

### 5.3.8 Efficacy Results

(Content from P060021/A011, November 2007 Amendment, Section V, Clinical, Section 4, Pages 40-41)

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#### 5.3.8 EFFICACY RESULTS

The primary efficacy endpoint is Overall Success, a composite endpoint including measurements of improvement in pain/function (ODI score), absence of retreatment, absence of treatment-related serious adverse events, absence of decrease in neurological status, and achievement of radiographic success (itself a composite measure of presence of bone formation, and extent of angular motion and translational movement). As prespecified in the SAP, the primary analysis of Overall Success is conducted at 24 months (with radiographic and retreatment subcomponents at 36+ months) on the mITT population using a variable non-inferiority margin. The original study protocol used a non-inferiority margin set at 10%. In the statistical analysis plan finalized prior to unblinding the study data, the non-inferiority margin was modified to be fixed at 0.14 as measured in radians, based on the arc sine transformation of the proportion, rather than fixed as measured in percent. This modification was made to reflect the fact that the underlying variance of the proportion of success varies with the value of the proportion itself. Use of the arc sine transformation, considered a variance stabilizing transformation, is a standard statistical technique used with proportions to address just this issue. The value of 0.14 was selected so that the range of non-inferiority margins as expressed in percent would be in the vicinity of the original 10% margin.

Additional analyses of Overall Success at 24 months (with radiographic and retreatment subcomponents at 36+ months) in the mITT population include analyses stratified by center size, age, and gender; analysis using an equivalence limit of 0.10 to test for noninferiority; and analysis using presence of bridging bone rather than presence of bone. Analyses of Overall Success as originally presented for S01-01US are also presented for historical reference, although not considered a reliable measure of the comparative safety and efficacy of OP-1 Putty due to the inadequacy of the plain films assessment technique for presence of bone at 24 months.

Secondary efficacy endpoints include analyses of the five subcomponents of Overall Success both at 24 months (from S01-01US) and at 36+ months (from 06-UPLF-01), along with additional analyses of radiographic data from both S01-01US and 06-UPLF-01. Finally, tertiary efficacy data includes analyses of visual analog scales for pain through 36+ months, analyses of donor site pain through 36+ months, analyses of general health survey results through 36+ months (SF-36), and analyses of operative time and blood loss associated with the study procedure.

The clinical study reports for S01-01US (Appendix B to section V of the original PMA) and for 06-UPLF-01 (Appendix B to section V of the PMA Amendment) contain further details for each study. The results of both studies are summarized here.

Note that the percentage of patients achieving success in the secondary endpoints related to ODI success, absence of treatment-related serious adverse events, absence of decrease in neurological status, and the subcomponents of overall radiographic success (presence of bone, angulation success, and translation success) have been calculated with all patients who were a retreatment failure subsequent to the posterolateral fusion set to failure. As previously discussed, this is a different method than was used for the 24-month success rates originally presented in

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CSR S01-01US (where patients who were failures due to retreatment were excluded from the analyses); however, Stryker Biotech believes that this method is more appropriate than the previous method because excluding patients who were failures due to retreatment may artificially inflate the success results for the other subcomponents, and because, clinically, it is not reasonable to consider a patient who is a failure due to retreatment as a success in these other clinical measures. The success rates for the primary outcome measure of overall success as well as overall radiographic success as originally presented in CSR S01-01US are unaffected, because patients who were retreatment failures had always been counted as failures for determination of these two measures in S01-01US and 06-UPLF-01.