

5.4 Conclusions Drawn from the Study

(Content from P060021 Minor Amendment Executive Summary February 2009, Pages 7-9)

5.4 Conclusions Drawn from the Study**Efficacy Summary**

The results for modified overall success and the subcomponents of the modified overall success are summarized below:

Modified Overall Success (with Radiographic and Retreatment subcomponents at 36+ months and clinical outcome assessments at 24 months) :mITT Population

| Outcome | OP-1 Putty | Autograft | P Value Non-inferiority |
|---------------------------------------|------------|-----------|-------------------------|
| Modified overall success ¹ | 47.2% | 46.8% | 0.025 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.

Subcomponents of Modified Overall Success

| Outcome | OP-1 Putty | Autograft | P Value Superiority |
|--|------------|-----------|---------------------|
| Components of Overall Radiographic Success at 36+ Months | | | |
| ▪ Presence of Bone by 36+ month CT Scan | 74.8% | 77.4% | 0.852 |
| ▪ Angular motion $\leq 5^\circ$ at 36+ Months | 69.3% | 68.4% | 1.000 |
| ▪ Translational movement ≤ 3 mm at 36+ Months | 75.7% | 75.4% | 1.000 |
| ODI Success (24 Months) | 74.5% | 75.7% | 0.839 |
| Absence of Retreatment (36+ Months) | 87.7% | 83.3% | 0.529 |
| Absence of Serious Treatment-related AEs (24 Months) | 85.6% | 84.7% | 0.863 |
| Neurological Success (24 Months) | 92.1% | 84.1% | 0.057 |

P Value is based on Fisher's exact test

Missing or non-evaluable data are excluded

OP-1 Putty was demonstrated to be statistically non-inferior to autograft with regard to the modified Overall Success (47.2% for OP-1 Putty and 46.8% for autograft, P=0.025), demonstrating that OP-1 Putty is comparable to autograft in the important parameters of radiographic success, clinical success and safety.

The CT scan analysis conducted under the follow-up study, in addition to the accompanying assessments of angulation and translation by flexion/extension films, demonstrated that radiographic success did occur at comparable rates between the OP-1 Putty and autograft groups

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at 36+ months. In support of our original hypothesis, that led us to collect these additional data, of the OP-1 Putty subjects who were judged negative for the presence of bone based on plain films at 24 months, 71% (27/38) were judged positive for presence of bone based on CT scans at 36+ months and of those 81% (22/27) demonstrated medial bone formation.

In summary, the modified Overall Success composite is an appropriate measure to assess the safety and effectiveness of OP-1 Putty for the proposed indication. The composite includes assessments of key parameters that are important to patients undergoing fusion surgery, including radiographic success, clinical success, neurological success and freedom from reoperation and device related serious adverse events. The modified composite includes data collected at both 24 months and 36+ months. This provides important additional long-term follow-up information in the analysis without introducing bias. Patients who have undergone decompression with arthrodesis for degenerative spondylolisthesis may exhibit similar clinical improvements at early time points regardless of whether they have achieved definitive fusion or pseudarthrosis; however, significant differences in clinical outcomes have become apparent between these two groups with longer-term follow-up starting at 3 year. It is felt that 36+ month data represents a significant positive addition to the submission by providing longer-term safety and efficacy data than is typically available for spinal devices under consideration for approval. Evaluation of the radiographic and clinical data through the 24-month interval collected in the pivotal study along with the radiographic and clinical data collected through the 36+ month interval in the extension study provides a reliable comparison of the critical factors relevant to an assessment of both the early and longer-term safety and effectiveness of OP-1 Putty as compared to autograft, and demonstrates that OP-1 Putty has equivalent clinical and radiographic outcomes to autograft without the additional comorbidities associated with autograft harvest.

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Safety Conclusions

Data from the OP-1 Putty clinical studies, as presented within this PMA, demonstrate the following:

- The safety profile of OP-1 Putty is clinically comparable to that of autograft treatment with respect to all of the following parameters:
 - o The proportion of patients experiencing treatment-emergent AEs, severe AEs, treatment-related AEs, SAEs, treatment-related SAEs, neoplasms, or death
 - o The occurrence of clinically important laboratory abnormalities
 - o The occurrence of local AEs involving the lumbar spine
 - o The occurrence of immunologically-related adverse or other clinical events, despite the occurrence of neutralizing anti-OP-1 antibodies in 25.6% of treated patients. Neutralizing antibodies were present in 2 patients (1.1%) by 12 months and no patients at 24 months or at 36+ months.
- There was a higher reported rate of AEs in the cardiac SOC in the OP-1 Putty treated group during pivotal study S01-01US (using a very conservative test for significance of $p \leq 0.2$); however, a substantial majority (25/27) of OP-1 Subjects with cardiac adverse events had clinically significant cardiac risk factors or underlying cardiac disease at baseline. (See narratives for all cardiac-related events reported in S01-01-US in Appendix A-2.) No difference between treatment groups with regard to the proportion of patients with new serious adverse events or new medical conditions or physical findings in this SOC was seen at the 36+ month interval in extension study 06-UPLF-01. Although there is no preclinical basis for an increase in cardiac-related events being causally related to OP-1 Putty in this patient population; one can not rule out the possibility that OP-1 Putty may have exacerbated underlying cardiac conditions. Therefore, to minimize this potential risk, the following precaution is proposed for the package labeling: *OP-1 Putty should be used with caution in patients with a history of underlying cardiac diseases; close follow-up post-operatively is advised.*
- There was a higher reported rate of AEs in the infections and infestations SOC in the OP-1 Putty treated groups during pivotal study S01-01US (using a very conservative test for significance of $p \leq 0.2$); however, no patterns of particular types of infections emerged (infections were disparate), and there was no evidence of an increased incidence of surgically-related wound infections in the OP-1 Putty group compared to autograft. No difference between treatment groups with regard to the proportion of patients with new serious adverse events or new medical conditions or physical findings in the infections and infestations SOC was seen at the 36+ month interval in extension study 06-UPLF-01.

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- There was a higher reported rate of AEs in the blood and lymphatic system disorders SOC in the autograft group during pivotal study S01-01US (using a very conservative test of statistical significance of $p \leq 0.2$). The difference in blood and lymphatic system disorders, which was largely related to donor site complications and anemia in study S01-01US, did not persist at 36+ months based on data from study 06-UPLF-01.
- There was a higher reported rate of AEs in the injury, poisoning and procedural complications SOC in the autograft group during pivotal study S01-01US (using a very conservative test of statistical significance of $p \leq 0.2$). At the 36+ month visit for 06-UPLF-01, there was still a higher percentage of patients in the autograft group than in the OP-1 Putty group with new serious AEs and new medical conditions and physical findings for this SOC, although the difference was not statistically significant. The higher incidence of events in this SOC at 36+ months with regard to new medical conditions and physical findings appeared to be related primarily to the preferred term, “fall.”
- Although respiratory and gastrointestinal SOC categories were identified (using a very conservative test of statistical significance at $p \leq 0.2$) as having a higher rate of AEs in the OP-1 Putty group compared to autograft in study S01-01US, there were no clinically relevant patterns of AEs that emerged in these areas. At the 36+ month evaluation in study 06-UPLF-01, there was no apparent difference between groups in the proportion of patients who had new SAEs or new medical conditions/physical findings in these SOC categories.
- OP-1 Putty treatment is generally safe and well-tolerated in the PLF population.

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Benefits of OP-1 Putty

The key benefits of OP-1 Putty treatment in PLF are summarized as follows:

- Like autograft, OP-1 Putty stimulates new bone growth needed for a successful fusion in patients requiring decompression and lumbar spinal fusion. OP-1 Putty's ability to substitute for autograft in stimulating lumbar spinal fusion after decompression has been demonstrated primarily through a comparison between OP-1 Putty and autograft groups with regard to the primary endpoint of overall success (a composite measure of improvement in pain/function as measured by ODI, absence of retreatment, absence of device-related serious adverse events, absence of decrease in neurological success, and radiographic assessment of fusion), and secondarily by comparisons between groups for each subcomponent of overall success in addition to comparisons of pain scales and general health surveys.
- Unlike autograft, OP-1 Putty eliminates the pain and morbidity associated with surgical harvesting of autograft bone from the iliac crest.
- The use of OP-1 Putty also reduced the time of the operation by 20 minutes ($p=0.006$) and significantly reduced blood loss ($p=.0004$)

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Risk/Benefit Ratio

OP-1 Putty met the primary endpoint by demonstrating non-inferiority to autograft with respect to the primary outcome of Overall Success at 24 months (with clinical assessments performed at 24 months and radiographic and retreatment components at 36+ months). In addition, OP-1 Putty has an acceptable safety profile, and offers an attractive alternative to autograft since it allows surgeons to avoid autograft related surgical morbidity and pain.

The pivotal trial and extension study trial results were consistent across multiple clinical and radiographic efficacy endpoints. With respect to pain and disability scores; avoidance of reoperation and serious treatment-related complications; maintenance or improvement of neurologic function; radiographic evidence of new bone formation (using CT scan data to assess presence of bone); functional stability (measured by angulation and translation); and long-term durability of success in patients followed for a mean of 4.4 years, OP-1 Putty achieved uniformly high and clinically meaningful results. The durability of the results at a mean 4.4 years follow-up is important because research indicates that although patients who have undergone decompression with arthrodesis for degenerative spondylolisthesis may exhibit similar clinical improvements at two years regardless of whether they have achieved fusion or pseudarthrosis²⁵, differences in clinical outcomes become apparent with longer-term follow-up, with patients who have not achieved fusion experiencing worse outcomes as compared with patients who achieved fusion.²⁶ The consistent pattern of clinical benefit in the OP-1 Putty group over a mean follow-up of 4.4 years argues strongly in favor of a truly relevant clinical benefit for OP-1 Putty.

The safety of OP-1 Putty treatment in PLF is similar to that of autograft treatment with respect to the proportion of patients experiencing treatment-emergent AEs, severe AEs, treatment-related AEs, SAEs, unanticipated AEs, neoplasia, and death. OP-1 Putty treatment is generally safe and well-tolerated in the PLF population.

While autograft is widely recognized as the standard of care for bone grafting in spinal surgery, alternative therapies are needed due to the high rates of donor site morbidity associated with iliac crest harvest. Consistent with reports of donor site pain in the literature²², the results of S01-01US/06-UPLF-01 reported 44% (32/72) of patients reporting mild pain at one year, and 35% (18/52) of patients reporting mild to moderate pain at 3+ years, as well as increased operating room time and blood loss.

As described in the paper developed by the North American Spine Society for Contemporary Concepts in Spine Care, the current alternatives to autologous bone graft include allograft bone, demineralized bone matrix, recombinant growth factors and synthetic implants²⁷. Of these alternatives, recombinant growth factors (ie, BMPs) are the only option that provide an adequate osteoinductive material for optimal bone formation. Given this unique physiologic property, positive balance of clinical benefits and safety profile, and avoidance of autograft harvest morbidities, OP-1 Putty has a favorable risk benefit ratio that makes it a very attractive alternative to autograft in PLF.

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Reference

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