*: treated patients who received study treatment, and had at least 1 post-treatment visit.
- *Per Protocol (PP)*: treated patients who did not violate the inclusion/exclusion criteria (in the analysis patients without at least 1 post-treatment visit were excluded).

All analyses of success were conducted on both the mITT and PP populations. Additionally, several ancillary efficacy analyses were conducted on the safety population. The definition of these populations varied slightly from the original protocol and is described in Section 9.8.

Table 8: Study Populations for SAP Analysis

Parameter	Number (%) of Patients		
	Overall	OP-1 Putty	Autograft
Safety Population	295 (100.0)	208 (100.0)	87 (100.0)
Modified ITT Population	293 (99.3)	207 (99.5)	86 (98.9)
Per Protocol Population	289 (98.0)	204 (98.1)	85 (97.7)

Source: Table 14.1-Table .1.1, A1.1

Note: Percentages are based on total number of safety patients for each treatment group or overall as appropriate.

Table 9: Study Populations for SAP Analysis by Visit

	Operative^a (<28 Days)	6 Weeks (28-77 Days)	3 Months (78-152 Days)	6 Months (153- 305 Days)	12 Months (306- 670 Days)	24 Months (671- 1035 Days)
OP-1 Putty						
Patients Included in Data Listings	208	206	205	202	199	193
Patients Included in Modified ITT Analysis Tables	207	206	205	202	199	193
Patients Included in Per Protocol Analysis Tables	204	203	202	199	196	190
Autograft						
Patients Included in Data Listings	87	86	84	83	80	67
Patients Included in Modified ITT Analysis Tables	86	86	84	83	80	67
Patients Included in Per Protocol Analysis Tables	85	85	83	82	79	67

(a) Occurring on or prior to the day of surgery.

11.2 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Table 10 presents demographics and baseline characteristics by treatment group and overall for the mITT population. No statistically significant differences between treatment groups were noted. Statistical Tables 2.1 through 2.3 in Section 14 present these data for the safety population, mITT population, and PP population, respectively. Listings 2 through 4 in Section 16 present these data by patient.

Age and Gender

Overall mean age was 68 years, with the range among groups of 36 to 84 years. The groups were similar in age distribution, with a majority of patients in each group aged >65 years. Approximately two-thirds of the patients were women.

Weight and Height

Weight and height were similar across both treatment groups.

Diagnosis

Ninety-three percent of patients in the OP-1 Putty group and 92% of patients in the autograft group had lumbar spinal stenosis with a definitive diagnosis of Grade 1 degenerative lumbar spondylolisthesis.

Treated Level

Eighty-six percent of patients in both treatment groups had disease involvement at the L4-L5 level.

Disease Severity Indices

The ODI and measurements of degree of angular motion and translational movement were assessed at baseline and at specified time points throughout the study period. There were no statistically significant differences between groups.

Method Used to Determine Diagnosis

Statistical Table 2.2 in Section 14 presents methods used to determine diagnosis. Greater than 90% of patients in both treatment groups were diagnosed via AP radiograph, lateral radiograph, flexion/extension radiograph and/or MRI.

Prior Treatments to Affect Level

Statistical Table 2.2 in Section 14 presents prior treatment history. Overall the most commonly used treatment modalities used by patients prior to study enrollment included non-steroidal medication (75.1%), physical therapy (72.4%), and steroidal medication (58.0%).

Worker's Compensation Status

Statistical Table 2.2 in Section 14 presents worker's compensation status. Fewer than 4% of patients were currently on worker's compensation.

Table 10: Selected Demographic and Baseline Characteristics (Modified ITT Population)

Parameter	Statistic	Overall	OP-1 Putty	Autograft	P Value ^a	
Age (years)	N	293	207	86	0.129	
	Mean	68	68	69		
	Median	69	68	71		
	Std. Dev.	9.4	9.8	8.3		
Sex: Male	N (%)	97 (33.1)	71 (34.3)	26 (30.2)	0.501	
Female	N (%)	196 (66.9)	136 (65.7)	60 (69.8)		
Weight (kg)	N	292	206	86	0.200	
	Mean	79.6	78.8	81.5		
	Median	79.4	78.1	82.4		
	Std. Dev.	16.32	16.06	16.88		
Height (cm)	N	293	207	86	0.268	
	Mean	165.8	165.4	166.8		
	Median	165.1	165.0	165.8		
	Std. Dev.	9.53	9.25	10.17		
Level Fused ^b :	L3-L4	n (%)	31 (10.6)	21 (10.1)	10 (11.6)	0.760
	L4-L5	n (%)	252 (86.0)	178 (86.0)	74 (86.0)	
	L5-S1	n (%)	10 (3.4)	8 (3.9)	2 (2.3)	
ODI	n	293	207	86	0.998	
	Mean	48.8	48.8	48.8		
	Median	48.0	48.9	48.0		
	Std. Dev.	12.19	11.60	13.59		
Degree of Angular Motion ^c (degrees)	n	271	195	76	0.086	
	Mean	4.1	3.9	4.7		
	Median	3.1	2.8	4.2		
	Std. Dev.	3.36	3.40	3.20		
Translational Movement ^c (mm)	n	268	193	75	0.802	
	Mean	1.7	1.7	1.6		
	Median	1.4	1.4	1.1		
	Std. Dev.	1.45	1.44	1.49		
Diagnosis of degenerative lumbar spondylolisthesis with spinal stenosis	n (%)	293 (100.0)	207 (100.0)	86 (100.0)	---	
	Grade 1	n (%)	272 (92.8)	193 (93.2)	79 (91.9)	
	Grade 2	n (%)	10 (3.4)	8 (3.9)	2 (2.3)	
	Unable to distinguish between Grade 1 and 2	n (%)	11 (3.8)	6 (2.9)	5 (5.8)	

Note: Percentages are based on total number of patients for each treatment group or overall as appropriate.

(a) P Value is based on Chi-Square test for the categorical variables, and is based on 2-sample *t* test for the continuous variables.

(b) Subject 3101 had involved level L5-S1 different from level fused L3-L4.

(c) The average scores from the 2 reviewers were used in the analysis.

11.3 EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL PATIENT DATA

This study demonstrated the following results at 24 months:

- Overall Success: OP-1 Putty treatment was not demonstrated to be non-inferior to autograft ($P=0.331$). The estimated success rates were 38.7% for OP-1 Putty and 49.4% for autograft.
- ODI success: the treatment groups were similar (80.4% for OP-1 Putty, and 85.5% for autograft). While statistical testing of non-inferiority did not show that OP-1 Putty was non-inferior to autograft with respect to ODI ($P=0.178$), neither did statistical testing of superiority indicate that autograft was superior to OP-1 Putty ($P=0.376$).
- Absence of retreatment: OP-1 Putty was statistically non-inferior to autograft at 24 months (92.3% for OP-1 Putty and 88.6% for autograft, $P=0.001$).
- Absence of serious treatment-related AEs: OP-1 Putty was statistically non-inferior to autograft (88.7% for OP-1 Putty and 91.4% for autograft, $P=0.038$).
- Neurological success: OP-1 Putty was statistically non-inferior to autograft (100% for OP-1 Putty, and 93.9% for autograft, $P<0.001$).
- Radiographic success: OP-1 Putty patients had a statistically significantly lower rate of overall radiographic success than autograft patients (52.4% for OP-1 Putty and 74.6% for autograft, $P=0.003$). *Post hoc* analyses revealed:
 - Presence of bone on plain film: presence of bone on plain film was statistically significantly lower in the OP-1 Putty patients compared to autograft (61.7% for OP-1 Putty and 83.1% for autograft, $P<0.001$).
 - Translational movement success: OP-1 Putty was non-inferior to autograft (93.6% for OP-1 Putty and 96.3% for autograft, $P=0.004$).
 - Angulation success: OP-1 Putty was similar to autograft (76.6% for OP-1 Putty and 79.3% for autograft). While statistical testing of non-inferiority did not show that OP-1 Putty was non-inferior to autograft with respect to angulation success ($P=0.087$), neither did statistical testing of superiority indicate that autograft was superior to OP-1 Putty ($P=0.629$).
 - Presence of bone on CT at 9 months: OP-1 Putty was clinically similar to autograft (84.9% for OP-1 Putty and 98.6% for autograft). Statistical testing of non-inferiority did not show that OP-1 Putty was non-inferior to autograft with respect to presence of bone by CT ($P=0.929$).
- Additional patient outcome measures of SF-36 and VAS pain scales suggest early and durable improvements for patients in both groups. In addition, the avoidance of a second surgical procedure resulted in decreased operative time, decreased

blood loss, and absence of donor site pain, all of which are clinical benefits of OP-1 Putty versus autograft.

- OP-1 Putty was statistically non-inferior to autograft with regard to overall clinical success, a composite parameter consisting of ODI success, absence of retreatment, absence of serious treatment-related AEs, and neurological success (71.2% in the OP-1 Putty group, and 69.0% in the autograft group, $P=0.029$).

Efficacy of OP-1 Putty is further demonstrated by consistency of success rates, and similarity between groups, in all clinically-relevant outcomes.

Table 11 presents a summary of success outcomes.

Table 11: Success Outcomes at 24 Months Follow-Up: SAP Analysis, mITT Population

Outcome	OP-1 Putty	Autograft	<i>P</i> Value Non-inferiority	<i>P</i> Value ³
Overall Success ¹	38.7%	49.4%	0.331 ²	----
ODI Success	80.4%	85.5%	0.178 ⁴	0.376
Absence of Retreatment	92.3%	88.6%	0.001 ⁴	0.347
Absence of Serious Treatment-related AEs	88.7%	91.4%	0.038 ⁴	0.519
Neurological Success	100%	93.9%	<0.001 ⁴	0.004
Radiographic Success ¹	53.0%	68.9%	0.622 ²	----

¹ Calculated with imputation of missing data.

² *P* Value is based on one-sided 2-sample test for non-inferiority in the angular scale with a non-inferiority margin of 0.14 (radians); estimates and standard errors are based on logistic regression and multiple imputation.

³ *P* value is based on chi-square or Fisher's exact test, as appropriate, to test the difference between treatment groups.

⁴ *P* Value is based on one-sided two-sample t-test for non-inferiority with an equivalence limit of 0.10.

11.3.1 Analysis of Efficacy

Efficacy outcomes were assessed based on results of both the SAP analyses, and the analyses described in the original protocol. SAP analyses on the mITT population will be the focus of the discussion in this report. Results based on the original protocol ITT population (referenced in the SAP addendum, Section 14.2) will be described briefly and tables and listings of more detailed results will be referenced. Results for the Per Protocol populations for both the SAP and original protocol analyses were consistent with the results discussed in this report. Results of the PP analyses will not be discussed within the report and may be located in Section 14.

Overall success is a composite measure with the following components:

- Improvement of at least 20% in the ODI from baseline
- Absence of retreatment
- Absence of treatment-emergent serious adverse events (SAEs)
- Absence of a decrease in neurological status (assessing muscle strength, reflexes, sensory and straight leg raise), unless attributable to a concurrent medical condition or to the surgical procedure by a blinded Independent Neurological Reviewer.
- Radiographic demonstration of spinal fusion, which was also a composite measure comprising all of the following:
 - Presence of bone formation
 - Angulation of $\leq 5^\circ$ on flexion/extension radiographs of the affected level
 - Translational movement of ≤ 3 mm on flexion/extension radiographs of the affected level

11.3.1.1 Primary Efficacy: Overall Success at 24 Months

The primary efficacy endpoint was the 24 month Overall Success rate for the mITT population, in which missing data were imputed. Results for the composite measure Overall Success will be described, and followed by a description of results for each of the individual components of overall success.

Table 12 presents the Overall Success rate at 24 months in the mITT population using the SAP analyses. OP-1 Putty treatment was not demonstrated to be non-inferior to autograft ($P=0.331$). The estimated success rates were 38.7% for OP-1 Putty and 49.4% for autograft.

Table 12: Overall Success Rate at 24 Months (mITT Population)

OP-1 Putty		Autograft		95% Upper Confidence Bound ² (%)	P Value for Non-Inferiority ³
Number of Patients	Success Rate (%) ^a	Number of Patients	Success Rate (%) ¹		
207	38.7%	86	49.4%	22.8%	0.331

Source: Statistical Table 3.2 in Section 14.

Note: Missing values were imputed.

(1) The percentage of successes and its standard error are based on estimates of the treatment effect adjusted for covariates in logistic regression and on variance estimates obtained from multiple imputation.

(2) The 95% upper confidence bound is for the difference between the angular-scale values corresponding to the success rates in the two treatment groups.

(3) *P Value* is based on one-sided two-sample test for non-inferiority in the angular scale with a non-inferiority margin of 0.14 (radians); estimates and standard errors are based on logistic regression and multiple imputation.

Results were similar for the analysis defined by the original protocol (31.7% for the OP-1 Putty group and 47.6% the autograft using the ITT population, $P= 0.824$, Statistical Table A1.2 in Section 14).

11.3.1.2 Secondary Efficacy Endpoints

11.3.1.2.1 Overall Success at 12, 24, and 36 Months

Table 13 presents overall success rates at 12, 24, and 36 months for the mITT population, in which data were not imputed. OP-1 Putty treatment was not demonstrated to be non-inferior to autograft at 24 months. However, it should be noted that the success rate in the OP-1 Putty group tended to improve over time, and the rate in the autograft group tended to decline.

Table 13: Overall Success Rate at 12, 24, and 36 months (mITT Population)

Time Point	OP-1 Putty		Autograft		95% Upper Confidence Bound (%) ¹	P Value for Non-Inferiority ²
	Number of Patients	Number (%) of Successes	Number of Patients	Number (%) of Successes		
12 Months	192	69 (35.9)	72	42 (58.3)	33.6	0.966
24 Months	183	69 (37.7)	70	34 (48.6)	22.4	0.549
36 Months	39	14 (35.9)	16	6 (37.5)	25.6	0.280

Source: Statistical Table 3.2.2 in Section 14.

Note: Missing data were not imputed.

Note: Patients of 36 months visit include those who had a 36 months visit or who were treated prior to November 29, 2002 and had a retreatment before the end of the 36 month window.

(1) 95% confidence bound is for the difference between the success rates in the two treatment groups.

(2) P Value is based on one-sided two-sample t-test for non-inferiority with an equivalence limit of 0.10.

Results were similar for the analysis defined by the original protocol (Statistical Table A1.2 in Section 14).

11.3.1.2.2 Oswestry Disability Index

Table 14 presents success as measured by 20% improvement in the ODI, a patient-completed questionnaire that reflects perceptions of components of disability: pain, activities of daily living, and mobility.

The treatment groups were similar at 24 months (80.4% for OP-1 Putty, and 85.5% for autograft). While statistical testing of non-inferiority did not show that OP-1 Putty was non-inferior to autograft with respect to ODI ($P=0.178$), neither did statistical testing of superiority indicate that autograft was superior to OP-1 Putty ($P=0.376$).

Table 14: Success Rate Based on Oswestry Disability Index at 12, 24, and 36 Months (mITT Population)

Time Point	OP-1 Putty		Autograft		95% Upper Confidence Bound (%) ¹	P Value Non-Inferiority ²	P Value ³
	Number of Patients	Number (%) of Successes	Number of Patients	Number (%) of Successes			
12 Months	187	155 (82.9)	77	65 (84.4)	9.7	0.045	0.762
24 Months	179	144 (80.4)	62	53 (85.5)	13.9	0.178	0.376
36 Months	35	30 (85.7)	14	12 (85.7)	18.6	0.185	1.000

Source: Section 14.2-Table 5.2

Note: Missing or non-evaluable data will be excluded from the analysis

(1) 95% confidence bound is for the difference between the success rates in the two treatment groups.

(2) P Value is based on one-sided two-sample t-test for non-inferiority with an equivalence limit of 0.10.

(3) P value is based on chi-square or Fisher's exact test, as appropriate, to test the difference between treatment groups.

Source: Section 14.2-Table 5.4; Section 16.2 Listing 9.1

Results were similar for the analysis defined by the original protocol (80.4% for the OP-1 Putty group and 85.5% for the autograft group, $P=0.180$, Statistical Table A3.2 in Section 14.)

Table 15 presents changes over time within and between treatment groups in ODI in the mITT population. Overall, both groups experienced clinically and statistically significant improvements in pain and function over time as assessed by ODI. No statistically significant difference at 24 months was noted between treatment groups with respect to change from baseline. Mean and median values for ODI scores at 24 months were also very comparable.

Section 16.2 Listing 5 displays these data by subject.

Table 15: Oswestry Disability Index Modified Intent-to-Treat Population

Time Point	Statistic	OP-1 Putty		Autograft		P Value ¹
		Actual	Change from Baseline	Actual	Change from Baseline	

Time Point	Statistic	OP-1 Putty		Autograft		P Value ¹
		Actual	Change from Baseline	Actual	Change from Baseline	
Baseline	N	207		86		
	Mean	48.8		48.8		
	Median	48.9		48.0		
	Std. Dev.	11.60		13.59		
	Minimum	20.0		24.0		
	Maximum	84.0		88.9		
3 Months	n	199	199	82	82	0.606
	Mean	27.3	-21.7	25.6	-22.8	
	Median	24.4	-20.0	26.0	-21.0	
	Std. Dev.	16.94	17.78	11.12	14.92	
	P Value ²		<0.001		<0.001	
6 Months	n	195	195	79	79	0.967
	Mean	22.5	-26.3	23.2	-26.3	
	Median	20.0	-26.0	22.0	-24.0	
	Std. Dev.	17.21	19.06	15.04	15.38	
	P Value ²		<0.001		<0.001	
12 Months	n	187	187	77	77	0.742
	Mean	20.8	-27.9	21.6	-27.0	
	Median	16.0	-28.0	20.0	-24.4	
	Std. Dev.	18.03	18.97	14.91	17.46	
	P Value ²		<0.001		<0.001	
24 Months	n	179	179	62	62	0.865
	Mean	21.7	-27.1	22.8	-27.6	
	Median	18.0	-28.0	20.0	-28.0	
	Std. Dev.	18.08	20.51	16.00	16.85	
	P Value ²		<0.001		<0.001	
36 Months	n	35	35	14	14	0.768
	Mean	20.7	-26.8	19.9	-25.3	
	Median	18.0	-28.7	21.0	-23.0	
	Std. Dev.	15.02	16.55	11.57	14.16	
	P Value ²		<0.001		<0.001	

Source: Statistical Table 5.11 in Section 14.

Note: Missing or non-evaluable data were excluded from the analysis.

(1) P Value is based on 2-sample t-test to test the difference in change from baseline between treatment groups.

(2) P Value is based on one-sample t-test to test the mean change within each treatment group.

11.3.1.2.3 Absence of Retreatment

Table 16 presents the success rate based on the absence of retreatment. OP-1 Putty was statistically non-inferior to autograft at 24 months (92.3% for OP-1 Putty and 88.6% for autograft, $P=0.001$).

Table 16: Success Rate Based on Absence of Retreatment at 12, 24, and 36 Months (mITT Population)

Time Point	OP-1 Putty		Autograft		95% Upper Confidence Bound (%) ¹	<i>P Value</i> Non-Inferiority ^b	<i>P Value</i> ²
	Number of Patients	Number (%) of Successes	Number of Patients	Number (%) of Successes			
12 Months	200	190 (95.0)	81	78 (96.3)	5.6	<0.001	0.763
24 Months	194	179 (92.3)	70	62 (88.6)	3.3	0.001	0.347
36 Months	43	36 (83.7)	17	14 (82.4)	16.7	0.149	1.000

Note: Missing or non-evaluable data will be excluded from the analysis Note: Patients of 36 months visit include those who had a 36 months visit or who were treated prior to November 29, 2002 and had a retreatment before the end of the 36 month window.

(1) 95% confidence bound is for the difference between the success rates in the two treatment groups.

(2) *P Value* is based on one-sided two-sample t-test for non-inferiority with an equivalence limit of 0.10.

Source: Section 14.2-Table 5.3; Section 16.2 Listing 9.3

Results were similar for the analysis defined by the original protocol (At 24 months: 92.7% for OP-1 Putty and 92.5% for autograft, $P=0.003$, Statistical Table A3.3).

Listing 9.1 in Section 16 displays concurrent medical events, including retreatment, by patient. Listing 9.3 in Section 16 displays patients requiring a retreatment.

11.3.1.2.4 Absence of Serious Treatment-Related Adverse Events

Table 17 presents success rate based on the absence of serious treatment-related AEs. Investigators were asked to rate the causality of each AE as “not related,” “suspected related” or “unknown.”

Table 17 presents Serious Treatment-Related Adverse Events that were rated as either “suspected related” or “unknown.” OP-1 Putty was statistically non-inferior to autograft (88.7% for OP-1 Putty and 91.4% for autograft, $P=0.038$).

Table 17: Success Rate Based on Absence of Serious Treatment-Related Adverse Events at 12, 24, and 36 Months (mITT Population)

Time Point	OP-1 Putty		Autograft		95% Upper Confidence Bound (%) ¹	P Value Non-Inferiority ²	P Value ³
	Number of Patients	Number (%) of Successes	Number of Patients	Number (%) of Successes			
12 Months	200	181 (90.5)	81	78 (96.3)	10.7	0.078	0.101
24 Months	194	172 (88.7)	70	64 (91.4)	9.4	0.038	0.519
36 Months	43	35 (81.4)	17	14 (82.4)	19.3	0.207	1.000

Source: Statistical Table 5.4 in Section 14.

Note 1: Missing or non-evaluable data will be excluded from the analysis

Note: Patients of 36 months visit include those who had a 36 months visit or who had a serious AE before the end of 36 months window.

(1) 95% confidence bound is for the difference between the success rates in the two treatment groups.

(2) p-value is based on one-sided two-sample t-test for non-inferiority with an equivalence limit of 0.10.

(3) P value is based on chi-square or Fisher's exact test, as appropriate, to test the difference between treatment groups.

Source: Section 14.2-Table 5.4; Section 16.2 Listing 9.1

Results were similar for the analysis defined by the original protocol (89.1% for OP-1 Putty and 95.5% for autograft, $P=0.141$, Statistical Table A3.4 in Section 14).

11.3.1.2.5 Neurological Success

Table 18 presents overall neurological success. OP-1 Putty was statistically non-inferior to autograft (100% for OP-1 Putty and 93.9% for autograft, $P<0.001$).

Table 18: Overall Neurological Success Rate at 12, 24, and 36 Months (mITT Population)

Time Point	OP-1 Putty		Autograft		95% Upper Confidence Bound (%) ¹	P Value Non-Inferiority ²	P Value ³
	Number of Patients	Number (%) of Successes	Number of Patients	Number (%) of Successes			
12 Months	193	189 (97.9)	75	73 (97.3)	2.9	<0.001	0.673
24 Months	189	189 (100)	66	62 (93.9)	-1.2	<0.001	0.004
36 Months	34	34 (100)	14	13 (92.9)	4.4	0.008	0.292

Source: Section 14.2-Table 5.5

Note: Missing or non-evaluable data will be excluded from the analysis

(1) 95% confidence bound is for the difference between the success rates in the two treatment groups.

(2) p-value is based on one-sided two-sample t-test for non-inferiority with an equivalence limit of 0.10.

(3) p-value is based on chi-square or Fisher's exact test, as appropriate, to test the difference between treatment groups..

Results were similar for the analysis defined by the original protocol (100% for OP-1 Putty and 93.9% for autograft, $P<0.001$, Statistical Table A3.5 in Section 14).

Listing 7 in Section 16 displays neurological evaluation data for each patient.

Statistical Tables 9.1 to 9.4 in Section 14.1 present change in neurological status over time. Muscle strength for all 24 muscle groups evaluated in both treatment groups was stable through 36 months, with the majority of patients having normal muscle strength. Patients in both groups demonstrated improvement or no change from baseline in reflex function, sensory function and straight leg raises through 36 months. There were some statistically significant improvements in change from baseline at several time points in both groups for reflex function, sensory function, and straight leg raises.

11.3.1.2.6 Overall Radiographic Success

Table 19 presents overall radiographic success rate at 24 months in the mITT population in which missing data were imputed in addition to summarizing overall success rates at 12, 24, and 36 months without imputing missing data. OP-1 Putty patients had a statistically significantly lower rate of overall radiographic success than autograft patients (52.4% for OP-1 Putty and 74.6% for autograft, $P=0.003$).

Table 19: Overall Radiographic Success Rate at 12, 24 and 36 Months (mITT Population)

Time Point	OP-1 Putty		Autograft		95% Upper Confidence Bound (%) ^a	<i>P Value</i> Non-Inferiority	<i>P Value</i> ^f
	Number of Patients	Number (%) of Successes	Number of Patients	Number (%) of Successes			
12 Months	179	88 (49.2)	71	52 (73.2)	34.7	0.985 ^b	0.001
24 Months	166	87 (52.4)	59	44 (74.6)	33.5	0.961 ^b	0.003
24 Months ^c	207	109.8 (53.0)	86	59.3 (68.9)	29.1 ^d	0.622 ^e	----
36 Months ^a	31	15 (48.4)	13	6 (46.2)	25.5	0.231 ^b	0.892

Note: Missing or non-evaluable data were excluded from the analysis

(a) 95% confidence bound is for the difference between the success rates in the 2 treatment groups.

(b) *P Value* is based on one-sided 2-sample t-test for non-inferiority with an equivalence limit of 0.10.

(c) Note: Missing values were imputed. The percentage of successes is based on estimates from multiple imputation.

(d) The 95% upper confidence bound is for the difference between the angular-scale values corresponding to the success rates in the 2 treatment groups.

(e) *P Value* is based on one-sided 2-sample test for non-inferiority in the angular scale with a non-inferiority margin of 0.14 (radians); estimates and standard errors are based on multiple imputation.

(f) *P value* is based on chi-square or Fisher's exact test, as appropriate, to test the difference between treatment groups.

Source: Section 14.2 Table 5.1

Statistical Table A3.1 presents the results of the original protocol analyses of radiographic success. The original protocol analysis of radiographic success included assessment of bridging bone, rather than presence of bone. Not unexpectedly, the rates of radiographic success in both groups by this definition were lower (At 24 months: 40.2% OP-1 Putty and 64.6% in autograft $P=0.989$, Statistical Table A3.1 in Section 14) than in the SAP analyses.

Listings 6.1 and 6.2 in Section 16 display radiographic data for each patient.

These overall radiographic success results were inconsistent with the positive clinical outcomes presented in previous sections. Patients in both groups demonstrated improvement in pain and function, maintenance of neurological status, and low rates of treatment related SAEs and retreatments. Additional *post hoc* analyses of the components of radiographic success (presence of bone, angulation =5 degrees and translation =3 mm) will be presented in the following sections. These additional analyses suggest that OP-1 Putty patients experienced clinically significant improvements in translational movement and angulation, and the overall radiographic success differences between groups was primarily due to differences in the presence of bone on X-rays.

11.3.1.2.7 Translational Movement

Table 20 presents translational movement success in the mITT population, in which missing data were imputed by LOCF (with the exception of the 36-month data). Successful translational movement was considered to be movement of ≤ 3 mm.

OP-1 Putty was non-inferior to autograft (93.6% for OP-1 Putty and 96.3% for autograft, $P=0.004$). In addition, a test for superiority was performed and no statistically significant differences were noted between groups.

Table 20: Post Hoc Table: Translational Movement Success Rate at 3, 6, 12, 24, and 36 Months mITT Population

Time Point	OP-1 Putty		Autograft		95% Upper Confidence Bound (%) ¹	P Value Non-inferiority ²	P Value ³
	Number of Patients	Number (%) of Successes	Number of Patients	Number (%) of Successes			
3 Months	189	165 (87.3)	77	66 (85.7)	6.1	0.007	0.728
6 Months	201	184 (91.5)	81	72 (88.9)	4.0	0.001	0.486
12 Months	202	182 (90.1)	82	77 (93.9)	9.4	0.034	0.305
24 Months	202	189 (93.6)	82	79 (96.3)	7.2	0.004	0.570
36 Months	30	28 (93.3)	14	11 (78.6)	5.2	0.022	0.307

Note: The mean scores of all reviewers are used in the analysis. Missing data were imputed using the last observation carried forward approach for 6, 12 and 24 months. Missing data were not imputed for 36 months.

(1) 95% confidence bound is for the difference between the success rates in the 2 treatment groups.

(2) P Value is based on one-sided 2-sample t-test for non-inferiority with an equivalence limit of 0.10.

(3) P Value is based on Chi-square or Fisher's exact test, as appropriate, to test the difference between treatment groups.

Source: Section 14.2-Table B1.1.

Table 21 presents the mean extent of translational movement and the change from baseline within and between treatment groups. Both groups experienced statistically significant improvements in translational movement over time. No statistically significant difference at 24 months was noted between treatment groups in change from baseline.

Section 16.2.6-Listings 6.1 and 6.2 displays these data by subject.

Table 21: Translational Movement Modified Intent-to-Treat Population

Time Point	Statistic	OP-1 Putty		Autograft		P Value ¹
		Actual	Change from Baseline	Actual	Change from Baseline	
Baseline	n	193		75		
	Mean	1.7		1.6		
	Median	1.4		1.1		
	Std. Dev.	1.44		1.49		
3 Months	n	189	177	77	66	0.699
	Mean	1.5	-0.2	1.3	-0.3	
	Median	1.2	-0.2	1.1	-0.3	
	Std. Dev.	1.34	1.80	1.27	1.91	
	P Value ²		0.121		0.190	
6 Months	n	192	179	79	69	0.698
	Mean	1.4	-0.3	1.5	-0.2	
	Median	1.2	-0.1	1.0	-0.1	
	Std. Dev.	1.15	1.60	1.48	2.14	
	P Value ²		0.010		0.439	
12 Months	n	179	168	71	62	0.717
	Mean	1.2	-0.4	1.1	-0.5	
	Median	1.0	-0.3	0.8	-0.5	
	Std. Dev.	1.21	1.75	1.31	2.01	
	P Value ²		0.004		0.059	
24 Months	n	163	151	58	50	0.704
	Mean	0.9	-0.8	0.6	-0.7	
	Median	0.5	-0.8	0.3	-0.6	
	Std. Dev.	1.03	1.68	0.89	1.78	
	P Value ²		<0.001		0.005	
36 Months	n	30	29	14	12	0.558
	Mean	1.0	-0.7	1.5	-0.3	
	Median	0.6	-0.8	0.7	-0.4	
	Std. Dev.	1.23	1.92	1.60	2.94	
	P Value ²		0.049		0.752	

Note: Missing or non-evaluable data were excluded from the analysis.

Note: The results from the third reviewer are used in the analysis. If there is no third review assessment, the average scores from the first 2 reviewers are used.

(1) P Value is based on 2-sample t-test to test the difference in change from baseline between treatment groups.

(2) P Value is based on one-sample t-test to test the mean change within each treatment group.

11.3.1.2.8 Angulation

Table 22 presents angulation success in the mITT population, in which missing data were imputed by LOCF (with the exception of the 36-month data). Success in angular motion was considered to be motion of ≤ 5 degrees. OP-1 Putty was similar to autograft (76.6% for OP-1 Putty and 79.3% for autograft). While statistical testing of non-inferiority did not show that OP-1 Putty was non-inferior to autograft with respect to angulation success ($P=0.087$), neither did statistical testing of superiority indicate that autograft was superior to OP-1 Putty ($P=0.629$). In addition, a test for superiority was performed and no statistically significant differences were noted between groups.

Table 22: Post Hoc Table: Angulation Success Rate at 3, 6, 12, 24, and 36 Months mITT Population

Time Point	OP-1 Putty		Autograft		95% Upper Confidence Bound (%) ¹	P Value for Non-inferiority ²	P Value Superiority ³
	Number of Patients	Number (%) of Successes	Number of Patients	Number (%) of Successes			
3 Months	187	126 (67.4)	78	59 (75.6)	18.1	0.385	0.182
6 Months	199	141 (70.9)	81	58 (71.6)	10.6	0.061	0.900
12 Months	200	149 (74.5)	82	62 (75.6)	10.4	0.059	0.845
24 Months	201	154 (76.6)	82	65 (79.3)	11.5	0.087	0.629
36 Months	32	28 (87.5)	14	10 (71.4)	6.5	0.029	0.222

Note: The mean scores of all reviewers are used in the analysis.

Missing data were imputed using the last observation carried forward approach for 6, 12 and 24 months.

Missing data were not imputed for 36 months.

(1) 95% confidence bound is for the difference between the success rates in the two treatment groups.

(2) p-value is based on one-sided two-sample t-test for non-inferiority with an equivalence limit of 0.10.

(3) p-value is based on Chi-square or Fisher's exact test, as appropriate, to test the difference between treatment groups.

Source: Section 14.2-Table B1.2.

Table 23 presents the mean extent of angulation and the change from baseline within and between treatment groups. Change from baseline was statistically significant for both groups at 24 months. No statistically significant differences were noted between treatment groups with respect to change from baseline. Furthermore, mean and median values of both groups at 24 months were clinically comparable.

Table 23: Degree of Angular Motion Modified Intent-to-Treat Population

Time Point	Statistic	OP-1 Putty		Autograft		P Value ¹
		Actual	Change from Baseline	Actual	Change from Baseline	
Baseline	n	195		76		
	Mean	3.9		4.7		
	Median	2.8		4.2		
	Std. Dev.	3.40		3.20		
3 Months	n	187	178	78	68	0.383
	Mean	4.1	0.1	3.9	-0.4	
	Median	3.6	0.2	2.8	-1.0	
	Std. Dev.	3.19	3.89	3.68	4.16	
	P Value ²		0.763		0.423	
6 Months	n	190	180	79	70	0.483
	Mean	4.0	0.1	4.2	-0.3	
	Median	3.0	0.1	3.4	-0.4	
	Std. Dev.	3.37	4.07	3.29	3.58	
	P Value ²		0.775		0.482	
12 Months	n	175	167	70	63	0.939
	Mean	3.5	-0.5	3.6	-0.5	
	Median	2.7	-0.3	2.4	-0.7	
	Std. Dev.	3.05	3.88	3.47	4.18	
	P Value ²		0.095		0.301	
24 Months	n	162	153	58	50	0.484
	Mean	3.3	-0.7	2.8	-1.2	
	Median	1.7	-0.6	1.9	-1.3	
	Std. Dev.	3.52	4.17	2.93	3.85	
	P Value ²		0.032		0.033	
36 Months	n	32	31	14	12	0.701
	Mean	2.5	-1.5	3.7	-2.0	
	Median	1.6	-0.9	3.3	-1.6	
	Std. Dev.	2.34	3.88	3.18	5.10	
	P Value ²		0.042		0.194	

Source: Statistical Table 5.9 in Section 14.

Note: Missing or non-evaluable data were excluded from the analysis.

Note: The results from the third reviewer are used in the analysis. If there is no third review assessment, the average scores from the first 2 reviewers are used.

(1) P Value is based on 2-sample t-test to test the difference in change from baseline between treatment groups.

(2) P Value is based on one-sample t-test to test the mean change within each treatment group.

11.3.1.2.9 Presence of Bone on Plain Film (AP View)

Table 24 presents the rate of success based on presence of bone visualized on X-rays. Presence of bone on plain film was statistically significantly lower in the OP-1 Putty patients compared to autograft (61.7% for OP-1 Putty and 83.1% for autograft, $P < 0.001$).

Table 24: Post Hoc Table: Success Rate Based on Presence of Bone at 3, 6, 12, 24, and 36 Months mITT Population

Time Point	OP-1 Putty		Autograft		95% Upper Confidence Bound (%) ¹	P Value Non-inferiority ²	P Value ³
	Number of Patients	Proportion (%) of Successes	Number of Patients	Proportion (%) of Successes			
3 Months	200	51.8	81	82.7	39.027	1.000	<0.001
6 Months	204	60.0	82	86.6	34.126	1.000	<0.001
12 Months	205	61.7	83	83.7	29.906	0.994	<0.001
24 Months	205	61.7	83	83.1	29.451	0.990	<0.001
36 Months	34	63.2	14	85.7	43.277	0.840	0.104

Note: The mean scores of all reviewers are used in the analysis.

Missing data were imputed using the last observation carried forward approach for 6, 12, 24 months.

Missing data were not imputed for 36 months.

(1) 95% confidence bound is for the difference between the success rates in the two treatment groups.

(2) p-value is based on one-sided two-sample t-test for non-inferiority with an equivalence limit of 0.10.

(3) p-value is based on two sample t-test to test the difference between treatment groups.

Source: Section 14.2-Table B1.3.

11.3.1.3 Other Radiographic Findings

11.3.1.3.1 Presence of Bridging Bone by Computed Tomography

Statistical Table 5.6 in Section 14 presents presence of bridging bone at the operative level, based on the CT scans at 9 months for the mITT Population, while *post hoc* Table B1.4 tabulates success rate based on presence of bone by CT at 9 months.

OP-1 Putty had a statistically significantly lower rate of bridging than autograft patients (31.3% for OP-1 Putty and 53.6% for autograft). Section 16.2 Listing 6.4 displays these data by subject.

11.3.1.3.2 Presence of Pseudarthrosis by Computed Tomography

Statistical Table 5.7 in Section 14 presents presence of pseudarthrosis based on the CT scans at 9 months for the mITT Population. This table presents pseudarthrosis at 9 months as assessed by either blinded radiographic reader. Pseudarthrosis AEs are discussed in Section 12.2.2.1.

Although a lower percent of patients in the OP-1 Putty group experienced pseudarthrosis versus patients in the autograft group (3.3% versus 9.5% for OP-1 Putty and autograft, respectively), this difference between groups only approached statistical significance ($P=0.058$).

Section 16.2-Listing 6.4 displays these data by subject.

11.3.1.3.3 Change from Baseline in Lateral Disc Height

Statistical Table 5.8 in Section 14 presents changes over time within and between treatment groups in lateral disc height in the mITT population. There were no statistically significant differences between treatment groups with respect to change from baseline value to any post-baseline assessments through 24 months.

Section 16.2-Listing 6.2 displays these data by subject.

11.3.2 Additional Analyses

11.3.2.1 Visual Analog Scale for Pain Assessment

Table 25 presents changes over time within treatment group, and differences between treatment groups, in Visual Analog Scale assessments of right and left leg/buttock pain assessment using the safety population. Patients in both groups experienced statistically significant decreases in pain over time. No statistically significant differences between treatment groups were noted with respect to change from baseline.

Table 25: Changes from Baseline in Visual Analog Scale of Right and Left Leg/Buttock Pain Assessment at 12, 24, and 36 Months (Safety Population)

Time Point	Statistic	OP-1 Putty Change from Baseline	Autograft Change from Baseline	P Value ^a
Right Leg/Buttock				
12 Months	N	176	77	0.558
	Mean	-3.2	-2.9	
	Median	-3.1	-2.6	
	Std. Dev.	3.44	3.58	
	P Value ^b	<0.001	<0.001	
24 Months	N	166	60	0.681
	Mean	-3.1	-2.9	
	Median	-2.9	-2.6	
	Std. Dev.	3.47	3.47	
	P Value ^b	<0.001	<0.001	
36 Months	N	35	14	0.561
	Mean	-2.7	-2.0	
	Median	-3.8	-1.6	
	Std. Dev.	4.07	3.28	
	P Value ^b	<0.001	0.043	
Left Leg/Buttock				
12 Months	N	180	77	0.565
	Mean	-3.1	-3.4	
	Median	-2.9	-3.4	
	Std. Dev.	3.78	3.81	
	P Value ^b	<0.001	<0.001	
24 Months	N	170	60	0.910
	Mean	-3.4	-3.4	
	Median	-3.3	-3.5	
	Std. Dev.	3.65	3.62	
	P Value ^b	<0.001	<0.001	
36 Months	N	34	14	0.638
	Mean	-3.6	-3.1	
	Median	-3.6	-3.5	
	Std. Dev.	3.39	3.03	
	P Value ^b	<0.001	0.002	

Note: Missing or non-evaluable data were excluded from the analysis.

Note: The results from the third reviewer are used in the analysis. If there is no third review assessment, the average scores from the first 2 reviewers are used.

(1) P Value is based on 2-sample t-test to test the difference in change from baseline between treatment groups.

(2) P Value is based on one-sample t-test to test the mean change within each treatment group.

Source: Section 14.2-Table 10.

11.3.2.1.1 Donor Site Pain

Table 26 presents Visual Analog Scale assessments of donor site pain using the safety population. At 6 weeks follow-up, mean donor site pain was 2.1 (on a scale of 0 to 10, where 0 indicated no pain and 10 indicated most severe pain). At 24 months follow-up, mean donor site pain was 1.2.

Table 26: Donor Site Pain-Visual Analog Scale at 12, 24, and 36 Months (Safety Population, Autograft Only)

Visit	Statistic	Autograft
6 Weeks	N	80
	Mean (Std Dev)	2.1 (2.40)
	Median	1.1
12 Months	N	77
	Mean (Std Dev)	1.6 (2.27)
	Median	0.3
24 Months	N	56
	Mean (Std Dev)	1.2 (2.05)
	Median	0.3
36 Months	N	14
	Mean (Std Dev)	1.5 (2.39)
	Median	0.5

Note: Missing or non-evaluable data are excluded from the analysis.

Source: Section 14.2-Table 11.01; Section 16.2.6-Listing 11

Table 27 presents donor site pain by severity using the safety population. Approximately half of the patients reported pain at the donor site at the 12, 24, or 36 month follow-up visit. Moderate to severe pain still persisted at 24 months for approximately 16% of patients with autograft. Severe pain was reported by 1 patient at 24 months.

Listing 11 in Section 16.2 displays Visual Analog Scale for Pain Assessment data by patient.

Table 27: Donor Site Pain Status at 12, 24, and 36 Months (Safety Population, Autograft Only)

Visit	Statistic	Autograft				
		None	Mild	Moderate	Severe	Total
12 Months	n (%)	40 (55.6)	17 (23.6)	15 (20.8)	0 (0.0)	72
24 Months	n (%)	30 (54.5)	16 (29.1)	8 (14.5)	1 (1.8)	55
36 Months	n (%)	8 (57.1)	2 (14.3)	4 (28.6)	0 (0.0)	14

Note: The percentages are based on the total number of patients with data at each visit.

Source: Section 14.2-Table 11.02; Section 16.2-Listing 11

11.3.2.2 Medication Use

Statistical Table 12 in Section 15 presents current medication use among the safety population. Similar results were found in both treatment groups.

Listing 12 in Section 16 displays current medication use by patient.

11.3.2.3 Surgical Procedure and Hospitalization Data

Table 28 presents surgical procedure characteristics for the safety population. Mean operative time was shorter for the OP-1 Putty group (144 minutes) than for the autograft group (164 minutes). Longer mean operative time in the autograft group is presumed to be attributed to additional operative time required to harvest the iliac crest.

Mean estimated blood loss was also lower for the OP-1 Putty group (309 cc) than for the autograft group (471 cc). Mean length of stay post surgery, however, was comparable for the two treatment groups: 4.5 days in the OP-1 Putty group and 4.4 days in the autograft group. No inferential testing of surgical procedure characteristics between treatment groups was performed.

Listing 13 in Section 16 displays hospitalization data by patient.

Table 28: Surgical Procedure Characteristics (Safety Population)

	Statistic	OP-1 Putty	Autograft
Operative Time (min)	n	204	86
	Mean	144	164
	Median	133	156
	Std. Dev.	53.3	62.4
Estimated Blood Loss (cc)	n	205	87
	Mean	309	471
	Median	250	400
	Std. Dev.	244.5	379.7
Length of Stay Post Surgery (Days)	n	208	87
	Mean	4.5	4.4
	Median	4	4
	Std. Dev.	2.9	1.7

Note: Percentages are based on the total number of patients for each treatment group.

Source: Section 14.2 Table 13; Section 16.2.6-Listing 13

11.3.2.4 General Health Survey (SF-36)

Patients completed the SF-36 questionnaire, a general health survey designed to measure a patient's perception of his/her overall health, functional status, and well being, at

specified time points during the study period. SF-36 measures consist of overall physical summary measure and an overall mental summary measure, in addition to 8 component scores: physical functioning, role-physical, bodily pain, mental health, role-emotional, social functioning, vitality, and general health perceptions. Increases in scores over time indicate improvement in the patient's perception of health status.

Table 29 presents physical component summary scores during the study period. At 6 weeks, patients in both groups had a statistically significant change from baseline. This improvement was maintained through 36 months. No statistically significant differences between treatment groups were observed for changes from baseline.

Table 29: SF-36 Physical Component Score (Safety Population)

Visit	Statistic	OP-1 Putty		Autograft		P Value ^a
		Actual Value	Change from Baseline	Actual Value	Change from Baseline	
Baseline	n	206	N/A	87	N/A	
	Mean	28.9	N/A	29.7	N/A	
	Median	28.6	N/A	28.7	N/A	
	Std. Dev.	6.13	N/A	6.38	N/A	
6 Weeks	n	200	198	83	83	0.483
	Mean	34.2	5.4	33.7	4.3	
	Median	33.1	4.6	33.8	4.6	
	Std. Dev.	6.99	8.43	6.36	7.55	
	P Value ^b	<0.001		<0.001		
3 Months	n	198	196	78	78	0.673
	Mean	38.1	9.5	38.0	8.5	
	Median	37.3	8.0	38.2	8.5	
	Std. Dev.	8.95	9.57	7.59	7.89	
	P Value ^b	<0.001		<0.001		
6 Months	n	195	194	78	78	0.325
	Mean	40.6	11.8	39.9	10.2	
	Median	39.8	11.4	40.0	9.9	
	Std. Dev.	10.19	11.15	10.04	10.33	
	P Value ^b	<0.001		<0.001		
9 Months	n	188	186	79	79	0.576
	Mean	40.6	11.8	40.6	11.1	
	Median	39.0	10.8	41.6	10.9	
	Std. Dev.	10.77	11.19	10.41	9.97	
	P Value ^b	<0.001		<0.001		
12 Months	n	188	186	78	78	0.265
	Mean	41.8	12.8	41.1	11.2	
	Median	41.3	12.4	40.9	10.4	
	Std. Dev.	10.90	11.28	10.31	10.65	
	P Value ^b	<0.001		<0.001		
24 Months	n	181	179	62	62	0.578
	Mean	40.2	11.0	39.7	10.3	
	Median	38.0	9.4	37.3	7.4	
	Std. Dev.	11.56	12.15	10.80	12.04	
	P Value ^b	<0.001		<0.001		
36 Months	n	28	28	13	13	0.268
	Mean	42.5	13.3	40.3	10.4	
	Median	47.0	16.0	40.9	8.1	
	Std. Dev.	11.98	10.71	11.13	11.87	
	P Value ^b	<0.001		0.008		

(a) P Value is based on Wilcoxon rank-sum test that tests the change from baseline between treatment groups.

(b) P Value is based on Wilcoxon signed-rank test that tests the mean change from baseline within each treatment group.

Source: Section 14.2-Table 14.1; Section 16.2.6-Listing 14

Table 30 presents physical functioning scores during the study period. The changes from baseline for these score are similar to those of the physical component summary scores previously described and were not statistically significantly different between treatment groups at any follow-up visit.

Listing 14 in Section 16 displays SF-36 data by patient.

Table 30: SF-36 Physical Functioning (Safety Population)

Visit	Statistic	OP-1 Putty		Autograft		P Value ¹
		Actual Value	Change from Baseline	Actual Value	Change from Baseline	
Baseline	n	208	N/A	87	N/A	
	Mean	26.8	N/A	26.6	N/A	
	Median	25.7	N/A	25.7	N/A	
	Std. Dev.	7.79	N/A	6.95	N/A	
6 Weeks	n	202	202	83	83	0.711
	Mean	31.2	4.4	31.5	5.2	
	Median	29.9	4.2	30.9	4.2	
	Std. Dev.	9.23	10.18	8.60	9.92	
	P Value ²	<0.001		<0.001		
3 Months	N	201	201	81	81	0.959
	Mean	36.1	9.4	35.7	9.0	
	Median	36.2	8.4	36.2	8.4	
	Std. Dev.	10.23	10.80	8.44	8.59	
	P Value ²	<0.001		<0.001		
6 Months	N	197	197	79	79	0.689
	Mean	38.9	12.1	38.1	11.5	
	Median	40.4	10.5	38.5	10.5	
	Std. Dev.	11.39	12.03	9.79	9.52	
	P Value ²	<0.001		<0.001		
9 Months	N	189	189	79	79	0.655
	Mean	39.1	12.2	38.5	12.0	
	Median	40.4	12.6	40.4	12.6	
	Std. Dev.	11.75	11.89	10.52	10.01	
	P Value ²	<0.001		<0.001		
12 Months	N	189	189	78	78	0.301
	Mean	40.1	13.1	38.9	11.9	
	Median	40.4	12.6	38.3	10.5	
	Std. Dev.	11.35	11.46	10.59	10.70	
	P Value ²	<0.001		<0.001		
24 Months	N	181	181	62	62	0.636
	Mean	38.8	11.8	37.7	11.3	
	Median	38.3	12.6	36.2	9.4	
	Std. Dev.	12.77	13.05	11.07	10.97	
	P Value ²	<0.001		<0.001		
36 Months	N	28	28	14	14	0.566
	Mean	40.2	13.0	39.9	11.7	
	Median	40.6	14.9	41.4	12.6	
	Std. Dev.	11.69	11.00	9.42	9.69	
	P Value ²	<0.001		0.001		

Note1: p-value is based on Wilcoxon rank-sum test to test the change from baseline between treatment groups.

Note2: p-value is based on Wilcoxon signed-rank test to test the mean change within each treatment group.

Source: Statistical Table 14.3 in Section 14.

11.3.3 Statistical/Analytical Issues

11.3.3.1 Adjustments for Covariates

For the mITT population, the SAP analysis used a logistic regression model to take into account the effects on success rate of baseline characteristics that were statistically significant at the 0.10 significance level. The model yielded adjusted success rates. The characteristics considered in this analysis were:

- Age: <45 years old, 45-65 years old, >65 years old
- Clinical site
- Gender: male, female
- Level fused: L3-L4, L4-L5, L5-S1
- Grade of spondylolisthesis: Grade 1 or Grade 2
- Prior treatment: surgical (laminectomy, facetectomy, foraminotomy, discectomy), not surgical (includes no previous treatment)
- Concurrent medical condition: metabolic bone disease and/or osteoporosis (yes/no)
- Concurrent medical condition: diabetes (yes/no)
- Workers' compensation status: no or yes (includes current, pending, litigation, and other)
- BMI (continuous variable)
- ODI (continuous variable)

The characteristics found to be statistically significant and included in the analysis were the following:

- Level fused: L3-L4, L4-L5, L5-S1
- Concurrent medical condition: diabetes (yes/no)
- Workers' compensation status: no or yes (includes current, pending, litigation, and other)
- ODI (continuous variable)

11.3.3.2 Handling of Dropouts or Missing Data

The number of mITT patients who had missing data for the 24-month overall success rate are tabulated in Section 14.2-Table 3.1. Within the OP-1 Putty group 21.7% of patients

had missing data for the 24 month overall success rate. This is lower than the 32.6% of patients with missing data in the autograft group, but this difference only approached statistical significance ($P=0.055$, Statistical Table 3.1 in Section 14). Statistical Table 3.1.1 in Section 14 presents the number of patients who had missing data which required imputation for the 24 month overall success rates.

Various approaches were used to handle missing data. Refer to the SAP in Section 0.

11.3.3.3 Interim Analyses and Data Monitoring

Not applicable.

11.3.3.4 Multicenter Studies

Clinical site was incorporated into the adjustment model for the primary efficacy assessment. Because clinical site (pooled for sites with small numbers of patients) did not contribute significantly to the model, treatment-by-center interactions were not required for analysis of the primary efficacy assessment of Overall Success at 24 months.

11.3.3.5 Multiple Comparisons/Multiplicity

No adjustments for multiple comparisons are made.

11.3.3.6 Examination of Subgroups

Table 31 presents the overall success rate at 24 months by gender and age group among the mITT Population. Statistical Table 4.2 in Section 14 presents these data for the Per Protocol Population. Based on these analyses, it cannot be concluded that OP-1 Putty's performance, relative to that of autograft, is influenced by patient age or sex.

Table 31: Overall Success Rate at 24 Months by Gender and Age Groups (mITT Population)

Patient Subgroup	OP-1 Putty		Autograft		95% Upper Confidence Bound (%) ¹	P Value for Non-Inferiority ²
	Number of Patients	Number (%) of Successes	Number of Patients	Number (%) of Successes		
Male	60	26 (43.3)	22	9 (40.9)	18.0	0.157
Female	123	43 (35.0)	48	25 (52.1)	31.0	0.801
<45 Years	3	0 (0.0)	0	0	N/A	N/A
45-65 Years	70	25 (35.7)	24	12 (50.0)	33.7	0.642
>65 Years	110	44 (40.0)	46	22 (47.8)	22.3	0.402

Note: Missing data were not imputed.

(1) 95% confidence bound is for the difference between the success rates in the two treatment groups.

(2) p-value is based on one-sided two-sample t-test for non-inferiority with an equivalence limit of 0.10.

Source data: Section 14.2 – Table 3.3; Listing 16.2.6-Listing xxx

11.4 EFFICACY *POST HOC* ANALYSES

Evidence for presence of bone on X-ray was inconsistent with the beneficial effects noted in angulation and translational movement. Although the angulation and translational movement success rates indicating spinal stability were similar for the 2 treatment groups, the OP-1 Putty group was not comparable to autograft with respect to presence of bone on plain film. This outcome regarding presence of bone on plain film seems anomalous and requires further evaluation. Therefore, we also evaluated the clinical outcomes as a composite without including radiographic parameters in the analytical model.

11.4.1 Presence of Bone Using Computed Tomography

To test the possibility that plain radiography was insensitive to OP-1-mediated osteoinduction in the clinical setting of PLF, other existing radiographic data were reviewed to see if more could be learned about characteristics of imaging in this patient population. Specifically, CT scans of the spine had been obtained at 9 months, not as success outcomes but to further understand the process of osteoinduction following PLF. CT scans were felt by the Sponsor's consultants to offer a complementary and potentially quite meaningful way of evaluating new bone formation because of their superior ability to image, in the sagittal plane, juxta-facet bone. In fact, CT scan is a more sensitive indicator of new bone formation under the conditions of this trial, demonstrating new bone in 84.9% of patients in the OP-1 Putty group, in contrast to the 61.7% demonstrated on plain films.

Statistical Table B1.4 in Section 14 presents the proportion of patients in whom bone was visualized by CT at 9 months post-procedure (CT scans were only performed at this time point). OP-1 Putty was similar to autograft (84.9% for OP-1 Putty and 98.6% for autograft). Statistical testing of non-inferiority did not show that OP-1 Putty was non-inferior to autograft with respect to presence of bone success ($P=0.929$).

11.4.2 Additional Analyses of Translation and Angulation Motion

Analyses of descriptive population statistics of the extent of translation and angulation motion over time, presented in previous sections (Table 21 and Table 23, respectively), showed similar behavior of both treatment group means over time. There appeared, however, to be wide variation within the populations at baseline as evidenced by the minimum and maximum values (Section 14.1, Tables 5.9 and 5.10). Based on the baseline mean values it was apparent that some proportion of patients in each group would have met the criteria for translational movement (≤ 3 mm) and/or angulation (≤ 5 degrees) success prior to surgery. Additional analyses were performed to better understand the rates of translational movement and angulation success over time compared to baseline status (success or failure).

Table 32 and Table 33 present shifts in success status for translational movement and angular motion, respectively. These tables demonstrate that within each group the majority of patients who would have been considered translational movement/angulation successes at baseline, remained successes at later time points. Even in patients with significant pre-operative instability, OP-1 Putty treatment was capable of inducing spinal stabilization comparable to that achieved by autograft treatment.

Table 32: Post Hoc Table: Success Rate Based on Translational Movement - Shifts in Status from Baseline to Post-Baseline Time-Points Modified Intent-to-Treat Population

Time Point	Post-baseline Status	Baseline Status				P Value ¹
		OP-1 Putty		Autograft		
		Failure	Success	Failure	Success	
12 Months	Failure	4	8	0	1	0.194
	Success	21	133	10	50	
	P Value ²		0.016		0.007	
24 Months	Failure	5	0	0	1	1.000
	Success	20	126	7	42	
	P Value ²		<0.001		0.034	
36 Months	Failure	0	2	1	2	0.139
	Success	4	23	2	7	
	P Value ²		0.414		1.000	

Note: Missing or non-evaluable data were excluded from the analysis.

The results from the third reviewer are used in the analysis. If there is no third review assessment, the average scores from the first 2 reviewers are used.

(1) P Value is based on Fisher's exact test to test the difference between treatment groups at each specified visit.

(2) P Value is based on McNemar's test to test the shifts in status within treatment.

Table 33: Post Hoc Table: Success Rate Based on Degree of Angular Motion - Shifts in Status from Baseline to Post-Baseline Time Points Modified Intent-to-Treat Population

Time Point	Post-baseline Status	Baseline Status				P Value ¹
		OP-1 Putty		Autograft		
		Failure	Success	Failure	Success	
12 Months	Failure	14	23	7	6	1.000
	Success	33	96	16	33	
	P Value ²		0.181		0.033	
24 Months	Failure	16	16	3	6	0.691
	Success	29	91	16	25	
	P Value ²		0.053		0.033	
36 Months	Failure	1	1	2	2	0.035
	Success	7	21	5	2	
	P Value ²		0.034		0.257	

Note: Missing or non-evaluable data were excluded from the analysis.

The results from the third reviewer are used in the analysis. If there is no third review assessment, the average scores from the first 2 reviewers are used.

(1) P Value is based on Fisher's exact test to test the difference between treatment groups at each specified visit.

(2) P Value is based on McNemar's test to test the shifts in status within treatment.

11.4.3 Clinical Outcomes as a Composite Measure

Table 53 presents overall clinical success in the OP-1 Putty group compared to the autograft group. Overall clinical success is a composite outcome, which includes ODI success, absence of retreatment, absence of serious treatment-related AEs, and neurological success. OP-1 Putty was statistically non-inferior to autograft with regard to overall clinical success (71.2% in the OP-1 Putty group, and 69.0% in the autograft group, $P=0.029$).

Table 34: Post Hoc Table: Clinical Success

Outcome	OP-1 Putty	Autograft	<i>P</i> Value Non-Inferiority ¹
ODI Success	80.4%	85.5%	0.178
Absence of Retreatment	92.3%	88.6%	0.001
Absence of Serious Treatment-related AEs	88.7%	91.4%	0.038
Neurological Success	100%	93.9%	<0.001
Overall Success	71.2%	69.0%	0.029

Source: Statistical Tables 5.2.2, 5.3.2, 5.4.2, 5.5.2, B3.2.1 in Section 14.

¹ *P* Value is based on one-sided two-sample t-test for non-inferiority with an equivalence limit of 0.10.

11.4.4 Post Hoc Analyses Summary and Conclusions

Based on *post hoc* analyses, CT images were more sensitive indicators of presence of bone than plain films.

- CT scan is a sensitive indicator of new bone formation under the conditions of this trial, demonstrating new bone in 84.9% of patients in the OP-1 Putty group, in contrast to the 61.7% demonstrated on plain films.
- OP-1 Putty was similar to autograft (84.9% for OP-1 Putty and 98.6% for autograft). Statistical testing of non-inferiority did not show that OP-1 Putty was non-inferior to autograft with respect to presence of bone by CT ($P=0.929$).
- The majority of patients who would have been considered translational movement/angulation successes at baseline, remained successes at later time points. Even in patients with significant pre-operative instability, OP-1 Putty treatment was capable of inducing spinal stabilization comparable to that achieved by autograft treatment.
- OP-1 Putty was statistically non-inferior to autograft with regard to overall clinical success, a composite parameter consisting of ODI success, absence of retreatment, absence of serious treatment-related AEs, and neurological success (71.2% in the OP-1 Putty group, and 69.0% in the autograft group, $P=0.029$).

11.5 EFFICACY CONCLUSIONS

This study demonstrated the following results at 24 months:

- Overall Success: OP-1 Putty treatment was not demonstrated to be non-inferior to autograft ($P=0.331$). The estimated success rates were 38.7% for OP-1 Putty and 49.4% for autograft.
- ODI success: the treatment groups were similar (80.4% for OP-1 Putty, and 85.5% for autograft). While statistical testing of non-inferiority did not show that OP-1 Putty was non-inferior to autograft with respect to ODI ($P=0.178$), neither did statistical testing of superiority indicate that autograft was superior to OP-1 Putty ($P=0.376$).
- Absence of retreatment: OP-1 Putty was statistically non-inferior to autograft at 24 months (92.3% for OP-1 Putty and 88.6% for autograft, $P=0.001$).
- Absence of serious treatment-related AEs: OP-1 Putty was statistically non-inferior to autograft (88.7% for OP-1 Putty and 91.4% for autograft, $P=0.038$).
- Neurological success: OP-1 Putty was statistically non-inferior to autograft (100% for OP-1 Putty, and 93.9% for autograft, $P<0.001$).
- Radiographic success: OP-1 Putty patients had a statistically significantly lower rate of overall radiographic success than autograft patients (52.4% for OP-1 Putty and 74.6% for autograft, $P=0.003$). *Post hoc* analyses revealed:
 - Presence of bone on plain film: presence of bone on plain film was statistically significantly lower in the OP-1 Putty patients compared to autograft (61.7% for OP-1 Putty and 83.1% for autograft, $P<0.001$).
 - Translational movement success: OP-1 Putty was non-inferior to autograft (93.6% for OP-1 Putty and 96.3% for autograft, $P=0.004$).
 - Angulation success: OP-1 Putty was similar to autograft (76.6% for OP-1 Putty and 79.3% for autograft). While statistical testing of non-inferiority did not show that OP-1 Putty was non-inferior to autograft with respect to angulation success ($P=0.087$), neither did statistical testing of superiority indicate that autograft was superior to OP-1 Putty ($P=0.629$).
 - Presence of bone on CT at 9 months: OP-1 Putty was clinically similar to autograft (84.9% for OP-1 Putty and 98.6% for autograft). Statistical testing of non-inferiority did not show that OP-1 Putty was non-inferior to autograft with respect to presence of bone by CT ($P=0.929$).
- Additional patient outcome measures of SF-36 and VAS pain scales suggest early and durable improvements for patients in both groups. In addition, the avoidance of a second surgical procedure resulted in decreased operative time, decreased

blood loss, and absence of donor site pain, all of which are clinical benefits of OP-1 Putty versus autograft.

- In a *post hoc* analysis, OP-1 Putty was statistically non-inferior to autograft with regard to overall clinical success, a composite parameter consisting of ODI success, absence of retreatment, absence of serious treatment-related AEs, and neurological success (71.2% in the OP-1 Putty group, and 69.0% in the autograft group, $P=0.029$).

Efficacy of OP-1 Putty is further demonstrated by consistency of success rates, and similarity between groups, in all clinically-relevant outcomes.

12. SAFETY EVALUATION

Safety data were analyzed using the Safety Population.

12.1 DURATION OF OBSERVATION

All 208 patients in the OP-1 Putty group were treated once with 2 units (7.0 mg) of OP-1 Putty and followed for up to 36 months. All 87 patients in the autograft group were treated with autologous iliac crest bone graft and followed for up to 36 months.

12.2 ADVERSE EVENTS

12.2.1 Summary of Adverse Events

In this pivotal study, 96.6% of patients in the OP-1 Putty treatment group reported at least 1 AE, and in the autograft treatment group 94.3% of patients reported at least 1 AE ($P=0.345$).

A conservative statistical cut-off ($P=0.2$) was imposed to identify potential differences in AEs between treatment groups. While the safety profiles of the 2 treatment groups were generally comparable, there were 4 System Organ Class (SOC) categories in which the OP-1 Putty group showed an overall higher incidence of AEs than did the autograft group based on this statistical cut-off. The categories were:

- Cardiac Disorders: 13% in OP-1 Putty patients, 5.7% in Autograft ($P=0.098$)
- Infections and Infestations: 23.6% in OP-1 Putty patients, 14.9% in Autograft patients ($P=0.117$)
- Respiratory, Thoracic And Mediastinal Disorders: 15.9% in OP-1 Putty patients, 6.9% in autograft patients ($P=0.039$)
- Gastrointestinal Disorders: 21.6% in OP-1 Putty patients, 13.8% in autograft patients ($P=0.145$)

There were 2 SOCs that had AEs reported more frequently in the autograft group than in the OP-1 Putty group:

- Blood And Lymphatic System Disorders: 5.8% in OP-1 Putty patients, 14.9% in autograft patients ($P=0.019$)
- Injury, Poisoning and Procedural Complications: 33.7% in OP-1 Putty patients, 47.1% Autograft patients ($P=0.035$)

The AEs in the remaining SOCs were reported with similar frequency in both treatment groups. The number of treatment-related AEs was small and relatively evenly distributed.

Approximately half of the patients in each treatment group experienced AEs post surgery and prior to discharge date: 47% of all OP-1 Putty patients (48.3% of OP-1 Putty patients with AEs) and 54% of all Autograft patients (57.3% of Autograft patients with AEs). The most common AEs during the hospitalization period in the OP-1 Putty group were dural tear, urinary retention, nausea, anemia and pyrexia. The most common AEs prior to discharge in the autograft group were anemia, dural tear, urinary retention, and confusional state.

The proportion of patients who reported AEs that were considered Suspected Related (includes events assessed as “unknown” causality) to treatment by the Principal Investigator was similar between both treatment groups (26.0% for patients in the OP-1 Putty-treated patients, and 26.4% for patients in the autograft-treated patients).

The majority of AEs suspected to be related to treatment were in the Musculoskeletal and Connective Tissue Disorders SOC (72.3% of all treatment-related AEs in the OP-1 Putty treatment group, and 52.2% of all treatment-related AEs in the autograft treatment group were in this SOC).

SAEs were reported with similar frequencies in both treatment groups, and no trends were identified that would suggest an excess risk for patients exposed to OP-1 Putty. Half of the patients in both the OP-1 Putty and autograft treatment groups (50.0% and 49.4% respectively) experienced at least 1 SAE over the course of the study. The most frequently reported SAEs were in the SOC Musculoskeletal and Connective Disorders (22.1% in the OP-1 Putty group, and 20.7% in the autograft group).

There were 31 patients (10.5%) across both treatment groups who reported 44 SAEs that were determined to be “suspected related” to study treatment, or were assessed as “relationship unknown” by the Principal Investigator. For the purposes of this analysis, events assessed as “relationship unknown” were considered to be treatment-related. In the OP-1 Putty treatment group, 12.0% of patients experienced 38 treatment-related SAEs, and 6.9% of patients in the autograft treatment group experienced 6 treatment-related SAEs.

There were 5 patients (2.4%) in the OP-1 Putty treatment group who reported 7 SAEs that were determined to be Unanticipated by the Principal Investigator. The SAEs were thyroid gland cancer (patient 1320), atrial fibrillation and transient ischemic attack (patient 1507), extradural haematoma (Patient 2405), lumbar spinal stenosis (patient 2514), and pulmonary oedema and hypotension (patient 3008). None of the patients in the autograft treatment group experienced an Unanticipated SAE.

There were 17 patients who received OP-1 Putty who had radiographic evidence of heterotopic ossification at any time point during the study, and 6 other patients who had evidence of heterotopic ossification identified on the 9-month CT scan. Three patients

(1501, 4405, and 4702) who received OP-1 Putty experienced heterotopic bone formation that was reported as an AE. Each of the patients who had heterotopic bone formation designated as an AE had radiographic evaluations indicating “exuberant bone growth” or “exuberant ossification” prior to reporting heterotopic bone formation as an adverse event.

Patients across both treatment groups reported events in the Neoplasms, Benign and Malignant (including polyps and cysts) SOC over the course of this study: 12 in the OP-1 Putty group (5.8%) and 8 in the autograft group (9.2%). None of the reported malignancies were determined to have a causal relationship to either OP-1 Putty or autograft. Two events, Lung Neoplasm Malignant in Patient 2519 who received Autograft, and Renal cyst in patient 1123 who received OP-1 Putty, were assessed as relationship “Unknown.” The causality of these events was, therefore, considered “Suspected Related” to the respective treatment. There were no patterns or specific events of concern identified with respect to type of cancer, time to onset post surgery, or frequency.

A total of 11 patients (3.7%) died over the course of the study: 3.4% in the OP-1 Putty group, and 4.6% in the autograft group. A complete description of deaths on study may be found in the SAE narratives Section 14.4. No patterns of concern emerged with respect to etiology of death, or the time to occurrence post surgery.

Twenty-five point six percent (25.6%) of patients in the OP-1 Putty group had evidence of neutralizing antibodies against OP-1 Putty versus 1.2% of autograft patients. There does not appear to be any association between antibody status and the development of potentially immunologically-related AEs or SAEs of any kind.

Three AEs were not included in the statistical analyses presented in this CSR, as these AEs were discovered during final study closeout visits which were conducted by the Sponsor after the database lock. All 3 AEs were reviewed by the head of Stryker Biotech Medical Affairs and assessed as having no significant effect on the safety results or conclusions. The following is a summary of the AEs:

- Patient 2104 had basal cell carcinoma of the lip, which was reported on the 27th of December 2004, was moderate in severity, and was not related to treatment. This was treated with radiation therapy and was ongoing at the last visit.
- Patient 4707 had a serum glucose level of 189 mg/dL, considered to be mild and not related to treatment. This patient also had a low serum potassium level (2.9 mEq/L), also considered mild and not related to treatment. No treatment was required for either of these AEs, and both were ongoing at the last visit.

12.2.2 Display of Adverse Events

12.2.2.1 Overall Incidence of Treatment Emergent Adverse Events

Table 35 presents the number and percent of patients who reported at least 1 treatment-emergent AE. In this pivotal study, 96.6% of patients in the OP-1 Putty treatment group reported at least 1 AE, and in the autograft treatment group 94.3% of patients reported at least 1 AE ($P=0.345$).

Serious AEs and treatment-related AEs were reported by a similar proportion of patients in each treatment group (50% and 26.0% respectively for patients in the OP-1 Putty group, and 49.4% and 26.4% respectively for patients in the autograft group). Treatment-related SAEs were reported by 12.0% of patients in the OP-1 Putty treatment group and 6.9% of patients in the autograft treatment group. A total of 11 patients died over the course of the study: 3.4% in the OP-1 Putty group, and 4.6% in the autograft group. Narratives describing all SAEs may be found in Section 14.4.

Statistical Table 6.5 in Section 14 presents treatment-adverse AEs by type of event.

Table 35: Treatment-Emergent Adverse Events (Safety Population)

Parameter	OP-1 Putty (N=208)		Autograft (N=87)	
	Number (%) of Patients with Events	95% CI	Number (%) of Patients with Events	95% CI
Any Adverse Event	201 (96.6)	(93.2, 98.6)	82 (94.3)	(87.1, 98.1)
Severe Adverse Event	43 (20.7)	(15.4, 26.8)	17 (19.5)	(11.8, 29.4)
Treatment-related Adverse Event	54 (26.0)	(20.1, 32.5)	23 (26.4)	(17.6, 37.0)
Unanticipated Adverse Event	6 (2.9)	(1.1, 6.2)	0 (0.0)	(0.0, 4.2)
Serious Adverse Event	104 (50.0)	(43.0, 57.0)	43 (49.4)	(38.5, 60.4)
Serious and Unanticipated Adverse Event	5 (2.4)	(0.8, 5.5)	0 (0.0)	(0.0, 4.2)
Treatment-related Serious Adverse Event	25 (12.0)	(7.9, 17.2)	6 (6.9)	(2.6, 14.4)
Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyyps)	12 (5.8)	(3.0, 9.9)	8 (9.2)	(4.1, 17.3)
Death	7 (3.4)	(1.4, 6.8)	4 (4.6)	(1.3, 11.4)

Note: Percentages are based on total number of enrolled subjects.

Note2: The 95% confidence interval for the proportion of patients with AEs is based on the exact (Clopper-Pearson) method. Note: The 95% confidence interval for the proportion of patients with AEs is based on the exact (Clopper – Pearson) method.

Table 36 presents treatment-emergent AEs by SOC. AEs were reported by most patients in both treatment groups, and the majority occurred with similar frequency in the groups.

The percentages of patients reporting AEs were generally similar between the treatment groups, and the frequency of individual AEs was also fairly similar. Utilizing a statistical cut-off of $P=0.2$, there were 4 SOC categories in which the OP-1 Putty treatment group had an overall higher incidence of AEs than did the autograft group. Conversely, there were 2 SOC categories that had a higher incidence of AEs reported in the autograft treatment group.

Specific AEs within the Cardiac disorders, Respiratory disorders, Infections and infestations, Gastrointestinal disorders, Blood and lymphatic disorders and Injury, poisoning and procedural complications SOCs will be discussed following Table 36.

The most frequently reported AEs in both treatment groups were in the SOC Musculoskeletal and Connective Tissue Disorders SOC. Seventy-five percent (75%) of patients in the OP-1 Putty group, and 69% of patients in the autograft group reported AEs in this SOC. As reported in Section 14.1 Tables 6.2 – 6.4, the most frequently occurring AE preferred terms, including arthralgia, back pain, pain in the extremity, and pseudarthrosis, were evenly distributed, as were the proportions of “mild”, “moderate” and “severe” events and events classified by the Principal Investigator to be “Suspected Related” to study treatment. Pain in Extremity was the most frequently reported AE in this SOC and in the study overall (25% of patients in the OP-1 Putty group, and 23% of patients in the autograft group). Pseudarthrosis was observed in 11.1% of patients in the OP-1 Putty group, and 11.5% of patients in the autograft group.

Of the Musculoskeletal and Connective Tissue Disorders AEs, 2 Preferred Terms of direct relevance to patients with degenerative spondylolisthesis appear to show a preponderance of events in the OP-1 Putty treatment group relative to the autograft group: Buttock Pain and Lumbar Spinal Stenosis (each, 4.8% versus 1.1% of patients); while 2 Preferred Terms appear to show fewer events in the OP-1 Putty treatment groups relative to the autograft group: Spondylolisthesis and Spondylolisthesis Acquired (summed, 0.5% versus 3.4% of patients). Any or all of these 4 Preferred Terms may indicate the progression or recurrence of underlying disease or the occurrence of post-operative complications in the lumbar spine. However, given the general similarity across treatment groups of Musculoskeletal and Connective Tissue Disorders in general, and the balance and low incidence of the lumbar spine-specific AEs in particular, neither treatment appears to entail excessive local risk in lumbar spinal surgery.

Table 36: Incidence of Treatment-Emergent Adverse Events by MedDRA System Organ Class (Safety Population)

System Organ Class/Preferred Term	Number (%) of Patients		P Value(a)	Number (%) of Events	
	OP-1 Putty (N=208)	Autograft (N=87)		OP-1 Putty	Autograft
Total	201 (96.6)	82 (94.3)	0.345	919 (100.0)	392 (100.0)
Blood and Lymphatic System Disorders	12 (5.8)	13 (14.9)	0.019	12 (1.3)	14 (3.6)
Cardiac Disorders	27 (13.0)	5 (5.7)	0.098	30 (3.3)	5 (1.3)
Ear And Labyrinth Disorders	4 (1.9)	1 (1.1)	1.000	5 (0.5)	1 (0.3)
Endocrine Disorders	2 (1.0)	0 (0)	1.000	2 (0.2)	0 (0.0)
Eye Disorders	7 (3.4)	3 (3.4)	1.000	8 (0.9)	3 (0.8)
Gastrointestinal Disorders	45 (21.6)	12 (13.8)	0.145	66 (7.2)	15 (3.8)
General Disorders and Administration Site Conditions	29 (13.9)	17 (19.5)	0.224	32 (3.5)	19 (4.8)
General System Disorders Nec	2 (1.0)	0 (0)	1.000	2 (0.2)	0 (0)
Hepatobiliary Disorders	1 (0.5)	1 (1.1)	0.503	1 (0.1)	1 (0.3)
Immune System Disorders	3 (1.4)	2 (2.3)	0.633	3 (0.3)	2 (0.5)
Infections And Infestations	49 (23.6)	13 (14.9)	0.117	61 (6.6)	18 (4.6)
Injury, Poisoning and Procedural Complications	70 (33.7)	41 (47.1)	0.035	93 (10.1)	51 (13.0)
Investigations	20 (9.6)	13 (14.9)	0.223	24 (2.6)	15 (3.8)
Metabolism and Nutritional Disorders	12 (5.8)	6 (6.9)	0.790	13 (1.4)	6 (1.5)
Musculoskeletal and Connective Tissue Disorders	156 (75.0)	60 (69.0)	0.313	322 (35.0)	135 (34.4)
Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps)	12 (5.8)	8 (9.2)	0.313	12 (1.3)	9 (2.3)
Nervous System Disorders	65 (31.3)	33 (37.9)	0.280	95 (10.3)	52 (13.3)
Psychiatric Disorders	17 (8.2)	7 (8.0)	1.000	17 (1.8)	7 (1.8)
Renal and Urinary Disorders	24 (11.5)	10 (11.5)	1.000	28 (3.0)	11 (2.8)
Reproductive System and Breast Disorders	2 (1.0)	2 (2.3)	0.584	4 (0.4)	2 (0.5)
Respiratory, Thoracic and Mediastinal Disorders	33 (15.9)	6 (6.9)	0.039	38 (4.1)	10 (2.6)
Skin And Subcutaneous Tissue Disorders	16 (7.7)	4 (4.6)	0.449	18 (2.0)	4 (1.0)
Surgical and Medical Procedures	4 (1.9)	0 (0.0)	0.323	4 (0.4)	0 (0.0)
Vascular Disorders	25 (12.0)	12 (13.8)	0.701	29 (3.2)	12 (3.1)

Note: Number of patients refers to patients with at least one adverse event of the indicated type. Number of events refers to all events of the indicated type. Percentages are based on the total number of patients or the total number of adverse events, as appropriate.

Patients experiencing multiple events under the same system organ class/preferred term are counted only once for that system organ class/preferred term.

(a) P values are calculated for all SOC terms and PT terms that happened to $\geq 5\%$ patients in at least one treatment group, using Fisher's exact test.

Table 37 presents the SOC **Blood and Lymphatic System Disorders**. Post-operative anemia was reported more frequently in the autograft group (13.8% of patients) versus the OP-1 Putty group (4.8% of patients, $P=0.013$). This is presumed to be related to the additional surgical procedure (i.e., autograft harvest) and is corroborated by findings of increase operative time and estimated blood loss in this treatment group (See Section 11.3.2.3)

Table 37: Incidence of Treatment -Emergent Blood and Lymphatic System Disorders (Safety Population)

System Organ Class/Preferred Term	Number (%) of Patients		Number (%) of Events	
	OP-1 Putty (N=208)	Autograft (N=87)	OP-1 Putty	Autograft
Total	201 (96.6)	82 (94.3)	919 (100.0)	392 (100.0)
Blood and Lymphatic System Disorders	12 (5.8)	13 (14.9)	12 (1.3)	14 (3.6)
Anaemia	10 (4.8)	12 (13.8)	10 (1.1)	12 (3.1)
Anaemia Postoperative	0 (0)	1 (1.1)	0 (0)	1 (0.3)
Leukocytosis	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Thrombocytthaemia	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Thrombocytopenia	0 (0)	1 (1.1)	0 (0)	1 (0.3)

Note: Number of patients refers to patients with at least one adverse event of the indicated type. Number of events refers to all events of the indicated type. Percentages are based on the total number of patients or the total number of adverse events, as appropriate. Patients experiencing multiple events under the same system organ class/preferred term are counted only once for that system organ class/preferred term.

Table 38 presents **Cardiac Disorders** by treatment group. In this category, 13.0% of the OP-1 Putty group patients experienced AEs, representing 3.3% of the events, while 5.7% of the autograft group patients experienced AEs, representing 1.3% of the events ($P=0.098$).

Table 38: Incidence of Treatment-Emergent Cardiac Disorders (Safety Population)

System Organ Class/Preferred Term	Number (%) of Patients		Number (%) of Events	
	OP-1 Putty (N=208)	Autograft (N=87)	OP-1 Putty	Autograft
Cardiac Disorders	27 (13.0)	5 (5.7)	30 (3.3)	5 (1.3)
Acute Coronary Syndrome	2 (1.0)	0 (0)	2 (0.2)	0 (0)
Atrial Fibrillation	5 (2.4)	0 (0)	5 (0.5)	0 (0)
Cardiac Failure	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Cardiac Failure Congestive	3 (1.4)	0 (0)	3 (0.3)	0 (0)
Chest Discomfort	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Chest Pain	7 (3.4)	3 (3.4)	7 (0.8)	3 (0.8)
Coronary Artery Disease	2 (1.0)	0 (0)	2 (0.2)	0 (0)
Myocardial Infarction	5 (2.4)	1 (1.1)	5 (0.5)	1 (0.3)
Myocardial Ischaemia	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Supraventricular Tachycardia	0 (0)	1 (1.1)	0 (0)	1 (0.3)
Tachycardia	3 (1.4)	0 (0)	3 (0.3)	0 (0)

Note: Number of patients refers to patients with at least one adverse event of the indicated type. Number of events refers to all events of the indicated type. Percentages are based on the total number of patients or the total number of AEs, as appropriate. Patients experiencing multiple events under the same system organ class/preferred term are counted only once for that system organ class/preferred term.

Source: Table 6.2, Section 14.

The following AEs were reported only by patients randomized to the OP-1 Putty treatment group: acute coronary syndrome (1.0%), atrial fibrillation (2.4%), cardiac failure (0.5%), cardiac failure congestive (1.4%), chest discomfort (0.5%), coronary artery disease (1.0%), myocardial ischaemia (0.5%), and tachycardia (1.4%). Of the 3 patients who experienced cardiac failure congestive, 1 was determined by the Principal Investigator to be ‘suspected related’ to OP-1 Putty, and of the 3 patients who experienced tachycardia, 1 event was assessed as ‘suspected related’ to OP-1 Putty.

Chest pain was equally distributed between the OP-1 Putty and autograft treatment patients (3.4% and 3.4% respectively). Of note, myocardial infarction was reported more frequently in OP-1 Putty patients as opposed to autograft patients (2.4% and 1.1% respectively). Supraventricular tachycardia was reported once by a patient who received autograft (1.1%), and this event was assessed as ‘not related’ to the autograft.

Most of the events in the OP-1 Putty group, and all in the autograft group, were classified as “mild” or “moderate” in severity. Patients in the OP-1 Putty group who experienced “severe” events reported myocardial infarction (1.4%), coronary artery disease (1.0%), chest pain (0.5%), and cardiac failure (0.5%).

The clinical significance of these findings is unclear. The patient population studied in this trial was generally elderly, with a mean age of 68 years, and many patients had preexisting cardiac risk factors such as cardiovascular disease, hypertension,

hypercholesterolemia, and diabetes reported pre-operatively. There is no known basis for suspecting that OP-1 Putty contributed to these events based on mechanism of action or preclinical studies of pharmacology or toxicology. Furthermore, a detailed cardiac medical history was not obtained at enrollment, making interpretation of the significance of these events more difficult. In addition, there has been no clinically significant pattern of cardiac events observed in extensive post-marketing safety surveillance.

In the **Infections and Infestations** category, 23.6% of OP-1 Putty patients experienced AEs, representing 6.6% of the events, while 14.9% of the autograft group patients experienced AEs, representing 4.6% of the events ($P=0.117$), as shown in Table 39.

Of patients receiving autograft, 1 (1.1%) reported 1 event each of abdominal discomfort, colitis ischaemic, haematochezia, oesophagitis, and small intestinal obstruction.

The events that were reported by patients in both the OP-1 Putty and autograft treatment groups respectively included colitis (0.5% vs 1.1%), constipation (4.3% vs 3.4%), gastroesophageal reflux disease (1.4% vs 1.1%), and nausea (4.8% vs 3.4%).

All AEs noted above in the OP-1 Putty group were “mild” with the exception of 1 “moderate” episode of Ileus. One report of “mild” diarrhea and 1 report of “severe” impaired gastric emptying were classified by the Principal Investigator to be “Suspected Related” to study treatment.

None of the events reported were determined to be ‘suspected related’ to the autograft.

The following AEs were reported only by patients randomized to the OP-1 Putty treatment group: clostridium colitis (1.9%), cystitis (0.5%), ear infection (1.0%), gastroenteritis viral (0.5%), herpes virus infection (0.5%), meningitis (0.5%), nasopharyngitis (0.5%), oral infection (0.5%), parotitis (0.5%), post-polio syndrome (0.5%), sepsis (0.5%), upper respiratory tract infection (0.5%), urosepsis (0.5%), and wound infection staphylococcal (0.5%).

Bone infection, larynthritis, and stitch abscess were only reported by one patient each who received autograft (1.1%).

The events that were reported by patients in both the OP-1 Putty and autograft treatment groups respectively included cellulitis (1.0% vs 3/3.4%), herpes zoster (2.9% vs 1.1%), infection (5.8% vs 5.7%), pneumonia (2.9% vs 1.1%), sinusitis (2.4% vs 1.1%), urinary tract infection (5.3% vs 3.4%) and viral infection (0.5% vs 1.1%).

None of the events in either treatment group were determined to be ‘suspected related’ by the Principal Investigator.

Of the Infections and Infestations AEs, there were 4 preferred terms that appeared to show a preponderance of events in the OP-1 Putty treatment group over the autograft

group: *Clostridium colitis* (1.9% vs 0%), herpes zoster (2.9% vs 1.1%), pneumonia (2.9% vs 1.1%), and urinary tract infection (5.3% vs 3.4%).

Infections are commonly observed in the post-operative setting. There is no known basis for suspecting that OP-1 Putty contributed to these events, whether from mechanism of action, preclinical studies of pharmacology or toxicology, or post-market surveillance. Future clinical use of OP-1 Putty should carefully assess patients for infection risk pre-operatively and for infectious events post-operatively.

Table 39: Incidence of Treatment -Emergent Infections and Infestations (Safety Population)

System Organ Class/Preferred Term	Number (%) of Patients		Number (%) of Events	
	OP-1 Putty (N=208)	Autograft (N=87)	OP-1 Putty	Autograft
Infections and Infestations	49 (23.6)	13 (14.9)	61 (6.6)	18 (4.6)
Bone Infection	0 (0)	1 (1.1)	0 (0)	1 (0.3)
Cellulitis	2 (1.0)	3 (3.4)	2 (0.2)	3 (0.8)
Clostridium Colitis	4 (1.9)	0 (0)	4 (0.4)	0 (0)
Cystitis	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Ear Infection	2 (1.0)	0 (0)	2 (0.2)	0 (0)
Gastroenteritis Viral	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Herpes Virus Infection	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Herpes Zoster	6 (2.9)	1 (1.1)	6 (0.7)	1 (0.3)
Infection	12 (5.8)	5 (5.7)	12 (1.3)	5 (1.3)
Labyrinthitis	0 (0)	1 (1.1)	0 (0)	1 (0.3)
Meningitis	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Nasopharyngitis	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Oral Infection	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Parotitis	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Pneumonia	6 (2.9)	1 (1.1)	6 (0.7)	1 (0.3)
Post Polio Syndrome	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Sepsis	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Sinusitis	5 (2.4)	1 (1.1)	5 (0.5)	1 (0.3)
Stitch Abscess	0 (0)	1 (1.1)	0 (0)	1 (0.3)
Upper Respiratory Tract Infection	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Urinary Tract Infection	11 (5.3)	3 (3.4)	11 (1.2)	3 (0.8)
Urosepsis	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Viral Infection	1 (0.5)	1 (1.1)	1 (0.1)	1 (0.3)
Wound Infection Staphylococcal	1 (0.5)	0 (0)	1 (0.1)	0 (0)

Note: Number of patients refers to patients with at least one adverse event of the indicated type. Number of events refers to all events of the indicated type. Percentages are based on the total number of patients or the total number of AEs, as appropriate. Patients experiencing multiple events under the same system organ class/preferred term are counted only once for that system organ class/preferred term.

Source: Table 6.2, Section 14

Table 40 presents **Gastrointestinal Disorders** by treatment group. In this category, 45 (21.6%) of the OP-1 Putty group patients experienced AEs, representing 66 (7.2%) of the events, while 12 (13.8%) of the autograft group patients experienced AEs, representing 15 (3.8%) of the events, as shown in Table 36. Although the 2 treatment groups were statistically identified as potentially different based on the conservative criteria SOC $P=0.2$ level, no concerning pattern of clinical events emerged in the OP-1 Putty treatment group

Table 40: Incidence of Treatment -Emergent Gastrointestinal Disorders (Safety Population)

System Organ Class/Preferred Term	Number (%) of Patients		Number (%) of Events	
	OP-1 Putty (N=208)	Autograft (N=87)	OP-1 Putty	Autograft
Gastrointestinal Disorders	45 (21.6)	12 (13.8)	66 (7.2)	15 (3.8)
Abdominal Discomfort	0 (0)	1 (1.1)	0 (0)	1 (0.3)
Abdominal Distension	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Abdominal Pain	3 (1.4)	0 (0)	4 (0.4)	0 (0)
Appendicitis	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Colitis	1 (0.5)	1 (1.1)	1 (0.1)	1 (0.3)
Colitis Ischaemic	0 (0)	1 (1.1)	0 (0)	1 (0.3)
Constipation	9 (4.3)	3 (3.4)	10 (1.1)	3 (0.8)
Crohn's Disease	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Diarrhoea	6 (2.9)	0 (0)	6 (0.7)	0 (0)
Diverticulitis	2 (1.0)	0 (0)	2 (0.2)	0 (0)
Dyspepsia	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Faecal Incontinence	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Flatulence	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Gastric Ulcer	2 (1.0)	0 (0)	2 (0.2)	0 (0)
Gastroenteritis Norwalk Virus	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Gastroenteritis Viral	2 (1.0)	0 (0)	2 (0.2)	0 (0)
Gastrointestinal Haemorrhage	2 (1.0)	0 (0)	2 (0.2)	0 (0)
Gastrooesophageal Reflux Disease	3 (1.4)	1 (1.1)	3 (0.3)	1 (0.3)
Haematochezia	0 (0)	1 (1.1)	0 (0)	1 (0.3)
Haemorrhoids	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Ileus	3 (1.4)	0 (0)	3 (0.3)	0 (0)
Impaired Gastric Emptying	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Irritable Bowel Syndrome	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Nausea	10 (4.8)	3 (3.4)	10 (1.1)	3 (0.8)
Oesophagitis	0 (0)	1 (1.1)	0 (0)	1 (0.3)
Pancreatitis	2 (1.0)	0 (0)	2 (0.2)	0 (0)
Postoperative Ileus	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Rectal Haemorrhage	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Small Intestinal Obstruction	0 (0)	1 (1.1)	0 (0)	3 (0.8)
Toothache	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Vomiting	5 (2.4)	0 (0)	5 (0.5)	0 (0)
Vomiting Projectile	1 (0.5)	0 (0)	1 (0.1)	0 (0)

Note: Number of patients refers to patients with at least one adverse event of the indicated type. Number of events refers to all events of the indicated type. Percentages are based on the total number of patients or the total number of adverse events, as appropriate. Patients experiencing multiple events under the same system organ class/preferred term are counted only once for that system organ class/preferred term.

Source: Table 6.2, Section 14.

The following adverse events were reported only by patients randomized to the OP-1 Putty treatment group: abdominal distension (0.5%), abdominal pain (1.4%), appendicitis (0.5%), Crohn's disease (0.5%), diverticulitis (1.0%), diarrhea 6 (2.9%), dyspepsia (0.5%), faecal incontinence (0.5%), flatulence (0.5%), gastric ulcer (1.0%), gastroenteritis Norwalk virus (0.5%), gastroenteritis viral (1.0%), gastrointestinal haemorrhage (1.0%), haemorrhoids (0.5%), ileus (1.4%), impaired gastric emptying (0.5%), irritable bowel syndrome (0.5%), pancreatitis (1.0%), postoperative ileus (0.5%), rectal haemorrhage (0.5%), toothache (0.5%), vomiting (2.4%), and vomiting projectile (0.5%).

Table 41 presents the SOC **Injury, Poisoning And Procedural Complications**.

Differences between groups (33.7% in the OP-1 putty group and 47.1% in the autograft group) were attributed to donor site complications ($P < 0.0001$).

Table 41: Incidence of Injury, Poisoning and Procedural Complications (Safety Population)

System Organ Class/Preferred Term	Number (%) of Patients		Number (%) of Events	
	OP-1 Putty (N=208)	Autograft (N=87)	OP-1 Putty	Autograft
Injury, Poisoning and Procedural Complications	70 (33.7)	41 (47.1)	93 (10.1)	51 (13.0)
Ankle Fracture	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Back Injury	3 (1.4)	1 (1.1)	3 (0.3)	1 (0.3)
Cerebrospinal Fluid Leakage	1 (0.5)	1 (1.1)	1 (0.1)	1 (0.3)
Cervical Vertebral Fracture	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Compression Fracture	2 (1.0)	1 (1.1)	2 (0.2)	1 (0.3)
Dermatitis Artefacta	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Donor Site Complication	0 (0)	8 (9.2)	0 (0)	8 (2.0)
Dural Tear	16 (7.7)	7 (8.0)	16 (1.7)	7 (1.8)
Excoriation	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Extradural Haematoma	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Failure of Implant	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Fall	12 (5.8)	8 (9.2)	12 (1.3)	9 (2.3)
Foot Fracture	3 (1.4)	0 (0)	3 (0.3)	0 (0)
Graft Complication	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Graft Dysfunction	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Hand Fracture	2 (1.0)	0 (0)	2 (0.2)	0 (0)
Iliotibial Band Syndrome	0 (0)	1 (1.1)	0 (0)	1 (0.3)
Incision Site Complication	0 (0)	1 (1.1)	0 (0)	1 (0.3)
Injury	2 (1.0)	1 (1.1)	2 (0.2)	1 (0.3)
Jaw Fracture	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Joint Dislocation	0 (0)	1 (1.1)	0 (0)	1 (0.3)
Limb Injury	0 (0)	1 (1.1)	0 (0)	1 (0.3)
Lower Limb Fracture	0 (0)	1 (1.1)	0 (0)	1 (0.3)
Lumbar Vertebral Fracture	3 (1.4)	0 (0)	4 (0.4)	0 (0)
Meniscus Lesion	4 (1.9)	1 (1.1)	4 (0.4)	1 (0.3)
Muscle Strain	0 (0)	1 (1.1)	0 (0)	1 (0.3)
Nerve Injury	0 (0)	1 (1.1)	0 (0)	1 (0.3)
Nerve Root Injury	0 (0)	1 (1.1)	0 (0)	1 (0.3)
Operative Haemorrhage	2 (1.0)	1 (1.1)	2 (0.2)	1 (0.3)
Patella Fracture	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Pelvic Fracture	0 (0)	1 (1.1)	0 (0)	1 (0.3)
Periorbital Haematoma	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Post Procedural Complication	3 (1.4)	0 (0)	3 (0.3)	0 (0)
Post Procedural Haemorrhage	1 (0.5)	0 (0)	1 (0.1)	0 (0)

(Continued on next page)

System Organ Class/Preferred Term	Number (%) of Patients		Number (%) of Events	
	OP-1 Putty (N=208)	Autograft (N=87)	OP-1 Putty	Autograft
<i>(Continued from previous page)</i>				
Post Procedural Nausea	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Post Procedural Vomiting	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Postoperative Heterotopic Calcification	3 (1.4)	0 (0)	3 (0.3)	0 (0)
Procedural Complication	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Procedural Site Reaction	0 (0)	1 (1.1)	0 (0)	1 (0.3)
Road Traffic Accident	3 (1.4)	1 (1.1)	3 (0.3)	1 (0.3)
Seroma	2 (1.0)	0 (0)	2 (0.2)	0 (0)
Skin Laceration	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Spinal Compression Fracture	4 (1.9)	1 (1.1)	4 (0.4)	1 (0.3)
Spinal Fracture	0 (0)	1 (1.1)	0 (0)	1 (0.3)
Stress Fracture	0 (0)	1 (1.1)	0 (0)	1 (0.3)
Tibia Fracture	0 (0)	1 (1.1)	0 (0)	1 (0.3)
Ulnar Nerve Injury	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Vertebral Injury	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Wound	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Wound Complication	0 (0)	1 (1.1)	0 (0)	1 (0.3)
Wound Dehiscence	3 (1.4)	1 (1.1)	3 (0.3)	1 (0.3)
Wound Secretion	3 (1.4)	3 (3.4)	3 (0.3)	4 (1.0)
Wrist Fracture	2 (1.0)	0 (0)	2 (0.2)	0 (0)

Source: Section 14.3, Table 6.2; Section 16.2.7-Listing 9.3;

Note: Number of patients refers to patients with at least one adverse event of the indicated type. Number of events refers to all events of the indicated type. Percentages are based on the total number of patients or the total number of adverse events, as appropriate. Patients experiencing multiple events under the same system organ class/preferred term are counted only once for that system organ class/preferred term.

Table 42 presents the SOC Respiratory, Thoracic and Mediastinal Disorders.

Although the 2 treatment groups were statistically identified as potentially different based on the conservative criteria SOC P=0.2 level (15.9% in the OP-1 Putty group and 6.9% in the autograft group) ($P=0.039$), no concerning pattern of clinical events emerged in the OP-1 Putty treatment group.

Table 42: Incidence of Respiratory, Thoracic and Mediastinal Disorders (Safety Population)

System Organ Class/Preferred Term	Number (%) of Patients		Number (%) of Events	
	OP-1 Putty (N=208)	Autograft (N=87)	OP-1 Putty	Autograft
Respiratory, Thoracic and Mediastinal Disorders	33 (15.9)	6 (6.9)	38 (4.1)	10 (2.6)
Asthma	0 (0)	1 (1.1)	0 (0)	1 (0.3)
Atelectasis	1 (0.5)	1 (1.1)	1 (0.1)	1 (0.3)
Bronchitis	4 (1.9)	1 (1.1)	4 (0.4)	1 (0.3)
Bronchitis Acute	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Chest Pain	2 (1.0)	0 (0)	2 (0.2)	0 (0)
Chronic Obstructive Pulmonary Disease	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Cough	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Diaphragmatic Disorder	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Dysphonia	0 (0)	1 (1.1)	0 (0)	1 (0.3)
Dyspnoea	3 (1.4)	0 (0)	3 (0.3)	0 (0)
Dyspnoea Exertional	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Epistaxis	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Hiccups	0 (0)	1 (1.1)	0 (0)	1 (0.3)
Hypoxia	5 (2.4)	3 (3.4)	5 (0.5)	3 (0.8)
Laryngeal Oedema	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Pharyngolaryngeal Pain	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Pleurisy	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Postnasal Drip	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Pulmonary Embolism	4 (1.9)	1 (1.1)	4 (0.4)	1 (0.3)
Pulmonary Fibrosis	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Pulmonary Oedema	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Respiratory Depression	0 (0)	1 (1.1)	0 (0)	1 (0.3)
Tachypnoea	1 (0.5)	0 (0)	1 (0.1)	0 (0)
Upper Respiratory Tract Infection	2 (1.0)	0 (0)	2 (0.2)	0 (0)
Wheezing	4 (1.9)	0 (0)	4 (0.4)	0 (0)

Source: Section 14.3, Table 6.2; Section 16.2.7-Listing 9.1;

Note: Number of patients refers to patients with at least one adverse event of the indicated type. Number of events refers to all events of the indicated type. Percentages are based on the total number of patients or the total number of adverse events, as appropriate. Patients experiencing multiple events under the same system organ class/preferred term are counted only once for that system organ class/preferred term.

12.2.2.2 Incidence of Peri-Operative Adverse Events

Statistical Tables 6.6 and 6.7 in Section 14 presents the incidence of treatment-emergent AEs over time. Approximately half of the patients in each treatment group experienced AEs post surgery and prior to discharge date: 48% of all OP-1 Putty patients and 54% of

all Autograft patients (48.3% of OP-1 Putty patients with AEs and 57.3% of Autograft patients with AEs respectively). The most common AEs during the hospitalization period in the OP-1 Putty group were Dural Tear, Urinary Retention, Nausea, Anemia and Pyrexia. The most common AEs prior to discharge in the Autograft group were Anemia, Dural Tear, Urinary Retention, and Confusional State.

12.2.2.3 Treatment Emergent Adverse Events by Causality

Table 43 presents treatment-emergent AEs by SOC and relationship to treatment. The proportion of patients who reported an AE considered as Suspected Related^c to treatment was similar for the treatment groups (26.0% for patients in the OP-1 Putty group, and 26.4% for patients in the autograft group).

The majority of AEs suspected to be related to treatment were in the Musculoskeletal and Connective Tissue Disorders SOC (18.8% in the OP-1 Putty group, and 13.8% in the autograft group). Pseudarthrosis suspected to be causally associated with treatment was reported in 19 patients in the OP-1 Putty group (9.1%), and 6 patients in the autograft group (6.9%). The significance of the difference in causality between groups is somewhat unclear given the open-label nature of the study.

^c AEs considered to have an Unknown relationship have been included with Suspected Related AEs.

Table 43: Treatment-Emergent Adverse Events by System Organ Class and Relationship to Study Treatment

System Organ Class/Preferred Term	Number (%) of Patients			
	OP-1 Putty (N=208)		Autograft (N=87)	
	Not Related	Suspected Related/Unknown	Not Related	Suspected Related/Unknown
Total	147 (70.7)	54 (26.0)	59 (67.8)	23 (26.4)
Blood And Lymphatic System Disorders	12 (5.8)	0 (0)	12 (13.8)	1 (1.1)
Cardiac Disorders	25 (12.0)	2 (1.0)	5 (5.7)	0 (0)
Ear And Labyrinth Disorders	4 (1.9)	0 (0)	1 (1.1)	0 (0)
Endocrine Disorders	2 (1.0)	0 (0)	0 (0)	0 (0)
Eye Disorders	7 (3.4)	0 (0)	3 (3.4)	0 (0)
Gastrointestinal Disorders	43 (20.7)	2 (1.0)	12 (13.8)	0 (0)
General Disorders And Administration Site Conditions	25 (12.0)	4 (1.9)	16 (18.4)	1 (1.1)
General System Disorders Nec	1 (0.5)	1 (0.5)	0 (0)	0 (0)
Hepatobiliary Disorders	0 (0)	1 (0.5)	1 (1.1)	0 (0)
Immune System Disorders	3 (1.4)	0 (0)	2 (2.3)	0 (0)
Infections And Infestations	49 (23.6)	0 (0)	13 (14.9)	0 (0)
Injury, Poisoning And Procedural Complications	66 (31.7)	4 (1.9)	33 (37.9)	8 (9.2)
Investigations	20 (9.6)	0 (0)	13 (14.9)	0 (0)
Metabolism And Nutrition Disorders	11 (5.3)	1 (0.5)	6 (6.9)	0 (0)
Musculoskeletal And Connective Tissue Disorders	117 (56.3)	39 (18.8)	48 (55.2)	12 (13.8)
Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps)	11 (5.3)	1 (0.5)	7 (8.0)	1 (1.1)
Nervous System Disorders	64 (30.8)	1 (0.5)	32 (36.8)	1 (1.1)
Psychiatric Disorders	17 (8.2)	0 (0)	7 (8.0)	0 (0)
Renal And Urinary Disorders	24 (11.5)	0 (0)	10 (11.5)	0 (0)
Reproductive System And Breast Disorders	2 (1.0)	0 (0)	2 (2.3)	0 (0)
Respiratory, Thoracic And Mediastinal Disorders	30 (14.4)	3 (1.4)	6 (6.9)	0 (0)
Asthma	0 (0)	0 (0)	1 (1.1)	0 (0)
Skin And Subcutaneous Tissue Disorders	13 (6.3)	3 (1.4)	4 (4.6)	0 (0)
Surgical And Medical Procedures	4 (1.9)	0 (0)	0 (0)	0 (0)
Vascular Disorders	23 (11.1)	2 (1.0)	11 (12.6)	1 (1.1)

Source: Section 14.3, Table 6.4

Note: Number of patients refers to patients with at least one adverse event of the indicated type. Percentages are based on the total number of patients in each treatment group. Patients experiencing multiple events under the same system organ class/preferred term are counted only once for that system organ class/preferred term under the closest relationship. If the patient is missing the relationship for an event, the patient is counted as suspected related events for the same system organ class/preferred term.

12.2.3 Listing of Adverse Events by Patient

A patient listing of AEs, regardless of whether they are treatment-emergent, is presented in Section 16.2, Listing 9.1.

12.3 DEATH, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

12.3.1 Deaths

A total of 11 patients died over the course of the study: 3.4% in the OP-1 Putty group, and 4.6% in the autograft group. A complete description of all deaths may be found in the SAE narratives Section 14.4. No patterns of concern emerged with respect to etiology of death, or the time to occurrence post surgery.

Table 44: Deaths

Treatment Group	Patient ID	Cause of Death	Days From Surgery	Relationship to Treatment
OP-1 Putty	1305	Bone and liver cancer secondary to renal cell carcinoma	1016 days*	Not related
	1326	Pulmonary embolism	18 days	Not related
	1706	Cerebral haemorrhage	200 days	Not related
	2506	Myocardial infarction	192 days	Not related
	4120	Small cell lung carcinoma	738 days	Not related
	4207	Cardiac failure	730 days	Not related
	5010	Multiple myeloma	241 days	Not related
Autograft	2519	Lung neoplasm malignant	757 days	Not related
	3010	Endometrial cancer metastatic	257 days	Not related
	4401	Small cell lung cancer	1020 days*	Not related
	5012	Refractory anemia with excess blasts	584 days	Not related

* Death occurred >24 months post-procedure.

12.3.2 Other Serious Adverse Events

Table 6.11 in Section 14 summarizes treatment-emergent SAEs which occurred by SOC and preferred term.

SAEs occurred with equal frequency in both treatment groups, and no trends were identified that would suggest an excess risk for patients exposed to OP-1 Putty. Half of the patients in both the OP-1 Putty and autograft treatment groups (50.0% and 49.4%

respectively) experienced at least 1 SAE over the course of the study. The most frequently reported SAEs were in the SOC Musculoskeletal and Connective Disorders (22.1% in the OP-1 Putty group, and 20.7% in the autograft group).

Lumbar spinal stenosis was reported only by patients who received OP-1 Putty (2.9%), and pain in extremity and osteoarthritis were reported by 4.3% and 3.8% of OP-1 Putty patients as opposed to 2.3% and 1.1% of those in the autograft treatment group.

In the Cardiac disorders SOC, 19 patients (9.1%) who received OP-1 Putty and 4 patients (4.6%) who received autograft reported SAEs. Atrial fibrillation, cardiac failure, congestive cardiac failure, coronary artery disease, myocardial ischaemia, and tachycardia were reported only by patients who received OP-1 Putty. Chest pain was reported in 4 OP-1 Putty patients (1.9%) and 3 autograft patients (3.4%). Myocardial infarction was reported by 5 (2.4%) OP-1 Putty patients and by 1 (1.1%) autograft patient.

In the Injury, poisoning and procedural complications SOC, 20 patients in the OP-1 Putty treatment group (9.6%) reported SAEs, and 6 patients (6.9%) in the Autograft treatment group reported SAEs.

There were 15 OP-1 Putty patients (7.2%) and 3 Autograft patients (3.4%) who reported SAEs in the Infections and infestations SOC.

SAEs reported in the Injury, poisoning and procedural complications SOC and the Infections and infestations SOC were equally distributed between the treatment groups, with no specific event having a clinically significant incidence in one treatment group or the other.

There were 6 autograft patients (6.9%) and 2 OP-1 Putty patients (1.0%) who reported SAEs in the Investigations SOC. Half of the patients in the autograft group (3.4%) reported decreased hematocrit. The higher percentage of autograft patients reporting events in this SOC is presumed to be related to the additional surgical procedure (i.e., autograft harvest) and is corroborated by findings of increase operative time and estimated blood loss in this treatment group (See Section 11.3.2.3).

Events reported in the remaining SOC categories were equally distributed between the OP-1 Putty and autograft treatment groups, with no specific event having a significant incidence in one treatment group or the other.

Statistical Table 6.9 in Section 14 presents treatment-emergent SAEs by severity. Statistical Tables 6.12 through 6.17 tabulate treatment-emergent serious and unanticipated AEs.

Table 45 presents treatment-related SAEs for individual patients. Across both treatment groups, 10.5% of patients reported 44 SAEs that were determined to be “suspected related” to study treatment, or were assessed as “relationship unknown” by the Principal

Investigator. For the purposes of this analysis, events assessed as “relationship unknown” were considered to be treatment-related. In the OP-1 Putty treatment group, 12.0% of patients experienced 38 treatment-related SAEs, and 6.9% of patients in the autograft treatment group experienced 6 treatment-related SAEs.

Of the 25 patients who had treatment-related SAEs in the OP-1 Putty treatment group, the majority of patients (72.0%) had treatment-related SAEs in the Musculoskeletal and connective tissue disorders SOC., Pain in extremity, and pseudarthrosis were reported in 4 and 9 patients, respectively. The other treatment-related SAEs in this SOC included back pain (3 patients), arthralgia (2 patients), and atlantoaxial instability, bursitis, buttock pain, intervertebral disc compression, intervertebral disc degeneration and Psoas sign (1 patient each event).

In the Respiratory, thoracic and mediastinal disorders SOC, of those patient having an SAE, 3 patients in the OP-1 Putty treatment group reported treatment-related hypoxia, pulmonary embolism, and pulmonary oedema, or tachypnoea. Hypoxia and tachypnoea were reported by the same patient (1305). There were 2 patients (8.0%) in the OP-1 Putty treatment group who had treatment-related SAEs in the General disorders and administration site conditions SOC (asthenia and pyrexia). In all other SOCs, the following treatment-related SAEs in the OP-1 Putty treatment group were also reported once by a single patient: cardiac failure congestive, cholangitis, hypokalemia, hypotension, impaired gastric emptying, lumbar vertebral fracture, pyrexia and tachycardia.

Of the 6 patients who had treatment-related SAEs in the autograft treatment group, half of the patients (50.0%) had treatment-related SAEs in the Musculoskeletal and connective tissue disorders SOC, in which pseudarthrosis was reported for all 3 patients. The following treatment-related SAEs were reported once by a single patient: anaemia, lung neoplasm malignant, and operative haemorrhage.

**Table 45: Treatment-Related Serious Adverse Events (Safety Population)
 Events with “Relationship Unknown” Indicated by an Asterisk (*)**

Patient ID	System Organ Class	Preferred Term*	Days from Surgery
OP-1 Putty			
1105	Musculoskeletal and connective tissue disorders	Pseudarthrosis*	714
1107	Musculoskeletal and connective tissue disorders	Pseudarthrosis*	1258
1305	Cardiac disorders	Tachycardia*	17
	Musculoskeletal and connective tissue disorders	Psoas sign*	2
	Respiratory, thoracic and mediastinal disorders	Hypoxia*	17
		Tachypnoea*	17
1310	Musculoskeletal and connective tissue disorders	Pseudarthrosis*	479
1311	Injury, poisoning and procedural complications	Lumbar vertebral fracture*	364
	Musculoskeletal and connective tissue disorders	Arthralgia*	280
		Buttock pain*	280
		Pain in extremity*	280
1326	Respiratory, thoracic and mediastinal disorders	Pulmonary embolism*	19
1509	Musculoskeletal and connective tissue disorders	Pseudarthrosis	396
2102	Musculoskeletal and connective tissue disorders	Pseudarthrosis	289
2303	Musculoskeletal and connective tissue disorders	Intervertebral disc compression*	1058
2321	Musculoskeletal and connective tissue disorders	Pseudarthrosis	276
2408	General disorders and administration site conditions	Asthenia*	79
2509	Musculoskeletal and connective tissue disorders	Pain in extremity	168
3005	Musculoskeletal and connective tissue disorders	Intervertebral disc degeneration	340
3008	Respiratory, thoracic and mediastinal disorders	Pulmonary oedema*	5
	Vascular disorders	Hypotension*	1

(Continued on next page)

Patient ID	System Organ Class	Preferred Term*	Days from Surgery
<i>(Continued from previous page)</i>			
4003	Musculoskeletal and connective tissue disorders	Arthralgia*	74
		Back pain*	74
4204	Musculoskeletal and connective tissue disorders	Pain in extremity	332
4205	General disorders and administration site conditions	Pyrexia*	1
	Metabolism and nutrition disorders	Hypokalaemia*	8
4209	Hepatobiliary disorders	Cholangitis*	325
4507	Cardiac disorders	Cardiac failure* congestive	521
4510	Musculoskeletal and connective tissue disorders	Back pain	72
		Pain in extremity	72
4702	Gastrointestinal disorders	Impaired gastric emptying*	112
4703	Musculoskeletal and connective tissue disorders	Pseudarthrosis	248
	Musculoskeletal and connective tissue disorders	Pseudarthrosis	596
4805	Musculoskeletal and connective tissue disorders	Atlantoaxial instability	672
		Back pain	279
		Pseudarthrosis	672
5003	Musculoskeletal and connective tissue disorders	Bursitis*	90
5004	Musculoskeletal and connective tissue disorders	Pseudarthrosis*	178
Autograft			
1116	Musculoskeletal and connective tissue disorders	Pseudarthrosis	210
1306	Musculoskeletal and connective tissue disorders	Pseudarthrosis	627
2301	Musculoskeletal and connective tissue disorders	Pseudarthrosis	624
2519	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lung neoplasm malignant	692
4303	Blood and lymphatic system disorders	Anaemia	3
5012	Injury, poisoning and procedural complications	Operative haemorrhage	1

* If an AE was assessed at any time point as being 'suspected related' or 'unknown', that assessment is represented here.

Source: Table 6.1.2 in Section 14.

12.3.3 Other Significant Adverse Events

12.3.3.1 Heterotopic Bone Formation

There were 17 patients who received OP-1 Putty that had radiographic evidence of heterotopic ossification at any time point during the study and 6 patients that had evidence of heterotopic ossification identified on the 9-month CT scan. (Section 16.2 Listing 6.2 and 6.4 respectively)

Three patients (1501, 4405, and 4702) who received OP-1 Putty experienced heterotopic bone formation that was recorded as an AE. Each of the patients who had heterotopic bone formation designated as an AE had radiographic evaluations indicating “exuberant bone growth” or “exuberant ossification” prior to reporting heterotopic bone formation as an adverse event.

- Patient 1501 received OP-1 Putty at level L3-4 on 21 March 2002. She reported excessive bone pain over the right posterior iliac region in September 2002. Heterotopic bone formation was reported as an AE on 11 December 2002, and again on 6 March 2004, and 24 March 2005. The patient was subsequently diagnosed with recurrent lumbar spinal stenosis at L4-5 which required hospitalization and a revision micro-decompression of L4-L5 on 01 Jan 2005 (1017 days post initial surgery). The event was considered resolved on 23 June 2005.
- Patient 4405 had discogenic bridging documented which was reported as an intervertebral disc disorder and required treatment with physical therapy.
- Patient 4702 patient received OP-1 Putty at level L4-L5 on 10 January 2003. On 28 October 2003 she was found to have heterotopic ossification extending from the right side of the fusion mass and the interval between the iliacus and psoas, extending into the pelvis.

The following patients had radiographic evidence of heterotopic ossification and subsequently developed spine-related adverse events which required surgical treatment:

- Patient 1123 received OP-1 Putty at level L4-L5 on 26 November 2002, and had evidence of heterotopic ossification on her 9-month CT scan. The patient developed lumbar spinal stenosis at L3-L5 which occurred in November 2004 (approximately 720 days post surgery). She had a L2-L5 decompressive lumbar laminectomy with supplemental fixation performed and the event resolved on 21 Jan 2005.
- Patient 1310 received OP-1 Putty at level L4-L5 on 04 November 2002. On 25 February 2004 (478 days post surgery) the patient developed pseudoarthrosis

which required hospitalization. The patient subsequently underwent a posterior lumbar interbody fusion on 28 Jan 2005 with bone morphogenic protein (not specified) and a supplemental fixation (not specified). The event was considered continuing at the end of the study.

There were 5 patients who received autograft that had radiographic evidence of heterotopic bone formation. Two patients (1116 and 2301) reported a spine-related SAE.

- Patient 1116 received autograft at L4-5 on 12 January 2003 and reported pseudarthrosis as an AE on 6 August 2003. On 08 March 2004 the patient underwent a posterior fusion L4-5, and posterior instrumentation L4-5 with supplemental fixation.
- Patient 2301 received an autograft at L4-5 on 04 December 2001. The patient developed pseudarthrosis on 19 August 2003 (623 days post surgery) which required hospitalization and resulted in persistent or significant disability or incapacity. The patient had a re-exploration decompression of L4-L5, a takedown of the nonunion lateral mass fusion, and a supplemental fixation which included pedicular fixation with an interbody fusion cage, and a structural bone graft in the right disc space. The event resolved on 16 September 2003.

12.3.3.2 Malignancies

As presented in Table 46, 20 patients across both treatment groups reported events in the SOC Neoplasms, Benign and Malignant (including cysts and polyps) over the course of this study: 12 in the OP-1 Putty group (5.8%), and 8 in the autograft group (9.2%). Eleven of these were considered to be SAEs: 6 in the OP-1 Putty group, and 5 in the autograft group. The malignancies reported as SAEs in the OP-1 Putty group include breast cancer, multiple myeloma, small cell lung cancer stage unspecified, thyroid gland cancer (1 each), and renal cell carcinoma stage unspecified (2). In the autograft group, one occurrence each of cerebral haemangioma, endometrial cancer metastatic, lung neoplasm malignant, refractory anaemia with an excess of blasts, and small cell lung cancer stage unspecified were reported as an SAE. Full narratives of the neoplasms, benign and malignant (including cysts and polyps) reported as serious may be found in Section 14.4.

None of the reported malignancies were determined to have a causal relationship to either OP-1 Putty or autograft. Renal cyst was reported by Patient 1129 who received OP-1 Putty, and Lung neoplasm malignant in Patient 2513 who received Autograft, were assessed as “Unknown.” The causality of these events was, therefore, considered “Suspected Related” to Autograft. There were no patterns or specific events of concern

identified with respect to type of cancer, time to onset post surgery, or distribution between treatment groups.

Table 46: Patients with Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps) System Organ Class

Treatment Group	Patient ID	Event	Relationship	Severity	Approximate Days to Onset
OP-1 Putty	4006	Benign Neoplasm	Not Related	Mild	330
	4707	Breast Cancer	Not Related	Moderate	706
	2303	Lipoma	Not Related	Mild	1111
	5010	Multiple Myeloma	Not Related	Severe	241
	1602	Neuroma	Not Related	Moderate	238
	1215	Renal Cell Carcinoma	Not Related	Moderate	196
	1305	Renal Cell Carcinoma	Not Related	Severe	286
	1129	Renal Cyst	Suspected Related/Unknown	Moderate	1060
	1310	Renal Cyst	Not Related	Mild	813
	1610	Renal Cyst	Not Related	Moderate	136
	4120	Small Cell Lung Cancer	Not Related	Severe	728
1320	Thyroid Cancer	Not Related	Severe	559	
Autograft	1304	Benign Neoplasm	Not Related	Mild	91
	3013	Cerebral Haemangioma	Not Related	Severe	706
	3010	Endometrial Cancer Metastatic	Not Related	Severe	238
	1508	Lung Neoplasm	Not Related	Mild	576
	2519	Lung Neoplasm Malignant	Suspected Related/Unknown	Severe	691
	5012	Refractory Anaemia with Excess of Blasts	Not Related	Severe	314
	1203	Renal Cyst	Not Related	Mild	325
	4401	Small Cell Lung Cancer	Not related	Severe	1020

12.4 SECONDARY PROCEDURES

Table 7 in Section 14 presents secondary procedures by visit for each of the treatment groups. Secondary procedures include revisions, removals, supplemental fixations and all reoperations, regardless if the reoperation was intended to promote fusion. Table 16 in Section 11.3.1.2.3 presented the absence of retreatments as criterion of Overall Success.

Only those patients who had a reoperation intended to promote fusion were counted as a retreatment failure.

A total of 22 patients in the OP-1 Putty group (10.6%), and 9 patients in the autograft group (10.3%) had a secondary procedure within the 36 months post-initial procedure. An additional OP-1 Putty patient [1107] had a supplemental fixation 41 months post treatment, and is included in Listing 9.3 only.^d

Of the 22 OP-1 Putty patients reported in Table 7 in Section 14, 18 patients had secondary procedures within the 24 month window. For 15 patients, the procedures were intended to promote fusion at the treated level.^e One patient in this group (4703) had 2 secondary procedures in consecutive visit windows with both procedures indicated in Table 7: a supplemental fixation at 12 months and a reoperation intended to promote fusion at 24 months. The remaining 3 patients (1220, 2408, 4805) had reoperations for reasons other than to promote fusion at the treated level.

An additional 4 OP-1 Putty patients had secondary procedures beyond the end of the 24 month window. Three of these patients (1105, 1310, 5011) had secondary procedures to promote fusion at the treated level, while an additional patient (2303) had a reoperation not intended to treat an absence of fusion.

Of the 9 Autograft patients with secondary procedures, 8 (9.2%) had secondary procedures to promote fusion at the treated level, while the remaining patient had a reoperation in the 6 week follow-up period for a reason other than an absence of fusion. All 8 secondary procedures intended to promote fusion at the treated level occurred within the 24 month follow-up period.^f

12.5 CLINICAL LABORATORY EVALUATION

12.5.1 Listing of Individual Laboratory Measurements by Patient

By-patient listings of all biochemistry and hematology assessments are presented in Appendix 16.2.8, Listing 17 and 18.

^d Patient 4501 (Autograft) is included in Listing 9.3 only as this patient is excluded from the mITT population.

^e Patient 4410 (OP-1 Putty) experienced a dural tear during the initial surgery. This adverse event was incorrectly reported on the CRF as a supplemental fixation. This resulted in the patient having been improperly assessed as a study failure due to retreatment.

^f Patient 3110 (Autograft) had a supplemental fixation within the 24 month study window and was improperly categorized as a study success.

12.5.2 Evaluation of Each Laboratory Parameter

Several statistically significant differences between treatment groups were noted for laboratory parameters, but none were clinically meaningful.

12.5.2.1 Laboratory Values over Time

Descriptive statistics summarizing the baseline, last evaluation, and change from baseline to last evaluation hematology and biochemistry laboratory data are presented in Section 14.3, Table 8.1 and Table 8.3. Statistically significant changes from Baseline values in both treatment groups were also noted for several laboratory parameters, but were not deemed to be clinically relevant. The majority of statistically significant shifts from baseline occurred in the immediate post-operative period and were expected given general anesthesia administration and the surgical procedure.

12.5.2.2 Individual Patient Changes

Frequencies and percentages of patients having changes over time in laboratory parameters, relative to normal values are tabulated in Section 14.3-Table 8.2 and Table 8.4. No trends reflecting abnormalities of hematologic, hepatic, renal, or other metabolic functions were noted.

12.5.2.3 Individual Clinically Significant Abnormalities

Not applicable.

12.6 IMMUNOGENICITY

12.6.1 Test Methods

Immunogenicity evaluation was carried out using patient serum samples collected pre-operatively (baseline), post-operatively, and at the 6 week, 3, 6, 12 and 24 month follow-up visits, as described in the study protocol.

Enzyme-linked immunosorbent assays (ELISA) were performed to detect the presence of anti-OP-1 antibodies in all samples. ELISA methods were validated to detect human anti-human OP-1 antibodies with IgG, IgM, and IgE isotypes. The ELISA cut point for this study was statistically based and reflects a false positive rate of 5 %, as recommended in Mire-Sluis, et al., 2004.²⁴

Positive samples in the screening ELISA were evaluated in a titer ELISA to quantitate the level of anti-OP-1 antibodies in the sample. The results of this assay are reported as a log titer which corresponds to the lowest dilution of the sample that yields a positive result.

The measurable log titer range in this assay extends from 1.90 to 6.11. Titers below and above this range were given the arbitrary numbers of 111 and 999, respectively. Complete results of the evaluation of anti-OP-1 levels in serum samples as determined by ELISA are provided in an attached technical report (TR-1081, Section 16.5.1).

Samples found to be positive in the titer ELISA were further analyzed to determine whether antibodies to OP-1 had the ability to neutralize its activity in vitro. Initially, ELISA positive samples were tested in an alkaline phosphatase-based neutralizing antibody assay using a rat osteosarcoma cell line (ROS 17/2.8). In this assay, anti-OP-1 neutralizing antibodies are detected based on their ability to reduce the OP-1-induced alkaline phosphatase activity measured 48 hours post treatment. The cut point for this Nab assay was determined statistically, based on the variability of the response of pre-operative (N=245) serum samples from this study. As described above for the ELISA, this Nab assay cut point was set to reflect a 5% false positive rate.

The presence of neutralizing anti-OP-1 antibodies could not be assessed using the alkaline phosphatase Nab assay in 8 samples from this study. These 8 samples had baseline alkaline phosphatase values that fell well below the normal range such that OP-1 induced levels were not deemed reliable. As a result these samples were referred to as “compromised”. In order to more reliably determine neutralizing activity, these samples were later tested in a polymerase chain reaction (PCR)-based secondary neutralizing antibody assay that was developed recently. In this assay, neutralizing anti-OP-1 antibodies are detected based on their ability to reduce OP-1 induced ID-1 gene expression in the human cell line, A549. ID-1 gene expression was detected by PCR, and was normalized to that of the house keeping gene, GAPDH. Thus, the reported neutralizing antibody status for the 8 compromised samples reflects the results obtained in the secondary assay. Neutralizing antibody data for serum samples with positive antibody titers are presented in a detailed technical report (TR 1084, Section 16.5.2).

The following is a brief summary of the immunogenicity results for this study. A complete description of results may be found in TR 1081 in Section 16.5.1.

12.6.2 Immunological Status

Using the screening ELISA test for anti-OP-1 antibodies, 93.2% of patients on OP-1 Putty were antibody positive at any time point versus 20.9% of patients who received autograft (Table 47). In the OP-1 Putty group 25.6% of patients had evidence of neutralizing antibodies versus 1.2% of autograft patients. The peak presence of neutralizing antibodies was observed at 6 weeks and 3 months and declined thereafter. By 24 months, none of the patients had neutralizing antibodies present.

Individual profiles of patients who had neutralizing antibodies at any time point are presented in Section 14.1 in Statistical Table 15.3. No significant patterns emerge from these profiles except that the peak presence of antibody titers was observed between 6 weeks and 3 months and declined thereafter.

Table 47. Patients with Positive Screening Test and Anti-OP-1 Neutralizing Antibody at Any Visit (Safety Population)

Parameter	Any Visit	Pre-Operative	Operative (1)	6 Weeks	3 Months	6 Months	12 Months	24 Months
OP-1 Putty								
Total Number of Patients	207	185	134	180	184	185	181	173
Number (%) of ELISA Positive	194 (93.7)	5 (8.1)	8 (6.0)	164 (91.1)	176 (95.7)	159 (85.9)	133 (73.5)	71 (41.0)
Number (%) of Neutralizing	53 (25.6)	1 (0.5)	1 (0.7)	31 (17.2)	36 (19.6)	13 (7.0)	2 (1.1)	0 (0.0)
Autograft								
Total Number of Patients	86	75	62	70	73	72	68	56
Number (%) of ELISA Positive	18 (20.9)	10 (13.3)	3 (4.8)	9 (12.9)	7 (9.6)	7 (9.7)	6 (8.8)	4 (7.1)
Number (%) of Neutralizing	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)

Note: Neutralizing is Anti-OP-1 positive.

(1) Operative includes hospitalization (surgical procedure) and within 72 hours of postoperative.

12.6.3 Potentially Immunologically-Related Adverse Events by Neutralizing Antibody Status

Table 48 presents the incidence of potentially immunologically-related treatment emergent AEs in the OP-1 Putty group. Treatment-emergent potentially immunologically-related AEs were defined as the following:^g

^g On March 30, 2006, the Sponsor's Medical Officer, Dr. Silverman, reviewed the list of preferred terms coded in MedDRA for the study and reviewed the SAP pre-classified terms to confirm which preferred terms should be utilized in the statistical analyses.

Adverse drug reaction	Haemoglobin decreased
Anaemia	Hyperkalaemia Infection
Angiopathy	Leukocytosis
Arthralgia	Procedural site reaction
Arthritis	Pyrexia
Arthropathy	Rach maculo-papular
Blood potassium abnormal	Renal failure
Blood potassium decreased	Systemic lupus erthematosus
Blood potassium increased	Thrombocythaemia
Drug eruption	Thrombocytopenia
Drug hypersensitivity	White blood cell count increased or decreased
Haematocrit decreased	Wound complication, dehiscence, drainage, or secretion
Haematuria	

There was no evidence of an increase in these AEs at any time point in the neutralizing positive patients versus the neutralizing negative patients.

Section 14.1 Statistical Tables 15.5 and 15.6 present the incidence of AEs and SAEs in the neutralizing antibody positive versus negative OP-1 Putty patients. There does not appear to be any increase in the incidence of AEs or SAEs at any time point in the neutralizing antibody positive patients versus the neutralizing negative patients.

Table 49 presents the incidence of potentially immunologically-related treatment emergent SAEs in the neutralizing antibody positive versus negative OP-1 Putty patients. Again, there does not appear to be an increase in these potentially immunologically-related SAEs at any time point in the neutralizing antibody positive patients versus the neutralizing negative patients.

Table 48: Potentially Immunologically-Related Treatment-Emergent Adverse Events by Neutralizing Antibody Status and Visit

Treatment	Neutralizing Status	Number (%) of Patients								
		Total No. with Neutralizing Antibodies	Total No. with AEs	Operative (Surgical Discharge Date)	6 Weeks (Discharge Date - 66 Days)	3 Months (67 - 136 Days)	6 Months (137- 273 Days)	12 Months (274 - 547 Days)	24 Months (548 - 913 Days)	36 Months (>913 Days)
OP-1 Putty	Positive	53 (100.0)	19 (35.8)	4 (7.5)	7 (13.2)	3 (5.7)	3 (5.7)	4 (7.5)	2 (3.8)	0 (0.0)
	Negative	154 (100.0)	61 (39.6)	14 (9.1)	16 (10.4)	11 (7.1)	15 (9.7)	9 (5.8)	11 (7.1)	0 (0.0)
Autograft	Positive	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Negative	85 (100.0)	44 (51.8)	25 (29.4)	10 (11.8)	1 (1.2)	4 (4.7)	12 (14.1)	6 (7.1)	1 (1.2)

Source: Section 14 Table 15.7

Note: Patients experiencing multiple events per time interval are counted only once.

Table 49: Potentially Immunologically-Related Treatment-Emergent Serious Adverse Events by Neutralizing Antibody Status and Visit

Treatment	Neutralizing Status	Number (%) of Patients								
		Total No. with Neutralizing Antibodies	Total No. with SAEs	Operative (Surgical - Discharge Date)	6 Weeks (Discharge Date-66 Days)	3 Months (67 - 136 Days)	6 Months (137- 273 Days)	12 Months (274-547 Days)	24 Months (548-913 Days)	36 Months (>913 Days)
OP-1 Putty	Positive	53 (100.0)	6 (11.3)	2 (3.8)	0 (0.0)	3 (5.7)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)
	Negative	154 (100.0)	19 (12.3)	5 (3.2)	6 (3.9)	1 (0.6)	6 (3.9)	1 (0.6)	2 (1.3)	0 (0.0)
Autograft	Positive	1 (100.0)	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Negative	85 (100.0)	17 (20.0)	11 (12.9)	1 (1.2)	0 (0.0)	2 (2.4)	2 (2.4)	1 (1.2)	0 (0.0)

Source: Section 14 Table 15.8

Note: Patients experiencing multiple events per time interval are counted only once

12.6.4 Success Outcomes at 24 Months by Neutralizing Antibodies

Table 50 presents potential associations between neutralizing antibody status and clinical outcome measures specified by the SAP. While none of these associations were statistically significant, overall patient success rates and overall radiographic success rates in the neutralizing antibody positive patients were slightly lower than in the neutralizing negative patients. Within the radiographic success criteria, this was mainly driven by the decrease in presence of bone by plain X-ray in patients with neutralizing antibodies compared to patients without neutralizing antibodies. As seen in Table 51 in a *post hoc* analysis, this association appears to diminish if one examines the relationship between presence of bone by CT, a potentially more sensitive marker of bone presence, and neutralizing antibody status. ODI success, success based on absence of retreatment rates, absence of serious AEs, and overall neurological success were comparable between those with neutralizing antibodies and those without.

Table 50: Success Outcome at 24 Months by Neutralizing Antibodies (Safety Population, OP-1 Putty Only)

Success Criteria	Neutralizing n/N (%)	Not Neutralizing n/N (%)	P Value ¹
Overall Patient Success	14/47 (29.8)	55/135 (40.7)	0.223
Overall Radiographic Success	17/41 (41.5)	70/125 (56.0)	0.149
ODI Success	35/45 (77.8)	109/134 (81.3)	0.665
Success Based on Absence of Retreatment	46/49 (93.9)	133/144 (92.4)	1.000
Absence of Serious Adverse Event	41/49 (83.7)	131/144 (91.0)	0.185
Overall Neurological Success	49/49 (100.0)	140/140 (100.0)	---

Neutralizing is Anti-OP-1 positive at any time point.

P Value is based on Fisher's exact test.

Source: Table 15.4.2 Section 14.

Table 51: Post Hoc Analysis: Radiological Success Components Based on Neutralizing Antibody Status (Safety Population, OP-1 Putty Only)

Success Criteria	Neutralizing Antibody Status		P
	Positive	Negative	
Success based on translation movement	92.7%	95.1%	0.693
Success based angulation	75.6%	80.2%	0.515
Success based on presence of bone by plain film at 24 months	45.2%	60.9%	0.105
Success based on presence of bone by CT at 9 months	73.2%	81.5%	0.271

12.7 SAFETY CONCLUSIONS

As summarized in Table 52, the 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 AEs
- Severe AEs
- Treatment-related AEs
- SAEs
- Unanticipated AEs
- Neoplasm
- Death

Table 52: Treatment-Emergent Adverse Events (Safety Population)

Parameter	OP-1 Putty (N=208)		Autograft (N=87)	
	Number (%) of Patients with Events	95% CI	Number (%) of Patients with Events	95% CI
Any AE	201 (96.6)	(93.2, 98.6)	82 (94.3)	(87.1, 98.1)
Severe AE	43 (20.7)	(15.4, 26.8)	17 (19.5)	(11.8, 29.4)
Treatment-related AE	54 (26.0)	(20.1, 32.5)	23 (26.4)	(17.6, 37.0)
Unanticipated AE	6 (2.9)	(1.1, 6.2)	0 (0.0)	(0.0, 4.2)
Serious AE	104 (50.0)	(43.0, 57.0)	43 (49.4)	(38.5, 60.4)
Serious and Unanticipated AE	5 (2.4)	(0.8, 5.5)	0 (0.0)	(0.0, 4.2)
Treatment-related Serious AE	25 (12.0)	(7.9, 17.2)	6 (6.9)	(2.6, 14.4)
Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyyps)	12 (5.8)	(3.0, 9.9)	8 (9.2)	(4.1, 17.3)
Death	7 (3.4)	(1.4, 6.8)	4 (4.6)	(1.3, 11.4)

- No clinically significant changes in clinical laboratory parameters have been associated with OP-1 Putty treatment.
- There does not appear to be any association of neutralizing antibodies and the development of potentially immunologically-related AEs or SAEs of any kind.
- The presence of neutralizing antibodies is not statistically correlated with clinical success outcomes.

- The risk of post-operative AEs related to the lumbar spine is clinically comparable for OP-1 Putty and autograft treatments.
- There was a higher reported rate of AEs in the Cardiac and Infections and Infestations SOCs in the OP-1 Putty treated groups. In the autograft group there was a higher reported rate of AEs in Blood and Lymphatic system Disorders and Injury, Poisoning and Procedural Complications SOCs.
- Future clinical use of OP-1 Putty should carefully assess patients for infection risks pre-operatively and for cardiac and infectious events post-operatively.
- Although respiratory and gastrointestinal SOC categories were identified (statistical significance at $P=0.2$) as having a higher rate of AEs in the OP-1 Putty group compared to autograft, there were no clinically relevant patterns of AEs that emerged in these areas.
- OP-1 Putty treatment is generally safe and well-tolerated in the PLF population.
- Although respiratory and gastrointestinal SOC categories were identified (statistical significance at $P=0.2$) as having a higher rate of AEs in the OP-1 Putty group compared to autograft, there were no clinically relevant patterns of AEs that emerged in these areas.
- OP-1 Putty treatment is generally safe and well-tolerated in the PLF population.

13. DISCUSSION AND OVERALL CONCLUSIONS

Results of this pivotal study demonstrate that OP-1 Putty is safe and effective when used in patients with single level degenerative lumbar spondylolisthesis with spinal stenosis who are undergoing decompression and spinal fusion.

In recent years, there has been focus on BMPs as bone graft material. OP-1 is one such BMP (BMP-7). Implants containing OP-1 and collagen matrix have been shown to be osteoinductive and osteoconductive, to speed the rate of bone healing, and to improve the performance of autograft in animals. Implants containing OP-1 and collagen matrix have also been shown to promote stable spinal fusions in animal models. Safety and efficacy of other BMPs in spinal applications have also been reported in animal models.

The trial reported herein represents an effort to translate these promising animal data into human therapeutic benefit. This clinical trial was designed specifically to test the pharmacologic activity of OP-1 – namely, osteoinduction – in humans undergoing PLF with an intent to create lumbar spinal fusion.

Of the primary efficacy endpoints prospectively defined and captured in this pivotal trial, 4 can be considered as clinical outcomes, i.e., outcomes which represent direct clinical benefit as perceived by the patient and his/her family. The ODI is a well-accepted, validated patient-reported scale for assessing pain and function during activities of daily living, commonly utilized in lumbar spinal surgery trials and publications. Retreatments intended to promote fusion represent not only a failure of the device, but, from the patient's standpoint, entail considerable anxiety, morbidity, risk, expense, and time loss; in an important way, avoidance of this outcome can be considered the ultimate test of product success. Serious device-related adverse events are, by definition, events of major clinical import, making avoidance of such events critical for a successful outcome. Finally, in the context of spinal surgery, preservation or improvement of neurological function indicates that the device does not predispose to clinically devastating adverse effects on spinal cord and radicular function.

In this trial, the 24 month success rates with respect to these 4 clinical outcome measures can be summarized in Table 53.

Table 53: Post Hoc Table: Clinical Success

Outcome	OP-1 Putty	Autograft	P Value Non-inferiority ¹
ODI Success	80.4%	85.5%	0.178
Absence of Retreatment	92.3%	88.6%	0.001
Absence of Serious Treatment-related AEs	88.7%	91.4%	0.038
Neurological Success	100%	93.9%	<0.001
Overall Success	71.2%	69.0%	0.029

Source: Statistical Tables 5.2.2, 5.3.2, 5.4.2, 5.5.2, B3.2.1 in Section 14.

¹ P Value is based on one-sided two-sample t-test for non-inferiority with an equivalence limit of 0.10.

Thus, for all patient-perceived and -reported efficacy outcomes, OP-1 Putty treatment was highly successful and was clinically similar to autograft treatment. OP-1 Putty was statistically non-inferior to autograft with regard to overall clinical success, a composite parameter consisting of ODI success, absence of retreatment, absence of serious treatment-related AEs, and neurological success (71.2% in the OP-1 Putty group, and 69.0% in the autograft group, $P=0.029$).

In other words, from the perspective of the patient undergoing PLF surgery under the conditions of the trial, OP-1 Putty was highly efficacious and comparable in every way to autograft. Furthermore, although not captured explicitly in any of the trial assessment instruments, these clinical outcomes are highly relevant to the treating surgeon, whose view of success is based almost exclusively on patient-reported pain, patient-reported function, and the absence of the need for repeat operation.

Several additional clinical benefits are evident in the OP-1 Putty-treated patients, corroborating the findings summarized above:

- OP-1 Putty treated patients do not suffer the pain associated with autograft harvest; in this trial, 16.3% of patients in the autograft group reported moderate or severe graft site pain at 24 months.
- OP-1 Putty treated patients do not suffer the morbidity associated with autograft harvest; in this trial, autograft patients experienced (for reasons that are likely due to the second surgical procedure) longer operative times, greater estimated intra-operative blood loss, anemia, and donor-site related adverse events.
- OP-1 Putty group patients had improvements in SF-36 measures that were equivalent to those seen in the autograft group.
- Analysis of translational motion and angulation data show that, even in patients with significant preoperative instability, OP-1 Putty treatment is capable of inducing spinal stabilization comparable to that achieved by autograft treatment.

- In the subset of patients followed to 36 months, the 24 month success outcomes persisted consistently across clinical outcomes.

As important as clinical results are, radiographic assessments are indispensable for determining the anatomical effects of lumbar spinal interventions and assessing the progression of degenerative or destabilizing pathologies. In this OP-1 Putty trial, extensive radiographic evaluation was performed, with 2 complementary objectives. Static imaging – plain films in neutral anteroposterior and lateral views, and CT scans – demonstrate anatomy, presence of bone, and presence of “bridging” bone (which joins the transverse processes at 2 adjacent spinal levels). On the other hand, dynamic imaging – paired flexion/extension films in lateral view – is designed to determine the functional status of the lumbar spine, particularly with respect to spinal stability or instability as measured by angular and translational motion between 2 segments on the 2 sequential views.

Dynamic imaging is regarded by orthopedists, spine surgeons, and musculoskeletal radiologists as being a critical indicator of the functional success of lumbar fusion surgery, having been employed as an important outcome variable in a variety of published trials that studied a heterogeneous spectrum of fusion approaches, surgical techniques, and fixation devices^{25,26,27,28}; and biological growth factors, including BMPs^{29,30,31}. Of particular note is the fact that dynamic imaging has been reported to be highly sensitive technique for establishing successful stabilization in patients with interbody cages²⁸, a situation in which—just as in the current trial—no posterior instrumentation is implanted for fixation.

The results of dynamic imaging in this trial are very favorable for the OP-1 Putty group, showing 93.6% success in translational motion (versus 96.3% in the autograft group), and 76.6% in angulation (versus 79.3% in the autograft group). These data indicate that OP-1 Putty treatment is capable, through its osteoinductive activity, of producing successful functional lumbar spinal stabilization in this patient population at a rate that is comparable that of the standard of care, iliac crest bone autograft. Post-operative spinal stability is essential for long-term functional and symptomatic success.³² Furthermore, since some authors have found correlations between radiographic stability and clinical outcomes^{33,34,35}, these 24 month OP-1 Putty data corroborate the clinical success data presented above, painting a consistent and coherent picture of therapeutic benefit.

In addition to the dynamic radiographic outcomes, this clinical trial also captured static outcomes, i.e., presence of bone on plain radiographs (anteroposterior and lateral views) or on CT scans. These films were evaluated specifically for the post-operative appearance of bone in and around the operative field, as an indicator of osteoinductive activity of the test material.

The data reviewed and discussed thus far have all pointed strongly towards a clinical benefit of OP-1 Putty in PLF: the clinical outcome associated with improved symptoms and function, the ODI, shows comparability to autograft; other clinically important endpoints, relating to adverse device or neurological events and to reoperations, also compare very favorably; and the benchmark radiographic indicator of post-operative spinal stability, dynamic imaging, indicates functional success. Therefore, it may be anticipated that the static radiographic endpoint of bone formation would also document OP-1 Putty success.

In fact, the radiographic results at 24 months in this Pivotal trial did demonstrate that OP-1 Putty treatment was successful in achieving the protocol-specified definition of “success” – i.e., presence of bone on plain films – in a clear majority of patients, 61.7%. However, statistical comparability between the OP-1 Putty and autograft groups could not be demonstrated. In light of the observations of clinical benefit noted above, and the radiographic evidence of lumbar spinal stabilization (both of which pointed towards successful fusion outcomes mediated by new bone growth), this outcome on plain film radiographic success seems anomalous and in need of explanation. The importance of understanding this anomaly is underscored by studies which call into question the accuracy of plain radiography in the assessment of lumbar fusion status in PLF. Blumenthal and Gill state that by radiography, “in one in five cases the degree of fusion was underestimated.”³⁶ Moreover, Kant et al document a 10.3% rate of radiographic false negatives and conclude that “using plain radiographs alone to determine the solidity of spinal fusion can be misleading.”³⁷

A variety of potential explanations exist for this discrepancy, focusing on specific aspects of this trial which might diminish the sensitivity of plain films in diagnosing new bone; 2 of these have experimental and/or empirical support:

- OP-1 may exert its osteoinductive effect through the production of intramembranous, rather than endochondral, ossification, a finding which has been reported in animals.³⁸ Intramembranous bone may be more closely apposed to existing bone and less densely trabecularized as compared to endochondral bone, making radiographic distinction more difficult in man. It should be noted that in the Cunningham study that, despite the process of intramembranous bone formation, OP-1 Putty-treated spines showed increased fusion rates and lower range of post-operative motion relative to autograft-treated spines.
- The anatomic placement of OP-1 Putty may obscure ready visualization by plain radiographs. Many of the Sponsor’s surgeon consultants have pointed out that the placement of OP-1 Putty in the operative field may, for technical reasons of product consistency and its conformation to anatomic tissue planes, be more medial than is customary for autograft. Such a medial location could place OP-1

Putty and, by extension, newly induced bone, adjacent or posterior to the facet joints where it would be obscured by normal bony structures on either anteroposterior or lateral X-rays. In fact, Santos et al have pointed out that plain films are insufficiently sensitive because they are limited to 2 dimensions, whereas post-PLF bone growth and stabilization are 3-dimensional phenomena.²⁸

To test the possibility that, for these reasons, plain radiography was insensitive to OP-1-mediated osteoinduction, other existing radiographic data were reviewed to see if more could be learned about characteristics of imaging in these trials. Specifically, CT scans of the spine had been obtained at 9 months, to further understand the process of osteoinduction following PLF. CT scans were felt by the Sponsor's consultants to offer a complementary and potentially quite meaningful way of evaluating new bone formation because of their superior ability to image, in the sagittal plane, juxta-facet bone.

In fact, such a review revealed that CT scans are much more sensitive than plain films in identifying OP-1 Putty-related osteogenesis in PLF, as these views demonstrated presence of bone in 84.9% of patients in the OP-1 Putty treatment group. In an informal review with the consulting radiologists who read all films from both the Pilot and the Pivotal studies, several cases were identified in which new bone not visualized on plain radiographs was seen by CT scan posterior to facet joints. Thus, it is the view of the Sponsor and its consultants that in this clinical setting, CT scans provide a more sensitive tool for identified new bone induced by OP-1 Putty, and that this new bone is sufficient to contribute to the clinical and functional radiographic outcomes observed in the Pivotal trial.

This trial was designed specifically to isolate and test the primary pharmacologic activity of OP-1, i.e., osteoinduction, in humans undergoing PLF with an intent to create lumbar spinal fusion. To accomplish this, no other "facilitators" of spinal fusion were used in this study. The focus of this trial was OP-1 Putty treatment alone, unaugmented by fixation hardware (e.g., rods, screws, or cages), or by osteoconductive materials (e.g., tricalcium phosphate or allograft bone), or by additional osteoinductive stimuli (specifically, autologous bone). Thus, the environment created in these clinical trials was the most challenging possible in which OP-1 could be asked to exert its osteogenic effects. As the results described above indicate, despite this considerable challenge, OP-1 Putty treatment was highly effective, showing:

- Pharmacologic success as judged by osteoinduction;
- Clinical success as shown by improvements in ODI and success in other clinical outcome measures;
- Radiographic success, as shown by success on both dynamic and static outcomes; and

- Durability of success, demonstrated through follow-up periods as long as 3 years.

Finally, the safety profile of OP-1 Putty is generally comparable to that of autograft treatment with respect to all of the following parameters:

- The proportion of patients experiencing treatment-emergent AEs, severe AEs, treatment-related AEs, SAEs, treatment-related SAEs, neoplasms, or death;
- The occurrence of clinically important laboratory abnormalities;
- The occurrence of local adverse events involving the lumbar spine;
- The occurrence of immunologically-related adverse or other clinical events, despite the occurrence of neutralizing anti-OP-1 antibodies in 25.6% of treated patients.

Given its favorable profile with respect to clinically relevant efficacy and safety outcomes, OP-1 Putty offers an attractive alternative to the use of autograft in patients undergoing lumbar posterolateral spinal fusion.

Absence of retreatment is a clinically meaningful endpoint. Retreatments intended to promote fusion represent not only a failure of the device, but, from the patient's standpoint entail considerable anxiety, morbidity, risk, expense, and time loss.

This study demonstrated the following results at 24 months:

- Overall Success: OP-1 Putty treatment was not demonstrated to be non-inferior to autograft ($P=0.331$). The estimated success rates were 38.7% for OP-1 Putty and 49.4% for autograft.
- ODI success: the treatment groups were similar (80.4% for OP-1 Putty, and 85.5% for autograft). While statistical testing of non-inferiority did not show that OP-1 Putty was non-inferior to autograft with respect to ODI ($P=0.178$), neither did statistical testing of superiority indicate that autograft was superior to OP-1 Putty ($P=0.376$).
- Absence of retreatment: OP-1 Putty was statistically non-inferior to autograft at 24 months (92.3% for OP-1 Putty and 88.6% for autograft, $P=0.001$).
- Absence of serious treatment-related AEs: OP-1 Putty was statistically non-inferior to autograft (88.7% for OP-1 Putty and 91.4% for autograft, $P=0.038$).
- Neurological success: OP-1 Putty was statistically non-inferior to autograft (100% for OP-1 Putty, and 93.9% for autograft, $P<0.001$).
- Radiographic success: OP-1 Putty patients had a statistically significantly lower rate of overall radiographic success than autograft patients (52.4% for OP-1 Putty and 74.6% for autograft, $P=0.003$). *Post hoc* analyses revealed:

- Presence of bone on plain film: presence of bone on plain film was statistically significantly lower in the OP-1 Putty patients compared to autograft (61.7% for OP-1 Putty and 83.1% for autograft, $P < 0.001$).
- Translational movement success: OP-1 Putty was non-inferior to autograft (93.6% for OP-1 Putty and 96.3% for autograft, $P = 0.004$).
- Angulation success: OP-1 Putty was similar to autograft (76.6% for OP-1 Putty and 79.3% for autograft). While statistical testing of non-inferiority did not show that OP-1 Putty was non-inferior to autograft with respect to angulation success ($P = 0.087$), neither did statistical testing of superiority indicate that autograft was superior to OP-1 Putty ($P = 0.629$).
- Presence of bone on CT at 9 months: OP-1 Putty was clinically similar to autograft (84.9% for OP-1 Putty and 98.6% for autograft). Statistical testing of non-inferiority did not show that OP-1 Putty was non-inferior to autograft with respect to presence of bone by CT ($P = 0.929$).
- Additional patient outcome measures of SF-36 and VAS pain scales suggest early and durable improvements for patients in both groups. In addition, the avoidance of a second surgical procedure resulted in decreased operative time, decreased blood loss, and absence of donor site pain, all of which are clinical benefits of OP-1 Putty versus autograft.
- In a *post hoc* analysis, OP-1 Putty was statistically non-inferior to autograft with regard to overall clinical success, a composite parameter consisting of ODI success, absence of retreatment, absence of serious treatment-related AEs, and neurological success (71.2% in the OP-1 Putty group, and 69.0% in the autograft group, $P = 0.029$).

Efficacy of OP-1 Putty is further demonstrated by consistency of success rates, and similarity between groups, in all clinically-relevant outcomes.

In conclusion:

OP-1 Putty treatment was highly effective, showing:

- Pharmacologic success as judged by osteoinduction;
- Clinical success as shown by improvements in ODI and success in other clinical outcome measures;
- Radiographic success, as shown by success on both dynamic and static outcomes; and
- Durability of success, demonstrated through follow-up periods as long as 3 years.

Additionally, OP-1 Putty is generally comparable to autograft treatment with respect to all of the following parameters:

- The proportion of patients experiencing treatment-emergent AEs, severe AEs, treatment-related AEs, SAEs, treatment-related SAEs, neoplasms, or death;
- The occurrence of clinically important laboratory abnormalities;
- The occurrence of local adverse events involving the lumbar spine;
- The occurrence of immunologically-related adverse events or clinical outcomes, despite the occurrence of neutralizing anti-OP-1 antibodies in 25.6% of treated patients.

Given its favorable profile with respect to clinically relevant efficacy and safety outcomes, OP-1 Putty offers an attractive alternative to the use of autograft in patients undergoing lumbar posterolateral spinal fusion.