

Stryker Biotech
OP-1 Putty[®] for Posterolateral Fusions
Clinical Study Report: S01-01US

16.1.9 Documentation of Statistical Methods Pivotal Study S01-01US

**Analysis Plan for A
Prospective,
Randomized,
Controlled,
Multicenter, Pivotal
Study of OP-1 Putty in
Uninstrumented
Posterolateral Fusions**

Protocol No. S01-01US

December 29, 2005

Prepared for
**Stryker Biotech
35 South Street
Hopkinton, MA 01748**

Prepared by
**Eugene C. Poggio, Ph.D.
Managing Vice President and
Executive Director**

**Biostatistics and Epidemiology
Abt Associates Clinical Trials
181 Spring Street
Lexington, MA 02421**

Signature Page for Analysis Plan

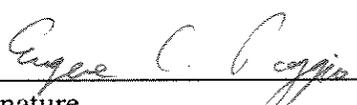
Sponsor: Stryker Biotech

Study Number: S01-01US

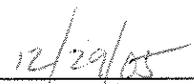
Protocol Title: A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Abt Associates Clinical Trials:

Eugene C. Poggio, Ph.D.
Managing Vice President
and Executive Director



Signature

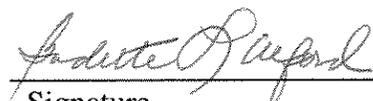


Date

Abt Associates Clinical Trials
55 Wheeler Street
Cambridge, MA 02138

Sponsor:

Bernadette L. Alford, Ph.D.
Vice President
Regulatory Affairs

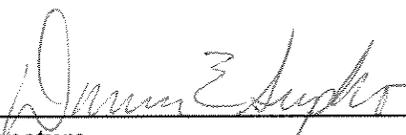


Signature



Date

Donna E. Supko, Ph.D.
Director, Regulatory Affairs



Signature



Date

Stryker Biotech
35 South Street
Hopkinton, MA 01748

Table of Contents

Signature Page for Analysis Plan.....	i
Table of Contents.....	ii
List of Tables	iv
List of Figures.....	vii
List of Listings	viii
1.0 INTRODUCTION	1
2.0 STUDY OBJECTIVES.....	3
3.0 STUDY INVESTIGATIONAL PLAN	4
3.1 Study Design.....	4
3.2 Randomization.....	4
3.3 Selection of Study Population	4
3.3.1 Inclusion Criteria	5
3.3.2 Exclusion Criteria	5
3.4 Study Product.....	6
3.5 Changes in the Conduct of the Study or Planned Analyses.....	6
3.6 Evaluation Schedule	7
4.0 STATISTICAL METHODOLOGY	9
4.1 General Considerations.....	9
4.2 Hypothesis Testing	9
4.3 Sample Size Estimation	10
4.4 Efficacy Assessments	11
4.5 Safety Assessments.....	11
4.6 Additional Information	11
4.7 Handling of Dropouts or Missing Data	11
4.8 Adjustments for Covariates	14
4.9 Multiple Comparisons/Multiplicity	14
4.10 Multicenter.....	14
4.11 Examination of Subgroups	14
5.0 STATISTICAL ANALYSES	15
5.1 Analysis Populations	15
5.1.1 Enrolled Population	15
5.1.2 Intent-to-Treat Population.....	15
5.1.3 Per Protocol Population	15
5.1.4 Safety Population	15
5.2 Subject Accountability.....	15
5.3 Demographic and Baseline Characteristics	16
5.4 Efficacy Analysis.....	16

5.4.1	Primary Efficacy Endpoint	16
5.4.2	Secondary Efficacy Endpoints	20
5.4.3	Additional Efficacy Measurements.....	20
5.5	Safety Analysis	21
5.5.1	Adverse Events	21
5.5.2	Secondary Procedures	23
5.5.3	Clinical Laboratory Evaluations	23
5.5.4	Neurological Status.....	23
5.6	Additional Analysis.....	24
5.6.1	Visual Analog Scale for Pain Assessment.....	25
5.6.2	Donor Site Pain	25
5.6.3	Current Medication Use	25
5.6.4	Surgical Procedure Characteristics	25
5.6.5	General Health Survey (SF-36)	25
5.7	Immunology.....	26
Appendix 1: Testing the Hypothesis of Inferiority.....		28
Appendix 2: References.....		29
Addendum: Statistical Analysis Plan Per the Protocol		

List of Tables

<u>Table</u>	<u>Title</u>
1.1	Patient Populations and Disposition – Enrolled Population
1.2	Patient Accounting Over Time – Safety Population
2.1	Demographic and Baseline Characteristics – Safety Population
2.2	Demographic and Baseline Characteristics – Intent-to-Treat Population
2.3	Demographic and Baseline Characteristics – Per Protocol Population
3.1	Number of Patients Who Had Missing Data for the 24 Month Overall Success Rate - Intent-to-Treat Population
3.2	Overall Success Rate at 12, 24 and 36 Months – Intent-to-Treat Population
3.3	24 Month Overall Success Rate by Gender and Age Group – Intent-to-Treat Population
4.1	Overall Success Rate at 12, 24 and 36 Months – Per Protocol Population
4.2	24 Month Overall Success Rate by Gender and Age Group – Per Protocol Population
5.1	Overall Radiographic Success Rate at 12, 24 and 36 Months – Intent-to-Treat Population
5.1.1	Overall Radiographic Success Rate at 12, 24 and 36 Months – Per Protocol Population
5.2	Success Rate Based on Oswestry Disability (Overall Success Criterion #2) at 12, 24 and 36 Months – Intent-to-Treat Population
5.2.1	Success Rate Based on Oswestry Disability (Overall Success Criterion #2) at 12, 24 and 36 Months – Per Protocol Population
5.3	Success Rate Based on Absence of Retreatment (Overall Success Criterion #3) at 12, 24 and 36 Months – Intent-to-Treat Population
5.3.1	Success Rate Based on Absence of Retreatment (Overall Success Criterion #3) at 12, 24 and 36 Months – Per Protocol Population
5.4	Success Rate Based on Absence of Serious Treatment-related Adverse Events at 12, 24 and 36 Months – Intent-to-Treat Population
5.4.1	Success Rate Based on Absence of Serious Treatment-related Adverse Events at 12, 24 and 36 Months – Per Protocol Population
5.5	Overall Neurological Success Rate at 12, 24 and 36 Months – Intent-to-Treat Population
5.5.1	Overall Neurological Success Rate at 12, 24 and 36 Months – Per Protocol Population
5.6	Presence of Bridging at Operated Level Based on CT Scans at 9 Months – Intent-to-Treat Population
5.6.1	Presence of Bridging at Operated Level Based on CT Scans at 9 Months – Per Protocol Population
5.7	Presence of Pseudoarthrosis and Fusion at 9 Months – Intent-to-Treat Population
5.7.1	Presence of Pseudoarthrosis and Fusion at 9 Months – Per Protocol Population
5.8	Lateral Disc Height (Mm) Measurement – Intent-to-Treat Population
5.8.1	Lateral Disc Height (Mm) Measurement – Per Protocol Population
5.9	Degree of Angular Motion – Intent-to-Treat Population

List of Tables (Cont'd)

<u>Table</u>	<u>Title</u>
5.9.1	Degree of Angular Motion – Per Protocol Population
5.10	Translational Movement – Intent-to-Treat Population
5.10.1	Translational Movement – Per Protocol Population
5.11	Oswestry Disability Index – Intent-to-Treat Population
5.11.1	Oswestry Disability Index – Per Protocol Population
6.1	Treatment-Emergent Adverse Events – Safety Population
6.2	Treatment-emergent Adverse Events by System Organ Class and Preferred Term – Safety Population
6.3	Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Severity – Safety Population
6.4	Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Treatment – Safety Population
6.5	Treatment-emergent Adverse Events by Type of Event – Safety Population
6.6	Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Visit – Safety Population
6.7	Treatment-emergent Adverse Events by Type of Event and Visit – Safety Population
6.8	Serious/Unanticipated Treatment-emergent Adverse Events by System Organ Class and Preferred Term – Safety Population
6.9	Serious/Unanticipated Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Severity – Safety Population
6.10	Serious/Unanticipated Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Treatment – Safety Population
6.11	Serious/Unanticipated Treatment-emergent Adverse Events by Type of Event – Safety Population
6.12	Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Visit – Safety Population
6.13	Treatment-emergent Adverse Events by Type of Event and Visit – Safety Population
7	Secondary Procedures by Visit – Safety Population
8.1	Clinical Laboratory Evaluations – Hematology – Actual Value and Change from Baseline – Safety Population
8.2	Clinical Laboratory Evaluations – Hematology – Shifts in Status from Baseline to Post-Baseline Time-points – Safety Population
8.3	Clinical Laboratory Evaluations – Biochemistry – Actual Value and Change from Baseline – Safety Population
8.4	Clinical Laboratory Evaluations – Biochemistry – Shifts in Status from Baseline to Post-Baseline Time-points – Safety Population
9	Shifts in Neurological Status from Baseline to Post-Baseline Time-points – Safety Population
10	Visual Analog Scale for Pain Assessment – Actual Value and Change from Baseline – Safety Population

List of Tables (Cont'd)

<u>Table</u>	<u>Title</u>
11.1	Donor Site Pain – Visual Analog Scale – Safety Population
11.2	Donor Site Pain Status – Safety Population
12	Current Medication Use – Safety Population
13	Hospitalization Data – Safety Population
14.1	SF-36 Health Survey Scale: Physical Component Score – Safety Population
14.2	SF-36 Health Survey Scale: Mental Component Score – Safety Population
14.3	SF-36 Health Survey Scale: Physical Functioning Scale – Actual Value and Change from Baseline – Safety Population
14.4	SF-36 Health Survey Scale: Role-Physical Scale – Safety Population
14.5	SF-36 Health Survey Scale: Bodily Pain Scale – Safety Population
14.6	SF-36 Health Survey Scale: Mental Health Scale – Safety Population
14.7	SF-36 Health Survey Scale: Role-Emotional Scale – Safety Population
14.8	SF-36 Health Survey Scale: Social Functioning Scale – Safety Population
14.9	SF-36 Health Survey Scale: Vitality Scale – Safety Population
14.10	SF-36 Health Survey Scale: General Health Perceptions Scale – Safety Population
15.1	Anti-OP-1 Antibody Status by Visit – Safety Population
14.10	SF-36 Health Survey Scale: General Health Perceptions Scale – Safety Population
15.1	Anti-OP-1 Antibody Status by Visit – Safety Population
15.2	Anti-OP-1 Titer – Safety Population
15.3	Profile for Patients with Neutralizing Antibodies – Safety Population
15.4	Success Outcome by Neutralizing Antibody Status – Safety Population
15.5	Treatment-emergent Serious Adverse Events by Neutralizing Antibody Status and Visit – Safety Population
15.6	Treatment-emergent Adverse Events by Neutralizing Antibody Status and Visit – Safety Population
15.7	Immunologically-related Adverse Events by Neutralizing Antibody Status and Visit – Safety Population
15.8	Immunologically-related Serious Adverse Events by Neutralizing Antibody Status and Visit – Safety Population

List of Figures

<u>Figure</u>	<u>Title</u>
1	Patient Disposition – Enrolled Population

List of Listings

<u>Listing</u>	<u>Title</u>
1.1	Inclusion Criteria
1.2	Exclusion Criteria
1.3	Subject Randomization
1.4	Patients with Missing 24 Month Patient Success Data
2	Demographics and Worker Compensation Status
3	Disease Diagnosis
4.1	Medical History – Prior Treatment to Affected Level, Level Planned for Fusion
4.2	Medical History – Prior Treatment to Level(s) of Lumbar – Sacral Region Other Than Affected Level
4.3	Medical History – Current Medical Condition
4.4	Medical History – Comments
5	Oswestry Low Back Pain Disability Questionnaire
6.1	Radiographic Evaluation – Preoperative
6.2	Radiographic Evaluation – Postoperative
6.3	Additional Postoperative Radiographic Evaluation
7	Neurological Evaluation
8	Physical Exam
9.1	Concurrent Medical Event
9.2	Serious/unanticipated Concurrent Medical Event
10.1	Laboratory Evaluations – Hematology
10.2	Laboratory Evaluations – Biochemistry
11	Visual Analog Scale for Pain Assessment
12	Current Medication Use
13	Hospitalization Data
14	General Health Survey (SF-36)
15	Subjects Excluded from Per Protocol Population
16	Subject Disposition
17.1	Immunology
17.2	Antibody Status and Adverse Events – Patients with Any Antibody Status Data

1.0 INTRODUCTION

This document details the analysis plan for a prospective, randomized, controlled, multicenter, pivotal study of OP-1 Putty in uninstrumented posterolateral fusions. It describes the proposed safety and efficacy analyses, including planned summary tables and by-subject listings.

It has been estimated that up to seventy percent of the adult population suffers from some form of low back (lumbar-sacral) pain.³¹ Though there are multiple disease processes, which cause these phenomena, symptoms are usually attributed to a degenerative disease process within the vertebral spine.

One of the diagnoses attributed to the degenerative disc disease process is spondylolisthesis. Spondylolisthesis is characterized by a slipping of one vertebral segment on the one below in the presence of an intact neural arch.¹³ It stems from an erosion of the facet cartilage, which permits vertebral displacement. Such displacement can in turn lead to the formation of osteophytes causing stenosis and nerve root compression.²⁸

Spondylolisthesis is divided into four categories (grades) dependent on the severity of displacement between the affected vertebrae. Grades I and II spondylolisthesis, defined as displacement of $\leq 25\%$ and displacement of 25% to 50%, respectively, are to be evaluated in the current study. Spondylolisthesis is classified into five types: dysplastic, isthmic, degenerative, traumatic and pathologic. Only one of the five types of spondylolisthesis, that of degenerative spondylolisthesis, is to be evaluated in the current study.

If patient pain, neurological deficit, and instability do not respond to conservative management such as rest, exercise, medication, use of a back brace, epidural steroids, Back School (good posture, exercise, body mechanics), and physical therapy, surgical intervention is often required.¹⁸

Decompression and lumbar spinal fusion are the surgical treatments of choice for degenerative spondylolisthesis. A primary means of surgical treatment for stenosis involves decompression at the affected level in order to relieve the pressure on the cauda equina or the exiting nerve roots. An increasing body of literature suggests that decompression without arthrodesis (spinal fusion) may have a less favorable outcome than previously thought, particularly when spinal stenosis is associated with degenerative lumbar spondylolisthesis at a single level.^{15,18,30} Therefore currently, the most common surgical option for the patient suffering from progressive degenerative spondylolisthesis with spinal stenosis is decompression and spinal fusion.⁷

Spinal fusion is a surgically created bony union across the involved vertebrae and approximately 70,000 posterolateral lumbar spinal fusions are performed annually.²⁷ However it is estimated that 20 to 55 percent of all posterolateral lumbar spine fusions (uninstrumented and instrumented) fail necessitating re-operation and/or resulting in continued patient pain and loss of function.^{14,27} A major cause of failed spinal fusion is pseudoarthrosis.¹⁷ For purposes of this study, pseudoarthrosis is defined as documented failure of solid fusion one year after the initial operation.²⁹ Contemporary spinal arthrodesis (fusion) procedures include anterior, posterior, posterolateral, and lateral fusion techniques, employed with the use of allograft and/or autograft

with and without the use of instrumentation systems. Although common, much controversy exists concerning the use of instrumentation in spinal fusion with regard to efficacy and safety.^{3,18,24}

The use of bone graft to stimulate bone growth is a standard surgical technique in spinal fusion 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 it is preferred over allograft bone.^{1,2,6,16} The most common site for harvesting autograft material is the iliac crest; however, this increases operative time, blood loss and the morbidity associated with spinal fusion.²⁵

In recent years, there has been focus on Bone Morphogenetic Proteins (BMPs) as bone graft material.²³ 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 and to improve the performance of autograft (Cook, ORS 1997) in animals.^{8,9,10,11,26} Implants containing OP-1 and collagen matrix have also been shown to promote stable spinal fusions in a significantly more rapid fashion than autograft.^{12,21} Safety and efficacy of other BMPs in spinal applications have also been reported.^{4,5,20,22,25}

It is postulated that the use of OP-1 Putty will prove beneficial in the treatment of patients requiring decompression and lumbar spinal fusion while also eliminating the pain and morbidity associated with the harvesting of autograft bone from the iliac crest. For purposes of the study, this disease process is restricted to Grade I and II degenerative spondylolisthesis with stenosis affecting one level of the lumbar spine (L-3 to S-1).

2.0 STUDY OBJECTIVES

The objectives of this pivotal study are to demonstrate the safety and efficacy of OP-1 Putty as a replacement for autograft in patients undergoing posterolateral spinal fusion as measured by:

1. Safety: By comparison of the complications (adverse events) and neurological status between the OP-1 Putty group and the control autograft group.
2. Efficacy: By comparison of overall patient success considering radiographic evidence along with pain/function outcomes, absence of retreatment, absence of serious treatment-related adverse events, and neurological outcomes between the OP-1 Putty group and the control autograft group.

3.0 STUDY INVESTIGATIONAL PLAN

3.1 Study Design

This is a controlled, randomized, prospective, multicenter, multinational pivotal study in which all subjects will receive decompression and spinal fusion. There are two arms: a treatment arm with OP-1 Putty and a control arm using autogenous bone graft from the iliac crest (autograft). Subjects having single level (L3-S1) degenerative lumbar spondylolisthesis (Grade I/II) with spinal stenosis will be treated by decompression and arthrodesis using either OP-1 Putty or autograft.

Subjects enrolled in the OP-1 Putty and the control groups will come from a maximum of 25 institutions in the United States and Canada. Both treatment and control subjects are to be scheduled to receive operative procedures for purpose of decompression and lumbar spinal fusion. If an intraoperative decision will be made to perform something other than what is intended for study enrollment, the subject will be considered a withdrawal. If a randomized patient is withdrawn prior to treatment, the next patient will be assigned the next randomly determined treatment as per the study randomization plan.

This study is a one-sided non-inferiority trial comparing the overall success between the OP-1 Putty group and the control autograft group. It is anticipated that the overall success rate for the OP-1 Putty group will be comparable to the success rate in the autograft group.

The expected duration of the study is approximately three years from the commencement of subject enrollment. Subject enrollment is expected to take one year. All subjects will be followed for at least two years after surgery and annually thereafter until the last subject achieves two year follow-up.

A total of 312 subjects will be treated during this investigation.

3.2 Randomization

The randomization scheme was produced in SAS using the PLAN procedure and was stratified by investigational site. The randomization scheme is maintained at Stryker Biotech. The Investigator or designee is to contact Stryker Biotech by phone to receive the randomization assignment. The randomization scheme is in the ratio of 2 (OP-1 Putty) to 1 (autograft). Study enrollment will be terminated upon treatment of 208 OP-1 Putty patients or a maximum of 312 patients total.

3.3 Selection of Study Population

Subjects diagnosed with degenerative lumbar spondylolisthesis with spinal stenosis qualifying for decompression and fusion of one spinal level (L3-S1) with the use of autograft are recruited through the medical institutions of participating investigators. All subjects are to have undergone non-operative treatment for at least six months prior to study enrollment.

3.3.1 Inclusion Criteria

- (1) The subject or legal guardian is willing and able to understand, sign, and date the study specific Patient Informed Consent, which has been approved by the Institutional Review Board.
- (2) The subject is a skeletally mature male or female less than 85 years of age.
- (3) The subject has a diagnosis of degenerative lumbar spondylolisthesis of Grade I or II with spinal stenosis demonstrated by medical history, physical examination, and radiographic imaging. Radiographic diagnosis has been performed showing a cross sectional image using a CT scan or MRI demonstrating an intact pars interarticularis with evidence of central or lateral recess stenosis accompanied by an anterolisthesis on upright lateral radiographs. The subject has leg and/or back pain and the manifestation of one or more of the following phenomena:
 - radiculopathy
 - sensory deficit
 - motor weakness
 - reflex changes
 - disc herniation
 - neurogenic claudication
 - instability (defined as greater than 0% and less than 50% translation of the vertebrae and/or greater than 10 degrees and less than 20 degrees angular motion) measured on flexion/extension radiographs
 - osteophyte formation or hypertrophy of the facet joint.
- (4) The subject is a candidate for decompression and spinal fusion with the use of autograft from the iliac crest.
- (5) The subject requires one level lumbar fusion (L-3 to S-1).
- (6) The subject agrees to participate in post-operative clinical and radiographic evaluations and required rehabilitation regimen.
- (7) The subject has no history of previous fusion attempt(s) to the affected spinal level.
- (8) The subject has been non-responsive to at least 6 months of non-operative treatment prior to study enrollment.
- (9) The subject has a preoperative Oswestry Disability Index of 30-100.

3.3.2 Exclusion Criteria

- (1) The subject has non degenerative spondylolisthesis of any grade at the affected level.
- (2) The subject has degenerative spondylolisthesis of Grade III or IV.
- (3) The subject has active spinal and/or systemic infection.
- (4) The subject has a systemic disease or condition, which would affect his/her ability to participate in the study requirements or the ability to evaluate the efficacy of the investigational product (i.e., active malignancy, neuropathy).
- (5) The subject is a prisoner, a transient, or has been treated for alcohol and/or drug abuse in an inpatient substance abuse program within six months prior to proposed study enrollment.
- (6) The subject has participated in clinical trials evaluating investigational devices, pharmaceuticals, or biologics within 3 months of enrollment in the study.

- (7) The subject is a woman who is able to bear children, e.g., not post-menopausal, has not had a hysterectomy, etc.
- (8) The subject is morbidly obese (defined as weight ≥ 60 percent over the recommended ideal weight as described in the 1996 Metropolitan Height and Weight Tables for Men and Women).
- (9) The subject has a known sensitivity to any component of OP-1 Putty.
- (10) The subject is known to require at the time of treatment, additional surgery to the lumbar spinal region within the next six months.
- (11) The subject has spinal instability measured on flexion/extension radiographs of greater than or equal to 50% translation of the vertebrae or greater than or equal to 20 degrees of angular motion.
- (12) The subject uses tobacco or nicotine or is prescribed steroids such as cortisone.

3.4 Study Product

The investigational product being evaluated in this study is 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 sodium (CMC), an anionic cellulose derivative which yields a putty-like consistency. OP-1 Putty is provided as two components:

- A large vial containing a sterile dry power consisting of 3.5 mg of human recombinant osteogenic protein-1 (OP-1) in 1 gm 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, one product unit will be used on each side of the spine, i.e., two product units per patient.

The control system being utilized in this study is lumbar spinal fusion with the use of autogenous bone graft from the iliac crest (autograft).

3.5 Changes in the Conduct of the Study or Planned Analyses

1. The protocol defines overall success using six individual criteria. The wording of individual criterion #4 has been changed from “absence of serious device-related adverse event during the course of the study” to “absence of serious treatment-related adverse event during the course of the study” to provide clarity.
2. Individual neurologic status success criteria #5 and #6 have been combined into one criterion in the analysis that takes into consideration the overall neurological status of the patient. The overall neurological success is defined in section 5.4.1.
3. Individual success criteria #1, overall radiographic success, is determined from three conditions: the presence of bone, the extent of angulation, and translational movement. The first and third condition have been changed as follows:

Previous Definition	Revised Definition
i. Presence of bridging bone	i. Presence of bone
ii. Angulation of $\leq 5^\circ$	ii. Angulation of $\leq 5^\circ$ (no change)
iii. Translational movement of $\leq 2\text{mm}$	iii. Translational movement of $\leq 3\text{mm}$

4. Patient success will be presented for the overall success rate and for each of the individual success criterion rates at 12, 24, and 36. The success rates at 3 and 6 months will not be analyzed.
5. The following analysis specified in the study protocol will not be performed: “The baseline characteristics will also be presented by investigational site to evaluate the poolability of data across sites. Differences in the distribution of baseline characteristics across sites will be addressed in the study report.”
6. The (modified) intent-to-treat population will be defined as “all subjects who are randomized and have at least one post-treatment visit”. The study protocol defined the intent-to-treat population as “all treated patients”.
7. The per protocol population will be defined as all randomized patients who meet the inclusion/exclusion criteria. The study protocol indicated that the following patients would be excluded: if (1) they are missing an Oswestry assessment at 24 months, (2) their 24 month radiographic results are missing or not evaluable, or (3) the patient is missing a neurological assessment.
8. The study protocol defines an abnormal laboratory value as a value that is $> 10\%$ outside of the normal range and a normal laboratory value as a value that is within 10% of the normal range. Instead, the laboratory status will now be classified as follows in the analysis:
 - Low (below the lower normal range)
 - Normal (within the normal range)
 - High (above the upper normal range)
9. The fixed non-inferiority margin of 10 percentage points specified in the study protocol is replaced by a fixed margin of 0.14 in the angular scale (as described in Section 4.2). A fixed margin in the angular scale corresponds to a margin in the percentage scale that varies with the hypothesized proportion of successes in the control arm, in such a way that that non-inferiority margin is lower when the underlying statistical variation is smaller and higher when the statistical variation is larger. Also, the hypothesis test in the angular scale will have the correct Type I error rate.

3.6 Evaluation Schedule

Subjects are to have the following scheduled visits: preoperative, hospitalization (surgical procedure), postoperative (within 72 hours of operative), six weeks (± 14 days), three months (± 14 days), six months (± 30 days), nine months (± 30 days), one year (± 60 days), two years (± 60 days), and annually thereafter until the last subject achieves at least two year follow-up.

The subject's evaluation schedule is presented in Table 1.

Table 1. Schedule of Events for Protocol S01-01US

Study Evaluations	Pre-operative	Operative ¹	6 Weeks	3 Months	6 Months	9 Months	12 Months	24 Months	Annual
Inclusion/Exclusion Criteria	X								
Informed Consent	X								
Randomization	X								
Demographics and Baseline Characteristics	X								
Medical History	X								
Oswestry Index	X		X	X	X	X	X	X	X
Visual Analog Scale	X		X	X	X	X	X	X	X
SF-36 Health Survey	X		X	X	X	X	X	X	X
Physical Exam	X		X	X	X	X	X	X	X
Laboratory Evaluation ²	X	X	X	X	X		X	X	
Radiographic Evaluation	X		X	X	X		X	X	X
Surgical Intervention		X							
CT Evaluation						X			
Disposition								X	
Current Medication	X		X	X	X	X	X	X	X
Concurrent Medical Events ³		X	X	X	X	X	X	X	X

¹ Operative includes hospitalization (surgical procedure) and within 72 hours of postoperative.

² Immunological, hematology and biochemistry; no immunological assessment beyond the 24 months.

³ Concurrent Medical Events are assessed at each post-treatment visit.

4.0 STATISTICAL METHODOLOGY

4.1 General Considerations

All summary tables will be produced and all statistical analyses will be performed using SAS software.

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

Inferential tests will be performed at the 5% level of significance. All p-values will be rounded to 3 decimal places. If a rounded p-value is 0.000 (i.e. the actual p-value is less than 0.0005), then this will be presented as a p-value of '<0.001'.

Information displayed in the tables generally will be presented for both treatments (the OP-1 Putty group and the autograft group).

Data listings will be based on all patients and will be sorted by treatment and subject ID. All date fields will be presented in a format of ddmmmyyyy (i.e., 01Jan2004) in the listings.

4.2 Hypothesis Testing

The objective of the study is to establish OP-1 Putty as a safe alternative to autograft for posterolateral fusion of the lumbar spine. A product that has similar efficacy, but avoids the pain and morbidity associated with iliac crest bone harvest is clinically desirable. Therefore, the trial is designed to demonstrate that the comprehensive success rate in the OP-1 Putty treatment group is comparable to the success rate in the autograft treatment group.

The null hypothesis for this study is 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 ($P_A - P_O \geq \delta_p$). The alternative hypothesis for this study is that this difference is less than δ_p ($P_A - P_O < \delta_p$). If the null hypothesis of inferiority of OP-1 is rejected, a test of superiority will be performed.

The actual testing of the hypothesis will involve the "angular transformation" (a standard transformation in statistical analyses of proportions, developed to remove the dependence of the variability of observed proportions on the underlying proportion --- P_A or P_O). Mathematically, this transformation begins with the observed proportion of successes, x/n from x successes in n trials, and applies the function $\sin^{-1} \sqrt{x/n}$ to produce the corresponding angle (in radians). Because the statistical variation in these angles is constant across the angular scale (in sizable samples the variance is $1/(4n)$), a non-inferiority margin δ_A that is constant in the angular scale has uniform impact, relative to the variation. Further, because the distribution in the angular scale is well approximated by a normal distribution, the customary hypothesis test in that scale (based on the normal distribution) will have the specified Type I error rate, .05.

If the angular values corresponding to P_A and P_O are A_A and A_O , respectively, then the null hypothesis becomes $A_A - A_O \geq \delta_A$. Specifying a constant non-inferiority margin in the angular scale (δ_A) corresponds to allowing the non-inferiority margin in the proportion scale, δ_p , to vary. The relation between δ_p and δ_A is anchored at P_A and A_A : $A_A = \sin^{-1} \sqrt{P_A}$, subtracting δ_A gives $A_O = A_A - \delta_A$, inverting the angular transformation yields $P_O = (\sin(A_O))^2$, and $\delta_p = P_A - P_O$. For an appropriate choice of δ_A , the corresponding values of δ_p are lower when the underlying statistical variation (in the proportion scale) is smaller and higher when that statistical variation is larger. The testing of the null hypothesis in this study will use $\delta_A = 0.14$. The choice of $\delta_A = 0.14$ maintains δ_p close to 0.1 for the extreme values of the success rates, and is greater in the middle of the scale to allow for the greater corresponding variability. The non-inferiority margin δ_p thus has the following values:

P_A	δ_p
0.1	0.0673
0.2	0.0989
0.3	0.1189
0.4	0.1315
0.5	0.1382
0.6	0.1393
0.7	0.1344
0.8	0.1222
0.9	0.0985

4.3 Sample Size Estimation

The number of treated subjects in this trial was based on hypothesized overall success rates of 53% for the OP-1 Putty group as compared to 47% for the autograft group. The hypothesized success rate for the OP-1 Putty group was based on the 58% overall 6 months success rate observed in the pilot study interim analysis (intent-to treat). The hypothesized success rate for autograft is higher than the overall success rate of 42% obtained in the pilot study (intent-to treat).

The maximum allowable difference between the treatment groups that could be used to conclude that OP-1 Putty is not inferior to autograft was set in the protocol at 10%. Using a 2:1 treatment to control group randomization assignment, an alpha level of 0.05 and power of 80%, 270 treated subjects (180 OP-1 Putty and 90 autograft) were determined to be needed for this study. Assuming that approximately 15% of treated subjects would not be evaluable at 24 months due to a number of reasons (lost-to-follow-up, withdrawn from study, visit outside of the established visit window), it was assumed that 42 additional subjects would need to be treated during the study. This assumption increased the number of treated subjects to 312.

4.4 Efficacy Assessments

Efficacy will be measured by calculating the 12, 24, and 36 month overall success rates in the OP-1 Putty and the autograft groups. The following assessments will be used for the patient success criteria:

- Radiographic evaluation at affected level, assessed by presence of bone; angular motion; translational movement
- Oswestry Disability Index
- Retreatment, reported as revision; removal; supplemental fixation; reoperation
- Neurological evaluation
- Absence of serious treatment-related adverse event during the course of the study

The following efficacy measurements will also be collected for each patient:

- CT scans at 9 months
- Presence of pseudoarthrosis at 9 months
- Fusion occurred at operated level at 9 months
- Lateral disc height measurement at baseline and 3, 6, 12, 24 and 36 months
- Degree of angular motion at baseline and 3, 6, 12, 24 and 36 months
- Translational movement at baseline and 3, 6, 12, 24 and 36 months
- Radiographic evaluation for the presence of bone at 3, 6, 12, 24 and 36 months
- Oswestry Disability Index at baseline, 6 weeks, 3, 6, 12, 24 and 36 months
- Neurological status at baseline, 6 weeks, 3, 6, 12, 24 and 36 months

4.5 Safety Assessments

Safety will be assessed principally by adverse events, clinical laboratory evaluations, and neurological status. The terms “complication” (used in the protocol) and “concurrent medical event” (used in the CRFs) will be considered synonymous with the term “adverse event”.

4.6 Additional Information

The following additional information will also be collected for each patient:

- Visual Analog Scale Results for Pain Assessment
- Donor Site Pain (autograft patients only)
- Medication Use
- Hospitalization Data
- General Health Survey (SF-36)
- Quality and Quantity of Bone Formation

4.7 Multiple Imputations for Handling of Dropouts or Missing Data

Patients who are considered as no longer participating in the study at a given visit, patients who have missed a visit, and patients who have missing data at a visit will be considered to have missing data at that visit. For the analysis of the primary endpoint for patient success and the analysis of overall radiographic success (overall success criterion #1) at 24 months for the intent-to-treat population, missing values will be imputed using a multiple imputation (MI) technique. The imputations of the missing data will be based on the following potentially relevant covariates:

Model 1: Patients who have 36 month data

- Patient overall success at 36 months
- Radiographic success at 36 months
- Presence of bone formation at 36 months (supplemented by data on quality and quantity of bone formation)
- Success of angulation of $\leq 5^\circ$ at 36 months
- Success of translational movement of ≤ 3 mm at 36 months
- Neurologic success at 36 months
- Oswestry Disability Index at 36 months
- Workers compensation status at baseline
- At least 2 morbidities at baseline (assessed by medical history)

Model 2: Patients who have 12 month data, but do not have 36 month data

- Patient overall success at 12 months
- Radiographic success at 12 months
- Presence of bone formation at 12 months (supplemented by data on quality and quantity of bone formation)
- Success of angulation of $\leq 5^\circ$ at 12 months
- Success of translational movement of ≤ 3 mm at 12 months
- Neurologic success at 12 months
- Oswestry Disability Index at 12 months
- Workers compensation status at baseline
- At least 2 morbidities at baseline (assessed by medical history)

Model 3: Patients who have 6 month data, but do not have 12 month or 36 month data

- Patient overall success at 6 months
- Radiographic success at 6 months
- Presence of bone formation at 6 months (supplemented by data on quality and quantity of bone formation)
- Success of angulation of $\leq 5^\circ$ at 6 months
- Success of translational movement of ≤ 3 mm at 6 months
- Neurologic success at 6 months
- Oswestry Disability Index at 6 months
- Workers compensation status at baseline
- At least 2 morbidities at baseline (assessed by medical history)

The data on quality and quantity of bone formation are based on previous and current radiographic evaluations, yielding five possible responses: NA – no bone, Progressing, Stable, Regressing, and Not Evaluable [because of problems with the film]. The data on presence of bone formation have three possible values: Yes, No, and Not Evaluable. By including two indicator (0-1) variables, for Progressing and Regressing, respectively, the analysis will provide for the following five reports:

- No bone formation (stable)
- No bone formation (regressing)
- Bone formation (progressing)
- Bone formation (stable)
- Bone formation (regressing).

(“Not Evaluable” yields a missing value.)

To carry out the MI, we will use a parametric model unless the data indicate that no model is required (e.g., among patients who have 12-month data and 24-month data, all successes at 12 months are also successes at 24 months). The parametric model will be a logistic regression where the outcome is success/failure at month 24 and the predictors are as listed under Models 1 through 3. Imputation will be done separately for each treatment arm. Two multiple imputations will be done: 1) for the primary endpoint, which is an aggregate across five different measures, and 2) for the overall radiographic success alone. The MI procedure begins by fitting the logistic regression model to data on the complete cases and estimating the parameters associated with each covariate (predictor) as well as the variance-covariance matrix. Separate models will be developed for patients who have 36-month data, patients who have 12-month data but not 36-month data, and patients who have 6-month data but neither 12-month nor 36-month data. Selection of the best logistic regression model will begin with identifying candidate models using a step-up approach including candidate covariates as described above. The choice of the best of the candidate models will be based on the Schwarz criterion (SC), which tends to produce parsimonious models.

It is possible that some patients whose outcomes are to be imputed have missing values on one or more of the predictors in the chosen model. In that situation we will identify the actual patterns of missing values. For each such pattern, we will develop an additional model (specific to the treatment arm, as needed) that does not involve the predictors whose values are missing. That model will be used in the imputation for each patient who has that pattern of missing values.

Once the model has been selected, imputation begins by sampling a value for the vector of model parameters from a multivariate normal distribution whose mean and variance-covariate matrix equal those estimated from the complete data. Each missing observation is imputed by sampling from the conditional distribution of this observation given the sampled parameter values and the observed covariates. Here the probability of a success for the missing observation is assumed to be Bernoulli-distributed, with the Bernoulli parameter obtained by the logistic regression equation with the sampled parameter estimates. The number of imputations will be 4, reflecting Rubin’s assertion that for moderate fractions of missing information (<30%), a small number of

imputations (3 or 4) results in nearly fully efficient estimates of the population quantity of interest.

Within each treatment arm each of the multiple imputations will produce a completed-data estimate of the quantity to be used in the hypothesis test, along with an associated estimate of its within-imputation variance. The inferences will be based on the average of those completed-data estimates and on a variance estimate that incorporates the average within-estimate variance and the between-imputation variance. If the multiply imputed data are used in an adjustment for covariates (Sections 4.8 and 5.4.1), the model will involve data from both arms and will yield estimates of the adjusted treatment difference and associated estimates of its within-imputation variance.

For other efficacy analyses, missing values will not be imputed except as otherwise specified. Missing data will not be imputed for the safety data except the SF-36 data.

4.8 Adjustments for Covariates

An analysis, described in Section 5.4.1, will adjust for covariates (if a statistically significant adjustment is found).

4.9 Multiple Comparisons/Multiplicity

No adjustments for multiple comparisons will be made.

4.10 Multicenter

For the primary efficacy endpoint, an analysis will be conducted to test for treatment by center interaction. If the interaction is significant, results will be presented by center.

4.11 Examination of Subgroups

Analysis of the primary efficacy endpoint, overall success at 24 months, will be presented by sex and age category, as well as overall.

5.0 STATISTICAL ANALYSES

5.1 Analysis Populations

5.1.1 Enrolled Population

The enrolled population includes all subjects who are enrolled in the study.

5.1.2 Intent-to-Treat Population

The (modified) intent-to-treat population includes all subjects who are randomized and have at least one post-treatment visit. All efficacy analysis will be conducted on the intent-to-treat population (ITT).

5.1.3 Per Protocol Population

The per protocol population includes all OP-1 Putty or autograft treated patients who do not violate the inclusion/exclusion criteria. Analysis of overall patient success will be repeated on the per protocol population using descriptive statistics to aid in the interpretation of the primary efficacy analysis on the ITT population. All other efficacy analysis will also be repeated on the per protocol population.

5.1.4 Safety Population

The safety population includes all subjects who are treated using either OP-1 Putty or autograft. The safety analysis will be based on the safety population.

5.2 Subject Accountability

A summary of each patient population will be presented in Table 1.1 by treatment group for all enrolled patients. It will include a tabulation of the number and percent of patients who participated in the study and who are in the enrolled, safety, intent-to-treat, and per protocol populations. The number and percentage of patients who complete the study will also be presented. The primary reason for withdrawal from the study will be tabulated for those patients who do not complete the study.

Patient accounting will be presented for each treatment group in Table 1.2 for the safety population. This includes an accounting of patient status at all time points: preoperative, operative, 6 weeks, 3, 6, 12, 24, and 36 months as follows:

- All patients (theoretically due)
- Deaths
- Withdrawals
 - Voluntary subject withdrawal
 - Subject illness/concurrent medical condition
 - Lost to follow-up

- Subject withdrawn by investigator
- Did not have surgical procedure specified in protocol
- Withdrawal due to other reason
- Number of patients included in data listings
- Number of patients included in ITT analysis tables
- Number of patients included in per protocol analysis tables
- Follow-up rate (percent of patients with data)

5.3 Demographic and Baseline Characteristics

Frequencies and percentages will be presented for age category, sex, disease diagnosis (diagnosis, involved level, method used to determine diagnosis), prior treatment to affected level, and workers compensation status for the safety, intent-to-treat, and per protocol populations in Tables 2.1, 2.2, and 2.3, respectively. Descriptive statistics for age, weight (kg), height (cm), BMI, Oswestry score, degree of angular motion, and translational movement will also be presented. For the categorical variables, Chi-square test will be used to test the difference between treatment groups. For the continuous variables, a two-sample t-test will be used to test the difference between treatment groups.

Age will be categorized as follows in the analysis:

- <45 years old
- 45 – 65 years old
- >65 years old

5.4 Efficacy Analysis

5.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the 24 month overall success rate for the intent-to-treat population. Individual patient success is defined as below:

A patient is considered a success if he or she meets all five of the following criteria.

- 1) Individual patient will be considered as overall radiographic success if all three of the following conditions are satisfied:
 - Presence of bone formation, and
 - Angulation of $\leq 5^\circ$, and
 - Translational movement of ≤ 3 mm

The angulation angle and translational movement are demonstrated on flexion/extension radiographs of the affected level. The values of angulation and translational movement will be rounded to the nearest integer in the analysis.

Copies of subject supine (anteroposterior) and standing (lateral and flexion/extension) radiographs will be reviewed by two independent radiologists. The reviewers will be

blinded to treatment group. The radiographs will be read in sequence according to the study specific procedure for evaluation of radiology. The findings from the two reviewers will be recorded on the CRF. A third independent, masked radiologist will perform a secondary radiographic evaluation if the two initial evaluations differ on the assessment of Overall Radiographic Success at any of the time points. The third radiologist will be provided with the results from the primary radiographic evaluation and asked to determine whether reviewer A's or B's assessment for each discrepant time point is the most accurate assessment, based on his/her radiographic evaluation.

All three criteria must be met in order to be classified as an overall radiographic success. A patient will be considered as not evaluable in the analysis if both AP and flexion and extension films are not evaluable.

- 2) Oswestry Disability Index improvement of at least 20% from the pre-treatment visit. The improvement will be measured by change in the percent disability from pre-treatment. The percent disability will be calculated as sum of all non-missing individual scores divided by the number of non-missing score times five, and multiplied by 100.
- 3) No revisions, removals or supplemental fixations. All reoperations that are intended to promote fusion at the treated level will be considered failures. Reoperations that are not intended to promote fusion, such as drain removal, will not be considered failures. Revision, removals, supplemental fixations, and reoperations are defined (definitions based on the Guidance Document for Preparation of IDEs for Spinal Systems, January 13, 2000) as follows:
 - a) A revision is a procedure that adjusts or in any way modifies or removes *part* of the original implant configuration, with or without replacement of a component. A revision may also include adjusting the position of the original configuration.
 - b) A removal is a procedure where *all* of the original system configuration is removed with or without replacement.
 - c) A reoperation is any surgical procedure at the involved level(s) that does not remove, modify, or add any components to the system.
 - d) A supplemental fixation is a procedure in which additional instrumentation not under study in the protocol is implanted (e.g., supplemental placement of a rod/screw system or a plate/screw system).

The term retreatment will be used to refer to a revision, removal, supplemental fixation, or reoperation intended to promote fusion at the treated level. Any patient who experiences a retreatment will be considered a failure, regardless of the timing of the procedure.

- 4) The absence of serious treatment-related adverse events during the course of the study.
- 5) Patient will be considered an overall neurological success in the absence of a decrease in neurological status, unless attributable to a concurrent medical condition or to the surgical procedure, defined as follows:
 - A patient will be considered to have a decrease in neurological status and will be considered an overall neurological FAILURE if either of the following conditions are met:
 - i. Muscle Strength: decrease of at least 2 or more grades in ≥ 1 of the 24 muscle groups that are assessed parameters;
 - ii. At least two of the following three changes occur:
 - Reflexes: Change of ≥ 1 of the 4 reflex assessments from normal (1) to absent (3);
 - Sensory: Change of ≥ 1 of the 8 sensory assessments from normal (2) to absent (0);
 - Change in straight leg raise pain from negative to positive.
 - For patients who are failures as defined above, the Neurological Patient Profile and Safety Patient Profile will be reviewed by a blinded Independent Neurological Reviewer to determine if the neurological status failure is attributed to
 - i. a concurrent medical condition;
 - ii. surgical procedure (decompression and posterolateral fusion)
 - iii. study treatment (OP-1 Putty or autologous bone graft)
 - iv. unable to determine based on the available information
 - Patients will be considered an Overall Neurological SUCCESS if any of the following conditions are satisfied:
 - i. Not an overall neurological FAILURE
 - ii. FAILURE in overall neurological status but attributed to a concurrent medical condition, as assessed by Independent Neurological Reviewer
 - iii. FAILURE in overall neurological status but attributed to the surgical procedure, as assessed by independent Neurological Reviewer.

The null hypothesis is that the difference between the success rate for the autograft treatment group (P_A) and the success rate for the OP-1 Putty treatment group (P_O) is greater than or equal to the non-inferiority margin δ_p ($P_A - P_O \geq \delta_p$). This hypothesis will be examined estimating the difference between the success rates in the two treatment groups (expressed in the angular scale

as $A_A - A_O$) and the associated standard error. A 95% confidence upper bound on $A_A - A_O$ will also be computed. If the null hypothesis of inferiority of OP-1 is rejected, a test of superiority of OP-1 will be performed. If an adjustment for covariates is made (as discussed below), additional test(s) and confidence bound will be based on the adjusted treatment difference.

The primary analysis of the primary efficacy endpoint will be based on the intent-to-treat population. The statistical procedure that accommodates missing data is described in detail in Section 4.7. This endpoint will also be analyzed with descriptive statistics based on the per protocol population to aid in the interpretation of the primary analysis of this endpoint.

The number and percentage of patients in each treatment group with missing data for the overall success will be presented in Table 3.1 to assess the potential impact of missing data for the intent-to-treat population. Fisher's exact test will be used to test the difference in number of patients with missing data between treatment groups. The patients with missing data will also be listed in the data listings.

Tables 3.2 and 4.1 will summarize the overall success rate for the intent-to-treat population and per protocol population, respectively.

For the intent-to-treat population, the main analysis will use a logistic regression model to take into account the combined effect on success rate of baseline characteristics that show statistically significant differences (at the .10 significance level). The model will yield adjusted success rates (which may be more precise than the unadjusted rates). The characteristics to be considered for this analysis are

- 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 I or Grade II
- 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)
- Oswestry Disability Index (continuous variable)

Inferences will be based on estimates of treatment effects adjusted for co-variates and on variance estimates obtained through multiple imputation as described in Section 4.7.

Additionally, analysis of treatment by center interaction for the primary efficacy endpoints will be presented in Table 3.2 using logistic regression. If the interaction is significant at the 0.05 level, success rates for each treatment group will be presented by center. Even if there is a

significant interaction, the significance of the unadjusted difference between groups on the primary endpoint will be based on the pooled data.

The overall success rate for the primary efficacy endpoint will also be presented separately for male and female and for each age category (<45 years old, 45 – 65 years old, >65 years old) in Tables 3.3 and 4.2 for the intent-to-treat population and per protocol population, respectively. If there are statistically significant differences in baseline characteristics (Oswestry score, level fused, degree of angular motion, and translational movement and Worker's Compensation Status) between treatment groups, the overall success rate for the primary efficacy endpoint will also be stratified by those characteristics which are statistically significant. The results will be presented in additional analysis tables.

5.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are defined as follows:

- Overall success rate at 12, 24 and 36 months for the per protocol population and overall success rate at 12 and 36 months for the ITT population (Tables 3.2 and 4.1 for the ITT and per protocol population, respectively)
- Overall radiographic success rate (overall success criterion #1) at 12, 24, and 36 months (Table 5.1 and 5.1.1 for the ITT and per protocol population, respectively)
- Success rate based on Oswestry disability (overall success criterion #2) at 12, 24, and 36 months (Table 5.2 and 5.2.1 for the ITT and per protocol population, respectively)
- Success rate based on the absence of retreatment (overall success criterion #3) at 12, 24, and 36 months (Table 5.3 and 5.3.1 for the ITT and per protocol population, respectively)
- Success rate based on absence of serious treatment-related adverse events (overall success criterion #4) at 12, 24, and 36 months (Table 5.4 and 5.4.1 for the ITT and per protocol population, respectively)
- Overall neurological success rate (overall success criterion #5) at 12, 24, and 36 months (Table 5.5 and 5.5.1 for the ITT and per protocol population, respectively)

5.4.3 Additional Efficacy Measurements

The following efficacy measurements will be reported using available data:

- Presence of bridging at operated level based on the CT scans at 9 months (Table 5.6 and 5.6.1 for the ITT and per protocol population, respectively)
- Presence of pseudoarthrosis at 9 months (Table 5.7 and 5.7.1 for the ITT and per protocol population, respectively)
- Change from baseline in lateral disc height measurement at 3, 6, 12, 24 and 36 months (Table 5.8 and 5.8.1 for the ITT and per protocol population, respectively)
- Change from baseline in degree of angular motion at 3, 6, 12, 24 and 36 months (Table 5.9 and 5.9.1 for the ITT and per protocol population, respectively)

- Change from baseline in translational movement at 3, 6, 12, 24 and 36 months (Table 5.10 and 5.10.1 for the ITT and per protocol population, respectively)
- Change from baseline in Oswestry Disability Index at 6 weeks, 3, 6, 12, 24 and 36 months (Table 5.11 and 5.11.1 for the ITT and per protocol population, respectively)

At nine months all subjects will receive a CT scan to evaluate bridging at the operative level. Sagittal, planar and curved coronal reformatted three-dimension (3D) will be used, with cut sections of 1-2 mm. Two independent masked radiologists will evaluate the CT scan for bridging. Success based on the CT scans will be defined as the presence of bridging at the right or left side of the operated level. A patient will be deemed a success if bone is present with bridging and/or solid bridging is apparent at the right or left side of the operated level. A patient will be deemed a failure if there is no evidence of bone or bone is present without bridging.

The radiologists will also assess the CT scans for the occurrence of pseudoarthrosis and fusion at the operated level at 9 month. Pseudoarthrosis is defined as a nonunion or a break in the fusion mass at the operated level. The occurrence of pseudoarthrosis and of fusion at the operated level will be summarized by presenting frequencies and percentages. The number and percentage of subjects with pseudoarthrosis and fusion will be summarized for each treatment group. Fisher's exact test will be used to test the difference in percentages of subjects with pseudoarthrosis and fusion between treatment groups.

Actual value and change from baseline to post-baseline time points for lateral disc height, degree of angular motion, and translational movement will be summarized by treatment group. Two-sample t-tests will be used to test the difference in change from baseline between the OP-1 Putty group and the autograft group. The change from baseline will also be examined using one-sample t-test to test the mean change within each treatment group.

Lateral disc height measurement recorded at the 6-week postoperative radiograph will be considered as the baseline measurement. For degree of angular motion and translational movement, the results from the third independent reviewer will be used in the analysis. If there was no third reviewer assessment, the average scores from the first two reviewers will be used.

5.5 Safety Analysis

Safety will be assessed principally based on the examination of adverse events, secondary procedures, clinical laboratory evaluations and neurological status.

5.5.1 Adverse Events

Adverse events (Concurrent Medical Events) will be coded using MedDRA coding dictionary. The adverse event summary tables will be based on treatment-emergent adverse events for the safety population.

The following adverse events are defined as treatment-emergent:

- Adverse events that occurred after study treatment,

- or
- Adverse events that occurred before study treatment, but increased in severity after study treatment

The following will be tabulated for the treatment-emergent adverse events in Table 6.1 for each treatment group:

- Number and percentage of patients with at least one adverse event.
- Number and percentage of patients with at least one severe adverse event.
- Number and percentage of patients with at least one treatment-related adverse event.
- Number and percentage of patients with at least one unanticipated adverse event.
- Number and percentage of patients with at least one serious adverse event.
- Number and percentage of patients with at least one treatment-related serious adverse event.
- Number and percentage of deaths.

The 95% exact Clopper-Pearson confidence intervals will be calculated for the incidence of adverse events specified above for each treatment group.

The following events will be classified as serious:

- Hospitalization or prolongation of hospitalization
- Life-threatening
- Persistent or significant disability/incapacity adverse event
- Deaths

The treatment-related events include suspected related events and events with unknown relationship to treatment.

The number and percentage of subjects experiencing treatment-emergent adverse events and the number and percentage of events will be summarized by system organ class (SOC), and by preferred term for each treatment in Table 6.2.

The number and percentage of subjects experiencing treatment-emergent adverse events will also be summarized by severity, by relationship to study treatment, and by type of event (e.g., intraoperative) for each treatment group in Tables 6.3, 6.4, and 6.5, respectively.

Time course distribution of all events will be analyzed by presenting the numbers and percentages of subjects experiencing treatment-emergent adverse events for the following time periods: operative (from start of operation to discharge from hospital), operative-6 weeks, 7 weeks-3 months, 4-6 months, 7-12 months, 13-24 months and 25-36 months. The results will be presented by SOC and preferred term in Table 6.6 and by type of event in Table 6.7.

The analyses presented in Tables 6.2 through 6.7 will be repeated for serious and/or unanticipated adverse events in Tables 6.8 through 6.13, respectively.

Detailed listings of treatment-emergent, and serious/unanticipated adverse events will be presented in the listings.

5.5.2 Secondary Procedures

The number and percent of patients who had a retreatment (e.g., revision, removal, supplemental fixation, and reoperation) at operative (from start of operation to discharge from hospital), operative-6 weeks, 7 weeks-3 months, 4-6 months, 7-12 months, 13-24 months and 25-36 months will be presented in Table 7.

5.5.3 Clinical Laboratory Evaluations

Blood will be drawn preoperatively (baseline), postoperatively, and at the 6 week, 3 month, 6 month, 12 month, 24 month and 36 month follow-up visits. No immunological assessment will be conducted beyond 24 months. Immunological testing will be conducted on serum and whole blood or plasma will be evaluated for the following:

- **Hematology:** Hematocrit, hemoglobin, neutrophils (bands, abs.), basophils abs., eosinophils abs., lymphocytes abs., MCHC, MCV, monocytes abs., neutrophils abs., platelet count, red cell count, white cell count
- **Biochemistry:** Albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), creatinine, CO₂ content, chloride, glucose, potassium, sodium, uric acid, bilirubin (total), protein, urea nitrogen

Descriptive statistics will be presented for actual value and change from baseline to the post-baseline time points for hematology and biochemistry parameters by treatment in Tables 8.1 and 8.3, respectively. Differences in change from baseline will be examined using the two-sample t-test to test for differences between treatment groups for each laboratory parameter. Additionally, change from baseline will be examined using one-sample t-test to test the mean change for each laboratory parameter within each treatment group.

All chemistry and hematology values will be classified as low (below the lower normal range), normal (within the normal range), or high (above the upper normal range) based on normal ranges supplied by the laboratory. Shift tables will be used to examine shifts in status (low, normal, high) from baseline to the post-baseline time points for hematology and biochemistry parameters in Tables 8.2 and 8.4, respectively. Chi-square or Fisher's exact test will be used to test the difference in status between the OP-1 Putty group and the autograft group, as appropriate. Additionally, shifts in status from baseline to post-baseline timepoints within treatment group will be tested using Stuart-Maxwell test or Stuart-Maxwell test or McNemar's test for each treatment group and laboratory test, as appropriate.

5.5.4 Neurological Status

The neurological status of each patient will be reported preoperatively (baseline), and at the 6 week, 3 month, 6 month, 12 month, 24 month, and 36 month follow-up visits. Shifts in status

(normal, abnormal, not evaluable) from baseline to the post-baseline time points will be examined in Table 9 by treatment group for muscle strength, reflexes, straight leg raises, and sensory evaluation. Chi-square or Fisher's exact test will be used to test the difference in status between the OP-1 Putty group and the autograft group, as appropriate. Additionally, shifts in status from baseline to post-baseline time points within treatment group will be tested using McNemar's test within each treatment group.

The normal/abnormal status for muscle strength, reflexes, straight leg raises, and sensory evaluation is defined as follows:

Muscle strength – hip, knee, ankle, and toe:

- Abnormal: “Absent”, “Trace”, “Poor”, or “Fair” is entered for any of the three hip segments (flexion, adductors, extensors) for either side.
- Not Evaluable: At least one of the three hip segments is missing for either side.
- Normal: “Good” or “Normal” is entered for all three hip segments for both sides.

Reflexes:

- Abnormal: “Decreased” or “Absent” is entered for any of the reflex segments (right knee jerk, right ankle jerk, left knee jerk, and left ankle jerk).
- Not Evaluable: At least one of the four reflex segments is missing.
- Normal: “Normal” is entered for all four reflex segments.

Straight leg raises:

- Abnormal: “Positive (pain)” is entered for either or both legs.
- Not Evaluable: Status is missing for any leg.
- Normal: “Negative (no pain)” is entered for both legs.

Sensory evaluation:

- Abnormal: “Impaired” or “Absent” is entered for any of the sensory segments (L3, L4, L5, and S1).
- Not Evaluable: At least one of the four sensory segments is missing.
- Normal: “Normal” is entered for all four sensory segments.

5.6 Additional analysis

Additional analysis will also be conducted on the following measurements:

- Visual Analog Scale Results for Pain Assessment
- Donor Site Pain (autograft patients only)
- Medication Use
- Hospitalization Data
- General Health Survey (SF-36)

5.6.1 Visual Analog Scale for Pain Assessment

The visual analog scale for pain will be reported preoperatively (baseline) and at the 6 week, and 3, 6, 9, 12, 24, and 36 month follow-up visits.

Descriptive statistics will be presented for actual value and change from baseline to the post-baseline time points for each treatment in Table 10. Difference in change from baseline will be examined using the two-sample t-test to test a difference in mean between treatment groups. Additionally, change from baseline will be examined using one-sample t-test to test the mean change within each treatment group.

5.6.2 Donor Site Pain

The donor site pain will be assessed at the 6 week, and 3, 6, 9, 12, 24, and 36 month follow-up visits for autograft patients only. The donor site pain will be rated using both visual analog scale and pain status (none, mild, moderate, severe).

Descriptive statistics will be presented for the visual analog scale for each timepoint in Table 11.1 for autograft patients only. Pain status will be summarized by frequencies and percentages in Table 11.2 for each category.

5.6.3 Current Medication Use

The current medication use will be recorded preoperatively and at the 6 week, 3 month, 6 month, 9 month, 12 month, 24 month, and 36 month follow-up visits.

Frequency and percentage will be presented for the current medications for each time point by treatment in Table 12.

5.6.4 Surgical Procedure Characteristics

Frequencies and percentages will be presented in Table 13 for level fused, spinal fusion approach, surgical incision, device/equipment used in positioning, and other procedures performed for each treatment.

Descriptive statistics for anesthetic time, operative time, estimated blood loss, and amount of blood reinfused during surgery will also be presented.

5.6.5 General Health Survey (SF-36)

The General Health Survey Scale will be collected preoperatively and at the 6 week, 3 month, 6 month, 9 month, 12 month, 24 month and 36 month follow-up visits.

If a subscale of SF-36 is missing an item, then means of the items in the subscale for that patient will be used to impute the missing value. This will only be done if fewer than one-half of the items in the subscale are missing.

The SF-36 yields an 8-scale profile of functional health and well-being scores as well as psychometrically based summary measures – the Physical Component Score (PCS) and Mental Component Score (MCS). The 8-scale profiles of functional health are:

- SF-36 Health Survey Scale: Physical Functioning Scale
- SF-36 Health Survey Scale: Role-Physical Scale
- SF-36 Health Survey Scale: Bodily Pain Scale
- SF-36 Health Survey Scale: Mental Health Scale
- SF-36 Health Survey Scale: Role-Emotional Scale
- SF-36 Health Survey Scale: Social Functioning Scale
- SF-36 Health Survey Scale: Vitality Scale
- SF-36 Health Survey Scale: General Health Perceptions Scale

Descriptive statistics will be presented for the actual value and change from baseline to the post-baseline time points for PCS and MCS as well as for each of the 8-scale profile of functional health by treatment in Tables 14.1 through 14.10. The change from baseline will be examined using Wilcoxon rank-sum test to test the difference in mean between treatment groups.

5.7 Immunology

Serum samples will be analyzed for anti-OP-1 antibodies preoperatively (baseline), and at the 6 week, 3 month, 6 month, 12 month and 24 month follow-up visits. Samples that are positive in an ELISA screen will be further tested to determine antibody titer and neutralizing capacity.

The number (%) of patients with a positive screen and with neutralizing antibodies will be summarized in Table 15.1 for each treatment group at each time point. Descriptive statistics will be presented for the titer result for each treatment at each time point in Table 15.2. Patient profiles for patients with neutralizing antibodies will be presented in Table 15.3. The following information will be summarized in each profile:

- Overall patient success at 12, 24 and 36 months
- Overall radiographic success (overall success criterion #1) at 12, 24, and 36 months
- Success based on Oswestry Disability Index (overall success criterion #2) at 12, 24, and 36 months
- Success based on absence of retreatment at 12, 24, and 36 months (overall success criterion #3)
- Success based on the absence of treatment-related serious adverse events at 6 weeks, and 3, 12, 24, and 36 months (overall success criterion #4)
- Overall neurological success (overall success criterion #5) at 12, 24, and 36 months
- Neutralizing antibodies status at baseline, 6 weeks, and 3, 12, and 24 months
- Antibody titer results over time figure
- Overview of adverse events (system organ class, preferred term, days onset since operation, duration, serious (yes/no), and potentially immunologically related (yes/no).

The following events will be classified as potentially immunologically related events:

Category	Term
Systemic symptoms	Allergic reaction, angioedema, hypersensitivity reaction, systemic infection, flu syndrome, pyrexia, malaise, lymphadenopathy
Local reactions	Inflammation, edema, erythema, pain, drainage, infection
Hematologic	ITP, leukocytosis, coagulopathy, thrombocytopenia, anemia, neutropenia
Impaired Renal function	BUN abnormal, creatinine abnormal, hyperkalemia, hyponatremia, hypocalcemia, hyperphosphatemia, hyperproteinemia , hyperproteinuria, acidosis
Other	Complement abnormalities, CD4 decreased, CD8 decreased, Raynaud's disease

Success outcomes (overall patient success, overall radiographic success, success based on Oswestry Disability Index, success based on absence of retreatment, success based on the absence of serious treatment-related adverse events, and overall neurological success) for patients with and without neutralizing antibodies will be summarized in Table 15.4 by presenting the number (%) of successes for each treatment group at 12, 24, and 36 months.

The number and percentage of subjects experiencing treatment-emergent adverse events will be summarized in Table 15.5 by treatment group and neutralizing antibody status for the following time periods: any time point, Operative-6 weeks, 6weeks-3 months, 3-6 months, 6-12 months, 12-24 months and 24-36 months. The analysis will be repeated for serious treatment-emergent adverse events in Table 15.6, immunologically related adverse events in Table 15.7, and immunologically related serious adverse events in Table 15.8.

Appendix 1: Testing The Hypothesis of Inferiority

The null hypothesis for this study is 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 ($P_A - P_O \geq \delta_p$). Initially, the study protocol based the test on the difference $P_A - P_O$ and defined $\delta_p = .10$ for all values of P_A (and P_O). Subsequent examination of this approach led to the proposal that a non-constant value of δ_p be used, in part so that larger values of δ_p could be used where the statistical variation of the observed success rates is greater and smaller values of δ_p could be used where that variation is less. This proposal was discussed with CDRH during a meeting on October 18, 2005; it varied the value of δ_p as a step-function of P_A . (Recall that, when the numbers of successes follow a binomial distribution, the variance of the observed proportion of successes is $P(1-P)/n$, where P is the true success rate and n is the number of trials.) Because of concerns about the statistical properties of a test based on a step-function, we also evaluated a similar proposal that varied the value of δ_p continuously with P_A as follows:

$$\delta_p = 0.15 - \{I \times |P_A - 0.5| \times 0.07 / 0.4\} - (1 - I) \times 0.07,$$

where I is an indicator variable whose value is 1 when $0.1 < P_A < 0.9$ and 0 otherwise. In conducting the customary significance test with this definition, however, the value of δ_p must be calculated (i.e., estimated) from the observed success rate in the autograft group. Simulation studies showed that the resulting Type I error rate departed substantially from the intended .05. Thus, that proposal was not satisfactory.

The current analysis plan resolves the difficulty of the Type I error rate by conducting the significance test in a transformed scale, related to the proportion scale by a straightforward mathematical function. The “angular transformation” begins with the observed proportion of successes, x/n from x successes in n trials, and applies the function $\sin^{-1} \sqrt{x/n}$ to produce the corresponding angle (in radians). The variance of the resulting angle is closely approximated by $1/(4n)$ for all but the most extreme values of P , and its distribution in sizable samples is well approximated by a normal distribution. Thus, one can use a non-inferiority margin in the angular scale, δ_A , chosen with attention to the likely values of P_A and the initial constant value of δ_p but not dependent on P_A . With such a constant value of δ_A the customary hypothesis test (based on the angular transforms of the observed success rates in the two groups and using the .05 level) will have the specified Type I error rate. (Statistical analyses of proportions often recognize that the interpretation and practical impact of a given difference in proportions depend on the proportions involved. For example, in many situations the difference between 10% and 12% is not regarded as equivalent to the difference between 50% and 52%. Thus, statisticians employ nonlinear transformations of percentages to scales in which a given amount of difference is more nearly equivalent at all points of the scale. The angular transformation is one such transformation, and the logit or log-odds is another.)

Appendix 2: References

- ¹An HS, Simpson JM, Glover JM, Stephany J, "Comparison Between Allograft Plus Demineralized Bone Matrix Versus Autograft in Anterior Cervical Fusion," *Spine*, 1995;20(20): 2211-2216.
- ²An HS, Lynch K, Toth J, "Prospective Comparison of Autograft vs. Allograft for Adult Posterolateral Lumbar Spine Fusion: Differences Among Freeze-Dried, Frozen, and Mixed Grafts," *J of Spine Disord*, 1993;8(2):131-135.
- ³Bernhardt M, Swartz DE, Clothiaux PL, Cronwell RR, White AA, "Posterolateral Lumbar and Lumbosacral Fusion with and without Pedicle Screw Internal Fixation," *Clin Orthop*, 1992;284: 109-115.
- ⁴Boden SD, Monroe MA, Martin G, Hutton WC, "Posterolateral Lumbar Spinal Arthrodesis with rhBMP-2/HA-TCP Following Laminectomy in the non-human Primate," *Trans ORS*, 1998;19: 249.
- ⁵Boden SD, Schimandle JH, Hutton WC, Chen MI, "The Use of an Osteoinductive Growth Factor for Lumbar Spinal Fusion," *Spine* 1995;20(24)2626-2632.
- ⁶Brantigan JW, "Pseudarthrosis Rate After Allograft Posterior Lumbar Interbody Fusion with Pedicle Screw and Plate Fixation," *Spine* 1995;19(11)1271-1280.
- ⁷Campbell's Operative Orthopaedics, Eighth Edition, AH Crenshaw, (ed.), Mosby , Boston, 1992.
- ⁸Cook SD, Wolfe MW, Salkeld SL, Rueger DC, "Effect of Recombinant Human Osteogenic Protein-1 on Healing of Segmental Defects in Non-Human Primates", *JBJS* 1995;77A: 734-750.
- ⁹Cook SD, Baffes GC, Wolfe MW, et al, "The effect of Recombinant Human Osteogenic Protein-1 on Healing of Large Segmental Bone Defects", *JBJS* 1994;76A: 827-838.
- ¹⁰Cook SD, Baffes GC, Wolfe MW, et al, " Recombinant Human Bone Morphogenic Protein-7 induces Healing in Canine Long Bone Segmental Defect Model", *Clin. Orthop*. 1994;301:302-312.
- ¹¹Cook SD, Rueger DC, "Osteogenic Protein-1," *Clin Orthop*, Number 1996;324: 29-38.
- ¹²Cook SD, Dalton JE, Tan EH, Whitecloud TS and Rueger DC, "In vivo evaluation of Recombinant Human Osteogenic Protein (rhOP-1) Implants as a Bone Graft Substitute for Spine Fusions", *Spine*, 1994;19(15):1655-1663.
- ¹³Dall BE, Rowe DE, "Degenerative Spondylolisthesis : Its Surgical Management," *Spine*, 1985;10(7):668-673.

¹⁴Fischgrund JS, Mackay M, Herkowitz HN, Brower R, Montgomery DM, Kurz LT, “Degenerative Lumbar Spondylolisthesis with Spinal Stenosis: A Prospective, Randomized Study Comparing Decompressive Laminectomy and Arthrodesis with and Without Spinal Instrumentation,” *Spine*, 1997;22(24):2807-2812.

¹⁵Herkowitz HN, Kurz LT, “Degenerative Lumbar Spondylolisthesis with Spinal Stenosis,” *JBJS*, 1991;73-A(6): 802-808.

¹⁶Jorgenson SS, Lowe TG, France J, Sabin J, “A Prospective Analysis of Autograft vs. Allograft in Posterolateral Lumbar Fusion in the Same Patient,” *Spine*, 1994;19(18): 2048-2053.

¹⁷Kant AP, Daum WJ, Dean SM, Uchida T, “Evaluation of Lumbar Spine Fusion,” *Spine*, 1995; 20(21): 2313-2317.

¹⁸Katz JN, Lipson SJ, Larson MG, McInnes JM, Fossel AH, Liang MH, “The Outcome of Decompressive Laminectomy for Degenerative Lumbar Stenosis,” *JBJS*, 1991;73-A(6): 809-816.

¹⁹Katz JN, Lipson SJ, Lew RA, Grobler LJ, Weinstein JN, Brick GW, Fossel AH, Liang MH, “Lumbar Laminectomy Alone or With Instrumented or Noninstrumented Arthrodesis in Degenerative Lumbar Spinal Stenosis,” *Spine*, 1997;22(10): 1123-1131.

²⁰Kwiatkowski TC, Meyer RA, Gruber HE, Tabor JR, Murakami T, Howard BA, Wozney JN, Hanley EN, “Spinal Laminectomy with rhBMP-2 in the Canine: A Safety Study,” *Trans ORS*, 1997;18: 189..

²¹Magin MN, “Enhancement of Lumbar Vertebral Interbody Fusion by Human Recombinant Osteogenic Protein-1, OP-1, in a Sheep Model”, American Association of Orthopedic Surgeons (AAOS), 1998, New Orleans.

²²Minamide A, Tamakit T, Kawakami M, Hashizume H, Sakatar R, “An Experimental Spinal Fusion with Wintered Bovine Bone and Recombinant Human Bone Morphogenetic Protein-2,” *Trans ORS*, 1998;(19): 659.

²³Mundy DR, “Regulation of bone formation by bone morphogenetic proteins and other growth factors,” *Clin Orthop*, 1997;323: 24-28.

²⁴Rompe JD, Eysel P, Hopf C, “Clinical Efficacy of Pedicle Instrumentation and Posterolateral Fusion in the Symptomatic Degenerative Lumbar Spine,” *Eur Spine J*, 1995;4: 231-237.

²⁵Sandhu HS, “Spinal Applications for Recombinant Bone Morphogenetic Protein: Early Experimental Results,” 1996.

²⁶Sampath TK, Rueger DC, “Structure, Function and Orthopedic Applications of Osteogenic Protein-1 (OP-1).” *Complications in Orthopedics* Winter, 101-107, 1994.

²⁷Spengler DM, "Fusion of the Lumbosacral Spine: An Excellent Treatment Option for Selected Patients with a Variety of Spinal Disorders," in Instrumented Fusion of the Degenerative Lumbar Spine: State of the Art, Questions, and Controversies, M Szpalski, R Gunzburg, DM Spengler, A Nachemson (eds.), Lippincott-Raven Publishers, Philadelphia, 1996.

²⁸The Spine, RH Rothman and FA Simeone (eds.), WB Saunders Co., Philadelphia, 1992.

²⁹Steinmann JC, Herkowitz HN, "Pseudarthrosis of the Spine," *Clin Orthop*, 1992; 284:80-90.

³⁰Yone K, Sakou T, Kawauchi Y, Yamaguchi M, Yanase M, "Indication of Fusion for Lumbar Spinal Stenosis in Elderly Patients and Its Significance," *Spine*, 1996;21(2):242 -248.

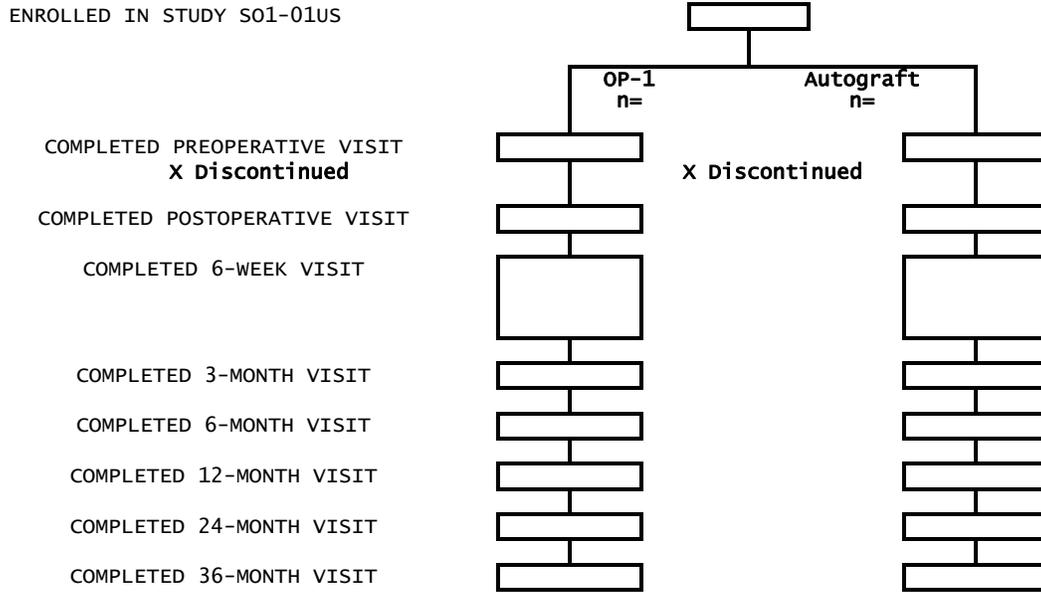
³¹Zdeblick TA, "The Treatment of Degenerative Lumbar Disorders: a Critical Review of the Literature," *Spine*, 1995;20(24S):126S-137S.

List of Tables and Listings

<u>Table</u>	<u>Title</u>
A1.1	Number of Patients Who Had Missing Data for the 24 Month Overall Success Rate (Protocol Defined) - Intent-to-Treat Population
A1.2	Overall Success Rate (Protocol Defined) at 3, 6, 12, 24 and 36 Months – Intent-to-Treat Population
A1.3	24 Month Overall Success Rate (Protocol Defined) by Gender and Age Group – Intent-to-Treat Population
A2.1	Overall Success Rate (Protocol Defined) at 3, 6, 12, 24 and 36 Months – Per Protocol Population
A2.2	24 Month Overall Success Rate (Protocol Defined) by Gender and Age Group – Per Protocol Population
A3.1	Overall Radiographic Success Rate (Protocol Defined) at 3, 6, 12, 24 and 36 Months – Intent-to-Treat Population
A3.1.1	Overall Radiographic Success Rate (Protocol Defined) at 3, 6, 12, 24 and 36 Months – Per Protocol Population
A3.2	Success Rate Based on Oswestry Disability (Protocol Defined) at 3, 6, 12, 24 and 36 Months – Intent-to-Treat Population
A3.2.1	Success Rate Based on Oswestry Disability (Protocol Defined) at 3, 6, 12, 24 and 36 Months – Per Protocol Population
A3.3	Success Rate Based on Absence of Retreatment (Protocol Defined) at 6-weeks, and at 6, 12, 24 and 36 Months – Intent-to-Treat Population
A3.3.1	Success Rate Based on Absence of Retreatment (Protocol Defined) at 6-weeks, and at 6, 12, 24 and 36 Months – Per Protocol Population
A3.4	Success Rate Based on Absence of Serious Treatment-related Adverse Events (Protocol Defined) at 3, 6, 12, 24 and 36 Months – Per Protocol Population
A3.4.1	Success Rate Based on Absence of Serious Treatment-related Adverse Events (Protocol Defined) at 3, 6, 12, 24 and 36 Months – Per Protocol Population
A3.5	Overall Neurological Success Rate (Protocol Defined) at 3, 6, 12, 24 and 36 Months – Intent-to-Treat Population
A3.5.1	Overall Neurological Success Rate (Protocol Defined) at 3, 6, 12, 24 and 36 Months – Per Protocol Population

<u>Listing</u>	<u>Title</u>
A1	Patient with Missing 24 Month Patient Success Data (Protocol Defined)

Figure 1
Patient Disposition Tree
Enrolled Population



Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 1.1
 Patient Populations and Disposition
 Enrolled Population

Parameter	Number (%) of Patients		
	Overall	OP-1 Putty	Autograft
All Enrolled Patients			
Safety Population			
ITT Population			
Per Protocol Population			
Disposition			
Completed 24 Month Visit			
Did not Complete 24 Month Visit			
Voluntary Subject Withdrawal			
Prior to Randomization			
Prior to Surgery			
After Surgery			
Subject Illness/Concurrent Medical Condition			
Lost to Follow-up			
Subject withdrawn by Investigator			
Did Not Have Surgical Procedure Specified in Protocol			
Death			
Other			

Program Name: _____ Creation date, time: _____
 Note: Percentages are based on total number of enrolled patients for each treatment group or overall as appropriate.

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 1.2
Patient Accounting Over Time
Safety Population
OP-1 Putty

	Preoperative	Operative	6 Weeks	3 Months	6 Months	12 Months	24 Months	36 Months
All patients (theoretically due)								
Deaths								
Withdrawals								
Voluntary Subject Withdrawal								
Subject Illness/Concurrent Medical Condition								
Lost to Follow-up								
Subject Withdrawn by Investigator								
Did Not Have Surgical Procedure Specified in Protocol								
Withdrawal Due to Other Reason								
Patients Included in Data Listings								
Patients Included in ITT Analysis Tables								
Patients Included in Per Protocol Analysis Tables								
Follow-up rate (Percent of Patients with Data)								

Program Name:

Creation date, time:

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 1.2
Patient Populations and Disposition
Safety Population
Autograft

	Preoperative	6 Weeks	3 Months	6 Months	12 Months	24 Months	36 Months
All Patients (theoretically due)							
Deaths							
Withdrawals							
Voluntary Subject Withdrawal							
Subject Illness/Concurrent Medical Condition							
Lost to Follow-up							
Subject Withdrawn by Investigator							
Did Not Have Surgical Procedure Specified in Protocol							
Withdrawal Due to Other Reason							
Patients Included in Data Listings							
Patients Included in ITT Analysis Tables							
Patients Included in Per Protocol Analysis Tables							
Follow-up rate (Percent of Patients With Data)							

Program Name:

Creation date, time:

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 2.1
 Demographic and Baseline Characteristics
 Safety Population

Parameter	Statistic	Overall	OP-1 Putty	Autograft	p-value
Age (years)	n Mean Median Std. Dev. Minimum Maximum				
Age (years)					
<45	n (%)				
45 - 65	n (%)				
>65	n (%)				
Sex					
Male	n (%)				
Female	n (%)				
weight (kg)	n Mean Median Std. Dev. Minimum Maximum				
Height (cm)	n Mean Median Std. Dev. Minimum Maximum				

Program Name: _____ Creation date, time: _____
 Note: Percentages are based on total number of patients for each treatment group or overall as appropriate.
 p-value is based on Chi-Square test for the categorical variables, and is based on two-sample t-test for the continuous variables.

[Note: This table will be repeated for intent-to-treat population (Table 2.2), and for per protocol population (Table 2.3)]

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 2.1
 Demographic and Baseline Characteristics
 Safety Population

Parameter	Statistic	Overall	OP-1 Putty	Autograft	p-value
Diagnosis					
Degenerate Lumbar Spondylolisthesis With Spinal Stenosis	n (%)				
Grade I	n (%)				
Grade II	n (%)				
Unable to Distinguish Between Grade I or II	n (%)				
Other	n (%)				
Involved Level					
L3-L4	n (%)				
L4-L5	n (%)				
L5-S1	n (%)				
Level Fused					
L3-L4	n (%)				
L4-L5	n (%)				
L5-S1	n (%)				
Method Used To Determine Diagnosis					
AP Radiograph	n (%)				
Lateral Radiograph	n (%)				
Flexion/Extension Radiographs	n (%)				
CT with Myelogram	n (%)				
MRI	n (%)				
CT	n (%)				
Other	n (%)				

Program Name: _____ Creation date, time: _____
 Note: Percentages are based on total number of patients for each treatment group or overall as appropriate.
 p-value is based on Chi-Square test for the categorical variables, and is based on two-sample t-test for the continuous variables.

[Note: This table will be repeated for intent-to-treat population (Table 2.2), and for per protocol population (Table 2.3)]

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 2.1
 Demographic and Baseline Characteristics
 Safety Population

Parameter	Statistic	Overall	OP-1 Putty	Autograft	p-value
Prior Treatment To Affected Level					
None	n (%)				
Laminectomy	n (%)				
Facetectomy	n (%)				
Foramenotomy	n (%)				
Dissectomy	n (%)				
Medication - Steroidal	n (%)				
Medication - Nonsteroidal	n (%)				
Physical Therapy	n (%)				
Rest	n (%)				
Immobilization/Brace	n (%)				
Heat, Ice Treatment	n (%)				
Manipulation/Chiropractic	n (%)				
Ultrasound	n (%)				
Tens/Electrical Stim.	n (%)				
Other	n (%)				
Workers Compensation Status					
Subject Not on Work's Compensation	n (%)				
Subject Currently on Work's Compensation	n (%)				
Subject Pending Work's Compensation	n (%)				
Subject Involved in Litigation	n (%)				
Other	n (%)				

Program Name: _____ Creation date, time: _____
 Note: Percentages are based on total number of patients for each treatment group or overall as appropriate.
 p-value is based on Chi-Square test for the categorical variables, and is based on two-sample t-test for the continuous variables.

[Note: This table will be repeated for intent-to-treat population (Table 2.2), and for per protocol population (Table 2.3)]

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 2.1
 Demographic and Baseline Characteristics
 Safety Population

Parameter	Statistic	Overall	OP-1 Putty	Autograft	p-value
Oswestry Score	n Mean Median Std. Dev. Minimum Maximum				
Degree of Angular Motion	n Mean Median Std. Dev. Minimum Maximum				
Translational Movement	n Mean Median Std. Dev. Minimum Maximum				

Program Name: _____ Creation date, time: _____
 Note: Percentages are based on total number of patients for each treatment group or overall as appropriate.
 p-value is based on Chi-Square test for the categorical variables, and is based on two-sample t-test for the continuous variables.

[Note: This table will be repeated for intent-to-treat population (Table 2.2), and for per protocol population (Table 2.3)]

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 3.1
 Number of Patients Who Had Missing Data for the 24 Month Overall Success Rate
 Intent-to-Treat Population

Total Number of Patients	OP-1 Putty		Total Number of Patients	Autograft		p-value
	Number of Patients With Missing Data	Percent of Patients With Missing Data		Number of Patients With Missing Data	Percent of Patients With Missing Data	

Program Name: _____ Creation date, time: _____
 Note: Percentages are based on total number of patients for each treatment group.
 p-value is based on Fisher's exact test to test the difference in number of patients with missing data between treatment groups.

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 3.2
 Overall Success Rate at 12, 24 and 36 Months
 Intent-to-Treat Population

Time-points	OP-1 Putty			Autograft			95% Confidence Bound (1)	p-value for Non- inferiority (2)	p-value for Superiority (3)	p-value for Treatment by Center Interaction (4)
	Number of Patients	Number (%) of Successes	Standard Error	Number of Patients	Number (%) of Successes	Standard Error				
12 Months										
24 Months										
36 Months										

Program Name:

Creation date, time:

Note: Missing data were imputed.

- (1) 95% confidence bound is for the difference between the success rates in the two treatment groups.
- (2) p-value is based on one-sided two-sample asymptotic test for non-inferiority with an equivalence limit of 0.10.
- (3) p-value is based on Fisher's exact test for superiority.
- (4) p-value is based on logistic regression.

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 3.3
 24 Month Overall Success Rate by Gender and Age Group
 Intent-to-Treat Population

Patient Subgroup	OP-1 Putty			Autograft			95% Confidence Bound (1)	p-value for Non-inferiority (2)	p-value for Superiority (3)
	Number of Patients	Number (%) of Successes	Standard Error	Number of Patients	Number (%) of Successes	Standard Error			
Male Patients									
Female Patients									
<45 Years Old									
45-65 Years Old									
>65 Years Old									

Program Name:

Creation date, time:

Note: Missing data were imputed.

- (1) 95% confidence bound is for the difference between the success rates in the two treatment groups.
- (2) p-value is based on one-sided two-sample t-test for non-inferiority with an equivalence limit of 0.10.
- (3) p-value is based on Fisher's exact test for superiority.

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 4.1
Overall Success Rate at 12, 24 and 36 Months
Per Protocol Population

Time-points	OP-1 Putty			Autograft		
	Number of Patients	Number (%) of Successes	Standard Error	Number of Patients	Number (%) of Successes	Standard Error
12 Months						
24 Months						
36 Months						

Program Name:
Note: Missing data were not imputed.

Creation date, time:

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 4.2
24 Month Overall Success Rate by Gender and Age Group
Per Protocol Population

Patient Subgroup	OP-1 Putty			Autograft		
	Number of Patients	Number (%) of Successes	Standard Error	Number of Patients	Number (%) of Successes	Standard Error
Male Patients						
Female Patients						
<45 Years Old						
45-65 Years Old						
>65 Years Old						

Program Name:
Note: Missing data were not imputed.

Creation date, time:

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 5.1
 Overall Radiographic Success Rate at 12, 24 and 36 Months
 Intent-to-Treat Population

Time-points	OP-1 Putty			Autograft			95% Confidence Bound (1)	p-value for Non-inferiority (2)	p-value for Superiority (3)
	Number of Patients	Number (%) of Successes	Standard Error	Number of Patients	Number (%) of Successes	Standard Error			
6 Months									
12 Months									
24 Months									
36 Months									

Program Name: _____ Creation date, time: _____

Note: Missing or non-evaluable data will be excluded in the analysis.
 (1) 95% confidence bound is for the difference between the success rates in the two treatment groups.
 (2) p-value is based on one-sided two-sample t-test for non-inferiority with an equivalence limit of 0.10.
 (3) p-value is based on Fisher's exact test for superiority.

- {Note: This table will be repeated for**
- Success rate based on overall radiographic success rate at 12, 24, and 36 months - per protocol -Table 5.1.1
 - Success rate based on Oswestry disability (overall success criterion #2) at 12, 24, and 36 months - intent-to-treat population - Table 5.2
 - Success rate based on Oswestry disability (overall success criterion #2) at 12, 24, and 36 months - per protocol population - Table 5.2.1
 - Success rate based on absence of retreatment (overall success criterion #3) at 12, 24, and 36 months - intent-to-treat population -Table 5.3
 - Success rate based on absence of retreatment (overall success criterion #3) at 12, 24, and 36 months - per protocol population - Table 5.3.1
 - Success rate based on absence of serious treatment-related adverse events at 12, 24, and 36 months - intent-to-treat population -Table 5.4}
 - Success rate based on absence of serious treatment-related adverse events at 12, 24, and 36 months - per protocol population - Table 5.4.1}
 - Overall neurological success rate at 12, 24, and 36 months - intent-to-treat population - Table 5.5
 - Overall neurological success rate at 12, 24, and 36 months - per protocol population - Table 5.5.1

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 5.6
Presence of Bridging at Operated Level Based on the CT Scans at 9 Months
Intent-to-Treat Population

OP-1 Putty		Autograft		p-value
Present n (%)	Absent n (%)	Present n (%)	Absent n (%)	

Program Name:

Creation date, time:

Note: Missing or non-evaluable data will be excluded in the analysis.
p-value is based on Fisher's exact test.

This table will be repeated for

- *Presence of pseudoarthrosis at 9 months - intent-to-treat population - Table 5.7*
- *Presence of pseudoarthrosis at 9 months - per protocol population - Table 5.7.1}*

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 5.8
 Lateral Disc Height (mm)
 Intent-to-Treat Population

Time Points	Statistic	OP-1 Putty		Autograft		p-value (1)
		Actual	Change from Baseline	Actual	Change from Baseline	
Baseline (6-week)	n					
	Mean					
	Median					
	Std. Dev.					
	Minimum					
3 Months	Maximum					
	n					
	Mean					
	Median					
	Std. Dev.					
6 Months	Minimum					
	Maximum					
	p-value (2)					
	n					
	Mean					
	Median					
	Std. Dev.					
	Minimum					
	Maximum					
	p-value (2)					

Program Name:

Creation date, time:

Note: Missing or non-evaluable data will be excluded in the analysis.

(1) p-value is based on two-sample t-test to test the difference in 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.

{Note: This table will be repeated for

- *degree of angular motion - intent-to-treat population - Table 5.9*
- *degree of angular motion - per protocol population - Table 5.9.1*
- *translational movement - intent-to-treat population - Table 5.10*
- *translational movement - per protocol population - Table 5.10.1*
- *Oswestry Disability Index - intent-to-treat population - Table 5.11*
- *Oswestry Disability Index - per protocol population - Table 5.11.1*

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 5.8
 Lateral Disc Height (mm)
 Intent-to-Treat Population

Time Points	Statistic	OP-1 Putty		Autograft		p-value (1)
		Actual	Change from Baseline	Actual	Change from Baseline	
12 Months	n Mean Median Std. Dev. Minimum Maximum p-value (2)					
24 Months	n Mean Median Std. Dev. Minimum Maximum p-value (2)					
36 Months	n Mean Median Std. Dev. Minimum Maximum p-value (2)					

Program Name: _____ Creation date, time: _____

Note: Missing or non-evaluable data will be excluded in the analysis.
 (1) p-value is based on two-sample t-test to test the difference in 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.

- {Note: This table will be repeated for**
- **degree of angular motion - intent-to-treat population - Table 5.9**
 - **degree of angular motion - per protocol population - Table 5.9.1**
 - **translational movement - intent-to-treat population - Table 5.10**
 - **translational movement - per protocol population - Table 5.10.1**
 - **Oswestry Disability Index - intent-to-treat population - Table 5.11**
 - **Oswestry Disability Index - per protocol population - Table 5.11.1**

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 6.1
 Treatment-emergent Adverse Events
 Safety Population

Type of Event	OP-1 Putty (n=)		Autograft (n=)	
	Number (%) of Patients with Events	95% CI	Number (%) of Patients with Events	95% CI
Any Adverse Event				
Severe Adverse Event				
Treatment-related Adverse Event				
Unanticipated Adverse Event				
Serious Adverse Event				
Treatment-related Serious Adverse Event				
Death				

Program Name: _____ Creation date, time: _____
 The 95% confidence interval for the proportion of patients with adverse events is based on the exact (Clopper-Pearson) method.

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 6.2
 Treatment-emergent Adverse Events by System Organ Class and Preferred Term
 Safety Population

System Organ Class/ Preferred Term	Statistic	Number (%) of Patients		Number (%) of Events	
		OP-1 Putty (n=)	Autograft (n=)	OP-1 Putty (n=)	Autograft (n=)
Total	n (%)				
System Organ Class 1	n (%)				
Preferred Term 1	n (%)				
Preferred Term 2	n (%)				
⋮	n (%)				
⋮	n (%)				
Preferred Term n	n (%)				
⋮					
⋮					
System Organ Class m	n (%)				
Preferred Term 1	n (%)				
⋮	n (%)				
⋮	n (%)				
Preferred Term n	n (%)				

Program Name: _____ Creation date, time: _____
 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.

[Note: This table will be repeated for serious/unanticipated adverse events (Table 6.8)]

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 6.3
 Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Severity
 Safety Population

System Organ Class/ Preferred Term	Statistic	Number (%) of Patients					
		OP-1 Putty			Autograft		
		Mild	Moderate	Severe	Mild	Moderate	Severe
Total	n (%)						
System Organ Class 1	n (%)						
Preferred Term 1	n (%)						
Preferred Term 2	n (%)						
⋮	n (%)						
⋮	n (%)						
Preferred Term n	n (%)						
⋮							
⋮							
System Organ Class m	n (%)						
Preferred Term 1	n (%)						
⋮	n (%)						
⋮	n (%)						
Preferred Term n	n (%)						

Program Name: _____ Creation date, time: _____
 Note: Number of patients refers to patients with at least one adverse 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 greatest severity.

[Note: This table will be repeated for serious/unanticipated adverse events (Table 6.9)]

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 6.4
 Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Treatment
 Safety Population

System Organ Class/ Preferred Term	Statistic	Number (%) of Patients					
		Not Related	OP-1 Putty Suspected Related	Unknown	Not Related	Autograft Suspected Related	Unknown
Total	n (%)						
System Organ Class 1	n (%)						
Preferred Term 1	n (%)						
Preferred Term 2	n (%)						
⋮	n (%)						
⋮	n (%)						
Preferred Term n	n (%)						
⋮							
⋮							
System Organ Class m	n (%)						
Preferred Term 1	n (%)						
⋮	n (%)						
⋮	n (%)						
Preferred Term n	n (%)						

Program Name: _____ Creation date, time: _____
 Note: Number of patients refers to patients with at least one adverse 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 closest relationship.

[Note: This table will be repeated for serious/unanticipated adverse events (Table 6.10)]

Confidential

Section V, Volume 1, Book 33 of 78, Page 9333

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 6.5
 Treatment-emergent Adverse Events by Type of Event
 Safety Population

Type of Event	Statistic	Number (%) of Patients		Number (%) of Events	
		OP-1 Putty (n=)	Autograft (n=)	OP-1 Putty (n=)	Autograft (n=)
General Surgical					
Intraoperative Events					
Organ/Bowel Injury					
.....					
Postoperative Events					
Superficial Infection					
.....					
Systemic Events					
.....					

Program Name: _____ Creation date, time: _____
 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 type are counted only once for that type.
[Note: This table will be repeated for serious/unanticipated adverse events (Table 6.11)]

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 6.6
 Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Visit
 Safety Population
 OP-1 Putty

System Organ Class/ Preferred Term	Statistic	Number (%) of Patients						
		Operative (n=)	6 weeks (n=)	6 weeks - 3 Months (n=)	3-6 Months (n=)	6-12 Months (n=)	12-24 Months (n=)	24-36 Months (n=)
Total	n (%)							
System Organ Class 1	n (%)							
Preferred Term 1	n (%)							
Preferred Term 2	n (%)							
⋮	n (%)							
⋮	n (%)							
Preferred Term n	n (%)							
⋮								
⋮								
System Organ Class m	n (%)							
Preferred Term 1	n (%)							
⋮	n (%)							
⋮	n (%)							
Preferred Term n	n (%)							

Program Name: _____ Creation date, time: _____
 Note: Number of patients refers to patients with at least one adverse 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.

[Note: *This table will also be produced for Autograft.
 This table will be repeated for serious/unanticipated adverse events (Table 6.12)*]

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 6.7
 Treatment-emergent Adverse Events by Type of Event and Visit
 Safety Population
 OP-1 Putty

Type of Event	Statistic	Number (%) of Patients						
		Operative (n=)	6 weeks (n=)	6 weeks - 3 Months (n=)	3-6 Months (n=)	6-12 Months (n=)	12-24 Months (n=)	24-36 Months (n=)
General Surgical	n (%)							
Intraoperative Events	n (%)							
Organ/Bowel Injury	n (%)							
.....	n (%)							
Postoperative Events	n (%)							
Superficial Infection	n (%)							
.....	n (%)							
Systemic Events	n (%)							
.....	n (%)							

Program Name: _____ Creation date, time: _____
 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 type are counted only once for that type.
[Note: This table will also be produced for Autograft. This table will be repeated for serious/unanticipated adverse events (Table 6.13)]

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 7
 Secondary Procedures by Visit
 Safety Population
 OP-1 Putty

Type of Event	Statistic	Number (%) of Patients						
		Operative (n=)	6 weeks (n=)	6 weeks - 3 Months (n=)	3-6 Months (n=)	6-12 Months (n=)	12-24 Months (n=)	24-36 Months (n=)
Any Secondary Procedure	n (%)							
Revision	n (%)							
Removal	n (%)							
Supplemental Fixation	n (%)							
Reoperation	n (%)							

Program Name:
[Note: This table will also be produced for Autograft.]

Creation date, time:

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 8.1
 Clinical Laboratory Evaluations - Hematology - Actual Value and Change from Baseline
 Safety Population

Parameter	Visit	Statistic	OP-1 Putty		Autograft		p-value (1)
			Actual Value	Change from Baseline	Actual Value	Change from Baseline	
Hematocrit	Baseline	n					
		Mean					
		Median					
		Std. Dev.					
		Minimum					
	Postoperatively	n					
		Mean					
		Median					
		Std. Dev.					
		Minimum					
	6 weeks	Maximum					
		p-value (2)					
n							
Mean							
Median							
3 Months	Std. Dev.						
	Minimum						
	Maximum						
	p-value (2)						

Program Name: _____ Creation date, time: _____
 (1) p-value is based on two-sample t-test to test the difference in 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.
 [Note: This table will also be produced for the following hematology parameters: hemoglobin, neutrophils (bands, abs.), basophils abs., eosinophils abs., lymphocytes abs., MCHC, MCV, monocytes abs., platelet count, red cell count, and white cell count]

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 8.1
 Clinical Laboratory Evaluations - Hematology - Actual Value and Change from Baseline
 Safety Population

Parameter	Visit	Statistic	OP-1 Putty		Autograft		p-value	
			Actual Value	Change from Baseline	Actual Value	Change from Baseline		
Hematocrit	6 Months	n						
		Mean						
		Median						
			Std. Dev.					
			Minimum					
			Maximum					
			p-value (2)					
	12 Months	n						
		Mean						
Median								
		Std. Dev.						
		Minimum						
		Maximum						
		p-value (2)						
24 Months	n							
	Mean							
	Median							
		Std. Dev.						
		Minimum						
		Maximum						
		p-value (2)						

Program Name: _____ Creation date, time: _____

(1) p-value is based on two-sample t-test to test the difference in 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.

[Note: This table will also be produced for the following hematology parameters: hemoglobin, Neutrophils (bands, abs.), basophils abs., eosinophils abs., lymphocytes abs., MCHC, MCV, monocytes abs., platelet count, red cell count, and white cell count]

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 8.2
 Clinical Laboratory Evaluations - Hematology - Shifts in Status from Baseline to Post-Baseline Time-points
 Safety Population

Parameter	Visit	Post-baseline Status	Baseline Status						p-value (2)
			OP-1 Putty			Autograft			
			Low	Normal	High	Low	Normal	High	
Hematocrit	Postoperatively	Low Normal High p-value (1)							
	6 Weeks	Low Normal High p-value (1)							
	3 Months	Low Normal High p-value (1)							
	6 Months	Low Normal High p-value (1)							
	12 Months	Low Normal High p-value (1)							
	24 Months	Low Normal High p-value (1)							

Program Name: _____ Creation date, time: _____
 Note: A low value is below the lower normal limit. A normal value is within the normal range. A high value is above the upper normal limit.

(1) p-value is based on Stuart-Maxwell test or McNemar's test to test the shifts in status within treatment, as appropriate.

(2) p-value is based on chi-square or Fisher's exact test to test the difference between treatment groups, as appropriate.

**[Note: This table will also be produced for the following hematology parameters:
 hemoglobin, Neutrophils (bands, abs.), basophils abs., eosinophils abs., lymphocytes abs., MCHC, MCV, monocytes abs., platelet count, red cell count, and white cell count]**

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 8.3
 Clinical Laboratory Evaluations - Biochemistry - Actual Value and Change from Baseline
 Safety Population

Parameter	Visit	Statistic	OP-1 Putty		Autograft		p-value (1)
			Actual Value	Change from Baseline	Actual Value	Change from Baseline	
Albumin	Baseline	n					
		Mean					
		Median					
		Std. Dev.					
		Minimum					
		Maximum					
	Postoperatively	n					
		Mean					
		Median					
		Std. Dev.					
		Minimum					
		Maximum					
6 weeks	p-value (2)						
	n						
	Mean						
	Median						
	Std. Dev.						
	Minimum						
3 Months	Maximum						
	p-value (2)						
	n						
	Mean						
	Median						
	Std. Dev.						

Program Name: _____ Creation date, time: _____
 (1) p-value is based on two-sample t-test to test the difference in 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.

[Note: This table will also be produced for the following Biochemistry parameters:
 alkaline phosphatase, ALT (SGPT), AST (SGOT), creatinine, CO2 content, chloride, glucose, potassium, sodium, uric acid,
 bilirubin (total), protein, and urea nitrogen.]

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 8.3
 Clinical Laboratory Evaluations - Biochemistry - Actual Value and Change from Baseline
 Safety Population

Parameter	Visit	Statistic	OP-1 Putty		Autograft		p-value (1)
			Actual Value	Change from Baseline	Actual Value	Change from Baseline	
Albumin	6 Months	n					
		Mean					
		Median					
	12 Months	Std. Dev.					
		Minimum					
		Maximum					
	24 Months	p-value (2)					
		n					
		Mean					
		Median					
		Std. Dev.					
		Minimum					
		Maximum					
		p-value (2)					

Program Name: _____ Creation date, time: _____

(1) p-value is based on two-sample t-test to test the difference in 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.

**[Note: This table will also be produced for the following Biochemistry parameters:
 alkaline phosphatase, ALT (SGPT), AST (SGOT), creatinine, CO2 content, chloride, glucose, potassium, sodium, uric acid,
 bilirubin (total), protein, and urea nitrogen.]**

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 8.4
 Clinical Laboratory Evaluations - Biochemistry - Shifts In Status From Baseline To Post-Baseline Time-points
 Safety Population

Parameter	Visit	Post-baseline Status	Baseline Status						p-value (2)
			OP-1 Putty			Autograft			
			Low	Normal	High	Low	Normal	High	
Hematocrit	Postoperatively	Low Normal High p-value (1)							
	6 Weeks	Low Normal High p-value (1)							
	3 Months	Low Normal High p-value (1)							
	6 Months	Low Normal High p-value (1)							
	12 Months	Low Normal High p-value (1)							
	24 Months	Low Normal High p-value (1)							

Program Name: _____ Creation date, time: _____
 Note: A low value is below the lower normal limit. A normal value is within the normal range. A high value is above the upper normal limit.
 (1) p-value is based on Stuart-Maxwell test or McNemar's test to test the shifts in status within treatment, as appropriate.
 (2) p-value is based on chi-square or Fisher's exact test to test the deference between treatment groups, as appropriate.

[Note: This table will also be produced for the following Biochemistry parameters:
 alkaline phosphatase, ALT (SGPT), AST (SGOT), creatinine, CO2 content, chloride, glucose, potassium, sodium, uric acid, bilirubin (total), protein, and urea nitrogen.]

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 9
 Shifts In Neurological Status From Baseline To Post-Baseline Time-points
 Safety Population

Parameter	Visit	Post-baseline Status	Baseline Status						p-value (2)
			OP-1 Putty			Autograft			
			Normal	Abnormal	Not Evaluable	Normal	Abnormal	Not Evaluable	
Muscle Strength - Hip	6 Weeks	Normal Abnormal Not Evaluable p-value (1)							
	3 Months	Normal Abnormal Not Evaluable p-value (1)							
	6 Months	Normal Abnormal Not Evaluable p-value (1)							
	12 Months	Normal Abnormal Not Evaluable p-value (1)							
	24 Months	Normal Abnormal Not Evaluable p-value (1)							
	24 Months	Normal Abnormal Not Evaluable p-value (1)							

Program Name:

Creation date, time:

(1) p-value is based on McNemar's test to test the shifts in status within treatment.

(2) p-value is based on chi-square test to test the difference between treatment groups, as appropriate.

[Note: This table will also be produced for the following parameters: muscle strength - knee, muscle strength - ankle, muscle strength - toe, reflexes, straight leg raises, and sensory evaluation]

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 10
 Visual Analog Scale for Pain Assessment - Actual Value and Change from Baseline
 Safety Population

Parameter	Visit	Statistic	OP-1 Putty		Autograft		p-value
			Actual Value	Change from Baseline	Actual Value	Change from Baseline	
Right Leg/Buttock	Baseline	n Mean Median Std. Dev. Minimum Maximum					
	6 weeks	n Mean Median Std. Dev. Minimum Maximum p-value (1)					
	3 Months	n Mean Median Std. Dev. Minimum Maximum p-value (1)					
	6 Months	n Mean Median Std. Dev. Minimum Maximum p-value (1)					

Program Name: _____ Creation date, time: _____
 (1) p-value is based on two-sample t-test to test the difference in 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.

[Note: This table will be repeated for left leg/buttock.]

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 10
 Visual Analog Scale for Pain Assessment - Actual Value and Change from Baseline
 Safety Population

Parameter	Visit	Statistic	OP-1 Putty		Autograft		p-value
			Actual Value	Change from Baseline	Actual Value	Change from Baseline	
Right Leg/Buttock	12 Months	n					
		Mean					
		Median					
		Std. Dev.					
		Minimum					
	p-value (1)						
	24 Months	n					
		Mean					
		Median					
		Std. Dev.					
p-value (1)							

Program Name: _____ Creation date, time: _____
 (1) p-value is based on two-sample t-test to test the difference in 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.

[Note: This table will be repeated for left leg/buttock.]

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 11.1
 Donor Site Pain - Visual Analog Scale
 Safety Population

Visit	Statistic	Autograft
6 Weeks	n Mean Median Std. Dev. Minimum Maximum	
3 Months	n Mean Median Std. Dev. Minimum Maximum	
6 Months	n Mean Median Std. Dev. Minimum Maximum	
12 Months	n Mean Median Std. Dev. Minimum Maximum	
24 Months	n Mean Median Std. Dev. Minimum Maximum	
Program Name:		Creation date, time:

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 11.2
Donor Site Pain Status
Safety Population

Visit	Statistic	Autograft			Total
		None	Mild	Moderate	
6 weeks	n (%)				
3 Months	n (%)				
6 Months	n (%)				
9 Months	n (%)				
12 Months	n (%)				
24 Months	n (%)				

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

Creation date, time:

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 12
Current Medication Use
Safety Population

Visit	Current Medication	OP-1 Putty n (%)	Autograft n (%)
Preoperative			
6 Weeks			
3 Months			
6 Months			
9 Months			
12 Months			
24 Months			

Program Name: _____ Creation date, time: _____

Confidential

Section V, Volume 1, Book 33 of 78, Page 9349

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 13
 Surgical Procedure Characteristics
 Safety Population

Parameter	Statistic	OP-1 Putty	Autograft
Anesthetic Time (min)	Mean Median Std. Dev. Minimum Maximum		
Operative Time (min)	Mean Median Std. Dev. Minimum Maximum		
Estimated Blood Loss (cc)	n Mean Median Std. Dev. Minimum Maximum		
Amount of Blood Reinfused During Surgery	n Mean Median Std. Dev. Minimum Maximum		

Program Name:
 Note: Percentages are based on total number of patients for each treatment group.

Creation date, time:

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 13
 Surgical Procedure Characteristics
 Safety Population

Parameter	Statistic	OP-1 Putty	Autograft
Spinal Fusion Approach			
Posterolateral	n (%)		
Other	n (%)		
Surgical Incision			
Midline	n (%)		
Other	n (%)		
Used In Positioning			
Andrews Frame	n (%)		
Jackson Table	n (%)		
Wilson Frame	n (%)		
Gel-Rolls	n (%)		
Other	n (%)		
Other Procedures Performed			
Laminectomy	n (%)		
Foraminotomy	n (%)		
Facetecomy	n (%)		
Other	n (%)		

Program Name:
 Note: Percentages are based on total number of patients for each treatment group.

Creation date, time:

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 14.1
 SF-36 Health Survey Scale: Physical Component Score
 Safety Population

Visit	Statistic	OP-1 Putty	Autograft	p-value
Baseline	Mean			
	Median			
	Std. Dev.			
	Minimum			
	Maximum			
6 Weeks	Mean			
	Median			
	Std. Dev.			
	Minimum			
	Maximum			
3 Months	n			
	Mean			
	Median			
	Std. Dev.			
	Minimum			
6 Months	n			
	Mean			
	Median			
	Std. Dev.			
	Minimum			

Program Name: _____ Creation date, time: _____
 Note: p-value is based on wilcoxon rank-sum test to test the change from baseline between treatment groups.

[Note: This table will be repeated for the following SF-36 parameters:
 - SF-36 Health Survey Scale: Mental Component Score (Table 14.2)
 - SF-36 Health Survey Scale: Physical Functioning Scale (Table 14.3)
 - SF-36 Health Survey Scale: Role-Physical scale (Table 14.4)
 - SF-36 Health Survey Scale: Bodily Pain Scale (Table 14.5)
 - SF-36 Health Survey Scale: Mental Health Scale (Table 14.6)
 - SF-36 Health Survey Scale: Role-Emotional Scale (Table 14.7)
 - SF-36 Health Survey Scale: Social Functioning Scale (Table 14.8)
 - SF-36 Health Survey Scale: Vitality Scale (Table 14.9)
 - SF-36 Health Survey Scale: General Health Perceptions Scale (Table 14.10)]

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 14.1
 SF-36 Health Survey Scale: Physical Component Score
 Safety Population

Visit	Statistic	OP-1 Putty	Autograft	p-value
9 Months	Mean			
	Median			
	Std. Dev.			
	Minimum			
12 Months	Mean			
	Median			
	Std. Dev.			
	Minimum			
24 Months	n			
	Mean			
	Median			
	Std. Dev.			
	Minimum			
	Maximum			

Program Name: _____ Creation date, time: _____
 Note: p-value is based on wilcoxon rank-sum test to test the change from baseline between treatment groups.

[Note: This table will be repeated for the following SF-36 parameters:
 - SF-36 Health Survey Scale: Mental Component Score (Table 14.2)
 - SF-36 Health Survey Scale: Physical Functioning Scale (Table 14.3)
 - SF-36 Health Survey Scale: Role-Physical Scale (Table 14.4)
 - SF-36 Health Survey Scale: Bodily Pain Scale (Table 14.5)
 - SF-36 Health Survey Scale: Mental Health Scale (Table 14.6)
 - SF-36 Health Survey Scale: Role-Emotional Scale (Table 14.7)
 - SF-36 Health Survey Scale: Social Functioning Scale (Table 14.8)
 - SF-36 Health Survey Scale: Vitality Scale (Table 14.9)
 - SF-36 Health Survey Scale: General Health Perceptions Scale (Table 14.10)]

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 15.1
Anti-OP-1 Antibody Status by Visit
Safety Population

Treatment	Parameter	Any Visit	Pre-operative	6 weeks	3 Months	6 Months	12 Months	24 Months	36 Months
OP-1	Total Number of Patients								
	Number (%) of Screening Positive								
	Number (%) of Neutralizing								
Autograft	Total Number of Patients								
	Number (%) of Screening Positive								
	Number (%) of Neutralizing								

Program Name:
Note: Neutralizing is Anti-OP-1 positive.

Creation date, time:

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 15.2
 Anti-OP-1 Titer
 Safety Population

Treatment	Statistic	Number (%) of Patients						
		Pre-operative	6 Weeks	3 Months	6 Months	12 Months	24 Months	36 Months
OP-1	n							
	Mean							
	Median							
	Std. Dev.							
	Minimum							
	Maximum							
Autograft	n							
	Mean							
	Median							
	Std. Dev.							
	Minimum							
	Maximum							

Program Name:
 Note: Neutralizing is Anti-OP-1 positive.

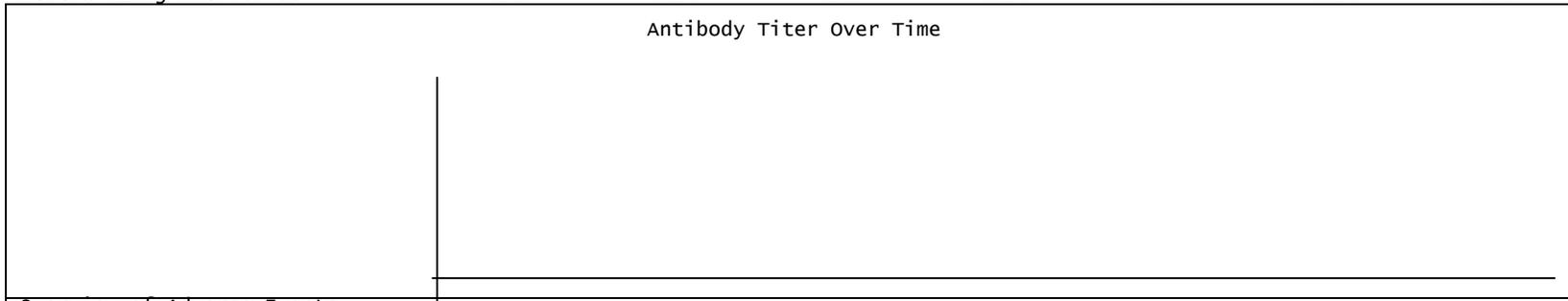
Creation date, time:

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 15.3
 Profile for Patients with Neutralizing Antibodies
 Safety Population

	Baseline	6 weeks	3 Months	6 Months	12 Months	24 Months	36 Months
Overall Clinical Success					XXX	XXX	XXX
Radiographic Success					XXX	XXX	XXX
ODI Success					XXX	XXX	XXX
Absence of Retreatment	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Absence of Treatment-related SAE	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Neurological Success					XXX	XXX	XXX
Neutralizing Antibodies	XXX	XXX	XXX	XXX	XXX	XXX	XXX



Overview of Adverse Events		Days Onset Since Operation (days)	Duration (days)	Serious (Y/N)	Potentially Immunologically Related (Y/N)
System Organ Class	Preferred Term				

Program Name:

Creation date, time:

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 15.4
 Success Outcome by Neutralizing Antibody Status
 Safety Population

Treatment	Success Criteria	6 Months		12 Months		24 Months		36 Months	
		Neutralizing (n=)	Not Neutralizing (n=)						
OP-1	Overall Patient Success								
	Overall Radiographic Success								
OP-1	Oswestry Disability Success								
	Success Based on Absence of Retreatment								
OP-1	Absence of Serious Adverse Event								
	Overall Neurological Success								
OP-1	Overall Patient Success								
	Overall Radiographic Success								
OP-1	Oswestry Disability Success								
	Success Based on Absence of Retreatment								
OP-1	Absence of Serious Adverse Event								
	Overall Neurological Success								

Program Name:
 Note: Neutralizing is Anti-OP-1 positive.

Creation date, time:

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table 15.5
 Treatment-emergent Adverse Events by Neutralizing Antibody Status and Visit
 Safety Population

Treatment	Neutralizing Status	Number of Patients	Number (%) of Patients						
			Any Time-Point	Operative-6 Weeks	6 weeks - 3 Months	3-6 Months	6-12 Months	12-24 Months	24-36 Months
OP-1 Putty	Positive								
	Negative								
Autograft	Positive								
	Negative								

Program Name:

Creation date, time:

Note: Patients experiencing multiple events are counted only once.

[Note: This table will be repeated for:

- serious treatment-emergent adverse events (Table 15.6)
- immunologically-related adverse events (Table 15.7)
- immunologically-related serious adverse events (Table 15.8)]

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table A1.1

Number of Patients Who Had Missing Data for the 24 Month Overall Success Rate (Protocol Defined)
 Intent-to-Treat Population

Total Number of Patients	OP-1 Putty		Total Number of Patients	Autograft		p-value
	Number of Patients With Missing Data	Percent of Patients With Missing Data		Number of Patients With Missing Data	Percent of Patients With Missing Data	

Program Name:

Creation date, time:

Note: Percentages are based on total number of patients for each treatment group.
 p-value is based on Fisher's exact test to test the difference in number of patients with missing data between treatment groups.

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table A1.2
 Overall Success Rate (Protocol Defined) at 3, 6, 12, 24 and 36 Months
 Intent-to-Treat Population

Time-points	OP-1 Putty			Autograft			95% Confidence Bound (1)	p-value for Non- inferiority (2)	p-value for Superiority (3)	p-value for Treatment by Center Interaction (4)
	Number of Patients	Number (%) of Successes	Standard Error	Number of Patients	Number (%) of Successes	Standard Error				
3 Months										
6 Months										
12 Months										
24 Months										
36 Months										

Program Name:

Creation date, time:

Note: Missing data were imputed using the last value carried forward approach.

- (1) 95% confidence bound is for the difference between the success rates in the two treatment groups.
- (2) p-value is based on one-sided two-sample asymptotic test for non-inferiority with an equivalence limit of 0.10.
- (3) p-value is based on Fisher's exact test for superiority.
- (4) p-value is based on logistic regression.

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table A1.3
 24 Month Overall Success Rate (Protocol Defined) by Gender and Age Group
 Intent-to-Treat Population

Patient Subgroup	OP-1 Putty			Autograft			95% Confidence Bound (1)	p-value for Non-inferiority (2)	p-value for Superiority (3)
	Number of Patients	Number (%) of Successes	Standard Error	Number of Patients	Number (%) of Successes	Standard Error			
Male Patients									
Female Patients									
<45 Years Old									
45-65 Years Old									
>65 Years Old									

Program Name:

Creation date, time:

Note: Missing data were imputed using the last value carried forward approach.

- (1) 95% confidence bound is for the difference between the success rates in the two treatment groups.
- (2) p-value is based on one-sided two-sample t-test for non-inferiority with an equivalence limit of 0.10.
- (3) p-value is based on Fisher's exact test for superiority.

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table A2.1
Overall Success Rate (Protocol Defined) at 3, 6, 12, 24 and 36 Months
Per Protocol Population

Time-points	OP-1 Putty			Autograft		
	Number of Patients	Number (%) of Successes	Standard Error	Number of Patients	Number (%) of Successes	Standard Error
3 Months						
6 Months						
12 Months						
24 Months						
36 Months						

Program Name:
Note: Missing data were not imputed.

Creation date, time:

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table A2.2
 24 Month Overall Success Rate (Protocol Defined) by Gender and Age Group
 Per Protocol Population

Patient Subgroup	OP-1 Putty			Autograft		
	Number of Patients	Number (%) of Successes	Standard Error	Number of Patients	Number (%) of Successes	Standard Error
Male Patients						
Female Patients						
<45 Years Old						
45-65 Years Old						
>65 Years Old						

Program Name:
 Note: Missing data were not imputed.

Creation date, time:

Stryker Biotech
 Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Table A3.1
 Overall Radiographic Success Rate (Protocol Defined) at 3, 6, 12, 24 and 36 Months
 Intent-to-Treat Population

Time-points	OP-1 Putty			Autograft			95% Confidence Bound (1)	p-value for Non- inferiority (2)	p-value for Superiority (3)
	Number of Patients	Number (%) of Successes	Standard Error	Number of Patients	Number (%) of Successes	Standard Error			
3 Months									
6 Months									
12 Months									
24 Months									
36 Months									

Program Name:

Creation date, time:

Note: Missing data were imputed using the last value carried forward approach.

- (1) 95% confidence bound is for the difference between the success rates in the two treatment groups.
- (2) p-value is based on one-sided two-sample t-test for non-inferiority with an equivalence limit of 0.10.
- (3) p-value is based on Fisher's exact test for superiority.

{Note: This table will be repeated for

- **Success rate based on overall radiographic success rate at 12, 24, and 36 months - per protocol -Table A3.1.1**
- **Success rate based on Oswestry disability (overall success criterion #2) at 12, 24, and 36 months - intent-to-treat population - Table A3.2**
- **Success rate based on Oswestry disability (overall success criterion #2) at 12, 24, and 36 months - per protocol population - Table A3.2.1**
- **Success rate based on Absence of retreatment (overall success criterion #3) at 12, 24, and 36 months - intent-to-treat population -Table A3.3**
- **Success rate based on Absence of retreatment (overall success criterion #3) at 12, 24, and 36 months - per protocol population - Table A3.3.1**
- **Success rate based on absence of serious treatment-related adverse events at 12, 24, and 36 months - intent-to-treat population -Table A3.4}**
- **Success rate based on absence of serious treatment-related adverse events at 12, 24, and 36 months - per protocol population - Table A3.4.1}**
- **Overall neurological success rate at 12, 24, and 36 months - intent-to-treat population - Table A3.5**
- **Overall neurological success rate at 12, 24, and 36 months - per protocol population - Table A3.5.1**

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 1.1

Inclusion Criteria

Treatment	Subject ID	Subject Initial	Date	Inclusion Criteria								
				#1	#2	#3	#4	#5	#6	#7	#8	#9

Program Name:

Creation date, time:

Note: See Section G.1 of the protocol for inclusion criteria.

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 1.2

Exclusion Criteria

Treatment	Subject ID	Subject Initial	Date	Exclusion Criteria												Name of Investigator	Signature	Date of Signature
				#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	#12			

Program Name:

Creation date, time:

Note: See Section G.2 of the protocol for exclusion criteria.

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 1.3

Subject Randomization
Part 1 of 2

Treatment	Subject ID	Subject Initial	Site	Hospital	Date of Surgery	Surgeon's Last Name	Met All Inclusion Criteria?	Met All Exclusion Criteria?
-----------	------------	-----------------	------	----------	-----------------	---------------------	-----------------------------	-----------------------------

Program Name:

Creation date, time:

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 1.3

Subject Randomization

Treatment	Subject ID	Subject Initial	Signed Consent Form?	Date of Consent Signed	Subject Randomized To	Explain If Not Randomized	Date of Sponsor Signature	Surgery Performed as Randomized?	Explain
-----------	------------	-----------------	----------------------	------------------------	-----------------------	---------------------------	---------------------------	----------------------------------	---------

Program Name:

Creation date, time:

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 1.4

Patients with Missing 24 Month Patient Success Data

Treatment	Subject ID	Radiographic Success	Oswestry Disability Index	Retreatment	Neurological Success
-----------	------------	----------------------	---------------------------	-------------	----------------------

Program Name:

Creation date, time:

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 2

Demographics and Worker Compensation Status

Treatment	Subject ID	Evaluation Date	Date of Birth	Age (years)	Sex	Worker Compensation Status
-----------	------------	-----------------	---------------	-------------	-----	----------------------------

Program Name:

Creation date, time:

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 3

Disease Diagnosis

Treatment	Subject ID	Evaluation Date	Diagnosis	Diagnosis Specify	Involved Level	Method of Diagnosis
-----------	------------	-----------------	-----------	-------------------	----------------	---------------------

Program Name:

Creation date, time:

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 4.1

Medical History - Prior Treatment to Affected Level, Level Planned for Fusion

Treatment	Subject ID	Evaluation Date	Prior Treatment to Affected Level, Level Planned for Fusion	Date Treatment Began (mon/yr)
-----------	------------	-----------------	---	-------------------------------

Program Name:

Creation date, time:

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 4.2

Medical History - Prior Treatment to Level(s) of Lumbar - Sacral Region Other Than Affected Level

Treatment	Subject ID	Evaluation Date	Prior Treatment to Level(s) of Lumbar	Type	Vertebral Level	Completion Date
-----------	------------	-----------------	---------------------------------------	------	-----------------	-----------------

Program Name:

Creation date, time:

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 4.3

Medical History - Current Medical Condition

Treatment	Subject ID	Evaluation Date	Current Medical Condition
-----------	------------	-----------------	---------------------------

Program Name:

Creation date, time:

Listing 4.4

Medical History - Comments

Treatment	Subject ID	Evaluation Date	Comment
-----------	------------	-----------------	---------

Program Name:

Creation date, time:

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 5

Oswestry Low Back Pain Disability Questionnaire

Treatment	Subject ID	Visit	Date	Pain Intensity	Personal Care	Lifting	Walking	Sitting	Standing	Sleeping	Sex Life	Social Life	Traveling	Percent Disability
-----------	------------	-------	------	----------------	---------------	---------	---------	---------	----------	----------	----------	-------------	-----------	--------------------

Program Name:

Creation date, time:

Note: Oswestry Pain Disability scores range from 0 (no pain) to 5 (maximum pain or unable to perform the tasks at all due to pain).

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 6.1

Radiographic Evaluation
Preoperative
Part 1 of 2

Treat- ment	Subject ID	Date	Reviewer Initial	Date of Review	Date of Film			Affected Level	Angular Motion (degree)	Transla- tional (mm)	>=50% Transla- tional
					AP	Lateral	Flexion Extension				

Program Name:

Creation date, time:

Note: N/O = Not obtained, N/E = Not evaluable.

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 6.1

Radiographic Evaluation - Preoperative
Part 2 of 2

Treatment	Subject ID	Date	Reviewer Initial	Date of Review	Comments
-----------	------------	------	------------------	----------------	----------

Program Name:

Creation date, time:

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 6.2

Radiographic Evaluation - Postoperative
Part 1 of 4

Treatment	Subject ID	Visit	Date	Reviewer Initial	Date of Review	Date of Film			Operated Level Treated	Angular Motion (degree)	Translational Movement (mm)
						AP	Lateral	Flexion Extension			

Program Name:

Creation date, time:

Note: N/O = Not obtained, N/E = Not evaluable.

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 6.2

Radiographic Evaluation - Postoperative
Part 2 of 4

Treatment	Subject ID	Visit	Date	Reviewer Initial	Date of Review	Presence of Bridging at Operated Level On AP Film		Presence of Bridging at Operated Level On Lateral Film	Heterotopic Ossification
						Left Side	Right Side		

Program Name:

Creation date, time:

Note: N/E = Not evaluable.

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 6.2

Radiographic Evaluation - Postoperative
Part 3 of 4

Treatment	Subject ID	Visit	Date	Reviewer Initial	Date of Review	Presence of Pseudoarthrosis	Lateral Disc Height Changed from 6 wk Measurement?	Film Quality Assessment		
								Penetration	Beam Angle	Rotation

Program Name:

Creation date, time:

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 6.2

Radiographic Evaluation - Postoperative
Part 4 of 4

Treatment	Subject ID	Visit	Date	Reviewer Initial	Date of Review	Comments
-----------	------------	-------	------	------------------	----------------	----------

Program Name:

Creation date, time:

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 6.3

Additional Postoperative Radiographic Evaluation

Treatment	Subject ID	Visit	Operated Level Treated	Reviewer Initial	Date of Review	Date of Film	Presence of Bone at Operative Level on AP Film?	Based on previous and current AP films is the quality and quantity of bone formation?
-----------	------------	-------	------------------------	------------------	----------------	--------------	---	---

Program Name:

Creation date, time:

Stryker Biotech
 Protocol Number: S01-01us

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 7
 Neurological Evaluation

Treatment	Subject ID	Visit	Evaluation Date	Category	Segment	Exam Result	
						Left Side	Right Side
				Reflex	Knee Jerk Ankle Jerk		
				Muscle strength - Hip	Flexion Adductors Extensors		
				Muscle strength - Knee	Extension Flexion		
				Muscle strength - Ankle	Dorsi Flexion Plantar Flexion Ankle Inversion Ankle Eversion		
				Muscle strength - Toe	Flexors Extensors Big Toe Extension		
				Sensory/Dermatomal Distribution	L3 Dermatomes L4 Dermatomes L5 Dermatomes S1 Dermatomes		
				Straight Leg Raises	Status Specify Degrees		

Program Name:

Creation date, time:

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 8
Physical Exam
Part 1 of 2

Treatment	Subject ID	Visit	Date	Height (cm)	Weight (kg)	Current work Status			Blood Drawn for Testing?	Wearing Brace or Other Back Support?	Any New Concurrent Medical Events Since Last Visit?	Any Unresolved Medical Events
						Employed?	Full/Part Time	If No, Related to Back Problem?				

Program Name:

Creation date, time:

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 8
Physical Exam
Part 2 of 2

Treatment	Subject ID	Visit	Date	Comments
-----------	------------	-------	------	----------

Program Name: _____ Creation date, time: _____

Stryker Biotech
Protocol Number: S01-01us

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 9.1

Concurrent Medical Event
Part 1 of 4

Treatment	Subject ID	Event Id	Date of Onset	Event Category	Event Time	Event Specify	System Class	Organ	Preferred Term
				General Surgery Systemic Lumbar Spine Specific Autograft Specific Investigational Product Specific		Intraoperative Post Operative Not Applicable (systemic)			

Program Name:

Creation date, time:

[Note: This listing will be repeated for serious/unanticipated concurrent medical event in Listing 9.2.]

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 9.1

Concurrent Medical Event
Part 2 of 4

Treatment	Subject ID	Event Id	Date of Onset	Evaluation Date	Any Changes or Additional Treatment?	Related to Autograft or OP-1 Putty	Unanticipated Event?	Hospitalization or Prolongation of Hospitalization?	Intensity	Life-threatening?	Persistent or Significant Disability/Incapacity?
-----------	------------	----------	---------------	-----------------	--------------------------------------	------------------------------------	----------------------	---	-----------	-------------------	--

Program Name:

Creation date, time:

[Note: This listing will be repeated for serious/unanticipated concurrent medical event in Listing 9.2.]

Stryker Biotech
Protocol Number: S01-01us

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 9.1

Concurrent Medical Event
Part 3 of 4

				Treatment					
Treatment	Subject ID	Event Id	Evaluation Date	Type	Date	Details	Describe Surgical Intervention	Outcome	Date of Resolved
				No Treatment or Observation Only Surgery to Study Site Operative Level Surgery to Other Spinal Levels Other					

Program Name:

Creation date, time:

[Note: This listing will be repeated for serious/unanticipated concurrent medical event in Listing 9.2.]

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 9.1

Concurrent Medical Event
Part 4 of 4

Treatment	Subject ID	Event Id	Evaluation Date	Comments
-----------	------------	----------	-----------------	----------

Program Name:

Creation date, time:

[Note: This listing will be repeated for serious/unanticipated concurrent medical event in Listing 9.2.]

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 10.1

Laboratory Evaluations - Hematology

Treatment	Subject ID	Visit	Draw Date	Draw Time	Comment	Laboratory Test	Results	Units	Normal Range	Abnormal Flag [1]
-----------	------------	-------	-----------	-----------	---------	-----------------	---------	-------	--------------	-------------------

Program Name:

Creation date, time:

[1] L = below lower limit, H = above upper limit.

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 10.2

Laboratory Evaluations - Biochemistry

Treatment	Subject ID	Visit	Draw Date	Draw Time	Comment	Laboratory Test	Results	Units	Normal Range	Abnormal Flag [1]
-----------	------------	-------	-----------	-----------	---------	-----------------	---------	-------	--------------	-------------------

Program Name:

Creation date, time:

[1] L = below lower limit, H = above upper limit.

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 11

Visual Analog Scale for Pain Assessment

Treatment	Subject ID	Visit	Date	Right Leg/ Buttock	Left Leg/ Buttock	Donor Site Pain (Bone Graft)	How You Rate Donor Site Pain
-----------	------------	-------	------	-----------------------	----------------------	---------------------------------	---------------------------------

Program Name:

Creation date, time:

Note: The Visual Analog Scale ranges from 0 (no pain) to 10 (most severe pain).
Donor site pain was assessed for the autograft patients only.

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 12

Current Medication Use

Treatment	Subject ID	Visit	Date	Current Medication Use
-----------	------------	-------	------	------------------------

Program Name:

Creation date, time:

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 13

Hospitalization Data
Part 1 of 4

Treatment	Subject ID	Date of Surgery	Surgeon's Last Name	Hospital	Medical Record #	Date of Discharge	Level Fused	Anesthetic Time (minutes)	Operative Time (minutes)
-----------	------------	-----------------	---------------------	----------	------------------	-------------------	-------------	---------------------------	--------------------------

Program Name:

Creation date, time:

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 13

Hospitalization Data
Part 2 of 4

Treatment	Subject ID	Estimate Blood Loss (cc)	Amount of Blood Reinfused (cc)	Spinal Fusion Approach	Surgical Incision	Used in Positioning	Other Procedures Performed / Level Treated
-----------	------------	--------------------------	--------------------------------	------------------------	-------------------	---------------------	--

Program Name:

Creation date, time:

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 13

Hospitalization Data
Part 3 of 4

Treatment	Subject ID	Graft Material Implanted	OP-1 Putty Lot #		Additional OP-1 Opened/Retained/ Discarded?	Additional OP-1 #1		Additional OP-1 #2		Any Intraoperative/ Pre-discharge Medical Events?
			Lot 1	Lot 2		Lot #	Code	Lot #	Code	

Program Name:

Creation date, time:

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 13

Hospitalization Data
Part 4 of 4

Treatment	Subject ID	Comments
-----------	------------	----------

Program Name: _____ Creation date, time: _____

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 14

General Health Survey (SF-36)
Part 1 of 6

Treatment	Subject ID	Visit	Date	In General, Your Health Is	Health in General Compare to One Year Ago	Activities		
						Vigorous Activities	Moderate Activities	Lifting or Carrying Groceries

Program Name:

Creation date, time:

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 14

General Health Survey (SF-36)
Part 2 of 6

Treatment	Subject ID	Visit	Date	Activities					
				Climbing One Flight of Stairs	Bending, Kneeling, or Stopping	walking More Than a Mile	walking Several Blocks	Walking One Block	Bathing or Dressing Yourself

Program Name:

Creation date, time:

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 14

General Health Survey (SF-36)
Part 3 of 6

Treatment	Subject ID	Visit	Date	Past 4 weeks, Any Problems as Result of Physical Health			Past 4 weeks, Any Problems as Result of Emotional Problems		
				Cut Down Amount of Time	Accomplished Less	Limit in Kind of Work	Difficulty Performing Work	Cut Down Amount of Time	Accomplished Less

Program Name:

Creation date, time:

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 14

General Health Survey (SF-36)
Part 4 of 6

Treatment	Subject ID	Visit	Date	What Extent Interfered with Social Activities	Bodily Pain During Past 4 Weeks	How Much Pain Interfered with Normal Work	How Much Time During Past 4 Weeks		
							Full of Pep	Nervous Person	Felt So Down

Program Name:

Creation date, time:

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 14

General Health Survey (SF-36)
Part 5 of 6

Treatment	Subject ID	Visit	Date	How Much Time During Past 4 Weeks					
				Felt Calm and Peaceful	Have Lot of Energy	Felt Downhearted and Blue	Felt worn Out	Been a Happy Person	Felt Tired

Program Name:

Creation date, time:

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 14

General Health Survey (SF-36)
Part 6 of 6

Treatment	Subject ID	Visit	Date	Physical Health or Emotional Problem Interfered Social Activities	True or False of the Statement for You			
					Get Sick a Little Easier Than Other Person	Healthy As Anybody I Know	Expect My Health To Get Worse	My Health Is Excellent

Program Name:

Creation date, time:

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 15

Subjects Excluded from Per Protocol Population

Treatment	Subject ID	Date Subject Last Seen	Completed 24 Month Visit?	Reason Subject Was Excluded
-----------	------------	------------------------	---------------------------	-----------------------------

Program Name:

Creation date, time:

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 16

Subject Disposition

Treatment	Subject ID	Date Subject Last Seen	Completed 24 Month Visit?	Primary Reason Subject Was Removed	Date of Event	Specify or Explain
-----------	------------	------------------------	---------------------------	------------------------------------	---------------	--------------------

Program Name:

Creation date, time:

Stryker Biotech
Protocol Number: S01-01us

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 17.1

Immunology

Treatment	Subject ID	Parameter	Pre-Operative	6 Weeks	6 Months	12 Months	24 Months	36 Months
		Draw Date						
		Screening						
		Titer						
		Neutralizing						

Program Name:

Creation date, time:

Stryker Biotech
Protocol Number: S01-01us

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing 17.2

Antibody Status and Adverse Events
Patients with Any Antibody Status Data

Treatment: OP-1

Subject ID	Neutralizing Antibody Status at Each Visit						SOC	Preferred Term	Onset Date	Duration	SAE?	P. Imm. Related (1)
	6 wk	3 mon	6 mon	12 mon	24 mon	36 mon						

Program Name:

Creation date, time:

(1) All adverse events are reviewed by styker Biotech to be classified as potentially or not potentially immunologically related.

Stryker Biotech
Protocol Number: S01-01US

A Prospective, Randomized, Controlled, Multicenter, Pivotal Study of OP-1 Putty in Uninstrumented Posterolateral Fusions

Listing A1

Patients with Missing 24 Month Patient Success Data (Protocol Defined)

Treatment	Subject ID	Radiographic Success	Oswestry Disability Index	Retreatment	Neurological Success
-----------	------------	----------------------	---------------------------	-------------	----------------------

Program Name:

Creation date, time: