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# The Safety and Efficacy of OP-1 (rhBMP-7) as a Replacement for Iliac Crest Autograft in Posterolateral Lumbar Arthrodesis

## A Long-term (>4 Years) Pivotal Study

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**Study Design.** Randomized controlled trial comparing OP-1 (rhBMP-7) with iliac crest autograft in patients with symptomatic degenerative spondylolisthesis and spinal stenosis treated with decompression and uninstrumented posterolateral arthrodesis.

**Objective.** To determine the safety and the clinical and radiographic efficacy of OP-1 (rhBMP-7) Putty as compared with an iliac crest bone autograft control in uninstrumented, single-level posterolateral spinal arthrodesis.

**Summary of Background Data.** Preclinical and preliminary clinical data have demonstrated successful fusion and clinical outcomes with the use of OP-1 Putty in posterolateral spinal arthrodesis. No prior randomized controlled trial with adequate study power has been performed.

**Methods.** A total of 335 patients were randomized in 2:1 fashion to receive either OP-1 Putty or autograft in the setting of an uninstrumented posterolateral arthrodesis performed for degenerative spondylolisthesis and symptomatic spinal stenosis. Patients were observed serially with radiographs, clinical examinations, and appropriate clinical indicators, including ODI, Short-Form 36, and visual analog scale scores. Serum samples were examined at regular intervals to assess the presence of antibodies to OP-1. The primary end point, Overall Success, was analyzed at 24 months. The study was extended to include additional imaging data and long-term clinical follow-up at 36+ months. At the 36+ month time point, CT scans were obtained in addition to plain radiographs to evaluate the presence and location of new bone formation. Modified Overall Success, including improvements in ODI, absence of retreatment, neurologic success, absence of device-related serious adverse events, angulation and translation success, and new bone formation by CT scan (at 36+ months), was then calculated using the 24-month primary clinical endpoints, updated retreatment data, and CT imaging and radiographic end points.

**Results.** OP-1 Putty was demonstrated to be statistically equivalent to autograft with respect to the primary end point of modified overall success. The use of OP-1 Putty when compared to autograft was associated with statistically lower intraoperative blood loss and shorter operative times. Although patients in the OP-1 Putty group demonstrated an early propensity for formation of anti-OP-1 antibodies, this resolved completely in all patients with no clinical sequelae.

**Conclusion.** OP-1 Putty is a safe and effective alternative to autograft in the setting of uninstrumented posterolateral spinal arthrodesis performed for degenerative spondylolisthesis and symptomatic spinal stenosis.

**Key words:** spinal fusion, bone morphogenetic protein, spondylolisthesis. **Spine 2008;33:2850–2862**

Posterolateral spinal arthrodesis is commonly used for the treatment of patients with symptomatic degenerative spondylolisthesis unresponsive to nonoperative treatment. However, failure of fusion remains a common complication after surgery.[1,2] In addition to the lack of successful arthrodesis, donor site morbidity related to the bone graft harvest continues to present a problem affecting as many as 25% of patients after traditional spinal fusion using autogenous iliac crest bone graft.[3–6] Therefore, a plethora of bone graft extenders and alternatives have been developed in an attempt to improve the rates of healing and avoid the complications of autograft harvest.[7,8] The discovery of osteogenic proteins by Urist in the mid-1960s ushered in a new era of molecular biology in bone formation and healing.[9] This family of proteins has been subsequently named bone morphogenetic proteins (BMPs), and many members of this family have been isolated and characterized. BMPs exert their action by recruiting and stimulating pluripotent mesenchymal cells along an osteoblastic lineage resulting in the formation of bone.[10] Because of the powerful osteogenic potential of these proteins, they have been studied with considerable interest as a possible replacement or augmentation for autograft bone in the setting of spinal fusion. Several BMP preparations have been studied in preclinical and clinical trials for spinal applications.[11–16]

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Osteogenic Protein-1 (OP-1), also called recombinant human BMP-7 (rhBMP-7), is one such protein. OP-1 is a member of the TGF-$\beta$ superfamily, and, like other members in this family, can induce the formation of bone when implanted in ectopic locations. Implants containing OP-1 and collagen matrix have been shown to be osteoinductive, osteoconductive, and to speed the rate of bone healing and to improve the performance of autograft in animals.[17–20] The human OP-1 gene has been cloned and introduced into a commercial cell line, facilitating the production of large quantities of recombinant human OP-1 (rhOP-1). OP-1, with various carrier preparations, has been studied in a number of animal models of spinal fusion.[12,13,21–23] The available human data involving BMPs suggest that these molecules are associated with a low risk of protein-related complications when used to promote bone healing or spinal fusion. These complications, although not recognized to date after the administration of OP-1, can consist of hypersensitivity to the administration of the protein, autoimmune reactions, or loss of efficacy of the protein at the intended target resulting from immune complex formation.

Several human pilot studies involving the use of OP-1 as both an adjunct to and a replacement for autograft in posterolateral spinal fusion studies have been performed to date. Fehlings and coworkers have reported that OP-1 can be used safely to achieve successful fusions in patients at higher risk for pseudarthrosis.[24,25] Conditions placing patients at higher risk over the general population after lumbar arthrodesis include nicotine usage, previous irradiation, administered chemotherapy, and continuous postoperative use of nonsteroidal anti-inflammatories. Vaccaro *et al* reported 1-year, 2-year, and minimum 4-year results of a prospective randomized, controlled, multicenter clinical pilot study comparing autograft *versus* OP-1 alone in the setting of uninstrumented posterolateral arthrodesis for degenerative spondylolisthesis.[26–28] These results consistently indicated the safety and efficacy of OP-1 and its comparability with autograft. At each time point, the groups treated with OP-1 demonstrated higher fusion rates, higher rates of clinical success (20% increase in the Oswestry scores), and no incidents of local or systemic toxicity, ectopic bone formation, or other adverse events related to the use of OP-1 Putty.

The purpose of this pivotal study was to establish the clinical and radiographic noninferiority of OP-1 Putty as a replacement for autograft bone when performing uninstrumented posterolateral spinal arthrodesis in a randomized controlled population of patients with symptomatic lumbar spinal stenosis and degenerative spondylolisthesis.

## ■ Materials and Methods

### *Study Design*

This study was approved as an Investigational Device Exception study by the Food and Drug Administration and by the institutional review boards of the participating institutions. The design was a controlled, open-label (with blinded radiographic assessment), randomized, prospective, multicenter trial in which patients underwent single-level uninstrumented posterolateral lumbar arthrodesis for degenerative spondylolisthesis and spinal stenosis. The primary goal of the study was to demonstrate the safety and efficacy of OP-1 Putty and to demonstrate noninferiority *versus* the autograft control. The study was performed at 24 centers. After obtaining informed consent, patients were randomized to treatment with either OP-1 Putty or a control arm in which autogenous bone graft from the iliac crest (autograft) was used. A total of 335 patients were enrolled and randomized, of which 295 were treated. There was an attrition of 40 patients from the "intent-to-treat" population; 20 patients from the autograft group either refused the autograft part of the procedure or did not qualify after randomization based on the inclusion/exclusion criteria and 20 patients in the OP-1 group who were from the OP-1 Putty group either voluntarily withdrew from the study or were disqualified based on the inclusion/exclusion criteria. A total of 208 patients received OP-1 Putty and 87 received autograft. After surgery, patients were evaluated clinically and radiographically at 6 weeks, and at 3, 6, 9, 12, 24, and at a minimum of 36 months. Clinical assessments consisted of an evaluation of subjective pain and function using the Oswestry Low Back Pain Disability (ODI) questionnaire, the Visual Analog Scale (VAS), neurologic evaluation, and functional outcome assessment via completion of the Short-Form 36 (SF-36) outcomes survey. Imaging consisted of anteroposterior (AP), lateral, and flexion-extension radiographs. After the 24-month time point, patients were recruited to participate in the 36+ month assessment. At the latest follow-up at 36+ months, 202 of the original protocol patients (144 patients in the OP-1 Putty group and 58 patients in the autograft group) were evaluated with flexion-extension radiographs and helical CT scans with multiplanar reformatted imaging and three-dimensional (3-D) reconstructions. In addition, clinical assessments consisting of physical examination, SF-36 forms, and ODI questionnaires were repeated. Updated retreatment and serious adverse events (SAE) data were compiled through 36+ months.

### *Fusion Materials*

A single package of OP-1 Putty implant consists of 3.5 mg of rhOP-1 formulated with 1 g of Type 1 bovine-derived collagen and 230 mg of carboxymethylcellulose. This powdered mixture was reconstituted at the time of surgery by the addition of saline to achieve a final implant concentration of rhOP-1 protein of 0.875 mg/mL. One package of implant was used per side, so that each patient received a total dose of 7 mg of rhOP-1 protein. No autogenous bone was used for the fusion in those patients randomized to receive the OP-1 Putty implants. Patients who were randomized to the autograft group were treated with corticocancellous bone harvested from the posterior iliac crest. No local bone graft was used for the fusion procedures. In both groups, the implanted fusion material was placed between the decorticated transverse processes and on the lateral border of the facets on both sides of the listhetic segment (*e.g.*, for a L4–L5 spondylolisthesis, the fusion material was used to bridge the space between the decorticated L4 and L5 transverse processes).

### *Inclusion and Exclusion Criteria*

All study patients had Grade I or II degenerative spondylolisthesis of the L3–L4, L4–L5, or L5–S1 segments with coexistent spinal stenosis as confirmed by history, physical examination, and imaging, including AP and lateral plain radiography, flex-

ion-extension radiographs, and MRI or postmyelographic CT. Clinically, the patients presented with symptoms of neurogenic claudication. All the patients were skeletally mature, and none had undergone previous lumbar surgery. All patients had failed at least 6 months of nonoperative treatment, including physical therapy, lumbar epidural injections, anti-inflammatory medications, and activity modifications for their spinal symptoms. Exclusion criteria involved a spondylolisthesis of greater than Grade II, nondegenerative spondylolisthesis of any grade, spinal instability on flexion-extension radiographs measuring >50% translation of the vertebral body or >20° of angular motion, active spinal or systemic infection, systemic disease precluding participation (*e.g.*, neuropathy), current nicotine use, a history of smoking, morbid obesity, or a known sensitivity to collagen. Women of child-bearing potential who had not had a hysterectomy were also excluded.

### Randomization and Demographics

Patients were randomized in a 2:1 ratio to receive OP-1 Putty or iliac crest autograft for the spinal arthrodesis aspect of the procedure. Randomization was performed after enrollment but before surgery using a computerized algorithm (SAS using the PLAN procedure). Patients and physicians became aware of the treatment assignment at the time of the randomization and before surgery so the study was unblinded; however, radiographic assessments of fusion and determination of neurologic success were performed by independent assessors in a blinded manner.

### Surgical and Postoperative Protocol

All patients received general anesthesia and prophylactic antibiotics. A posterior midline exposure was performed and carried out to the tips of the transverse processes of the listhetic segment. A bilateral laminectomy and bilateral medial facetectomies were performed to decompress the neural elements. The transverse processes of the levels cephalad and caudad to the slip were decorticated to expose the marrow elements of the bone. The lateral border of the facets and the pars interarticularis were also decorticated. The fusion material (either 3.5 mg OP-1 Putty implant per side or half of the autograft bone graft per side) was placed in the intertransverse region to bridge the space between the decorticated transverse processes. Although a standardized technique was used to harvest corticocancellous bone from the posterior iliac crest, no formal method for quantification of the volume of autograft bone was used in the protocol. No irrigation was performed after placement of the fusion material.

### Postoperative Management

Each patient was fitted with a lumbosacral orthosis of choice and instructed to wear the brace when out of bed for 3 months. Early ambulation was encouraged on the first day after surgery. Formal organized physical therapy emphasizing active exercises was begun 6 to 8 weeks after surgery. Each patient was scheduled for follow-up visits with their surgeon at 6-week, and 3, 6, 9, 12, 24-month time points after surgery. At each visit, a clinical neurologic and radiographic assessment was performed, including AP, lateral and flexion-extension plain radiographs (at the 3-month follow-up and later). Oswestry Disability Index (ODI), and Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) were administered. VAS scores were assessed at the 12 and 24-month visits. At 36+ months, all available patients were brought back for clinical and radiographic reassessment. The criteria for recruitment of patients to the 36+ month group were that the patient had to be alive and had not been previously categorized as a retreatment failure earlier in the study. The repeat clinical assessments included ODI assessments, VAS scores, neurologic testing, retreatment analysis (*i.e.*, revision, removal, supplemental fixation, or reoperation) at the original treated level, and compilation of SAEs.

### Radiographic Assessments

AP and flexion-extension radiographs through 24 months were interpreted by 2 radiologists blinded to the treatment group. A third, blinded radiologist evaluated those radiographs in which the 2 radiologists were in disagreement. Radiographs were used for the identification of the treatment level, assessment for bridging trabecular bone between the transverse processes, and identification of angulation and translation. The presence of new bone formation bridging across the transverse processes, angulation $\leq 5°$, and $\leq 3$ mm of translation were all required to meet the standard of radiographic fusion. The postoperative flexion-extension radiographs were performed as part of the assessment of radiographic fusion only. They were not performed to allow a comparison with preoperative flexion-extension values. Because the performed surgery involved a decompressive laminectomy and partial medial facetectomy of a degenerative spondylolisthesis, the postoperative condition of the spine before the development of fusion was considered to be unstable and, therefore, unsuitable for comparison with the preoperative condition. At the 36+ month interval, helical CT scans and flexion-extension plain films were taken and assessed using a prospective, multireviewer, blinded radiographic assessment protocol designed to minimize bias. The CT scans were performed using a standardized imaging algorithm and protocol to assess the presence of new bone formation and the presence of bridging bone across the transverse processes. The CT scans were also used to determine the location of bone formation (medial *vs.* lateral, in reference to the transverse process and pars interarticularis). Medial bone formation was determined to be across the pars interarticularis or the medial one-third of the transverse process region, whereas lateral bone formation was defined as bone formation extending across the lateral two-thirds of the transverse process region. Both the 36+ month CT scans and flexion-extension plain radiographs were interpreted by 2 primary spine surgeon readers not associated with the clinical trial and blinded to the treatment arm. When the 2 primary readers did not agree, a third reader was used to adjudicate the results and the majority assessment was used.

### Immunologic Assessments

Enzyme-linked immunosorbent assays (ELISA) were performed to detect the presence of anti-OP-1 antibodies in all samples. ELISA methods were validated to detect human anti-human OP-1 antibodies with IgG, IgM, and IgE isotypes. The ELISA cutoff point for this study was statistically based and reflects a false positive rate of 5%, as recommended by Mire-Sluis *et al*.[29] Positive samples in screening ELISA were considered potentially positive for anti-OP-1 antibodies and tested in a validated confirmatory competition ELISA. Positive samples in the competition ELISA were further evaluated in a titer ELISA to quantify the level of anti-OP-1 antibodies in the sample. The results of this assay are reported as a log titer, which corresponds to the log of the lowest dilution of the sample that yields a positive result.

Samples found to be positive in the titer ELISA were further analyzed to determine whether antibodies to OP-1 had the

ability to neutralize its activity *in vitro*. Samples were initially tested in a luciferase reporter-based primary neutralizing antibody assay (nab). The presence or absence of antibodies (both anti-OP-1 antibodies and anti-OP-1 neutralizing antibodies) was determined following blood draw and centrifugation using ELISA analysis (Genetics Institute, Cambridge, MA). All patients who were antibody-positive at 24 months had repeat serum samples obtained at the 36+ month visit.

### *Primary Outcome Assessments*

**Safety and Adverse Outcome Reporting.** The safety of the investigational product was evaluated by comparing the nature and frequency of adverse events in each of the 2 treatment groups. Adverse events included all minor and major medical events for which the patient sought medical attention regardless of the nature of the event or its severity. An adverse event was defined as any clinically adverse sign, symptom, syndrome, or illness that occurred or worsened during the operative or postoperative period of the trial, regardless of causality. All reoperations (revisions or supplemental fixations) over the study period were recorded. Reoperations performed to promote fusion at the treated level were deemed failures. Laboratory testing for immunologic, hematologic, and biochemical evaluation was performed before surgery (baseline), at 6 weeks, and at 3, 6, 12, and 24 months.

### *Primary End Points*

The primary end points for the study were evaluated at 24 and at 36+ months. The primary end point at 24 months was designed for FDA submission evaluating the safety and efficacy of OP-1 Putty as a replacement for autologous iliac crest in the setting of a posterolateral fusion for degenerative spondylolisthesis. Primary Overall Success at 24 months was defined as a composite measure that required a 20% improvement in ODI, absence of treatment-emergent SAEs related to the treatment device, absence of a decrease in neurologic status (assessing muscle strength, reflexes, sensation, and straight leg raise), and radiographic fusion success. Radiographic fusion success was also a composite measure, requiring the presence of bridging bone as assessed on AP radiographs, angular motion $\leq 5°$, and translational movement $\leq 3$ mm as assessed by flexion-extension radiographs. The primary outcome assessment for the study at 36+ months, Modified Overall Success, was also defined as a composite measure requiring success on each of the following components: improvement of at least 20% in the ODI from baseline, absence of treatment-emergent SAEs related to the treatment device, absence of a decrease in neurologic status (assessing muscle strength, reflexes, sensation, and straight leg raise) at 24 months, and presence of new bone formation by CT scan, angulation of $\leq 5°$ and translational movement of $\leq 3$ mm on flexion/extension radiographs, and absence of retreatment intended to promote fusion at 36+ months.

### *Data Analysis and Statistics*

A power analysis performed before the initiation of the study demonstrated, using an alpha level of 0.05 and a power of 80%, that 270 treated subjects (180 OP-1 Putty, 90 autograft) were needed for the study. The number of treated patients in this trial was based on hypothesized overall success rates of 53% for the OP-1 Putty group in comparison with 47% for the autograft group based on data from a pilot study conducted on a similar population of patients with a similar endpoint. The maximum allowable difference between the treatment groups that could be used to conclude that OP-1 Putty was not inferior to autograft was variable.

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

The primary efficacy end points were the 24-month and the 36+ month overall success rates. The 36+ month rate of overall success included the 24-month overall success rate data with radiographic and retreatment (need for revision surgery at the index surgical level) data at 36+ months for the intent-to-treat population with missing data imputed using a multiple imputation technique. The percentage of successes (and standard error) was based on estimates of the treatment effect adjusted for covariates in logistic regression and on variance estimates obtained from multiple imputations. Secondary efficacy end points included analyses of overall success stratified by center size, age category, and gender.

For imputed modified overall success at 24 months (with radiographic and retreatment data at 36+ months), a one-sided two-sample asymptotic test for noninferiority was used. For both the primary efficacy analyses of success, the 95% upper confidence bound was generated corresponding to the difference in success rates (autograft minus OP-1 Putty) in the 2 treatment groups.

For adverse events, each SOC and each preferred term reported by $\geq 5\%$ of patients in either treatment arm were tested for treatment differences using Fisher exact test. For neurologic status, $\chi^2$ or Fisher exact test was used to test the difference between treatments groups and McNemar's test was used to test the shifts in status within treatment group.

## ■ Results

### *Demographic Information*

Demographic and baseline data for the patients enrolled in the study are presented in Table 1. Overall mean age at baseline was 68 years (range 36–84 years). There were no significant differences between the OP-1 and autograft groups with respect to age, gender, weight, height, level treated, preoperative ODI, preoperative translation, or diagnosis.

At the 36+ month assessment time point, 80% (80.5%) of eligible patients (79.7% of autograft group and 80.8% of the OP-1 Putty group) returned or had died before study follow-up and were, therefore, accounted for in the long-term evaluation. All key demographic characteristics and 24-month outcome variables of the patients who participated in the long-term evaluation compared to those eligible to participate were similar and not statistically different (Table 2).

### *Surgical Indications and Prior Treatments*

The indications for surgery are summarized in Tables 1 and 2. At baseline, all the patients carried a diagnosis of degenerative lumbar spondylolisthesis with spinal stenosis. Of these 272 of 293 (92.8%) had Grade I spondylolisthesis by the Meyerding classification,[30] 10 of 293 (3.4%) had Grade II, and 11 of 293 (3.8%) had spondylolisthesis that could not be distinguished between

**Table 1. Demographics and Baseline Characteristics (Modified ITT)**

| Parameter | Statistic | Mean | OP-1 Putty | Autograft | *P* |
|---|---|---|---|---|---|
| Age (yrs) | | | | | |
| Mean | | 68 | 68 | 69 | 0.129 |
| Median | | 69 | 68 | 71 | |
| Std. Dev. | | 9.4 | 9.8 | 8.3 | |
| Sex | | | | | |
| Male | N (%) | 97 (33.1) | 71 (34.3) | 26 (30.2) | 0.501 |
| Female | N (%) | 196 (66.9) | 136 (65.7) | 60 (69.8) | |
| Level fused | | | | | |
| L3–L4 | n (%) | 31 (10.6) | 21 (10.1) | 10 (11.6) | 0.76 |
| L4–L5 | n (%) | 252 (86.0) | 178 (86.0) | 74 (86.0) | |
| L5–S1 | n (%) | 10 (3.4) | 8 (3.9) | 2 (2.3) | |
| ODI | N | 293 | 207 | 86 | |
| Mean | | 48.8 | 48.8 | 48.8 | 0.998 |
| Median | | 48 | 48.9 | 48 | |
| Std. Dev. | | 12.19 | 11.6 | 13.59 | |
| Angular motion (degrees) | N | 271 | 195 | 76 | |
| Mean | | 4.1 | 3.9 | 4.7 | 0.086 |
| Median | | 3.1 | 2.8 | 4.2 | |
| Std. Dev. | | 3.36 | 3.4 | 3.2 | |
| Translational movement (mm) | N | 268 | 193 | 75 | |
| Mean | | 1.7 | 1.7 | 1.6 | 0.802 |
| Median | | 1.4 | 1.4 | 1.1 | |
| Std. Dev. | | 1.45 | 1.44 | 1.49 | |
| Diagnosis of degenerative lumbar spondylolisthesis with spinal stenosis | n (%) | 293 (100.0) | 207 (100.0) | 86 (100.0) | — |
| Grade 1 | n (%) | 272 (92.8) | 193 (93.2) | 79 (91.9) | |
| Grade 2 | n (%) | 10 (3.4) | 8 (3.9) | 2 (2.3) | |
| Unable to distinguish between Grade 1/2 | n (%) | 11 (3.8) | 6 (2.9) | 5 (5.8) | |

Grade I and Grade II. Two hundred fifty-two of 293 (86.0%) patients had disease at the L4–L5 level, 31 of 293 (10.6%) patients had disease at the L3–L4 level, and 10 of 293 (3.4%) patients had disease at the L5–S1 level.

All patients had failed at least 6 months of nonoperative treatment, including physical therapy, lumbar epidural injections, anti-inflammatory medications, and activity modifications for their spinal symptoms.

**Table 2. Demographic and Baseline Characteristics for 36+ Months Eligible Patients**

| | | OP-1 Putty | | Autograft | |
|---|---|---|---|---|---|
| Parameter | Statistic | 24 mo | 36+ mo | 24 mo | 36+ mo |
| Age (yrs) | N | 183 | 144 | 74 | 58 |
| Mean | | 67.6 | 66.8 | 69.3 | 68.7 |
| Median | | 69 | 67 | 71 | 70 |
| Std. Dev. | | 9.54 | 9.25 | 8.72 | 8.66 |
| Sex | | | | | |
| Male | N (%) | 64 (35.0) | 50 (34.7) | 19 (25.7) | 16 (27.6) |
| Female | N (%) | 119 (65.0) | 94 (65.3) | 55 (74.3) | 42 (72.4) |
| Level fused | | | | | |
| L3–L4 | n (%) | 19 (10.4) | 17 (11.8) | 10 (13.5) | 9 (15.5) |
| L4–L5 | n (%) | 156 (85.2) | 124 (86.1) | 62 (83.8) | 48 (82.8) |
| L5–S1 | n (%) | 8 (4.4) | 3 (2.1) | 2 (2.7) | 1 (1.7) |
| ODI | n | 183 | 144 | 74 | 58 |
| Mean | | 48.5 | 48.2 | 50.1 | 50.7 |
| Median | | 48.9 | 48.9 | 48 | 48 |
| Std. Dev. | | 11.11 | 10.74 | 13.48 | 12.47 |
| Angular motion (degrees) | n | 174 | 138 | 66 | 51 |
| Mean | | 4 | 4.1 | 4.7 | 4.3 |
| Median | | 2.8 | 2.9 | 4.1 | 3.6 |
| Std. Dev. | | 3.42 | 3.53 | 3.24 | 3.03 |
| Translational movement (mm) | n | 171 | 136 | 65 | 51 |
| Mean | | 1.7 | 1.8 | 1.6 | 1.5 |
| Median | | 1.4 | 1.5 | 1 | 0.8 |
| Std. Dev. | | 1.48 | 1.55 | 1.52 | 1.42 |
| Diagnosis of degenerative lumbar spondylolisthesis with spinal stenosis | n (%) | 183 (100) | 144 (100) | 74 (100) | 58 (100) |
| Grade 1 | n (%) | 169 (92.3) | 135 (93.8) | 68 (91.9) | 54 (93.1) |
| Grade 2 | n (%) | 8 (4.4) | 5 (3.5) | 2 (2.7) | 2 (3.4) |
| Unable to distinguish between Grade 1/2 | n (%) | 6 (3.3) | 4 (2.8) | 4 (5.4) | 2 (3.4) |
| Prior overall success at 24 mo | % | 42.9 | 43.8 | 57.6 | 60 |

**Table 3. Overall Success at 24 Months (MITT)**

| Parameter | OP-1 Putty | Autograft | *P* for Noninferiority |
|---|---|---|---|
| Overall success | 38.7% | 49.4% | 0.33 |

Of the 202 patients available at 36+ months, 169 of 183 (92.3%) had Grade I spondylolisthesis, 8 of 183 (4.4%) had Grade II spondylolisthesis, and 6 of 183 (3.3%) had spondylolisthesis that could not be distinguished between Grade I and Grade II. One hundred fifty-six of 183 (85.2%) patients had disease at the L4–L5 level, 19 of 183(10.4%) patients had disease at the L3–L4 level, and 8 of 183 (4.4%) patients had disease at the L5–S1 level.

### *36+ Month Follow-up Evaluation*

Of the 257 patients eligible for 36+ month follow-up, 80.5% (202/257) were available. These consisted of 144 of the original 208 OP-1 patients (69%) and 58 of the original 87 (67%) autograft patients. Of the 55 of 257 who did not have 36+ month follow-up, 5 patients had died, 23 refused to participate, 15 could not be located, 3 were unable to participate because of the unavailability of the participating site, and 9 could not participate for other reasons. Therefore, 80.5% (202/257) of the eligible patients (79.7% of the autograft group, and 80.8% of the OP-1 Putty Group) at 24 months were accounted for at the time of final follow-up (36+ months). The mean time to final follow-up was 4.4 years (range 3.68–5.46, SD 0.4) for all enrolled patients, 4.38 years (range 3.68–5.42, SD 0.4) for the OP-1 Putty group, and 4.47 years (range 3.76–5.46, SD 0.4) for the autograft group. There were no significant difference in times to follow-up ($P = 0.143$). Although a small percentage of the total eligible population was lost to follow-up at the 36+ month interval, the reasons for nonparticipation in 36+ month extension part of the study were equally distributed across the study groups.

### *Primary Outcome*

The Overall Success outcome composite end point at 24 months revealed that statistical equivalence was not achieved between the 2 groups at 24 months (38.7% for the OP-1 Putty group and 49.4% for the Autograft group, $P = 0.33$) (Table 3). Among the subcomponents of Overall Success, there was a statistically significant difference between the groups in terms of the presence of bridging bone as assessed by plain radiographs (61.7% for the OP-1 Putty group and 83.1% for the Autograft group, $P < 0.001$). There were no other statistically significant differences among the clinical or radiographic subcomponents of Overall Success (Table 4).

**Table 4. Subcomponents of Overall Success at 24 Months**

| Parameter | OP-1 Putty | Autograft | *P* for Difference |
|---|---|---|---|
| Components of overall radiographic success | | | |
| Presence of bridging bone by plain film | 61.7% | 83.1% | <0.001 |
| Angulation ≤5° on flexion/extension films | 73.3% | 75.6% | 0.684 |
| Translation ≤3 mm on flexion/extension films | 87.7% | 87.8% | 0.978 |
| ODI success | 74.5% | 75.7% | 0.839 |
| Absence of retreatment | 92.3% | 88.6% | 0.347 |
| Absence of serious treatment-related AEs | 85.6% | 84.7% | 0.863 |
| Neurological success | 92.1% | 84.1% | 0.057 |

**Table 5. Modified Overall Success at 36+ Months**

| Parameter | OP-1 Putty | Autograft | *P* for Noninferiority |
|---|---|---|---|
| Overall success | 47.2% | 46.8% | 0.025 |

The Modified Overall Success outcome end point at 36+ months revealed no difference and statistical comparability between the 2 study groups (47.2% for the OP-1 Putty group and 46.8% for the Autograft group, $P = 0.025$) (Table 5). Furthermore, there were no statistically significant differences among the subcomponents of Modified Overall Success at 36+ months (Table 6).

### *Imaging Findings*

At 24 months, 73.3% of OP-1 subjects and 75.6% of autograft subjects had ≤ 5° of angular motion ($P = 0.684$) and at 36+ months 69.3% of OP-1 subjects, and 68.4% of autograft subjects had ≤5° of angular motion ($P = 1.0$). At 24 months, 87.7% of OP-1 subjects and 87.8% of autograft subjects had ≤3 mm translation ($P = 0.978$). At 36+ months, 75.7% of OP-1 subjects and 75.4% of autograft subjects had ≤3 mm translation ($P = 1.0$). There were no statistical differences between the study groups in terms of angular or translational motion at either time point.

CT scans were obtained on 196 of 202 (97%) patients available at 36+ months: 143 from the OP-1 Putty group and 53 from the autograft group. One hundred seven of 143 (74.8%) of the OP-1 Putty patients and 41 of 53 (77.4%) of the autograft patients had presence of new bone on CT scan. The results were clinically comparable and not statistically significantly different ($P = 0.852$).

**Table 6. Subcomponents of Modified Overall Success at 36+ Months**

| Parameter | OP-1 Putty | Autograft | *P* |
|---|---|---|---|
| Presence of Bone on CT Scan (36+ months) | 74.8% | 77.4% | 0.852 |
| Angulation ≤5° on flexion/extension films (36+ months) | 69.3% | 68.4% | 1 |
| Translation ≤3 mm on flexion/extension films (36+ months) | 75.7% | 75.4% | 1 |
| ODI success (24 mo) | 74.5% | 75.7% | 0.839 |
| Absence of retreatment (36 mo) | 87.0% | 83.3% | 0.529 |
| Absence of serious treatment-related adverse events (24 mo) | 85.6% | 84.7% | 0.863 |
| Neurologic success (24 mo) | 92.1% | 84.1% | 0.057 |

**Table 7. Presence of Bone Assessed *via* CT Scan for Patients Without Bone Formation *via* Plain Films at 24 Months (mITT)**

| Presence of Bone Assessed *via* CT Scan | OP-1 Putty | Autograft |
|---|---|---|
| Present | 27/38 (71.0%) | 5/6 (83.3%) |
| Present medial | 22/27 (81.5%) | 3/5 (60.0%) |
| Present lateral/transverse | 5/27 (18.5%) | 2/5 (40.0%) |
| Absent | 11/38 (29.0%) | 1/6 (16.7%) |

Analysis of the OP-1 Putty patients who had previously been assigned as failures because of lack of bone formation (38 patients) based on the 24-month plain radiographs and had undergone CT scans at 36+ months demonstrated that 27 of 38 (71%) exhibited bone formation on CT scan. Furthermore, of these 27 patients who did form bone, 22 of 27 (81.5%) were found to have bone formation that was classified as medial, and 5 of 27 (18.5%) had bone formation that was classified as lateral (Table 7).

Although stability of the fusion was not different between the treatment groups, the presence of bridging bone across the intertransverse process region was dissimilar in the 36+ month CT data. Bridging bone was detected in 56% of patients in the OP-1 Putty group and 83% ($P = 0.001$) of patients in the autograft group. Detection of bridging bone was more difficult medially as shown by a higher disagreement rate between the readers' assessment of bridging bone with OP-1 Putty (29%) compared with autograft (8%) ($P = 0.0124$).

### *Device-Related Serious Adverse Events and Retreatment Failures*

Table 8 presents the success rate based on the absence of treatment-related SAEs categorized as related to the device. At 24 months, the OP-1 Putty group exhibited a higher proportion of patients free from treatment-related SAEs than did the autograft group (85.6% for OP-1 Putty and 84.7% for autograft, $P = 0.863$). At 36+ months the OP-1 Putty group again experienced a higher proportion of patients free from treatment-related SAEs (79.5% for OP-1 Putty and 73.5% for autograft, $P = 0.387$). These differences did not reach statistical significance.

### *Retreatment Failures*

The OP-1 Putty group demonstrated a higher proportion of patients who were free from retreatment failures at 24 months (179/194 patients, or 92.3% for OP-1 Putty and 62/70 patients, or 88.6% for autograft, $P = 0.347$) and at 36+ months (141/162 patients, or 87.0% for OP-1 Putty and 55/66 patients, or 83.3% for autograft, $P = 0.529$). These values were statistically not different.

**Table 8. Success Rates by Absence of Treatment-Related Serious Adverse Events (SAEs) at 24 and 36+ Months**

| | OP-1 Putty | | Autograft | | |
|---|---|---|---|---|---|
| Time Point | No. Patient | No. (%) Successes | No. Patient | No. (%) Successes | *P* |
| 24 mo | 194 | 166 (85.6) | 72 | 61 (84.7) | 0.863 |
| 36+ mo | 166 | 132 (79.5) | 68 | 50 (73.5) | 0.387 |

There were 32 total retreatments (*i.e.*, failures for the absence of retreatment criteria): 21 in the OP-1 Putty group (17 reported at 24 months and 4 reported at 24–36+ months) and 11 in the autograft group (10 reported at 24 months and 1 reported at 24–36+ months). Retreatments occurring over time for both treatment groups are illustrated in Table 9. In both treatment groups, the majority of retreatment events occurred in the interval between the immediate postoperative period and the 24-month interval, with the balance of events occurring by the 48-month interval, and no events occurring at or after the 60-month interval.

At the 24-month follow-up point, 21 of 257 (8.2%) of the OP-1 Putty patients and 11 of 87 (13%) of the autograft patients had undergone further surgery to promote fusion at the index level. At the time of latest follow-up (>36 months), an additional 3 of 144 (2.1%) OP-1 Putty patients and 3 of 58 (5.2%) autograft patients had undergone further surgery for retreatment failure. These rates were not statistically different ($P = 0.242$).

### *Secondary Outcomes*

**Oswestry Disability Index.** Tables 10 and 11 present the success rates for the study groups at 24 and 36+ months as measured by a 20% improvement in the ODI. At 24 months, 74.5% of OP-1 subjects and 75.7% of autograft subjects had a ≥20% improvement from baseline in ODI. At 36+ months, 68.6% of OP-1 subjects and 77.3% of autograft subjects had a ≥20% improvement from baseline in ODI. There were no statistical differences between the groups at either time point ($P = 0.839$ at 24 months, $P = 0.201$ at 36+ months). The mean percent improvements from baseline 24 months (54.0% for OP-1 Putty and 54.5% for autograft) and 36+ months (52.0% for OP-1 Putty and 54.4% for autograft) were similar and not statistically different between treatment groups.

Because the 20% ODI improvement from baseline is an arbitrary cut point for determining clinical improvement, additional analyses were conducted to compare the proportions of patients in each treatment group achieving more robust levels of improvement that should be more clinically meaningful to both physicians and patients. The number of patients in each treatment group achieving improvements over baseline of 100%, ≥80%, ≥50%, ≥30%, and ≥20% at both 24 months and 36+ months was evaluated (Figure 1). These results indicate that although the OP-1 Putty group had slightly lower proportions of patients who achieved ODI success in the ≥20% and ≥30% improvement in ODI categories (differences not statistically significant), the OP-1 Putty group had higher proportions of patients achieving

**Table 9. Retreatment Failures by Time Interval (Safety Population)**

| Treatment Group | Operative (<28 d) | 24 mo (28–1035 d) | 36 mo (1036–1401 d) | 48 mo (1402–1766 d) | 60 mo (1767–2131 d) | >60 mo (>2131 d) | Totals |
|---|---|---|---|---|---|---|---|
| OP-1 Putty | 0 | 17 | 3 | 1 | 0 | 0 | 21 |
| Autograft | 0 | 10 | 0 | 1 | 0 | 0 | 11 |

≥50%, ≥80%, and 100% improvements at both the 24 month and 36+ month intervals (differences not statistically significant).

### *Neurologic Success*

The patient was considered an overall neurologic success in the absence of a decrease in neurologic status unless attributable to a concurrent medical condition or to the surgical procedure. Patients in the OP-1 Putty group had a higher neurologic success rate at 24 months (92.1% for OP-1 Putty and 84.1% for autograft, $P = 0.057$), although this difference was not statistically significant. Neurologic success was similar for both groups at 36+ months, and the difference between treatment groups was not statistically significant (84.4% for OP-1 Putty and 80.0% for autograft, $P = 0.54$).

### *Visual Analog Scale and Short-Form 36*

Patients in both the OP-1 Putty and Autograft Groups had significant decreases in pain over time noted on VAS at 24 months and at 36 months. There were no significant differences between the 2 groups in terms of VAS scores. By 6 weeks, patients in both groups demonstrated statistically significant improvements over baselines in SF-36 scores. There were no significant differences between group SF-36 scores at any point in the study (Figure 2).

### *Donor Site Pain After Autograft Harvest*

VASs assessments of donor site pain in the autograft population demonstrated that at 12 months, 32 of 72 (44%) of autograft patients reported pain at the donor site, at 24 months 25 of 55 (45%) patients reported pain, and at 36 months 18 of 52 (35%) reported persistent mild/moderate pain. Donor site pain was persistent and decreased slowly over time, reported as a 2.1 on the VAS (scale of 1–10, 10 being most severe) at 6 weeks, 1.6 at 12 months, 1.2 at 24 months, and 1.1 at 36 months.

### *Surgery and Hospitalization Data*

Mean operative time for the OP-1 Putty group was significantly shorter than the autograft group (144 minutes for the OP-1 Putty group and 164 minutes for the autograft group, $P = 0.006$). Mean operative blood loss was also significantly lower for the OP-1 Putty group than the autograft group (309 cc *vs.* 471 cc, $P = 0.00004$). There were no differences in the mean length of stay after surgery ($P = 0.529$).

### *Immunologic Results*

Serum samples for OP-1 antibody testing for the study were performed immediately after surgery, and at 6 weeks, 3, 6, 12, and 24 months from 293 patients. One patient in the OP-1 group had died just after surgery and 1 patient in the autograft group had no postbaseline visit. In the 36+ month group, serum samples were analyzed at the time of latest follow-up for patients who had been positive for anti-OP-1 antibodies at the 24-month follow-up visit and for patients who had not completed the 24-month follow-up visit but had been antibody positive at their last recorded visit. There were 54 patients who underwent this testing (49 patients from the OP-1 Putty group, 5 from the autograft group) at 36+ months.

93.7% of patients receiving OP-1 Putty were antibody-positive at any time point *versus* 20.9% of the patients receiving autograft. In the OP-1 Putty group, 25.6% of patients became positive for anti-OP-1 neutralizing antibodies *versus* 1.2% of the autograft patients. The peak presence of neutralizing antibodies was observed between 6 weeks and 3 months. However, at both 24 and 36+ months no patients had neutralizing antibodies present.

### *Neutralizing Activity Status and Clinical Outcomes*

No significant associations were observed between neutralizing activity status, clinical success, and safety parameters. Overall success of patients with neutralizing activity (36.4%) was not statistically different from the overall success of patients without detectable neutralizing activity (38.2%). When the overall success end point was broken down into the individual components of radiographic success, ODI success and absence of retreatment, no associations between clinical success and neutralizing activity were seen. Furthermore, there was no evidence of an increase in AEs, SAES, or immunologically-related AEs or SAEs at any time point in the neutralizing positive patients *versus* the neutralizing negative patients in the study.

**Table 10. ODI Scores at 24 Months**

| | OP-1 Putty | | Autograft | | | |
|---|---|---|---|---|---|---|
| Time Point | No. Patients | No. (%) Successes | No. Patients | No. (%) Successes | 95% Upper Confidence Bound (%) | *P* |
| 24 mo | 192 | 143 (74.5) | 70 | 53 (75.7) | 11.2 | 0.839 |

**Table 11. ODI Scores at 36+ Months (mITT Population)**

| | OP-1 Putty | | Autograft | | |
|---|---|---|---|---|---|
| Time Point/Population | No. Patients | No. (%) Successes | No. Patients | No. (%) Successes | *P* |
| 36+ mo | 159 | 109 (68.6) | 66 | 51 (77.3) | 0.201 |

## ■ Discussion

This study was a randomized controlled trial comparing 2 similar groups of patients with degenerative spondylolisthesis and spinal stenosis. The study population was reflective of the general population with degenerative spondylolisthesis, given the relatively higher number of women (approximately 2/3) and the mean age of 68 (range 36–84). The preoperative status of the patients in the respective study groups was similar, with no differences between groups in terms of demographic characteristics, disease status, the involved segment, motion or instability at the involved level, clinical status based on the ODI, previous treatments, or worker's compensation status.

This pivotal study was originally designed to report on patient outcomes as part of the 24-month randomized, prospective, multicenter trial conducted under an Investigational Device Exemption Study as permitted by the US FDA. In the original 24-month investigational study, patients in the OP-1 Putty group achieved clinical and functional radiographic improvements comparable to the autograft group measured along a composite measure of clinical success. Although there were no statistical differences between the OP-1 Putty group and the autograft group in terms of overall success by these composite end points, there was a statistical difference between the groups in terms of the presence of bridging bone on plain radiography. As assessed by plain films, the OP-1 Putty group demonstrated a significantly lower percentage of patients with presence of bridging trabecular bone. There were no differences seen in angulation or translation on flexion-extension films suggestive of a true difference in the fusion mass. A long-term follow-up was performed to see if clinical and radiographic results were maintained over time and to see if patients who seemed to demonstrate radiographic success at 2 years maintained success as reported in other clinical IDE fusion studies.[31] One interesting finding in this study was the presence of bone formation in the OP-1 Putty fusion group medially along the transverse processes and along the lateral border of the facet joints on the 9-month and 36+ month CT scans. These results suggest that plain films may be less than reliable in assessing fusion or bone formation with the present physical formulation of OP-1 Putty, as they are less sensitive when compared with CT in assessing bone formation along the lateral border of the facet joints.

The finding of bone formation medial to the transverse processes was unexpected, because it had been assumed that OP-1 Putty-directed new bone formation would occur as it does for autograft, laterally along the transverse processes. A probable explanation lies in the differences in the physical properties of the graft materials studied: OP-1 Putty is a compressible, moldable material (putty that does not harden), whereas autograft is not malleable (has a noncompressible physical structure). During the spinal fusion procedure used in the clinical study, the surgeon retracts the paraspinal muscles to lay down the OP-1 Putty or autograft material (Figures 3A, B). When the retractors are removed and the muscles are released, the OP-1 Putty product may be compressed medially (Figure 3C), leading to medialized bone formation not easily detected by plain radiographs. On plain radiographs, the medial location of the OP-1 putty may be obscured by the lateral border of the ver-

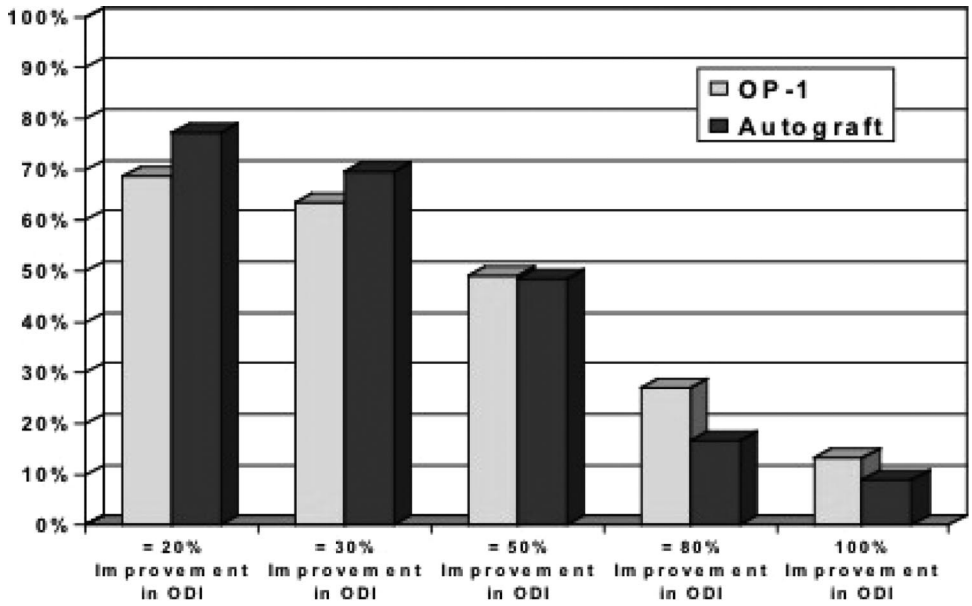


Figure 1. Proportions of patients with percentage improvements in ODI at 36+ months.

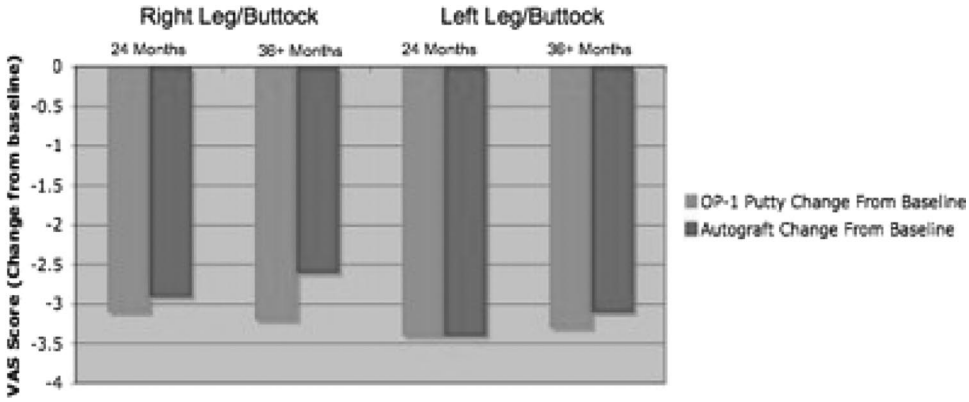


Figure 2. VAS scores at 24 and 36+ months.

tebral body, hypertrophied facet joints, and overlying bowel gas (Figure 4A), but may be better illustrated with the usage of CT scanning (Figure 4B). A similar phenomenon was reported by Boden and coworkers during a study of posterolateral intertransverse process fusion using a compressible collagen carrier and rhBMP-2 in a primate model.[32]

Therefore, to adequately investigate whether patients in the OP-1 Putty group experienced fusion rates comparable to autograft, a radiographic assessment tool more sensitive than the plain films used at 24 months was needed. As a result, prospective collection of additional radiographic and clinical data was conducted on all available study patients at the longer term follow-up interval of 36+ months. Patients received CT scans to assess for the presence of bone and repeat flexion/extension films to allow measurement of angulation and translation at the same time point. All key clinical outcome measures collected in the original study were also collected at the 36+ month interval.

Eighty-seven percent of the originally randomized 295 patients were eligible for review at 24 months. Of the 257 patients eligible for 36+ month follow-up, 202 of 257 (80%) were available. Patients who returned for follow-up at 36+ months did not differ significantly from the original population with regard to demographics, baseline disease characteristics, or key outcome variables at 24 months. The mean time to final follow-up for all enrolled patients was 4.4 years and there was no significant difference in times to follow-up between treatment groups.

At 36+ months, OP-1 Putty demonstrated statistical comparability to autograft with regard to the primary endpoint (Modified Overall Success), and each of the individual subcomponents. Although the 24-month radiographic data did not show comparability of OP-1 Putty and autograph in terms of rates of new bone formation by plain radiograph despite comparable results for angulation and translation, the 36+ month imaging data found no difference between groups in terms of the presence of bone on CT (74.8% for OP-1 Putty and 77.4% for autograft, $P = 0.85$). There are several possible reasons for these differences in findings. First, the original readers may have underestimated the presence of bone as they were not aware of the medial repositioning of OP-1 Putty. Second, CT scanning represents a more sensitive imaging modality for bone formation given the increase in spatial resolution. Finally, the CT scan data demonstrate that the OP-1 Putty group formed bone in a more medial location with greater frequency (Figures 5A, B).

Because of the medial fusion mass when OP-1 Putty is used, CT assessment of fusion may not accurately reflect the degree of bridging bone. Although some patients in the OP-1 Putty arm did show bridging bone between the transverse processes, the majority of the bone formation was more medial. CT imaging of the spine has improved greatly over the last decade with advancements in image acquisition. However, the radiologist must review an increased number of slices and images and visualize a complex 3-D model. Bone seen in the area of the transverse process most likely represents graft because degenerative

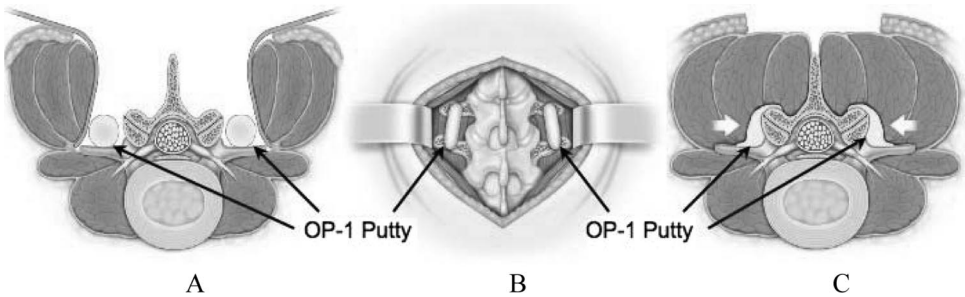


Figure 3. Implantation of OP-1 Putty and the paraspinal musculature. **A,** Axial illustration demonstrating retraction of paraspinal muscles and placement of OP-1 Putty across the decorticated transverse processes. **B,** Coronal view demonstrating OP-1 Putty placement across the intranverse region. **C,** After paraspinal muscle release, OP-1 Putty is compressed medial to the transverse processes.

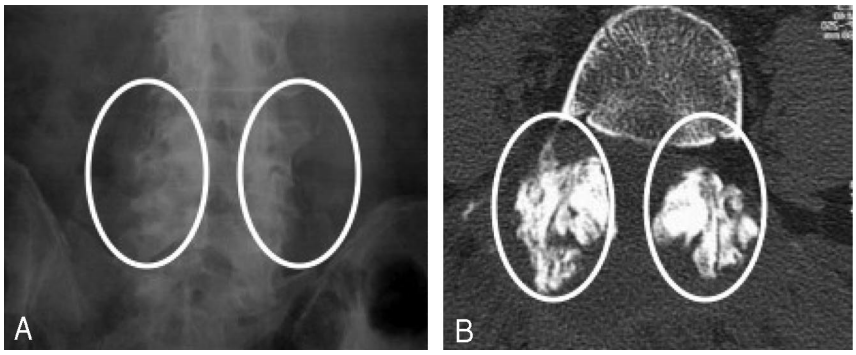


Figure 4. AP radiograph (**A**) taken at 24 months compared to axial CT (**B**) scan in a patient after receiving OP-1 Putty. While the radiograph (**A**) fails to illustrate bridging bone between the transverse processes, axial CT scan (**B**) demonstrates profuse bone formation more medially. The obtained plain radiograph was interpreted by blinded observers as having no bone formation at 24 months.

changes in the spine are not seen in that area. If the same amount of bone is seen more medially near the facet, it could easily be misinterpreted as an osteophyte rather than bone being generated from biologic material placed medially. Because bone that has formed medial to the transverse processes is more difficult to assess for bridging, one could easily underestimate the degree of fusion with OP-1 compared to autograft across transverse processes. A future prospect may lie in the use of multiplanar reformatted images and the ability to generate 3-D models (Figures 6A and 6), which may serve to provide more usable information on bony fusion.

With regard to fusion outcomes, it is interesting to compare bone formation rates in the 50% to 70% range relative to previously published studies on bone morphogenetic factors with claimed fusion success rates of 95% to 100%. This comparison highlights the strength of a prospective randomized study evaluating fusion success in an unstable (spondylolisthesis) degenerative model in the absence of instrumentation or an opaque carrier, which may be confused with new bone formation. In the seminal paper by Fischgrund *et al* on fusion success in the presence or absence of instrumentation, the authors noted a fusion success of only 45% in the absence of instrumentation.[1] Clearly, without confounding variables such as instrumentation or carriers that contain calcium or hydroxyapatite, fusion rates in degenerative disorders are expected to be in the 40% to 70% success rate range, depending on patient characteristics. This further supports the premise that OP-1 Putty in the stated dosage and with its compressible carrier is an adequate replacement for autologous iliac crest bone graft in fusion for degenerative spondylolisthesis. With use of instrumentation, the current gold standard for treatment, higher rates of fusion and overall success would be anticipated. All patients in this study were considered to be "unstable" before fusion because of the destabilization occurring secondary to the laminectomy and partial facetectomy. When evaluating the final radiographs, the absence of motion on flexion and extension views may be because of bone formation from either OP-1 Putty, autograft, or a stable fibrous nonunion. It is assumed that successful fusion occurs when there is sufficient bone formation to confer stability to the spine (by meeting the stringent translation and angulation criteria for successful fusion). This argument would be invalid if instrumentation had been placedbecause of the presence of hardware restricting motion.

Patients receiving OP-1 Putty as part of the arthrodesis surgery had significantly lower blood loss at the time of surgery and lower operative times. Although these numbers did not result in a lower rate of treatment-related serious adverse events, the decreased operative time, decreased exposure to anesthesia, and expected lower transfusion requirements are potential benefit to this elderly surgical population in terms of an expected quicker recovery and lower rate of transfusion-related complications, in addition to providing a possible eco-

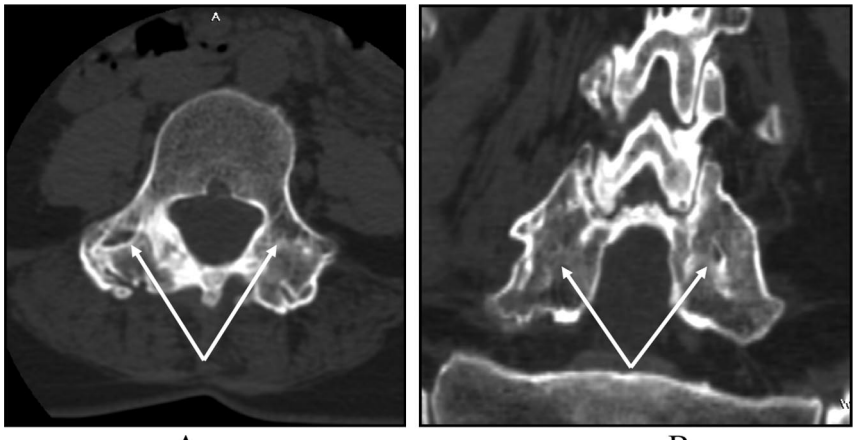


Figure 5. Axial CT (**A**) and coronal multiplanar reformatted image (**B**). Axial CT and multiplanar reformatted coronal images demonstrate a solid fusion mass in a patient receiving OP-1 Putty. Note the medial positioning of the fusion mass (white arrows).

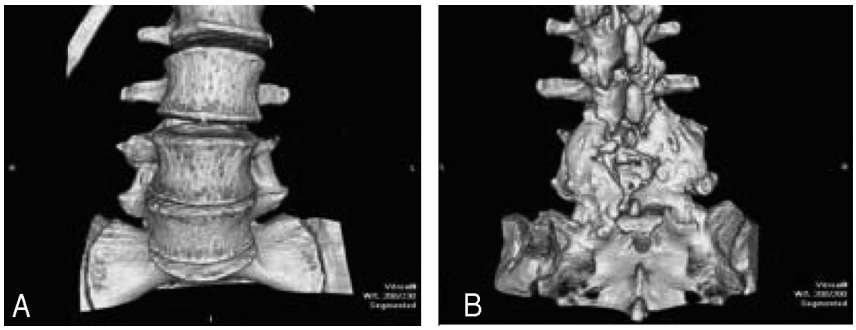


Figure 6. Three-dimensional CT reconstructions in the depiction of bony fusion following posterolateral arthrodesis with OP-1 Putty. AP (**A**) and posteroanterior (**B**) 3D CT scans illustrate the nature of bony fusion following an L45 posterolateral fusion with the use of OP-1 Putty.

nomic benefit to the hospital and/or provider system. Finally, the autograft patients were found to experience mild/moderate donor site pain in 35% of cases at 36+ months, demonstrating that the pain associated with autograft harvest can be both significant and of lasting duration.

There were no significant differences in the occurrence rates of serious adverse events related to device between the study groups at either 24 or 36+ months in the study. There were also no complications or adverse events directly attributable to the OP-1 Putty. Testing for anti-OP-1 antibodies and anti-OP-1 neutralizing antibodies demonstrated transient occurrences between the 6-week and 3-month periods. However, by 24 and 36+ months, no patients had neutralizing antibodies present. It seems based on the data that the formation of anti-OP-1 antibodies does not have any clinically significant effects on either safety or efficacy. Most importantly, the presence of neutralizing antibodies was not correlated with any safety concerns or clinical outcomes.

In terms of the key variable, revision surgery to promote fusion, the overall rates were low in both treatment groups considering the challenging surgical model and the OP-1 group and autograft group showed no significant differences over the course of the study period. At the 36-month follow-up point, 21 of 257 (8.2%) of the OP-1 Putty patients and 11 of 87 (13%) of the autograft patients had undergone further surgery to promote fusion at the index level. At the time of latest follow-up at a mean of over 4 years after the original surgery, only an additional 3 of 144 (2.2%) OP-1 Putty patients and 3 of 58 (5.2%) autograft patients had undergone further surgery for retreatment failure.

## ■ Conclusion

OP-1 Putty has been designed as an alternative to autograft harvest in posterolateral spinal fusion. In multiple preclinical and early clinical models, OP-1 has produced fusion success results equivalent or superior to that of autograft. Based on this large prospective randomized controlled trial of uninstrumented posterolateral arthrodesis performed for degenerative spondylolisthesis and spinal stenosis, OP-1 Putty is a safe and effective alternative to autograft that results in equivalent overall success outcomes, shorter operative times, and lower intraoperative blood loss, while avoiding the morbidity associated with autograft harvest.

### ■ Key Points

- OP-1 Putty is a safe and effective alternative to autograft in uninstrumented posterolateral fusion performed for degenerative spondylolisthesis and spinal stenosis.
- At 36+ months, OP-1 Putty resulted in equivalent outcomes in terms of overall success and all clinical and radiographic endpoints.
- The OP-1 Putty group had significantly lower blood loss during surgery and significantly shorter operative times.
- Although antibodies to OP-1 did develop, they resolved in all patients without clinical sequelae.

## References

1. Fischgrund JS, Mackay M, Herkowitz HN, et al. 1997 Volvo Award winner in clinical studies. Degenerative lumbar spondylolisthesis with spinal stenosis: a prospective, randomized study comparing decompressive laminectomy and arthrodesis with and without spinal instrumentation. *Spine* 1997;22:2807–12.
2. Herkowitz HN, Kurz LT. Degenerative lumbar spondylolisthesis with spinal stenosis. A prospective study comparing decompression with decompression and intertransverse process arthrodesis. *J Bone Joint Surg Am* 1991;73:802–08.
3. Beirne JC, Barry HJ, Brady FA, et al. Donor site morbidity of the anterior iliac crest following cancellous bone harvest. *Int J Oral Maxillofac Surg* 1996;25:268–71.
4. Cotler JM, Star AM. "Complications of spinal fusion." In: Cotler JM, Cotler HB, eds. *Spine Fusions: Science and Technique*. New York, NY: Springer-Verlag; 1990.
5. Younger EM, Chapman MW. Morbidity at bone graft donor sites. *J Orthop Trauma* 1989;3:192–5.
6. Arrington ED, Smith WJ, Chambers HG, et al. Complications of iliac crest bone graft harvesting. *Clin Orthop Relat Res* 1996;329:300–09.
7. Boden SD. Biology of lumbar spine fusion and use of bone graft substitutes: present, future, and next generation. *Tissue Eng* 2000;6:383–99.
8. Hadjipavlou AG, Simmons JW, Tzermiadianos MN, et al. Plaster of Paris as bone substitute in spinal surgery. *Eur Spine J* 2001;10(suppl 2):189–96.
9. Urist MR. Bone: formation by autoinduction. *Science* 1965;150:893–9.
10. Uludag H, Gao T, Porter TJ, et al. Delivery systems for BMPs: factors contributing to protein retention at an application site. *J Bone Joint Surg Am* 2001;83-A(1 pt 2):128–135.
11. Cook SD, Dalton JE, Tan EH, et al. In-vivo evaluation of recombinant human osteogenic protein (rhOP-1) implants as a bone graft substitute for spinal fusions. *Spine* 1994;19:1655–63.
12. Grauer JN, Patel TC, Erulkar JS, et al. 2000 Young Investigator Research Award winner: evaluation of OP-1 as a graft substitute for intertransverse process lumbar fusion. *Spine* 2001;26:127–33.

13. Johnsson R, Stromqvist B, Aspenberg P. Randomized radiostereometric study comparing osteogenic protein-1 (BMP-7) and autograft bone in human noninstrumented posterolateral lumbar fusion: 2002 Volvo Award in clinical studies. *Spine* 2002;27:2654–61.
14. Liao SS, Guan K, Cui FZ, et al. Lumbar spinal fusion with a mineralized collagen matrix and rhBMP-2 in a rabbit model. *Spine* 2003;28:1954–60.
15. Sidhu KS, Prochnow TD, Schmitt P, et al. Anterior cervical interbody fusion with rhBMP-2 and tantalum in a goat model. *Spine J* 2001;1:331–40.
16. Takahashi J, Saito N, Ebara S, et al. Anterior thoracic spinal fusion in dogs by injection of recombinant human bone morphogenetic protein-2 and a synthetic polymer. *J Spinal Disord Tech* 2003;16:137–43.
17. Cook SD, Baffes GC, Wolfe MW, et al. The effect of recombinant human osteogenic protein-1 on healing of large segmental bone defects. *J Bone Joint Surg Am* 1994;76A:827–38.
18. Cook SD, Baffes GC, Wolfe MW, et al., Recombinant human bone morphogenic protein-7 induces healing in canine long bone segmental defect model. *Clin Orthop* 1994;301:302–12.
19. Cook SD, Wolfe MW, Salkeld SL, et al. Effect of recombinant human osteogenic protein-1 on healing of segmental defects in non-human primates. *J Bone Joint Surg Am* 1995;77:734–50.
20. Cook SD, Rueger DC. Osteogenic protein-1. *Clin Orthop* 1996;324:29–38.
21. Cunningham BW, Kanayama M, Parker LM, et al. Osteogenic protein versus autologous interbody arthrodesis in the sheep thoracic spine. A comparative endoscopic study using the Bagby and Kuslich interbody fusion device. *Spine* 1999;24:509–18.
22. Paramore CG, Lauryssen C, Rauzzino MJ, et al. The safety of OP-1 for lumbar fusion with decompression: a canine study. *Neurosurgery* 1999;44:1151–5.
23. Magin MN, Delling G. Improved lumbar vertebral interbody fusion using rhOP-1: a comparison of autogenous bone graft, bovine hydroxylapatite (Bio-Oss), and BMP-7 (rhOP-1) in sheep. *Spine* 2001;26:469–78.
24. Furlan JC, Perrin RG, Govender PV, Petrenko Y, et al. Use of osteogenic protein-1 in patients at high risk for spinal pseudarthrosis: a prospective cohort study assessing safety, health-related quality of life, and radiographic fusion. Invited submission from the joint section on disorders of the spine and peripheral nerves, March 2007. *J Neurosurg Spine* 2007;7:486–95.
25. Govender PV, Rampersaud YR, Rickards L, et al. Use of osteogenic protein-1 in spinal fusion: literature review and preliminary results in a prospective series of high-risk cases. *Neurosurg Focus* 2002;13:e4.
26. Vaccaro AR, Patel T, Fischgrund J, et al. 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. *Spine* 2004;29:1885–92.
27. Vaccaro AR, Anderson DG, 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. *Spine* 2005;30:2709–16.
28. Vaccaro AR, Whang PG, Patel T, et al. The safety and efficacy of OP-1 (rhBMP-7) as a replacement for iliac crest autograft for posterolateral lumbar arthrodesis: minimum 4-year follow-up of a pilot study. *Spine J* 2008;8:457–65.
29. Mire-Sluis AR, Barrett YC, Devanarayan V, et al., Recommendations for the design and optimization of immunoassays used in the detection of host antibodies against biotechnology product. *J Immunol Methods* 2004;289:1–16.
30. Meyerding HW. Spondylolisthesis. *Surg Gynecol Obstet* 1932;54:371–7.
31. Mooney V. A randomized double-blind prospective study of the efficacy of pulsed electromagnetic fields for lumber interbody fusion. *Spine* 1990;15:708–12.
32. Martin GJ, Boden SD, Morone MA, et al. Posterolateral intertransverse process spinal arthrodesis with rhBMP-2 in a nonhuman primate: important lessons learned regarding dose, carrier, and safety. *J Spinal Disord* 1999;12:179–86.