5.3.10.5 Immunogenicity

In pivotal study S01-01US, immunogenicity evaluation was carried out using patient serum samples collected pre-operatively (baseline), post-operatively, and at the 6 week, 3, 6, 12 and 24 month follow-up visits, as described in the study protocol. Bio-analytical methods are described in Appendix C of Section V of the original PMA.

Using the screening enzyme-linked immunosorbent assay (ELISA) test for anti-OP-1 antibodies, 93.7% of patients on OP-1 Putty were antibody positive at any time point versus 20.9% of patients who received autograft. In the OP-1 Putty group 25.6% of patients had evidence of anti-OP-1 neutralizing antibodies versus 1.2% of autograft patients. The peak presence of neutralizing antibodies was observed at 3 months and declined thereafter. By 24 months, none of the patients had neutralizing antibodies present (Table 40). In follow-up study 06-UPLF-01, all patients who had been antibody positive at 24 months (or, if they did not have a 24-month visit, were positive at their last visit in S01-01US) had serum samples analyzed at the 36+ month visit. Even using a more sensitive assay than was available in S01-01US, none of the patients in either treatment group were positive for neutralizing antibodies at the 36+ month interval. (Source: Statistical Table S.24.1 and S.24.2 in Section 14.1 of CSR 06-UPLF-01, Appendix B, Section V, PMA Amendment)

Individual profiles of patients who had neutralizing antibodies at any time point were assessed in S01-01US. No significant patterns emerge from these profiles except that the peak presence of antibody titers was observed between 6 weeks and 3 months and declined thereafter.

Table 40: Patients with Positive Screening Test and Anti-OP-1 Neutralizing Antibody at Any Visit (Safety Population)

Parameter	Any Visit	Pre-Operative	Operative[1]	6 Weeks	3 Months	6 Months	12 Months	24 Months
OP-1 Putty								
Total Number Patients	207	185	134	180	184	185	181	173
Number (%) ELISA Positive	194 (93.7)	5 (8.1)	8 (6.0)	164 (91.1)	176 (95.7)	159 (85.9)	133 (73.5)	71 (41.0)
Number (%) Neutralizing	53 (25.6)	1 (0.5)	1 (0.7)	31 (17.2)	36 (19.6)	13 (7.0)	2 (1.1)	0 (0.0)
Autograft								
Total Number Patients	86	75	62	70	73	72	68	56
Number (%) ELISA Positive	18 (20.9)	10 (13.3)	3 (4.8)	9 (12.9)	7 (9.6)	7 (9.7)	6 (8.8)	4 (7.1)
Number (%) Neutralizing	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)

Note: Neutralizing is anti-OP-1 antibody positive.
(1) Operative includes hospitalization (surgical procedure) and within 72 hours of postoperative.

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 S01-01US.

5.3.10.5 Immunogenicity

(Content from P060021/A011, November 2007 Amendment, Section V, Clinical, Section 5.7, Pages 91-93)

Table 41 presents potential associations between neutralizing antibody status and clinical outcome measures for patients who were antibody positive at any time throughout S01-01US and 06-UPLF-01. The clinical outcome measures presented are Overall Success at at 24 months using the modified criteria for radiographic success (including presence of bone by CT scan, angulation and translation at 36+ months) and absence of retreatment at 36+ months. The subcomponents for each definition of Overall Success are also presented. The overall success analysis using radiographic and retreatment data at 36+ months shows comparable overall success and subcomponents of overall success between those with and without neutralizing antibodies at any time during the study.

Table 41: Success Outcomes by Neutralizing Antibodies (Safety Population, OP-1 Putty Only)

Success Criteria	Neutralizing n/N (%)	Not Neutralizing n/N (%)
24 Month Interval (with 36+ month radiographic data including CT scans, and 36+ absence of retreatment data)		
Overall Patient Success	16/44 (36.4)	39/102 (38.2)
Overall Radiographic Success (1) at 36+ months	21/40 (52.5)	53/93 (57.0)
ODI Success at 24 months	34/50 (68.0)	104/142 (73.2)
Success Based on Absence of Retreatment at 36+ months	47/53 (88.7)	139/154 (90.3)
Absence of Serious Adverse Event at 24 months	41/53 (77.4)	134/154 (87.0)
Overall Neurological Success at 24 months	44/50 (88.0)	127/142 (89.4)

Percentage is based on patients with antibody analysis performed during S01-01US or 06-UPLF-01
Missing data are not imputed. Patients with retreatment subsequent to the PFL are set to failure for Radiographic success, Oswestry Disability success, Absence of serious adverse events success, and neurological success.
Source: Statistical Table S.24.4 and S.24.4.A in CSR 06-UPLF-01, Appendix B, Section V, PMA Amendment.