

Protocol 06-UPLF-001

Final Clinical Study Report

Prospective Data Collection from the Stryker Biotech Pivotal IDE Study of OP-1[®] Putty in Uninstrumented Posterolateral Fusions

Protocol Number: 06-UPLF-001

SPONSOR:

Stryker Biotech
35 South Street
Hopkinton, MA 01748

Report Date: November 21, 2007

Stryker Biotech considers the information contained within this Protocol to be
PROPRIETARY and CONFIDENTIAL.

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty® for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

1. TITLE PAGE

Title:	Prospective Data Collection from the Stryker Biotech Pivotal IDE Study of OP-1 Putty in Uninstrumented Posterolateral Fusions (<i>Extension to Pivotal IDE Study S01-01US</i>)
Investigational Device:	OP-1 Putty
Indication:	To be used as a replacement for autograft for an uninstrumented posterolateral fusion of the lumbar spine for patients with degenerative spondylolisthesis (Grade 1 or 2) with spinal stenosis.
Methods:	Prospective data collection of long-term follow-up on a controlled, prospective, randomized, multicenter, pivotal clinical trial
Sponsor Name and Address:	Stryker Biotech 35 South Street Hopkinton, MA 01748
Protocol Identification:	06-UPLF-01
Development Phase:	Pivotal Study (longer-term data collection)
Study Initiation Dates: Study Completion Dates:	First patient had study visit May 15, 2007 and last patient had study visit August 10, 2007.
Compliance Statement:	This study was conducted in accordance with standards of Good Clinical Practice, as defined by the International Conference on Harmonization, the Food and Drug Administration, and all applicable federal and local regulations.
Company Sponsor/Representative	Julie Krop, MD Vice President Clinical Development and Medical Affairs
Date of Report:	November 21, 2007
Confidential Information:	The information contained within this report is confidential and may not be used, divulged, published, or otherwise disclosed without the prior written consent of Stryker Biotech.

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty® for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

1. TITLE PAGE

Title:	Prospective Data Collection from the Stryker Biotech Pivotal IDE Study of OP-1 Putty in Uninstrumented Posterolateral Fusions (<i>Extension to Pivotal IDE Study S01-01US</i>)
Investigational Device:	OP-1 Putty
Indication:	To be used as a replacement for autograft for an uninstrumented posterolateral fusion of the lumbar spine for patients with degenerative spondylolisthesis (Grade 1 or 2) with spinal stenosis.
Methods:	Prospective data collection of long-term follow-up on a controlled, prospective, randomized, multicenter, pivotal clinical trial
Sponsor Name and Address:	Stryker Biotech 35 South Street Hopkinton, MA 01748
Protocol Identification:	06-UPLF-01
Development Phase:	Pivotal Study (longer-term data collection)
Study Initiation Dates: Study Completion Dates:	First patient had study visit May 15, 2007 and last patient had study visit August 10, 2007.
Compliance Statement:	This study was conducted in accordance with standards of Good Clinical Practice, as defined by the International Conference on Harmonization, the Food and Drug Administration, and all applicable federal and local regulations.
Company Sponsor/Representative	Julie Krop, MD Vice President Clinical Development and Medical Affairs
Date of Report:	November 21, 2007
Confidential Information:	The information contained within this report is confidential and may not be used, divulged, published, or otherwise disclosed without the prior written consent of Stryker Biotech.

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

SIGNATURE PAGE

STUDY TITLE: Prospective Data Collection from the Stryker Biotech Pivotal IDE Study of OP-1 Putty in Uninstrumented Posterolateral Fusions (*Extension to Pivotal IDE Study S01-01US*)

STUDY NUMBER: 06-UPLF-01

I have read this report and confirm that to the best of my knowledge it accurately describes the results of the study.

Approved by:

Julie Krop, MD
Vice President Clinical Development and Medical Affairs
Stryker Biotech, LLC

Date

Monique Duncan
Director, Clinical Operations
Stryker Biotech, LLC

Date

Eugene C. Poggio PhD
President and Chief Biostatistician
Biostatistical Consulting Inc.

Date

Bonnie S. Bielefeld MS
Director and Principal Biostatistician
Biostatistics and Epidemiology
Abt Associates Clinical Trials

Date

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

2. SYNOPSIS

Name of Sponsor/Company: Stryker Biotech	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: OP-1 [®] Putty		
Name of Active Ingredient: Human recombinant Osteogenic Protein-1 (OP-1)		
Title of Study: Prospective Data Collection from the Stryker Biotech Pivotal IDE Study of OP-1 Putty in Uninstrumented Posterolateral Fusions (<i>Extension to Pivotal IDE Study S01-01US</i>)		
Investigators: See complete investigator list in Section 16.1.4.		
Study Centers: Patients were enrolled from 23 institutions in the United States and Canada. See complete list of study centers in Section 16.1.4.		
Publication (reference): Not applicable		
Study Period: Duration of the extension study for collection of longer-term follow-up data from the pivotal IDE S01-01US was approximately three months from May 15, 2007 through August 10, 2007.		
Phase of Development: Pivotal Study		

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

Name of Sponsor/Company: Stryker Biotech	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: OP-1 [®] Putty		
Name of Active Ingredient: Human recombinant Osteogenic Protein-1 (OP-1)		
<p>Objectives: To provide additional data to support the safety and efficacy of OP-1 Putty as a replacement for autograft in patients undergoing posterolateral spinal fusion as measured by:</p> <ul style="list-style-type: none"> • Collecting additional radiographic data on all patients at least three years beyond (36+ months) initial treatment in this study. The prospectively collected data will be used to analyze primary efficacy as measured by calculating overall success rates with clinical data previously collected and analyzed, but using the new 36+ months radiographic data and reoperation data up to and including 36+ months, in the OP-1 Putty and the autograft groups. • Secondly, all data, including clinical outcome and safety data at 36+ months or more beyond initial treatment, will be used to complement the primary analysis. <p>The principal goal of this current protocol is to show that patients treated with OP-1 Putty not only experienced clinical benefits comparable to those of patients receiving autograft, but also that these patients have comparable evidence of new bone formation and dynamic radiographic stability.</p>		
<p>Number of Patients (planned and analyzed): Of 257 patients eligible for participation in this extension study, 5 patients were identified as having died after completion of S01-01US and prior to the start of follow-up study 06-UPLF-01, and 202 returned for evaluation (202/252 = 80.1%).</p>		
<p>Diagnosis and Main Criteria for Inclusion: Patients who had not died or been retreatment failures in pivotal study S01-01US were eligible for inclusion in this extension study to collect longer-term follow-up data. Patients in pivotal study S01-01US had been diagnosed with degenerative lumbar spondylolisthesis (Grade 1 or 2) with spinal stenosis and required decompression and spinal fusion treatment.</p>		

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

Name of Sponsor/Company: Stryker Biotech	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: OP-1 [®] Putty		
Name of Active Ingredient: Human recombinant Osteogenic Protein-1 (OP-1)		
Test Product: OP-1 Putty. OP-1 Putty is composed of recombinant human osteogenic protein (rhOP-1), Type I bovine bone collagen matrix, and a putty additive of carboxymethylcellulose (CMC) sodium, an anionic cellulose derivative, which yields a product with putty-like consistency. Two product units of OP-1 Putty were provided, each consisting of 2 components: <ul style="list-style-type: none">• A large vial containing a sterile dry powder consisting of 3.5 mg of human recombinant osteogenic protein-1 (OP-1) in 1 g of collagen matrix• A small vial containing the putty additive consisting of a sterile dry powder composed of 230 mg CMC		
Dose and Mode of Administration For the OP-1 Putty arm, 1 product unit was used on each side of the spine at the level of fusion, i.e., 2 product units per patient.		
Duration of Treatment: The treatment took place only once under pivotal study S01-01US, at the time of surgery.		
Reference Therapy, Dose and Mode of Administration: Lumbar spinal fusion with the use of autogenous bone graft from the iliac crest (autograft).		

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

Name of Sponsor/Company: Stryker Biotech	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: OP-1 [®] Putty		
Name of Active Ingredient: Human recombinant Osteogenic Protein-1 (OP-1)		
<p>Criteria for Evaluation:</p> <p><u>Efficacy:</u></p> <p><i>Primary Efficacy Endpoint:</i> overall success rate in the OP-1 Putty and the autograft groups using a multiple imputation technique.</p> <p>Overall success was a composite measure with the following components:</p> <ul style="list-style-type: none"> • Improvement of at least 20% in the ODI from baseline (at 24 months) • Absence of retreatment (up to and including 36+ month data) • Absence of treatment-emergent serious adverse events (SAEs) (at 24 months) • Absence of a decrease in neurological status (assessing muscle strength, reflexes, sensory and straight leg raise), unless attributable to a concurrent medical condition or to the surgical procedure by a blinded Independent Neurological Reviewer (at 24 months). • Radiographic demonstration of spinal fusion (at 36+ months), which was also a composite measure comprising all of the following: <ul style="list-style-type: none"> ○ Presence of bone formation by CT scan ○ Angulation of $\leq 5^\circ$ on flexion/extension radiographs of the affected level ○ Translational movement of ≤ 3 mm on flexion/extension radiographs of the affected level <p><i>Secondary Efficacy Endpoints:</i></p> <ul style="list-style-type: none"> • Components of overall success: success based on Oswestry Disability Index, absence of serious treatment related adverse events, absence of retreatment to promote fusion, neurologic success, and overall radiographic success at 36+ months without imputation of missing data • Overall radiographic success at 36+ months with missing data imputed <p><u>Safety:</u> New serious adverse events, new medical history/physical findings, status of events ongoing as of last study visit in Pivotal Study S01-01US.</p>		

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty® for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

Name of Sponsor/Company: Stryker Biotech	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: OP-1® Putty		
Name of Active Ingredient: Human recombinant Osteogenic Protein-1 (OP-1)		
<p>Statistical Methods:</p> <p>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.</p> <p>The primary efficacy endpoint was the 24-month overall success rate (with radiographic and retreatment at 36+ months) for the (modified) 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 endpoints included analyses of overall success stratified by center size, age category, and gender; overall success with bridging bone via CT using 36+ CT and radiographic data; overall success presented with an alternate equivalence limit of 0.10 to test for non-inferiority; success rates for each of the subcomponent measures of overall success (success based on Oswestry Disability Index, success based upon absence of serious treatment related adverse events, success based upon absence of retreatment to promote fusion, neurologic success, overall radiographic success using presence of bone, and the subcomponents of overall radiographic success) at 36+ months without imputation of missing data, and overall radiographic success at 36+ months with missing data imputed (for mITT population only). Additional analyses included overall radiographic success using presence of bridging bone; presence and location of bone, and presence of bridging bone, at operated level based on the CT scans at 36+ months; extent of angular motion and translational movement at 36+ months and at baseline, changes from baseline in the Oswestry Disability Index at 36+ months, and reanalysis of the 9 month CT data collected during the Pivotal IDE study. Analyses were also performed for the supplemental per protocol population to aid in interpretation of the primary efficacy analysis.</p> <p>The null hypothesis was that the difference in overall success rates between the autograft treatment group and the OP-1 Putty treatment group were comparable. For both imputed overall success at 24 months (with radiographic and retreatment data at 36+ months) and</p>		

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

Name of Sponsor/Company: Stryker Biotech	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: OP-1 [®] Putty		
Name of Active Ingredient: Human recombinant Osteogenic Protein-1 (OP-1)		
<p>imputed overall radiographic success at 36+ months, a one-sided two-sample asymptotic test for non-inferiority was used to test for non-inferiority in the angular scale with a fixed non-inferiority margin of .14 radians. This fixed margin in the angular scale corresponds to margins ranging from 6.9-13.9%. For the primary endpoint the equivalence limit for the test of non-inferiority was also tested at 0.10, and was not based upon an angular transformation.</p> <p>For both the primary and secondary 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 two treatment groups.</p> <p>For adverse events, each SOC and each preferred term reported by \geq of 5% of patients in either treatment arm were tested for treatment differences using Fisher's exact test. For neurological status Chi-square or Fisher's 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.</p>		

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

Name of Sponsor/Company: Stryker Biotech	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: OP-1 [®] Putty		
Name of Active Ingredient: Human recombinant Osteogenic Protein-1 (OP-1)		
<p>Summary – Conclusions:</p> <p><u>Efficacy:</u></p> <p>This study demonstrated the following results with regard to overall success at 24 months, with subcomponents related to radiographic success and retreatment success based on the 36+ month interval data:</p> <ul style="list-style-type: none"> • Overall Success (with ODI success, absence of SAE success, and neurological success at 24 months, and radiographic success and retreatment success at 36+ months): OP-1 Putty treatment was demonstrated to be non-inferior to autograft (p=0.025). The estimated success rates were 47.2% for OP-1 Putty and 46.8% for autograft. <p>In addition, the study demonstrated the following results with regard to clinical outcomes measures at the 36+ month interval.</p> <ul style="list-style-type: none"> • ODI success: 68.6% of OP-1 Putty patients experienced at least a 20% improvement over baseline scores at 36+ months, as compared to 77.3% of autograft patients. The difference between groups was not statistically significant, p=0.201. Mean ODI scores at 36+ months were similar between treatment groups (22.9 for OP-1 Putty and 22.3 for autograft), as were mean improvements from baseline (25.3 for OP-1 Putty and 27.4 for autograft) and mean percent improvement from baseline (54.0% for OP-1 Putty and 54.5% for autograft). • Absence of retreatment: 87.0% of OP-1 Putty patients were free from retreatment by 36+ months, whereas 83.3% of autograft patients were free from retreatment at 36+ months. The difference between groups was not statistically significant (p=0.529) • Absence of serious treatment-related AEs: OP-1 Putty and autograft demonstrated comparable success rates for patients free from serious treatment-related adverse events up to and including the 36+ month interval (79.5% for OP-1 Putty and 73.5% for autograft). The difference between groups was not statistically significant (p=0.387). • Neurological success: 84.4% of OP-1 Putty and 80.0% of autograft patients were neurological successes up through and including the 36+ months interval. The 		

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

Name of Sponsor/Company: Stryker Biotech	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: OP-1 [®] Putty		
Name of Active Ingredient: Human recombinant Osteogenic Protein-1 (OP-1)		
<p>difference between groups was not statistically significant (p=0.540).</p> <ul style="list-style-type: none"> • Radiographic success: 60.7% of OP-1 Putty patients and 63.1% of autograft patients achieved radiographic success at 36+ months. The OP-1 Putty group was not statistically non-inferior to the autograft group with regard to this secondary endpoint (p=0.138); however, there were no statistically significant differences between the OP-1 Putty and autograft groups with regard to the three subcomponents of Overall Radiographic Success at 36+ Months (non-imputed): <ul style="list-style-type: none"> ○ Presence of bone on 36+ month CT scans: 74.8% of OP-1 Putty patients demonstrated presence of bone by 36+ month CT scans, as compared to 77.4% of autograft patients (p=0.852). ○ Translational movement success: 75.7% of OP-1 Putty patients demonstrated success, and 75.4% of autograft patients demonstrated success (p=1.000). ○ Angulation success: 69.3% of OP-1 Putty patients demonstrated success, and 68.4% of autograft patients demonstrated success (p=1.000). • Presence of bone on CT at 9 months (using same radiographic assessment protocol used for 36+ month CT scans): OP-1 Putty demonstrated presence of bone in 73.0% of patients. While autograft demonstrated presence of bone in 97.5% of patients, it is difficult to distinguish in this group whether the visible bone at 9 months is <i>de novo</i> bone formation or the autograft itself. In the OP-1 Putty group, all bone visible on CT scans is <i>de novo</i> bone formation because there is no other graft material present and the OP-1 Putty itself is not radiopaque. While 9 months is not an adequate length of time post surgery to assess peak <i>de novo</i> bone formation, this analysis demonstrates that the majority of patients in the OP-1 Putty group who had presence of bone by 36+ months also showed presence of bone by 9 months. • SF-36 and VAS pain scales demonstrated significant improvements for patients in both treatment groups. In addition, the avoidance of a second surgical procedure resulted in absence of donor site pain in the OP-1 Putty group; whereas 35% of patients in the autograft group had mild to moderate donor site pain even 36+ months after surgery. 		

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty® for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

Name of Sponsor/Company: Stryker Biotech	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: OP-1® Putty		
Name of Active Ingredient: Human recombinant Osteogenic Protein-1 (OP-1)		
<p>OP-1 Putty is equivalent to autograft with regard to the primary composite endpoint of overall success. OP-1 Putty was also shown to be clinically comparable to autograft with regard to the secondary measures of overall radiographic success, improvement in Oswestry Disability Index, absence of decrease in neurological success, incidence of treatment-related serious adverse events, and retreatment rate at the longer-term 36+ month follow-up interval. OP-1 Putty achieved improvements in VAS and SF-36 measures that were comparable to the improvements achieved by the autograft group, but without the additional comorbidities and surgical time associated with autograft harvest from the patient’s iliac crest.</p>		
<p><u>Safety:</u></p> <p>The safety of OP-1 Putty treatment in posterolateral fusion (PLF) is similar to that of autograft treatment with respect to the percentage of patients experiencing the following events in the longer-term follow-up interval (36+ months):</p> <ul style="list-style-type: none"> • New serious adverse events • New serious adverse events – treatment related • New serious adverse events – severe • Neoplasms 		

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty® for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (Extension to Pivotal Study S01-01US)

Name of Sponsor/Company: Stryker Biotech	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: OP-1® Putty		
Name of Active Ingredient: Human recombinant Osteogenic Protein-1 (OP-1)		

Table 1: New Serious Adverse Events (Safety Population)

Parameter	OP-1 Putty (N=208)	Autograft (N=87)
	Number (%) of Patients with Events	Number (%) of Patients with Events
Any New Serious Adverse Event	24 (11.5)	17 (19.5)
New Serious Adverse Events – Treatment Related (Suspected-related or unknown)	2 (1.0)	5 (5.7)
New Serious Adverse Events – Severe	15 (7.2)	9 (10.3)
Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps)	1 (0.5)	2 (2.3)

New serious adverse events reported at 36+ months were evaluated by System Organ Class (SOC) and preferred term. There were 33 new SAEs occurring in 24 patients (11.5% of patients) in the OP-1 Putty group, and 22 new SAEs occurring in 17 patients (19.5% of patients) in the autograft group (p=0.095). New serious adverse events were classified by System Organ Class (SOC), and a conservative statistical cut-off (p≤0.2) was imposed to identify potential differences in new serious adverse events by SOC between treatment groups (for SOC terms reported by ≥5% of patients in at least one treatment group). The safety profiles of the two treatment groups were generally comparable, with no statistically significant differences observed between treatment groups in any of the SOC categories using a conservative statistical cut off of p≤0.2. The percentages of patients with new serious adverse events that were considered severe or device-related were no higher for the OP-1 Putty group than for the autograft group.

New medical history and physical findings reported at 36+ months were also evaluated by SOC and preferred term. The percentage of patients with new medical history or physical findings was 31.7% in the OP-1 Putty group and 43.7% in the autograft group (p=0.061). A conservative statistical cut-off (p≤0.2) was imposed to identify potential differences in new findings by SOC between treatment groups (for SOC terms reported by ≥5% of patients in at least one treatment group). While the new medical history and

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

Name of Sponsor/Company: Stryker Biotech	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: OP-1 [®] Putty		
Name of Active Ingredient: Human recombinant Osteogenic Protein-1 (OP-1)		
<p>physical findings profiles of the two treatment groups were generally comparable, for the SOC of Nervous System Disorders, the autograft group showed an overall higher incidence of new SAEs than did the OP-1 Putty group based on this statistical cut-off: 10.% of patients for OP-1 Putty, 16.1% of patients for autograft, p=0.167. The percentages of patients with new findings that were considered severe or device-related was no higher for the OP-1 Putty group than for the autograft group.</p> <p>Of the adverse events that were classified as “ongoing” at the close of Pivotal IDE S01-01US, the balance of events that continued to be ongoing versus events that had resolved was similar between treatment groups: 75.9% of the events remained ongoing in the OP-1 Putty group, and 82.0% of the events remained ongoing in the autograft group. The percentage of ongoing events that had become serious adverse events since Pivotal Study S01-01US was low in both groups, although was higher for the autograft group: 4.4% for the OP-1 Putty group and 9.0% for the autograft group. The percentage of ongoing events that had resulted in spine surgery since Pivotal IDE S01-01US was also low in both groups, although was higher in the autograft group: 1.5% for the OP-1 Putty group and 5.1% for the autograft group. The system organ class General Disorders and Administration Site Conditions was the only SOC category for the Ongoing AE analysis where the difference between treatment groups was statistically significant using the conservative cut-off of p≤0.2: events were reported in 2.9% of OP-1 Putty patients, and 6.9% of autograft patients (p=0.191).</p> <p>Patients in both treatment groups reported new medical history and physical findings in the SOC Neoplasms, Benign and Malignant (including cysts and polyps) at 36+ months: 2 patients in the OP-1 Putty group (1.0%) reported 3 events, and 2 patients in the autograft group (2.3%) reported 2 events. In addition, prostate cancer was reported as a new SAE for one autograft patient under the SOC category of Investigations. None of the reported malignancies were determined to have a causal relationship to either OP-1 Putty or autograft. There were no patterns or specific events of concern identified at the 36+ month interval with respect to type of cancer or distribution between treatment groups.</p> <p>Five patients had died subsequent to pivotal study S01-01US and prior to enrollment in extension study 06-UPLF-01: four in the OP-1 Putty group and one in the autograft</p>		

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

Name of Sponsor/Company: Stryker Biotech	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: OP-1 [®] Putty		
Name of Active Ingredient: Human recombinant Osteogenic Protein-1 (OP-1)		
<p>group. No patterns of concern emerged with respect to the frequency or etiology of these deaths.</p> <p>No patients in either study group had evidence of neutralizing antibodies against OP-1 Putty by the 36+ month visit. There did not appear to be any clinically significant differences in overall success at 24 months (with radiographic and retreatment assessed at 36+ months) or its subcomponents between patients who had neutralizing antibodies at any time and those who did not have neutralizing antibodies.</p>		

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

Name of Sponsor/Company: Stryker Biotech	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Name of Finished Product: OP-1 [®] Putty		
Name of Active Ingredient: Human recombinant Osteogenic Protein-1 (OP-1)		
<p>Conclusion:</p> <p>Results of this pivotal study demonstrate that OP-1 Putty is safe and effective when used in patients with single level degenerative lumbar spondylolisthesis with spinal stenosis who are undergoing decompression and spinal fusion.</p> <ul style="list-style-type: none"> • OP-1 Putty has been shown to be non-inferior to autograft with respect to the primary outcome of Overall Success at 24 months (with radiographic and retreatment components at 36+ months). • There were no statistically significant differences between OP-1 Putty and autograft with regard to the following clinical outcome measurements at 36+ months: improvement in ODI, absence of retreatment, absence of serious treatment-related adverse events, and absence of decrease in neurological status. • OP-1 Putty was not demonstrated to be non-inferior to autograft with regard to overall radiographic success at 36+ months; however, there were no statistically significant differences between OP-1 and autograft with regard to the three subcomponents of overall radiographic success at 36+ months: presence of bone assessed by CT scan, angular motion ≤ 5 degrees, and translational movement ≤ 3mm. • OP-1 Putty demonstrated improvements in VAS and SF-36 outcomes that were clinically meaningful and not statistically different from autograft. OP-1 patients avoided the autograft-harvest-related donor site pain experienced by the autograft group. • OP-1 Putty demonstrated a safety profile that was similar to autograft as supported by a comparison of ongoing adverse events from study S01-01US, new serious adverse events, and new medical history and physical findings. <p>OP-1 Putty's good clinical outcomes, acceptable safety profile, and ability to avoid autograft-related surgical morbidity and pain make it an attractive alternative to autograft in the setting of PLF.</p>		
<p>Date of the Report: November 21, 2007</p>		

3. TABLE OF CONTENTS

1. Title Page	1
2. Synopsis	3
3. Table of Contents	16
3.1 List of In-Text Tables	20
3.2 List of In-Text Figures	23
4. Abbreviations and Definitions of Terms	24
5. Ethics	25
5.1 Institutional Review Board (IRB)	25
5.2 Ethical Conduct of the Study	25
5.3 Patient Information and Consent	25
6. Investigators and Study Administrative Structure	26
6.1 Investigators	26
6.2 Study Conduct	26
7. Introduction	27
8. Study Objectives	32
9. Investigational Plan	33
9.1 Overall Study Design and Plan	33
9.2 Description and Discussion of the Design and Choice of Control	33
9.3 Selection of Study Population	33
9.3.1 Inclusion Criteria	33
9.3.2 Exclusion Criteria	34
9.3.3 Removal of Patients from Therapy or Assessment	34
9.4 Treatments	34
9.4.1 Treatments Administered	34
9.4.2 Identity of Investigational Product	34
9.4.3 Method of Assigning Treatment	35
9.4.4 Blinding	35
9.5 Efficacy and Safety Variables	36
9.5.1 Efficacy and Safety Measurements Assessed and Study Schedule	36
9.5.2 Appropriateness of Measurements	37
9.5.3 Primary Efficacy Variable	38
9.6 Data Quality Assurance	38
9.6.1 Site Training	38
9.6.2 Data Monitoring	39
9.6.3 Data Management	39

9.7	Protocol-specified Statistical Methods and Determination of Sample Size.....	39
9.7.1	Statistical and Analytical Plans.....	39
9.7.1.1	Hypothesis Testing.....	40
9.7.1.2	Populations for Statistical Analyses.....	40
9.7.1.3	Non-Response Bias.....	41
9.7.1.4	Demographic and Baseline Characteristics.....	41
9.7.1.5	Analysis of Efficacy.....	41
9.7.1.6	Safety Analysis.....	43
9.7.1.7	Additional Analysis.....	44
9.7.1.8	Immunology.....	45
9.8	Change from the Protocol and Planned Analyses.....	45
9.8.1	Changes in the Conduct of the Radiographic Evaluation.....	45
9.8.2	Changes in Collection of Serious Adverse Events.....	46
9.8.3	Changes in Planned Statistical Analyses.....	46
10.	Study Patients.....	57
10.1	Patient Disposition.....	57
10.2	Protocol Deviations.....	64
11.	Efficacy Evaluation.....	65
11.1	Data Sets Analyzed.....	65
11.2	Demographics and Other Baseline Characteristics.....	66
11.3	Efficacy Results and Tabulations of Individual Patient Data.....	69
11.3.1	Primary Efficacy: Overall Success.....	69
11.3.2	Secondary Efficacy Endpoints.....	73
11.3.2.1	Oswestry Disability Index Success at 36+ Months.....	74
11.3.2.2	Absence of Retreatment at 36+ Months.....	80
11.3.2.3	Absence of Serious Treatment-Related Adverse Events up to and including 36+ Months.....	80
11.3.2.4	Neurological Success at 36+ Months.....	81
11.3.2.5	Overall Radiographic Success at 36+ Months.....	83
11.3.3	Other Radiographic Findings.....	87
11.3.3.1	Overall Radiographic Success with Presence of Bridging Bone by CT Scan at 36+ Months.....	87
11.3.3.2	Presence of Bone on 9-Month CT Scans Compared to 36+ Month CT Scans.....	89
11.3.3.3	Differences in Location of Bone Formation.....	91
11.3.4	Additional Analyses.....	91
11.3.4.1	Visual Analog Scale for Pain Assessment at 36+ Months.....	91

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

11.3.4.2	Donor Site Pain at 36+ Months.....	92
11.3.2.3	General Health Survey (SF-36).....	93
11.3.5	Statistical/Analytical Issues	95
11.3.5.1	Adjustments for Covariates.....	95
11.3.5.2	Handling of Dropouts or Missing Data.....	95
11.3.5.3	Interim Analyses and Data Monitoring.....	96
11.3.5.4	Multicenter Studies	96
11.3.5.5	Multiple Comparisons/Multiplicity.....	96
11.3.5.6	Examination of Subgroups.....	96
11.4	Efficacy Conclusions	97
12.	Safety Evaluations	100
12.1	Duration of Observation.....	100
12.2	Adverse Events – Ongoing at Close of S01-01US	100
12.3	New Serious Adverse Events.....	103
12.3.1	Overall Incidence of New Treatment Emergent Serious Adverse Events.....	103
12.3.2	New Treatment Emergent Serious Adverse Events by Causality.....	106
12.3.3	Listings and Tables of New Serious Adverse Events.....	107
12.4	New Medical History and Physical Findings.....	107
12.4.1	Overall Incidence of New Medical History and Physical Findings.....	108
12.4.2	New Medical History and Physical Findings by Causality	112
12.4.3	Listings and Tables of New Medical History and Physical Findings.....	114
12.5	Secondary Procedures	115
12.6	Neurological Status	116
12.7	Death, Other Serious Adverse Events, and Other Significant Adverse Events.....	116
12.7.1	Deaths	116
12.7.2	Heterotopic Bone Formation.....	116
12.7.3	Malignancies.....	118
12.8	Immunogenicity	119
12.8.1	Test Methods.....	119
12.8.2	Immunological Status	120
12.9	Safety Conclusions.....	122
13.	Discussion and Overall Conclusions	126

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

Additional Contents

- 14. Tables, Figures, and Graphs for Study 06-UPLF-01
 - 14.1 Statistical Analysis Plan Tables
 - 14.2 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events
 - 14.3 Narratives of Patients Lost to Follow-Up
- 15. Reference List
- 16. Appendices Pivotal Study 06-UPLF-01
 - 16.1 Study Information Pivotal Study 06-UPLF-01
 - 16.1.1 Protocol and Amendments Pivotal Study Extension 06-UPLF-01
 - 16.1.2 Sample Case Report Forms Pivotal Study Extension 06-UPLF-01
 - 16.1.3 List of IRBs and Sample Informed Consent Pivotal Study Extension 06-UPLF-01
 - 16.1.4 List and Description of Investigators and Other Important Participants Pivotal Study Extension 06-UPLF-01
 - 16.1.5 Signatures of Principal or Coordinating Investigator(s) or Sponsor's Responsible Medical Officer Pivotal Study Extension 06-UPLF-01
 - 16.1.6 Documentation of Statistical Methods Pivotal Study Extension 06-UPLF-01
 - 16.1.7 Randomization Scheme and Codes, Study 06-UPLF-01
 - 16.1.8 Audit Certificates, Study 06-UPLF-01
 - 16.1.9 Documentation of Statistical Methods, Study 06-UPLF-01
 - 16.1.10 Documentation of Inter-Laboratory Standardization Methods, and Quality Assurance Procedures, Study 06-UPLF-01
 - 16.1.11 Publications Based on Study 06-UPLF-01
 - 16.1.12 Important Publications Referenced in the Report, Study 06-UPLF-01
 - 16.2 Patient Data Listing Pivotal Study Extension 06-UPLF-01
 - 16.3 Case Report Forms Pivotal Study Extension 06-UPLF-01
 - 16.4 Individual Patient Data Listings Pivotal Study Extension 06-UPLF-01
 - 16.5 Immunology Results

3.1 LIST OF IN-TEXT TABLES

Table 1:	New Serious Adverse Events (Safety Population)	12
Table 2:	Changes in Planned Statistical Analyses	48
Table 3:	Disposition of Patients Eligible for Follow-up in 06-UPLF-01	57
Table 4:	Patient accounting through 36+ Months, S01-01US and 06-UPLF-01 (safety population).....	60
Table 5:	Study Populations for SAP Analyses	65
Table 6:	Summary of Key Demographic Parameters and S01-01US Success Outcomes for Extension Study 06-UPLF-06	67
Table 7:	Overall Success at 24 Months (with Radiographic and Retreatment Success Subcomponents at 36+ Months), mITT Population.....	70
Table 8:	Subcomponents of Overall Success at 24 months (with Radiographic and Retreatment subcomponents at 36+ months), mITT Population	71
Table 9:	Success Outcomes at 36+ months Follow-Up: SAP Analysis, mITT Population.....	74
Table 10:	Success Rate Based on Oswestry Disability Index at 36+ Months (mITT Population and SPP Population)	75
Table 11:	Oswestry Disability Index, Change from Baseline, 36+ Months (mITT Population).....	76
Table 12:	ODI Percent Changes at 36+ Months Compared to Baseline, mITT Population.....	76
Table 13:	ODI Improvements Using Varying Percent Improvements, mITT Population.....	77
Table 14:	Success Rate Based on Absence of Retreatments up to and including 36+ Months (mITT Population and SPP Population).....	80
Table 15:	Success Rate Based on Absence of Serious Treatment-Related Adverse Events at 36+ Months (mITT Population and SPP Population)	81
Table 16:	Overall Neurological Success Rates at 36+ Months (mITT and SPP Populations).....	82
Table 17:	Overall Radiographic Success Rate at 36+ Months (mITT Population)	84
Table 18:	Translational Movement at 36+ Months (mITT Population).....	85
Table 19:	Angular Motion at 36+ Months (mITT Population).....	86
Table 20:	Presence of Bone Based on 36+ Month CT Scan, mITT Population.....	87

Table 21:	Presence of Bone on 9 Month CT Scan Cross-Tabulated Against Presence of Bone on 36+ Month CT Scan (mITT Population).....	89
Table 22:	Presence of Bone Assessed via CT Scan for Patients Who Did Not Have Presence of Bone via 24 Month Plain Films (mITT).....	90
Table 23:	Changes from Baseline in Visual Analog Scale of Right and Left Leg/Buttock Pain Assessment at 36+ Months (Safety Population).....	92
Table 24:	Donor Site Pain-Visual Analog Scale at 6 Weeks and at 12, 24, and 36+ Months (Safety Population, Autograft Only).....	92
Table 25:	Donor Site Pain Status at 12, 24, and 36+ Months (Safety Population, Autograft Only)	93
Table 26:	SF-36 Physical Component Score (Safety Population).....	94
Table 27:	SF-36 Physical Functioning (Safety Population)	94
Table 28:	Overall Success Rate at 24 Months (with radiographic and retreatment subcomponents at 36+ months) by Gender and Age Groups (mITT Population).....	97
Table 29:	Outcome and Action Taken Since Last IDE Visit for Ongoing Adverse Events.....	101
Table 30:	New Serious Adverse Events (Safety Population)	103
Table 31:	Incidence of New Adverse Events by MedDRA System Organ Class (Safety Population).....	104
Table 32:	Incidence of Musculoskeletal and Connective Tissue Disorders at 36+ Months (Safety Population)	105
Table 33:	New Treatment-Related (Suspected Related or Unknown) Serious Adverse Events.....	107
Table 34:	New Medical History and Physical Findings by SOC for any SOC with Difference $p \leq 0.2$ (Safety Population)	109
Table 35:	New Medical History and Physical Findings, Occurrence of Potentially Spine-Related Preferred Terms within Musculoskeletal and Connective Tissue Disorders SOCs.....	110
Table 36:	New Medical History and Physical Findings, Occurrence of Potentially Spine-Related Preferred Terms within Nervous Systems Disorders SOCs	111
Table 37:	Incidence of Injury, Poisoning and Procedural Complications – New Medical History/Physical Findings (Safety Population)	112
Table 38:	Treatment-Related (Suspected Related or Unknown) New Medical History or Physical Findings	113
Table 39:	Failures due to Retreatment Identified in 06-UPLF-01.....	115

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

Table 40:	Deaths Recorded After S01-01US.....	116
Table 41:	Additional Information on Patients Who Experienced HTO-Related Adverse Events in S01-01US	117
Table 42:	Patients with Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps) System Organ Class.....	119
Table 43:	Success Outcomes by Neutralizing Antibodies (Safety Population, OP-1 Putty Only).....	121
Table 44:	New Serious Adverse Events (Safety Population).....	122

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty® for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

3.2 LIST OF IN-TEXT FIGURES

Figure 1:	Disposition of Patients in S01-01US and 06-UPLF-01	58
Figure 2:	% Improvements in ODI at 24 Months	78
Figure 3:	% Improvements in ODI at 36+ Months	79

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

4. ABBREVIATIONS AND DEFINITIONS OF TERMS

AACT	Abt Associates Clinical Trials
AE	Adverse Event
AP	Anteroposterior
BMP	Bone Morphogenetic Proteins
CI	Co-Investigator
CMC	Carboxymethylcellulose
CO ₂	Carbon Dioxide
CRA	Clinical Research Associate
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computerized Tomography
ELISA	Enzyme-Linked Immunosorbent Assay
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IDE	Investigational Device Exemption
IRB	Institutional Review Board
ITT	Intent-to-Treat
MCHC	Mean Corpuscular Hemoglobin Concentration
MCS	Mental Component Score
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
mITT	Modified Intent-to-treat
MRI	Magnetic Resonance Imaging.
Nab	Neutralizing antibody
ODI	Oswestry Disability Index
OP-1	Osteogenic Protein-1
PCS	Physical Component Score
PI	Principal Investigator
PLF	Posterolateral fusion
RPD	Radiographic Procedure Document
SAE	Severe Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software (SAS Institute Inc., Cary, NC)
SD	Standard Deviation
SLR	Straight Leg Raises
SOC	System Organ Class
SPP	Supplemental Per Protocol
VAS	Visual Analog Scale

5. ETHICS

5.1 INSTITUTIONAL REVIEW BOARD (IRB)

The protocol and informed consent documents were approved by the sites' IRBs.

The protocol is provided in Appendix 16.1.1. Information on the IRBs, with the names of the committee chairs, is provided in Appendix 16.1.3.

5.2 ETHICAL CONDUCT OF THE STUDY

This study was conducted with adherence to the principles of Good Clinical Practice (GCP), as required by the US Code of Federal Regulations (21 CFR parts 50, 54, 56, and 812); the International Conference on Harmonization Guidelines, effective 17 January 1997; and in accordance with the ethical principles contained in the Declaration of Helsinki.

5.3 PATIENT INFORMATION AND CONSENT

All patients in this study were informed in accordance with GCP and local regulatory authority requirements concerning the pertinent details and purpose of the study, potential risks, and treatment options. A signed Patient Informed Consent was to be obtained by the Investigator, or designee, prior to study participation.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

6.1 INVESTIGATORS

This study was sponsored by Stryker Biotech and was conducted at 23 centers. The Principal Investigator at each center assumed ultimate responsibility for the conduct of the trial at that center. The institutional affiliations and qualifications of the study investigators are provided in Section 16.1.4.

6.2 STUDY CONDUCT

Stryker Biotech was responsible for the overall conduct of this study. The signature of the Sponsor's medical monitor is provided in Section 16.1.5.

Study monitors employed by M Squared Associates (901 King Street, Alexandria, VA 22314) were assigned to monitor the progress of the study, assure site compliance with GCP and appropriate federal regulations, and ensure that accurate data were collected.

Serum samples for immunological testing were stored at ICON Laboratories and then shipped to Stryker Biotech for testing.

Patient radiographs (plain films and CT scans) were sent to BioImaging Technologies, Inc. and initially reviewed for quality parameters by an Image Analysis Technician with accreditation in CT. The radiographic data was loaded into a Cedara read system. Great care was taken to standardize the prospective CT scan including the imaging algorithm and a standard imaging protocol. Upon acceptance of films based on quality parameters the radiographic images were read by 3 spine surgeons not previously involved with the pivotal study: 2 primary readers, and 1 adjudicating reader. If the primary readers were not in agreement regarding radiographic success or failure, then the adjudicating review was used, and success or failure with regard to radiographic parameters was determined by the majority of readers. The qualifications of the study radiographic readers are provided in Section 16.1.4.

Final determination of overall neurological status was performed by an orthopedic spine surgeon, Lou Jenis, MD, from the Boston Spine Group at The New England Baptist Hospital (Boston, MA), based on neurological exams performed by the Investigator and on review of the patient history and any reported adverse events. This individual was not involved in the conduct of the study. The qualifications of this orthopedic spine surgeon are provided in Section 16.1.4.

Data entry, data cleaning, and statistical analyses were performed by Abt Associates Clinical Trials (AACT) (Lexington, MA).

Medical writing was performed by Stryker Biotech and by M Squared Associates, Inc. (Alexandria, VA).

7. INTRODUCTION

The study was designed to evaluate the safety and efficacy of OP-1[®] Putty as a replacement for autograft in posterolateral fusion of the lumbar spine in patients with degenerative spondylolisthesis with spinal stenosis.

It has been estimated that up to 70% of the adult population suffers from some form of low back (lumbar sacral) pain,¹ which is usually attributed to a degenerative disease process within the vertebral spine. Degenerative spondylolisthesis, a condition characterized by the slippage of one vertebral segment on the one below in the presence of an intact neural arch,² is one of the diagnoses attributed to the degenerative disc disease process. Spinal stenosis is often associated with the spondylolisthesis due to facet hypertrophy, ligamentum flavum thickening and osteophyte formation. If patient pain, neurological deficits, and instability do not respond to conservative management, decompression and lumbar spinal fusion are the most common surgical treatments of choice for degenerative spondylolisthesis and spinal stenosis.³

Spinal fusion is a surgically created bony union across the involved vertebrae.

Approximately 70,000 posterolateral lumbar spinal fusions are performed annually in the US.⁴ The use of bone graft to stimulate new bone growth is a standard surgical technique in spinal fusion, both with and without instrumentation. Bone graft stimulates new bone formation and acts as a matrix or scaffold into or over which new bone can grow.

Currently, autologous bone (autograft) is considered the most successful bone grafting material and is preferred over allograft bone.^{5,6,7,8} The most common site for harvesting autograft material is the iliac crest.⁹ However, this procedure increases operative time, blood loss, and the morbidity associated with spinal fusion.¹⁰

In recent years, there has been a focus on Bone Morphogenetic Proteins (BMPs) as bone graft material.¹¹ Osteogenic Protein-1 (OP-1) is one such BMP. Implants containing OP-1 and collagen matrix have been shown to be osteoinductive and osteoconductive, to speed the rate of bone healing^{12,13,14,15,16} and to improve the performance of autograft in animals. Implants containing OP-1 and collagen matrix have also been shown to promote stable spinal fusions significantly faster than autograft.^{17,18} Safety and efficacy of other BMPs in spinal applications have also been reported in animal models.^{10,19,20,21, 22}

It was postulated that the use of OP-1 Putty would prove beneficial in the treatment of patients requiring decompression and lumbar spinal fusion while also eliminating the pain and morbidity associated with harvesting autograft bone from the iliac crest. For the purposes of this study, the disease process was restricted to Grade 1 and 2 degenerative spondylolisthesis with stenosis affecting one level of the lumbar spine (L3 to S1).

This study described in this study report was a prospective data collection on patients who participated in the Pivotal IDE study (S01-01US) and who were three years plus (36+ months) beyond study treatment. All data that was previously evaluated in the patients in S01-01US was collected again at a single, longer-term follow-up, 36+ month evaluation, with the exception of laboratory assessments and anteroposterior (AP) and lateral plain films.

This study expanded the information regarding efficacy as well as the long-term safety of OP-1 Putty in uninstrumented PLF. In the original Pivotal IDE study previously reported in CSR S01-01US, only a small number of patients in each group (34 in OP-1 Putty and 14 in autograft) were assessed clinically at 36 months. This study captured 36+ month data on all eligible patients to enable a more complete assessment of the efficacy and patient outcomes following PLF with either OP-1 Putty or autograft.

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 of angulation and translation at 24 months was also observed.

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
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.

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

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

Outcome	OP-1 Putty	Autograft	P Value for difference
Components of Overall Radiographic Success			
- presence of bone by plain ² film	61.7	83.1	<0.001
- angulation ≤ 5 degrees on ² flexion/extension films	73.3%	75.6%	0.684
- translation ≤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) of the patients treated with OP-1 and the presence of new bone formation reported by plain film x-ray for those patients. Given that clinical experience and the literature demonstrates a high correlation between fusion and positive clinical outcomes in patients undergoing decompression with laminectomy, these results were unexpected^{23,24}. Since the OP-1 Putty patients had comparable clinical outcomes to the autograft patients, 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.

Since the patients in the OP-1 Putty group achieved clinical and functional radiographic (angulation and translation) improvements 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 not previously involved with the study and 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 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 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

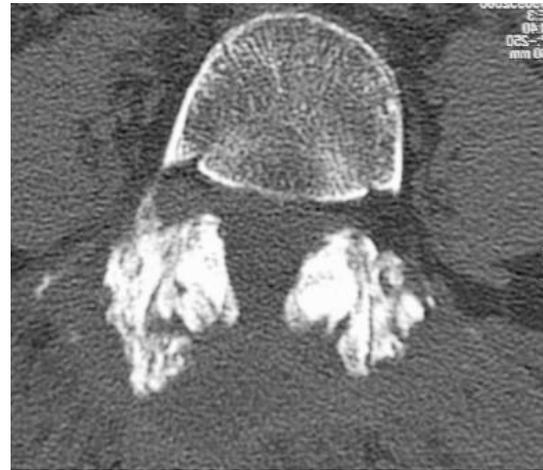


Figure 2

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 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 1). When the retractors are removed and the muscles are released, the OP-1 Putty product is compressed medially (See Figure 2), 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.

Given the greater sensitivity of CT scans in assessing presence of bone, it was imperative to collect follow-up CT images for the determination of radiographic success following treatment with OP-1 Putty for an accurate assessment of overall patient success.

Therefore, this extension study protocol prospectively collected follow-up CT scans in as many patients as possible in both arms of the Pivotal IDE study. All patients were at least 3.5 years post procedure with some out as far as 5.5 years (mean 4.4 years).

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

In addition to CT assessments, all patients enrolled in this study were brought back for re-assessments of all clinical parameters including ODI assessments, neurological testing, surgical retreatment (i.e., revision, removal, supplemental fixation or reoperation to promote fusion) at the original treated level, as well as flexion and extension plain films for evaluation of angulation and translation. Serum was also collected for assessment of OP-1 immunogenicity at the follow-up visit in patients who were antibody positive at their last recorded visit in the original Pivotal IDE. Finally, the safety of OP-1 Putty was further supported by capturing follow-up from on-going adverse events (AE) and occurrence of new serious adverse events (SAE) and new medical history/physical findings since the last Pivotal IDE study visit.

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

8. STUDY OBJECTIVES

The objective of this prospective data collection was to evaluate the long-term safety and durable efficacy of OP-1 Putty as a replacement for autograft in patients undergoing posterolateral spinal fusion.

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

9. INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN

This study was a prospective data collection at a single visit 36+ months post-treatment of patients from the Pivotal IDE study for the purpose of obtaining additional efficacy and safety data on as many patients as possible treated in the Pivotal IDE study.

Stryker Biotech attempted to contact all eligible patients for participation in the study. The number of eligible patients (excludes deaths and retreatment failures) from the Pivotal IDE study is shown in the following table.

Pivotal IDE Study: Number of Eligible Patients

Treatment Group	Treated	Deaths*	Retreatments*	Eligible for Follow-up
OP-1 Putty	208	7	18	183
Autograft	87	4	8	74

*Includes all deaths or retreatments reported during the Pivotal IDE study (i.e., may include deaths/retreatments after 24 months)

9.2 DESCRIPTION AND DISCUSSION OF THE DESIGN AND CHOICE OF CONTROL

The objective of the study was to evaluate the long-term safety and durable efficacy of OP-1 Putty as a replacement for autograft in patients undergoing posterolateral spinal fusion. A product with effectiveness similar to autograft, but that avoids the pain and morbidity associated with iliac crest bone harvest, is clinically desirable. The control group consisted of patients who received autograft. This was considered appropriate, as autograft is the current standard of care for spinal fusion.

9.3 SELECTION OF STUDY POPULATION

All patients who participated in Pivotal IDE S01-01US, and who had not died or been retreatment failures during the Pivotal IDE, were eligible for participation in this extension study. Stryker Biotech attempted to contact all eligible patients for participation in the study.

9.3.1 Inclusion Criteria

To be eligible for study participation, a patient must have met all of the following criteria:

1. The patient was treated in Stryker Biotech clinical protocol S01-01US (Pivotal IDE study) and was not a retreatment failure at the time of completion of the Pivotal IDE study.

2. The patient or legal guardian was willing and able to understand, sign and date the study-specific Patient Informed Consent, which had been approved by the Institutional Review Board (IRB).
3. The patient agreed to complete the necessary clinical and radiographic evaluations. Radiographic evaluations were not required if the patient was pregnant.

9.3.2 Exclusion Criteria

There were no exclusion criteria for participation in this study. Patients who died subsequent to the Pivotal IDE study S01-01US were considered missing for analyses of data at 36+ months.

9.3.3 Removal of Patients from Therapy or Assessment

This study constituted a single office visit. Patients who agreed to participate in this follow-up study were free to decline the radiographic assessments or clinical evaluations associated with the single visit.

9.4 TREATMENTS

9.4.1 Treatments Administered

No treatment was administered in this follow-up study. Treatment had been administered under the Pivotal IDE S01-01US. Under Pivotal IDE S01-01US, all patients received posterior decompression with concomitant posterolateral intertransverse process arthrodesis. Multiple-level decompression was permitted, however, only 1 level could be fused. The product under investigation (OP-1 Putty) or autogenous bone graft from the iliac crest was implanted, according to the randomization schedule, using standard surgical procedures for lumbar spinal fusion.

9.4.2 Identity of Investigational Product

The Investigational product evaluated in this study was OP-1 Putty. OP-1 Putty is composed of recombinant human Osteogenic Protein-1 (rhOP-1), Type I bovine bone collagen matrix and a putty additive of carboxymethylcellulose (CMC) sodium, an anionic cellulose derivative, which yields a product with putty-like consistency.

As described in the study report for S01-01US, two product units of OP-1 Putty were provided for each patient randomized to the OP-1 Putty group, each consisting of 2 components:

- A large vial containing a sterile dry powder consisting of 3.5 mg of human recombinant Osteogenic Protein-1 (OP-1) in 1 g of collagen matrix
- A small vial containing the putty additive consisting of a sterile dry powder composed of 230 mg CMC.

For the OP-1 Putty arm, 1 product unit had been used during Pivotal IDE S01-01US on each side of the spine at the level of fusion, i.e., 2 product units per patient.

9.4.3 Method of Assigning Treatment

No treatment was assigned in this study which involves prospective data collection at a single visit 36+ months after surgery for all eligible patients who had participated in Pivotal IDE S01-01US.

In Pivotal IDE S01-01US, patients were randomly assigned to receive either OP-1 Putty or autograft. The randomization scheme was at the ratio of 2:1 (OP-1 Putty: autograft). Details regarding randomization have previously been presented in CSR S01-01US.

9.4.4 Blinding

No treatment was assigned in this study, which involves prospective data collection at a single visit 36+ months after surgery for all eligible patients who had participated in Pivotal IDE S01-01US.

To minimize bias in the current study, the radiographic outcomes and neurologic success determinations were evaluated by reviewers who were blinded to treatment group assignments and who had not previously been involved in Pivotal IDE S01-01US.

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 Efficacy and Safety Measurements Assessed and Study Schedule

Efficacy measurements collected in this extension study at 36+ months included the following:

- Radiographic success defined as: Presence of bone assessed by CT scans at 36+ months, and angulation of $\leq 5^\circ$ * and translational movement of ≤ 3 mm* demonstrated on flexion/extension radiographs at 36+ months of the affected level. Presence of bridging bone and location of bone were also evaluated.
- ODI improvement of at least 20% from the pre-treatment visit.
- Incidence of retreatment. (The term retreatment refers to a revision, removal, supplemental fixation, or reoperation intended to promote fusion at the treated level).
- Incidence of serious device-related adverse events occurring subsequent to Pivotal IDE S01-01US.
- Incidence of decreases in neurological status at the final examination from the preoperative evaluation, unless the decrease was due to a concurrent medical condition. Decreases in neurological status due to a concurrent medical condition were not considered failures.

Safety for this extension study was assessed principally based on the examination of: 1) 'ongoing' adverse events at the time of the last Pivotal IDE study visit, 2) new serious adverse events, 3) new medical conditions/physical findings since last study visit under Pivotal IDE S01-01US; 4) occurrence of any retreatment to the original treated spinal level; and 5) neurological status. In addition, all patients who were positive for anti-OP-1 antibodies at the 24 month visit in the Pivotal IDE S01-01US (or who missed the 24 month visit but were antibody positive at their last recorded visit) had serum samples taken at the 36+ month visit in this extension study. Patients who had neutralizing antibodies at any time prior to or at 36+ months were to be analyzed separately for effectiveness outcomes.

The following additional information was also collected for each patient in this extension study:

- Visual Analog Scale Results for Pain Assessment

* Rounded to the nearest integer.

- Donor Site Pain (autograft patients only)
- General Health Survey (SF-36)

The data collected in this extension study are being used with data collected in the Pivotal IDE S01-01US to calculate Overall Success, which is the primary efficacy measure for comparing the performance of OP-1 Putty to autograft. Overall Success is a composite endpoint. To be considered an Overall Success, patients must meet all of the following:

1. Improvement of at least 20% in the Oswestry Disability Index from baseline at 24 months
2. Absence of retreatment up to and including 36+ months
3. Absence of treatment-related serious adverse events at 24 months
4. Absence of a decrease in neurological status unless attributable to a concurrent medical condition or to the surgical procedure at 24 months.
5. Radiographic success at 36+ months consisting of all of the following:
 - Presence of bone formation as assessed by CT scan
 - Angulation $\leq 5^\circ$ on flexion/extension plain films radiographs of the affected level
 - Translational movement of ≤ 3 mm on flexion/extension plain films radiographs of the affected level

For patients who report a retreatment to the operative spinal level prior to the 36+ month assessment, the patient was designated as a failure in this study, regardless of the classification assigned during the Pivotal IDE study, and whether or not the patient participated in the current study. This is because retreatment at any time point is a critical component of overall success, and radiographic measures (CT scans and plain films) at 36+ months are meaningless if there has been a retreatment.

The current study, Protocol 06-UPLF-01, was designed as a single visit; however, the study assessments may have been completed in a single visit or multiple visits (e.g., clinical evaluations and radiographic evaluations may have been performed on separate dates) after obtaining informed consent. The patient's participation in this study was considered complete following collection of all specified evaluations.

9.5.2 Appropriateness of Measurements

The assessments performed were appropriate toward meeting the study objectives, and were consistent with the recommendations for key safety and effectiveness assessments presented in FDA's Guidance Document for Preparation of IDEs for Spinal Systems (Jan 2000). As described in section 11.3.1, the primary efficacy endpoint is the Overall Success rate for the mITT population, in which missing data were imputed. Success

regarding the improvement of ODI, absence of neurological compromise, and absence of serious treatment-related adverse events is determined at 24 months from the data collected in the original pivotal study, S01-01US. Success regarding radiographic evidence of fusion (presence of bone by CT scan, angular motion success and translational movement success by plain films) is based on the 36+ months data collected in this study (because CT scans were not taken at 24 months, and because plain films such as those taken at 24 months are now known to be invalid for assessing medial bone formation). Stryker Biotech acknowledges that it would be preferable to have all components of a composite measure assessed at the same time point; however, this was not possible for this study given that CT scans were not obtained at 24 months. Combining the 36+ radiographic assessment with the original 24 month clinical outcome assessments (with the exception of retreatment, discussed below) does not introduce bias because radiographic results would be expected to remain constant between 24 months and 36 months.²⁵ Therefore, a 36+ month radiographic assessment is an accurate representation of the expected results at 24 months and can be used in the modified Overall Success measure. Success regarding absence of retreatment is also based on the 36+ months data, because retreatment at any time point is a critical component of overall success, and because radiographic results at 36+ months would not be meaningful if a patient had been retreated at any time prior to the 36+ month visit.

9.5.3 Primary Efficacy Variable

The primary efficacy variable is overall success rate at 24 months (using the radiographic and retreatment data at 36+ months collected under this extension study) in the OP-1 Putty and the autograft groups. The components of the primary endpoint for this study are the same as the original study except for substituting a more sensitive and specific measure of new bone formation, CT scan, instead of plain x-rays.

9.6 DATA QUALITY ASSURANCE

Stryker Biotech, as the Sponsor, was responsible for the conduct of this study.

9.6.1 Site Training

Prior to the initiation of the study, the sponsor or sponsor's representative conducted an orientation in order to train the Investigator and/or the Investigator's designee in the protocol as well as appropriate use and completion of all patient Case Report Forms (CRFs) utilized in the study. All communications with the site, concerning this training,

were documented by the sponsor or delegate and maintained as part of the sponsor's study files.

9.6.2 Data Monitoring

All submitted CRFs were reviewed by trained, experienced clinical monitors for completeness, accuracy, and any evidence of unforeseen patient risk. Any issue concerning incomplete or discrepant data was resolved by documented clarification/correction communication with the site. Accuracy of submitted data was verified during monitoring site visits.

9.6.3 Data Management

Data entry, data cleaning, and statistical analyses were performed by Abt Associates Clinical Trials (Abt), a contract research organization located in Lexington, MA. Abt followed applicable quality control procedures regarding the database, statistical analysis plan (SAP), analyses, and report writing.

9.7 PROTOCOL-SPECIFIED STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

9.7.1 Statistical and Analytical Plans

The statistical analyses described here reflect those in the SAP. A description of the changes to statistical analyses as specified in the SAP may be found in Section 9.6. The SAP for the study is provided in Section 16.1.9. All summary tables and listings were produced and all statistical analyses were performed using the SAS[®] statistical software system.

Continuous variables were summarized using descriptive statistics, specifically the mean, median, standard deviation, minimum, and maximum. Categorical variables were summarized using frequencies and percentages.

Inferential tests were performed at the 5% level of significance. All *P-values* were rounded to 3 decimal places. If a rounded p-value was 0.000 (i.e., $P\text{-value} < 0.0005$), then this was presented as a p-value of <0.001 .

All data entered into the database were displayed in data listings.

9.7.1.1 Hypothesis Testing

The null hypothesis for this study is the same as for the Pivotal IDE study, specifically that the difference between the success rate in the autograft treatment group (P_A) and the success rate in the OP-1 Putty treatment group (P_O) is greater than or equal to the non-inferiority margin δ_p ($P_A - P_O \geq \delta_p$). Likewise, the alternative hypothesis for this study is the same as for the Pivotal IDE study, specifically that this difference is less than δ_p ($P_A - P_O < \delta_p$).

The following table summarizes which analyses have been tested for non-inferiority.

Protocol 06-UPLF-001 Post-text Table (Section 14.2)	Title
S.3.1.A	Overall Success Rate – mITT Population
S.3.3	Overall Success Rate with Test of Non-inferiority Using Equivalence Limit of 0.10 – mITT Population

9.7.1.2 Populations for Statistical Analyses

Three populations were identified for statistical analyses:

- Modified Intent-to-Treat Population:

The modified intent-to-treat (mITT) population includes all patients who were randomized in the Pivotal IDE study and had at least one post-treatment visit during that study. All efficacy analyses were conducted on the mITT population.

- Supplemental Per Protocol Population

The supplemental per protocol (SPP) population includes all OP-1 Putty or autograft treated patients who were in the per protocol population of the Pivotal IDE study and who had radiographic success measured at 36+ months. Analysis of overall patient success was repeated on the supplemental per protocol population using descriptive statistics to aid in the interpretation of the primary effectiveness analysis of the mITT population. All other efficacy analyses were also repeated on the supplemental per protocol population unless indicated otherwise.

- Safety Population

The safety population includes all patients who were treated using either OP-1 Putty or autograft in the Pivotal IDE study. The safety analyses will be based on the safety population.

9.7.1.3 Non-Response Bias

Baseline characteristics and select outcome criteria (presence of bone on 9 month CT, and 24-month overall success during Pivotal IDE study) were to be tabulated, by treatment group, stratified by participation status in the current study

9.7.1.4 Demographic and Baseline Characteristics

Baseline characteristics are summarized in the Pivotal IDE study, were not to be reanalyzed for this study.

9.7.1.5 Analysis of Efficacy

9.7.1.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint of this study is the overall success rate for the mITT population (missing values imputed) at 24 months, but substituting radiographic success at 36+ months (based on 36+ month CT scans for presence of bone and 36+ month flexion/extension plain films for angulation and translation) for radiographic success at 24 months (based on 24 month plain films for presence of bone, angulation and translation). All values are from the Pivotal IDE study, with the exception of the 36+ month radiographic data and retreatment data, which are from the current study.

A patient was to be considered an overall success if all five of the following components are met:

- 1) Radiographic success defined as meeting all three of the following conditions:
 - Presence of bone formation on CT at 36+ months
 - Angulation of $\leq 5^\circ$ at 36+ months via plain film
 - Translational movement of ≤ 3 mm at 36+ months assessed by plain film
- 2) Oswestry Disability Index improvement of at least 20% from the pre-treatment visit at 24 months
- 3) No retreatments up to and including 36+ months.

The term retreatment refers to a revision, removal, supplemental fixation, or reoperation intended to promote fusion at the treated level. Any patient who experienced a retreatment is considered a failure, regardless of the timing of the procedure. Patients who were a success at 24 months based upon the Pivotal IDE results, but who subsequently experienced a retreatment, will have their 24-month assessment reclassified as failure.

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

- 4) The absence of serious treatment-related adverse events before or at 24 months.
- 5) Patient was considered an overall neurological success at 24 months in the absence of a decrease in neurological status, unless attributable to a concurrent medical condition or to the surgical procedure.

Any patients who did not meet all the success criteria were to be classified as failures for the Overall Success study analysis.

The number and percentage of mITT patients in each treatment group with missing data and requiring imputation for overall success rate was to be tabulated in order to assess the potential impact of missing data for the mITT population. Fisher's exact test was to be used to test the difference in number of patients with missing data between treatment groups.

9.7.1.5.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints for the study are overall success with bridging bone via CT at 36+ months, and translational movement and angulation at 36+ months via plain film.

Additionally, although not specified in the protocol for Study 06-UPLF-01, for consistency with analyses performed for the Pivotal IDE study, the following secondary efficacy endpoints are being defined.

- 36+ month overall radiographic success. Only the analyses based on the mITT population will impute for missing data.
- 36+ month overall radiographic success with presence of bridging bone
- 36+ month success rate based on Oswestry disability score
- 36+ month success rate based on absence of retreatment
- 36+ month success rate based on absence of serious treatment-related adverse events
- 36+ month overall neurological success rate
- Presence of bone at operated level based on the CT scans at 36+ months
- Presence of bridging bone at operated level based on the CT scans at 36+ months
- Location of bone at operated level based on the CT scans at 36+ months
- Degree of angular motion at 36+ months
- Translational movement at 36+ months

- Change from baseline in Oswestry Disability Index at 36+ months.

All of the bulleted items above that involve success rates are calculated with patients who were retreatment failures subsequent to the posterolateral fusion set to failure. All other bulleted items that are not presentations of success rates are calculated with patients who were retreatment failures subsequent to the posterolateral fusion excluded.

9.7.1.6 Safety Analysis

Safety for this study was to be assessed principally based on the examination of: 1) 'ongoing' adverse events at the time of the last Pivotal IDE study visit, 2) new serious adverse events, 3) new medical conditions/physical finding since last IDE study visit; 4) occurrence of any retreatment to the original treated spinal level; and 5) neurological status.

9.7.1.6.1 Adverse Events

Adverse events collected in this study were to consist of new medical conditions/physical findings and new serious adverse events. New serious adverse events and new medical history and physical findings were coded using the MedDRA coding dictionary. Events were determined to be serious based upon the investigator's assessment, as recorded on the CRF. Additionally, there was follow-up on adverse events that were ongoing as of the time of the Pivotal study completion.

Details regarding ongoing adverse events, new serious adverse events, and new medical histories/physical findings are presented in the listings.

9.7.1.6.2 Analysis of Retirements

The following were to be tabulated for retirements:

- The number and percent of patients who had a retreatment subsequent to S01-01US as reported in extension study 06-UPLF-01
- The type of retreatment
- Hospitalization status, and whether the event was performed inpatient or outpatient

Additionally, data on retreatment were to be tabulated by time interval. Details of all surgical events other than retirements are presented in data listings only.

9.7.1.6.3 Neurological Status

The neurological status of each patient was to be summarized preoperatively (baseline), and at the 36+ month follow-up visits. Tables were to report the percent of patients in each treatment group who experienced abnormalities in muscle strength, reflexes, straight leg raises, and sensory evaluation. Overall neurological success is defined in Section 11.3.2.4.

9.7.1.7 Additional Analysis

The following additional analyses were also to be performed:

- Visual Analog Scale Results for Pain Assessment:

The visual analog scale for pain was summarized preoperatively (baseline) and at the 36+ month follow-up visit. Descriptive statistics were presented for actual value and change from baseline to the post-baseline time point. Difference in change from baseline was examined using the two-sample t-test to test a difference in mean between treatment groups. Additionally, change from baseline was examined using one-sample t-test to test the mean change within each treatment group.

- Donor Site Pain (autograft patients only)

The donor site pain was summarized at the 36+ month follow-up visit for autograft patients only. The donor site pain was rated using both visual analog scale and pain status (none, mild, moderate, severe). Descriptive statistics were presented for the visual analog scale at baseline and 36+ months. Pain status was summarized by frequencies and percentages for each category.

- General Health Survey (SF-36)

The General Health Survey Scale was summarized preoperatively and at the 36+ month follow-up visits. If a subscale of SF-36 was missing an item, then means of the items in the subscale for that patient were used to impute the missing value. This was only done if fewer than one-half of the items in the subscale are missing. Descriptive statistics were presented for the actual value and change from baseline to the post-baseline time point for PCS and MCS, as well as for each of the 8 scales, by treatment. The changes from baseline were examined using Wilcoxon rank-sum test to test the differences in means between treatment groups.

9.7.1.8 Immunology

Serum samples have been analyzed for patients who were positive for anti-OP-1 antibodies at the 24-month follow-up visit, and for patients who did not complete the 24-month follow-up visit but were antibody positive at their last recorded visit. Among this subset of patients, the number and percent of patients with neutralizing antibodies at 36+ months were to be reported, and those with neutralizing antibodies at 36+ months were to be analyzed separately for safety and effectiveness outcomes.

9.8 CHANGE FROM THE PROTOCOL AND PLANNED ANALYSES

9.8.1 Changes in the Conduct of the Radiographic Evaluation

There were two changes to the planned radiographic evaluation:

First, according to the radiographic protocol, 36+ month digitized scout films (two dimensional x-ray images similar to plain x-rays) derived from the 36+ month CT scan images were to be evaluated and compared to both 24 month plain films and 36+ month CT scan results to further investigate whether the CT scan offers improved sensitivity in assessing new bone formation in this patient population. However, because not all CT scan equipment at all study sites contained an algorithm needed to capture the scout films, the images were not captured by the radiographic imaging center. Therefore, analysis of the 36+ month digitized scout films was not performed.

Second, according to the radiographic assessment protocol, 36+ month and 9-month CT scans as well as 36+ month angulation and translation success were reviewed and scored by two blinded spine surgeons who had no other involvement in the study and no prior knowledge of study results. If there was disagreement between the two reviewers, then a third reviewer (adjudicating reviewer) independently read the scans, with success or failure being determined by the majority of reviewers. Harvinder S. Sandhu, MD, was originally selected as the adjudicating reviewer. After completing approximately 75% of the adjudicating reviews, Dr. Sandhu was suddenly prevented from continuing with his duties as adjudicating reviewer due to personal circumstances. The duties of adjudicating reviewer were then taken over by Christian Fras, MD. Therefore, the adjudicating review was actually conducted by two reviewers: Dr. Sandhu and Dr. Fras. All of Dr. Sandhu's evaluations were entered into the study database, and Dr. Fras conducted evaluations only on those cases that Dr. Sandhu had not evaluated (i.e., Dr. Fras's evaluations did not replace any evaluations previously done by Dr. Sandhu.) Both reviewers qualification are presented in Section 16.1.4.

9.8.2 Changes in Collection of Serious Adverse Events

The protocol called for reporting of any new treatment emergent serious adverse events. Several sites reported any new adverse event, whether serious or not. Therefore, all new treatment emergent adverse events that were reported to Stryker Biotech in this extension study, whether serious (as requested by the protocol) or not serious, are presented in Listing 9 in Section 16.2.

9.8.3 Changes in Planned Statistical Analyses

9.8.3.1 Changes in the Conduct of the Radiographic Evaluation

There were two changes to the planned radiographic evaluation:

First, according to the radiographic protocol, 36+ month digitized scout films (two dimensional x-ray images similar to plain x-rays) derived from the 36+ month CT scan images were to be evaluated and compared to both 24 month plain films and 36+ month CT scan results to further investigate whether the CT scan offers improved sensitivity in assessing new bone formation in this patient population. However, because not all CT scan equipment at all study sites contained an algorithm needed to capture the scout films, the images were not captured by the radiographic imaging center. Therefore, analysis of the 36+ month digitized scout films was not performed.

Second, according to the radiographic assessment protocol, 36+ month and 9-month CT scans as well as 36+ month angulation and translation success were reviewed and scored by two blinded spine surgeons who had no other involvement in the study and no prior knowledge of study results. If there was disagreement between the two reviewers, then a third reviewer (adjudicating reviewer) independently read the scans, with success or failure being determined by the majority of reviewers. Harvinder S. Sandhu, MD, was originally selected as the adjudicating reviewer. After completing approximately 75% of the adjudicating reviews, Dr. Sandhu was suddenly prevented from continuing with his duties as adjudicating reviewer due to personal circumstances. The duties of adjudicating reviewer were then taken over by Christian Fras, MD. Therefore, the adjudicating review was actually conducted by two reviewers: Dr. Sandhu and Dr. Fras. All of Dr. Sandhu's evaluations were entered into the study database, and Dr. Fras conducted evaluations only on those cases that Dr. Sandhu had not evaluated (i.e., Dr. Fras's evaluations did not replace any evaluations previously done by Dr. Sandhu.) Both reviewers qualification are presented in Section 16.1.4.

9.8.4 Changes in Collection of Serious Adverse Events

The protocol called for reporting of any new treatment emergent serious adverse events. Several sites reported any new adverse event, whether serious or not. Therefore, all new treatment emergent adverse events that were reported to Stryker Biotech in this extension study, whether serious (as requested by the protocol) or not serious, are presented in Listing 9 in Section 16.2.

9.8.5 Changes in Planned Statistical Analyses

After completion of the SAP for this study, but prior to database lock, it was felt that the supplemental per protocol population should also include all retreatment failures during or subsequent to the Pivotal IDE study. Additionally, for all components of overall success, rather than excluding retreatment failures from analyses, retreatment failures were considered to be failures. All changes to analyses specified in the SAP, which were made prior to database lock are summarized in Table 2 under the column “Criteria Specified Post SAP but Prior to Database Lock”.

For ease of interpretation, the primary efficacy variable was reanalyzed based directly upon the percentage rather than its angular scale transformation. All additional post hoc analyses are described in Table 2 under the column “Criteria Used in Analyses for Protocol 06-UPLF-001 – Post Database Lock”.

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty® for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (Extension to Pivotal Study S01-01US)

Table 2: Changes in Planned Statistical Analyses

Issue	Criteria Specified in Statistical Analysis Plan for Protocol 06-UPLF-001	Criteria Specified Post SAP but Prior to Database Lock	Criteria Used in Analyses for Protocol 06-UPLF-001 – Post Database Lock	Protocol 06-UPLF-001 Post-text Tables
Definition of SPP	All OP-1 Putty or autograft treated patients who were in the per protocol population of the Pivotal IDE study and who had radiographic success measured at 36+ months	Added that all retreatment failures during or subsequent to Pivotal IDE study would be considered as part of the SPP		1.2 All SPP tables
Patient status by time in study	Data to be presented cumulatively across both studies, in addition to 06-UPLF-001 alone	Analyses not presented		1.3.2
Demographics and baseline characteristics	No analyses specified in SAP	Parameters presented in S01-01US to be presented, by treatment group, separately for patients eligible for 06-UPLF-001 and patients enrolled in 06-UPLF-001		1.4
Success criteria by participation status in study	Presence of Bone on 9-month CT and Prior Overall Success at 24 months were to be tabulated for patients with at least one follow-up assessment in 06-UPLF-001 and for patients with no follow-up assessments in 06-UPLF-001	Success criteria were tabulated for patients eligible for 06-UPLF-001 in lieu of patients with no follow-up assessments in 06-UPLF-001.		2

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty® for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (Extension to Pivotal Study S01-01US)

Issue	Criteria Specified in Statistical Analysis Plan for Protocol 06-UPLF-001	Criteria Specified Post SAP but Prior to Database Lock	Criteria Used in Analyses for Protocol 06-UPLF-001 – Post Database Lock	Protocol 06-UPLF-001 Post-text Tables
Overall success rate – with missing data not imputed	No inferential testing planned Analysis based on mITT population not specified in SAP		Overall 24 Month Success Rate, non-imputed, summarized for mITT population. Fisher’s exact test used to test difference in proportions of successes between treatment groups	3.1.B, 3.1.B.2 3.5.A, 3.5.B
Overall success rate – missing data imputed	Analyses to be done on angular scale		Analyses also done on percentage scale	3.3
Overall success rate by size of center, gender, and age groups	No inferential testing planned		Fisher’s exact test used to test difference in proportions of successes between treatment groups	3.2 3.4.A, 3.4.B
ODI success rate	Retreatment failures through 36+ months were excluded from analyses at 36+ months ODI success criteria set at 20% Analyses of 24-month data not specified	For 36+ month analyses retreatment failures were set to ODI failures	For 24-month analyses, retreatment failures through 36+ months were set to ODI failures Fisher’s exact test calculated to test difference between treatment groups in proportion of patients considered success Definition of ODI success criteria presented at 20%, 30%, 50%, 80%, and 100% Patients with retreatment subsequent to the PLF through 24 month visit only, are set to ODI failures for 24 month reanalysis using 20% criteria	6.A, 6B 6A.adhoc.1A, 6B.adhoc.1A 6.A.adhoc.3 through 6.A.adhoc.9 6.B.adhoc.3 through 6.B.adhoc.9 5.2.2.adhoc

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

Issue	Criteria Specified in Statistical Analysis Plan for Protocol 06-UPLF-001	Criteria Specified Post SAP but Prior to Database Lock	Criteria Used in Analyses for Protocol 06-UPLF-001 – Post Database Lock	Protocol 06-UPLF-001 Post-text Tables
Overall success rate based on retreatment	No inferential testing specified		Fisher's exact test calculated to test difference between treatment groups in proportion of patients considered success	7.A, 7.B
Success rate based on absence of serious treatment-related adverse events	Retreatment failures through 36+ months were excluded from analyses at 36+ months Analyses of 24-month data not specified	For 36+ month analyses retreatment failures were set to SAE failures	For 24-month analyses, retreatment failures were set to SAE failures Fisher's exact test calculated to test difference between treatment groups in proportion of patients considered success Patients with retreatment subsequent to the PLF through 24 month visit only, are set to SAE failures for 24 months reanalysis	8.A., 8.B 5.4.2.adhoc
Overall neurological success rate	Retreatment failures through 36+ months were excluded from analyses at 36+ months Analyses of 24-month data not specified	For 36+ month analyses retreatment failures were set to neurological failures	For 24-month analyses, retreatment failures were set to neurological failures Fisher's exact test calculated to test difference between treatment groups in proportion of patients considered success Patients with retreatment subsequent to the PLF through 24 month visit only, are set to neurological failures for 24 months reanalysis	9.A, 9.B 5.5.2.adhoc

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty® for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

Issue	Criteria Specified in Statistical Analysis Plan for Protocol 06-UPLF-001	Criteria Specified Post SAP but Prior to Database Lock	Criteria Used in Analyses for Protocol 06-UPLF-001 – Post Database Lock	Protocol 06-UPLF-001 Post-text Tables
Presence of Bone Success Rate	Retreatment failures through 36+ months were excluded from analyses at 36+ months Analyses of 24-month data not specified	For 36+ month analyses retreatment failures were set to presence of bone failures	For 24-month analyses, retreatment failures were set to presence of bone failures Fisher’s exact test calculated to test difference between treatment groups in proportion of patients considered success Patients with retreatment subsequent to the PLF through 24 month visit only, are set to presence of bone failures for 24 months reanalysis	3.5.c, 3.5.d B.1.3.adhoc

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty® for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

Issue	Criteria Specified in Statistical Analysis Plan for Protocol 06-UPLF-001	Criteria Specified Post SAP but Prior to Database Lock	Criteria Used in Analyses for Protocol 06-UPLF-001 – Post Database Lock	Protocol 06-UPLF-001 Post-text Tables
Success outcomes by neutralizing antibody status	Patients with and without neutralizing antibodies during the current study were to be summarized by number and percentages of successes for each treatment group at 24 months and 36+ months		<p>Patients were considered to have neutralizing antibodies at 24 months if they experienced neutralizing antibodies any time since PLF surgery and prior to or at 24 months.</p> <p>No analyses at 36+ months performed</p> <p>Patients with retreatment subsequent to the PLF through 24 month visit only, are set to ODI failure, Presence of bone failure, SAE failure, and neurological failure for 24 months reanalysis</p>	24.4 24.4A.adhoc
36+ month overall radiographic success rate-mITT	Non-inferiority testing not specified in SAP		95% upper confidence bound for difference between angular-scale values corresponding to the success rates in the two treatment group was calculated, along with p-value based on one-sided two-sample test for non-inferiority in the angular scale with a non-inferiority margin of 0.14 (radians).	4.A

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty® for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (Extension to Pivotal Study S01-01US)

Issue	Criteria Specified in Statistical Analysis Plan for Protocol 06-UPLF-001	Criteria Specified Post SAP but Prior to Database Lock	Criteria Used in Analyses for Protocol 06-UPLF-001 – Post Database Lock	Protocol 06-UPLF-001 Post-text Tables
Angulation and translational movement success rates	Analyses not specified in SAP		Summarized based on 36+ month data for the mITT population, with retreatment subsequent to the PLF set to failure. Fisher's exact test calculated to test differences between treatment groups in proportion of patients considered success Patients with treatment subsequent to the PLF through 24-months set to failure for 24 month reanalysis	4.1, 4.2 B.1.1.adhoc, B1.2.adhoc
36+ month overall radiographic success rate – SPP	In SAP as Table S.4.B		Fisher's exact test calculated to test differences between treatment groups in proportion of patients considered success	4.3
36+ month overall radiographic success rate – mITT with missing data not imputed	Analyses not specified in SAP		36+ Month overall radiographic success rate calculated without imputing missing data Fisher's exact test calculated to test differences between treatment groups in proportion of patients considered success	4.3.A
36+ month overall radiographic success rate with presence of bridging bone	No inferential testing planned		Fisher's exact test calculated to test differences between treatment groups in proportion of patients considered success	5.A, 5.B
Location of bone	Analyses not		Patients with	10.3.adhoc

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

Issue	Criteria Specified in Statistical Analysis Plan for Protocol 06-UPLF-001	Criteria Specified Post SAP but Prior to Database Lock	Criteria Used in Analyses for Protocol 06-UPLF-001 – Post Database Lock	Protocol 06-UPLF-001 Post-text Tables
at operated level based on 36+ month CT for patients with no bone presence at 24 months	specified in SAP		retreatment subsequent to the PLF are excluded. Analyses done for the mITT population	
Presence of bone at operated level based on 9 month and 36+ month CT	Table S.12.1 specified in SAP		Change in table numbering only	S.12
Presence of bone based on 36+ month scout film vs. 24-month film of 36+ month CT	Table S.12.2 specified in SAP	No analyzed since scout film not available for analysis		N/A
Ongoing adverse events at last IDE visit by SOC and preferred term	No inferential statistics specified in SAP		p-values calculated for SOC terms reported by $\geq 5\%$ of patients in at least one treatment group, using Fisher's Exact test.	16.2
Ongoing AEs which became serious since last IDE visit by SOC and preferred term	Analyses not specified in SAP		New table. p-values calculated for SOC terms reported by $\geq 5\%$ of patients in at least one treatment group, using Fisher's Exact test.	16.3
New Treatment emergent serious adverse events by SOC and preferred Term	No inferential statistics specified in SAP		p-values calculated for SOC terms reported by $\geq 5\%$ of patients in at least one treatment group, using Fisher's Exact test.	17.1

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

Issue	Criteria Specified in Statistical Analysis Plan for Protocol 06-UPLF-001	Criteria Specified Post SAP but Prior to Database Lock	Criteria Used in Analyses for Protocol 06-UPLF-001 – Post Database Lock	Protocol 06-UPLF-001 Post-text Tables
New medical history or physical findings by SOC and preferred term	No inferential statistics specified in SAP		p-values calculated for SOC terms reported by >=5% of patients in at least one treatment group, using Fisher's Exact test.	18.1
New treatment-emergent serious adverse events by SOC, preferred term, and time since PLF	To be tabulated in Table S.17.4 for number (%) of patients	Combined treatment-emergent serious AE experience for studies S01-01US and 06-UPLF-001. Presented by treatment and at both patient and event level		17.4.A through 17.4.D
36+ month bridging bone agreement rate among primary reviewers	No analyses specified in SAP		For patients having bridging bone assessment completed by both primary reviewers, how often did both reviewers agree on presence of bridging bone, and when there was disagreement, what was location of bone?	T10.5 Adhoc
Mean percent change from ODI score from baseline at both 24- and 36+ month visits	No analyses specified in SAP		Summarize the ODI success criteria (mean percent change from baseline) at both 24 and 36+ month visits, by treatment	Odipercchg24, Odipercchg36
ODI change from baseline at 24 and 36+ months	Summary not presented in SAP		Data summarized at both time periods	15.5.Adhoc
36+ month bone	No analyses specified in SAP		Presence of bone at 36+ months for patients who were negative for bone at 24 months	T10.8.Adhoc T10.7.Adhoc T10.6.Adhoc

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty® for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

Issue	Criteria Specified in Statistical Analysis Plan for Protocol 06-UPLF-001	Criteria Specified Post SAP but Prior to Database Lock	Criteria Used in Analyses for Protocol 06-UPLF-001 – Post Database Lock	Protocol 06-UPLF-001 Post-text Tables
			36+ month bone location for patients who were bridging bone failures at 36+ months. Bone location at 36+ month bone presence	
36+ month ODI component scores by treatment and ODI success	No analyses specified in SAP		Done by mITT and SPP populations	Odichg.Adhoc
Presence of bone at operative level based on 36+ month CT	No analyses specified in SAP		Done by mITT and SPP populations	10.2.C.Adhoc 10.2.D.Adhoc
Surgical procedure characteristics	No analyses specified in SAP		Inferential statistics comparing treatment groups	13.Adhoc

10. STUDY PATIENTS

10.1 PATIENT DISPOSITION

Two hundred ninety five patients were enrolled and treated in the Pivotal IDE study S01-01US (208 for OP-1 and 87 for autograft), and 258 of these patients (183 for OP-1 Putty and 75 for autograft) had not been retreatment failures and had not died as of the database lock for S01-01US. Excluding one patient in the autograft group who had no post-baseline visit in pivotal study S01-01US, there were 257 patients identified as eligible for follow-up in the current extension study, 06-UPLF-01.

After receiving FDA approval for the 06-UPLF-01 protocol, and approval by all participating IRBs, Stryker Biotech made all reasonable attempts to contact the 257 patients identified as eligible for follow-up. The disposition of these 257 patients is summarized in Table 3:

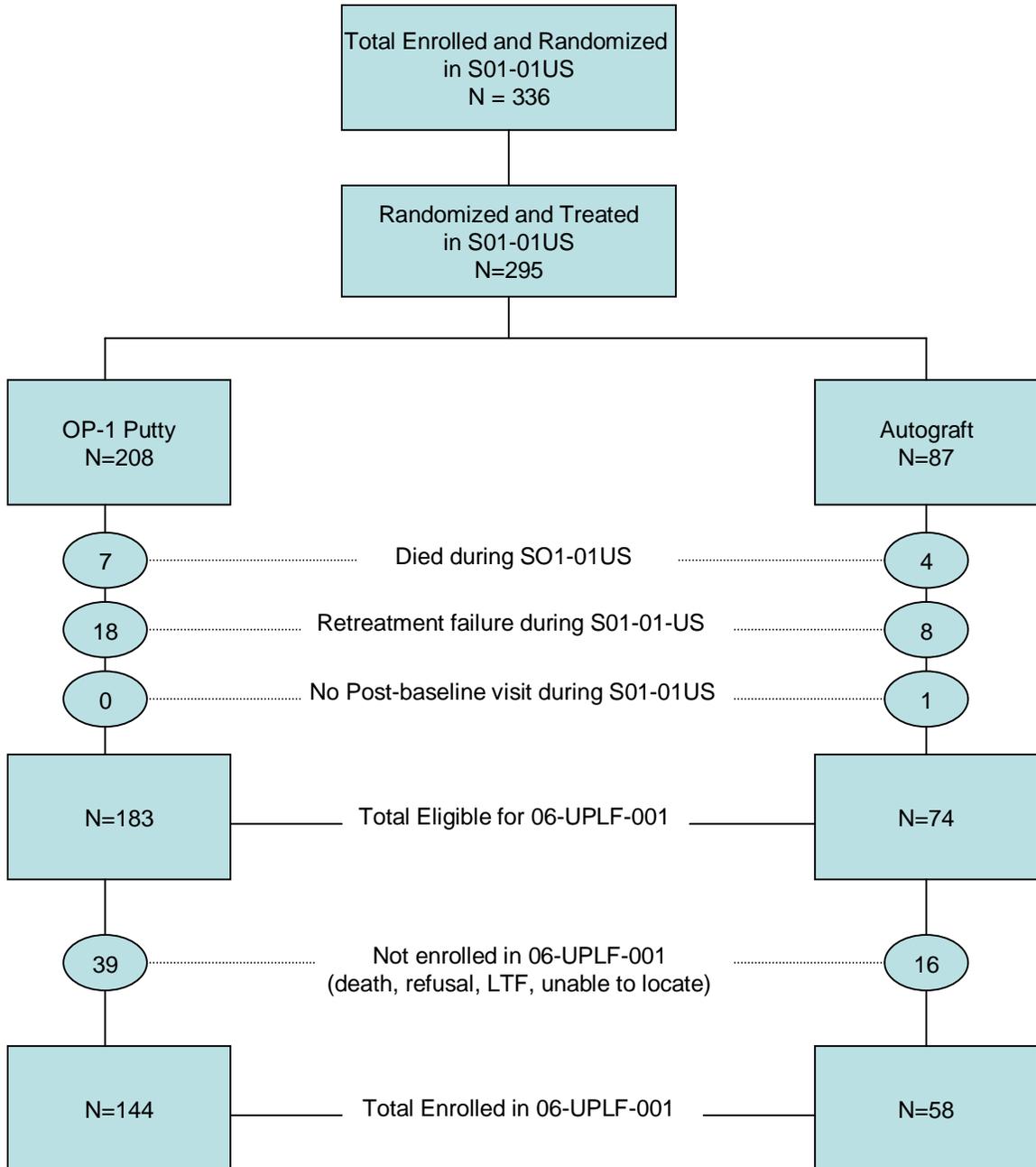
Table 3: Disposition of Patients Eligible for Follow-up in 06-UPLF-01

Parameter	Overall	OP-1 Putty	Autograft
Patients Eligible for 06-UPLF-01	257	183	74
Died subsequent to S01-01US	5	4	1
Refused to participate in 06-UPLF-01	23	16	7
Unable to locate	15	10	5
Site refused to participate in 06-UPLF-01	3	2	1
Other	9	7	2
Patients Enrolled in 06-UPLF-01	202	144	58

Source: Statistical Table S.1.1 in Section 14.1.

Of the 257 patients eligible for follow-up under 06-UPLF-01, 5 additional patients had died subsequent to S01-01US of causes unrelated to their study procedure. Stryker Biotech was successful in enrolling 202 of the 252 eligible patients (80.1%) who had not died subsequent to S01-01US (144 patients in the OP-1 Putty group and 58 patients in the autograft group), for the longer-term follow-up visit at 36+ months. See Figure 1 for an illustration of patient accounting from Pivotal IDE S01-01US through initiation of extension study 06-UPLF-01. (Source: Statistical Table S.1.1 in Section 14.1.)

Figure 1: Disposition of Patients in S01-01US and 06-UPLF-01



Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

The mean length of follow-up for the patients who participated in extension study 06-UPLF-01 was 1609 days (4.4 years), which was similar for the OP-1 Putty group (1599 days) and for the autograft group (1633 days). The range of follow up was from 3.7 years (1344 days) to 5.5 years (1995 days). (Source: Statistical Table S.1.3.1 in Section 14.1)

Some patients enrolled in 06-UPLF-01 were willing to provide only partial assessments for the extension study—for example, some patients were willing to complete the ODI questionnaire, but were unwilling to undergo another CT evaluation. Therefore, the number of patients represented in the analyses of the individual subcomponents of overall success (related to ODI, retreatment, serious adverse events, neurological compromise, and radiographic assessment) may differ from the total number of patients participating in 06-UPLF-01. Statistical Table S.1.3.2 in Section 14.1 presents the number of patients with full assessments and with partial assessments in 06-UPLF-01.

Table 4 displays the number of patients participating by time interval through the Pivotal IDE Study S01-01US and this extension study 06-UPLF-01.

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

Table 4: Patient accounting through 36+ Months, S01-01US and 06-UPL:F-01 (safety population)

	Operative^a (<28 Days)	6 Weeks (28-77 Days)	3 Months (78-152 Days)	6 Months (153-605 Days)	12 Months (306-670 Days)	24 Months (671- 1035 Days)	36+ Months (≥1036 Days)
OP-1 Putty							
Theoretical	208	208	208	208	208	208	208
Deaths (cumulative)	1	1	2	5	5	9	11
Failures (cumulative)	0	0	2	5	12	17	21
Expected	207	207	204	198	191	182	176
Actual ^b	23	201	195	195	187	176	140
% Follow-up ^c	11.1	97.1	95.6	98.5	97.9	96.7	79.5*
Autograft							
Theoretical	87	87	87	87	87	87	87
Deaths (cumulative)	0	0	0	0	2	4	5
Failures (cumulative)	0	0	0	0	8	10	11
Expected	87	87	87	87	77	73	71
Actual ^b	10	83	79	83	72	61	55
% Follow-up ^c	11.5	95.4	90.8	95.4	93.5	83.6	77.5*

(a) Occurring on or after the day of surgery.

(b) Two of the OP-1 deaths occurred during S01-01US but were not reported until the 36+ month visit.

(c) Patients with any assessment or visit data occurring within window time frame. Patient 1210 was flagged as enrolled at 36+ month (based on inclusion/exclusion criteria), but was excluded in actual counts because there were no assessments in 06-UPLF-001. For the Actual returned patients that died or had a retreatment failure occur during the same time period as their visit, they were only counted in the Death or Failures category.

* Percent follow-up rates are not the same as the percentage of patients for whom 36+ month follow-up assessments were collected, because retreatment failures were subtracted from follow-up rates.

Source: Statistical Table S.1.1.1.1 in Section 14.1

While the follow-up rate for visits at 36+ months is 79% (195/247) overall, the follow-up rate for assessments at 36+ months is 80% overall (represented by the number of patients who enrolled in 06-UPLF-01 divided by the number of patients eligible to enroll in 06-UPLF-01: 202/252). Stryker Biotech exhausted all reasonable means to contact all patients eligible for participation in 06-UPLF-01. Stryker Biotech contacted patients at their last known addresses. If patients could not be reached at their last known addresses, family members were contacted (if family contact information was available), credit bureau search engines were used, and/or Internet people search reports were obtained to

help locate patients. Primary care physicians were also asked if they had more current contact information. Stryker Biotech provided modest compensation to participating patients to cover personal expenses associated with the study visit (parking fees, lost wages, caretaker expenses, etc.) and reimbursed patients for extended travel costs and all medical costs associated with study evaluations. Stryker Biotech also allowed patients who had relocated since the pivotal trial to return to a geographically closer site for the follow-up visit.

For those patients who were eligible to participate in this extension study but did not participate, the reasons for non-participation are shown in Statistical Table S.1.1 in Section 14.1, and are presented in narratives in Section 14.3. The reasons for non-participation are summarized below:

- Five patients had died subsequent to closure of the database for S01-01US of causes believed to be unrelated to the study procedure (patient IDs: 1102, 1506, 2307, 2406, 3107). Four were from the OP-1 Putty group, and one was from the autograft group. These patients could not be enrolled in 06-UPLF-01, but anecdotal information collected during the follow-up attempts has been reported.
- 23 patients refused to participate and 9 patients were not enrolled for other reasons. The reasons for refusal or other non-participation are provided for each patient in Section 14.3, but fall into several main categories:
 - Reason not given (OP-1 Putty = 6, autograft = 3)
 - Wanted more money or was concerned with cost (OP-1 Putty 3, autograft = 2)
 - Could not take time from work or other domestic responsibilities (caring for dependents) (OP-1 Putty = 3)
 - Unable to participate due to illness or injury not related to study procedure (OP-1 Putty = 8, autograft = 3)
 - Dissatisfied with poor outcome from the study procedure (autograft = 1)
 - Difficulty traveling (OP-1 Putty = 1)
 - Patient withdrew during pivotal study S01-01US due to randomization assignment (autograft = 1)
 - Informed Consent Irregularity: Patient completed questionnaire before completing informed consent process, (OP-1 Putty = 1)
- Three patients (patient IDs 1801, 1802, 1803) were from the one site that refused to participate in the extension study. This site determined that the low enrollment

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

at their site (3 patients) did not justify the additional work associated with study participation. Two of these patients were from the OP-1 Putty group, and one was from the autograft group.

- Fifteen patients could not be located (patient IDs 1111, 1313, 1314, 1328, 2502, 2517, 2522, 4003, 4101, 4405, 4110, 4114, 4706, 5005, 5206). Ten were from the OP-1 Putty group, and five were from the autograft group.

Narratives for each patient who was a retreatment failure subsequent to S01-01US are provided in Section 14.2. Narratives for patients lost to follow-up are provided in Section 14.3.

Stryker Biotech's high follow-up rate at this long-term 36+ month interval is strong, and Stryker Biotech believes that higher follow-up rates would be unexpected for this study considering the following factors:

1. Age-related deterioration of general health: The study population for the pivotal IDE, S01-01US, was an elderly patient population (mean age at surgery of 68 for OP-1 and 69 for autograft), and patients are now 3.7 – 5.5 years older than when S01-01-US began. Several patients have experienced significant deterioration of general health attributable to aging, new diseases, or pre-existing disease progression, and were unwilling or unable to fulfill the requirements of this extension protocol.
2. Patient relocation: It had been 1.5 – 2.5 years since patients were last contacted for pivotal IDE S01-01US, and some patients were no longer at their last known addresses and had left no forwarding addresses. Many patients were at retirement age and likely to relocate.
3. Time: Stryker Biotech had six months to complete this data collection and analysis effort. Stryker Biotech received FDA's approval to conduct this extension study on May 15, 2007, and immediately obtained site approvals to contact patients. Patients were contacted and consented, and were scheduled for evaluations through August 10, 2007, after which time all data were collected, prepared for analysis, and compiled and analyzed in support of the PMA Amendment, due to FDA on November 30, 2007.

Although a small percentage of the total eligible population was lost to follow-up, the patient population that did return for the 36+ month assessments compares very well to the original pivotal study patient population in all key demographics and key outcome variables at 24 months as shown in Table 6. The high follow-up rate and the balance that has been maintained between the patients who returned for the extension study and the patients in the original pivotal study with regard to key demographics, overall success at

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

24 months (as calculated in the pivotal IDE), and presence of bone at 9 months by CT scan (as assessed in pivotal IDE), provides confidence that the data collected in the extension study 06-UPLF-01 are representative of the overall population from the Pivotal IDE S01-01US.

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

10.2 PROTOCOL DEVIATIONS

The current study involved a single follow-up visit at 36+ months. Therefore, no violations related to randomization, surgery, or rehabilitation were possible.

Deviations from the protocol regarding the reporting of adverse events are described in Section 9.8.2. Changes to the radiographic assessment methods are described in Section 9.8.1.

11. EFFICACY EVALUATION

11.1 DATA SETS ANALYZED

Table 5 presents populations used for SAP analysis. Populations were defined in the SAP as follows:

- *Safety*: all patients who were treated using either OP-1 Putty or autograft in the Pivotal IDE study. The safety analyses are based on the safety population.
- *Modified intent-to-treat (mITT)*: all patients who were randomized to the Pivotal IDE study and had at least one post-treatment visit during that study. All efficacy analyses are conducted on the mITT population.
- *Supplemental Per Protocol (SPP)*: All OP-1 Putty or autograft treated patients who were in the per protocol population of the Pivotal IDE study and who had radiographic success measured at 36+ months, or who were retreatment failures at any time up to and including 36+ months. Analysis of overall patient success is repeated on the supplemental per protocol population using descriptive statistics to aid in the interpretation of the primary efficacy analysis of the mITT population. All other efficacy analyses are also repeated on the supplemental per protocol population, unless indicated otherwise.

Table 5: Study Populations for SAP Analyses

Parameter	Number (%) of Patients		
	Overall	OP-1 Putty	Autograft
All patients enrolled in Pivotal Study S01-01US	295 (100.0)	208 (100.0)	87 (100.0)
Safety Population	295 (100.0)	208 (100.0)	87 (100.0)
Modified ITT Population	293 (99.3)	207 (99.5)	86 (98.9)
Per Protocol Population	289 (98.0)	204 (98.1)	85 (97.7)
All patients enrolled in Extension Study 06-UPLF-01	202 (68.5)	144 (69.2)	58 (66.7)
Safety Population (1) (subset of S01-01US Safety population who enrolled in 06-UPLF-01)	202 (68.5)	144 (69.2)	58 (66.7)
mITT Population (1) (subset of S01-01US mITT population who enrolled in (06-UPLF-01)	202 (68.5)	144 (69.2)	58 (66.7)
Supplemental Per Protocol Population (1,2)	211 (71.5)	150 (72.1)	61 (70.1)

Source: Statistical Table S.1.2 in Section 14.1

(1) Percentages are based on total number of patients enrolled in Pivotal IDE study (S01-01US) for each treatment group or overall, as appropriate.

(2) Supplemental Per Protocol Population defined as subset of S01-01US Per Protocol Population who have radiographic data in 06-UPLF-001 or who were a retreatment failure in S01-01US.

11.2 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

The OP-1 Putty group and the autograft group in the Safety population for S01-01US were very similar to each other with regard to key demographics including mean age, height, and weight at surgery, levels fused, mean pre-operative ODI scores, gender distribution, original diagnosis, and degree of angular motion and translational movement. Of all patients eligible for participation in 06-UPLF-01 (n=257, 183 for OP-1 Putty group and 74 for autograft group), the key demographics and baseline characteristics (including key clinical outcomes as measured in pivotal study S01-01US) between study groups for the patients who enrolled in 06-UPLF-01 versus the patients who were eligible for 06-UPLF-01 have been maintained.

The population that was eligible to participate in 06-UPLF-01 (had not died or been a retreatment failure in S01-01US) can be characterized as elderly (mean age at surgery of 67.6 for OP-1 and 69.3 for autograft), more females than males (65.0% for OP-1 Putty and 74.3% for autograft), with comparable mean weights (78.9kg for OP-1 Putty and 80.6kg for autograft), comparable mean heights (165.5cm for OP-1 Putty and 165.8 for autograft), similar mean pre-operative ODI scores (48.5 for OP-1 Putty and 50.1 for autograft), similar mean pre-operative angular motion (4.0° for OP-1 Putty and 4.7° for autograft), and similar mean pre-operative translational movement (1.7mm for OP-1 Putty and 1.6mm for autograft). Although spondylolisthesis of Grade 1 or Grade 2 with spinal stenosis was permitted in the study, both groups featured predominantly Grade 1 spondylolisthesis (92.3% Grade 1 for OP-1 Putty and 91.9% Grade 1 for autograft population). Almost all patients were not on Worker's Compensation (95.1% for OP-1 Putty and 98.6% for autograft). In addition to comparing baseline demographic characteristics, it should be noted that the percent of patients eligible for 06-UPLF-01 who had achieved Overall Success at 24 months as originally defined in the Pivotal IDE S01-01US was 42.9% for the OP-1 Putty group and 57.6% for the autograft group (Source: Statistical Table S.2 in Section 14.1), which reflects the higher success rate achieved in the autograft group by the overall population in the Pivotal Study S01-01US.

For those patients who returned for evaluation under protocol 06-UPLF-01, demographics between the OP-1 Putty group and the autograft group continue to be comparable to each other as well as to the corresponding groups for the entire population that was eligible to participate in 06-UPLF-01. The patients who returned for evaluation under 06-UPLF-01 can also be characterized as elderly (mean age at surgery of 66.8 for OP-1 and 68.7 for autograft), more females than males (65.3% for OP-1 Putty and 72.4% for autograft), with comparable mean weights (79.0kg for OP-1 Putty and 81.0kg for autograft), comparable mean heights (165.9cm for OP-1 Putty and 166.1cm for autograft), similar mean pre-operative ODI scores (48.2 for OP-1 Putty and 50.7 for autograft), similar mean pre-operative angular motion (4.1° for OP-1 Putty and 4.3° for

autograft), and similar mean pre-operative translational movement (1.8mm for OP-1 Putty and 1.5mm for autograft). Both study groups featured predominantly Grade 1 spondylolisthesis (93.8% Grade 1 for OP-1 Putty and 93.1% Grade 1 for autograft population). As with the original Pivotal IDE population, nearly all patients were not on Worker’s Compensation: 95.8% for OP-1 Putty and 98.3% for autograft. The percent of patients who had achieved Overall Success at 24 months as originally defined in the Pivotal IDE S01-01US was 43.8% for the OP-1 Putty group and 60.0% for the autograft group, which is consistent with the overall success rates at 24 months for the entire population eligible to return for 06-UPLF-01. (Source: Statistical Table S.2 in Section 14.1)

Table 6 presents a comparison of demographic and baseline characteristics and key outcomes from pivotal study S01-01US by treatment group between the population eligible for 06-UPLF-01 and the population who actually returned to participate in extension study 06-UPLF-01. The comparison of demographics and baseline characteristics and key clinical outcomes from S01-01US between the population from Pivotal IDE S01-01US who were eligible to return for follow-up in Extension Study 06-UPLF-01 and the population who actually participated in 06-UPLF-01 demonstrates that there were no apparent differences in these factors, thus providing reasonable assurance that the results of the 36+ month analyses are representative of the entire study population, and that the extension study does not appear to have introduced a source of bias by disproportionately representing those patients pre-disposed to success or failure in either treatment group.

Table 6: Summary of Key Demographic Parameters and S01-01US Success Outcomes for Extension Study 06-UPLF-06

Parameter	Statistic	OP-1 Putty		Autograft		
		Eligible for 06-UPLF-01	Enrolled in 06-UPLF-01	Eligible for 06-UPLF-01	Enrolled in 06-UPLF-01	
Age (years)	N	183	144	74	58	
	Mean	67.6	66.8	69.3	68.7	
	Median	69.0	67.0	71.0	70.0	
	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)
Weight (kg)	N	183	144	74	58	
	Mean	78.9	79.0	80.6	81.0	
	Median	79.4	79.4	81.6	82.4	
	Std. Dev.	16.08	15.71	17.41	17.98	

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty® for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

Parameter	Statistic	OP-1 Putty		Autograft		
		Eligible for 06-UPLF-01	Enrolled in 06-UPLF-01	Eligible for 06-UPLF-01	Enrolled in 06-UPLF-01	
Height (cm)	N	183	144	74	58	
	Mean	165.5	165.9	165.8	166.1	
	Median	165.1	165.1	165.1	165.1	
	Std. Dev.	9.26	9.18	10.20	9.36	
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	48.0	48.0	
	Std. Dev.	11.11	10.74	13.48	12.47	
Degree of Angular Motion ^b (degrees)	n	174	138	66	51	
	Mean	4.0	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 ^b (mm)	n	171	136	65	51	
	Mean	1.7	1.8	1.6	1.5	
	Median	1.4	1.5	1.0	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 and 2	n (%)	6 (3.3)	4 (2.8)	4 (5.4)	2 (3.4)	
Prior overall success at 24 months as determined in pivotal study S01-01US	%	42.9	43.8	57.6	60.0	
Prior success in presence of bone assessment by 9 month CT scan in pivotal study S01-01US	%	91.2	89.7	98.4	100.0	

(a) Subject 3101 in S01-01US had involved level L5-S1 different from level fused L3-L4.

(b) This represents the average scores from the 2 reviewers used in the analysis for the pivotal IDE S01-01US.

Source: Statistical Table S.1.4 and S.2 in Section 14.1 of CSR 06-UPLF-01

11.3 EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL PATIENT DATA

11.3.1 Primary Efficacy: Overall Success

The primary efficacy endpoint is the Overall Success rate for the mITT population, in which missing data were imputed. Overall success is a composite endpoint consisting of radiographic success, improvement in Oswestry Disability Index, absence of retreatment, absence of neurological compromise, and absence of serious treatment-related adverse events. Success regarding the improvement of ODI, absence of neurological compromise, and absence of serious treatment-related adverse events is determined at 24 months from the data collected in the original pivotal study, S01-01US. Success regarding radiographic evidence of fusion (presence of bone by CT scan, angular motion success and translational movement success by plain films) is based on the 36+ months data collected in this study (because CT scans were not taken at 24 months, and because plain films such as those taken at 24 months are now known to be inadequate for assessing medial bone formation). Stryker Biotech acknowledges that it would be preferable to have all components of a composite measure assessed at the same time point; however, this was not possible for this study given that CT scans were not obtained at 24 months. Combining the 36+ radiographic assessment with the original 24 month clinical outcome assessments (with the exception of retreatment, discussed below) does not introduce bias because radiographic results would be expected to remain constant between 24 months and 36 months.²⁶ Therefore, a 36+ month radiographic assessment is an accurate representation of the expected results at 24 months and can be used in the modified Overall Success measure. Success regarding absence of retreatment is also based on the 36+ months data, because retreatment at any time point is a critical component of overall success, and because radiographic results at 36+ months would not be meaningful if a patient had been retreated at any time prior to the 36+ month visit.

Table 7 presents the Overall Success rate at 24 months (with radiographic success and retreatment success at 36+ months) in the mITT population using the pre-specified SAP analyses. OP-1 Putty treatment was demonstrated to be statistically non-inferior to autograft ($p=0.025$). The estimated success rates were 47.2% for OP-1 Putty and 46.8% for autograft.

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

Table 7: Overall Success at 24 Months (with Radiographic and Retreatment Success Subcomponents at 36+ Months), mITT Population

OP-1 Putty		Autograft		95% Upper Confidence Bound ²	95% Upper Confidence Bound (%) ³	p-value for Non-Inferiority ⁴
Number of Patients	Success Rate (%) ¹	Number of Patients	Success Rate (%) ¹			
207	47.2%	86	46.8%	0.116	11.59%	0.025

Source: Statistical Table S.3.1.A in Section 14.1.

Note: Missing values were imputed.

(1) The percentage of successes and its standard error are based on estimates from multiple imputation.

(2) The 95% upper confidence bound is for the difference in success rates expressed in radians.

(3) The 95% upper confidence bound for the difference in success rates expressed as a percentage

(4) p-value is based on one-sided two-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 multiple imputation.

Table 8 summarizes the subcomponents of Overall Success at 24 months (with radiographic and retreatment success subcomponents at 36+ months).

Table 8: Subcomponents of Overall Success at 24 months (with Radiographic and Retreatment subcomponents at 36+ months), mITT Population

Outcome	OP-1 Putty		Autograft		p-value Non-inferiority
	Number of Patients	N (%) Successes	Number of Patients	N (%) Successes	
Radiographic Success ¹ (36+ Months)	207	125.75 (60.7)	86	54.25 (63.1)	0.138 ²
Outcome	OP-1 Putty		Autograft		p-value Difference
	Number of Patients	N (%) Successes	Number of Patients	N (%) Successes	
ODI Success (24 Months) ⁴	192	143 (74.5)	70	53 (75.7)	0.839 ³
Absence of Retreatment (36+ Months) ⁴	162	141 (87.0)	66	55 (83.3)	0.529 ³
Absence of Serious Treatment-related AEs (24 Months) ⁴	194	166 (85.6)	72	61 (84.7)	0.863 ³
Neurological Success (24 Months) ⁴	190	175 (92.1)	69	58 (84.1)	0.057 ³

¹ Missing values were imputed.

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 imputations.

³ p- value is based on Fisher's exact test.

⁴ Missing data are not imputed. Patients with retreatment subsequent to PLF are set to failure.

Sources: Statistical Tables S.4.A, S.7.A, 5.2.2 ADHOC, 5.4.2.ADHOC, 5.5.2.ADHOC in Section 14 of CSR 06-UPLF-01 (Appendix B, Section V, current PMA Amendment)

The number and percentage of mITT patients in each treatment group with missing data and requiring imputation for Overall Success is presented in Statistical Table S.3 in Section 14.1. The percentage of patients requiring imputation was 29.5% in the OP-1 Putty group and 32.6% in the autograft group, and the percentage of patients requiring imputation for missing data was not statistically different (p=0.676). See the SAP and for a discussion of imputation models.

Overall Success results were also analyzed without imputation for the mITT and the Supplemental Per Protocol populations. The non-imputed Overall Success results for the SPP population were 42.6% for OP-1 Putty and 44.2% for autograft, p=0.869 (Statistical Table S.3.1.B in Section 14.1) the difference between treatment groups was not statistically significant. The non-imputed Overall Success results for the mITT population

were 37.7% for OP-1 Putty and 39.7% for autograft, $p=0.873$ (Statistical Table S.3.1.B.2 in Section 14.1). The difference between treatment groups was not statistically significant.

In accordance with the SAP, the following additional analyses of Overall Success at 24 months (with radiographic and retreatment data at 36+ months) have also been conducted:

- Analysis of Overall Success (non-imputed) using presence of bridging bone rather than presence of bone as a factor in radiographic success is presented in Statistical Tables S.3.5.A and S.3.5.B in Section 14.1 for the mITT and SPP populations. In the mITT population, OP-1 Putty achieved 26.4% success (39/148) and autograft achieved 36.2% success (21/58), $p=0.175$. In the SPP population, OP-1 Putty achieved 29.8% success (39/131) and autograft achieved 40.4% success (21/52), $p=0.221$. Differences between groups were not statistically significant.
- Analysis of Overall Success stratified by center size (with large centers defined as $n \geq 12$ and small centers defined as $n < 12$) for the mITT population is presented in Statistical Table S.3.2. Missing data are not imputed. The analysis demonstrated that larger centers had a slightly higher success rate (39.4%) than smaller centers (34.6%) in the OP-1 Putty group. The finding of slightly higher success rates in larger centers for the OP-1 Putty group is not expected to be attributable to any characteristic of the OP-1 Putty device itself, but rather to the likelihood that centers/surgeons that perform a particular spinal procedure frequently will develop more expertise than centers/surgeons that perform the procedure less frequently. The difference between larger and smaller centers was more pronounced in the autograft group (48.6% for larger centers versus 23.8% for smaller centers); however, the number of patients in the autograft group at the smaller centers ($n=21$) was too small to justify any conclusions based on this group. The differences between treatment groups for larger and smaller centers were not statistically significant (Source: Statistical Table S.3.2., Section 14.1.)
- Analysis of Overall Success was to be conducted based on any statistically significant differences between the study groups with regard to key demographic and baseline characteristics. However, as there were no statistically significant differences between the study groups with regard to key demographic and baseline characteristics, such additional analysis of Overall Success was not necessary.
- An alternate equivalence limit of 0.10 was used to test for non-inferiority of OP-1 Putty to Autograft for Overall Success in the mITT population as presented in Statistical Table S.3.3. The success estimates are the same as presented for the

primary analysis presented in Table 7; however, OP-1 Putty was not demonstrated to be non-inferior to autograft using the equivalence limit of 0.10 ($p=0.076$). 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 discussion regarding the non-inferiority margin of 0.14 (radians) versus the non-inferiority margin in the percentage scale (using a margin of 10 percentage points, as requested by FDA) is provided in Section 16.1.9.

- Overall Success rates at 24 months (with radiographic and retreatment data at 36+ months, missing data not imputed) by study group for males and females, and for each age category (<45 years old, 45-65 years old, >65 years old) are presented in Statistical Tables S.3.4.A for the mITT population. In the OP-1 Putty group, males and females achieved overall success at similar rates (39.6% for males, 36.7% for females). In the autograft group, females achieved a higher percentage of overall success than males (31.6% for males, 43.6% for females). In the OP-1 Putty group, patients in the 45-65 years old category and in the >65 years old category achieved overall success at similar rates (36.1% for 45-65, 39.8% for >65), and there were only 2 patients in the <45 years old category (success rate 0.0%). In the autograft group, patients in the 45-65 years old category achieved higher rates of overall success as compared to patient in the >65 years old category (55.0% for 45-65, 31.6% for >65), and there were no patients in the <45 years old category. The difference in success rates in the autograft group between the 45-65 years old group and the >65 year old group may be due to the diminishing quality of autograft bone as patients age. The Supplemental Per Protocol population demonstrated similar results as illustrated in Statistical Table S.3.4.B.

11.3.2 Secondary Efficacy Endpoints

Table 9 summarizes key success outcomes at the 36+ month follow-up interval for the mITT population. The subsections following Table 9 present the analyses of each of the key clinical outcome measures collected at 36+ months. 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 radiographic success have been calculated with all patients who were a retreatment subsequent to the posterolateral fusion set to failure. This is a different method than was used for the 24-month success rates presented in CSR S01-01US; however, this method is thought to be more appropriate than the previous method (excluding patients who were failures due to retreatment) 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 other clinical measures.

Table 9: Success Outcomes at 36+ months Follow-Up: SAP Analysis, mITT Population

Outcome	OP-1 Putty	Autograft	p-value Non-inferiority ²
Radiographic Success ¹ (36+ Months)	60.7%	63.1%	0.138 ²
Outcome	OP-1 Putty	Autograft	p-value for Difference ³
ODI Success (36+ Months)	68.6%	77.3%	0.201
Absence of Retreatment (36+ Months)	87.0%	83.3%	0.529
Absence of Serious Treatment-related AEs (36+ Months)	79.5%	73.5%	0.387
Neurological Success (36+ Months)	84.4%	80.0%	0.540

¹ Radiographic Success 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 multiple imputation.

³ p-value is based on Fisher's Exact Test

Sources: Statistical Tables S.4.A, S.6.A, S.7.A, S.8.A, S.9.A in Section 14.2

11.3.2.1 Oswestry Disability Index Success at 36+ Months

Table 10 presents the percent of patients in both the mITT and SPP populations who achieved success as defined by at least a 20% improvement in the ODI, a patient-completed questionnaire that reflects perceptions of components of disability: pain, activities of daily living, and mobility. At the 36+ month interval, for the mITT population, the difference between the OP-1 Putty group and the autograft group for the percentage of patients who achieved the minimum 20% improvement in ODI as

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty® for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (Extension to Pivotal Study S01-01US)

compared to baseline was not statistically significant (68.6% for OP-1 Putty and 77.3% for autograft, $p=0.201$). The percentage of patients achieving success in each treatment group was similar for the SPP group. As shown in Table 11, for the mITT population, the OP-1 Putty group and the autograft group experienced nearly identical mean ODI scores at 36+ months (22.9 for OP-1 Putty and 22.3 for autograft), mean improvements from baseline at 36+ months (25.3 for OP-1 Putty and 27.4 for autograft), and median improvements from baseline at 36+ months (24.2 for OP-1 Putty and 24.4 for autograft). Both groups achieved changes from baseline that were statistically significant ($p<0.0001$), but the difference between groups was not statistically significant ($p=0.491$). In addition, the mean percent improvements from baseline (54.0% for OP-1 Putty and 54.5% for autograft), and median percent improvements from baseline (60.0% for OP-1 Putty and 57.2% for autograft) were also similar between treatment groups. (Source for mean and median percent changes: Statistical Table ODICHDCHEG.Adhoc, Section 14.1).

Table 10: Success Rate Based on Oswestry Disability Index at 36+ Months (mITT Population and SPP Population)

Time Point/Population	OP-1 Putty		Autograft		p-value For Difference
	Number of Patients	Number (%) of Successes	Number of Patients	Number (%) of Successes	
36+ Months/mITT	159	109 (68.6)	66	51 (77.3)	0.201
36+ Months/SPP	149	103 (69.1)	61	46 (75.4)	0.406

Source: Statistical Tables S.6.A and S.6.B in Section 14.1, Listing 5 in Section 16.2.

Note: p-value is based on Fisher's exact test. Missing data are not imputed. Patients with retreatment subsequent to the PLF are set to failure.

Table 11: Oswestry Disability Index, Change from Baseline, 36+ Months (mITT Population)

Time Point	Statistic	OP-1 Putty		Autograft		p-value ¹
		Actual	Change from Baseline	Actual	Change from Baseline	
Baseline	N	186		75		
	Mean	48.7		48.7		
	Median	48.9		48.0		
	Std. Dev.	11.16		13.13		
36+ Months	N	138	138	55	55	0.491
	Mean	22.9	-25.3	22.3	-27.4	
	Median	19.0	-24.2	22.0	-24.4	
	Std. Dev.	18.99	20.45	16.72	17.38	
	p-value ²		<0.0001		<0.0001	

Source: Statistical Table S.15.A in Section 14.1 of CSR 06-UPLF-01.

Note: Missing or non-evaluable data were excluded from the analysis. Patients with retreatment subsequent to the PLF are excluded.

(1) p-value is based on 2-sample t-test to test the difference in mean change from baseline between treatment groups.

(2) p-value is based on one-sample t-test to test the mean change within each treatment group.

Table 12: ODI Percent Changes at 36+ Months Compared to Baseline, mITT Population

Outcome	OP-1 Putty	Autograft
Mean % change from baseline at 36+ months	52.0%	54.4%
Median % change from baseline at 36+ months	59.1%	53.8%

Source: ad hoc Statistical Table 15.5.Adhoc.SAS, Section 14.1

The changes from baseline at 36+ months within and between treatment groups in ODI in the SPP population are presented in Statistical Table S.15.B in Section 14. Results were similar to those seen in the mITT population. Section 16.2, Listing 5, displays these data by subject.

Because the 20% ODI improvement from baseline is an arbitrary cut point for determining clinical improvement, additional analyses were conducted to compare the percentages 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. (See Table 11, Figure 2, and Figure 3.)

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty® for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

These results indicate that while the OP-1 Putty group had slightly lower proportions of patients who achieved ODI success in the $\geq 20\%$ and $\geq 30\%$ improvement in ODI categories (differences not statistically significant), the OP-1 Putty group had higher proportions of patients achieving $\geq 50\%$ improvements, and, more importantly, a greater proportion of patients who achieved $\geq 80\%$ and $\geq 100\%$ improvements at both the 24 month and 36+ month intervals (differences not statistically significant). While a 20% improvement in ODI is the minimum improvement from baseline that is generally considered clinically meaningful, it is also true that larger improvements in ODI are indicative of more clinically significant improvements in pain and function. The large percentage of patients in both groups achieving improvements of 50% or more at both 24- and 36+-months further supports the efficacy and durability of both treatments.

Table 13: ODI Improvements Using Varying Percent Improvements, mITT Population

% ODI improvement over baseline	OP-1 Putty N (%)	Autograft N (%)	p-value For Difference
At 24 Months			
$\geq 20\%$	139 (72.4)	53 (73.2)	1.000
$\geq 30\%$	128 (66.7)	48 (67.6)	1.000
$\geq 50\%$	107 (55.7)	38 (53.5)	0.781
$\geq 80\%$	60 (31.1)	13 (18.3)	0.044
100%	28 (14.6)	5 (7.0)	0.141
At 36+ Months			
$\geq 20\%$	109 (68.6)	51 (77.3)	0.201
$\geq 30\%$	101 (63.5)	46 (69.7)	0.443
$\geq 50\%$	78 (49.1)	32 (48.5)	1.000
$\geq 80\%$	43 (27.0)	11 (16.7)	0.123
100%	21 (13.2)	6 (9.1)	0.501

Source: Statistical Tables, S.6.A, S.6A.ADHOC.1A, S.6.A.ADHOC.3 through S.6.A.ADHOC.10 in Section 14.1.

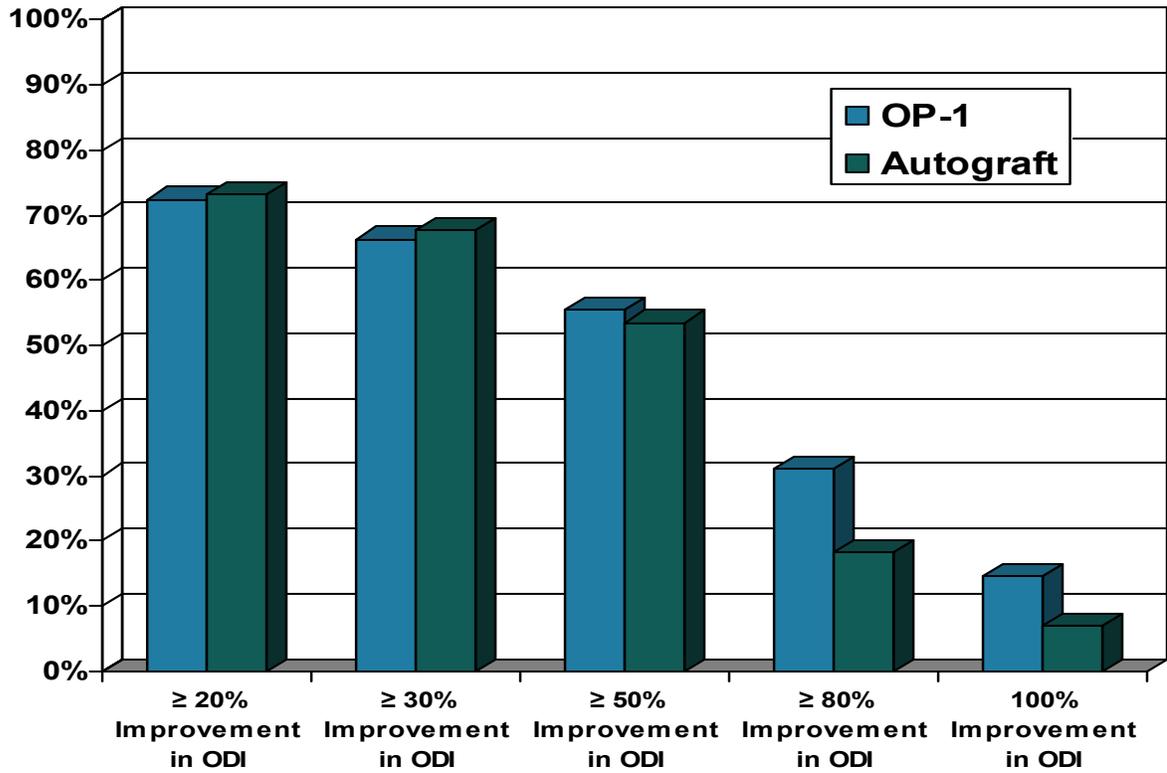
Notes: Missing data are not imputed. Patients with retreatment subsequent to the PFL are set to failure. p-value is based on Fisher's exact test.

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

Figure 2: % Improvements in ODI at 24 Months

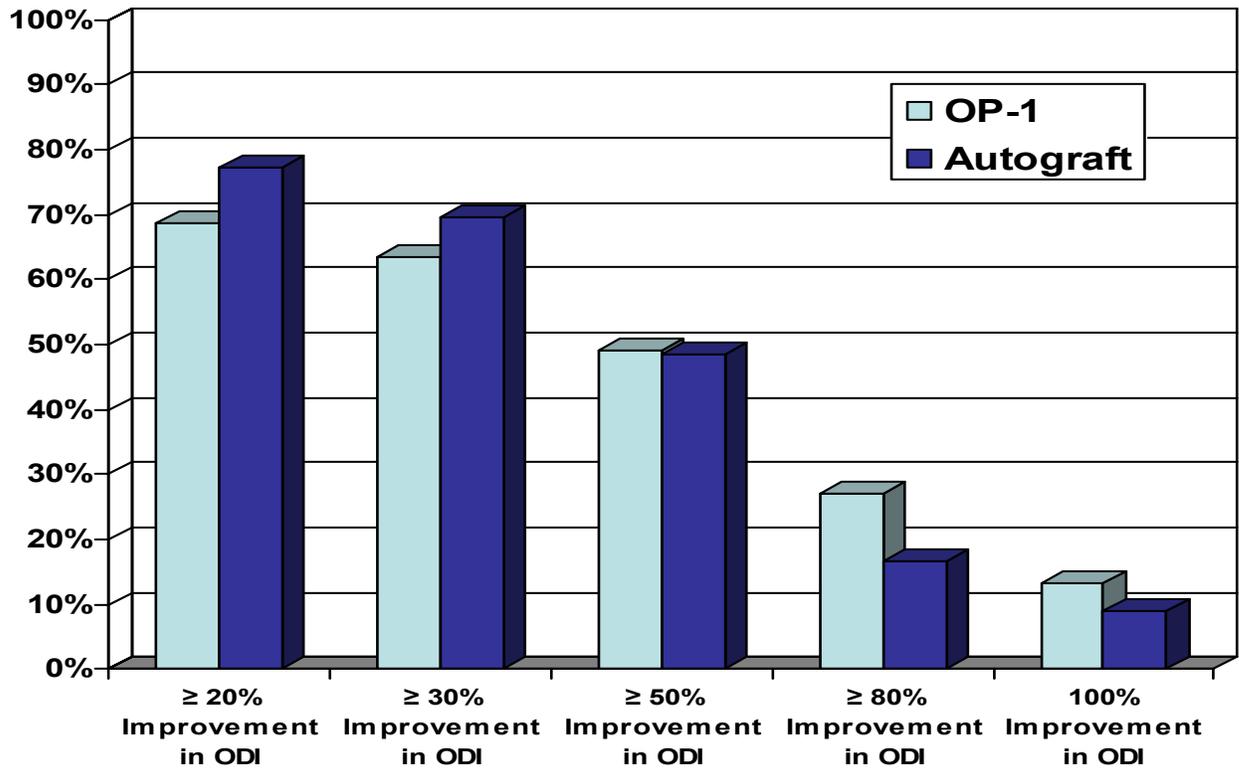


Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

Figure 3: % Improvements in ODI at 36+ Months



11.3.2.2 Absence of Retreatment at 36+ Months

Table 14 presents the success rate based on the absence of retreatment up to and including 36+ months, a key clinical outcome with great significance to both patients and surgeons. The term retreatment refers to a revision, removal, supplemental fixation, or reoperation intended to promote fusion at the treated level. In the mITT population, patients in the OP-1 Putty group experienced higher success rates (fewer retreatments up to and including 36+ months) than did patients in the autograft group, although the difference was not statistically significant (87.0% for OP-1 Putty and 83.3% for autograft, p=0.529). Results were similar in the SPP population.

Table 14: Success Rate Based on Absence of Retreatments up to and including 36+ Months (mITT Population and SPP Population)

Time Point/Population	OP-1 Putty		Autograft		p-value For Difference
	Number of Patients	Number (%) of Successes	Number of Patients	Number (%) of Successes	
36+ Months/mITT	162	141 (87.0)	66	55 (83.3)	0.529
36+ Months/SPP	150	129 (86.0)	61	50 (82.0)	0.526

Note: Missing data are not imputed. Patients with retreatment subsequent to PLF are set to failure. p-value is based on Fisher's Exact test.

Source: Statistical Tables S.7.A and S.7.B in Section 14.1.

Section 12.5 describes the retreatments that were reported under extension study 06-UPLF-01. Listing 10 in Section 16.2 displays all surgical procedures (including retreatments) reported in this extension study resulting from adverse events. Narratives of all serious adverse events and other significant adverse events (including retreatments) are provided in Section 14.2.

11.3.2.3 Absence of Serious Treatment-Related Adverse Events up to and including 36+ Months

Table 15 presents success rate based on the absence of serious treatment-related AEs by 36+ months. Investigators were asked to rate the causality of each AE as “not related,” “suspected related” or “unknown.”

Table 15 presents Serious Treatment-Related Adverse Events (i.e., SAEs that were classified as either “suspected related” or “unknown”). In the mITT population, patients in the OP-1 Putty group experienced absence of serious treatment related adverse events at rates comparable to those in the autograft group at 36+ months (79.5% for OP-1 Putty and 73.5% for autograft, p=0.387), and the difference between groups was not

statistically significant. The results in the SPP population were similar to those in the mITT population.

Table 15: Success Rate Based on Absence of Serious Treatment-Related Adverse Events at 36+ Months (mITT Population and SPP Population)

Time Point/Population	OP-1 Putty		Autograft		p-value for Difference
	Number of Patients	Number (%) of Successes	Number of Patients	Number (%) of Successes	
36+ Months/mITT	166	132 (79.5)	68	50 (73.5)	0.387
36+ Months/SPP	150	121 (80.7)	61	47 (77.0)	0.575

Source: Statistical Tables S.8.A and S.8.B in Section 14.1.

Note 1: Missing data are not imputed. Patients with retreatment subsequent to PLF are set to failure. p--value is based on Fisher's Exact test.

Listing 9 in Section 16.2 displays all new adverse events reported in the extension study. Listing 10 in Section 16.2 displays all surgical procedures reported in this extension study resulting from adverse events. Narratives of all deaths, other serious adverse events and other significant adverse events (including retreatments) are provided in Section 14.2.

Comparisons of new serious adverse events by system organ class/preferred term, device-relatedness, severity, and by time interval are presented and discussed in further detail in Section 12.2 of this report.

11.3.2.4 Neurological Success at 36+ Months

Table 16 presents the number and percent of patients who achieved overall neurological success at 36+ months in both the mITT and SPP populations. Overall neurological success was defined as the absence of a decrease in neurological status (assessing muscle strength, reflexes, sensory and straight leg raise), unless attributed to a concurrent medical condition or to the surgical procedure by a blinded Independent Neurological Reviewer. The percent of patients who achieved overall neurological success in the mITT population at 36+ months was 84.4% in the OP-1 Putty group, and 80.0% in the autograft group, and the difference between groups was not statistically significant (p=0.540). The results were similar for the SPP population.

Table 16: Overall Neurological Success Rates at 36+ Months (mITT and SPP Populations)

Time Point/Population	OP-1 Putty		Autograft		p-value for Difference
	Number of Patients	Number (%) of Successes	Number of Patients	Number (%) of Successes	
36+ Months/mITT	147	124 (84.4)	60	48 (80.0)	0.540
36+ Months/SPP	143	120 (83.9)	59	47 (79.7)	0.540

Source: Statistical Tables S.9.A and S.9.B, Section 14.1

Note: Missing data are not imputed. Patients with retreatment subsequent to the PLF are set to failure. p-value is based on Fisher's Exact test.

Listing 4 in Section 16.2 displays neurological evaluation data for each patient. Statistical Tables S.20.1 to S.20.4 in Section 14.1 present changes in neurological status over time. Muscle strength for all 24 muscle groups evaluated in both treatment groups was stable at 36+ months, with the majority of patients having normal muscle strength. The majority of patients in both groups demonstrated improvement or no change from baseline in reflex function, sensory function and straight leg raises at 36+ months.

Two patients in the OP-1 Putty group (patient IDs 1319 and 1501) and one patient in the autograft group (patient ID 2513) were failures in the overall neurological success criteria during extension study 06-UPLF-01 by the 36+ month visit. These patients experienced worsening in neurological status that could not be attributed to a concurrent medical condition or to the surgical procedure. (Table 16 indicates that there were more neurological failures than these three patients, because neurological success rates were calculated with all retreatments set to failure) The independent surgeon who assessed neurological failures could not determine if neurological changes seen for these three patients were due to the procedure itself or to the treatment assignment. A discussion of each of these patients follows:

- ID 2513: Clinical evaluation demonstrated absent reflexes for ankle (right and left) and knee (right and left), and poor ankle dorsi-flexion (right and left).
- ID 1319: Clinical evaluation demonstrated that right and left knee and ankle reflexes were decreased, and right L₃ dermatomes were impaired. Left ankle and toe muscle strength tests were fair.
- ID 1501: Clinical evaluation demonstrated that right ankle jerk and left ankle jerk reflexes were decreased. Right ankle inversion and eversion were fair, and left ankle inversion and eversion were good. Both right- and left-side ankle inversion/eversion scores were noted as clinically significant since previous visit.

11.3.2.5 Overall Radiographic Success at 36+ Months

Table 17 presents overall radiographic success rate at 36+ months in the mITT population (with missing data imputed), and the subcomponents of radiographic success at 36+ months (without missing data imputed). In the imputed mITT analysis, OP-1 Putty was clinically comparable to autograft with regard to the Overall Radiographic Success outcome using the 36+ month CT scan data (60.7% for OP-1 Putty and 63.1% for autograft, $p=0.138$). OP-1 Putty was not demonstrated to be non-inferior to autograft with regard to the secondary endpoint, Overall Radiographic Success; however, there were no statistically significant differences between the OP-1 Putty and autograft groups with regard to the three subcomponents of Overall Radiographic Success at 36+ Months (non-imputed): Presence of Bone, Angular Motion, and Translational Movement. In addition, there was no statistically significant difference with regard to overall radiographic success at 36+ months for the mITT population, non-imputed (OP-1 Putty 55.6%, autograft 59.3%, $p=0.745$) or for the SPP population, non-imputed (OP-1 Putty 55.7%, autograft 59.3%, $p=0.745$). (Source: Statistical Tables S.4.3.A and S.4.3 in Section 14.1.)

Table 17: Overall Radiographic Success Rate at 36+ Months (mITT Population)

Radiographic Measure	OP-1 Putty		Autograft		p-value Non-Inferiority ^b
	Number of Patients	Number (%) of Successes	Number of Patients	Number (%) of Successes	
Overall Radiographic Success ^a	207	125.75 (60.7)	86	54.25 (63.1)	0.138
Subcomponents of Overall Radiographic Success at 36+ Months:					p-value^c For Difference
• Presence of Bone by 36+ month CT	143	107 (74.8)	53	41 (77.4)	0.852
• Angular Motion $\leq 5^\circ$, 36+ months	137	95 (69.3)	57	39 (68.4)	1.000
• Translational Movement ≤ 3 mm, 36+ months	136	103 (75.7)	57	43 (75.4)	1.000

Note: Missing data were imputed for overall radiographic success. Missing data are not imputed for the subcomponents of radiographic success, and patients with retreatment subsequent to the PLF are set to failure.

(a) The percentage of successes and its standard error are based on estimates from multiple imputations

(b) 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 multiple imputation.

(c) P-value is based on Fisher's Exact test.

Source: Statistical Table S.4.A, S.4.1, S.4.2, and S.10.1.A in Section 14.1

Listings 11.1, 11.2, and 13 in Section 16.2 display radiographic data collected during 06-UPLF-01 for each patient.

In addition to the analyses on overall radiographic success presented above, a review of the three subcomponents of overall radiographic success at 36+ months follows.

11.3.2.5.1 Translational Movement at 36+ Months

Success for translational movement was defined as movement of ≤ 3 mm. Table 17 in section 11.3.2.5 of this report presents the percent of patients in each study group in the mITT population that achieved success in translational movement at 36+ months (75.7% for OP-1 Putty and 75.4% for autograft). The difference between groups was not statistically significant (p=1.000). Table 18 displays the mean extent of translation at baseline and at 36+ months for both study groups. Data show the two groups to be comparable with regard to mean and median values at baseline and at 36+ months.

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty® for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

Table 18: Translational Movement at 36+ Months (mITT Population)

Time Point	Statistic	Op-1 Putty	Autograft
		Actual	Actual
Baseline	N	193	75
	Mean	1.7	1.6
	Median	1.4	1.1
	Std. Dev.	1.44	1.49
36+ Months	N	108	41
	Mean	1.7	1.5
	Median	1.3	1.3
	Std. Dev.	1.28	0.89

Note 1: Missing or non-evaluable data were excluded from the analysis. Patients with retreatment subsequent to PLF were excluded.

Note 2: For baseline measurement, if an adjudicating review was required, then the adjudicating review was used. If there was no adjudicating review assessment, the average scores from the first two reviewers were used. For 36+ months measurement, the median of three reviewers was used in the analysis, if there was a third review assessment. Otherwise, the mean of the first two reviewers was used.

Source: Statistical Table S.14.A in Section 14.1

The analysis of translational movement for the SPP population is presented in Table S.14.B in Section 14.1 and demonstrates results similar to those in the mITT population.

Listing 12 in Section 16.2 displays the data on translational movement by subject.

11.3.2.5.2 Angular Motion at 36+ Months

Success for angular motion was defined as motion of ≤ 5 degrees. Table 17 in section 11.3.2.5 of this report presents the percent of patients in each study group in the mITT population that achieved success in angular motion at 36+ months (69.3% for OP-1 Putty and 68.4% for autograft). The difference between groups was not statistically significant ($p=1.000$). Table 19 displays the mean extent of angulation at baseline and at 36+ months for both study groups. Data show the two groups to be comparable.

Table 19: Angular Motion at 36+ Months (mITT Population)

Time Point	Statistic	Op-1 Putty	Autograft
		Actual	Actual
Baseline	N	195	76
	Mean	3.9	4.7
	Median	2.8	4.2
	Std. Dev.	3.40	3.20
36+ Months	N	109	41
	Mean	3.5	3.6
	Median	2.6	2.6
	Std. Dev.	2.87	2.85

Note 1: Missing or non-evaluable data were excluded from the analysis. Patients with retreatment subsequent to PLF were excluded.

Note 2: For baseline measurement, the results from the third reviewer were used in the analysis. If there was no third review assessment, the average scores from the first two reviewers were used. For 36+ months measurement, the median of three reviewers was used in the analysis, if there was a third review assessment. Otherwise, the mean of the first two reviewers was used.

Source: Statistical Table S.13.A in Section 14.1

The analysis of angular motion for the SPP population is presented in Table S.13.B in Section 14.1 and demonstrates results similar to those in the mITT population.

Listing 12 in Section 16.2 displays the data on angular motion measurements by subject.

11.3.2.5.3 Presence of Bone on CT Scans

Table 20 presents the rate of success based on presence of bone visualized on 36+ month CT scans in the mITT population. Presence of bone was seen in 74.8% of the OP-1 Putty patients and in 77.4% of the autograft patients at 36+ months. The difference between groups was not statistically significant ($p=0.852$).

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty® for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

Table 20: Presence of Bone Based on 36+ Month CT Scan, mITT Population

Time Point	OP-1 Putty		Autograft		p-value ¹ for Difference
	Number of Patients	Proportion (%) of Successes	Number of Patients	Proportion (%) of Successes	
36+ Months	143	74.8	53	77.4	0.852

Note: Presence of bone is established by majority of reviewers: If two primary reviewers did not agree, then adjudicating review was consulted, and majority opinion prevailed. Missing or non-evaluable data are excluded. Patients with retreatment subsequent to PLF are excluded.

(1) p-value is based on Fisher's exact test.

Source: Statistical Table S.3.5.C in Section 14.1.

The analysis for presence of bone as assessed by 36+ month CT scans in the SPP population yielded nearly identical results: 74.5% (105/141) for OP-1 Putty and 77.4% (41/53) for autograft, p=0.714. (Statistical Table S.3.5.D, Section 14.1)

Listing 11.1 in Section 16.2 presents the radiographic evaluation results of the 36+ month CT scans by patient.

11.3.3 Other Radiographic Findings

11.3.3.1 Overall Radiographic Success with Presence of Bridging Bone by CT Scan at 36+ Months

Analyses of presence of bridging bone assessed by 36+ month CT scans in both the mITT and SPP populations are presented in Statistical Tables S.10.2.A and S.10.2.B, respectively, in Section 14.1. Overall radiographic success based on presence of bridging bone rather than presence of bone was also calculated for the mITT and SPP populations in Statistical Tables S.5.A and S.5.B. Not unexpectedly, the rates of overall radiographic success in both treatment groups by this definition were lower. In the mITT population, the OP-1 Putty group achieved 37.8% success (51/135) and the autograft group achieved 54.5% (30/55). The difference between groups was statistically significant, p=0.037. The results were similar in the SPP population (37.6% for OP-1 Putty (50/133) and 54.5% (30/55) for autograft, p=0.036).

Analysis of presence of bridging bone at the operated level based on the 36+ month CT was also conducted. In the mITT population, the OP-1 group achieved 55.7% success (68/122) and the autograft group achieved 83.3% (35 /42). The differences between the groups was statically significant, p=.001(Source Statical Table 10.2.A) As a result of the differences between groups with regard to bridging bone, an ad hoc review of all patients from both treatment groups who did not demonstrate presence of bridging bone via 36+ month CT scan was conducted to look at potential differences in location of bone.

Consistent with other radiographic findings, of those patients who failed to show bridging bone at 36+ months, the OP-1 Putty group demonstrated a higher proportion of patients with medial bone formation as compared to autograft. In the OP-1 Putty group, 59% (23/39) of patients had presence of bone medially, and 41% (16/39) had presence of bone transversely. In the autograft group, 50% (3/6) of patients had presence of bone medially, and 50% (3/6) had presence of bone transversely. (Source: Statistical Table 10.7.Adhoc.SAS in Section 14.1.)

Axial Computed Tomography (CT) imaging of the spine has improved greatly over the last decade with advancements in image acquisition. Improvements in detector technology have resulted in reducing slice thickness to less than a mm. With this, spatial resolution has improved with better visualization of the anatomy and the ability to improve diagnoses. The downside to this has been the increased number of slices and the overall size of the imaging stack. To interpret this imagery, the radiologist has to be trained to mount these slices one on top of the another and build a complex three-dimensional model in his or her head.

Presence of new bone is generally easy to detect using CT as it is one of the four basic densities visible on a radiograph. However, CT imaging presents challenges for detecting bridging bone. Keeping in mind the increase in stack size, it can be exceedingly difficult to try to link one piece of bone to another, either above or below the image, and try to carry this cerebral reconstruction forward to determine if the fragments of bone have fused to one another (to assess bridging bone).

If bone is seen in the area of the transverse process, it most likely represents graft since degenerative 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. Thus, medial bone is more difficult to assess for bridging bone than transverse bone and, because OP-1 Putty-directed bone formation is more often located medially, bridging was more difficult to accurately assess for the OP-1 Putty group. This conclusion regarding the difficulty in reading medial bridging bone, particularly for OP-1 Putty, is supported by the observation that the primary radiographic readers disagreed on bridging bone assessments 29% of the time in OP-1 Putty subjects and only 8% of the time in autograft subjects (see Statistical Frequency Table 10.5ADHOC in Section 14.1). Furthermore, when the primary readers disagreed, the bone was medial 63.3% of the time (Table 10.5A.ADHOC).

11.3.3.2 Presence of Bone on 9-Month CT Scans Compared to 36+ Month CT Scans

At the time that pivotal study S01-01US was being designed, plain x-rays were the accepted standard of care for detecting new bone formation in the lumbar spine. However, at that time, CT scans were just beginning to be used for this purpose as well. Because of this, Stryker Biotech decided to include a CT scan at an early time point (9 months) when plain x-rays were not being collected for efficacy, in order to minimize radiation exposure to the patients. They were not designed to be part of the primary endpoint in the original study.

Table 21 presents the percent of patients in each treatment group who had and who did not have presence of bone as assessed by the 9-month CT scans taken during pivotal study S01-01US (re-read according to the same prospective, blinded, multi-reviewer evaluation protocol used for the 36+ month scans) cross-tabulated against the percent of patients who had and who did not have presence of bone as assessed by the 36+ month CT scans. The percent of patients who had presence of bone at 9 months and at 36+ months were 73.0% for the OP-1 Putty group and 97.5% for the autograft group. In the OP-1 Putty group, 84 out of 87 patients (96.5%) who had presence of bone at 9 months continued to have presence of bone at 36+ months, and 16 out of 28 patients (57.1%) who did not have presence of bone at 9 months progressed to having bone at 36+ months. In the autograft group, 39 out of 40 patients (97.5%) who had presence of bone at 9 months continued to show presence of bone at 36+ months. It should be noted that all patients in the autograft group show presence of bone on 9 month CT scans; however, it is difficult to distinguish in this group at this time point whether the visible bone is new bone formation or the autograft itself. In the OP-1 Putty group, all bone visible on CT scans is de-novo bone formation; because there is no other graft material present and the OP-1 Putty itself is not radiopaque. While 9 months is not an adequate length of time post surgery to assess peak de novo bone formation for OP-1 Putty, this analysis demonstrates that the majority of patients in the OP-1 Putty group who had presence of bone by 36+ months already showed presence of bone by 9 months.

Table 21: Presence of Bone on 9 Month CT Scan Cross-Tabulated Against Presence of Bone on 36+ Month CT Scan (mITT Population)

36+ Month CT Scan Results	9 Month CT Scan Results			
	OP-1 Putty		Autograft	
	Bone n (%)	No Bone n (%)	Bone n (%)	No Bone n (%)
Bone: n (%)	84 (73.0)	16 (13.9)	39 (97.5)	0 (0.0)
No Bone: n (%)	3 (2.6)	12(10.4)	1 (2.5)	0 (0.0)

Source: Statistical Table S.12 in Section 14.2.

Missing or non-evaluable data excluded. Patients with retreatment subsequent to PLF are excluded.

Table 22: Presence of Bone Assessed via CT Scan for Patients Who Did Not Have Presence of Bone via 24 Month Plain Films (mITT)

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

Source: Statistical Table ad hoc 10.3.Adhoc.SAS in Section 14.2.

Analysis of the 9-month CT scans under the original pivotal study S01-01US (not using the same protocol used for the 36+ month scans in 06-UPLF-01) also demonstrated the greater sensitivity of CT scans over plain films for assessing new bone: presence of bone was visualized in 84.9% of patients in the OP-1 Putty group, in contrast to the 61.7% demonstrated on plain films. Autograft showed a higher proportion of patients with presence of bone on the 9 month CT scans: 84.9% for OP-1 Putty and 98.6% for autograft, $P < 0.001$. (Source: Statistical Table B1.4 in Section 14, CSR S01-01US, Appendix B, Section V, original PMA.) Re-analysis of the 9-month CT scans under the same protocol used for the 36+ month CT scans showed results similar to the original reading: In the mITT population, OP-1 Putty had presence of bone in 79.5 % (147/185) of patients, and autograft had presence of bone in 100.0% (75/75) of patients, $P < 0.001$. (Source for mITT population is Statistical Table S.11.A and source for SPP population is Statistical Table S.11.B in Section 14.1). It should be noted, however, that visualization of bone at 9 months in the autograft group is not necessarily an indicator of de novo bone, as it is difficult to distinguish de novo bone formation from the graft material itself at 9 months post surgery. And, since 9 months is not long enough post surgery to evaluate peak de novo bone formation, OP-1 Putty would not be expected to demonstrate equivalence to autograft at the 9-month interval. Therefore, while the 9-month interval is not useful in comparing the relative abilities of OP-1 Putty and autograft to stimulate bone formation, the CT scans at 9 months are useful in that they demonstrate that the majority of OP-1 Putty patients who had presence of bone by 36+ months also had presence of bone by 9 months

Listings 11.1 and 11.2 in Section 16.2 present the results by patient of the 36+ month CT scans and of the 9-month CT scans (re-read according to the same prospective, blinded, evaluation protocol as the 36+ month CT scans), respectively.

11.3.3.3 Differences in Location of Bone Formation

Statistical Table S.10.3 in Section 14.1 demonstrates that the location of bone formation as assessed by CT scan at 36+ months differed by treatment group. Of patients with presence of bone assessed by 36+ month CT scan in the OP-1 Putty group, 47.7% (51/107) exhibited medial bone formation, while 52.3% (56/107) exhibited lateral bone formation (at the transverse processes). In the autograft group, 31.7% (13/41) of patients exhibited medial bone formation, while 68.3% (28/41) exhibited lateral bone formation. In addition, as presented in Table 22, of patients in the OP-1 Putty group who were judged not to have presence of bone based on plain films at 24 months, 71% (27/38) were judged to have presence of bone based on CT scans at 36+ months, with 81% (22/27) of those patients showing presence of bone medially rather than transversely. These analyses demonstrate that OP-1 Putty had a higher proportion of patients with medial bone formation and a lower proportion of patients with lateral bone formation as compared with the autograft group, and illustrates why the plain films assessment of presence of bone at 24 months was more likely to underestimate bone formation in the OP-1 Putty group as compared with the autograft group.

11.3.4 Additional Analyses

11.3.4.1 Visual Analog Scale for Pain Assessment at 36+ Months

Table 23 presents changes from baseline at 36+ months within treatment group, and differences between treatment groups, in Visual Analog Scale assessments of right and left leg/buttock pain assessment using the safety population. Patients in both groups experienced statistically significant decreases in pain at 36+ months. No statistically significant differences between treatment groups were noted with respect to change from baseline.

Table 23: Changes from Baseline in Visual Analog Scale of Right and Left Leg/Buttock Pain Assessment at 36+ Months (Safety Population)

Time Point	Statistic	OP-1 Putty Change from Baseline	Autograft Change from Baseline	p-value ^a
Right Leg/Buttock				
36+ Months	N	133	55	0.301
	Mean	-3.2	-2.6	
	Median	-3.4	-2.3	
	Std. Dev.	3.63	3.69	
	p-value ^b	<0.001	<0.001	
Left Leg/Buttock				
36+ Months	N	134	55	0.758
	Mean	-3.3	-3.1	
	Median	-3.3	-2.9	
	Std. Dev.	3.99	3.79	
	p-value ^b	<0.001	<0.001	

(a) p-value is based on 2-sample t-test to test the difference in mean change from baseline between treatment groups.

(b) p-value is based on one-sample t-test to test the mean change within each treatment group.

Source: Statistical Tables S.21 and S.22 in Section 14.1.

The improvements in Visual Analog Scale are consistent with the clinically relevant improvements seen in the ODI scores in both treatment groups.

11.3.4.2 Donor Site Pain at 36+ Months

Table 24 presents Visual Analog Scale assessments of donor site pain using the safety population. The data through 24 months follow-up have been presented in CSR S01-01US, and the data at 36+ months collected during this extension study are reported here. By 36+ months, mean donor site pain was 1.1.

Table 24: Donor Site Pain-Visual Analog Scale at 36+ Months (Safety Population, Autograft Only)

Visit	Statistic	Autograft
36+ Months	N	53
	Mean (Std Dev)	1.1 (2.09)
	Median	0.1

Note: Missing or non-evaluable data are excluded from the analysis.

Source for 36+ Month data: S.22.1 in Section 14.1 of this report, CSR 06-UPLF-01

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

Table 25 presents donor site pain by severity using the safety population. One third of the patients (35%) reported mild to moderate donor site pain at 36+ months. OP-1 Putty patients do not require autograft harvest and therefore avoid the pain and morbidity associated with the autograft harvest procedure.

Table 25: Donor Site Pain Status at 36+ Months (Safety Population, Autograft Only)

Visit	Statistic	Autograft				Total
		None	Mild	Moderate	Severe	
36+ Months	n (%)	34 (65.4)	9 (17.3)	9 (17.3)	0 (0.0)	52

Note: The percentages are based on the total number of patients with data at each visit.

Source: Statistical Table S.22.2 in Section 14.1 of this report, CSR 06-UPLF-01.

Listing 6 in Section 16.2 displays Visual Analog Scale for Pain Assessment data by patient.

11.3.2.3 General Health Survey (SF-36)

Patients completed the SF-36 questionnaire, a general health survey designed to measure a patient's perception of his/her overall health, functional status, and well being, at specified time points during the study period. SF-36 measures consist of an overall physical summary measure and an overall mental summary measure, in addition to 8 component scores: physical functioning, role-physical, bodily pain, mental health, role-emotional, social functioning, vitality, and general health perceptions. Increases in scores over time indicate improvement in the patient's perception of health status.

Table 26 presents physical component summary scores at 36+ months. Both treatment groups had statistically significant improvements from baseline. No statistically significant differences between treatment groups were observed for changes from baseline.

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty® for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (Extension to Pivotal Study S01-01US)

Table 26: SF-36 Physical Component Score (Safety Population)

Visit	Statistic	OP-1 Putty		Autograft		p-value ^a
		Actual Value	Change from Baseline	Actual Value	Change from Baseline	
Baseline	n	206	N/A	87	N/A	
	Mean	28.9	N/A	29.7	N/A	
	Median	28.6	N/A	28.7	N/A	
	Std. Dev.	6.13	N/A	6.38	N/A	
36+ Months	n	139	138	57	57	0.338
	Mean	41.0	11.8	39.3	10.4	
	Median	41.6	9.9	38.0	10.0	
	Std. Dev.	11.53	12.63	11.23	10.47	

(a) p-value is based on Wilcoxon rank-sum test that tests the change from baseline between treatment groups.

Source: Statistical Table S.23.1, Section 14.1, of this CSR 06-UPLF-01

Table 27 presents physical functioning scores at 36+ months. The changes from baseline for these score are similar to those of the physical component summary scores previously described and were not statistically significantly different between treatment groups.

Table 27: SF-36 Physical Functioning (Safety Population)

Visit	Statistic	OP-1 Putty		Autograft		p-value ¹
		Actual Value	Change from Baseline	Actual Value	Change from Baseline	
Baseline	n	208	N/A	87	N/A	
	Mean	26.8	N/A	26.6	N/A	
	Median	25.7	N/A	25.7	N/A	
	Std. Dev.	7.79	N/A	6.95	N/A	
36+ Months	N	141	141	57	57	0.206
	Mean	38.7	11.4	36.1	9.7	
	Median	40.4	10.5	36.2	7.9	
	Std. Dev.	12.87	13.17	11.96	10.84	

Note1: p-value is based on Wilcoxon rank-sum test to test the change from baseline between treatment groups.

Source for 36+ month data: Statistical Table S.23.3, Section 14.1

The improvements from baseline in both groups are consistent with the good results seen in the VAS and ODI analyses.

11.3.5 Statistical/Analytical Issues

11.3.5.1 Adjustments for Covariates

For the mITT population, the SAP analysis used a logistic regression model to take into account the effects on success rate of baseline characteristics that were statistically significant at the 0.10 significance level. The model yielded adjusted success rates. The characteristics considered in this analysis were:

- Age: <45 years old, 45-65 years old, >65 years old
- Clinical site
- Gender: male, female
- Level fused: L3-L4, L4-L5, L5-S1
- Grade of spondylolisthesis: Grade 1 or Grade 2
- Prior treatment: surgical (laminectomy, facetectomy, foraminotomy, discectomy), not surgical (includes no previous treatment)
- Concurrent medical condition: metabolic bone disease and/or osteoporosis (yes/no)
- Concurrent medical condition: diabetes (yes/no)
- Workers' compensation status: no or yes (includes current, pending, litigation, and other)
- BMI (continuous variable)
- ODI (continuous variable)

None of the characteristics was found to be statistically different between the two groups, therefore no adjustment analysis was conducted.

11.3.5.2 Handling of Dropouts or Missing Data

The number of mITT patients who had missing data and required imputation for the 24 month overall success rate (with radiographic and retreatment components at 36+ months) are tabulated in Section 14.2-Table S.3. Within the OP-1 Putty group, 29.5% of patients had missing data for the overall success rate. This is slightly lower than the 32.6% of patients with missing data in the autograft group, but this difference was not statistically significant ($p=0.676$, Statistical Table S.3.in Section 14.1).

Various approaches were used to handle missing data. Refer to the Statistical Analysis Plan (SAP) in Section 16.1.9.

11.3.5.3 Interim Analyses and Data Monitoring

Not applicable.

11.3.5.4 Multicenter Studies

The effect of clinical site (pooled for sites with small numbers of patients) on the primary efficacy endpoint was tested using a logistic regression model. Treatment-by-center interactions were examined for the analysis of the primary efficacy assessment of Overall Success at 24 months (with 36+ month radiographic and retreatment subcomponents) and were found not to be significant.

11.3.5.5 Multiple Comparisons/Multiplicity

No adjustments for multiple comparisons are made. A test of non-inferiority with respect to the primary efficacy endpoint was performed in the original study and, then, in the follow-on study a test of non-inferiority for a new version of the endpoint was performed. To some this may raise the issue of multiplicity and the potential need to make a multiplicity adjustment. It is Stryker's belief that the plain film x-rays taken at 24 months provided inaccurate and invalid assessments of radiographic success and hence should be disregarded.

Having arrived at this conclusion, we set about to obtain valid assessments of radiographic success. While ideally this would have been done at 24 months, since this was not possible, we obtained new assessments at the earliest possible time. It is our view that the resulting new version of the endpoint is simply, to the extent possible, a "corrected" version of the original endpoint. The non-inferiority test in the follow-on study is then a "corrected" version of the original test rather than a "new" test. As such, we do not think a multiplicity adjustment is appropriate.

11.3.5.6 Examination of Subgroups

Table 28 presents Overall Success rates at 24 months (with radiographic and retreatment data at 36+ months, missing data not imputed) by study group for males and females, and for each age category (<45 years old, 45-65 years old, >65 years old) are presented in Statistical Tables S.3.4.A for the mITT population. In the OP-1 Putty group, males and females achieved overall success at similar rates (39.6% for males, 36.7% for females).

In the autograft group, females achieved a higher percentage of overall success than males (31.6% for males, 43.6% for females). In the OP-1 Putty group, patients in the 45-65 years old category and in the >65 years old category achieved overall success at similar rates (36.1% for 45-65, 39.8% for >65), and there were only 2 patients in the <45 years old category (success rate 0.0%). In the autograft group, patients in the 45-65 years old category achieved higher rates of overall success as compared to patient in the >65 years old category (55.0% for 45-65, 31.6% for >65), and there were no patients in the <45 years old category. The difference in success rates in the autograft group between the 45-65 years old group and the >65 year old group may be due to the diminishing quality of autograft bone as patients age. Within each subgroup, no statistically significant difference was found between OP-1 Putty and autograft. The Supplemental Per Protocol population demonstrated similar results as illustrated in Statistical Table S.3.4.B (Section 14.1).

Table 28: Overall Success Rate at 24 Months (with radiographic and retreatment subcomponents at 36+ months) by Gender and Age Groups (mITT Population)

Patient Subgroup	OP-1 Putty		Autograft		p-value
	Number of Patients	Number (%) of Successes	Number of Patients	Number (%) of Successes	
Male	48	19 (39.6)	19	6 (31.6)	0.588
Female	98	36 (36.7)	39	17 (43.6)	0.560
<45 Years	2	0 (0.0)	0	0 (0.0)	---
45-65 Years	61	22 (36.1)	20	11 (55.0)	0.190
>65 Years	83	33 (39.8)	38	12 (31.6)	0.424

Note: Missing data were not imputed. Age determined at treatment in Pivotal Study S01-01US

Note: p-value is based on Fisher's Exact test.

Source data: Statistical Table S.3.4.A in Section 14.1, CSR 06-UPLF-01, Appendix B, Section V, PMA Amendment

11.4 EFFICACY CONCLUSIONS

This study demonstrated the following results with regard to overall success at 24 months with subcomponents related to radiographic success and retreatment success based on the 36+ month interval data:

- The primary endpoint, Overall Success (with ODI success, absence of SAE success, and neurological success at 24 months, and radiographic success and retreatment success at 36+ months), was met: OP-1 Putty treatment was demonstrated to be non-inferior to autograft (p=0.025). The estimated success rates were 47.2% for OP-1 Putty and 46.8% for autograft.

In addition, the study demonstrated the following results with regard to clinical outcomes measures at the 36+ month interval.

- ODI success: 68.6% of OP-1 Putty patients experienced at least a 20% improvement over baseline scores at 36+ months, as compared to 77.3% of autograft patients. The difference between groups was not statistically significant, $p=0.201$. Mean ODI scores at 36+ months were similar between treatment groups (22.9 for OP-1 Putty and 22.3 for autograft), as were mean improvements from baseline (25.3 for OP-1 Putty and 27.4 for autograft) and mean percent improvements from baseline (54.0% for OP-1 Putty and 54.5% for autograft).
- Absence of retreatment: 87.0% of OP-1 Putty patients were free from retreatment by 36+ months, whereas 83.3% of autograft patients were free from retreatment at 36+ months. The difference between groups is not statistically significant ($p=0.529$)
- Absence of serious treatment-related AEs: OP-1 Putty and autograft demonstrated comparable percentages of patients free from serious treatment-related adverse events up to and including the 36+ month interval (79.5% for OP-1 Putty and 73.5% for autograft). The difference between groups was not statistically significant ($p=0.387$).
- Neurological success: 84.4% of OP-1 Putty and 80.0% of autograft patients were neurological successes up through and including the 36+ months interval. The difference between groups was not statistically significant ($p=0.540$).
- Radiographic success: 60.7% of OP-1 Putty patients and 63.1% of autograft patients achieved radiographic success at 36+ months. The OP-1 Putty group was not statistically non-inferior to the autograft group with regard to this secondary outcome measure ($p=0.138$); however, there were no statistically significant differences between the OP-1 Putty and autograft groups with regard to the three subcomponents of Overall Radiographic Success at 36+ Months (non-imputed):
 - Presence of bone on 36+ month CT scans: 74.8% of OP-1 Putty patients demonstrated presence of bone by 36+ month CT scans, as compared to 77.4% of autograft patients ($p=0.852$).
 - Translational movement success: 75.7% of OP-1 Putty patients demonstrated success, and 75.4% of autograft patients demonstrated success ($p=1.000$).
 - Angulation success: 69.3% of OP-1 Putty patients demonstrated success, and 68.4% of autograft patients demonstrated success ($p=1.000$).
- Presence of bone on CT at 9 months (using same radiographic assessment protocol used for 36+ month CT scans): OP-1 Putty demonstrated presence of bone in 79.5% of patients. While autograft demonstrated presence of bone in 97.5% of patients, it is difficult to distinguish in this group whether the visible bone at 9 months is de novo

bone formation or the autograft itself. In the OP-1 Putty group, all bone visible on CT scans is de novo bone formation, because there is no other graft material present and the OP-1 Putty itself is not radiopaque. While 9 months is not an adequate length of time post surgery to assess peak de novo bone formation, this analysis demonstrates that the majority of patients in the OP-1 Putty group who had presence of bone by 36+ months also showed presence of bone by 9 months.

- SF-36 and VAS pain scales demonstrated significant improvements for patients in both treatment groups. In addition, the avoidance of a second surgical procedure resulted in absence of donor site pain in the OP-1 Putty group; whereas 35% of patients in the autograft group had mild to moderate donor site pain as long as 36+ months after surgery.

OP-1 Putty is equivalent to autograft with regard to the primary composite endpoint of overall success. OP-1 Putty was also shown to be clinically comparable to autograft with regard to the secondary measures of overall radiographic success, improvement in Oswestry Disability Index, absence of decrease in neurological success, incidence of treatment-related serious adverse events, and retreatment rate at the longer-term 36+ month follow-up interval. OP-1 Putty achieved improvements in VAS and SF-36 measures that were comparable to the improvements achieved by the autograft group, but without the additional comorbidities and surgical time associated with autograft harvest from the patient's iliac crest.

12. SAFETY EVALUATIONS

Safety data were analyzed using the safety population from pivotal study S01-01-US. Safety for this extension study was assessed principally based on the examination of:

- Adverse events assessed as ongoing at the time of the last study visit under Pivotal IDE S01-01US
- New serious adverse events
- New medical history and physical findings since last study visit under Pivotal IDE S01-01US
- Occurrence of any re-treatment to the original treated spinal level
- Neurological status

All patients who were positive for anti-OP-1 antibodies at the 24-month visit in the Pivotal IDE S01-01US (or who missed the 24-month visit but were antibody positive at their last recorded visit) had serum samples taken at the 36+ month visit in this extension study to assess any association between neutralizing antibodies and success outcomes.

Ongoing adverse events, new serious adverse events and new medical history and physical findings reported at 36+ months were classified by System Organ Class (SOC) and preferred term, and a conservative statistical cut-off ($p \leq 0.2$) was imposed to identify potential differences between treatment groups. (p -values were calculated for SOC terms reported by $\geq 5\%$ of patients in at least one treatment group using Fisher's exact test.)

12.1 DURATION OF OBSERVATION

Extension study 06-UPLF-01 consisted of a single follow-up evaluation at the 36+ month interval. Average duration of follow-up since the study treatment was 4.4 years (range 3.7 to 5.5 years).

12.2 ADVERSE EVENTS – ONGOING AT CLOSE OF S01-01US

At the time of the last patient visit for study S01-01US, there were 203 adverse events (AEs) in 99 (47.6%) patients in the OP-1 group and 78 AEs in 35 (40.2%) patients in the autograft group that were assessed as ongoing. Of these, the percentage of events that continued to be ongoing in 06-UPLF-01 versus events that had resolved was higher for the OP-1 Putty group: 154 (75.9%) AEs in the OP-1 group, and 64 (53.8%) AEs in the

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

autograft group were reported as still ongoing (not resolved) during the prospective data collection for 06-UPLF-01.

The percentage of ongoing events that had become serious adverse events since Pivotal Study S01-01US was low in both groups, although was higher for the autograft group: 4.4% for the OP-1 Putty group and 9.0% for the autograft group. The percentage of ongoing events that had resulted in spine surgery since Pivotal IDE S01-01US was also low in both groups, although was higher in the autograft group: 1.5% for the OP-1 Putty group and 5.1% for the autograft group. See Table 29.

Table 29: Outcome and Action Taken Since Last IDE Visit for Ongoing Adverse Events

	OP-1 Putty	Autograft
	Number (%) of Events	Number (%) of Events
Total Number of Ongoing AEs (last IDE visit)	203 (100.0)	78 (100.0)
Previously Reported as SAE		
Yes	22 (10.8)	1 (1.3)
No	181 (89.2)	77 (98.7)
Became an SAE Since Last Visit		
Yes	9 (4.4)	7 (9.0)
No	165 (81.3)	68 (87.2)
Not Applicable (already classified as SAE)	22 (10.8)	1 (1.3)
Missing	7 (3.4)	2 (2.6)
Current AE Status		
Ongoing	154 (75.9)	64 (53.8)
Resolved	42 (20.7)	12 (15.4)
Unknown	7 (3.4)	2 (2.6)
Action Taken Since Last Visit (a)		
None	134 (66.0)	42 (53.8)
Spine Surgery	3 (1.5)	4 (5.1)
Non-Spine Surgery	9 (4.4)	3 (3.8)
Medication	45 (22.2)	16 (20.5)
Other	18 (8.9)	13 (16.7)
Unknown	8 (3.9)	2 (2.6)

Source: Statistical Table S.16.1 in Section 14.1

(a) Because multiple actions could have been taken for an adverse event, the sum of percentages may exceed 100%

The system organ class **General Disorders and Administration Site Conditions** was the only SOC category where the difference between treatment groups was statistically significant at $p \leq 0.02$: events were reported in 6 (2.9%) OP-1 Putty patients and 6 (6.9%) autograft patients ($p=0.191$). The most frequently occurring preferred term within this SOC was asthenia: 2 (1.0%) patients for OP-1 Putty group, and 3 (3.4%) patients for the autograft group.

Statistical Table S.16.2 in Section 14.1 displays the adverse events from Pivotal Study S01-01US that were ongoing at the last S01-01US study visit by system organ class and preferred term. (These adverse events, which were ongoing from S01-01US, have already been reported and their relative frequencies analyzed during S01-01US.) Listing 8 in Section 16.2 displays the status of adverse events reported as ongoing at the last visit of Pivotal Study S01-01US.

The majority of ongoing AEs did not require treatment, 134 (66.0%) events in the OP-1 group and 42 (53.8%) events in the autograft group, or were treated with medication, 45 (22.2%) OP-1 events and 16 (20.5%) autograft events. Ongoing events that resulted in spine surgery since Pivotal IDE S01-01US included 3 (1.5%) events in the OP-1 group, and 4 (5.1%) events in the autograft group. (Source: Statistical Table S.16.1 in section 14.1.)

A total of 16 ongoing adverse events became serious during the time interval of the prospective data collection study: 9 (4.3%) ongoing AEs in the OP-1 group and 7 (9.0%) ongoing AEs in the autograft group. Fourteen of the events became serious due to surgery performed to treat the event, resulting in hospitalization. The remaining 2 SAEs, ventricular fibrillation and neuropathy peripheral, were assessed as serious upon medical review. The majority of the SAEs (13 [81%]) were assessed as not related to treatment. Two events were assessed as related to treatment – back pain in an autograft patient and pain in extremity in an OP-1 patient - both of which required spine surgery. One event of back pain in an OP-1 patient, which was treated with a multilevel laminectomy and discectomy, was assessed as relationship to treatment unknown. Narratives for ongoing AEs that became SAEs are included in Section 14.2 of this study report.

12.3 NEW SERIOUS ADVERSE EVENTS

12.3.1 Overall Incidence of New Treatment Emergent Serious Adverse Events

In this extension study, a total of 55 new treatment-emergent SAEs were experienced by 41 patients in the OP-1 and autograft treatment groups combined. In the OP-1 Putty group, 24 (11.5%) of patients experienced a total of 33 SAEs, compared to 17 (19.5%) patients who experienced a total of 22 SAEs in the autograft group ($p=0.095$). Table 30 presents the number and percent of patients who reported at least one new serious adverse event during extension study 06-UPLF-01.

New serious AEs that were treatment-related were reported infrequently in both study groups, although the percentage of patients with new SAEs that were treatment-related was higher in the control group (1.0% for the OP-1 Putty group, and 5.7% for the autograft group). The percentage of patients with new SAEs that were severe was similar between treatment groups: 7.2% for the OP-1 Putty group, and 10.3% for the autograft group. Narratives describing all new SAEs may be found in Section 14.2 and Listings are provided in Section 16.2.

Table 30: New Serious Adverse Events (Safety Population)

Parameter	OP-1 Putty (N=208)	Autograft (N=87)	p-value
	Number (%) of Patients with Events	Number (%) of Patients with Events	
Any New Serious Adverse Event	24 (11.5)	17 (19.5)	0.095
New Serious Adverse Events – Treatment Related (Suspected-related or unknown)	2 (1.0)	5 (5.7)	--
New Serious Adverse Events – Severe	15 (7.2)	9 (10.3)	--
Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps)	1 (0.5)	2 (2.3)	--

Source: Statistical Tables S.17.1, S.17.2, S.17.3 in Section 14.1.

The percentages of patients with new SAEs that were “mild”, “moderate” and “severe” were no higher for the OP-1 Putty group than for the autograft group. (Source: Statistical Table S.17.2 in Section 14.1.) Of the new serious adverse events, only 2 patients (1.0%) in the OP-1 Putty group and 5 patients (5.7%) in the autograft group had SAEs that were classified by the Principal Investigator as “Suspected Related” to study treatment or relationship to study treatment “Unknown.” (Source: Statistical Table S.17.3 in Section 14.1.)

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty® for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (Extension to Pivotal Study S01-01US)

Table 31 presents new SAEs by System Organ Class (SOC). New serious adverse events were classified by SOC, and a conservative statistical cut-off ($p \leq 0.2$) was imposed to identify potential differences in new serious adverse events by SOC between treatment groups. (p-values were calculated for SOC terms reported by $\geq 5\%$ of patients in at least one treatment group using Fisher's exact test.) The safety profiles of the two treatment groups were generally comparable, with no statistically significant differences at $p \leq 0.2$ between treatment groups regarding any particular SOC category.

Table 31: Incidence of New Adverse Events by MedDRA System Organ Class (Safety Population)

System Organ Class	Number (%) of Patients		p-value(a)	Number (%) of Events	
	OP-1 Putty (N=208)	Autograft (N=87)		OP-1 Putty	Autograft
Total	24 (11.5)	17 (19.5)	0.095	33 (100)	22 (100)
Congenital, Familial and Genetic Disorders	2 (1.0)	0 (0.0)		2 (6.1)	0 (0.0)
Gastrointestinal Disorders	3 (1.4)	1 (1.1)		3 (9.1)	1 (4.5)
Hepatobiliary Disorders	0 (0.0)	2 (2.3)		0 (0.0)	2 (9.1)
Infections And Infestations	1 (0.5)	1 (1.1)		1 (3.0)	1 (4.5)
Injury, Poisoning and Procedural Complications	6 (2.9)	4 (4.6)		8 (24.2)	5 (22.7)
Investigations	0 (0.0)	1 (1.1)		0 (0.0)	1 (4.5)
Metabolism and Nutritional Disorders	1 (0.5)	1 (1.1)		1 (3.0)	1 (4.5)
Musculoskeletal and Connective Tissue Disorders	7 (3.4)	6 (6.9)	0.214	9 (27.3)	7 (31.8)
Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps)	1 (0.5)	2 (2.3)		1 (3.0)	2 (9.1)
Nervous System Disorders	4 (1.9)	2 (2.3)		4 (12.1)	2 (9.1)
Renal and Urinary Disorders	2 (1.0)	0 (0.0)		2 (6.1)	0 (0.0)
Reproductive System and Breast Disorders	1 (0.5)	0 (0.0)		1 (3.0)	0 (0.0)
Surgical and Medical Procedures	1 (0.5)	0 (0.0)		1 (3.0)	0 (0.0)

Source: Statistical Table S.17.1 in Section 14.1.

Note: Number of patients refers to patients with at least one adverse event of the indicated type. Number of events refers to all events of the indicated type. Percentages are based on the total number of patients or the total number of adverse events, as appropriate. Patients experiencing multiple events under the same system organ class/preferred term are counted only once for that system organ class/preferred term.

(a) p-values are calculated for all SOC terms reported by $\geq 5\%$ patients in at least one treatment group, using Fisher's exact test.

The most frequently reported new serious adverse events in both treatment groups were in the **Musculoskeletal and Connective Tissue Disorders** SOC, with a greater percentage of events reported in the autograft group: seven patients (3.4%) in the OP-1 Putty group, and six patients (6.9%) in the autograft group (p=0.214). Table 32 compares the number of patients and events for each treatment group by the preferred terms within this SOC. There are no notable differences with regard to the frequency of specific preferred terms—all occurred in 1.1% or less of patients in either treatment group, with the exception of back pain, which occurred in 3 (3.4%) patients in the autograft group. Back pain was the preferred term most frequently reported as a new serious adverse event within this SOC: 4 (1.4%) of patients overall, with 1 (0.5%) patient in the OP-1 Putty group, and 3 (3.4%) patients in the autograft group (Source: Statistical Table S.17.1 in Section 14.1). In this SOC, 2 patients (1.0%) in the OP-1 Putty group and 2 patients (2.3%) in the autograft group experienced events that were classified as either “suspected related” to treatment or relationship to treatment “unknown.” (Source: Statistical Table S.17.3 in Section 14.1.) In this SOC, OP-1 Putty patients did not experience a higher rate of events classified as moderate or severe as compared with the autograft group: 6 (2.9%) moderate or severe for the OP-1 Putty group, and 5 (5.7%) moderate or severe for the autograft group. (Source: Statistical Table S.17.2 in Section 14.1)

Table 32: Incidence of Musculoskeletal and Connective Tissue Disorders at 36+ Months (Safety Population)

System Organ Class/Preferred Term	Number (%) of Patients		p-value	Number (%) of Events	
	OP-1 Putty (N=208)	Autograft (N=87)		OP-1 Putty	Autograft
Musculoskeletal and Connective Tissue Disorders	7 (3.4)	6 (6.9)	0.214	9 (27.3)	7 (31.8)
Arthralgia	1 (0.5)	1 (1.1)		1 (3.0)	1 (4.5)
Arthritis	1 (0.5)	1 (1.1)		1 (3.0)	1 (4.5)
Back Pain	1 (0.5)	3 (3.4)		1 (3.0)	3 (13.6)
Lumbar Spinal Stenosis	2 (1.0)	0 (0.0)		2 (6.1)	0 (0.0)
Musculoskeletal Stiffness	0 (0.0)	1 (1.1)		0 (0.0)	1 (4.5)
Osteoarthritis	2 (1.0)	1 (1.1)		2 (6.1)	1 (4.5)
Scoliosis	1 (0.5)	0 (0.0)		1 (3.0)	0 (0.0)
Spinal Column Stenosis	1 (0.5)	0 (0.0)		1 (3.0)	0 (0.0)

Note: Number of patients refers to patients with at least one adverse event of the indicated type. Number of events refers to all events of the indicated type. Percentages are based on the total number of patients or the total number of treatment emergent serious adverse events, as appropriate. Patients experiencing multiple events under the same system organ class/preferred term are counted only once for that system organ class/preferred term.

Source: Statistical Table S.17.1 in Section 14.1.

Injury, Poisoning, and Procedural Complications was the SOC with the second highest frequency. The OP-1 Putty group had events in 6 (2.9%) patients, and the autograft group had events in 4 (4.6%) patients. The preferred terms within this SOC that were potentially spine-related included spinal compression fracture and subdural haematoma, which occurred in one patient each in the OP-1 Putty group.

12.3.2 New Treatment Emergent Serious Adverse Events by Causality

In both treatment groups, the majority of patients experienced SAEs that were assessed as not related to study treatment. New SAEs for which relationship to treatment was considered “Suspected Related” or “Unknown” was low for both groups, although higher in the autograft group: 1.0% for patients in the OP-1 Putty group, and 5.7% for patients in the autograft group. (Source: Statistical Table S.17.3 in Section 14.1) Overall, 3 patients experienced SAEs that were assessed as suspected related to treatment: 2 patients in the autograft group each had a suspected related SAE of back pain, and 1 patient in the OP-1 group had suspected related SAEs of spondylolisthesis and lumbar spinal stenosis. The causality of SAEs in 4 patients was assessed as unknown: 2 autograft patients experienced 1 event each of fall, 1 autograft patient experienced an SAE of ovarian cancer, and 1 OP-1 patient experienced events of back pain, spondylolisthesis, and lumbar spinal stenosis. Table 33 summarizes new treatment related (suspected related or unknown) serious adverse events. There do not appear to be any emerging patterns of concern at 36+ months regarding the frequency of new SAEs attributed to OP-1 Putty treatment as compared to autograft.

Table 33: New Treatment-Related (Suspected Related or Unknown) Serious Adverse Events

System Organ Class/Event	Number (%) OP-1 Putty Patients (N=208)		Number (%) Autograft Patients (N=87)	
	Suspected Related	Unknown	Suspected Related	Unknown
Musculoskeletal and Connective Tissue Disorders				
Back Pain	0 (0.0)	1 (0.5)	2 (2.3)	0 (0.0)
Lumbar Spinal Stenosis	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
Injury, Poisoning and Procedural Complications				
Fall	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.3)
Congenital, Familial, and Genetic Disorders				
Spondylolisthesis	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
Neoplasms, Benign, Malignant, and Unspecified				
Ovarian Cancer	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)

Source: Statistical Table S.17.3 in Section 14.1

12.3.3 Listings and Tables of New Serious Adverse Events

A patient listing of new SAEs reported during this extension study is presented in Section 16.2, Listing 9. The following Statistical Tables in Section 14.1 present additional displays of new serious adverse events:

- Statistical Table S.17.1: New Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term – Safety Population
- Statistical Table S.17.2: New Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term, and Severity – Safety Population
- Statistical Table S.17.3: New Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term, and Relationship – Safety Population
- Statistical Table S.17.4.A through S.17.4.D: Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term, and Time Since PLF (for Study S01-01US and 06-UPLF-01 combined)
- Statistical Table S.17.5: Outcome and Action Taken for New Treatment-Emergent Serious Adverse Events– Safety Population

12.4 NEW MEDICAL HISTORY AND PHYSICAL FINDINGS

12.4.1 Overall Incidence of New Medical History and Physical Findings

New medical history and physical findings reported at 36+ months were also evaluated by SOC and preferred term (Statistical Table S.18.1 in Section 14.1). The percentage of patients with new medical history or physical findings was 31.7% in the OP-1 Putty group and 43.7% in the autograft group ($p=0.061$). A conservative statistical cut-off ($p\leq 0.2$) was imposed to identify potential differences in new findings by SOC between treatment groups. (p -values were calculated for SOC terms reported by $\geq 5\%$ of patients in at least one treatment group using Fisher's exact test.) While the new findings profiles of the two treatment groups were generally comparable, for the SOC of Nervous System Disorders, the autograft group showed an overall higher incidence of new SAEs than did the OP-1 Putty group based on this statistical cut-off (21 (10.1%) patients for OP_1 Putty, 14 (16.1%) patients for autograft, $p=0.167$). There were no SOC categories in which the OP-1 Putty group demonstrated an overall higher incidence than the autograft group based on this statistical cut-off. Table 34 presents the SOC categories where there was a difference between groups of $p\leq 0.2$.

The new medical history and physical findings in the remaining SOCs were reported with similar frequency in both treatment groups. Further, an analysis of the SOCs by the preferred terms that were of particular relevance to an assessment of spinal fusion success (spondylolisthesis, gait disturbance, back injury, back pain, buttock pain, lumbar spinal stenosis, pseudarthrosis, spinal column stenosis, and spinal osteoarthritis, dysaesthesia, hypoaesthesia, hyporeflexia, radiculopathy, sciatica, back injury) revealed no clinically meaningful differences. (See Table 35, Table 36, and Table 37.) The percentages of patients with new medical histories or physical findings that were "moderate" or "severe" were no higher for the OP-1 Putty group than for the autograft group. In the OP-1 Putty group, of the patients who had new findings, 24 (11.5%) were moderate, and 17 (8.2%) were severe. In the autograft group, of the patients who had new findings, 15 (17.2) were moderate, and 12 (13.8%) were severe. (Source: Statistical Table S.18.2 in Section 14.1.)

Table 34: New Medical History and Physical Findings by SOC for any SOC with Difference $p \leq 0.2$ (Safety Population)

System Organ Class	Number (%) of Patients		p-value (a)	Number (%) of Events	
	OP-1 Putty (N=208)	Autograft (N=87)		OP-1 Putty (N=140)	Autograft (N=86)
Nervous Systems Disorders	21 (10.1)	14 (16.1)	0.167	37 (26.4)	22 (25.6)

Source: Statistical Table S.18.1 in Section 14.1.

Note: Number of patients refers to patients with at least one event of the indicated type. Number of events refers to all events of the indicated type. Percentages are based on the total number of patients or the total number of adverse events, as appropriate. Patients experiencing multiple events under the same system organ class/preferred term are counted only once for that system organ class/preferred term.

(a) p-values calculated for SOC terms reported by $\geq 5\%$ patients in at least one treatment group, using Fisher's exact test.

The most frequent new medical history and physical findings were in the SOCs of Musculoskeletal and Connective Tissue Disorders; Nervous Systems Disorders; and Injury, Poisoning and Procedural Complications. Each of these SOCs is discussed below.

New findings in both treatment groups were most frequently reported in the **Musculoskeletal and Connective Tissue Disorders** SOC. Thirty-five patients (16.8%) in the OP-1 Putty group, and twenty patients (23.0%) in the autograft group had new medical history or physical findings reported at 36+ months for this SOC ($p=0.251$). The preferred terms within this SOC that are most relevant to an assessment of the comparative safety of OP-1 Putty for spinal fusion include back pain, buttock pain, lumbar spinal stenosis, muscle spasms, pain in extremity, pseudarthrosis, spinal column stenosis, and spinal osteoarthritis. Table 35 displays the comparative frequencies of new findings for the spine-related preferred terms within the Musculoskeletal and Connective Tissues Disorders SOC for the OP-1 Putty and autograft groups at 36+ months. There do not appear to be any notable differences between groups with regard to these preferred terms, except for back pain, which occurred in fewer OP-1 Putty patients (3.4% for OP_1 Putty and 12.6% for autograft). Section 12.4.2 presents an analysis of new medical history and physical findings by relationship to treatment.

Table 35: New Medical History and Physical Findings, Occurrence of Potentially Spine-Related Preferred Terms within Musculoskeletal and Connective Tissue Disorders SOCs

System Organ Class/Preferred Term	Number (%) of Patients		p-value for difference	Number (%) of Events	
	OP-1 Putty (N=208)	Autograft (N=87)		OP-1 Putty (N=140)	Autograft (N=86)
Musculoskeletal and Connective Tissue Disorders*	35 (16.8)	20 (23.0)	0.251	53 (37.9)	29 (33.7)
Back Pain	7 (3.4)	11 (12.6)		7 (5.0)	12 (14.0)
Buttock Pain	2 (1.0)	1 (1.1)		2 (1.4)	1 (1.2)
Lumbar Spinal Stenosis	3 (1.4)	0 (0.0)		3 (2.1)	0 (0.0)
Muscle Spasms	2 (1.0)	0 (0.0)		3 (2.1)	0 (0.0)
Pain in Extremity	7 (3.4)	4 (4.6)		9 (6.4)	5 (5.8)
Pseudarthrosis	0 (0.0)	2 (2.3)		0 (0.0)	2 (2.3)
Spinal Column Stenosis	1 (0.5)	0 (0.0)		1 (0.7)	0 (0.0)
Spinal Osteoarthritis	0 (0.0)	1 (1.1)		0 (0.0)	1 (1.2)

* Numbers and percents are shown for overall SOC, and for only those preferred terms within the SOC that are relevant to spinal fusion surgery.

Note: p-value calculated using Fisher's Exact test

Source: Statistical Table S.18.1 in Section 14.1.

The second most frequently reported SOC for new medical history and physical findings was **Nervous System Disorders**. Twenty-one patients (10.1%) in the OP-1 Putty group, and fourteen patients (16.1%) in the autograft group had new medical history or physical findings reported at 36+ months for this SOC, and the difference was statistically significant based on the conservative cutoff of $p \leq 0.2$ (difference between groups $p = 0.167$). The preferred terms within this SOC that are considered relevant to an assessment of the comparative safety of OP-1 Putty for spinal fusion surgery include dysaesthesia, hypoaesthesia, hyporeflexia, radiculopathy, and sciatica. Table 36 displays the comparative frequencies of new findings for the potentially spine-related preferred terms within the Nervous System Disorders SOC for the OP-1 Putty and autograft groups at 36+ months. There do not appear to be any notable differences in the percent of patients reporting these potentially spine-related preferred terms. Section 12.4.2 presents an analysis of new medical history and physical findings by relationship to treatment.

Table 36: New Medical History and Physical Findings, Occurrence of Potentially Spine-Related Preferred Terms within Nervous Systems Disorders SOCs

System Organ Class/Preferred Term	Number (%) of Patients		p-value for difference	Number (%) of Events	
	OP-1 Putty (N=208)	Autograft (N=87)		OP-1 Putty (N=140)	Autograft (N=86)
Nervous Systems Disorders*	21 (10.1)	14 (16.1)	0.167	37 (26.4)	22 (25.6)
Dysaesthesia	5 (2.4)	2 (2.3)		14 (10.0)	6 (7.0)
Hypoaesthesia	2 (1.0)	1 (1.1)		2 (1.4)	1 (1.2)
Hyporeflexia	7 (3.4)	1 (1.1)		10 (7.1)	2 (2.3)
Radiculopathy	1 (0.5)	2 (2.3)		1 (0.7)	2 (2.3)
Sciatica	1 (0.5)	0 (0.0)		1 (0.7)	0 (0.0)

* Numbers and percents are shown for overall SOC, and for only those preferred terms within the SOC that are relevant to spinal fusion surgery.

Note: p-value calculated using Fisher's Exact test

Source: Statistical Table S.18.1 in Section 14.1.

In the SOC **Injury, Poisoning and Procedural Complications**, the autograft group reported an overall higher percentage of patients reporting events: 9 patients (4.3%) reported new findings in the OP-1 Putty group, and 7 patients (8.0%) reported new findings in the autograft group (p=0.257). The difference appears to be primarily related to the higher incidence of the preferred term “fall” within the autograft group (0.5% patients in the OP-1 Putty group and 6.9% in the autograft group). Of the preferred terms within this SOC, Back Injury, were identified as relevant to assessing the comparative safety of OP-1 Putty, and these findings occurred only in the OP-1 Putty group. Back Injury occurred in one patient (0.5%); however, these findings were classified as not related to OP-1 Putty treatment. Table 37 Presents the new findings reported at 36+ months under the SOC Injury, Poisoning and Procedural Complications.

Table 37: Incidence of Injury, Poisoning and Procedural Complications – New Medical History/Physical Findings (Safety Population)

System Organ Class/Preferred Term	Number (%) of Patients		p-value for difference	Number (%) of Events	
	OP-1 Putty (N=208)	Autograft (N=87)		OP-1 Putty (N=140)	Autograft (N=86)
Injury, Poisoning and Procedural Complications	9 (4.3)	7 (8.0)	0.257	11(7.9)	10 (11.6)
Back Injury	1 (0.5)	0 (0.0)		1 (0.7)	0 (0.0)
Concussion	0 (0.0)	1 (1.1)		0 (0.0)	1 (1.2)
Fall	1 (0.5)	6 (6.9)		1 (0.7)	7 (8.1)
Femur Fracture	1 (0.5)	0 (0.0)		1 (0.7)	0 (0.0)
Hip Fracture	2 (1.0)	0 (0.0)		2 (1.4)	0 (0.0)
Joint Dislocation	1 (0.5)	0 (0.0)		1 (0.7)	0 (0.0)
Lower Limb Fracture	1 (0.5)	0 (0.0)		2 (1.4)	0 (0.0)
Pelvic Fracture	0 (0.0)	1 (1.1)		0 (0.0)	1 (1.2)
Upper Limb Fracture	0 (0.0)	1 (1.1)		0 (0.0)	1 (1.2)

Source: Statistical Table S.18.1 in Section 14.1

Note: p-value calculated using Fisher’s Exact test

Note: Number of patients refers to patients with at least one event of the indicated type. Number of events refers to all events of the indicated type. Percentages are based on the total number of patients or the total number of events, as appropriate. Patients experiencing multiple events under the same system organ class/preferred term are counted only once for that system organ class/preferred term. New medical history/physical findings that are classified as serious are also reported in serious adverse event tables.

12.4.2 New Medical History and Physical Findings by Causality

The percentage of patients for whom new medical history and physical findings was considered “Suspected Related” or “Unknown” was 6.3% in the OP-1 Putty group and 12.6% in the autograft group. (Source: Statistical Table S.18.3 in Section 14.1.) Table 38 presents new medical history and physical findings by SOC and relationship to treatment for those events that were classified as “Suspected Related” to treatment or relationship to treatment “Unknown.” The new medical history and physical findings in the OP-1 Putty group where relationship to treatment was suspected related or unknown included the following: back pain (n=3), spinal stenosis (n=2), buttock pain (n=2), pain in extremity (n=1), muscle spasms (n=1), dysaesthesia (n=3), hypoaesthesia (n=1), hypotonia (n=1), hyporeflexia (n=1), spondylolisthesis (n=2), precancerous cells (n=1), , depression (n=1), and renal failure (n=1). The new medical history and physical findings in the autograft group where relationship to treatment was suspected related or unknown included the following: back pain (n=7), pain in extremity (n=1), pseudarthrosis (n=1), hyporeflexia (n=1), ovarian cancer (n=1), and fall (n=3). This analysis did not suggest that OP-1 Putty was more likely than autograft to be causally related to any concerning new medical history/physical findings.

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

Table 38: Treatment-Related (Suspected Related or Unknown) New Medical History or Physical Findings

System Organ Class/Event		Number (%) OP-1 Putty Patients (N=208)		Number (%) Autograft Patients (N=87)	
		Suspected Related	Unknown	Suspected Related	Unknown
Musculoskeletal and Connective Tissue Disorders					
	Back Pain	0 (0.0)	3 (1.4)	3 (3.4)	4 (4.6)
	Lumbar Spinal Stenosis	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
	Buttock Pain	0 (0.0)	2 (1.0)	0 (0.0)	0 (0.0)
	Pain in Extremity	0 (0.0)	1 (0.5)	0 (0.0)	1 (1.1)
	Muscle Spasm	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
	Pseudoarthrosis	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
Nervous System Disorders					
	Dysaesthesia	0 (0.0)	3 (1.4)	0 (0.0)	0 (0.0)
	Hypoaesthesia	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
	Hypotonia	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
	Hyporeflexia	0 (0.0)	1 (0.5)	1 (1.1)	0 (0.0)
Congenital, Familial, and Genetic Disorders					
	Spondylolisthesis	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
Neoplasms, Benign, Malignant, and Unspecified					
	Ovarian Cancer	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
General Disorders and Administration Site Conditions					
	Pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
Investigations					
	Precancerous Cells Present	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Injury, Poisoning, and Procedural					
	Fall	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.4)
Psychiatric Disorders					
	Depression	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Renal and Urinary Disorders					
	Renal Failure	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)

Source: Statistical Table S.18.3 in Section 14.1

Note: Number of patients refers to patients with at least one event of the indicated type. Percentages are based on the total number of patients with the event. Patients experiencing multiple events under the same system organ class/preferred term are counted only once for that system organ class/preferred term under the most related category in the order of suspected related, unknown, and not related. New medical history/physical findings that are classified as serious are also reported in serious adverse event tables.

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

12.4.3 Listings and Tables of New Medical History and Physical Findings

The following listings and tables display data new medical history and physical findings:

- Statistical Table S.18.1: New Medical History or Physical Findings by System Organ Class and Preferred Term – Safety Population
- Statistical Table S.18.2: New Medical History or Physical Findings by System Organ Class, Preferred Term, and Severity – Safety Population
- Statistical Table S.18.3: New Medical History or Physical Findings by System Organ Class, Preferred Term, and Relationship – Safety Population
- Statistical Table S.18.4: Outcome and Action Taken for New Medical History or Physical Findings – Safety Population
- Listing 3: Physical Exam and Medical History

12.5 SECONDARY PROCEDURES

In the study, a patient was a failure due to retreatment if the patient had a retreatment defined as a revision, removal, supplemental fixation, or reoperation intended to promote fusion at the treated level.

There were four patients (1.9%) in the OP-1 Putty group and 3 patients (3.4%) in the autograft group who had any surgical intervention to the treated spinal level reported at the 36+ month visit. (Source: Statistical Table S.19.1) Of these, one intervention (in the OP-1 Putty group) was not a study failure due to retreatment, because the surgical intervention at the treated level was not intended to promote fusion. The other six patients were failures due to retreatment as recorded in study 06-UPLF-01: 3 (1.4%) patients in the OP-1 group, and 3 (3.4%) patients in the autograft group. Table 39 presents the reasons for each failure due to retreatment reported in 06-UPLF-01:

Table 39: Failures due to Retreatment Identified in 06-UPLF-01

Treatment Group	Patient ID	Approximate Days to Retreatment	Description of Surgical Procedure	Hospitalization Status
OP-1 Putty	1117	1325	L3-S1 instrumented fusion	Inpatient
	2510	1506	L3 posterior revision decompression; transforaminal lumbar interbody fusion L3-L4; posterior instrumentation fusion L3-L4 with pedicle screws, rod, fluoroscopy; posteriolateral fusion with morcellized local autograft	Inpatient
	4506	1271	L3-5 instrumented fusion	Inpatient
Autograft	1202	1729	L4, L5 transforaminal lumbar interbody fusion	Inpatient
	2516	509*	Revision lumbar decompression bilateral; post lateral spinal fusion-all; post lumbar interbody fusion: 4-5; instrumented interbody prosthesis: 4-5; segment instrument: 1-5; local autologous bone graft; reduction lumbar kyphosis; intraoperative interpretive fluoroscopy	Inpatient
	4701	861	Spine surgery L3-L4; posterior spinal fusion with instrumentation from L3 to L5 with a decompression at L5-S1	Inpatient

* Retreatment occurred during pivotal study interval, but was not reported until follow-up study 06-UPLF-01

Failures due to retreatment are also discussed in Section 11.3.2.2, because absence of retreatment is a secondary efficacy measure as well as a safety measure. Listing 10 in Section 16.2 displays surgical procedures resulting from adverse events that were reported in this extension study. Statistical Tables S.19.1 and S.19.2 present surgical interventions to the treated spinal level, and describe the classification of surgical

intervention (revision, removal, supplemental fixation, reoperation intended to promote fusion, reoperation not intended to promote fusion).

12.6 NEUROLOGICAL STATUS

While neurological status was cited in the SAP as a safety measurement, absence of a decrease in neurological status is also one of the secondary effectiveness measures, and neurological status results have therefore been presented and discussed in Section 11.3.2.4 of this document.

12.7 DEATH, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

12.7.1 Deaths

A total of 11 patients died over the course of the Pivotal Study S01-01US, as described in clinical study report S01-01US (seven in OP-1 Putty group, and four in the autograft group). An additional five patients died after S01-01US (four from the OP-1 Putty group and one from the autograft group), and could not therefore be enrolled in extension study 06-UPLF-01. Anecdotal information regarding the causes of death for these five patients was collected during attempts to locate and enroll patients for 06-UPLF-01, and this information is presented in Table 40. No information linking any of these deaths to the study procedure was provided to the sponsor, and neither the causes of death reported nor the time at which these events occurred suggests any causal link between the deaths and the study procedures.

Table 40: Deaths Recorded After S01-01US

Treatment Group	Patient ID	Cause of Death	Date of Death
OP-1 Putty	1506	Cerebrovascular Accident	15 Aug 2003
	2307	Pulmonary fibrosis	15 Aug 2006
	2406	Brain mass consistent with glioblastoma	18 Nov 2005
	3107	Unknown	Unknown
Autograft	1102	Subarachnoid hemorrhage	15 Mar 2007

12.7.2 Heterotopic Bone Formation

There were no new serious adverse events or new medical history/physical findings of heterotopic bone formation reported in extension study 06-UPLF-01.

As previously reported in clinical study report CSR S01-01US, there were 3 patients in the Pivotal Study who experienced heterotopic ossification as an adverse event but who had not required surgical intervention as of the close of Pivotal IDE S01-01US. These patients were therefore eligible for participation in 06-UPLF-01 (because they were not retreatment failures), and any additional information received about these patients during the extension study 06-UPLF-01 is summarized below:

Table 41: Additional Information on Patients Who Experienced HTO-Related Adverse Events in S01-01US

Patient ID	Information reported in CSR S01-01US	New information collected during 06-UPLF-01
1501	Received OP-1 Putty at level L3-4 on 21 March 2002. Reported excessive bone pain over the right posterior iliac region in September 2002. Heterotopic bone formation was reported as an AE on 11 December 2002, and again on 6 March 2004, and 24 March 2005. The patient was subsequently diagnosed with recurrent lumbar spinal stenosis at L4-5 which required hospitalization and a revision micro-decompression of L4-L5 on 11 Jan 2005 (1017 days post initial surgery). CT scans for this patient were reviewed by the independent reviewer for neurological success/failure assessments, who determined that the spinal stenosis at this level was unrelated to the heterotopic bone formation. The event was considered resolved on 23 June 2005	This patient experienced an additional event reported as an SAE: right total knee arthroplasty on October 30, 2006. No new complaints or findings of L4-L5 lumbar spinal stenosis (although date of micro-decompression of L4-L5 previously reported as occurring on 11 Jan 2005 has since been reported as occurring on 11 May 2005), nor any reports of HTO at the iliac crest have been reported in 06-UPLF-01.
4405	Received OP-1 Putty. Had discogenic bridging documented which was reported as an intervertebral disc disorder and required treatment with physical therapy.	This patient did not return to participate in 06-UPLF-01. No further information has been provided in 06-UPLF-01.
4702	Received OP-1 Putty at level L4-L5 on 10 January 2003. On 28 October 2003, was found to have heterotopic ossification extending from the right side of the fusion mass and the interval between the iliacus and psoas, extending into the pelvis	No new SAEs have been reported for this patient.

Source: Listing 9. Narratives in Section 14.2

12.7.3 Malignancies

As presented in Table 42, 4 patients across both treatment groups reported 5 new medical conditions/physical findings events in the SOC Neoplasms, Benign and Malignant (including cysts and polyps) at 36+ months: 2 patients in the OP-1 Putty group (1.0%) and 2 patients in the autograft group (2.3%). Three of five events were considered to be SAEs: 1 in the OP-1 Putty group, and 2 in the autograft group. The malignancy reported as an SAE in the OP-1 Putty group included vaginal cancer. In the autograft group, one occurrence each of ovarian cancer and breast cancer was reported as an SAE. Narratives of the events reported under the SOC for neoplasms, benign and malignant (including cysts and polyps) reported as serious adverse events may be found in Section 14.2. The two events that were not reported as SAEs (but only as new medical history/physical findings) occurred in the OP-1 Putty group and included basal cell carcinoma and benign neoplasm. In addition, one patient in the autograft group developed prostate cancer, although this event was reported as a new SAE under the SOC category of Investigations (Prostatic Specific Antigen Increase). The event was classified as severe, but not related to the study procedure. Finally, the cause of death for one patient in the OP-1 Putty group who died subsequent to pivotal study S01-01US (patient ID 2406) and prior to extension study 06-UPLF-01 was reported during attempts at follow-up as having died of a “brain mass consistent with glioblastoma.” However, as this patient could not be enrolled in 06-UPLF-01, no further information was available for this event, nor could the cause of death be confirmed.

None of the five malignancies reported within the study were determined to have a causal relationship to either OP-1 Putty or autograft, although the ovarian cancer that occurred in the autograft group was classified as relationship to treatment “unknown.” There were no patterns or specific events of concern identified at the 36+ month interval with respect to type of cancer or distribution between treatment groups.

Table 42: Patients with Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps) System Organ Class

Treatment Group	Patient ID	Event	Relationship	Severity	Approximate Days to Onset
OP-1 Putty	1101	Vaginal Cancer	Not Related	Severe	1530
	2315	Basal Cell Carcinoma	Not Related	Mild	1593
	2315	Benign Neoplasm	Not Related	Mild	1350
Autograft	2309	Breast Cancer	Not Related	Mild	1570
	2328	Ovarian Cancer	Unknown	Severe	1734

Does not include patient 2328 in autograft group who reported prostate cancer under the SOC category Investigations (elevated PSA), or patient 2406 in OP-1 Putty group who was reported to have died of brain mass consistent with glioblastoma subsequent to S01-01US (and was therefore not enrolled in 06-UPLF-01).

Source: Statistical Table S.18.3 in Section 14.1, Narratives in Section 14.2.

12.8 IMMUNOGENICITY

12.8.1 Test Methods

In this extension study, serum samples were analyzed for patients who had been positive for anti-OP-1 antibodies at the 24-month follow-up visit for Pivotal IDE S01-01US, and for patients who had not completed the 24-month follow-up visit for S01-01US but had been antibody positive at their last recorded visit.

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 cut point for this study was statistically based and reflects a false positive rate of 5 %, as recommended in Mire-Sluis, et al., 2004.²⁷

Positive samples in the screening ELISA were considered potential positive for anti-Op-1 antibodies and tested in a newly validated confirmatory competition ELISA. Positive samples in the competition ELISA were further evaluated in a titer ELISA to quantitate 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 lowest dilution of the sample that yields a positive result. The measurable log titer range in this assay extends from 0.3 to 3.4. Titers below and above this range were given the arbitrary numbers of 111 and 999, respectively.

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 recently developed luciferase reporter-based primary neutralizing antibody assay (nab). This assay was developed to replace the alkaline-phosphatase-

based assay, used in the Pivotal IDE S01-01US study. In the luciferase-based nab assay, anti-OP-1 neutralizing antibodies interfere with the ability of OP-1 to induce luciferase expression in a genetically engineered human cell line (A549-BRE-LUC).

Positive samples identified in the primary nab assay were confirmed in a quantitative polymerase chain reaction (QPCR)-based secondary neutralizing antibody assay. In this assay, neutralizing anti-OP-1 antibodies are detected based on their ability to reduce OP-1 induced ID-1 gene expression in the human cell line, A549. ID-1 gene expression was detected by PCR, and was normalized to that of the house keeping gene, GAPDH.

12.8.2 Immunological Status

In follow-up study 06-UPLF-01, all patients who had been anti-body 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. Of the 202 patients enrolled in 06-UPLF-01, 49 (34.0%) patients in the OP-1 Putty group and 5 (8.6%) in the autograft group had serum samples analyzed, and 18/49 (36.7%) patients in the OP-1 Putty group and 1/5 (20.0%) in the autograft group were positive for anti-OP-1-Putty antibodies at 36+ months. The mean anti-OP-1 Titer for the OP-1 Putty group was 1.62 (s.d. 0.378) and for the autograft group was 1.00 (s.d. N/A) at 36+ months. None of the patients in either study 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) (Source: Appendix 16.5 Immunology Results)

According to the SAP, the following analyses were planned to examine safety and effectiveness outcomes for patients who had neutralizing antibodies at 36+ as compared to patients who did not have neutralizing antibodies at 36+ months:

- Planned Statistical Table S.24.3: Profile for Patients with Neutralizing Antibodies
- Planned Statistical Table S.24.4: Success Outcome by Neutralizing Antibody Status
- Planned Statistical Table S.24.5: New Treatment-Emergent Serious Adverse, Events, Medical History, or Physical Findings by Neutralizing Antibody Status and Visit
- Planned Statistical Table S.24.6: New Immunologically-Related Treatment-Emergent Serious Adverse Events, Medical History, or Physical Findings by Neutralizing Antibody Status and Visit

As no patients in either study group had neutralizing antibodies as 36+ months, these additional planned analyses were not conducted. However, an analysis of Overall

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty® for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

Success (non-imputed) at 24 months (with radiographic and retreatment data at 36+ months) and its subcomponents was conducted to compare the clinical outcomes for OP-1 Putty patients who had neutralizing antibodies at any time during S01-01US or 06-UPLF-01 to those who did not have neutralizing antibodies at any time. Results are summarized in Table 43. The analysis suggests no clinically significant differences in outcomes between patients who had neutralizing antibodies and those who did not.

Table 43: Success Outcomes by Neutralizing Antibodies (Safety Population, OP-1 Putty Only)

Success Criteria	Neutralizing n/N (%)	Not Neutralizing n/N (%)
Overall Patient Success at 24 months (with radiographic and retreatment data at 36+ months)	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 up to and including 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 in Section 14.1.

12.9 SAFETY CONCLUSIONS

As summarized in Table 44, the safety of OP-1 Putty treatment in PLF is similar to that of autograft treatment with respect to the percentage of patients experiencing:

- Any new serious adverse event
- New serious adverse events that are treatment related (suspected related or unknown)
- New serious adverse events that are severe
- Neoplasms

Table 44: New Serious Adverse Events (Safety Population)

Parameter	OP-1 Putty (N=208)	Autograft (N=87)	p-value
	Number (%) of Patients with Events	Number (%) of Patients with Events	
Any New Serious Adverse Event	24 (11.5)	17 (19.5)	0.095
New Serious Adverse Events – Treatment Related (Suspected-related or unknown)	2 (1.0)	5 (5.7)	--
New Serious Adverse Events – Severe	15 (7.2)	9 (10.3)	--
Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps)	1 (0.5)	2 (2.3)	--

Source: Statistical Tables S.17.1, S.17.2, S.17.3 in Section 14.1.
 p-value calculated using Fisher's Exact test

In this extension study, 11.5% of patients in the OP-1 Putty treatment group reported at least 1 new serious adverse event (SAE), and 19.5% of patients in the autograft group reported at least one new SAE (p=0.095).

New serious adverse events were classified by System Organ Class (SOC), and a conservative statistical cut-off (p≤0.2) was imposed to identify potential differences in new serious adverse events by SOC between treatment groups. (p-values were calculated for SOC terms reported by ≥5% of patients in at least one treatment group using Fisher's exact test.) The safety profiles of the two treatment groups were generally comparable, with no statistically significant differences observed between treatment groups in any of the SOC categories,

The most frequently reported new serious adverse events in both treatment groups were in the Musculoskeletal and Connective Tissue Disorders SOC, with a greater percentage

of events reported in the autograft group: seven patients (3.4%) in the OP-1 Putty group, and six patients (6.9%) in the autograft group ($p=0.214$).

An analysis of the SOCs by the preferred terms that are of particular relevance to an assessment of spinal fusion success (spondylolisthesis, back pain, lumbar spinal stenosis, spinal column stenosis) revealed no clinically meaningful differences.

The number of patients with new SAEs that were device related (ruled “unknown” or “suspected related” by the investigator) was small for both groups, although represented a higher percentage in the control group: 2 (1%) for the OP-1 Putty group and 5 (5.7%) for the autograft group.

New medical history and physical findings were reported at 36+ months for 31.7% of OP-1 Putty patients and 43.7% of autograft patients ($p=0.061$). These new findings were evaluated by SOC and preferred term, and a conservative statistical cut-off ($p\leq 0.2$) was imposed to identify potential differences in new findings by SOC between treatment groups. (p -values were calculated for SOC terms reported by $\geq 5\%$ of patients in at least one treatment group using Fisher’s exact test.) While the new medical history and physical findings profiles of the two treatment groups were generally comparable, for the SOC of Nervous System Disorders, the autograft group showed an overall higher incidence of new SAEs than did the OP-1 Putty group based on this statistical cut-off: 21 (10.1%) patients for OP_1 Putty, 14 (16.1%) patients for autograft, $p=0.167$.

An analysis of the SOCs by the preferred terms that were of particular relevance to an assessment of spinal fusion success (spondylolisthesis, gait disturbance, back injury, spinal compression fracture, back pain, buttock pain, lumbar spinal stenosis, pseudarthrosis, spinal column stenosis, and spinal osteoarthritis, dysaesthesia, hypoaesthesia, hyporeflexia, radiculopathy, and sciatica) revealed no clinically meaningful differences between treatment groups.

The number of patients with new medical history or physical findings that were device related (ruled “unknown” or “suspected related” by the investigator) was small for both groups, although represented a higher percentage in the control group: 13 (6.2%) for the OP-1 Putty group and 11 (12.6%) for the autograft group. The new medical history or physical findings that were device related or possibly device related occurred primarily in the musculoskeletal and connective tissue disorders SOC. Back pain was the preferred term under this SOC most commonly ruled suspected-related or relationship unknown (1.4% in the OP-1 Putty group and 8.0% in the autograft group), with all other preferred terms under this SOC ruled as suspected related or relationship unknown in $\leq 1.1\%$ of patients in either treatment group.

The two most frequently reported SOC categories were Musculoskeletal and Connective Tissue Disorders (3.4% for OP-1 Putty group, 6.9% for autograft, $p=0.214$), and Injury, Poisoning and Procedural Complications (4.3% for OP-1 Putty group, 8.0% for autograft, $p=0.257$). Events in these SOCs occurred in a higher percentage of patients in the autograft group, although the differences between groups only approached statistical significance at $p \leq 0.2$.

Patients in both treatment groups reported events in the SOC Neoplasms, Benign and Malignant (including cysts and polyps) at 36+ months: 2 patients in the OP-1 Putty group (1.0%) reported 3 events, and 2 patients in the autograft group (2.3%) reported 2 events. Three of five events were considered to be SAEs: 1 in the OP-1 Putty group, and 2 in the autograft group. The malignancy reported as an SAE in the OP-1 Putty group included vaginal cancer. In the autograft group, one occurrence each of ovarian cancer and breast cancer was reported as an SAE. The two events that were not reported as SAEs (but only as new medical history/physical findings) occurred in the OP-1 Putty group and included basal cell carcinoma and benign neoplasm. In addition, one patient in the autograft group developed prostate cancer, although this event was reported as a new SAE under the SOC category of Investigations (Prostatic Specific Antigen Increase). The event was classified as severe, but not related to the study procedure. None of the reported malignancies were determined to have a causal relationship to either OP-1 Putty or autograft, although the ovarian cancer that occurred in the autograft group was classified as relationship to treatment “unknown.” Finally, the cause of death for one patient in the OP-1 Putty group who died subsequent to pivotal study S01-01US (patient ID 2406) and prior to extension study 06-UPLF-01 was reported as “brain mass consistent with glioblastoma.” However, as this patient could not be enrolled in 06-UPLF-01, no further information was available for this event, nor could the cause of death be confirmed. There were no patterns or specific events of concern identified at the 36+ month interval with respect to type of cancer or distribution between treatment groups.

Of the adverse events that were classified as “ongoing” at the close of Pivotal IDE S01-01US, the percentage of events that continued to be ongoing versus events that had resolved was higher for the OP-1 Putty group: 75.9% of the events remained ongoing in the OP-1 Putty group, and 53.8% of the events remained ongoing in the autograft group. The percentage of ongoing events that had become serious adverse events since Pivotal Study S01-01US was low in both groups, although was higher for the autograft group: 4.4% for the OP-1 Putty group and 9.0% for the autograft group. The percentage of ongoing events that had resulted in spine surgery since Pivotal IDE S01-01US was also low in both groups, although was higher in the autograft group: 1.5% for the OP-1 Putty group and 5.1% for the autograft group. The system organ class General Disorders and

Stryker Biotech

Prospective Data Collection from Pivotal IDE Study of OP-1 Putty[®] for Uninstrumented Posterolateral Fusions

Clinical Study Report: 06-UPLF-01 (*Extension to Pivotal Study S01-01US*)

Administration Site Conditions was the only SOC category for the Ongoing AE analysis where the difference between treatment groups was statistically significant using the conservative cut-off of $p \leq 0.02$: events were reported in 6 (2.9%) OP-1 Putty patients and 6 (6.9%) autograft patients ($p=0.191$). The most frequently occurring preferred term within this SOC was asthenia: 2 (1.0%) for OP-1 Putty group and 3 (3.4%) for the autograft group.

A total of 5 patients died subsequent to the Pivotal IDE S01-01US (four from the OP-1 Putty group, and one from the autograft group). These deaths were reported to Stryker Biotech during attempts to locate and enroll patients in extension study 06-UPLF-01. No patterns of concern emerged with respect to the frequency or etiology of death.

No patients in either study group had evidence of neutralizing antibodies against OP-1 Putty by the 36+ month visit. There does not appear to be any clinically significant differences in overall success at 24 months (with radiographic and retreatment assessed at 36+ months) or its subcomponents between patients who had neutralizing antibodies at any time and those who did not have neutralizing antibodies.

13. DISCUSSION AND OVERALL CONCLUSIONS

Results of this pivotal study demonstrate that OP-1 Putty is safe and effective when used in patients with single level degenerative lumbar spondylolisthesis with spinal stenosis who are undergoing decompression and spinal fusion.

- OP-1 Putty has been shown to be non-inferior to autograft with respect to the primary endpoint, Overall Success at 24 months (with radiographic and retreatment components at 36+ months).
- There were no statistically significant differences between OP-1 Putty and autograft with regard to the following clinical outcome measurements at 36+ months: improvement in ODI, absence of retreatment, absence of serious treatment-related adverse events, and absence of decrease in neurological status.
- OP-1 Putty was not demonstrated to be non-inferior to autograft with regard to overall radiographic success at 36+ months; however, there were no statistically significant differences between OP-1 and autograft with regard to the three subcomponents of overall radiographic success at 36+ months: presence of bone assessed by CT scan, angular motion ≤ 5 degrees, and translational movement ≤ 3 mm.
- OP-1 Putty demonstrated a safety profile that was similar to autograft as supported by a comparison of ongoing adverse events from study S01-01US, new serious adverse events, and new medical history and physical findings.
- OP-1 Putty demonstrated improvements in VAS and SF-36 outcomes that were clinically meaningful and not statistically different from autograft. OP-1 patients avoided the autograft-harvest-related donor site pain experienced by the autograft group.

OP-1 Putty's good clinical outcomes, acceptable safety profile, and ability to avoid autograft-related surgical morbidity and pain make it an attractive alternative to autograft in the setting of PLF.