

5.2 Pilot Study (Content from P060021 Original PMA, CSR S99-01US, Section 2)

Stryker Biotech

OP-1 Putty® for Posterolateral Fusions

Clinical Study Report: S99-01US

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, Pilot Study of OP-1 Putty in Uninstrumented Posterolateral Fusions		
Investigator: See complete investigator list in Section 16.1.4.		
Study Center: See complete list of study centers in Section 16.1.4.		
Publications (references): Vaccaro A, Anderson D, Patel T, et al. Comparison of OP-1 Putty (rhBMP-7) to Iliac Crest Autograft for Posterolateral Lumbar Arthrodesis. A Minimum 2-Year Follow-up Pilot Study. <i>Spine</i> . 2005;2709-16. Vaccaro A, Patel T, Fischgrund, et al. A Pilot Safety and Efficacy Study of OP-1 Putty (rhBMP-7) as an Adjunct Iliac Crest Autograft in Posterolateral Lumbar fusions. <i>Eur Spine J</i> . 2003;12(5):495-500. Vaccaro A, Patel T, Fischgrund J. A Pilot Study Evaluating the Safety and Efficacy of OP-1 Putty (rhBMP-7) as a Replacement for Iliac Crest Autograft in Posterolateral Lumbar Arthrodesis for Degenerative Spondylolisthesis. <i>Spine</i> . 2004;1885-92. Vaccaro A, Patel T, Fischgrund, et al. A 2-Year Follow-Up Pilot Study Evaluating the Safety and Efficacy of OP-1 Putty (rhBMP-7) as an adjunct to Iliac Crest Autograft in Posterolateral Lumbar fusions. <i>Eur Spine J</i> . 2005;14(7):623-9.		

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Name of Finished Product: OP-1 Putty		
Name of Active Ingredient: Human recombinant Osteogenic Protein-1 (OP-1)		
Study Period: First patient enrolled: 07 June 1999 Last patient completed: 13 July 2005 Phase of Development: Pilot		
Objectives: The objectives of this study were to demonstrate the feasibility of Osteogenic Protein-1 (OP-1) Putty alone or as an autograft adjunct as measured by: <ul style="list-style-type: none"> • Safety: comparison of complications and neurological status within the OP-1 Putty treatment groups and control group (autograft alone) • Efficacy: comparison of overall fusion success and time to fusion,^b and pain/function outcome within the OP-1 treatment groups, and in the control group (autograft alone). 		
Methodology: This was a controlled, randomized, multicenter, pilot clinical study to evaluate the safety and efficacy of OP-1 Putty for lumbar spinal fusion, both alone and as an adjunct to autogenous bone graft (autograft) in patients with single level (L3-S1) degenerative lumbar spondylolisthesis (Grade 1 or 2) with spinal stenosis. The initial protocol specified 2 treatment groups: an investigational arm of OP-1 Putty and autograft, and a control arm of autograft alone. A protocol revision added a new investigational arm of treatment with OP-1 Putty alone, and eliminated enrollment in the OP-1 Putty and autograft arm. At all times patients were randomized in a 2:1 manner to the OP-1 Putty-containing treatment arm versus the autograft treatment arm. Patients underwent standard surgical procedures for lumbar spinal posterior decompression with concomitant posterolateral intertransverse process arthrodesis using OP-1 Putty alone, OP-1 Putty with autograft, or with autograft alone, as specified by randomization. Patients were evaluated postoperatively at 6 weeks, and 3, 6, 9, 12, and 24 months, and annually thereafter until the last patient in the Pivotal study (S01-01US) achieved 2-year follow-up.		

^b As analysis of time to fusion was not defined prospectively, it will not be discussed further.

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<p>Number of Patients (planned and analyzed): The study planned 48 patients: 24 in the OP-1 Putty alone group, 12 in the OP-1 Putty and autograft group, and 12 in the autograft alone group.</p> <p>Fifty-seven patients were enrolled. Forty-eight patients were randomized to 1 of 3 treatment groups and were distributed across treatment groups as planned. Both analysis datasets (the intent-to-treat [ITT] dataset and the safety dataset) used all 48 treated patients. Of the 9 patients enrolled but not included in analyses, 8 patients were withdrawn prior to treatment, and 1 patient did not receive the protocol-specified treatment, so was not included in analyses.</p>																						
<p>Diagnosis and Main Criteria for Inclusion: Patients with single level (L3-S1) degenerative lumbar spondylolisthesis (Grade 1 or 2) with spinal stenosis.</p>																						
<p>Test Product, Dose and Mode of Administration, Batch Number: 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 putty-like consistency. OP-1 Putty is provided as 2 components:</p> <ul style="list-style-type: none"> • A large vial containing a sterile dry powder consisting of 3.5 mg of rhOP-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>For both OP-1 Putty treatment groups, 1 product unit was to be used on each side of the posterolateral fusion, i.e., 2 product units per patient.</p> <p>Batch Numbers:</p> <table border="1"> <thead> <tr> <th>Study Device</th> <th>Kit Numbers</th> <th>OP-1 Implant Lot No.</th> <th>Putty Additive Lot No.</th> </tr> </thead> <tbody> <tr> <td rowspan="5">OP-1 Putty</td> <td>FD9903001</td> <td>AH99A002</td> <td>AN00A001</td> </tr> <tr> <td>FD9908002</td> <td>AH99A001</td> <td>AN00A001</td> </tr> <tr> <td>FD0003002</td> <td>AH99A002</td> <td>AN00A001</td> </tr> <tr> <td>FD0008004</td> <td>AH9A001L</td> <td>AN8A001L</td> </tr> <tr> <td>FD0008005</td> <td>AH9A001L</td> <td>AN8A001L</td> </tr> </tbody> </table>			Study Device	Kit Numbers	OP-1 Implant Lot No.	Putty Additive Lot No.	OP-1 Putty	FD9903001	AH99A002	AN00A001	FD9908002	AH99A001	AN00A001	FD0003002	AH99A002	AN00A001	FD0008004	AH9A001L	AN8A001L	FD0008005	AH9A001L	AN8A001L
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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)		
Duration of Treatment: Periodic follow-up for at least 24 months post-operatively.		
Reference Therapy, Dose and Mode of Administration: Lumbar spinal fusion with the use of autogenous bone graft from the iliac crest (autograft).		
<p>Criteria for Evaluation:</p> <p>Efficacy: The clinical protocol did not categorically define outcome variables as primary or secondary endpoints. For the purposes of analysis and reporting, outcome variables have been identified as either a primary endpoint or ancillary clinical outcome.</p> <p>The primary efficacy variable was overall success, a composite measure consisting of radiographic demonstration of spinal fusion (presence of bridging bone and $\leq 5^\circ$ angular motion and ≤ 2 mm translational motion), improvement of at least 20% on the Oswestry Disability Index (ODI), and absence of retreatment. Ancillary clinical outcomes included SF-36 Health Outcomes Survey scores, leg/buttock pain and donor site pain as measured by a visual analog scale, disc height by radiographic assessment, and degree of angular motion and translational movement by radiographic assessment.</p> <p>Safety: Safety outcomes were adverse events and immunogenicity.</p>		
Statistical Methods: Descriptive statistics were used for data analysis. Analysis of the overall success rate was calculated both with and without a 'last observation carried forward' (LOCF) approach.		
<p>Summary and Conclusions:</p> <p>This was a feasibility study designed to assess safety and inform the design of future studies. Sample size was selected to allow descriptive statistics.</p> <p>Demographics and Baseline Characteristics: The groups were similar in age, weight, height distribution. Females accounted for more than half of the patients in each treatment group, and comprised 54.2% of the OP-1 Putty alone group, 58.3% of the autograft alone group, and 75% of the OP-1 Putty and autograft combination group.</p>		

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Name of Active Ingredient: Human recombinant Osteogenic Protein-1 (OP-1)		
<p>Efficacy:</p> <ul style="list-style-type: none"> • Overall Success: treatment groups appear to be comparable at 24 months • Greater Radiographic Success is noted in both OP-1 Putty groups versus autograft, but small sample sizes preclude the ability to assess differences between treatment groups. • Angular motion: The proportion of patients who achieved success in angular motion appeared to be greater in the OP-1 Putty alone treatment group versus other treatment groups at both 12 and 24 months. • ODI percent success for both OP-1 Putty treatment groups appeared to suggest an advantage for OP-1 Putty over autograft. • Patient 105 (OP-1 Putty and autograft) underwent retreatment for pseudarthrosis (supplemental fixation) at 7.6 months post-operatively. Two additional patients (Patients 153 and 455 in the OP-1 Putty alone group) underwent retreatment after 24 months. • Treatment groups were similar for disc height, leg/buttock pain, donor site pain, and SF-36 scores. <p>The following table is a summary of results for the primary endpoint, Overall Success, and for the 3 components of Overall Success: Radiographic Success, ODI, and Retreatment at 24 months.</p>		

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	OP-1 Putty Alone		OP-1 Putty/Autograft		Autograft Alone	
Outcome	Number Patients	Number (%) Successes	Number Patients	Number (%) Successes	Number Patients	Number (%) Successes
Overall success with LOCF	24	11 (45.8)	12	5 (41.7)	12	4 (33.3)
Overall success without LOCF	18	10 (55.6)	9	4 (44.4)	9	3 (33.3)
Radiographic success	19	11 (57.9)	10	5 (50.0)	10	4 (40.0)
Bridging Bone	19	15 (78.9)	10	7 (70.0)	10	9 (90.0)
Angulation Success	18	12 (66.7)	10	5 (50.0)	10	5 (50.0)
Translational Movement	18	16 (88.9)	10	6 (60.0)	10	7 (70.0)
ODI	18	17 (94.4)	9	8 (88.9)	10	6 (60.0)
No Retreatment	24	24 (100.0)	12	11 (91.7)	12	12 (100.0)
A potentially important and clinically meaningful advantage of OP-1 Putty over autograft is shown by greater success in angulation and ODI scores.						
Safety:						
<ul style="list-style-type: none"> Adverse events (AE) occurred in 100% of patients across all treatment groups: 149 in the 36 patients in the OP-1 Putty treatment groups (with or without autograft), and 51 in the 12 patients treat who received autograft. Thirty-six serious AEs (SAEs) were reported in 18 patients across all treatment groups, and none were attributed to the use of OP-1 Putty. Four patients across treatment groups reported 8 malignancies, none of which were attributed to the use of OP-1 Putty. One death, due to carcinomatosis, occurred in this study. Pseudarthrosis was reported predominantly between 6 and 12 months post-operatively and in 13 patients who received an OP-1 Putty-containing regimen. 						

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<p>Only 2 of these 13 patients required a surgical retreatment due to pseudarthrosis.</p> <ul style="list-style-type: none"> • Post-operative wound infections occurred in 4 patients who received OP-1 Putty alone, and did not occur in patients who received an autograft. • There was no evidence of neurological deterioration post-operatively in any treatment group. • Seven patients in the OP-1 Putty alone group had neutralizing antibodies at either 6 weeks or 6 months post-procedure, however no pattern of immunologically-mediated AEs has emerged. The Overall Success rates of OP-1 Putty patients with or without neutralizing antibodies appears comparable, 42.3% vs. 44.8%. In this trial, no relationship between antibody occurrence and clinical events was observed. <p>Overall, the AE profile in the groups treated with OP-1 Putty was comparable to that in the autograft alone treatment group. The small sample sizes, particularly in the autograft only group, preclude any broader conclusions. Although pseudarthrosis was reported only in the OP-1 Putty treatment groups, reporter bias cannot be ruled out in this unblinded trial, as pseudarthrosis is a known potential outcome of failed lumbar fusion surgery.</p>		
<p>Conclusion: OP-1 Putty, as a single modality and in combination with autograft, compares favorably with autograft alone in the treatment of degenerative lumbar spondylolisthesis.</p>		
<p>Date of the Report: 18 May 2006</p>		

7. INTRODUCTION

It has been estimated that up to 70%⁴⁵ of the adult population suffer from some form of low back (lumbar sacral) pain, usually attributed to degenerative processes within the vertebral spine. The cost of evaluation, treatment, and the restrictions on mobility associated with low back pain exert significant economic and social consequences for individual patients, their families and employers, health care providers, compensation systems, and society as a whole.

Degenerative disc disease is associated with spondylolisthesis, which is characterized by slippage of 1 vertebral segment onto the segment below. Spondylolisthesis results from erosion of the facet cartilage, in the presence of an intact neural arch.¹⁶ This in turn may lead to the formation of osteophytes that cause stenosis and root compression.⁴⁰

Symptoms of spondylolisthesis include: localized back pain and leg pain, originating both at the affected vertebrae and from nerve root compression; neurological deficit; and spinal instability due to excessive angulation and /or translational movement of the spinal vertebrae.

The severity of spondylolisthesis is determined by the degree of displacement between the affected vertebrae, and is classified into 4 grades. Grades 1 and 2, defined as displacement of $\leq 25\%$ and displacement of 25% to 50%, respectively, were evaluated in this study. Of the 5 types of spondylolisthesis (dysplastic, isthmic, degenerative, traumatic, and pathologic), only degenerative spondylolisthesis was evaluated in this study.

If initial conservative approaches to the management of pain, neurological deficit, and instability such as rest, exercise or physical therapy, medication including epidural steroids, use of a back brace, changes in posture and body mechanics do not result in improvement, surgical intervention is often required.²⁶

Decompression and lumbar spinal fusion are the surgical treatments of choice for degenerative spondylolisthesis. Decompression at the affected level relieves pressure of stenosis on the cauda equine or on the exiting nerve roots. Decompression without spinal fusion (arthrodesis) may have a less favorable outcome that was previously thought, particularly when spinal stenosis is associated with degenerative lumbar spondylolisthesis at a single level.^{22,26,43} Decompression with spinal fusion is currently the most common surgical approach to the management of progressive degenerative spondylolisthesis.⁹

Spinal fusion is the surgical creation of a bony union across the affected vertebrae. Of the estimated 70,000 posterolateral lumbar spinal fusions performed annually, approximately 20% to 55% fail, resulting in continued pain and loss of function, and require re-operation.^{19,39} A major cause of failure is pseudarthrosis, defined for the purposes of this study as documented failure of solid fusion 1 year after the initial operation.^{25,41} Current spinal fusion techniques include grafting of autologous or allogeneic bone tissue, with or without the use of instrumentation systems. The efficacy and safety of instrumentation remains controversial.^{4,27,35}

Bone grafts stimulate bone formation and acts as a matrix or scaffold into or over which new bone can grow. Autologous bone (autograft) is considered the most successful bone grafting material, and is preferred over allograft bone.^{1,2,7,24} The iliac crest is the most common source of autograft tissue, but the removal of tissue increases operative time, blood loss, and the morbidity associated with spinal fusion.^{36,40} An alternative source of graft material would reduce this risk profile.

Bone Morphogenetic Proteins (BMPs), such as Osteogenic Protein-1 (OP-1), in combination with collagen matrix, have been shown to be osteoinductive and osteoconductive, and to speed the rate of bone healing and autograft performance in animals.^{11,12,13,14,37} Other BMPs have also demonstrated safety and efficacy in spinal applications.^{5,6,28,32,36}

This pilot study was designed to determine whether the addition of OP-1 Putty to autologous bone graft material, or the use of OP-1 Putty alone, would be safe and effective when compared to autografting alone in patients requiring decompression and lumbar spinal fusion. Success of OP-1 as a single modality would eliminate the need for harvesting autograft tissue from the iliac crest, and its resulting pain and morbidity.

In patients with Grade 1 or 2 degenerative spondylolisthesis with stenosis affecting one level of the lumbar spine (L3 to S1), the use of OP-1 Putty alone, or in combination with autograft, and autograft alone (control group) were compared to assess rates of fusion success and time to fusion. Assessments of pain, function, and neurological status were also performed to determine and compare levels of improvement among the treatment groups, as well as to clarify the safety profiles of OP-1 alone and in combination with autograft.

8. OBJECTIVES

The objectives of this pilot study were to demonstrate the safety and efficacy of OP-1 Putty alone or as an autograft adjunct as measured by:

- Safety: comparison of complications and neurological status within the OP-1 Putty treatment groups and control group (autograft alone)
- Efficacy: comparison of overall fusion success and time to fusion,^d and pain/function outcome within the OP-1 treatment groups, and in the control group (autograft alone).

^d As time to fusion was not defined prospectively, it will not be discussed further.

9. INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN DESCRIPTION

This was a controlled, randomized, multicenter, pilot clinical study to evaluate the safety and efficacy of OP-1 Putty for lumbar spinal fusion, both alone and as an adjunct to autogenous bone graft (autograft) in patients with single level (L3-S1) degenerative lumbar spondylolisthesis (Grade 1 or 2) with spinal stenosis. Patients were randomized to treatment groups to undergo surgery for decompression and lumbar spinal fusion.

The initial protocol contained 2 treatment groups: an investigational arm of OP-1 Putty and autograft, and a control arm of autograft alone. Patients were randomized in a 2:1 manner to receive treatment with OP-1 Putty and autograft, or autograft alone. Protocol revision 5.0 was approved in December 1999, which added a new investigational arm of treatment with OP-1 Putty alone. Following the addition of the OP-1 Putty arm, enrollment in the OP-1 Putty and autograft arm was terminated with 12 patients treated. Subsequent patients continued to be randomized in a 2:1 manner to the OP-1 Putty arm or to the autograft arm, to reach enrollment of 24 and 12 patients, respectively. A total of 48 patients was planned.

In the initial protocol, the expected duration of the study was 24 months. A protocol revision in June 2002 required an additional annual evaluation until the last patient in the Pivotal Spine Study (S01-01US) achieved 2-year follow-up, which increased the study duration to up to 72 months. Patients were evaluated postoperatively at 6 weeks (± 14 days), 3 months (± 14 days), 6 months (± 30 days), 9 months (± 30 days), 12 months (± 60 days), 24 months (± 60 days) and annually thereafter (± 90 days) until the last patient in the Pivotal study (S01-01US) achieved 2-year follow-up.

Efficacy was demonstrated by a comparison of clinical outcomes and fusion success for the 3 groups. Efficacy assessments included radiographic evidence of fusion as determined by an independent radiographic evaluation, at least a 20% improvement on the Oswestry Disability Index (ODI) from the pre-operative visit, and no revisions, removals, or supplemental fixations intended to promote fusion at the treated location. Safety was assessed by medical events, surgery-related events, donor site pain, and neurological analysis.

An additional 5 mL of blood was drawn pre-operatively and at the 6-week and 6-month follow-up for patient immunological testing. Information on surgery specifics was collected post-surgery and included date of surgery, spinal level affected, additional surgical procedures performed, operative times, estimated blood loss, device lot number, and treatment group.

9.2 DISCUSSION OF STUDY DESIGN INCLUDING THE CHOICE OF CONTROL GROUPS

The most common surgical option for progressive degenerative spondylolisthesis with spinal stenosis is decompression and spinal fusion. Autograft is the current standard of care for lumbar spinal fusion, due to its osteoinductive and osteoconductive characteristics. Autograft is harvested from the patient's own bone, usually from the iliac

crest, which requires a second surgical site. Donor site pain and morbidity, and increased risk of infection, are associated with this second site surgery.

Allograft is another option currently available for spinal fusion. Allograft may be utilized when autograft bone is insufficient or when the patient prefers not to have a second surgical site. While this eliminates donor site morbidity, it is less desirable than autograft for a number of reasons. The bone used is primarily cadaveric, which does not have the same osteoinductive capacity as autograft bone, decreasing the patient success rates. Additionally, allograft bone has been linked to serious disease transmission, though improvements in screening have decreased this risk.

The use of OP-1 Putty in lumbar spinal fusion may eliminate both disease transmission and donor site morbidity associated with alternative treatments of autograft and allograft. A lack of options for this procedure indicates the need for an alternative, effective treatment, which is both osteoinductive and osteoconductive.

Efficacy in this study was evaluated by a comparison of clinical outcomes and fusion success for the 3 treatment groups: OP-1 Putty and autograft, OP-1 Putty alone, and autograft alone. Success and failure criteria included radiographic demonstration of spinal fusion, improvement of at least 20% in the ODI, and no revisions, removals or supplemental fixations at the surgical site.

9.3 PATIENT SELECTION

Patients were skeletally mature men and women less than 81 years of age with a diagnosis of Grade 1 or 2 degenerative lumbar spondylolisthesis with spinal stenosis, and who were candidates for decompression and spinal fusion with the use of autograft from the iliac crest. The investigator completed a physical, neurological, and radiographic assessment of the patient prior to enrollment into the study. Concurrent medical problems and prior treatment to the spine were also documented at this time. Demographic and medical history were collected including age, sex, smoking history, work status, height, weight, and pregnancy status. Women of childbearing potential received a pregnancy test, based on urine sample, approximately 72 hours prior to surgery. Patients, or their legal guardians, were required to sign an IRB approved Informed Consent Form prior to treatment.

The exclusion criteria were intended to prevent enrollment of patients who may not have had the ability to heal (e.g., conditions interfering with bone formation, infection, and tobacco or steroid use). The exclusion criteria regarding known sensitivity to OP-1 Putty components and pregnancy or breast-feeding were included as safety precautions. No modifications were made to the inclusion and exclusion criteria throughout the study.

9.3.1 Inclusion Criteria

Patients enrolled in the study met the following inclusion criteria:

1. Willing and able to understand, sign, and date the study specific Patient Informed Consent, which was approved by the Institutional Review Board

2. Skeletally mature men and women less than 81 years of age
3. Diagnosis of degenerative lumbar spondylolisthesis of Grade 1 or 2 with spinal stenosis demonstrated by medical history, physical examination and radiographic imaging (Radiographic diagnosis had been performed showing a cross sectional image using a computed tomography (CT) scan or magnetic resonance imaging (MRI) demonstrating an intact pars intra-articularis with evidence of central or lateral recessed stenosis accompanied by an anterolisthesis on upright lateral radiographs. The patient had leg and/or back pain and the manifestation of 1 or more of the following phenomena:
 - radiculopathy
 - sensory deficit
 - motor weakness
 - reflex changes
 - disc herniation
 - neurogenic and/or vascular claudication
 - instability (defined as greater than 0% and less than 50% translation of the vertebrae and/or greater than 10 degrees and less than 20 degrees angular motion) measured on flexion/extension radiographs
 - osteophyte formation or hypertrophy of the facet joint
4. Candidate for decompression and spinal fusion with the use of autograft from the iliac crest
5. Required 1 level lumbar fusion (L3 to S1)
6. Agreed to participate in post-operative clinical and radiographic evaluations and required rehabilitation regimen
7. Had no history of previous fusion attempt(s) to the affected spinal level
8. Had undergone non-operative treatment in the 6 months prior to study enrollment
9. Had a preoperative ODI of 30-100

9.3.2 Exclusion Criteria

Patients were excluded from participation in the study if they met any of the following exclusion criteria:

1. Non-degenerative spondylolisthesis of any Grade at the affected level
2. Degenerative spondylolisthesis of Grade 3 or 4
3. Active spinal and/or systemic infection

4. Systemic disease or condition, which would affect his/her ability to participate in the study requirements or the ability to evaluate the efficacy of the investigational device (i.e., active malignancy, neuropathy)
5. Was a prisoner, 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. Participated in clinical trials evaluating investigational devices, pharmaceuticals, or biologics within 3 months of enrollment in the study
7. Pregnant (as determined by testing within 72 hours prior to surgery) or lactating, or planned to become pregnant before completion of the study
8. Morbidly obese (defined as weight ≥ 60 percent over the recommended ideal weight as described in the 1983 Metropolitan Height and Weight Tables for Men and Women)
9. Known sensitivity to any component of the OP-1 Putty
10. Known to require, at the time of treatment, additional surgery to the lumbar spinal region within the following 6 months
11. Spinal instability measured on flexion/extension radiographs of greater than 50% translation of the vertebrae and greater than or equal to 20 degrees of angular motion
12. Use of tobacco or nicotine, or prescribed steroids such as cortisone

9.3.3 Removal of Patients from Therapy or Assessment

Patients were informed that they may withdraw voluntarily from the study at any time, and were not obligated to state their reason for withdrawal.

Any of the following occurrences were reasons for withdrawal from the study:

- death on study
- loss to follow up (documented attempts to locate patient have failed)
- refusal to return for follow-up evaluations
- relocation made follow-up impossible
- unable to continue participation in the study due to concurrent medical condition unrelated to the study.

If an intraoperative decision was made to perform a procedure other than that specified for enrollment in the study, the patient did not receive randomized treatment and was withdrawn from the study. If a patient was withdrawn prior to treatment, the following patient was assigned the next randomly determined treatment as per the study randomization plan.

Patients who had additional surgical intervention to the lumbosacral spine, other than at the operated level, within 6 months of index surgery, would be withdrawn from the study. These patients would be followed for safety, but not included in any efficacy analyses.

9.4 STUDY TREATMENT

9.4.1 Treatments Administered

Each patient received posterior decompression with concomitant posterolateral intertransverse process arthrodesis with OP-1 Putty alone, OP-1 Putty and autograft, or autograft alone. For the OP-1 Putty and autograft arm, 1 product unit of OP-1 Putty mixed with autograft was used on each side of the posterolateral fusion. For the OP-1 Putty alone arm, 1 product unit was used on each side of the posterolateral fusion. For patients in the OP-1 Putty and autograft arm and autograft alone arm, the current standard surgical technique was employed to harvest and implant autograft material.

9.4.2 Identity of Study Treatments

OP-1 Putty is composed of recombinant human osteogenic protein-1 (rhOP-1), Type 1 bovine bone collagen matrix, and carboxymethylcellulose (CMC) sodium, an anionic cellulose derivative which yields a putty-like consistency. OP-1 Putty was supplied by the sponsor as 2 components: a large vial containing OP-1 Implant, a sterile dry powder composed of 3.5 mg rhOP-1 and Type 1 bovine bone collagen matrix, and a small vial containing putty additive, a sterile dry powder composed of CMC. At the time of lumbar spinal fusion, the contents of the OP-1 Implant vial and the putty additive vial were mixed and wetted with sterile saline to form a putty-like material to be used for surgical implant. Kit numbers, which included the OP-1 Implant vial and the putty additive vial used in the pilot study are presented in Table 2.

Table 2. Study Treatment Kit Numbers

Study Device	Kit Numbers	OP-1 Implant Lot#	Putty Additive Lot #
OP-1 Putty	FD9903001	AH99A002	AN00A001
	FD9908002	AH99A001	AN00A001
	FD0003002	AH99A002	AN00A001
	FD0008004	AH9A001L	AN8A001L
	FD0008005	AH9A001L	AN8A001L

9.4.3 Method of Assigning Patients to Treatment Groups

The randomization scheme was developed by an independent biostatistician in SAS using the PLAN procedure, and was maintained by the sponsor. Investigators contacted the sponsor by phone to receive the patient randomization assignment. In the first phase of the study, patients were randomized in a 2:1 manner to receive OP-1 Putty and autograft

or autograft alone, for decompression and lumbar spinal fusion. Following the addition of the OP-1 Putty arm, enrollment in the OP-1 Putty and autograft arm was terminated with 12 patients treated. Subsequent patients continued to be randomized in a 2:1 manner to receive either OP-1 Putty or autograft, to reach enrollment of 24 and 12 patients, respectively. A randomization schedule is provided in Section 16.1.7.

9.4.4 Selection of Treatment in the Study

For the OP-1 Putty and autograft arm, 1 product unit mixed with autograft was used on each side of the posterolateral fusion. For the OP-1 Putty alone arm, 1 product unit was used on each side of the posterolateral fusion. The current standard surgical technique was employed to harvest and implant autograft material.

9.4.5 Blinding

The investigator and patient were not blinded to study treatment, as blinding was not possible because of the nature of the procedure. Patients enrolled in the OP-1 Putty and autograft arm or the autograft arm experienced an additional surgical site where the bone was grafted from the iliac crest. Hospital billing procedures of the investigational product also prevented blinding of patients in the study.

The radiographic review team was not informed of study treatment, patient identification, clinical history prior to and post treatment. Radiologists were told of the interval between the operative procedure and the X-ray under evaluation to reproduce more closely the manner in which radiographic data would be evaluated in a normal clinical practice.

Radiographs were reviewed by 2 independent radiologists who were blinded to treatment group, and were read in sequence using the pre-operative film for reference.

Discrepancies were resolved by a third reviewer.

The sponsor was not blinded to study treatment.

9.4.6 Prior and Concomitant Therapy

Patients must not have had a history of previous fusion attempts to the affected spinal level. All enrolled patients had undergone non-operative treatment in the 6 months prior to study enrollment. If an intraoperative decision was made to perform a procedure other than that specified for enrollment in the study, the patient did not receive OP-1 Putty and was withdrawn from the study. Patients who required additional surgical intervention to the lumbosacral spine (other than at the operated level) within 6 months of index surgery would be withdrawn from the study. These patients would be followed for safety, but not included in any efficacy analyses.

9.4.7 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 EVALUATIONS

The schedule of patient evaluations is summarized in Table 3.

Table 3. Schedule of Patient Evaluation and Case Report Forms

Time Interval	Clinical Evaluation	Neurologic Evaluation	Radiographic Evaluation	Immunogenicity Evaluation
Pre-operative	X	X	X	X
Hospitalization				
6 Weeks (± 14 days)	X	X	X	X
3 Months (± 14 days)	X	X	X	
6 Months (± 30 days)	X	X	X	X
9 Months (± 30 days)	X	X	X	
12 Months (± 30 days)	X	X	X	
24 Months (± 60 days)	X	X	X	
Annual (± 90 days)	X	X	X	

9.5.1 Efficacy and Safety Measurements Assessed

9.5.1.1 Safety

The safety of OP-1 Putty was evaluated by documenting the number of anticipated and unanticipated adverse events (AEs) that occurred within the study population compared to the frequency of events in the control population. All anticipated and unanticipated AEs, product-related or not, were reported and evaluated for the OP-1 alone group, the OP-1 autograft combination group, and the autograft alone group. The neurological function scores of the control and treatment groups were compared. It was expected that the control and treatment groups would be similar with respect to clinical and neurological function levels. Complication rates were expected to be similar in all groups, although the autograft arm and the OP-1 Putty and autograft arm were expected to exhibit donor site complications.

The severity of each AE was assessed by the investigator and graded as mild, moderate, or severe. The definitions of each grade of severity are as follows:

Mild: Symptom(s) barely noticeable to the patient or does not make the patient uncomfortable. The AE does not influence performance or function. Prescription drugs are not ordinarily needed for relief of symptom(s).

Moderate: Symptom(s) of a sufficient severity to make the patient uncomfortable. Performance of daily activities is influenced. Treatment of symptom(s) may be needed.

Severe: Symptom(s) of a sufficient severity to cause the patient severe discomfort. Severity may cause cessation of treatment with the study device. Treatment for symptom(s) may be given.

5.2 Pilot Study (Content from P060021 Original PMA, CSR S99-01US, Section 7-13)

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As this study was conducted under Investigational Device Exemption (IDE) regulations, the 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.”

In this study, investigators assessed the causal relationship between AEs and the administration of an OP-1 Putty-containing treatment only. Specific causality assessments were not made for AEs experienced by patients randomized to the autograft treatment arm. The relationship between the event and OP-1 Putty was categorized as follows:

- definitely not related
- probably not related
- possibly related
- probably related
- definitely related
- not applicable

For the purposes of this study, causality assessments other than “definitely not related”, or “probably not related” were assumed to causally related to OP-1 Putty.

All patients participating in the study were evaluated clinically and neurologically.

Patient pain and function was evaluated pre-operatively and at 6 weeks, 3 months, 6 months, 9 months, 12 months, 24 months, and annually thereafter until the last patient in the Pivotal spine study achieved 2-year follow-up.

Level of patient disability was measured by use of a patient-completed ODI. This questionnaire is divided into 10 questions, the responses to which describe the level of difficulty or pain associated with the activity described. Each question is scored from 0 (least amount of disability) to 5 (greatest level of disability). Parameters evaluated include:

1. pain intensity
2. personal care (washing, dressing, etc.)
3. lifting
4. walking
5. sitting
6. standing
7. sleeping
8. sex life
9. social life
10. travel

Scores for all questions were added to give a possible score of 50 points. The total was divided by 50 and expressed as a percentage. If a patient did not answer a parameter, the ODI score was calculated by dividing the actual score by the possible score (the number or parameters answered multiplied by 5) and expressing this result as a percentage.

Pre-operative and post-operative leg and buttock pain and post-operative donor site pain (for the 2 arms receiving autograft) were recorded at all evaluation points through the use of a visual analog scale.

Neurological safety was assessed using 4 criteria: abnormal reflexes, leg pain on straight leg raises, changes in sensory evaluation, and changes in muscle strength. Evaluations were conducted pre-operatively and at 6 weeks, 3 months, 6 months, 9 months, 12 months, 24 months, and annually thereafter until the last patient in the Pivotal spine study achieved 2-year follow-up.

Right and left reflexes were evaluated by knee and ankle jerk testing. Responses were graded as normal, decreased, or absent.

Straight leg raises for the right and left leg were performed and evaluated as degrees (positive and negative). Sensory evaluation was performed through dermatomal distribution above the left and right areas of the lower lumbar spine and evaluated as absent, impaired, or normal.

Muscle strength evaluation consisted of bilateral measurements of hip, knee, ankle, and toe strength. The scale for measurement ranged from 0 (absent) to 5 points (normal).

Neurological evaluations were regarded as normal or abnormal in analysis. Abnormal indicated the neurological response was diminished or absent.

9.5.1.2 Efficacy

Efficacy was demonstrated by a comparison of clinical outcomes and fusion success for the 3 groups. Patients must have met all of the following criteria to be considered successful.

1. Radiographic demonstration of spinal fusion

- Presence of bridging on anterior posterolateral (AP) or lateral radiographs between transverse processes of 2 vertebral bodies
 - Angular motion on flexion/extension radiographs of $\leq 5^{\circ}$ at the operated level
 - Translational movement of ≤ 2 mm demonstrated on flexion/extension radiographs at the affected level
2. Improvement of at least 20% on the ODI from the pre-operative visit
 3. No revisions, removals, or supplemental fixations. All re-operations that were intended to promote fusion at the treated level were considered failures. Re-operations that were not intended to promote fusion, such as drain removal, were not considered failures. Revision, removals, supplemental fixations, and re-operations are defined in the Guidance Document for Preparation of Investigational Device Exemptions (IDEs) for Spinal Assemblies, August 1998, as follows:
 - A revision is a procedure which adjusts or in any way modifies the original implant configuration that may include adjusting the position of the original implant or replacing part or all of the device.
 - A removal is a procedure where 1 or more components or the original device are removed without replacement.
 - A re-operation is any surgical procedure at the involved level which does not remove, modify, or add components to the device.
 - A supplemental fixation is a procedure in which instrumentation is implanted. This may include supplemental placement of a rod/screw, or plate/screw system.)

Failure to achieve any of the above constitutes individual patient failure.

Patient standing radiographs were reviewed by 2 independent radiologists who were blinded to treatment group. The radiographs were read in sequence using the pre-operative film for reference. A set of AP and lateral radiographs to measure disc height was evaluated at the 6-week follow-up visit. In addition, AP, lateral, and flexion/extension radiographs were evaluated pre-operatively, and at 3 months, 6 months, 9 months, 12 months, 24 months, and annually thereafter until the last patient in the Pivotal spine study achieved 2-year follow-up. A third blinded, independent radiologist evaluated those radiographs for which the 2 radiologists disagreed on the determination of overall radiographic success.

Overall patient satisfaction data were obtained using a patient-completed, standard SF-36 Outcomes Survey. The SF-36 had 8 individual scales designed to measure overall health, functional status, and well-being of the patient. Subsequent to the development of the initial SF-36 survey, the physical component scale (PCS) and mental component scale

^c All values were rounded to the nearest integer.

(MCS) were developed based on grouping and weighing the 8 individual scales. Outcomes information was obtained pre-operatively and at 6 weeks, 3 months, 6 months, 9 months, 12 months, 24 months, and annually thereafter until the last patient in the Pivotal spine study achieved 2-year follow-up.

9.5.2 Appropriateness of Measurements

Study assessments and measurements were derived from definitions based on the Guidance Document for Preparation of Investigational Device Exemptions (IDEs) for Spinal Assemblies, August 1998.

9.5.3 Primary Efficacy Endpoints

The clinical protocol did not categorically define outcome variables as primary endpoints or ancillary clinical outcomes. For the purposes of analysis and reporting, outcome variables have been identified as either a primary endpoint or ancillary clinical outcome.

Efficacy was demonstrated by comparing clinical outcomes and fusion success within the OP-1 Putty treatment groups and the control group. Patients must have met all of the following 3 criteria to be considered an overall success: radiographic demonstration of spinal fusion, improvement of at least 20% on the ODI from the pre-operative visit, and no revisions, removals, or supplemental fixations, or reoperations intended to promote fusion at the treated level.

9.5.4 Ancillary Clinical Outcomes

Ancillary clinical outcomes included SF-36 Health Outcomes Survey scores, leg/buttock pain and donor site pain as measured by a visual analog scale, disc height by radiographic assessment, and degree of angular motion and translational movement by radiographic assessment.

9.6 DATA QUALITY ASSURANCE

Prior to the initiation of the study, a representative of the sponsor conducted an orientation in order to train the investigator or the investigator's designee in the protocol, as well as appropriate use and completion of all patient CRFs used 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.

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 or correction communication with the site. Accuracy of submitted data was verified during monitoring site visits. Data entry was verified and the verification documented. The systems used for data management and report generation were validated.

9.7 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

Detailed methodology for the summary and statistical analyses of the data collected in this study was documented in a statistical analysis plan (refer to Section 16.1.9).

9.7.1 Statistical and Analytical Plans

Analyses were performed at 3, 6, 9, 12, and 24 months to compare the efficacy and safety endpoints of both treatment groups and the control group. Each patient was followed annually until the last patient in the Pivotal spine study achieved 2-year follow-up to reach the final safety endpoint. The 3 groups were compared with respect to the safety and efficacy endpoints using descriptive statistics.

Data collected outside of established visit windows were not excluded from analyses at that visit.

9.7.2 Determination of Sample Size

No formal determination of sample size was required in this pilot study.

9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

9.8.1 Changes to the Protocol

The original version of the Pilot Study protocol, Revision 1.0, was filed with the IDE on 29 January 1999. The first version under which patients were studied was Revision 2.0. Revisions 3.0 and 4.0 to the protocol were minor and/or editorial in nature. Subsequent revisions to the protocol are described briefly.

- Protocol Revision 5.0: eliminated the OP-1 Putty and autograft arm of the study, and added an OP-1 Putty alone arm. After this Revision, further enrollment to the OP-1 Putty and autograft arm was terminated with a total of 12 patients treated.
- Protocol Revision 5.1: increased the number of patients in the OP-1 Putty arm from 12 to 24, and set maximum enrollment at 48 patients.
- Protocol Revision 5.2: eliminated the 10-day follow-up visit because of low patient compliance and lack of potential safety and efficacy data resulting from this visit.
- Protocol Revision 5.3: allowed for inclusion of a third independent radiologist in cases where the primary radiographic reviewers disagreed on the evaluation of radiographic success.
- Protocol Revision 5.4: included an expansion of the 1-year follow-up visit window from ± 1 month to ± 2 months per the FDA Guidance Document for the Preparation of IDEs for Spinal Systems (13 January 2000).
- Protocol Revision 5.5: increased the follow-up to include an additional annual evaluation until the last patient in the Pivotal Spine Study achieved 2-year follow-up.

9.8.2 Changes to the Planned Analysis

The protocol objectives included assessment of time to fusion. As this variable was not defined prospectively, it will not be discussed further.

10. STUDY PATIENTS

10.1 PATIENT DISPOSITION

Figure 1 presents patient disposition at the time of enrollment, and Table 4 summarizes patient disposition up to and including the 24-month visit. Fifty-seven patients were enrolled. Forty-eight patients were randomized to the following treatment groups: OP-1 Putty alone (n=24), OP-1 Putty/autograft (n=12), and autograft alone (n=12).

Nine enrolled patients were not included in data analyses. Eight patients were withdrawn prior to treatment, of whom 3 chose not to participate, 1 withdrew due to “other” reasons not specified, 2 withdrew for unknown reasons, and 2 were withdrawn due to closed enrollment. One patient did not have the surgical procedure specified in the protocol. This patient was not included in analyses of either the ITT or safety populations, and consequently does not appear in Table 4.

Enrollment in these treatment arms was not concurrent, because the OP-1 Putty single-modality arm was added later in the study period and did not recruit in parallel with the OP-1 and autograft arm (see Section 9.8). Both analysis datasets (the intent-to-treat [ITT] dataset and the safety dataset) used all 48 treated patients.

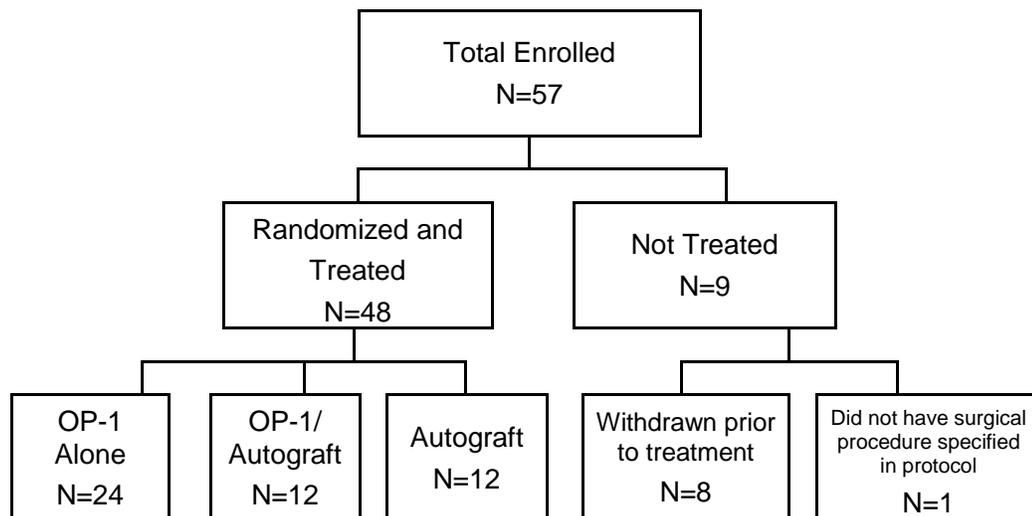


Figure 1. Patient Disposition at Time of Enrollment

5.2 Pilot Study (Content from P060021 Original PMA, CSR S99-01US, Section 7-13)

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As presented in Table 4, 20 patients in the OP-1 Putty alone group completed the 24-month visit, while 11 patients in each of the other treatment groups completed this visit. Of patients in the OP-1 Putty alone group who withdrew prior to the 24-month visit, 1 voluntarily withdrew, 2 were lost to follow up, and 1 could not be contacted. In the combination group, 1 patient voluntarily withdrew. In the autograft alone group, 1 patient could not be contacted.

Table 4. Patient Disposition Up to and Including the 24 Month Visit

Parameter	Number (%) of Patients			
	Overall	OP-1 Putty Alone	OP-1 Putty/Autograft	Autograft Alone
All Enrolled Patients	57 (100.0)			
Safety Population	48 (100.0)	24 (100.0)	12 (100.0)	12 (100.0)
ITT Population	48 (100.0)	24 (100.0)	12 (100.0)	12 (100.0)
Disposition				
Completed 24 Month Visit	42 (87.5)	20 (83.3)	11 (91.7)	11 (91.7)
Did not Complete 24 Month Visit	6 (12.5)	4 (16.7)	1 (8.3)	1 (8.3)
Voluntary Patient Withdrawal	2 (4.2)	1 (4.2)	1 (8.3)	0 (0.0)
Unable to Return	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patient Illness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to Follow-up	2 (4.2)	2 (8.3)	0 (0.0)	0 (0.0)
Patient Withdrawn by Investigator	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Did Not Have Surgical Procedure Specified in Protocol	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	2 (4.2)	1 (4.2)	0 (0.0)	1 (8.3)

Reference: Summary Table 1

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

Statistical Listing 15 in Section 16.2 provides information regarding withdrawal from the study after the 24-month visit. The following 9 patients withdrew from the study after completion of the 24-month visit:

- OP-1 Putty alone group: 1 patient was lost to follow-up
- OP-1 Putty/Autograft group: 1 patient withdrew voluntarily, 2 patients were lost to follow-up, 1 patient was unable to return, and 1 patient died of carcinomatosis
- Autograft alone group: 1 patient withdrew voluntarily, and 2 were lost to follow-up.

10.2 PROTOCOL DEVIATIONS

Several minor protocol deviations occurred during the course of the study and are not expected to affect safety and efficacy outcomes. Major protocol deviations are summarized below. All of these deviations have been reported to and acknowledged by the respective IRBs. None resulted in the removal of patients from the study or from the analysis.

10.2.1 Consent Process

Fifty-seven patients signed informed consent documents, and 48 of these patients proceeded to randomization and surgery. Deviations in the informed consent process were reported to the IRB.

10.2.2 Inclusion/Exclusion Criteria Deviations

Five deviations were noted:

- Patient 156 (49 year-old woman in the OP-1 Putty group) did not have a pregnancy test at study entry. The reason for this oversight was not documented.
- Patient 251 (OP-1 Putty) had a baseline ODI of 16, which is lower than the required score for study inclusion (30). The IRB was notified, and the patient continued on in the study.
- Patient 303 (OP-1 Putty and Autograft) was documented as having osteopenic bones which is a systemic condition that would affect the ability to evaluate the efficacy of the investigational product.
- Patient 356 (OP-1 Putty) was greater than 60% over the recommended ideal weight as described in the 1983 Metropolitan Height and Weight tables during enrollment. The IRB was notified of these protocol deviations.
- Patient 401 was discontinued from the study prior to surgery because the patient smoked tobacco.

10.2.3 Blood Collection

Patient 156 did not have blood drawn at 6 weeks. The IRB was notified of the deviation on February 13, 2003.

11. EFFICACY EVALUATION

11.1 DATA SETS ANALYZED

Forty-eight patients underwent surgery and constitute the Intent-to-Treat (ITT) population, and were evaluated for efficacy. The safety population consisted of all 48 patients who received treatment.

11.2 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Table 5 summarizes data for the 3 treatment groups.

11.2.1 Age and Gender

Mean age was 65 years, with the range among groups of 43 to 80 years. The groups were similar in age distribution, with a majority of patients in each group aged >65 years. Females accounted for more than half of the patients in each treatment group, and comprised 54.2% of the OP-1 Putty alone group, 58.3% of the autograft alone group, and 75% of the OP-1 Putty and autograft combination group.

11.2.2 Weight and Height

Weight and height were similar across the 3 treatment groups. The autograft alone group, however, demonstrated the least variance in these measurements within the group, whereas the OP-1 Putty group had the greatest variance.

11.2.3 Involved Level

The majority of patients in each treatment group had disease involvement at the L4-L5 level, with the OP-1 Putty alone group having more than 95% of patients with this presentation, with only a single patient (4.2%) having L3-L4 involvement. Involvement at L4-L5 was seen in 75% of patients and at L3-L4 in 25% of patients in both the combination OP-1 Putty with autograft group and the autograft alone group. Involvement of L5-S1 was not observed in any treatment group.

11.2.4 Disease Severity Indices

The ODI and measurements of degree of angular motion and translation movement were assessed at baseline and at specified time points throughout the study period. ODI scores pre-operatively were similar across the treatment groups, with a mean of 45.2 overall.

The mean extent of angular motion was 5.6 degrees, but the most motion was observed in the OP-1 Putty and autograft combination group, with a mean value of 7.0, compared to values of 5.9 in the OP-1 Putty alone group and 4.0 in the autograft alone groups.

Similarly, the mean extent of translational movement was 2.67 mm, but the most motion was observed in the combination treatment group, with a mean value of 3.55, compared with 2.40 in the OP-1 Putty alone group, and 2.60 in the autograft alone group. Based on

these data, the combination treatment group had the highest degree of instability at baseline.

11.2.5 Prior Treatments to Affected Level

Statistical Table 2.1 in Section 14 summarizes prior treatment history. Overall, the most commonly used treatment modalities used by patients prior to study enrollment included steroids (56.3%), non-steroidal medications (87.5%), physical therapy (79.2%), treatment with heat or ice (29.2%), rest (25%), and manipulation/chiropractic therapy (22.9%). Steroid usage was similar between the OP-1 Putty treatment groups, while more patients in the autograft alone group used physical therapy and non-steroidal medications, and fewer used steroids, although this difference was minor. Ultrasound and electrical stimulation were used by more patients in the OP-1 Putty alone group than in either of the other groups. Few patients in any group had undergone prior surgical procedures (laminectomy, facetectomy, foramenotomy, or discectomy).

Table 5. Demographic and Baseline Characteristics

Parameter	Statistic	Overall	OP-1 Putty Alone	OP-1 Putty/Autograft	Autograft Alone
Age (years)	N	48	24	12	12
	Mean	65	63	68	67
	Median	67	67	72	67
	Std. Dev.	10.4	11	11.1	7.8
Sex					
Male	n (%)	19 (39.6)	11 (45.8)	3 (25.0)	5 (41.7)
Female	n (%)	29 (60.4)	13 (54.2)	9 (75.0)	7 (58.3)
Weight (kg)	N	48	24	12	12
	Mean	85.3	90.3	80.2	80.3
	Median	82.8	91.2	76.7	82.8
	Std. Dev.	18.16	20.79	16.77	10.69
Height (cm)	N	48	24	12	12
	Mean	167.3	169.1	162.9	168.3
	Median	165.1	166.4	161.3	166.4
	Std. Dev.	10.79	11.6	10.89	8.26
Involved Level					
L3-L4	n (%)	7 (14.6)	1 (4.2)	3 (25.0)	3 (25.0)
L4-L5	n (%)	41 (85.4)	23 (95.8)	9 (75.0)	9 (75.0)
L5-S1	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Oswestry Disability Index	N	48	24	12	12
	Mean	45.2	45.9	42.3	46.6
	Median	44	45.6	40	45
	Std. Dev.	11.06	11.22	11.55	10.66
Degree of Angular Motion (degrees)^(a)	N	35	19	6	10
	Mean	5.6	5.9	7	4
	Median	4.8	5.6	6.9	3.9
	Std. Dev.	3.48	3.98	3.43	1.84
Translational Movement (mm)^(a)	N	37	20	7	10
	Mean	2.67	2.4	3.55	2.6
	Median	2.42	2.1	3.52	2.71
	Std. Dev.	1.575	1.441	1.749	1.655

Reference: Summary Table 2.1

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

(a) Average scores from 2 primary reviewers used.

11.3 MEASUREMENTS OF TREATMENT COMPLIANCE

Not applicable.

11.4 EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL PATIENT DATA

This was a feasibility study designed to assess safety and inform the design of future studies. Sample size was selected to allow descriptive statistics.

11.4.1 Analysis of Efficacy

Analysis of the overall success rate was calculated both with and without a ‘last observation carried forward’ (LOCF) approach using the ITT data set. LOCF analysis eliminates variation in the number of patients analyzed at specific time points due to patient withdrawals or missed study visits.

The primary focus will be efficacy at 24 months, although analyses have been performed on all available 3-, 6-, 9-, 12-, 24-, 36-, and 48-month data. Efficacy evaluations from the small number of patients who completed the 60-month and 72-month visits are provided in data listings found in Section 16.2.

Efficacy in this study was demonstrated by a comparison of clinical outcomes and fusion success for the 3 treatment groups: OP-1 Putty alone, OP-1 Putty and autograft, and autograft alone. The primary efficacy endpoint was overall success, a composite measure with the following components:

11.4.1.1 Overall Success

1. Radiographic demonstration of spinal fusion, which was also a composite measure comprising the following:
 - Presence of bridging (on AP or lateral radiographs) between transverse processes of 2 vertebral bodies
 - Angulation of $\leq 5^\circ$ on flexion/extension radiographs of the affected level
 - Translational movement of ≤ 2 mm on flexion/extension radiographs of the affected level
2. Improvement of at least 20% in the ODI from baseline
3. Absence of retreatments

Ancillary clinical outcomes included SF-36 Health Outcomes Survey scores, leg/buttock pain and donor site pain as measured by a visual analog scale, and disc height assessed radiographically.

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11.4.1.2 Overall Success Rates

Overall success will be described as a composite measure, and will be followed by descriptions of each component.

Table 6 summarizes overall success rates by study visit (3 months to 48 months) in the ITT population using the LOCF analysis, and Table 7 summarizes overall success rates without the LOCF. Percent success in these tables implies that patients in the OP-1 Putty groups may have experienced greater overall success than patients who received an autograft. However, wide variation was noted which suggests that sample sizes may not be sufficient to show precise estimates of success and therefore preclude the ability to assess differences between treatment groups.

Table 6. Overall Success Rate (LOCF, Intent-to-Treat Population)

Time Point	OP-1 Putty Alone			OP-1 Putty/Autograft			Autograft Alone		
	Pts. (N)	Number (%) of Successes	CI for % of Successes*	Pts. (N)	Number (%) of Successes	CI for % of Successes*	Pts. (N)	Number (%) of Successes	CI for % of Successes*
3 Months	24	10 (41.7)	(22.1, 63.4)	12	4 (33.3)	(9.9, 65.1)	12	4 (33.3)	(9.9, 65.1)
6 Months	24	14 (58.3)	(36.6, 77.9)	12	5 (41.7)	(15.2, 72.3)	12	4 (33.3)	(9.9, 65.1)
9 Months	24	11 (45.8)	(25.6, 67.2)	12	5 (41.7)	(15.2, 72.3)	12	3 (25.0)	(5.5, 57.2)
12 Months	24	11 (45.8)	(25.6, 67.2)	12	5 (41.7)	(15.2, 72.3)	12	4 (33.3)	(9.9, 65.1)
24 Months	24	11 (45.8)	(25.6, 67.2)	12	5 (41.7)	(15.2, 72.3)	12	4 (33.3)	(9.9, 65.1)
36 Months	24	11 (45.8)	(25.6, 67.2)	12	4 (33.3)	(9.9, 65.1)	12	3 (25.0)	(5.5, 57.2)
48 Months	24	11 (45.8)	(25.6, 67.2)	12	5 (41.7)	(15.2, 72.3)	12	3 (25.0)	(5.5, 57.2)

Reference: Summary Table 3

* The 95% confidence interval for the proportion of patients who succeed is based on the exact (Clopper-Pearson) method.

Note: Missing data were imputed based on last observation carried forward method.

Table 7. Overall Success Rate (Non-LOCF, Intent-to-Treat Population)

Time Point	OP-1 Putty Alone			OP-1 Putty/Autograft			Autograft Alone		
	Pts. (N)	Number (%) of Successes	CI for % of Successes*	Pts. (N)	Number (%) of Successes	CI for % of Successes*	Pts. (N)	Number (%) of Successes	CI for % of Successes*
3 Months	24	10 (41.7)	(22.1, 63.4)	12	4 (33.3)	(9.9, 65.1)	12	4 (33.3)	(9.9, 65.1)
6 Months	23	14 (60.9)	(38.5, 80.3)	11	5 (45.5)	(16.7, 76.6)	12	4 (33.3)	(9.9, 65.1)
9 Months	22	10 (45.5)	(24.4, 67.8)	10	5 (50.0)	(18.7, 81.3)	9	3 (33.3)	(7.5, 70.1)
12 Months	21	11 (52.4)	(29.8, 74.3)	10	5 (50.0)	(18.7, 81.3)	9	4 (44.4)	(13.7, 78.8)
24 Months	18	10 (55.6)	(30.8, 78.5)	9	4 (44.4)	(13.7, 78.8)	9	3 (33.3)	(7.5, 70.1)
36 Months	18	9 (50.0)	(26.0, 74.0)	8	3 (37.5)	(8.5, 75.5)	5	1 (20.0)	(0.5, 71.6)
48 Months	16	10 (62.5)	(35.4, 84.8)	7	3 (42.9)	(9.9, 81.6)	6	2 (33.3)	(4.3, 77.7)

Reference: Summary Table 3.2

* The 95% confidence interval for the proportion of patients who succeed is based on the exact (Clopper-Pearson) method.

Note: Missing data were not imputed.

11.4.1.3 Radiographic Success Rates

One of the components of the overall success rate, fusion success was determined radiographically by blinded radiologists. Radiographic success was a composite of evaluations of bridging bone development (Section 11.4.1.3.1), degree of angular motion (Section 11.4.1.3.2), and translational movement (Section 11.4.1.3.3). As shown in Table 8, patients in both OP-1 Putty groups appeared to demonstrate greater radiographic success versus autograft. However, wide variation was noted which suggests that sample sizes may not be sufficient to show precise estimates of success and therefore preclude the ability to assess differences between treatment groups.

Table 9 presents a summary of the 3 components of radiographic success at 12 months and 24 months. The proportion of patients who achieved success in angular motion appeared to be greater in the OP-1 Putty alone treatment group versus other treatment groups at both 12 and 24 months.

Table 8. Success Rate Based on Radiographic Results (Intent-to-Treat Population)

Time Point	OP-1 Putty Alone			OP-1 Putty/Autograft			Autograft Alone		
	Pts. (N)	Number (%) of Successes	CI for % of Successes*	Pts. (N)	Number (%) of Successes	CI for % of Successes*	Pts. (N)	Number (%) of Successes	CI for % of Successes*
3 Mo.	24	11 (45.8)	(25.6, 67.2)	12	5 (41.7)	(15.2, 72.3)	12	7 (58.3)	(27.7, 84.8)
6 Mo.	24	15 (62.5)	(40.6, 81.2)	11	6 (54.5)	(23.4, 83.3)	12	6 (50.0)	(21.1, 78.9)
9 Mo.	23	12 (52.2)	(30.6, 73.2)	10	6 (60.0)	(26.2, 87.8)	9	5 (55.6)	(21.2, 86.3)
12 Mo.	21	14 (66.7)	(43.0, 85.4)	10	6 (60.0)	(26.2, 87.8)	10	6 (60.0)	(26.2, 87.8)
24 Mo.	19	11 (57.9)	(33.5, 79.7)	10	5 (50.0)	(18.7, 81.3)	10	4 (40.0)	(12.2, 73.8)
36 Mo.	18	10 (55.6)	(30.8, 78.5)	8	4 (50.0)	(15.7, 84.3)	6	3 (50.0)	(11.8, 88.2)
48 Mo.	16	11 (68.8)	(41.3, 89.0)	7	4 (57.1)	(18.4, 90.1)	6	3 (50.0)	(11.8, 88.2)

Reference: Summary Table 4.1

* The 95% confidence interval for the proportion of patients who succeed is based on the exact (Clopper-Pearson) method.

Note: Missing data were not imputed.

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Table 9. Components of Radiographic Success Rates: Bridging Bone, Degree of Angular Motion, Translational Movement

	OP-1 Putty Alone n (%)	OP-1 Putty/Autograft n (%)	Autograft Alone n (%)
Bridging Bone			
12 Months	17/21 (81.0)	10/10 (100.0)	9/10 (90.0)
24 Months	15/19 (78.9)	7/10 (70.0)	9/10 (90.0)
Angulation Success			
12 Months	15/21 (71.4)	6/10 (60.0)	6/10 (60.0)
24 Months	12/18 (66.7)	5/10 (50.0)	5/10 (50.0)
Translational Movement			
12 Months	16/20 (80.0)	9/10 (90.0)	10/10 (100.0)
24 Months	16/18 (88.9)	6/10 (60.0)	7/10 (70.0)

Reference: Summary Tables 4.1.2A, 4.1.2B, 4.1.3A, 4.1.3B, and 5.5.

11.4.1.3.1 Bridging Bone Development

Evidence of bridging bone development was seen in all treatment groups, as shown in Table 10.

Table 10. Presence of Bridging Bone on AP or Lateral Radiographs

Time Point	OP-1 Putty Alone	OP-1 Putty/ Autograft	Autograft Alone
	n (%)	n (%)	n (%)
3 Months	18 (75.0)	11 (91.7)	11 (91.7)
6 Months	22 (91.7)	11 (100.0)	11 (91.7)
9 Months	20 (87.0)	9 (90.0)	8 (88.9)
12 Months	17 (81.0)	10 (100.0)	9 (90.0)
24 Months	15 (78.9)	7 (70.0)	9 (90.0)
36 Months	15 (83.3)	5 (62.5)	5 (83.3)
48 Months	13 (81.3)	4 (57.1)	3 (50.0)

Reference: Summary Table 5.5

Note: The analysis data only include patients with an evaluation at the specified time point. When reviewers disagreed and no secondary review was performed because the reviewers were in agreement with regard to the overall radiographic assessment, the patient is considered as not having bridging bone for the associated time point.

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11.4.1.3.2 Angular Motion

Table 11 summarizes changes in angular motion at the treated level at specified time points as compared to baseline. Mean degree of angular motion decreased from baseline in the OP-1 Putty alone treatment group at both 12 and 24 months, indicating improvement in spinal stability. However, mean angular motion increased in autograft, suggesting an advantage in stabilization with OP-1 Putty.

Table 11. Angular Motion (Degrees)

Time Point	Statistic	OP-1 Putty Alone		OP-1 Putty/Autograft		Autograft Alone	
		Actual	Change from Baseline	Actual	Change from Baseline	Actual	Change from Baseline
Baseline	n	19		6		10	
	Mean	5.9		7		4	
	Median	5.6		6.9		3.9	
	Std. Dev.	3.98		3.43		1.84	
3 Months	n	24	19	11	5	11	10
	Mean	5.1	-0.7	5.4	-1.4	4.3	0.6
	Median	3.5	-1.4	4.6	-0.6	2.8	1.7
	Std. Dev.	4.94	6.07	2.67	3.1	4.09	4.08
6 Months	n	24	19	11	5	12	10
	Mean	5.4	-0.8	5.7	-1.2	4.6	0.3
	Median	3.7	-0.5	3.6	-0.2	4.2	-0.1
	Std. Dev.	5.32	6.26	5.03	5.99	2.6	3.01
12 Months	n	20	17	10	4	10	8
	Mean	3.8	-2.5	4.7	-0.4	4.5	0.7
	Median	2.4	-1	3	-1	2.8	0.8
	Std. Dev.	4.42	4.3	4.12	3.36	3.39	3.17
24 Months	n	19	17	9	4	10	8
	Mean	3.8	-1.8	5.5	2.4	5.7	2.5
	Median	3.3	-1.4	2.1	4.2	5.5	3.2
	Std. Dev.	2.86	3.61	5.5	4.29	3.49	3.56
36 Months	n	17	14	8	3	5	4
	Mean	4.5	-1.2	5.9	-2.8	2.7	-1.7
	Median	3.5	-2.7	2.1	-4.4	2.2	-1.2
	Std. Dev.	4.02	5.4	6.34	6.11	2.47	1.59
48 Months	n	15	14	7	4	6	5
	Mean	3.2	-2.8	3.2	-3	0.9	-2.5
	Median	1.8	-2.6	1.3	-2.9	0.7	-2.2
	Std. Dev.	3.43	2.76	3.51	2.47	0.59	1.52

Reference: Summary Table 5.3

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

Note: The results from the third independent reviewer were used in the analysis. If there was no third reviewer assessment, the average scores from the first two reviewers were used.

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11.4.1.3.3 Translational Movement

Table 12 summarizes changes in translational movement at the treated level at specified time points as compared to baseline. No specific trends are suggested by these data.

Table 12. Translational Movement (mm)

Time Point	Statistic	OP-1 Putty Alone		OP-1 Putty/Autograft		Autograft Alone	
		Actual	Change from Baseline	Actual	Change from Baseline	Actual	Change from Baseline
Baseline	n	20		7		10	
	Mean	2.4		3.55		2.6	
	Median	2.1		3.52		2.71	
	Std. Dev.	1.441		1.749		1.655	
3 Months	n	24	20	11	6	11	10
	Mean	1.8	-1.1	1.22	-1.94	1.2	-1.35
	Median	1.04	-1.07	0.92	-2.22	1.21	-1.66
	Std. Dev.	1.798	2.265	1.223	1.721	0.688	2
6 Months	n	24	20	11	6	12	10
	Mean	1.84	-0.58	1.39	-1.71	1.46	-0.95
	Median	1.46	-1.02	1.16	-1.59	1.29	-0.47
	Std. Dev.	1.698	2.151	0.866	1.298	0.967	2.01
12 Months	n	20	17	10	5	10	8
	Mean	1.29	-0.95	1.46	-1.93	0.81	-2.03
	Median	0.98	-1.2	1.13	-3.65	0.78	-2.26
	Std. Dev.	1.208	1.627	1.47	3.443	0.734	2.388
24 Months	n	18	16	9	4	10	8
	Mean	0.99	-1.34	2.16	0.4	1.47	-1.25
	Median	0.85	-1.43	0.91	1.66	1.13	-1.61
	Std. Dev.	1.014	1.54	2.228	3.839	1.458	1.413
36 Months	n	17	14	8	4	5	4
	Mean	1.25	-1.18	1.33	-2.93	0.62	-2.71
	Median	1.26	-1.06	0.66	-3.76	0.1	-2.36
	Std. Dev.	1.21	1.251	1.336	2.907	0.804	1.558
48 Months	n	15	14	7	5	6	5
	Mean	0.8	-1.7	1.39	-1.9	0.45	-1.76
	Median	0.31	-1.45	1.36	-2.01	0.5	-1.78
	Std. Dev.	1.048	1.545	1.03	2.82	0.406	1.381

Reference: Summary Table 5.4

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

Note: The results from the third independent reviewer were used in the analysis. If there was no third reviewer assessment, the average scores from the first two reviewers were used.

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11.4.1.4 Oswestry Disability Index

Table 13 summarizes success as measured by 20% improvement in the ODI, a questionnaire completed by patients that reflects their perceptions of components of disability: pain, activities of daily living, and mobility. The percent success for both OP-1 Putty treatment groups appeared to suggest an advantage for OP-1 Putty over autograft.

Table 14 summarizes mean changes in the ODI.

Table 13. Success Rate Based on Oswestry Disability Index (Intent-to-Treat Population)

Time Point	OP-1 Putty Alone			OP-1 Putty/Autograft			Autograft Alone		
	Pts. (N)	Number (%) of Successes	CI for % of Successes*	Pts. (N)	Number (%) of Successes	CI for % of Successes*	Pts. (N)	Number (%) of Successes	CI for % of Successes*
3 Months	24	21 (87.5)	(67.6, 97.3)	12	10 (83.3)	(51.6, 97.9)	12	8 (66.7)	(34.9, 90.1)
6 Months	23	21 (91.3)	(72.0, 98.9)	11	8 (72.7)	(39.0, 94.0)	12	8 (66.7)	(34.9, 90.1)
9 Months	23	20 (87.0)	(66.4, 97.2)	11	9 (81.8)	(48.2, 97.7)	9	6 (66.7)	(29.9, 92.5)
12 Months	21	18 (85.7)	(63.7, 97.0)	11	9 (81.8)	(48.2, 97.7)	10	8 (80.0)	(44.4, 97.5)
24 Months	18	17 (94.4)	(72.7, 99.9)	9	8 (88.9)	(51.8, 99.7)	10	6 (60.0)	(26.2, 87.8)
36 Months	19	16 (84.2)	(60.4, 96.6)	8	4 (50.0)	(15.7, 84.3)	6	3 (50.0)	(11.8, 88.2)
48 Months	19	14 (73.7)	(48.8, 90.9)	8	6 (75.0)	(34.9, 96.8)	7	4 (57.1)	(18.4, 90.1)

Reference: Summary Table 4.2

*The 95% confidence interval for the proportion of patients who succeed is based on the exact (Clopper-Pearson) method.

Note: Missing data were not imputed.

5.2 Pilot Study (Content from P060021 Original PMA, CSR S99-01US, Section 7-13)

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Table 14. Oswestry Disability Index (Intent-to-Treat Population)

Time Point	Statistic	OP-1 Putty Alone		OP-1 Putty/Autograft		Autograft Alone	
		Actual	Change from Baseline	Actual	Change from Baseline	Actual	Change from Baseline
Baseline	n	24		12		12	
	Mean	45.9		42.3		46.6	
	Median	45.6		40.0		45.0	
	Std. Dev.	11.22		11.55		10.66	
6 Weeks	n	23	23	11	11	12	12
	Mean	32.0	-13.3	27.1	-15.0	30.3	-16.3
	Median	26.0	-18.4	28.0	-15.8	27.4	-23.3
	Std. Dev.	17.52	19.95	14.73	11.43	15.26	16.36
3 Months	n	24	24	12	12	12	12
	Mean	21.4	-24.5	18.6	-23.7	25.5	-21.1
	Median	17.9	-28.2	17.8	-25.0	25.0	-28.6
	Std. Dev.	13.32	16.94	12.47	15.51	16.95	17.20
6 Months	n	23	23	11	11	12	12
	Mean	17.9	-27.6	24.1	-19.1	26.1	-20.5
	Median	18.0	-31.6	22.0	-26.0	25.3	-23.2
	Std. Dev.	10.94	13.75	18.68	21.82	16.15	18.78
12 Months	n	21	21	11	11	10	10
	Mean	16.2	-29.9	15.7	-26.7	19.6	-28.7
	Median	12.0	-34.0	14.0	-22.2	13.8	-35.6
	Std. Dev.	15.84	17.61	12.87	18.01	15.25	17.51
24 Months	n	18	18	9	9	10	10
	Mean	11.0	-35.0	17.2	-25.4	32.5	-15.8
	Median	7.0	-37.0	15.6	-26.0	36.9	-17.0
	Std. Dev.	13.85	16.10	15.81	18.41	15.22	19.17
36 Months	n	19	19	8	8	6	6
	Mean	19.3	-28.5	26.4	-13.1	27.8	-16.5
	Median	10.0	-28.0	28.3	-11.9	29.0	-9.0
	Std. Dev.	16.36	17.89	13.87	13.79	18.63	22.87
48 Months	n	18	18	8	8	7	7
	Mean	19.8	-27.1	22.4	-19.8	26.3	-17.3
	Median	13.0	-32.9	13.0	-19.0	24.0	-22.0
	Std. Dev.	17.58	20.43	20.51	26.07	20.57	26.33

Reference: Summary Table 11

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

11.4.1.5 Retreatment

Table 15 below shows that patients in all treatment groups experienced success rates greater than 90%, based upon the lack of need for retreatment. However, 3 patients in the OP-1 Putty-treated groups did require retreatment.

- Patient 105 (OP-1 Putty and autograft) underwent retreatment (supplemental fixation) at 7.6 months post-operatively for pseudarthrosis.
- Patient 153 (OP-1 Putty alone) underwent retreatment (reoperation intended to promote fusion) at 28 months post-operatively due to excessive back pain, not at the operative level.
- Patient 455 (OP-1 Putty alone) underwent retreatment (supplemental fixation) at 28.9 months post-operatively for pseudarthrosis.

These events were recorded as SAEs (refer to Section 12.3).

Table 15. Success Rate Based on Retreatment (Intent-to-Treat Population)

Time Point	OP-1 Putty Alone			OP-1 Putty/Autograft			Autograft Alone		
	Pts. (N)	Number (%) of Successes	CI for % of Successes*	Pts. (N)	Number (%) of Successes	CI for % of Successes*	Pts. (N)	Number (%) of Successes	CI for % of Successes*
3 Mo.	24	24 (100.0)	(85.8, 100)	12	12 (100.0)	(73.5, 100)	12	12 (100.0)	(73.5, 100)
6 Mo.	24	24 (100.0)	(85.8, 100)	12	12 (100.0)	(73.5, 100)	12	12 (100.0)	(73.5, 100)
9 Mo.	24	24 (100.0)	(85.8, 100)	12	11 (91.7)	(61.5,99.8)	12	12 (100.0)	(73.5, 100)
12 Mo.	24	24 (100.0)	(85.8, 100)	12	11 (91.7)	(61.5,99.8)	12	12 (100.0)	(73.5, 100)
24 Mo.	24	24 (100.0)	(85.8, 100)	12	11 (91.7)	(61.5,99.8)	12	12 (100.0)	(73.5, 100)
36 Mo.	24	22 (91.7)	(73.0,99.0)	12	11 (91.7)	(61.5,99.8)	12	12 (100.0)	(73.5, 100)
48 Mo.	24	22 (91.7)	(73.0,99.0)	12	11 (91.7)	(61.5,99.8)	12	12 (100.0)	(73.5, 100)

Reference: Summary Table 4.3

* The 95% confidence interval for the proportion of patients who succeed is based on the exact (Clopper-Pearson) method.

11.4.2 Ancillary Clinical Outcomes

The following are outcome measures identified in the protocol that may be relevant to both safety and efficacy.

11.4.2.1 Disc Height

An additional radiographic assessment of disc height is included here to show stability or change in disc height over time. Baseline for this assessment was measured post-operatively at 6 weeks. Table 16 summarizes changes from baseline in disc height for anteroposterior views at specified time points.

Table 17 summarizes measurements of disc height from lateral views.

5.2 Pilot Study (Content from P060021 Original PMA, CSR S99-01US, Section 7-13)

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Table 16. Disc Height (Anteroposterior View)

Time Point	Statistic	OP-1 Putty Alone		OP-1 Putty/Autograft		Autograft Alone	
		Actual (mm)	Change from Baseline (mm)	Actual (mm)	Change from Baseline (mm)	Actual (mm)	Change from Baseline (mm)
Baseline (6 weeks)	N	22		12		11	
	Mean	9.94		11.27		9.84	
	Median	10.5		11.56		10.64	
	Std. Dev.	3.036		2.986		2.757	
3 Months	n	24	22	12	12	12	11
	Mean	10.91	1.05	10.99	-0.28	10.08	0.26
	Median	11.18	1.06	10.49	-0.01	10.2	-0.01
	Std. Dev.	2.396	2.743	3.877	2.532	3.049	2.399
6 Months	n	24	22	10	10	12	11
	Mean	9.47	-0.37	10.2	-1.23	9.56	-0.22
	Median	9.59	0.23	9.19	-0.54	9.59	-1.01
	Std. Dev.	2.536	3.637	2.844	3.435	2.623	2.685
12 Months	n	21	19	10	10	10	9
	Mean	8.98	-0.78	9.71	-1.76	9.83	0.47
	Median	9.14	-0.9	8.15	-1.89	9.58	-0.6
	Std. Dev.	2.75	3.341	3.972	4.63	4.187	4.167
24 Months	n	15	14	9	9	8	7
	Mean	9.85	-0.41	8.18	-3.19	7.28	-2.79
	Median	10.05	-0.16	8.23	-2.1	8.15	-3.17
	Std. Dev.	3.21	3.052	2.242	3.874	2.38	3.316
36 Months	n	18	17	8	8	6	5
	Mean	8.11	-2.18	8.43	-3.29	7.76	-2.7
	Median	8.31	-1.97	7.68	-1.66	8.11	-2.15
	Std. Dev.	2.942	3.079	2.514	3.389	1.331	2.458
48 Months	n	15	14	5	5	6	5
	Mean	7.39	-2.62	6.63	-5.43	6.12	-4.3
	Median	6.82	-1.61	6.67	-6.83	6.68	-3.66
	Std. Dev.	3.045	3.414	3.008	4.246	2.247	2.144

Reference: Summary Table 5.1

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

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Table 17. Disc Height (Lateral Views)

Time Point	Statistic	OP-1 Putty Alone		OP-1 Putty/Autograft		Autograft Alone	
		Actual	Change from Baseline	Actual	Change from Baseline	Actual	Change from Baseline
Baseline (6 weeks)	n	23		12		11	
	Mean	10.46		9.88		10.95	
	Median	10.49		9.06		10.51	
	Std. Dev.	2.672		2.947		3.036	
3 Months	n	24	23	12	12	12	11
	Mean	11.41	1.18	10.79	0.9	11.28	0.18
	Median	11.56	1.39	10.95	-0.46	12.01	0.18
	Std. Dev.	2.67	1.507	3.188	2.888	3.584	1.505
6 Months	n	24	23	11	11	12	11
	Mean	10.31	0.02	10	-0.29	10.48	-0.49
	Median	10.57	0.29	9.9	0.47	10.55	-0.16
	Std. Dev.	3.174	2.601	2.914	2.988	3.127	1.092
12 Months	n	21	20	10	10	10	9
	Mean	9.94	0.01	9.51	-0.74	10.23	-1
	Median	9.89	-0.28	9.28	-0.41	10.4	-2.12
	Std. Dev.	3.074	1.69	2.963	2.032	3.451	3.716
24 Months	n	19	18	10	10	10	9
	Mean	8.83	-1.2	9.67	-0.57	8.14	-3.2
	Median	8.36	-1.12	9.67	-0.4	8.3	-3.37
	Std. Dev.	3.465	2.236	3.234	2.716	2.806	2.061
36 Months	n	18	18	8	8	6	5
	Mean	7.76	-2.55	7.4	-3.74	7.29	-3.62
	Median	7.81	-2.34	6.29	-3.89	6.89	-3.69
	Std. Dev.	2.792	1.803	2.797	2.774	1.568	2.584
48 Months	n	16	15	7	7	6	5
	Mean	7.21	-2.99	6.32	-3.21	6.35	-4.5
	Median	7.07	-2.74	5.61	-3.52	6.44	-3.81
	Std. Dev.	2.457	2.674	3.715	2.621	3.25	1.867

Reference: Summary Table 5.2

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

11.4.2.2 Pain Self-Assessment**11.4.2.2.1 Leg/Buttock Pain**

Patients completed an assessment of pre-operative and post-operative leg/buttock pain, and of post-operative donor site pain (for the 2 groups receiving autograft) using a visual analog scale (VAS) at specified time points during the study (refer to Statistical Table 6.1 in Section 14).

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11.4.2.2.2 Donor Site Pain

Analysis of VAS data for donor site pain is presented in Statistical Table 6.2 in Section 14. Overall, mean donor site pain was greater in the autograft alone group when compared with the OP-1 Putty and autograft combination group at 12, 24, and 36 months. However, wide variability was noted for all time points for both groups, which precluded the ability to make conclusions about group differences.

Table 18 summarizes severity of donor site pain in the autograft treatment groups.

Table 18. Donor Site Pain Status

Visit	Number (%) of Patients							
	OP-1 Putty/Autograft				Autograft Alone			
	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe
6 Months	5 (45.5)	3 (27.3)	2 (18.2)	1 (9.1)	2 (16.7)	6 (50.0)	2 (16.7)	2 (16.7)
12 Months	7 (63.6)	3 (27.3)	1 (9.1)	0 (0.0)	3 (30.0)	4 (40.0)	1 (10.0)	1 (10.0)
24 Months	5 (55.6)	0 (0.0)	3 (33.3)	0 (0.0)	3 (30.0)	2 (20.0)	4 (40.0)	0 (0.0)
36 Months	4 (50.0)	0 (0.0)	2 (25.0)	1 (12.5)	2 (33.3)	1 (16.7)	1 (16.7)	1 (16.7)
48 Months	5 (62.5)	1 (12.5)	1 (12.5)	1 (12.5)	2 (28.6)	2 (28.6)	2 (28.6)	1 (14.3)

Reference: Summary Table 6.3

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

There were 8 AEs of donor site complications reported during the study period, of which 2 occurred in the combination group, and 6 in the autograft alone group (see Section 12.2.2.2). These events may have contributed to both the incidence and severity of pain experienced by patients in the autograft groups.

11.4.2.3 SF-36 Questionnaire

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 data consist of an overall physical summary measure and an overall mental summary measure, in addition to 8 component scores: physical, mental, 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 19 reports physical component summary scores during the study period. The treatment groups were comparable at baseline (with average scores of between 31 and 33), and all groups showed improvements in scores post-treatment.

Table 20 summarizes physical functioning scores during the study period. These are highly correlated with the physical component summary scores previously described.

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Table 19. SF-36 Health Survey Scale: Physical Component

Visit	Statistic	OP-1 Putty Alone		OP-1 Putty/Autograft		Autograft Alone	
		Actual Value	Change from Baseline	Actual Value	Change from Baseline	Actual Value	Change from Baseline
Baseline	n	24	N/A	12	N/A	12	N/A
	Mean	31.3	N/A	30.4	N/A	32.8	N/A
	Median	31.7	N/A	29.7	N/A	30.4	N/A
	Std. Dev.	5.45	N/A	4.08	N/A	7.16	N/A
6 Weeks	n	23	23	11	11	11	11
	Mean	35.1	3.8	36	5.6	34.2	2.9
	Median	36.1	5.6	40.8	8.7	30.9	0.3
	Std. Dev.	7.33	7.85	11.22	9.89	8.13	9.05
3 Months	n	24	24	12	12	12	12
	Mean	39.4	8.1	40.2	9.8	38.9	6.1
	Median	38.7	8.7	41.6	9.6	35.4	7
	Std. Dev.	7.97	8.34	8.77	7.42	8.06	11.85
6 Months	n	23	23	11	11	12	12
	Mean	40.7	9.3	40.7	10.6	38.1	5.4
	Median	39.3	7.4	39.3	11.6	36.5	3.7
	Std. Dev.	8.4	8.76	12.4	12.31	10.4	13.12
9 Months	n	23	23	11	11	9	9
	Mean	45.9	14.6	41.6	11	38.1	5.7
	Median	44.2	15.5	44.2	12.8	38.4	4.1
	Std. Dev.	9.14	9.4	9.84	9.97	10.53	12.68
12 Months	n	21	21	10	10	10	10
	Mean	46	14.3	45.2	14.5	40.5	8.8
	Median	49.4	16.2	47.9	15.7	41.3	8.9
	Std. Dev.	10.41	10.29	7.53	6.33	10.34	12.86
24 Months	n	18	18	9	9	10	10
	Mean	48	16	42.3	11.5	31.5	-0.3
	Median	51.5	21.3	43.5	10.9	34	2.4
	Std. Dev.	11.54	13.37	9.79	8.23	6.68	8.4
36 Months	n	19	19	8	8	6	6
	Mean	43	11.9	37.5	7.1	37.6	8.5
	Median	42.1	6.2	39.2	8.8	38.1	10.3
	Std. Dev.	12.9	14.13	11.36	11.18	12.31	12.01
48 Months	n	18	18	8	8	7	7
	Mean	43.1	11.1	38.5	8.1	34.9	5.8
	Median	43.5	10.4	42.6	6	32.3	4.6
	Std. Dev.	11.73	13.59	14.75	13.44	10.89	8.28

Reference: Summary Table 7.1

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Table 20. SF-36 Health Survey Scale: Physical Functioning Scale (Intent-to-Treat Population)

Visit	Statistic	OP-1 Putty Alone		OP-1 Putty/Autograft		Autograft Alone	
		Actual Value	Change from Baseline	Actual Value	Change from Baseline	Actual Value	Change from Baseline
Baseline	n	24	N/A	12	N/A	12	N/A
	Mean	25.7	N/A	27.4	N/A	30.1	N/A
	Median	23.6	N/A	26.7	N/A	28.8	N/A
	Std. Dev.	6.62	N/A	5.78	N/A	9.53	N/A
6 Weeks	n	23	23	11	11	12	12
	Mean	33.7	7.5	32.9	5.5	32.5	2.4
	Median	36.2	10.5	32	6.3	29.9	4.2
	Std. Dev.	9.2	9.87	9.9	10.07	8.68	13.99
3 Months	n	24	24	12	12	12	12
	Mean	39	13.3	40.4	13	34.9	4.9
	Median	41.4	14.7	40.6	12.6	35.1	3.1
	Std. Dev.	9.41	9.35	8.53	7.55	8.69	12.85
6 Months	n	23	23	11	11	12	12
	Mean	39	13.4	37.1	10.1	35.8	5.7
	Median	40.4	14.7	38.3	10.5	35.1	3.1
	Std. Dev.	9.54	8.54	13.41	9.23	9.43	15.26
9 Months	n	23	23	11	11	9	9
	Mean	43.3	17.4	39.6	11.8	36.4	6.8
	Median	42.5	18.9	40.4	12.6	32	4.2
	Std. Dev.	9.75	10.74	7.1	6.78	9.41	15.55
12 Months	n	21	21	10	10	10	10
	Mean	43.4	17.7	41.7	13.5	39.5	10.3
	Median	46.7	18.9	43.5	11.5	40.4	15.7
	Std. Dev.	9.74	11.23	7.72	6.63	9.02	14.14
24 Months	n	18	18	9	9	10	10
	Mean	46.8	21	39.4	11.2	31.8	2.7
	Median	48.8	24.1	40.4	6.3	32	2.1
	Std. Dev.	9.2	12.17	8.13	9.61	5.72	11.91
36 Months	n	19	19	8	8	6	6
	Mean	41.8	16.7	34.3	6.3	33.6	6.5
	Median	42.5	14.7	36.2	5.2	34.8	7.0
	Std. Dev.	11.99	13.57	9.61	8.83	11.34	11.30
48 Months	n	18	18	8	8	7	7
	Mean	42.2	16.5	36.2	8.4	34.1	7.2
	Median	44.6	12.6	35.1	7.3	34.1	6.3
	Std. Dev.	10.81	12.19	12.88	13.17	8.98	11.02

Reference: Summary Table 7.3

11.5 EFFICACY CONCLUSIONS

Table 21 presents a summary of results for the primary endpoint, Overall Success, and for the 3 components of Overall Success: Radiographic Success, ODI, and Retreatment, at 24 months post-procedure.

- Overall Success: treatment groups appear to be comparable at 24 months
- Greater Radiographic Success is noted in both OP-1 Putty groups versus autograft, but small sample sizes preclude the ability to assess differences between treatment groups.
- Angular motion: The proportion of patients who achieved success in angular motion appeared to be greater in the OP-1 Putty alone treatment group versus other treatment groups at both 12 and 24 months.
- ODI percent success for both OP-1 Putty treatment groups appeared to suggest an advantage for OP-1 Putty over autograft.
- Patient 105 (OP-1 Putty and autograft) underwent retreatment for pseudarthrosis (supplemental fixation) at 7.6 months post-operatively. Two additional patients (Patients 153 and 455 in the OP-1 Putty alone group) underwent retreatment after 24 months.
- Treatment groups were similar for disc height, leg/buttock pain, donor site pain, and SF-36 scores.

A potentially important and clinically meaningful advantage of OP-1 Putty over autograft is shown by greater success in angulation and ODI scores.

Table 21. Overall Success Rates, and Success for Components of Overall Success at 24 Months

Outcome	OP-1 Putty Alone		OP-1 Putty/Autograft		Autograft Alone	
	Number Patients	Number (%) Successes	Number Patients	Number (%) Successes	Number Patients	Number (%) Successes
Overall success with LOCF	24	11 (45.8)	12	5 (41.7)	12	4 (33.3)
Overall success without LOCF	18	10 (55.6)	9	4 (44.4)	9	3 (33.3)
Radiographic success						
Bridging Bone	19	11 (57.9)	10	5 (50.0)	10	4 (40.0)
Angulation Success	19	15 (78.9)	10	7 (70.0)	10	9 (90.0)
Translational Movement	18	14 (77.8)	10	5 (50.0)	10	5 (50.0)
ODI	18	16 (88.9)	10	6 (60.0)	10	7 (70.0)
ODI	18	17 (94.4)	9	8 (88.9)	10	6 (60.0)
No Retreatment	24	24 (100.0)	12	11 (91.7)	12	12 (100.0)

12. SAFETY EVALUATION

12.1 DURATION OF OBSERVATION

All 48 patients randomized in the study were treated once with 2 units (7.0 mg) of OP-1 Putty alone, 2 units (7.0 mg) of OP-1 Putty and autograft, or autograft alone. The overall duration of observation following treatment with OP-1 Putty alone, OP-1 Putty in combination with autograft, or autograft alone is presented by treatment group for the Safety Population in Table 22. The average length of observation after treatment with OP-1 Putty alone was 45.3 months (range 8.9 to 63.2 months); 51.1 months for patients after treatment with OP-1 Putty and autograft (range 8.9 to 71.8 months); and 46.5 months after treatment with autograft alone (range 26.3 to 69.9 months).

Table 22. Average Length (Months) of Observation After Randomized Treatment

Statistic	OP-1 Putty Alone	OP-1 Putty/Autograft	Autograft Alone
N	24	12	12
Mean	45.3	51.1	46.5
Median	48.4	57.8	49.8
Std. Dev.	15.82	17.97	14.34
Minimum	8.9	8.9	26.3
Maximum	63.2	71.8	69.9

Reference: Summary Table 8.1

12.2 ADVERSE EVENTS

The safety population consisted of all 48 patients who received treatment. AEs were reported for all patients in the study.

12.2.1 Summary of Adverse Events

A total of 48 patients were treated in the study. The treatment assignments were as follows: 24 patients (50%) were randomized to receive OP-1 Putty alone, 12 patients (25%) were randomized to receive OP-1 Putty and autograft, and 12 patients (25%) were randomized to receive autograft alone.

In this study, AEs occurred in all 48 patients (100%), and adverse reactions occurred in 5 patients (10%). A total of 200 AEs were reported in 48 patients across all treatment arms. As shown in Table 25, AEs occurred in 100% of patients across all treatment groups: 149 in the 36 patients in the OP-1 Putty treatment groups (with or without autograft), and 51 in the 12 patients treat who received autograft.

Over the course of the study, 8 malignancies were reported in 4 patients across all treatment arms (refer to Table 29). None of these events were attributed to OP-1 Putty

treatment. Malignancies were reported in all treatment groups; however, their occurrence was not unexpected in this patient population of generally older adults.

Eighteen patients (38%) experienced 36 SAEs for which narratives have been provided in Section 12.3.2.3. There were 18 SAEs in the OP-1 Putty alone group. The SAEs were: aortic valve disease, pleural effusion, cataract bilateral, and eye disorder (Patient 151); arthralgia and back pain (Patient 153); breast cancer and renal artery stenosis (Patient 154); chest pain (Patient 156); cosmetic surgery (Patient 351); arthralgia (2) (Patient 352); arthralgia and hip arthroplasty (Patient 358); knee arthropathy (Patient 452); pseudarthrosis (Patient 455); and lung and prostate carcinoma (Patient 553). In the OP-1 Putty and autograft combination treatment group, there were 12 SAEs: coronary artery disease, bowel volvulus, arthralgia, and groin pain (Patient 101); pseudarthrosis (Patient 105); diarrhea, malignant melanoma (2), and hypertension (Patient 107); upper extremity fracture and back pain (Patient 204); and pulmonary edema (Patient 302); There were 6 SAEs in the autograft alone group: chest pain (3) (Patient 152); abdominal pain (Patient 306); hip arthroplasty and wound hematoma (Patient 353).

None of the reported SAEs were determined to be attributed to the use of OP-1 Putty either alone, or in combination with autograft. All of the SAEs were attributed to procedural complications or comorbidities.

12.2.2 Display of Adverse Events

12.2.2.1 Overall Incidence of Treatment Emergent Adverse Events

All treated patients have reported at least 1 AE during the study.

Table 23 displays the overall incidence of treatment emergent AEs by number of patients.

Table 24 summarizes the number of patients who experienced treatment emergent AEs, for system organ classes (SOCs) with $\geq 5\%$ of all patients in either of the OP-1 Putty groups. In addition to the 2 separate OP-1 Putty groups, patients in the OP-1 Putty Alone group were combined with patients in the OP-1 Putty/Autograft group to assess the impact of exposure to OP-1 Putty versus autograft. These combined data are presented in the OP-1 Putty Exposed column of Table 24. Table 25 provides a similar presentation, but instead summarizes the number of events (as opposed to the number of patients experiencing the events).

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Table 23. Treatment-Emergent Adverse Events (Safety Population)

Parameter	Number (%) of Patients with Events		
	OP-1 Putty Alone	OP-1 Putty/Autograft	Autograft Alone
Any Adverse Event	24	12	12
Severe Adverse Event	2 (8.3)	4 (33.3)	0 (0.0)
OP-1 Putty Related Adverse Event	5 (20.8)	0 (0.0)	0 (0.0)
Unanticipated Adverse Event	0 (0.0)	1 (8.3)	0 (0.0)
Serious Adverse Event	10 (41.7)	5 (41.7)	3 (25.0)
Serious/Unanticipated Adverse Event	0 (0.0)	1 (8.3)	0 (0.0)
OP-1 Putty Related Serious Adverse Event	0 (0.0)	0 (0.0)	0 (0.0)

Reference: Summary Table 8.1

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

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Table 24. Number of Patients with Treatment-Emergent Adverse Events by System Organ Class and Preferred Term that Occurred in $\geq 5\%$ of Patients in Either of the OP-1 Putty Groups (Safety Population) by Treatment Group and OP-1 Putty Exposed Group

System Organ Class Preferred Term	Number (%) of Patients			OP-1 Putty Exposed* Number (%) of Patients
	OP-1 Putty Alone	OP-1 Putty/ Autograft	Autograft Alone	
Total number of patients	24	12	12	36
Cardiac disorders	2 (8.3)	2 (16.7)	0 (0.0)	4 (11.1)
Coronary artery disease	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.8)
Pulmonary oedema	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.8)
Gastrointestinal disorders	2 (8.3)	3 (25.0)	3 (25.0)	5 (13.9)
Diarrhoea	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.8)
Ileus paralytic	0 (0.0)	1 (8.3)	1 (8.3)	1 (2.8)
Intestinal functional disorder	2 (8.3)	0 (0.0)	0 (0.0)	2 (5.6)
Volvulus of bowel	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.8)
Vomiting	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.8)
General disorders and administration site conditions	2 (8.3)	3 (25.0)	2 (16.7)	5 (13.9)
Gait disturbance	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.8)
Injection site bruising	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.8)
Pain	1 (4.2)	2 (16.7)	1 (8.3)	3 (8.3)
Infections and infestations	6 (25.0)	2 (16.7)	1 (8.3)	8 (22.2)
Herpes viral infection	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.8)
Pneumonia	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.8)
Postoperative wound infection	4 (16.7)	0 (0.0)	0 (0.0)	4 (11.1)
Urinary tract infection	1 (4.2)	1 (8.3)	1 (8.3)	2 (5.6)
Injury, poisoning and procedural complications	10 (41.7)	6 (50.0)	8 (66.7)	16 (44.4)
Anaemia postoperative	3 (12.5)	0 (0.0)	1 (8.3)	3 (8.3)
Donor site complication	0 (0.0)	2 (16.7)	5 (41.7)	2 (5.6)
Dural tear	1 (4.2)	1 (8.3)	1 (8.3)	2 (5.6)
Fall	3 (12.5)	0 (0.0)	0 (0.0)	3 (8.3)
Haemorrhage	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.8)
Injury	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.8)
Post procedural haemorrhage	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.8)
Urinary retention postoperative	1 (4.2)	1 (8.3)	2 (16.7)	2 (5.6)

(Continued on next page)

5.2 Pilot Study (Content from P060021 Original PMA, CSR S99-01US, Section 7-13)

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System Organ Class Preferred Term	Number (%) of Patients			OP-1 Putty Exposed* Number (%) of Patients
	OP-1 Putty Alone	OP-1 Putty/ Autograft	Autograft Alone	
<i>(Continued from previous page)</i>				
Investigations	1 (4.2)	1 (8.3)	1 (8.3)	2 (5.6)
Colonoscopy normal	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.8)
Musculoskeletal and connective tissue disorders	20 (83.3)	12 (100.0)	8 (66.7)	32 (88.9)
Arthralgia	7 (29.2)	5 (41.7)	1 (8.3)	12 (33.3)
Arthritis	1 (4.2)	1 (8.3)	0 (0.0)	2 (5.6)
Back pain	8 (33.3)	7 (58.3)	7 (58.3)	15 (41.7)
Bone pain	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.8)
Bursitis	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.8)
Fibromyalgia	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.8)
Groin pain	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.8)
Joint range of motion decreased	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.8)
Lumbar spinal stenosis	1 (4.2)	1 (8.3)	0 (0.0)	2 (5.6)
Neck pain	0 (0.0)	1 (8.3)	3 (25.0)	1 (2.8)
Pain in extremity	5 (20.8)	3 (25.0)	3 (25.0)	8 (22.2)
Pain in limb	1 (4.2)	1 (8.3)	0 (0.0)	2 (5.6)
Pseudarthrosis	10 (41.7)	3 (25.0)	0 (0.0)	13 (36.1)
Spondylolisthesis	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.8)
Synovial cyst	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.8)
Upper limb fracture	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (8.3)	1 (8.3)	1 (8.3)	3 (8.3)
Bladder cancer	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.8)
Colon cancer	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.8)
Malignant melanoma	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.8)
Nervous system disorders	2 (8.3)	1 (8.3)	2 (16.7)	3 (8.3)
Neurological disorder	0 (0.0)	1 (8.3)	2 (16.7)	1 (2.8)
Vascular disorders	2 (8.3)	2 (16.7)	1 (8.3)	4 (11.1)
Haemangioma	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.8)
Hypertension	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.8)

Reference: Summary Tables 8.2 and 8.2.1.

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

* Note: OP-1 Putty Exposed refers to OP-1 Putty alone arm in addition to OP-1 Putty/Autograft arm.

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Table 25. Number of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term that Occurred in $\geq 5\%$ of Patients in Either of the OP-1 Putty Groups (Safety Population) by Treatment Group and OP-1 Putty Exposed Group

System Organ Class Preferred Term	Number (%) of Events			OP-1 Putty Exposed* Number (%) of Events
	OP-1 Putty Alone	OP-1 Putty/ Autograft	Autograft Alone	
TOTAL	89	60	51	149
Cardiac disorders	2 (2.2)	2 (3.3)	0 (0.0)	4 (2.7)
Coronary artery disease	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.7)
Pulmonary oedema	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.7)
Gastrointestinal disorders	2 (2.2)	4 (6.7)	3 (5.9)	6 (4.0)
Diarrhoea	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.7)
Ileus paralytic	0 (0.0)	1 (1.7)	1 (2.0)	1 (0.7)
Intestinal functional disorder	2 (2.2)	0 (0.0)	0 (0.0)	2 (1.3)
Volvulus of bowel	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.7)
Vomiting	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.7)
General disorders and administration site conditions	2 (2.2)	4 (6.7)	4 (7.8)	6 (4.0)
Gait disturbance	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.7)
Injection site bruising	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.7)
Pain	1 (1.1)	2 (3.3)	1 (2.0)	3 (2.0)
Infections and infestations	6 (6.7)	3 (5.0)	1 (2.0)	9 (6.0)
Herpes viral infection	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.7)
Pneumonia	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.7)
Postoperative wound infection	4 (4.5)	0 (0.0)	0 (0.0)	4 (2.7)
Urinary tract infection	1 (1.1)	1 (1.7)	1 (2.0)	2 (1.3)
Injury, poisoning and procedural complications	16 (18.0)	7 (11.7)	14 (27.5)	23 (15.4)
Anaemia postoperative	3 (3.4)	0 (0.0)	1 (2.0)	3 (2.0)
Donor site complication	0 (0.0)	2 (3.3)	6 (11.8)	2 (1.3)
Dural tear	1 (1.1)	1 (1.7)	1 (2.0)	2 (1.3)
Fall	5 (5.6)	0 (0.0)	0 (0.0)	5 (3.4)
Haemorrhage	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.7)
Injury	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.7)
Post procedural haemorrhage	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.7)
Urinary retention postoperative	1 (1.1)	1 (1.7)	2 (3.9)	2 (1.3)
Investigations	1 (1.1)	1 (1.7)	1 (2.0)	2 (1.3)
Colonoscopy normal	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.7)

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5.2 Pilot Study (Content from P060021 Original PMA, CSR S99-01US, Section 7-13)

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System Organ Class Preferred Term	Number (%) of Events			OP-1 Putty Exposed* Number (%) of Events
	OP-1 Putty Alone	OP-1 Putty/ Autograft	Autograft Alone	

(Continued from previous page)

Musculoskeletal and connective tissue disorders	40 (44.9)	31 (51.7)	21 (41.2)	71 (47.7)
Arthralgia	8 (9.0)	5 (8.3)	1 (2.0)	13 (8.7)
Arthritis	1 (1.1)	1 (1.7)	0 (0.0)	2 (1.3)
Back pain	9 (10.1)	7 (11.7)	10 (19.6)	16 (10.7)
Bone pain	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.7)
Bursitis	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.7)
Fibromyalgia	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.7)
Groin pain	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.7)
Joint range of motion decreased	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.7)
Lumbar spinal stenosis	1 (1.1)	1 (1.7)	0 (0.0)	2 (1.3)
Neck pain	0 (0.0)	1 (1.7)	3 (5.9)	1 (0.7)
Pain in extremity	6 (6.7)	4 (6.7)	5 (9.8)	10 (6.7)
Pain in limb	1 (1.1)	1 (1.7)	0 (0.0)	2 (1.3)
Pseudarthrosis	10 (11.2)	3 (5.0)	0 (0.0)	13 (8.7)
Spondylolisthesis	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.7)
Synovial cyst	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.7)
Upper limb fracture	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (3.4)	4 (6.7)	1 (2.0)	7 (4.7)
Bladder cancer	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.7)
Colon cancer	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.7)
Malignant melanoma	0 (0.0)	2 (3.3)	0 (0.0)	2 (1.3)
Nervous system disorders	2 (2.2)	2 (3.3)	3 (5.9)	4 (2.7)
Neurological disorder	0 (0.0)	2 (3.3)	2 (3.9)	2 (1.3)
Vascular disorders	2 (2.2)	2 (3.3)	1 (2.0)	4 (2.7)
Haemangioma	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.7)
Hypertension	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.7)

Reference: Summary Tables 8.2 and 8.2.1.

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

* Note: OP-1 Putty Exposed refers to OP-1 Putty alone arm in addition to OP-1/Autograft arm.

The AE pseudarthrosis occurred only in patients who received OP-1 Putty (13 patients, 36%), and most of these occurred in patients who received OP-1 Putty alone (10 patients, 28%). The majority of these events (6) were diagnosed between 6 and 12 months following surgery. One patient (Patient 105) in the OP-1 Putty and autograft combination treatment group developed pseudarthrosis that was considered to be serious and unanticipated, and was assessed by the investigator as “probably unrelated” to OP-1

Putty. Based upon the current version of the OP-1 Clinical Investigator's Brochure, pseudarthrosis is an anticipated event. This event was apparently inadvertently misclassified; however, the original classification was maintained for this analysis. There were no reports of pseudarthrosis in the autograft alone treatment group.

Pseudarthrosis may have resulted from failure to fuse, premature evaluation prior to fusion, or radiographic artifact due to the relative lack of opacity of the OP-1 Putty product. Two patients who reported pseudarthrosis required a surgical retreatment. Additional information on the surgical retreatments for Patients 105 and 455 are provided in Section 12.3.2.3. The remaining 11 patients with pseudarthrosis did not require surgical retreatment. In addition, due to the unblinded nature of the study, a reporting bias favoring the autograft groups cannot be ruled out.

There were 4 reports of post-operative wound infections that occurred only in patients who were treated with OP-1 Putty alone. It is unclear if these patients underwent more procedural manipulation in order to achieve optimal placement of the study product, or if there were environmental, procedural, or other pre-existing factors which could have contributed to the occurrence of wound infections in this treatment group.

In the SOC Neoplasms Benign and Malignant, 4 patients reported 8 malignancies across all treatment groups (refer to Table 29). Breast cancer, malignant melanoma (2), prostate cancer and lung neoplasm malignant were reported as SAEs. The malignancies reported in the OP-1 Putty-containing treatment arms had an onset of more than 24 months post-operatively. There was one report of prostate cancer in an autograft patient that occurred approximately 4 months post-operatively. None of the reported malignancies were attributed to the use of OP-1 Putty alone or in combination with autograft.

12.2.2.2 Incidence of Adverse Events Over Time

Statistical Table 8.7 in Section 14 presents incidence of AEs over time, from the date of operation. In the OP-1 Putty alone treatment group post-operative wound infections were reported within 6 weeks post-operatively. Pseudarthrosis was reported in several patients from after 3 months to after 24 months post-operatively, with a peak in events occurring between 6 and 12 months. Arthralgia was reported by 7 patients after 6 weeks to more than 24 months post-operatively, with an increased incidence between 6 and 24 months. Malignancies in the OP-1 Putty treatment group were reported only more than 24 months post-operatively.

Patients in the OP-1 Putty and autograft combination treatment group reported gastrointestinal disorders at 6 weeks, and more than 24 months post-operatively. There were no post-operative wound infections reported in this group. Pseudarthrosis was reported in 2 patients between 3 and 6 months post-operatively, and by 1 patient more than 24 months post-operatively. A single patient experienced malignancies more than 24 months post-operatively.

Two patients in the autograft alone treatment group reported anemia or secondary anemia at the time of operation. Donor site complications were reported from more than 6 weeks to more than 24 months post-operatively. Back pain was reported more frequently from

more than 3 months to more than 24 months post-operatively. One malignancy was reported between 3 and 6 months in this group. There were no reports of pseudarthrosis.

12.2.2.3 Treatment Emergent Adverse Events by Severity

As shown in Statistical Table 8.3 in Section 14, treatment-emergent AEs were graded by severity as mild, moderate, or severe. In the OP-1 Putty alone group, 17 of the 24 patients (71%) had AEs that were reported as moderate, 5 patients (21%) had events reported as mild, and 2 patients (8%) reported as severe. Severe events were prostate cancer and renal artery stenosis. In the OP-1 Putty and autograft combination group, 12 patients had AEs that were equally distributed among the categories, with 4 (33%) each classified as mild, moderate, or severe. Severe events in the combination group were volvulus of the bowel, back pain, pseudarthrosis, bladder cancer, and colon cancer. In the autograft alone group, 4 patients (33%) had AEs that were assessed as mild, and 8 (66%) that were assessed as moderate in severity. There were no AEs assessed as severe in the autograft alone group.

12.2.2.4 Treatment Emergent Adverse Events by Causality

As seen in Statistical Table 8.4 in Section 14, 5 events of pseudarthrosis that occurred in the OP-1 Putty alone treatment group have been classified as suspected related to the study treatment. Patients 252, 356 and 360 each experienced pseudarthrosis which was classified as “possibly related” to study treatment. One event of pseudarthrosis experienced by Patient 555 was considered “probably related” to OP-1 Putty. Pseudarthrosis reported by Patient 556 was assessed as “definitely related” to the study treatment. None of these events were classified as serious.

There were 3 reported events whose relationship to the use of OP-1 Putty was assessed as “unknown”. One event, arthralgia, was also assessed as serious. The second event was pseudarthrosis, reported in a patient who received OP-1 Putty and autograft. The third event was pain (see Statistical Table 8.4 in Section 14).

12.2.3 Analysis of Adverse Events

A total of 48 patients were randomized to receive OP-1 Putty alone (24), OP-1 Putty in combination with autograft (12), and autograft alone (12). AEs occurred in 100% of patients across all treatment groups: 149 in the 36 patients in the OP-1 Putty treatment groups (with or without autograft), and 51 in the 12 patients treat who received autografts.

In the OP-1 Putty alone treatment group, the most commonly reported AEs were in the Musculoskeletal and Connective Tissue Disorders SOC (20 patients, 83.3%). Of the patients who were randomized to the OP-1 Putty and autograft combination treatment group, 100% of the patients reported AEs in the Musculoskeletal and Connective Tissue Disorders SOC. Of the patients randomized to the autograft alone treatment group, the most commonly reported AEs were in the musculoskeletal and injury SOCs (8 patients, 66.7% in each SOC).

The events pseudarthrosis and wound infection were reported only by patients who received an OP-1 Putty-containing treatment regimen, and predominantly by those patients who received OP-1 Putty alone.

There was 1 death reported during the course of the study, which was secondary to bladder and colon cancer.

There were 8 malignancies reported of in 4 patients across all treatment groups (bowel, breast, colon, lung, malignant melanoma [2] and prostate cancer [2]). One patient in the autograft group reported prostate cancer at approximately 4 months post-operative. Five malignancies were reported as SAEs (breast, prostate, lung, and malignant melanoma [2]). None of the reported malignancies were attributed to OP-1 Putty.

There were 5 non-SAEs (pseudarthrosis) reported that were assessed by the Investigator as being possibly, probably or definitely related to OP-1 Putty. Three events, arthralgia (which was serious), pain, and pseudarthrosis, were assessed as causality unknown.

The majority of the AEs were assessed as being moderate in severity. Across all treatment arms, 6 patients (12.5%) had severe AEs.

There were no reports of any AEs associated with heterotopic bone formation.

Overall, the AE profile of the groups treated with OP-1 Putty was clinically comparable to that in the autograft alone group. The small sample sizes, particularly in the autograft group, preclude any broader conclusions. Although pseudarthrosis was reported only in the OP-1 Putty treatment groups, reporting bias cannot be ruled out in this unblinded trial; pseudarthrosis is a known potential outcome of failed lumbar fusion surgery.

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

12.3.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1.1 Deaths

A single death was reported during the course of the study. Patient 107 died of carcinomatosis involving the bladder and colon on 27 July 2005. A narrative for this patient is provided in Section 12.3.2.

12.3.1.2 Other Serious Adverse Events

Table 26 summarizes Treatment-Emergent SAEs by SOC and Preferred Term. Table 27 summarizes Treatment-Emergent SAEs by SOC, Preferred Term, and Relationship to OP-1 Putty. Eighteen patients across all treatment arms experienced 36 SAEs. None of the SAEs were determined to be attributed to OP-1 Putty either alone or in combination with autograft. All SAEs were attributed to procedural complications or comorbidities; thus, a true causal relationship could not be established.

5.2 Pilot Study (Content from P060021 Original PMA, CSR S99-01US, Section 7-13)

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Table 26. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	Number (%) of Patients			Number (%) of Events		
	OP-1 Putty Alone (n = 24)	OP-1 Putty/ Autograft (n = 12)	Autograft (n = 12)	OP-1 Putty Alone	OP-1 Putty/ Autograft	Autograft
Total	10 (41.7)	5 (41.7)	3 (25.0)	18 (100.0)	12 (100.0)	6 (100.0)
Cardiac disorders	1 (4.2)	2 (16.7)	0 (0.0)	1 (5.6)	2 (16.7)	0 (0.0)
Aortic valve disease	1 (4.2)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)
Coronary artery disease	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)
Pulmonary oedema	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)
Eye disorders	1 (4.2)	0 (0.0)	0 (0.0)	2 (11.1)	0 (0.0)	0 (0.0)
Cataract bilateral NOS	1 (4.2)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)
Eye disorder NOS	1 (4.2)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	0 (0.0)	2 (16.7)	1 (8.3)	0 (0.0)	2 (16.7)	1 (16.7)
Abdominal pain	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	1 (16.7)
Diarrhoea	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)
Volvulus of bowel	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)
General disorders and administration site conditions	1 (4.2)	0 (0.0)	1 (8.3)	1 (5.6)	0 (0.0)	3 (50.0)
Chest pain	1 (4.2)	0 (0.0)	1 (8.3)	1 (5.6)	0 (0.0)	3 (50.0)
Injury, poisoning and procedural complications	1 (4.2)	1 (8.3)	1 (8.3)	1 (5.6)	1 (8.3)	1 (16.7)
Incision site haemorrhage	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	1 (16.7)
Pseudarthrosis	1 (4.2)	1 (8.3)	0 (0.0)	1 (5.6)	1 (8.3)	0 (0.0)
Musculoskeletal and connective tissue disorders	3 (12.5)	2 (16.7)	1 (8.3)	5 (27.8)	4 (33.3)	1 (16.7)
Arthralgia	3 (12.5)	1 (8.3)	1 (8.3)	4 (22.2)	1 (8.3)	1 (16.7)
Back pain	1 (4.2)	1 (8.3)	0 (0.0)	1 (5.6)	1 (8.3)	0 (0.0)
Groin pain	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)
Upper limb fracture	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (8.3)	1 (8.3)	0 (0.0)	3 (16.7)	2 (16.7)	0 (0.0)
Breast cancer	1 (4.2)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)
Lung neoplasm malignant	1 (4.2)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)
Malignant melanoma	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	2 (16.7)	0 (0.0)
Prostate cancer	1 (4.2)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)
Respiratory thoracic and mediastinal disorders	1 (4.2)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)
Pleural effusion	1 (4.2)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)

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5.2 Pilot Study (Content from P060021 Original PMA, CSR S99-01US, Section 7-13)

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System Organ Class Preferred Term	Number (%) of Patients			Number (%) of Events		
	OP-1 Putty Alone (n = 24)	OP-1 Putty/ Autograft (n = 12)	Autograft (n = 12)	OP-1 Putty Alone	OP-1 Putty/ Autograft	Autograft

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Surgical and medical procedures	3 (12.5)	0 (0.0)	0 (0.0)	3 (16.7)	0 (0.0)	0 (0.0)
Breast cosmetic surgery	1 (4.2)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)
Hip arthroplasty	1 (4.2)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)
Knee arthroplasty	1 (4.2)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)
Vascular disorders	1 (4.2)	1 (8.3)	0 (0.0)	1 (5.6)	1 (8.3)	0 (0.0)
Hypertension	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)
Renal artery stenosis	1 (4.2)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)

Reference: Summary Table 8.5

Note: Number of patients refers to patients with at least one AE 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 in each treatment group, 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.

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Table 27. Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term, and Relationship to OP-1 Putty (Safety Population)

System Organ Class Preferred Term	Number(%) of Patients					
	OP-1 Putty Alone			OP-1 Putty/Autograft		
	Not Related	Suspected Related	Unknown	Not Related	Suspected Related	Unknown
Total	10	0	0	5	0	0
Cardiac disorders	1 (100.0)	0 (0.0)	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)
Aortic valve disease	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Coronary artery disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
Pulmonary oedema	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
Eye disorders	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cataract bilateral NOS	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eye disorder NOS	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)
Diarrhoea	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
Volvulus of bowel	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Chest pain	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
Pseudarthrosis	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	3 (100.0)	0 (0.0)	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)
Arthralgia	3 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
Back pain	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
Groin pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
Upper limb fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
Breast cancer	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lung neoplasm malignant	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Malignant melanoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
Prostate cancer	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory thoracic and mediastinal disorders	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pleural effusion	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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5.2 Pilot Study (Content from P060021 Original PMA, CSR S99-01US, Section 7-13)

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System Organ Class Preferred Term	Number(%) of Patients					
	OP-1 Putty Alone			OP-1 Putty/Autograft		
	Not Related	Suspected Related	Unknown	Not Related	Suspected Related	Unknown

(Continued from previous page)

Surgical and medical procedures	3 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Breast cosmetic surgery	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hip arthroplasty	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Knee arthroplasty	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
Hypertension	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
Renal artery stenosis	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Reference: Summary Table 8.5.1

Note: Number of patients refers to patients with at least one AE of the indicated type. Percentages are based on the total number of patients with the event 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, and has no suspected related events for the same system organ class/preferred term, the patient is counted as unknown.

Table 28 summarizes the incidence of malignancies by treatment group and SOC. Narratives for patients with serious malignancies are presented in Sections 12.3.2.2 and 12.3.2.3.

There were 8 reports of malignancies in 4 patients across all treatment groups (refer to Table 29). none of which were attributed to the use of OP-1 Putty.

5.2 Pilot Study (Content from P060021 Original PMA, CSR S99-01US, Section 7-13)

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Table 28. Incidence of Malignancies by Treatment Group

System Organ Class/ Preferred Term	Number (%) of Patients			Number (%) of Events		
	OP-1 Putty Alone	OP-1 Putty/ Autograft	Autograft Alone	OP-1 Putty Alone	OP-1 Putty/ Autograft	Autograft Alone
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (8.3)	1 (8.3)	1 (8.3)	3 (3.4)	4 (6.7)	1 (2.0)
Bladder cancer	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)
Breast cancer	1 (4.2)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)
Colon cancer	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)
Lung neoplasm malignant	1 (4.2)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)
Malignant melanoma	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	2 (3.3)	0 (0.0)
Prostate cancer	1 (4.2)	0 (0.0)	1 (8.3)	1 (1.1)	0 (0.0)	1 (2.0)

Table 29. Malignancies Reported as AEs for Four Patients

Treatment Group	Patient Number	Malignancy
OP-1 Putty alone	Patient 553 (2 SAEs)	Prostate carcinoma (day 1104) Bronchopulmonary carcinoma (day 1453)
	Patient 154 (1 SAE)	Breast carcinoma (day 1443)
OP-1 Putty/autograft	Patient 107 (4 SAEs)	Malignant melanoma (day 1212, with recurrence day 1640) Carcinomatosis with involvement of bladder and colon
Autograft alone	Patient 359 (1 SAE)	Prostate cancer (day 120)

12.3.1.3 Other Significant Adverse Events

Significant AEs were not defined in the protocol because the investigational product was used only once at the time of surgery; therefore, it was assumed that there would be no intervention should such an event occur (i.e., drug discontinuation, antidote, etc.).

12.3.1.4 Heterotopic Bone Formation

Heterotopic bone formation was identified radiographically in 3 patients who received OP-1 Putty, and in 1 patient who was treated with autograft alone. There were no AEs associated with the radiographic evidence of heterotopic bone formation.

12.3.2 Narratives of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.2.1 Deaths

Patient 107 (OP-1 Putty and Autograft)

A 78-year-old female patient received OP-1 Putty and an autograft at level L4-L5 on 13 September 1999. She experienced 4 SAEs over the course of the study. The events included melanoma (2), hypertension, and diarrhea. There were multiple hospitalizations for the melanoma and the hypertension.

The patient was hospitalized for treatment of a malignant melanoma on 06 January 2003 (1,212 days post surgery), which required excision of a scalp lesion and a skin graft. The event resolved on 12 November 2003. The duration of the event was 310 days. In March 2004 (approximately 1640 days post-surgery), the patient experienced a recurrence of the melanoma requiring hospitalization for an excision of a scalp lesion with skin grafting. The event resolved in March 2004 with duration of less than 1 month. The investigator assessed the recurrence of melanoma as moderate and definitely not related to OP-1 Putty.

In January 2004 (approximately 1215 days post surgery) the patient, who had a past medical history of hypertension, was hospitalized for worsening of her hypertension, and was treated with an unspecified medication. She was subsequently hospitalized for hypertension on three separate occasions (dates not specified) and was treated with unspecified medications. The event was ongoing.

In May 2004 (approximately 1700 days post surgery) she experienced diarrhea which required hospitalization and treatment with intravenous fluids and potassium. The duration of the event was less than 1 month and resolved in May 2004.

On 27 July 2005 the patient died from bladder cancer and colon cancer (2144 days post surgery). There was no treatment reported for the cancer. Concomitant medications included a non-narcotic pain medication, Noroxin® (norfloxacin), Prilosec® (omeprazole), Synthroid® (levothyroxine), verapamil, and Xanax® (alprazolam).

The melanoma, hypertension and diarrhea were assessed by the investigator as moderate in severity and definitely not related to OP-1 Putty.

12.3.2.2 Other Serious Adverse Events (Malignancies)

Patient 154 – OP-1 Putty

Invasive Ductal Breast Carcinoma

A 67-year-old male patient received OP-1 Putty at level L4-L5 on 15 May 2000. His medical history was significant for hypertension, gout, arthritis, and vascular calcification of abdominal aorta. The patient was diagnosed with renal artery stenosis and underwent a renal artery angioplasty with stent placement on 07 April 2003 (1058 days post-surgery). The event duration was 99 days, and was considered resolved on 15 July 2003. On 26 April 2004 (1,442 days post surgery) the patient was diagnosed with invasive ductal

carcinoma of the breast and was hospitalized. He subsequently underwent a left modified radical mastectomy. The event was considered resolved following surgery on 26 April 2004.

Concomitant medications included a non-narcotic pain medication (not specified), Maxzide® (hydrochlorothiazide and triamterene), Indocin® (indomethacin), Lipitor® (atorvastatin), and colchicine.

The investigator assessed the severity of the renal artery stenosis as severe and definitely not related to OP-1 Putty, and the severity of the invasive ductal carcinoma as moderate and definitely not related to OP-1 Putty.

Patient 553 – OP-1 Putty

Prostate Cancer, Metastatic Lung Cancer

A 75-year-old male patient received OP-1 Putty at level L4-L5 on 16 November 2000. His medical history was significant for cardiovascular disease, gastrointestinal disease, urogenital disease, and a family history of prostate cancer. The patient was hospitalized with prostate cancer on 24 November 2003 (1,104 days post surgery) and received treatment with androgen deprivation injections. On 05 November 2004 (1,450 days post surgery) he developed metastatic lung cancer and was hospitalized. Treatment included chemotherapy (not specified). The investigator initially assessed both the prostate cancer and the lung cancer as life-threatening events. The events were ongoing at the conclusion of the study.

Concomitant medications included non-narcotic pain medications (not specified).

The investigator assessed the severity of the prostate cancer as severe and probably not related to OP-1 Putty, and the severity of the lung cancer as moderate and probably not related to OP-1 Putty.

12.3.2.3 Narratives for Serious Adverse Events

Patient Number	Patient Initials	Narrative
<p>101 OP-1 Putty with autograft</p>	<p>RIA</p>	<p>Serious Adverse Event(s): Arthralgia, coronary artery disease. groin pain, volvulus of bowel</p> <p>Past Medical History: Cardiovascular disease, hiatal hernia, hypercholesterolemia, right total knee replacement, ulcerative colitis</p> <p>A 78-year-old male patient received OP-1 Putty with autograft at level L4-L5 on 15 June 1999. The patient experienced four SAEs over the course of the study. The events included right knee pain, groin pain, an exacerbation of coronary artery disease, and a sigmoid volvulus; all of which required hospitalization.</p> <p>The right knee pain occurred on 03 November 2000 (507 days post surgery) and the patient was hospitalized for a total right knee arthroplasty status post revision. The duration of the event was 38 days, and was considered resolved on 11 December 2000.. The investigator assessed the knee pain as moderately severe and definitely not related to OP-1. At the same time, on 03 November 2000 (507 days post surgery), the patient experienced groin pain which required a right total hip arthroplasty. The event resolved on 24 October 2001. The duration of the event was 355 days. The severity of the groin pain was assessed as mild and definitely not related to OP-1.</p> <p>On 07 October 2002 (1,210 days post surgery) the patient was hospitalized for an exacerbation of his coronary artery disease. He had a cardiac catheterization done and was discharged on the same day. This event was assessed as moderately severe and definitely not related to OP-1.</p> <p>The patient developed a sigmoid volvulus on 02 April 2003 (1,387 days post surgery). He was hospitalized and sigmoid colectomy was performed. The event duration was 12 days and resolved on 14 April 2003. The investigator assessed the volvulus as severe and definitely not related to OP-1.</p> <p>Steroids (dosage and dates of administration unknown) were the only concomitant medication documented.</p>

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Patient Number	Patient Initials	Narrative
105 OP-1 Putty with autograft	SJG	<p>Serious Adverse Event(s): Pseudarthrosis</p> <p>Past Medical History: Gastrointestinal disease, history of smoking</p> <p>A 58-year-old female received OP-1 Putty with autograft at level L3-L4 on 19 Aug 1999. She was hospitalized on 09 Feb 2000 (180 days post surgery) with pseudarthrosis. She underwent a lumbar laminectomy at L3-4 with iliac crest bone graft, and a supplemental fixation with Texas Scottish Rite Hospital instrumentation. Event duration was 57 days, and resolved on 06 Apr 2000.</p> <p>Concomitant meds included narcotic pain medication (NOS), Prilosec[®] (omeprazole), and Seldane[®] (terfenadine).</p> <p>The investigator assessed the pseudarthrosis as severe and definitely not related to OP-1 Putty.</p>

Patient Number	Patient Initials	Narrative
<p>107 OP-1 Putty with autograft</p>	<p>LJI</p>	<p>Serious Adverse Event(s): Diarrhoea, hypertension, malignant melanoma</p> <p>Past Medical History: Hypertension, hypothyroidism, urinary tract infection</p> <p>An 78-year-old female received OP-1 Putty with autograft at level L4-L5 on 13 Sep 1999. She experienced 3 SAEs during the study. Events included malignant melanoma, hypertension, and diarrhea. There were multiple hospitalizations for the malignant melanoma (2) and the hypertension (3).</p> <p>Patient was hospitalized for treatment of malignant melanoma on 06 Jan 2003 (1211 days post surgery) requiring excision of scalp lesion and skin graft. Event resolved 12 Nov 2003. Duration was 310 days. In Mar 2004 (approximately 1640 days post-surgery), she experienced recurrence of malignant melanoma requiring hospitalization for excision of scalp lesion and skin grafting. Event resolved in Mar 2004 with duration of less than 1 month, and was assessed as severe and definitely not related to OP-1 Putty.</p> <p>In January 2004 (approximately 1,215 days post surgery) the patient, who had a past medical history of hypertension, was hospitalized for worsening of her hypertension, and was treated with medication (not specified). She was subsequently hospitalized for hypertension on three separate occasions (dates not specified) and was treated with medication (not specified). The event was ongoing.</p> <p>In May 2004 (approximately 1,700 days post surgery) the patient experienced diarrhea which required hospitalization and treatment with intravenous fluids and potassium replacement. The duration of the event was less than 1 month and resolved in May 2004.</p>
<p>107 OP-1 Putty with autograft</p>	<p>LJI</p>	<p>On 27 July 2005 the patient died from bladder cancer and colon cancer (2,144 days post surgery). There was no treatment reported for the cancer. Concomitant medications included a non-narcotic pain medication (not specified), Noroxin® (norfloxacin), Prilosec® (omeprazole), Synthroid® (levothyroxine), verapamil, and Xanax® (alprazolam).</p> <p>The malignant melanoma, hypertension and diarrhea were assessed by the investigator as moderate in severity and definitely not related to OP-1 Putty.</p>

Patient Number	Patient Initials	Narrative
151 OP-1 Putty	EPH	<p>Serious Adverse Event(s): Aortic valve disease, cataracts bilateral, eye disorder (NOS), pleural effusion,</p> <p>Past Medical History: Arthritis, hypercholesterolemia, hypertension, neuropathy, paresthesia</p> <p>A 77-year-old female patient received OP-1 Putty at level L4-L5 on 24 February 2000. The patient experienced three SAEs over the course of the study.</p> <p>On 15 January 2002 (691 days post surgery), the patient was hospitalized for aortic disease which required a cardiac catheterization. The patient subsequently underwent a coronary artery bypass graft and an aortic valve replacement. The duration of the event was 12 days and the event was considered resolved on 17 January 2002. On 04 February 2002 (711 days post surgery) the patient developed a pleural effusion which required hospitalization and a thoracentesis. The duration of the event was less than 1 day and resolved on 04 February 2002.</p> <p>On 30 October 2002 (979 days post surgery) and on 05 February 2003 (1077 days post surgery) the patient was hospitalized for cataract removal. The duration of each event was less than 1 day, and the events were considered resolved.</p> <p>Concomitant medications included a non-narcotic pain medication (not specified), Lipitor® (atorvastatin), Tenormin® (atenolol), Procardia® (nifedipine), and Tylenol Sinus® (acetaminophen and pseudoephedrine).</p> <p>The investigator assessed the severity of the aortic disease and subsequent pleural effusion as moderate and definitely not related to OP-1 Putty, and both episodes of cataracts were assessed as mild in severity and definitely not related to OP-1 Putty.</p>

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Patient Number	Patient Initials	Narrative
152 Autograft	NLC	<p>Serious Adverse Event(s): Chest pain</p> <p>Past Medical History: Angioplasty, bilateral carpal tunnel, depression, diverticulitis, fibromyalgia, gastroesophageal reflux disease, leg numbness, rheumatoid arthritis, shoulder surgery</p> <p>A 57-year-old female patient received Autograft at level L3-L4 on 24 February 2000. The patient was hospitalized for chest pain on 3 separate occasions during the study: 07 July 2000 (134 days post surgery), 05 August 2000 (163 days post surgery), and 13 March 2002 (748 days post surgery). During her first hospitalization the patient underwent a cardiac catheterization. The duration of the initial event was 2 days and was considered resolved on 09 July 2000. The patient was subsequently hospitalized on two other occasions with a recurrence of chest pain. Each event resolved after two days, and was treated with sublingual and intravenous nitroglycerin.</p> <p>Concomitant medications included non-narcotic and narcotic pain medication (not specified), Dilacor® (diltiazem), Claritin® (loratadine), Prozac® (fluoxetine), Tranxene® (clorazepate), Lipitor® (atorvastatin), Prilosec® (omeprazole), Voltaren® (diclofenac), Cytotec® (misoprostol), Flexeril® (cyclobenzaprine), Epipen® (epinephrine), and acetylsalicylic acid.</p> <p>The investigator assessed the severity of all 3 episodes of chest pain as moderate.</p>

Patient Number	Patient Initials	Narrative
153 OP-1 Putty	ARA	<p>Serious Adverse Event(s): Arthralgia, back pain</p> <p>Past Medical History: Arthritis, carpal tunnel syndrome, hiatal hernia, hypertension, lymphedema right lower extremity, nausea,</p> <p>An 80-year-old female patient received OP-1 Putty at level L4-L5 on 18 April 2000. The patient experienced two SAEs over the course of the study. She was hospitalized for left knee pain on 20 October 2000 (185 days post surgery) and subsequently underwent a left total knee replacement. The event duration was 132 days and was considered resolved on 01 March 2001. The patient was hospitalized again on 20 March 2002 (701 days post surgery) with excessive back pain which required a L3-4, L4-5, and L5-S1 decompression, a supplemental fixation and fusion of L3-4 using local bone graft and demineralized matrix. The event was continuing at the conclusion of the study.</p> <p>Concomitant medications included non-narcotic and narcotic pain medication (not specified), Norvasc® (amlodipine), Dyazide® (hydrochlorothiazide and triamterene), and Oscal® (multivitamin).</p> <p>The investigator assessed the severity of both the arthralgia and the back pain as moderate and definitely not related to OP-1 Putty.</p>

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Patient Number	Patient Initials	Narrative
<p>154 OP-1 Putty</p>	<p>AEK</p>	<p>Serious Adverse Event(s): Breast cancer, renal artery stenosis</p> <p>Past Medical History: Arthritis, gout, hypertension, vascular calcification of abdominal aorta</p> <p>A 67-year-old male patient received OP-1 Putty at level L4-L5 on 15 May 2000. The patient was found to have renal artery stenosis and underwent a renal artery angioplasty with stent placement on 07 April 2003 (1057 days post-surgery). The event duration was 99 days, and was considered resolved on 15 July 2003.. On 26 April 2004 (1,442 days post surgery) the patient was diagnosed with invasive ductal carcinoma of the breast and was hospitalized. He subsequently underwent a left modified radical mastectomy. The event was considered resolved following surgery on 26 April 2004.</p> <p>Concomitant medications included a non-narcotic pain medication (not specified), Maxzide® (hydrochlorothiazide and triamterene), Indocin® (indomethacin), Lipitor® (atorvastatin), and colchicine.</p> <p>The investigator assessed the severity of the renal artery stenosis as severe and definitely not related to OP-1 Putty, and the severity of the invasive ductal carcinoma as moderate and definitely not related to OP-1 Putty.</p>
<p>156 OP-1 Putty</p>	<p>RCF</p>	<p>Serious Adverse Event(s): Chest pain</p> <p>Past Medical History: Carpal tunnel syndrome, right thigh paresthesia,</p> <p>A 49-year-old female patient received OP-1 Putty at level L4-L5 on 07 September 2000. The patient was hospitalized for an episode of chest pain on 17 August 2002 (709 days post surgery). The chest pain had a duration of one day and was considered resolved on 18 August 2002.</p> <p>Concomitant medications included Flexeril® (cyclobenzaprine), and Motrin® (ibuprofen).</p> <p>The investigator assessed the severity of the chest pain as moderate and definitely not related to OP-1 Putty.</p>

Patient Number	Patient Initials	Narrative
<p>204 OP-1 Putty with autograft</p>	<p>CDR</p>	<p>Serious Adverse Event(s): Back pain, upper limb fracture</p> <p>Past Medical History: Depression, esophageal hernia, hypertension, osteoarthritis</p> <p>A 62-year-old female patient received OP-1 Putty with autograft at level L4-L5 on 24 August 1999. She sustained a right shoulder fracture and back pain secondary to a fall on 26 August 2000 (368 days post surgery). The patient was hospitalized and underwent surgery to repair the right humerus and shoulder. There was no treatment reported for the back pain. The events were considered resolved on 02 October 2003, 1,125 days following the initial fracture.</p> <p>Concomitant medications included Norvasc® (amlodipine), Dyazide® (hydrochlorothiazide and triamterene), Prilosec® (omeprazole), Wellbutrin® (bupropion), triamterene, calcium, Theragran® (multivitamin), Estraderm® patch (estradiol), and Vicodin® (hydrocodone and acetaminophen).</p> <p>The investigator assessed the severity of the shoulder fracture and back pain as mild and definitely not related to OP-1 Putty.</p>
<p>302 OP-1 Putty with autograft</p>	<p>FXD</p>	<p>Serious Adverse Event(s): Pulmonary oedema</p> <p>Past Medical History: Hypercholesterolemia</p> <p>A 79-year-old male patient received OP-1 Putty with autograft at level L4-L5 on 10 June 1999. The patient developed post-operative pulmonary edema on 10 June 1999 which prolonged his hospitalization. No treatment was reported for the pulmonary edema. The etiology was suspected to be IV fluid administered during the surgical procedure coupled with patient immobility.</p> <p>Concomitant medications included a non-narcotic pain medication (not specified), Zocor® (simvastatin), Plavix® (clopidogrel), Celebrex® (celecoxib) and tetracycline.</p> <p>The investigator assessed the severity of the pulmonary edema as moderate and definitely not related to OP-1 Putty.</p>

Patient Number	Patient Initials	Narrative
306 Autograft	CAW	<p>Serious Adverse Event(s): Abdominal pain</p> <p>Past Medical History: Arthritis, asthma, excision of both axillae with skin grafting, hypertension, L1 hemangioma, osteoporosis right lower extremity, sacral Tarlov cyst, tonsillectomy,</p> <p>A 51-year-old female patient received Autograft at level L4-L5 on 23 August 1999. The patient experienced abdominal pain on 12 March 2002 (932 days post surgery) which required hospitalization. No treatment was reported for the abdominal pain. The event was considered resolved on 15 March 2003, one year after the onset.</p> <p>Concomitant medications included a non-narcotic pain medication (not specified), Prinivil® (lisinopril), Miacalcin® (calcitonin), calcium, and nortriptyline.</p> <p>The investigator assessed the severity of the abdominal pain as mild.</p>
351 OP-1 Putty	VJS	<p>Serious Adverse Event(s): Breast cosmetic surgery</p> <p>Past Medical History: Arthritis, bilateral gynecomasty, cardiovascular disease, chronic bilateral lymphedema, degenerative scoliosis L1- L5, left knee replacement surgery</p> <p>A 67-year-old male patient received OP-1 Putty at level L4-L5 on 12 February 2000. The patient was hospitalized on 09 November 2000 (271 days post surgery) for breast-reduction surgery. The event was considered resolved on the day of surgery.</p> <p>Concomitant medications included a non-narcotic pain medication (not specified), Trental® (pentoxifylline), Lasix® (furosemide), Neurontin® (gabapentin), and Aldactone® (spironolactone).</p> <p>The investigator assessed the severity of the bilateral gynecomastia as mild and definitely not related to OP-1 Putty.</p>

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Patient Number	Patient Initials	Narrative
352 OP-1 Putty	CML	<p>Serious Adverse Event(s): Arthralgia</p> <p>Past Medical History: Hypercholesterolemia, osteoporosis</p> <p>A 74-year-old female patient received OP-1 Putty at level L4-L5 on 13 April 2000. The patient experienced two SAEs during the course of the study. The patient developed left knee pain and on 02 October 2000 (172 days post-surgery) she was hospitalized and underwent a left total knee arthroplasty . Treatment included physical therapy. The event resolved on 27 February 2001. The duration of the event was 148 days. On 03 August 2001 (477 days post surgery) the patient was hospitalized for right knee pain and underwent a right knee arthroscopic meniscectomy. The duration of the event was 62 days and the event was considered resolved on 04 October 2001.</p> <p>Concomitant medications included Lipitor® (atorvastatin), Fosamax® (alendronate), OxyContin® (oxycodone), and a non-narcotic pain medication (not specified).</p> <p>The investigator assessed the severity of the left knee pain as moderate and definitely not related to OP-1 Putty, and the severity of the right knee pain as mild and definitely not related to OP-1 Putty.</p>

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Patient Number	Patient Initials	Narrative
353 Autograft	ERT	<p>Serious Adverse Event(s): Hip arthroplasty, incisional site hemorrhage</p> <p>Past Medical History: Depression, hypothyroidism, knee replacement, rotator cuff surgery</p> <p>A 67-year-old female patient received Autograft at level L4-L5 on 01 May 2000. The patient experienced three SAEs over the course of the study. On 10 July 2001 (435 days post surgery) she experienced excessive leg pain which required hospitalization. The patient subsequently underwent a right total hip replacement. The event was considered resolved on 09 September 2002, approximately 575 days after the event onset. On 27 September 2002 (879 days post initial surgery, approximately 8 days post total hip replacement) she developed an incisional hematoma which required hospitalization. An incision and drainage of the hematoma was performed. The event was considered resolved on 03 October 2002. The duration of the event was 6 days. During the course of this hospitalization the patient also had a pulmonary embolism which resolved. Concomitant medications included a non-narcotic pain medication (not specified), Folex® (methotrexate), Effexor® (venlafaxine), Celexa® (citalopram), Ritalin® (methylphenidate), Synthroid® (levothyroxine), trazodone and oxazepam.</p> <p>The investigator assessed the severity of both the leg pain and the hematoma as moderate.</p>

Patient Number	Patient Initials	Narrative
<p>358 OP-1 Putty</p>	<p>NCD</p>	<p>Serious Adverse Event(s): Left hip arthroplasty, arthralgia</p> <p>Past Medical History: Cervical radiculopathy, fissurectomy, osteoarthritis, mononucleosis, nasal endoscopy</p> <p>A 51-year-old female patient received OP-1 Putty at level L4-L5 on 13 June 2000. The patient experienced two SAEs over the course of the study. On 28 March 2001 (288 days post surgery) she developed left hip pain which required hospitalization. The patient subsequently had a total left hip replacement performed. The event was considered resolved on 06 November 2001. On 20 January 2004 (1,316 days post surgery) the patient experienced right hip pain which required hospitalization and a subsequent right total hip replacement. The event was considered resolved on 11 May 2004.</p> <p>Concomitant medications included narcotic and non-narcotic pain medication (not specified), Aldactone® (spironolactone), and Fiorinal® (butalbital, aspirin, and caffeine).</p> <p>The investigator assessed the severity of the left hip pain as moderate and probably not related to OP-1 Putty, and the severity of the right hip pain as moderate and definitely not related to OP-1 Putty.</p>
<p>452 OP-1 Putty</p>	<p>LDS</p>	<p>Serious Adverse Event(s): Knee arthroplasty</p> <p>Past Medical History: Hypertension, paresthesias</p> <p>A 53-year-old female patient received OP-1 Putty at level L4-L5 on 14 April 2000. In April 2003 (approximately 1,060 days post-surgery) she was hospitalized for a left total knee arthroplasty. No additional treatments were reported and the event resolved. The duration of the event was less than 1 month.</p> <p>Concomitant medications included a narcotic and non-narcotic pain medication (not specified).</p> <p>The investigator assessed the severity of the event as moderate and definitely not related to OP-1 Putty.</p>

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Patient Number	Patient Initials	Narrative
<p>455 OP-1 Putty</p>	<p>BAM</p>	<p>Serious Adverse Event(s): Pseudarthrosis Past Medical History: Hypercholesterolemia</p> <p>A 58-year-old female received OP-1 Putty at level L4-L5 on 21 Dec 2000. On 22 Oct 2001 (305 days post-surgery) she was hospitalized for leg pain secondary to pseudarthrosis. She underwent supplemental fixation that included an instrumented transforaminal lumbar interbody fusion, and L4-L5 decompression. The event resolved on 17 Jul 2003, approximately 605 days after the initial onset.</p> <p>Concomitant medications included narcotic pain medication (NOS), sulfa medication (NOS) and Lipitor® (atorvastatin).</p> <p>Investigator assessed severity of the pseudarthrosis as moderate and probably not related to OP-1 Putty.</p>
<p>553 OP-1 Putty</p>	<p>DEL</p>	<p>Serious Adverse Event(s): Lung neoplasm malignant, prostate cancer, Past Medical History: Cardiovascular disease, gastrointestinal disease, urogenital disease, family history of prostate cancer</p> <p>A 75-year-old male received OP-1 Putty at level L4-L5 on 16 Nov 2000. Patient was hospitalized with prostate cancer on 24 Nov 2003 (1102 days post surgery) and received treatment with androgen deprivation injections. On 05 Nov 2004 (1450 days post surgery) he developed metastatic lung cancer and was hospitalized. Treatment included chemotherapy (NOS). Investigator initially assessed both prostate cancer and the lung cancer as life-threatening events. Events were ongoing at conclusion of study.</p> <p>Concomitant medications included non-narcotic pain medications (not specified).</p> <p>The investigator assessed the severity of the prostate cancer as severe and probably not related to OP-1 Putty, and the severity of the lung cancer as moderate and probably not related to OP-1 Putty.</p>

12.4 NEUROLOGICAL EVALUATIONS

Statistical Tables 9 and 9.1 in Section 14 summarizes shifts from normal to abnormal in neurologic status, as assessed by tests of muscle strength in the hips, knees, ankles, toes, and by reflex testing. Overall, muscle strength was similar among the 3 treatment groups during the course of the study, with most patients having normal evaluations. Abnormal reflexes were elicited in all treatment groups, but no progressive deterioration was apparent during the course of the study.

Abnormal sensory evaluations were observed in the OP-1 Putty alone and autograft alone treatment groups, with higher proportion of patients who received autografts alone or in combination with OP-1 Putty demonstrating abnormalities than in the OP-1 Putty alone group. These findings remained stable over time.

In general, the components of neurologic function were insensitive indicators of alterations in clinical status in this study.

12.5 IMMUNOGENICITY EVALUATION

Serum samples for evaluation of immunogenicity were collected pre-operatively, and at 6 weeks and 6 months post-operatively as described in the study protocol. Enzyme-linked immunoabsorbent assays (ELISA) were performed to detect the presence of antibodies to OP-1 according to established procedures. ELISA methods were validated to detect human anti-human OP-1 antibodies with IgG, IgM, and IgE isotypes. Positive samples in a screening ELISA were evaluated in a Titer ELISA to determine the titer of Anti-OP-1 antibodies in the sample. A technical report (TR-0694, Section 16.5.1) provides detailed information on the evaluation of Anti-OP-1 levels in serum samples as determined by ELISA. Samples found to be positive in the Titer ELISA were further analyzed to determine whether antibodies to OP-1 had the ability to neutralize the activity of OP-1 in vitro. Neutralizing antibody data for serum samples with positive antibody titers are presented in a detailed technical report (TR-0735, Section 16.5.2). The following is a brief summary of the immunogenicity results for this study.

12.5.1 OP-1 Putty/Autograft

In the OP-1 Putty/autograft group, 8 of 12 patients (66.7%) developed measurable titers by the 6-week time point, and 7 patients maintained measurable titers at 6 months. Two patients never had detectable antibodies, 1 patient had a minimal titer at 6 months, and 1 patient was not analyzed at 6 weeks. Two additional patients, negative at 6 weeks, had measurable titers at 6 months (10 of 12, 83%). None of these 10 patients who were antibody-positive at either 6 weeks or 6 months demonstrated neutralizing activity.

12.5.2 OP-1 Putty Alone

In the OP-1 only group, 23 of 24 patients (95.8%) had detectable antibody titers 6 weeks postoperatively. At 6 months, 22 of these patients (91.7%) maintained antibody titers, and 1 patient had returned to baseline undetectable levels.

In the OP-1 Putty alone group, 7 of the 23 antibody-positive patients (30%) demonstrated neutralizing activity; however, in 6 of these patients (86%), neutralizing activity was detected only at the 6-week time point. In 1 patient, neutralizing activity was detected only at the 6-month time point. It therefore appears that in those patients who developed neutralizing antibodies by 6 weeks post-operatively, the antibodies diminished over time, and became undetectable by 6 months. No samples were collected beyond the 6-month time point, and thus, no further conclusions can be drawn regarding persistence of antibodies in this patient population.

Table 30 presents the efficacy results (overall success and radiographic success at 12, 24, and 36 months) for the 7 patients with neutralizing antibodies. No formal analyses of the effect of neutralizing OP-1 antibodies on safety or efficacy for the 7 patients with neutralizing antibodies were performed. However, the rate of overall success at 24 months for patients with neutralizing antibodies in either OP-1 Putty containing regimen (3 of 7 patients; 42.3%) is comparable to the rate of overall success for patients without neutralizing antibodies in either OP-1 Putty containing regimen (13 of 29 patients; 44.8%).

Table 31 presents the reported AEs (by preferred term) for these same 7 patients. Whether these immune responses were associated with occurrence of AEs has not been formally analyzed; however, no pattern of immunologically-mediated AEs has emerged. While many patients experienced musculoskeletal AEs, these generally appeared to be mechanical in nature, and no evidence of autoimmune syndromes has been observed. Pseudarthrosis was reported only in patients who received OP-1 Putty. The relationship of pseudarthrosis to the immune response initiated by OP-1 Putty is unknown at this time. None of these patients underwent retreatment.

Table 30. Seven Patients with Neutralizing Antibodies to OP-1

Patient ID	Time Point Positive	12 Months		24 Months	
		Overall Success	Radiographic Success	Overall Success	Radiographic Success
154	Baseline	N/A	N/A	N/A	N/A
	6 month	Failure	No radiographic data	Failure	No radiographic data
155	6 week	Failure	No radiographic data	Failure	No radiographic data
352	6 week	Failure	Failure	Success	Success
354	6 week	Success	Success	Success	Success
356	6 week	Failure	Failure	Failure	Failure
360	6 week	Failure	Failure	Failure	Failure
551	6 week	Success	Success	Success	Success
Total Success		2	2	3	3

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Table 31. Reported Adverse Events for Seven Patients with Neutralizing Antibodies to OP-1

PTID	Time Point(s) Positive	Preferred Term	Onset Date	Surgery Date
154	Baseline, 6 month	Urinary retention postoperative	15-May-00	15-May-00
		Anaemia postoperative	18-May-00	
		Pseudarthrosis	18-Oct-00	
		Renal artery stenosis	7-Apr-03	
		Breast cancer	26-Apr-04	
155	6 week	Post-procedure hematoma	21-Jun-00	15-Jun-00
		Vertigo	2-Jul-00	
		Arthritis	19-Jul-00	
		Pain in limb	30-Aug-00	
		Pseudarthrosis	14-Mar-01	
352	6 week	Postoperative wound infection	17-Apr-00	13-Apr-00
		Oedema peripheral	19-Apr-00	
		Arthralgia	2-Oct-00	
		Arthralgia	3-Aug-01	
354	6 week	Hypoaesthesia	10-Jan-01	11-May-00
356	6 week	Postoperative wound infection	14-Jun-00	6-Jun-00
		Back pain	11-Jan-01	
		Pseudarthrosis	5-Jun-01	
		Fall	8-Jun-01	
		Pain in extremity	24-Feb-04	
		Back pain	24-Feb-04	
360	6 week	Urinary tract infection	9-Nov-00	6-Nov-00
		Pain in extremity	10-Dec-00	
		Back pain	15-Jan-01	
		Pseudarthrosis	24-Jul-01	
		Pain in extremity	20-Nov-01	
551	6 week	Arthralgia	4-Jan-01	24-Oct-00
		Fall	31-Mar-02	
		Pain	15-Aug-03	
		Onychomycosis	1-Nov-03	
		Fall	22-Feb-04	
		Fall	8-Nov-04	

12.5.3 Autograft Alone

All samples from patients who received autograft tested negative for antibodies to OP-1 Putty.

12.6 SURGICAL PROCEDURE CHARACTERISTICS AND RISK PROFILE

Statistical Table 10 in Section 14 summarizes characteristics of the surgical procedure and its components, including level fused, anesthetic time, operative time, blood loss, reinfusion of autologous blood, prophylactic measures employed, equipment, and other procedures performed at the time of operation.

Most patients in each treatment group underwent fusion at the L4-L5 level. The OP-1 Putty alone treatment group required the least amount of operative procedure anesthesia time when compared to either the OP-1 Putty and autograft combination treatment group, or the autograft alone group. However, the estimated blood loss was greater in the OP-1 Putty alone group (408 mL) and in the combination treatment group (433mL) than in the autograft alone group (338mL). This was also reflected in the volume of blood reinfused to patients, with those in the OP-1 Putty alone group receiving 500 mL, and those in the OP-1 Putty and autograft and autograft alone groups receiving 292 mL and 250 mL, respectively.

12.7 SAFETY CONCLUSIONS

- Adverse events (AE) occurred in 100% of patients across all treatment groups: 149 in the 36 patients in the OP-1 Putty treatment groups (with or without autograft), and 51 in the 12 patients treat who received autografts.
- Thirty-six SAEs were reported in 18 patients across all treatment groups, and none were attributed to the use of OP-1 Putty.
- Four patients across treatment groups reported 8 malignancies, none of which were attributed to the use of OP-1 Putty.
- One death, due to carcinomatosis, occurred in this study.
- Pseudarthrosis was reported predominantly between 6 and 12 months post-operatively and in 13 patients who received an OP-1 Putty-containing regimen. Only 2 of these 13 patients required a surgical retreatment due to pseudarthrosis.
- Post-operative wound infections occurred only in patients who received OP-1 Putty alone.
- There was no evidence of neurological deterioration post-operatively in any treatment group.
- Seven patients in the OP-1 Putty alone group had neutralizing antibodies at either 6 weeks or 6 months post-procedure, however no pattern of immunologically-mediated AEs has emerged. The Overall Success rates of OP-1 Putty patients with or without neutralizing antibodies appears comparable, 42.3% vs. 44.8%. In

5.2 Pilot Study (Content from P060021 Original PMA, CSR S99-01US, Section 7-13)

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this trial, no relationship between antibody occurrence and clinical events was observed.

Overall, the AE profile in the groups treated with OP-1 Putty was comparable to that in the autograft alone treatment group. The small sample sizes, particularly in the autograft only group, preclude any broader conclusions. Although pseudarthrosis was reported only in the OP-1 Putty treatment groups, reporter bias cannot be ruled out in this unblinded trial, as pseudarthrosis is a known potential outcome of failed lumbar fusion surgery.

13. CONCLUSIONS

A large proportion of the adult population suffers from some form of low back (lumbosacral) pain, usually attributed to degenerative processes within the vertebral spine. The cost of evaluation, treatment, and the restrictions on mobility associated with low back pain exert significant economic and social consequences for individual patients, their families and employers, health care providers, compensation systems, and society as a whole.

Degenerative disc disease is associated with spondylolisthesis, which in turn may lead to the formation of osteophytes that cause stenosis and root compression. Symptoms of spondylolisthesis include: localized back pain and leg pain, originating both at the affected vertebrae and from nerve root compression; neurological deficit; and spinal instability due to excessive angulation and /or translational movement of the spinal vertebrae.

If initial conservative approaches to the management of pain, neurological deficit, and instability such as rest, exercise or physical therapy, medication including epidural steroids, use of a back brace, changes in posture and body mechanics do not result in improvement, surgical intervention is often required.

Decompression and lumbar spinal fusion are the surgical treatments of choice for degenerative spondylolisthesis. Decompression at the affected level relieves pressure of stenosis on the cauda equine or on the exiting nerve roots. Decompression without spinal fusion (arthrodesis) may have a less favorable outcome that was previously thought, particularly when spinal stenosis is associated with degenerative lumbar spondylolisthesis at a single level. Decompression with spinal fusion is currently the most common surgical approach to the management of progressive degenerative spondylolisthesis.

In this study, patients with single level (L3-S1) Grade 1 or 2 degenerative lumbar spondylolisthesis were randomized to undergo spinal fusion with OP-1 Putty alone, OP-1 Putty in combination with autograft, or with autograft alone. Safety was assessed by comparison of complications and neurological status within the OP-1 Putty treatment groups and the control group, autograft alone. Efficacy was assessed by comparison of overall fusion success and pain/function outcome within the OP-1 Putty treatment groups, and in the control group, autograft alone.

Of the 48 patients treated in this study, the mean age was 65 years, and females accounted for more than half of the patients in each treatment group. Weight and height were similar in all 3 treatment groups, and the majority of patients had disease involvement at the L4-L5 level. Few patients had had prior surgical intervention, and most had taken steroids and non-steroidal medications, and a variety of non-drug therapies prior to study enrollment.

13.1 EFFICACY

The focus of this pilot trial was safety, as the study was not statistically powered to sufficiently assess efficacy. Small sample size and wide variability in efficacy outcomes precluded the ability to definitively assess differences between treatment groups.

Nevertheless, the following observations can be made:

- Overall Success: treatment groups appear to be comparable at 24 months
- Greater Radiographic Success is noted in both OP-1 Putty groups versus autograft, but small sample sizes preclude the ability to assess differences between treatment groups.
- Angular motion: The proportion of patients who achieved success in angular motion appeared to be greater in the OP-1 Putty alone treatment group versus other treatment groups at both 12 and 24 months.
- ODI percent success for both OP-1 Putty treatment groups appeared to suggest an advantage for OP-1 Putty over autograft.
- Patient 105 (OP-1 Putty and autograft) underwent retreatment for pseudarthrosis (supplemental fixation) at 7.6 months post-operatively. Two additional patients (Patients 153 and 455 in the OP-1 Putty alone group) underwent retreatment after 24 months..
- Treatment groups were similar for disc height, leg/buttock pain, donor site pain, and SF-36 scores.

13.2 SAFETY

Forty-eight patients were randomized to 3 treatment arms and were treated once with 2 units of OP-1 Putty alone, 2 units of OP-1 Putty in combination with autograft, or with autograft alone. The mean follow-up was similar among all 3 treatment groups (45.3 months, 51.1 months, and 46.5 months, respectively). Adverse events occurred in all 48 patients (100%), with a total of 200 AEs reported across all treatment arms. Adverse events (AE) occurred in 100% of patients across all treatment groups: 149 in the 36 patients in the OP-1 Putty treatment groups (with or without autograft), and 51 in the 12 patients treat who received autografts.

Eighteen patients experienced 36 SAEs, none of which were attributed to the use of OP-1 Putty. There were 8 reports of malignancies in 4 patients across all treatment groups. One patient in the autograft treatment group reported prostate cancer approximately 4 months post-operatively. Five malignancies were reported as SAEs, and none of the reported malignancies were attributed to the use of OP-1 Putty. Malignancies were not unexpected in this population of generally older adults, and in general were noted later in the course of the study, at least 24 months post-operatively.

Pseudarthrosis occurred only in patients who received OP-1 Putty (13 patients, 36%), and most of these occurred in patients who received OP-1 Putty alone (10 patients, 28%). The

majority of these events (6) were diagnosed between 6 and 12 months following surgery. There were no reports of pseudarthrosis in the autograft alone treatment group.

Pseudarthrosis may have resulted from failure to fuse, premature evaluation prior to fusion, or radiographic artifact due to the relative lack of opacity of the OP-1 Putty product. Two patients who reported pseudarthrosis required a surgical retreatment. The remaining 11 patients with pseudarthrosis did not require surgical retreatment. In addition, due to the unblinded nature of the study, a reporting bias favoring the autograft groups cannot be ruled out.

There were 4 reports of post-operative wound infections that occurred only in patients who were treated with OP-1 Putty alone. It is unclear if these patients underwent more procedural manipulation in order to achieve optimal placement of the study product, or if there were environmental, procedural, or other pre-existing factors which could have contributed to the occurrence of wound infections in this treatment group.

There were no reports of AEs associated with the radiographic evidence of heterotopic bone formation.

Neurological evaluations of muscle strength were similar among the 3 treatment groups, with most patients having normal evaluations. Abnormal reflexes were noted in all treatment groups, but there was no evidence of progressive deterioration during the course of the study.

Immunologic evaluations demonstrated that the patients who received autograft only remained antibody-negative throughout the 6-month evaluation period, while the majority of patients who received OP-1 Putty either alone or in combination with autograft did mount an immune response to OP-1 as measured by anti-OP-1 antibody titers. Seven patients in the OP-1 Putty alone group had neutralizing antibodies at either 6 weeks or 6 months post-procedure, however no pattern of immunologically-mediated AEs has emerged. The Overall Success rates of OP-1 Putty patients with or without neutralizing antibodies appears comparable (42.3% versus 44.8%). In this trial, no relationship between antibody occurrence and clinical events was observed.

13.3 CONCLUSION

OP-1 Putty, as a single modality and in combination with autograft, compares favorably with autograft alone in the treatment of degenerative lumbar spondylolisthesis.