

5.3.9.2 Insensitivity of Plain Films for Evaluating Presence of Bone in OP-1 Patients

(Content from P060021 Minor Amendment Executive Summary February 2009, Pages 2-6)

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In the original study, OP-1 Putty failed to demonstrate non-inferiority to autograft according to the composite overall success endpoint. Failure to demonstrate non-inferiority of OP-1 compared with autograft was primarily attributable to one component of one parameter, the presence of bone as assessed by plain films. The OP-1 Putty group achieved clinically comparable improvements in all other key clinical outcomes at 24 months post surgery including Oswestry Disability Index (ODI), absence of retreatment, absence of treatment-related serious adverse effects and absence of decrease in neurological status. Comparable success in the other radiographic parameters measuring stability of the fused level (angulation and translation) at 24 months was also observed. In addition, OP-1 subjects had statistically shorter operative times and less blood loss during surgery on average than autograft subjects.

The results of the original pivotal trial at 24 months post-surgery for overall success and the subcomponents of overall success are summarized below:

Overall Success and Overall Radiographic Success at 24 Months Follow-Up: SAP Analysis, mITT Population

Outcome	OP-1 Putty	Autograft	P Value Non-inferiority
Overall Success ¹	38.7%	49.4%	0.331 ²

¹ Calculated with imputation of missing data.

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

Overall Radiographic Success at 24 Months Follow-Up: mITT Population

Outcome	OP-1 Putty	Autograft	P Value Non-inferiority
Radiographic Success ¹	53.0%	68.9%	0.622 ²

¹ Calculated with imputation of missing data.

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

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Subcomponents of Radiographic Success at 24 Months mITT Population

Outcome	OP-1 Putty	Autograft	P Value for difference
Components of Overall Radiographic Success			
- presence of bone by plain ² film	51.9	73.5	0.003
- angulation \leq 5 degrees on ² flexion/extension films	73.3%	75.6%	0.684
- translation \leq 3mm on ² 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

¹ P value is based on chi-square or Fisher's exact test, as appropriate, to test the difference between treatment groups.

² Calculated with missing data imputed by Last Observation Carried Forward

These data revealed a striking disparity between the positive clinical and functional radiographic outcomes (angulation and translation) and the presence of new bone formation reported by plain film x-ray for patients treated with OP-1. Given that clinical experience and the literature demonstrate a high correlation between fusion and positive clinical outcomes in patients undergoing decompression with laminectomy, these results were unexpected.^{13,14} Since the OP-1 Putty patients had comparable clinical outcomes to the autograft patients and comparable segmental stability, they should also have shown comparable results for the radiographic assessment of the presence of bone. That is, the OP-1 patients would not be expected to demonstrate improved and durable clinical outcomes at 24 months and beyond if fusion had not occurred. In addition, it would stand to reason that in the absence of a bony fusion, the Op-1 patients would have been expected to demonstrate increased angular and translational instability.

Since the patients in the OP-1 Putty group achieved clinical improvements and radiographic stability comparable to the autograft group, it was reasonable to question whether the radiographic assessments performed at 24 months accurately assessed the presence of bone. In order to better understand these anomalous results, Stryker Biotech brought together two nationally recognized spine surgeons and one academic musculoskeletal radiologist who were blinded to the study data, to examine the 24-month plain films as well as the 9 month CT scans in a subset of study patients. CT scans and plain films were selected from both the autograft and OP-1 group (although selection was heavily weighted towards patients who were failures for presence of bone by plain film) for this exploratory assessment. The independent expert assessment revealed that in many cases, bone was not seen on the 24-month plain films, but *was* seen on the 9-month CT scan medial to the transverse processes and along the lateral border of

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the facet joints. These findings suggested that the plain film technique used to assess fusion at 24 months was flawed for assessing the medial bone formation associated with OP-1 Putty. Figure 1 and 2 below represents an example where the plain x-ray at 24 months revealed no evidence of new bone formation, but the 9 month CT scan revealed significant new bone formation medially.

24 Month AP X-ray



Figure 1

9 Month Axial CT



Figure 2

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. Stryker Biotech in discussion with surgical experts believes that the difference in the observed pattern of bone formation may relate to the physical properties of the graft materials studied; OP-1 Putty is a compressible, moldable material that does not harden, whereas autograft is not malleable and has a non-compressible 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. (See Figure 3) When the retractors are removed and the muscles are released, the OP-1 Putty product is compressed medially (See Figure 4), leading to medial bone formation. This is not easily detected by plain x-ray because the lumbar vertebrae are retroperitoneal structures for which overlying abdominal organs, bowel, bowel contents, and bowel gas can easily obscure new bone formation. In addition, the medial location of the OP-1 putty – directed bone formation may be obscured by the lateral border of the vertebral body and hypertrophied facet joints.

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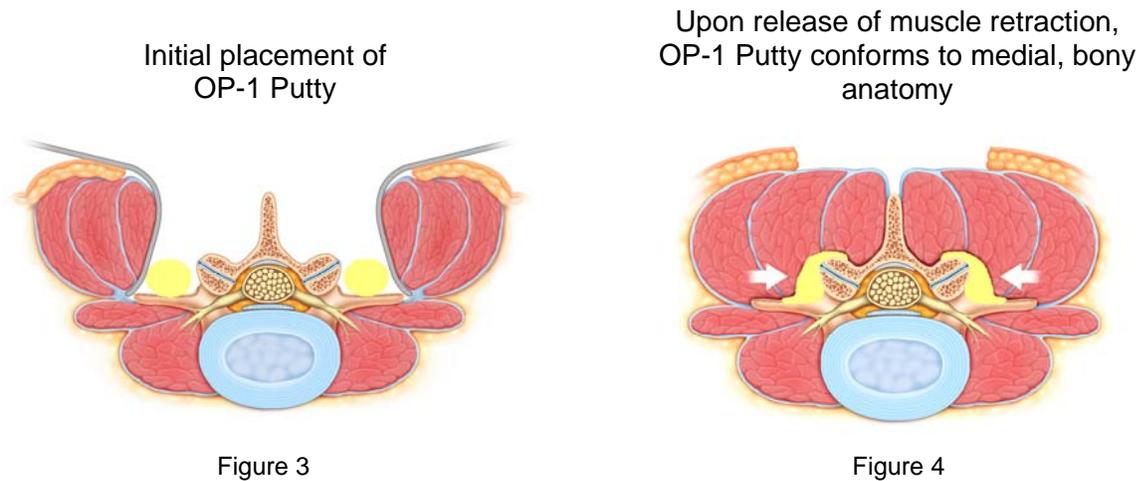


Figure 3 (left): Axial view of the lumbar spine with paraspinal muscle retraction and placement of OP- Putty across the transverse processes

Figure 4 (right): Axial view of the lumbar spine with release of traction and medial displacement of OP-1 Putty

Therefore, to resolve the apparent disparity in outcomes and adequately investigate whether patients in the OP-1 Putty group experienced fusion rates comparable to the autograft group, a radiographic assessment tool more sensitive than the plain films used at 24 months was needed. Stryker Biotech designed and conducted a prospective follow-up study to collect additional radiographic and clinical data on all available study patients at the longer-term follow-up interval of 36+ months. Considerable effort was expended to locate and evaluate as many patients as possible in both the autograft and OP-1 Putty groups. Patients received CT scans to assess for the presence of bone, and repeat flexion/extension films to provide measurements 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. Great care was taken to standardize the prospective CT scan including the imaging algorithm and the imaging protocol that was prospectively developed. Each CT scan was read by two blinded orthopedic spine surgeons according to a standardized protocol that was prospectively defined. In case of discrepant readings, the scan was read by a third blinded orthopedic spine surgeon and the opinion of the majority determined the outcome.

References

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