

Section II
Summary of Safety and Effectiveness Data

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1. GENERAL INFORMATION

The subject device is Stryker Biotech's OP-1[®] Putty device, which consists of osteogenic protein-1 (BMP 7) in a bioresorbable matrix of bovine collagen and carboxymethyl cellulose.

The applicant is Stryker Biotech LLC, 35 South Street, Hopkinton, MA 01748.

The application is PMA #P060021.

2. INDICATIONS FOR USE

OP-1[®] Putty is indicated for posterolateral lumbar spinal fusion in patients with spondylolisthesis who have failed at least six months of conservative non-surgical treatment.

3. DEVICE DESCRIPTION

OP-1[®] Putty device consists of a therapeutic protein in a bioresorbable matrix that is surgically implanted into the lumbar region of the spine. The components of OP-1[®] Putty device are packaged in two vials, each in separate blister packages, and stored together in one shelf box. Each vial must be aseptically combined with the other and reconstituted with sterile saline just prior to use. The contents of the two vials include:

- OP-1 protein and bovine collagen matrix (also known as OP-1[®] Implant);
- sodium carboxymethylcellulose (putty additive).

OP-1[®] Implant consists of one gram of sterile powder containing 3.5 mg OP-1 protein and Type 1 bovine bone collagen in a 2 ounce vial for reconstitution. The carboxymethylcellulose (CMC or putty additive) consists of 230 mg of sterile CMC in a 10 mL vial for reconstitution. At the time of surgery, the contents of each vial are transferred to a sterile mixing bowl, reconstituted with normal saline, and mixed with a spatula to produce a product with a putty-like consistency. This process is repeated to prepare a second unit for implantation into the contralateral side of the spine. The Product Preparation Instructions and Surgical Technique booklet contain complete directions for use.

4. CONTRAINDICATIONS, WARNINGS, PRECAUTIONS

4.1 Contraindications

OP-1[®] Putty should not be used in patients with the following conditions:

- A known hypersensitivity to recombinant human BMP-7, bovine Type I collagen or carboxymethylcellulose;
- Active infection at the operative site or history of reoccurring infections;
- Active malignancy or in patients undergoing treatment for a malignancy;

- Pregnancy. The potential effects of OP-1 treatment on the human fetus have not been evaluated. Studies in rats injected with high doses of OP-1 have shown that small amounts of OP-1 will cross the placental barrier.

4.2 Warnings

- Women of childbearing potential should be advised that antibody formation to OP-1 (rhBMP-7) and its influence on fetal development have not been assessed. In a clinical study assessing the safety and efficacy of OP-1[®] Putty, 194 out of 207 (94%) patients treated with OP-1[®] Putty and 18 out of 86 (21%) treated with autograft bone (without OP-1) developed antibodies to rhBMP-7. Within the OP-1[®] Putty treatment group, 26% of the patients produced antibodies with neutralizing capacity versus 1% in the autograft group. The peak antibody response was seen 3 months following treatment. There were no patients with neutralizing antibodies 2 years following treatment or at the later 36+ month follow-up period. Studies in genetically altered mice indicate that BMP-7 is critical for fetal development and that lack of BMP activity, as might be induced by antibodies, may cause neonatal death or birth defects.
- Women of childbearing potential should be advised to avoid becoming pregnant for 2 years following treatment with OP-1[®] Putty.
- There are no data on the excretion of OP-1 in the breast milk of female patients who are nursing. Women should discontinue breast-feeding following treatment with OP-1[®] Putty.

4.3 Precautions

- One unit of OP-1[®] Putty must be used on each side of the spine. The maximum dose should not exceed 2 units.
- OP-1[®] Putty has no biomechanical strength.
- The safety and effectiveness of repeat applications have not been established.
- OP-1[®] Putty should be used with caution in patients with a history of underlying cardiac disease; close follow-up post-operatively is advised.
- A two year rat bioassay, in which approximately 17.5-70 times the equivalent human dose of OP-1 in collagen was placed under the skin, produced more cancer growths at the site of implantation of the OP-1 compared to rats that had no OP-1. It is believed that this may be due to the Oppenheimer Solid State Tumor Effect, described as the formation of tumors at the site of implantation of inert objects under the skin in rats. This effect has not been reported in humans.
- OP-1 is important in the embryonic development of the kidney. Studies have not been performed to examine the effect of neutralizing antibodies to OP-1 in patients with impaired renal function.

- Inadequate vascularity in the surrounding tissues may diminish the effectiveness of OP-1[®] Putty. Make every effort to surround the product with viable tissue.
- Prior to use, inspect the packaging, vial and stopper for visible damage. If damage is visible, don't use the product. Retain the packaging and vial, and contact a Stryker Biotech representative.
- For single use only. Do not re-use OP-1[®] Putty. Discard unused product.
- Do not use after the printed expiration date on the label.

5. POTENTIAL ADVERSE EFFECTS ON HEALTH

The number and percent of patients in pivotal study S01-01US who experienced adverse events, and the number and percent of patients in the follow-up study to S01-01US (study 06-UPLF-01) who experienced new serious adverse events, are presented by MedDRA System Organ Class in [Table 1](#).

Table 1: Incidence of Treatment -Emergent Adverse Events from S01-01US and Treatment Emergent New Serious Adverse Events from 06-UPLF-01 by MedDRA System Organ Class (Safety Population)

System Organ Class	OP-1 Putty		Autograft	
	S01-01US (N=208)	06-UPLF-01 (N=208)	S01-01US (N=87)	06-UPLF-01 (N=87)
Total Patients	201 (96.6)	24 (11.5)	82 (94.3)	17 (19.5)
Blood and Lymphatic System Disorders	12 (5.8)	0 (0.0)	13 (14.9)	0 (0.0)
Cardiac Disorders	27 (13.0)	0 (0.0)	5 (5.7)	0 (0.0)
Congenital, Familial, and Genetic Disorders	0 (0.0)	2 (1.0)	0 (0.0)	0 (0.0)
Ear And Labyrinth Disorders	4 (1.9)	0 (0.0)	1 (1.1)	0 (0.0)
Endocrine Disorders	2 (1.0)	0 (0.0)	0 (0)	0 (0.0)
Eye Disorders	7 (3.4)	0 (0.0)	3 (3.4)	0 (0.0)
Gastrointestinal Disorders	45 (21.6)	3 (1.4)	12 (13.8)	1 (1.1)
General Disorders and Administration Site Conditions	29 (13.9)	0 (0.0)	17 (19.5)	0 (0.0)
General System Disorders	2 (1.0)	0 (0.0)	0 (0)	0 (0.0)
Hepatobiliary Disorders	1 (0.5)	0 (0.0)	1 (1.1)	2 (2.3)

System Organ Class	OP-1 Putty		Autograft	
	S01-01US (N=208)	06-UPLF-01 (N=208)	S01-01US (N=87)	06-UPLF-01 (N=87)
Immune System Disorders	3 (1.4)	0 (0.0)	2 (2.3)	0 (0.0)
Infections And Infestations	49 (23.6)	1 (0.5)	13 (14.9)	1 (1.1)
Injury, Poisoning and Procedural Complications	70 (33.7)	6 (2.9)	41 (47.1)	4 (4.6)
Investigations	20 (9.6)	0 (0.0)	13 (14.9)	1 (1.1)
Metabolism and Nutritional Disorders	12 (5.8)	1 (0.5)	6 (6.9)	1 (1.1)
Musculoskeletal and Connective Tissue Disorders	156 (75.0)	7 (3.4)	60 (69.0)	6 (6.9)
Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps)	12 (5.8)	1 (0.5)	8 (9.2)	2 (2.3)
Nervous System Disorders	65 (31.3)	4 (1.9)	33 (37.9)	2 (2.3)
Neurologic Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric Disorders	17 (8.2)	0 (0.0)	7 (8.0)	0 (0.0)
Renal and Urinary Disorders	24 (11.5)	2 (1.0)	10 (11.5)	0 (0.0)
Reproductive System and Breast Disorders	2 (1.0)	1 (0.5)	2 (2.3)	0 (0.0)
Respiratory, Thoracic and Mediastinal Disorders	33 (15.9)	0 (0.0)	6 (6.9)	0 (0.0)
Skin And Subcutaneous Tissue Disorders	16 (7.7)	0 (0.0)	4 (4.6)	0 (0.0)
Surgical and Medical Procedures	4 (1.9)	1 (0.5)	0 (0.0)	0 (0.0)
Vascular Disorders	25 (12.0)	0 (0.0)	12 (13.8)	0 (0.0)

Note: All AEs were collected in S01-01US. New serious AEs (SAEs) were collected in 06-UPLF-01.

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

6. ALTERNATIVE PRACTICES AND PROCEDURES

Spinal instrumentation (i.e. interlaminar fixation orthoses, pedicle screw spinal systems) and electrical stimulation devices are used for spinal fusion, but only in conjunction with autograft. Bone void fillers are also available but similarly require the use of autograft.

7. MARKETING HISTORY

OP-1[®] Putty was approved for use in the U.S. on April 7, 2004 via Humanitarian Device Exemption (HDE) No. H020008 for use as an alternative to autograft in compromised patients requiring revision posterolateral (intertransverse) lumbar spinal fusion, for whom autologous bone and bone marrow harvest are not feasible or are not expected to promote fusion. OP-1[®] Putty is not marketed in any other country.

OP-1[®] Implant (OP-1 Putty without the carboxymethylcellulose putty additive) was also approved for use in the U.S. on November 26, 2001 via an HDE for an alternative to autograft in the treatment of recalcitrant long bone non-unions where use of autograft is unfeasible and alternative treatments have failed. OP-1[®] Implant is also approved for use in the treatment of specific long bone non-unions in Canada and Australia.

8. SUMMARY OF PRECLINICAL STUDIES

Preclinical investigations consist of pharmacologic, toxicologic, and biodistribution studies in rodent and several non-rodent species.

8.1 Pharmacology Studies

This submission focuses on the use of OP-1[®] Putty as a device for treatment of patients requiring posterolateral lumbar spinal fusion. The goal of spinal fusion is to attain solid arthrodesis. Nonunion remains a significant challenge and may lead to added morbidity and requirements for additional surgeries. The pharmacology studies include efficacy evaluations in animal models of spinal fusion, trauma (long bone) injury repair and craniomaxillofacial (CMF) repair. In the efficacy studies much of the early dosing experience with OP-1 was derived from studies in trauma (long bone) and craniomaxillofacial (CMF) models. In total, we have evaluated OP-1 in 6 species. At least 25 studies have evaluated multiple dosages, both as different total mg of OP-1 and different concentrations of OP-1. Concentrations as high as 17.6 mg/mL (in dogs) and total amounts up to 48 mg (in baboons) have been used in these studies. These doses span the therapeutic range from minimal or inadequate bone formation to locally excessive bone at the specific site of implantation. The therapeutic OP-1 concentration range varies with the animal species tested in apparent accord with differences in the rate of bone formation inherent to that species. Thus, higher concentrations are required in dogs compared with rats, and even higher concentrations are required in nonhuman primates, reflective of the differential bone formation rates across phylogeny. In general, the therapeutic concentration of OP-1 used in human clinical trials of OP-1 Putty (1 mg/mL) was very effective in the large animal models of spinal fusion.

Vertebral Fusion Studies

Study Type/Species	Groups/No. Animals	BMP-7		Relevant Findings
		mg/mL	total mg	
07-012 Appendix 1a-1 Posterolateral Lumbar Transverse Process Fusion/Rabbit	5/3 each gender	0 1 2 4	0 3 6 12	All rabbits with BMP-7 had solid lumbar vertebral fusion.
07-003 Appendix 1a-2 Lumbar Spine Fusion with Internal Fixation/Baboon	6/4M	autograft 0 0.33 1 2 4	0 0 4 12 24 48	All animals treated with any dose of OP-1 or autograft had lumbar vertebral fusion at 4 months after surgery. The highest dose of OP-1 (4 mg/mL or 48 mg) had the earliest fusion detected by CT.
04-024 Appendix 1a-3 Posterolateral Lumbar Transverse Process Fusion/Rat	6/7F	empty Calstrux Calstrux + low lactose Calstrux + high lactose 0.08 0.23	0 0 0 0 0 0.03 0.09	High dose BMP-7 with Calstrux ¹ overcame inhibition of osteoporosis on spine fusion with 6/7 fusing by 21 days.
04-003 Appendix 1a-4 Posterolateral Lumbar Transverse Process Fusion/Sheep	4/4F	0 0.29 0.58 0.86	0 2.3 4.6 6.9	Dose dependent vertebral fusion response observed with BMP-7. Highest dose induced best fusion (100% by 12 weeks).

¹ Calstrux is bone void filler. Stryker Biotech is not proposing to market a version of OP-1 Putty that contains Calstrux.

Vertebral Fusion Studies

Study Type/Species	Groups/No. Animals	BMP-7		Relevant Findings
		mg/mL	total mg	
02-017 P060021, Section IV, Vol. I, Book 1, Page 19 Posterolateral Lumbar Transverse Process Fusion in Nicotine-Treated Animals/Rabbit	3/14F	empty autograft 1	0 0 2.4	82% fusion with OP-1 Putty, 42% with autograft, 10% no graft at 10 weeks. OP-1 overcame inhibitory effects of nicotine
02-005 P060021, Section IV, Vol. I, Book 1, Page 19 Posterolateral Lumbar Transverse Process Fusion/Sheep	4/7-9F	1	28	Fusion rate was 60-80% at week 6, and 80-100% at week 12. No significant differences in fusion rates or quality were observed between instrumented and uninstrumented animals
02-002 P060021, Section IV, Vol.I, Book 1, Page 18 Posterolateral Lumbar Transverse Process Fusion/Athymic Rat	2/30	Grafton DBM 1	0 0.6	Earlier fusion in OP-1-rats than Grafton rats. OP-1 Putty had higher fusion rate (100% at 3 & 6 wks vs. 13% at 3 & 39% at 6 wks) by histology, palpation & radiography

Vertebral Fusion Studies

Study Type/Species	Groups/No. Animals	BMP-7		Relevant Findings
		mg/mL	total mg	
99-038 Appendix 1a-5 Posterolateral Lumbar Transverse Process Fusion with Internal Fixation/Rabbit	4/8M	Autograft 1	0 3.5	All OP-1 Putty animals fused by 12 wks, while no autograft animals had fused. Fixation improved fusion at 3 wks, no effect at 12.
99-032 P060021, Section IV, Vol.I, Book 1, Page 16 Time course Posterolateral Lumbar Transverse Process Fusion/Dog	36 (72 levels) n=6 per time/group	Autograft autograft/0.5 1	0 3.5 7.0	OP-1 Putty with or without autograft was more effective than autograft alone. ² Fusion rates were 50% for autograft and 77% for OP-1 at 24 wks. OP-1 Putty-induced bone was normal histologically.
99-021 Appendix 1a-6 Posterolateral Lumbar Transverse Process Fusion in Nicotine-Treated Animals/Rabbit	2/9F	Autograft 1	0 2.4	OP-1 Putty induced 100% fusion, autograft 25% fusion in difficult nicotine treated model at 5 weeks.
98-020 Appendix 1a-7 Posterolateral Lumbar Transverse Process Fusion/Sheep	5/5F 1/2F	empty autograft autograft 1 1	0 0 0 3.2 3.5	OP-1 vertebral fusion equivalent to autograft in PEEK & titanium interbody cages. OP-1: 4/5 fused in PEEK, 3/5 Ti. Autograft: 2/4 fused in PEEK, 3/4 Ti. ³

² This was an exploratory study examining the effect of OP-1 when combined with autograft. Please note that Stryker Biotech does not intend to market OP-1 for use in combination with autograft.

³ This was an exploratory study examining the effect of OP-1 when used with an interbody cage. Stryker Biotech does not intend to market OP-1 Putty in combination with any interbody cage.

⁴ This study was done to explore the pharmacology of OP-1 in an interbody cage. Stryker is not seeking to market OP-1 in combination with the BAK cage

Vertebral Fusion Studies

Study Type/Species	Groups/No. Animals	BMP-7		Relevant Findings
		mg/mL	total mg	
96-031 Appendix 1a-8 Posterolateral Lumbar Transverse Process Fusion/Sheep	3/10F	autograft BioOss (a marketed bone void filler) 1	0 0 2.5	Fusion assessments were qualitative. OP-1 formed significantly more bone than autograft at 16, 20, 24 weeks
95-008 Appendix 1a-9 Posterolateral Lumbar Transverse Process Fusion/Sheep	1/2M 1/4M	autograft 1	0 20	OP-1 results (3/4 fused) similar to autograft (2/2 fused) biomechanically, radiographically and histologically. No deleterious effect on spinal cord morphology or function.
94-012 Appendix 1a-10 Posterolateral Thoracic Interbody Fusion/Sheep with Babgy & Kuslich (BAK) Titanium cage	12M (36 levels) 6/6 levels ea	non-surgical destabilization empty BAK autograft autograft/BAK 1/BAK	0 0 0 0 2.5	Fusion rate OP-1/BAK to autograft/BAK = 75% to 63%. Biomechanics and histologically also equivalent ⁴
94-011 Appendix 1a-11 Posterolateral Lumbar Transverse Process Fusion/Sheep	1/2M	1	5 (fusion) 5 (laminectomy)	Varied fusion quality observed at 4 months (1 fusion/1 partial fusion). No stenosis or negative effects on spinal cord from laminectomy.
93-001 Appendix 1a-12 Posterolateral Lumbar Transverse Process Fusion/Dog	6M (24 levels) 8/4	empty collagen autograft 1	0 0 0 10	OP-1 levels fused by 6 wks, complete fusion at 12 wks. Autograft fused at 26 wks. Controls (collagen or no implant) did not show fusion.

Long Bone Studies

Study Type/Species	Groups/No. Animals	BMP-7		Relevant Findings
		(mg/mL)	total mg	
02-003 Appendix 1a-13 Unilateral (5 cm) Tibial Osteotomy (with Nail)/Sheep	5/4 (20 total)	0 0.2 0.4 0.8	0 0.15 0.23 0.345	Tibias treated with OP-1 had the most bone growth and defect healing at 0.8 mg/mL OP-1.
01-008 Appendix 1a-14 Unilateral (5cm) Tibial Osteotomy (with Nail)/Sheep	3/6 to 10 (26 total)	0 1+collagen 1+collagen+CMC	0 3.5 3.5	Defects treated with OP-1 with collagen or OP-1 with collagen and CMC had better bone growth and healing than untreated controls
00-021 Appendix 1a-15 Femoral Osteotomy (6 mm)/Rat	8/6 to 18	0 0.010 0.400	0 0.0011 0.0050	Femoral defects treated with low or higher doses of OP-1 with or without bacterial infection healed; control defects did not heal.
97-039 Appendix 1a-16 Bilateral Ulnar Osteotomy (3 mm)/Dog	42 ulnas	0 1.0 4.84 9.55	0 0.1 0.484 0.484	Defects treated with any amount of OP-1 had better healing than control defects.
97-037 Appendix 1a-17 Bilateral Ulnar Osteotomy (3 mm) Timecourse/Dog	18 total (36 ulnas)	0 3.5 7.0	0 0.35 0.35	Extensive new bone was seen in all OP-1 treated defects. Biomechanical strength was better in legs treated at 6H after defect creation/
96-010 Appendix 1a-18 Bilateral Ulnar Osteotomy/Rabbit	3/4 (12 ulnas)	0 0.87 0.99 8.71	0 0.1 0.1 0.1	All OP-1 treated defects healed; better healing results were observed based on radiographs, histology, and biomechanical strength at higher concentrations of OP- 1.
96-007 Appendix 1a-19 Bilateral Ulnar Osteotomy (2.5 cm)/Dog	3 total dogs, 6 ulnas	0 1.7 3.4 17.6	0 1.75 1.75 1.75	All ulna bone defects treated with any concentration of OP- 1 healed well

Long Bone Studies

Study Type/Species	Groups/No. Animals	BMP-7		Relevant Findings
		(mg/mL)	total mg	
95-024 Bilateral Ulnar and Unilateral Tibial Osteotomy (with Nail)/Monkey	10 to 12/1 to 4 limbs/group (28 total monkeys)	autograft	0	Ulnas and tibias treated with 1 to 2 mg/mL OP-1 had good bone defect healing. Tibial defects treated with ≥ 1.0 mg/mL OP-1 had the most bone healing.
		collagen	0	
		0	0	
		0.625	0.25	
		1.25	0.5	
		2.5	1.0	
5.0	2.0			
95-016 Appendix 1a-21 & 1a-22 Tibial Fracture (with External Fixation)/Goat	4/10	0	0	Tibial fractures treated with OP-1 in solution or with OP-1 and collagen had better bone healing than untreated fractures.
		collagen	0	
		1.6	1.0	
		2.5	1.0	
95-007 Appendix 1a-23 Bilateral Ulnar Osteotomy (2.5 cm)/Dog	3/2	0	0	Ulnar defects treated with 1.0mg/mL OP-1 healed better than defects treated with 0.5 mg/mL OP-1.
		0.5	1.75	
		1.0	3.5	
94-020 Appendix 1a-24 Bilateral Ulnar Osteotomy (1.5 cm)/Rabbit	10 to 12 groups/1 to 6 ulnas/group	0	0	Ulnar defects healed well based on histology, radiographs, and biomechanical strength if treated with >0.02 mg/mL OP-1.
		0.01	0.003	
		0.02	0.006	
		0.04	0.025	
		0.08	0.05	
		0.16	0.1	
		0.32	0.2	
		0.64	0.25	
		1.0	0.3	
		1.3	0.4	
94-019 Appendix 1a-25 Bilateral Ulnar Osteotomy (2.5cm)/Dog	3/1, 1, 6 (8 total)	0	0	Healing of ulnar defects was seen at all OP-1 doses; some bone was observed outside original bone contours at 1.12 and 2 mg/mL. No associated clinical effects.
		0.6	0.625	
		1.12	1.2	
		2.0	2.5	
94-002 Appendix 1a-26 Bilateral Ulnar & Radius Osteotomy/Dog	2/1, 5 (6 total)	0	0	Ulnar and radial defect sites treated with 1 mg/mL OP-1 healed; OP-1 with PLA carrier had less healing than OP-1 with collagen carrier
		0.2	0.5	
		1.0	2.5	

CMF Studies

Study Type/Species	Groups/No. Animals	BMP-7		Relevant Findings
		mg/mL	total mg	
01-010 Appendix 1a-27 mandibular reconstruction & sinus augmentation/minipigs	5F (30 implants)	0 0.05 0.250 1.0	0 0.05 0.250 1.0	Dose dependent bone growth repair response with OP-1. 1 mg OP-1 per 1 g BioOSS.
00-037 Appendix 1a-28 calvarial defects/Baboon	14M (64 defects)	0 0.1 0.5 2.5	0 0.1 0.5 2.5	New bone with fully differentiated bone marrow elements seen as early as d 15. Restoration of internal and external cortices of calvaria seen at one year. Optimal activity seen between 0.1 and 0.5 mg/mL OP-1.
96-008 Appendix 1a-29 periodontal regeneration/Dogs	18M (36 defects)	0 0.80 2.5 7.5	0 0.80 2.5 7.5	OP-1 associated with concentration dependent stimulation of osteogenesis, regenerative cementum, and new attachment formation. Differences were statistically different from control therapies for all wound healing parameters (P < 0.0001).

CMF Studies

Study Type/Species	Groups/No. Animals	BMP-7		Relevant Findings
95-019 Appendix 1a-30 reparative dentine formation/ Monkeys	5M (90 teeth)	0 0.01 0.10 1.0 10	0 0.00001 0.0001 0.001 0.01	OP-1, when applied to freshly cut dentine, stimulated significantly more reparative dentine than did calcium hydroxide paste in permanent monkey teeth. Response was concentration dependent.
95-010 Appendix 1a-31 maxillary sinus augmentation/Monkeys	15 (30 defects)	0 0.25 0.6 2.5	0 0.58 1.38 5.75	High dose OP-1 resulted in almost complete closure of the osteotomy window without the use of an occlusive window.

Pharmacology Conclusions

As indicated by results of the efficacy studies, recombinant human OP-1 has a spectrum of beneficial therapeutic effects in animal models. It is active in a variety of species and models at doses that are similar to the human dose. The demonstration of spinal fusions in multiple species, and in many different spine fusion models that utilize multiple measures of efficacy, underscores the consistent and robust ability of OP-1 to initiate the bone-formation process necessary for spinal fusion. Additionally, the evaluation of multiple endpoints including histology, biomechanics, and gross morphology provides a direct measure of the efficacy. Direct endpoints are impossible to measure in a clinical setting due to the invasiveness of the measurement. Consequently, the animal models offer key insights to the true potential of OP-1 in bone formation and spinal fusion. OP-1 is most effective in spinal fusion models when combined with collagen, a resorbable matrix with osteoconductive activity. In conclusion, this promising pharmacologic profile fully supports the proposed clinical use of the molecule in posterolateral spinal fusion in humans.

8.2 Toxicology Studies

Toxicity was assessed primarily by the SC route (using OP-1[®] Putty or OP-1 with collagen matrix) or the IV route (using OP-1 protein). Rodents and nonhuman primates were used for most of the toxicology studies. Guinea pigs and rabbits were used as standard species for dermal sensitization and developmental toxicology studies, respectively. The findings are summarized as follows:

- **Single-dose IV Studies** - No adverse effects were identified in mice (10.7 mg/kg; 107 times the maximum human dose of approximately 0.1 mg/kg; based on 70 kg body weight) or rats (3.5 mg/kg; 35 times the maximum human dose).
- **Multiple Dose IV Studies** - In a multiple dose 28-day IV toxicity study in male and female rats, a variety of mild but significant adverse events were noted at 3.5 mg/kg/day. These events included lower body weights in males, minor changes in both red and white blood cell counts, and albumin and globulin concentrations, and minor changes in thymus weights in both males and females. These changes were small and not seen in the mid-dose group (the level at which no adverse effects were observed was 0.35 mg/kg/day; 3.5 times the maximum human dose given daily for 28 days). In female monkeys treated IV with 1.0 mg/kg/day (10 times the total human dose) given 3 days a week for 4 weeks (1/group), there was no evidence of systemic toxicity. Moderate to severe injection-site irritation and thrombophlebitis was observed in all drug-treated groups and the lesions were not reversed following an 8-week recovery period. Similar injection-site responses, including ossification, were also observed in rats.
- **Implant Studies** - No adverse events were noticed in implant studies (0.41-3.3 mg/kg; 4.1 to 33 times the maximum human dose) except for irritation at the SC site and some heterotopic bone, both expected in light of OP-1 pharmacology.
- **Genotoxicity** - Chromosomal aberrations and base-pair changes were evaluated in the CHO cell line (using OP-1[®] Implant) and Ames assays. At maximum concentrations, with and without S9, there was no evidence of clastogenicity or mutagenicity in either of these assays.
- **Dermal Sensitization** - The Buehler Method was used in male and female guinea pigs with OP-1[®] Putty. There was no evidence of cutaneous sensitization in these assays.
- **Hemocompatibility** – OP-1 mixed with collagen and carboxymethylcellulose was negative in a standard hemocompatibility test at a concentration of 0.2 g test article/mL rabbit blood.
- **Embryo-fetal Development** - OP-1 protein was administered to either rats or rabbits via the IV route. In two rat studies (0.004 to 3.5 mg/kg; up to 35 times the human dose given daily for 12 days), OP-1 did not cause maternal or developmental toxicity when administered on Days 6 to 17 of gestation. In rabbits (0.004 to 0.4 mg/kg; up to 4 times the human dose given daily for 13 days), OP-1 did not cause maternal or developmental toxicity when administered on Days 6 to 18 of gestation. In a different study, rabbits were

intentionally immunized with human OP-1 in complete Freund's adjuvant and boosted several times in incomplete Freund's adjuvant; no changes were noted in dam or kits that could be attributed to OP-1. The only effects were differences in organ weights that may be attributed either to stress (maternal) or an underlying small difference in kit body weight between groups (related to litter sizes).

- **Carcinogenicity** - Carcinogenic potential of OP-1 mixed with collagen and implanted SC was evaluated in rats over 104 weeks. Food and water consumption and laboratory values were unaffected throughout the study. Circumscribed SC ossification occurred at the implantation site in all groups treated with OP-1 and collagen and correlated with the quantity implanted. Pleomorphic sarcomas formed at the implantation site in association with ossified and fibrous tissue. This foreign body response was consistent with classical solid state carcinogenicity known as the Oppenheimer effect. There were no other neoplastic or non-neoplastic findings detected in the rats at any sites distal to the implantation site.
- **Tumor Cell Proliferation** - The effect of OP-1 on cell proliferation *in vitro* was evaluated using a panel of 12 human tumor cell lines. All 12 cell lines expressed mRNA for the Type I and Type II OP-1 receptors. OP-1 either inhibited or had no effect on proliferation in 10 of 12 cell lines. In 2 osteosarcoma cell lines, OP-1 stimulated proliferation in a dose-dependent manner. In *in vivo* studies, OP-1 was either pre-incubated or co-injected with several of the cell lines. In the pre-incubation study using cell lines that otherwise did not induce tumors in nude mice, the primary effect noted was the formation of bone nodules at the injection sites. In some of the nodules, small tumor foci were found, presumably due to entrapment of human tumor cells within the bone matrix. There was no evidence that the OP-1 induced additional tumor expansion within the foci. In the co-injection study utilizing a cell line (PC-3) capable of forming tumors in nude mice, mixing the tumor cells with OP-1 appeared to have a mildly inhibitory effect on subsequent tumor formation.
- **Pharmacologic Safety**
Pharmacologic safety studies were performed in rats and dogs. CNS effects were not observed at 3.5 mg/kg (35x the human dose) in rats using the Irwin test. In CV studies in rats, transient effects of OP-1 on BP, heart rate and body temperature were noted after a single IV dose at 3.5 mg/kg (35x the human dose). Because analogous clinical effects were not observed in other studies where the molecule was administered IV (e.g. 96-001, OP-1 administered at the same dose for up to 28 days), a study was done in dogs at 3.0 mg/kg (30x the human dose) to examine the CV effects more closely. In this study, care was taken to administer the compound very slowly because OP-1 is poorly soluble in an aqueous environment. In the dog study, no effects on cardiovascular parameters were observed at any time point. Moreover, OP-1 had no effect on respiratory function in dogs at 3.0 mg/kg (30x the human dose).

Study Type/Species	No. M/F per group	Dose & Dose Regimen/ Fold Human Dose*	Key Findings
98-005 OP-1 15 day acute IV toxicity test in mice	5 M 5 F	0–10.7 mg/kg Single IV dose. 107x human dose	No treatment-related toxicity
95-002 OP-1 14 day acute IV toxicity in rats	5 M 5 F	0–3.5 mg/kg Single IV dose. 35x human dose	No treatment-related toxicity
03-006 OP-1 14 day acute toxicity in rats	5 M 5 F	0–3.5 mg/kg Single IV dose. 35x human dose	No treatment-related toxicity
00-003 OP-1 28 day IV toxicity in cynomolgus monkeys	2 F (toxicity 4 wk); 1 F (8 wk recovery)	0–1.0 mg/kg per admin 12 doses over 4 weeks 10x human dose/day; 120x total	No systemic toxicity noted. Local injection site blood vessel irritation noted at all doses
96-001 OP-1 28 Day IV toxicity study in rats	10 M 10 F	0–3.5 mg/kg/day 28 daily doses 35x human dose/day; 980X total	No treatment-related mortalities. Local injection site toxicity based on gross findings of constricted white rings; hyperplastic, and ossified cartilage at injection site. Male & female rats treated w/ 3.5 mg/kg/day for 28 days had lower body wts, lower serum albumin, lower red cell parameters, & increased serum globulin. Reduced ovary & adrenal wts also noted in females.
97-011 OP-1 Putty 14 day implantation study in rats	5 M 5 F	0–5.6 mg/kg Single dose 56x human dose	No treatment related toxicities

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Study Type/Species	No. M/F per group	Dose & Dose Regimen/ Fold Human Dose*	Key Findings
97-012 OP-1 Putty 35 day implantation in rabbits	15 M 15 F	0-3 mg/kg Single Dose 30x human dose	No treatment-related toxicity
91-002 OP-1 Implant 15 day implantation study in rats	5 M 5 F	0-3.3 mg/kg Single dose 33x human dose	No treatment-related toxicity
92-001 OP-1 Implant 22 day implantation study in rats	5 M 5 F	0-0.35 mg/kg Single dose 3.5x human dose	No adverse toxic effects observed except for inflammatory response at implant site
98-024 OP-1 Implant 13 week implantation study in rats	15 M 15 F	0-6.9 mg/kg with duration Single dose 69x human dose	Small body wt changes at 500mg; encrust & discolor of skin at implant site at 250mg (3.5 mg/kg) & 500mg (7.0 mg/kg). Heterotopic bone observed near inject site at 500mg.
95-001 OP-1 Implant 14 day submucosal toxicity study in hamster	5 M 5 F	0-3.4mg/kg with duration Single dose 34x human dose	Very slight elevation of aspartate aminotransferase & alanine aminotransferase noted in high-dose males only.

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Study Type/Species	No. M/F per group	Dose & Dose Regimen/ Fold Human Dose*	Key Findings
96-004 Ames/Salmonella- <i>E coli</i> reverse mutation assay on OP-1 <i>S. Typhimurium</i> (5 strains) <i>E. coli</i> (1 strain)	Triplicate plates	69-6900 µg OP-1/plate +/- S9; positive & negative controls n/a	No cytotoxicity or genetic toxicity at highest concentration, 6900µg/plate
97-001 Ames/Salmonella- <i>E coli</i> reverse mutation assay on OP-1 Implant/CMC <i>S. Typhimurium</i> (5 strains) <i>E. coli</i> (1 strain)	Triplicate plates	69-6900 µg OP-1/plate +/- S9; positive & negative controls n/a	No cytotoxicity or genetic toxicity at highest concentration, 6900µg/plate
98-009 OP-1 Implant chromosomal aberrations with CHO cells <i>in vitro</i>	Triplicate slides	0.004% to 1% of DMSO extracts; 0.35% to 90% of Ham's F-10 extracts ± S9; positive & neg controls n/a	No cytotoxicity or clastogenic activity
97-002 L929 agar overlay test for cytotoxicity <i>in vitro</i>	Triplicate dishes	0.18 mg OP-1 n/a	OP-1 Putty scored a 1 (slight toxicity) on USP23 reactive grade scale vs. 4 by the pos control.
96-003 CHO mammalian cell cytotoxicity assay on OP-1 (OP-1 Implant)	Triplicate plates	0.23–6900 µg/mL exposure for 5 hours n/a	Invalid: test system incompatible w/ OP-1 implant. known bio-incompatibility w/ CHO cells

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Study Type/Species	No. M/F per group	Dose & Dose Regimen/ Fold Human Dose*	Key Findings
92-002 Dermal sensitization study of OP-1 Implant in guinea pigs	Phase 1: 2M, 2F Phase 2: 5M, 5F	Phase 1 Pre-induction: 0–1.19 mg/kg applied topically Phase 2 Induction/Challenge 0–1.17 mg/kg applied topically 1/week for 4 weeks 11.7-11.9x/dose; 46.8-47.9x total	OP-1 Implant is non-irritating & non-sensitizing
97-006 OP-1 Putty sensitization in guinea pigs (epicutaneous maximization test)	10 M 10 F	0–0.87 mg/kg 8 topical applications over 32 days 8.7x human/dose; 69.6x total	OP-1 Implant is non-irritating & non-sensitizing
97-004 Hemolytic test	TriPLICATE blood samples	.2 gram of test article/mL blood 0.7 mg OP-1 (for OP-1 putty) n/a	<5% hemolysis for OP-1 implant and CMC

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Study Type/Species	No. M/F per group	Dose & Dose Regimen/ Fold Human Dose*	Key Findings
00-004 OP-1 Implant 104 week carcinogenicity study in rats	20-50 M 20-50 F	0–8.4 mg/kg 84x human dose	Pleomorphic sarcomas at implant site deemed due to rodent-specific Oppenheimer effect ; bone formation at implant site; no systemic tox
02-007** OP-1 effect on mouse tumor cell proliferation	8 M for <i>in vivo</i> studies	tumor cell lines given with 25 mg/kg OP-1 250x human dose	Growth inhibition or no effect on 10/12 cell lines; prolif. in 2 osteosarcoma cell lines; No stimul. of appreciable tumor formation in 5 cell lines when co-incubated in nude mice; Growth inhib. of 1 cell line when co-admin. w/ cell line in nude mice
98-004 OP-1 developmental toxicity range-finding study in rats	6 F	0–3.5 mg/kg/day IV administration on gestation Days 6–17 35x human dose/day; 420x total	No treatment-related maternal or developmental toxicity
00-005 OP-1 effects on embryo-fetal development in rat	24 F	0 to 0.4 mg/kg/day IV administration on gestation Days 6–17 4.0x human dose/day; 48x total	No treatment-related maternal or developmental toxicity
00-006 OP-1 effects on embryo-fetal development in rabbits	23 F	0–0.4 mg/kg/day IV administration on gestation Days 6–18 4.0x human dose/day; 52x total	No treatment-related maternal or developmental toxicity
99-004 ¹²⁵ I-OP-1: Placental transfer in rat after IV administration	3 F	3.8 mg/kg single IV on gestation day 18 38X human dose	Placental transfer of ¹²⁵ I-OP-1 to rat fetal tissue <1%.
04-002 04-010 04-011 OP-1 Effects on fetal development in rabbits	25-27 F	350µg OP-1 in complete Freund's adjuvant; 3 boosts w/ OP-1 (350 µg) in incomplete Freund's adjuvant n/a	No definit. immuniz-assoc changes; all dams/kits (pre- & postnatal) developed IgM & IgG immunoreactivity
98-003 CNS Safety in Rats	6 M	0-3.5 mg/kg Single IV dose 35x human dose	No CNS effects observed

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Study Type/Species	No. M/F per group	Dose & Dose Regimen/ Fold Human Dose*	Key Findings
98-006 Cardiovascular safety in rats	6-7 M	0-3.5 mg/kg Single IV dose 35x human dose	Transient increases in arterial BP at 120 min preceded by transient bradycardia at 90 min, followed by transient tachycardia at 180 min. Small changes in body temp at 180-480 min
06-026 CV and respiratory safety in dogs	4 M 4 F	3 mg/kg Single IV dose 30X human dose	No adverse effects noted on BP, HR, body temp, electrocardiographic parameters (HR,PR,QRS,RR and QT/Qt _c), respiratory function (respiratory rate, saturated blood oxygen, and end tidal CO ₂)

*Human dose is approximately 0.1 mg/kg based on 70 kg body weight and 2 OP-1 Putty (7.0mg OP-1) Devices per single lumbar fusion level. It is either the highest dose tested or the highest dose demonstrating no adverse effects.

**Note: All studies in this table are GLP studies with the exception of Stryker Biotech Study 02-007, 98-003, 98-006 and 06-026. All GLP studies are included in P060021, Section IV.

Toxicology Conclusions

OP-1[®] Putty appears to be safe at doses that far exceed doses used in experimental models of spinal fusion and in clinical practice. The OP-1 remains confined to the site of administration and does not circulate at high levels in the blood or into distal tissues. As OP-1 diffuses from the implantation site it is cleared quickly by the kidneys. The lack of systemic distribution may be partially responsible for the large safety multiples observed in the use of OP-1. Even when given by repeat IV administration, however, the molecule is nontoxic at high multiples of the efficacious dose except for implantation-site irritation which is expected given the pharmacology of the molecule. When large amounts of the molecule were given in the form of OP-1[®] Implant, pleomorphic sarcomas were observed at the site of implantation. This response is attributable to a solid state carcinogenicity phenomenon that is unique to rodents. It might be expected, based on the role of OP-1 in development, that its use might cause developmental toxicity or teratogenicity. When administered at high repeated IV doses, however, OP-1 had no adverse maternal or perinatal effects. Even when rabbits were intentionally immunized with xenogeneic OP-1 using an adjuvant, there were no significant developmental abnormalities. OP-1 is also safe at a large multiple of the therapeutic dose in most standard safety pharmacology tests. Early studies in rats showed some transient effects on CV parameters, but these effects were not reproducible at a similar dose in dogs (using a slow infusion rate). In conclusion, there were no observations in the toxicology studies that would preclude the use of OP-1 at its intended dose for spinal fusion.

8.3 Biodistribution Studies

Several studies were completed to determine the PK and biodistribution of OP-1 following various routes of administration in several species. Rats were used for most

studies, but monkeys and rabbits were also employed. In general, OP-1 was not widely distributed in the body after administration. After IV administration, its half-life was about 0.3 to 1.5 hours in rats and monkeys. When administered as OP-1[®] Putty in spinal fusion models, blood levels were sustained but very low and never exceeded more than 3% of the total administered dose. These data indicate that OP-1 is released slowly from the implant site and/or rapidly cleared from the circulation. OP-1 did not accumulate to any significant extent in any major organs except the thyroid (representing free iodine as expected for a protein radiolabeled with iodine) and at the surgical sites. The majority of OP-1 was cleared by the kidneys. The pharmacokinetic (PK) results for OP-1 are consistent with the profile of a device whose effects are limited to the site (or compartment) of administration.

Summary of Bio-Distribution

Stryker Biotech Study ID Species	Dose (mg/kg)	C _{max} (ng/mL)	T _{max} (h)	T _{1/2elim} (h)	AUC (ng.h/mL)	K _{el} (hrs ⁻¹)	Cl (mL/min/kg)	Vd (L/kg)	Key Findings
00-038 Rat IV	0.025 (37B)	98.1	0.096	0.827	58.07	-	8.099	0.514	Rapid biphasic elimination at all doses. AUC proportionate w/dose & PK parameters linear. Cl similar to glomerular filtration rate suggests predominant renal Cl. Vd equivalent to total body water suggests minimal tissue penetration.
	0.25 (37B)	1293	0.086	1.053	746.1	-	5.962	0.526	
	2.5 (37B)	9200	0.096	1.426	8740	-	5.025	0.618	
	3.5 (37B)	8896	0.163	1.342	10081	-	5.975	0.673	
	0.25 (37A)	1288	0.077	1.636	849.1	-	5.025	0.704	
00-002 Monkey IV	0.025	188	0.100	0.328	97.55	-	4.152	0.118	Rapid biphasic elimination at 2.5mg/kg. AUC proportionate w/dose & PK parameters linear. Cl similar to glomerular filtration rate suggests predominant renal Cl. Vd equivalent to total body water suggests minimal tissue penetration.
	0.25	944	0.083	0.519	476.0	-	9.855	0.355	
	2.5	14133	0.083	1.417	10515	-	4.055	0.487	
97-024 Rat IV	0.035	83 ^a	.08	8.0	539.8	0.086	-	-	Dose independent linear kinetics observed over dose range. Majority sequestered at early time points by liver. Transient accumulations of radioactivity in liver, skin, lung, spleen, testis, & thyroid. Significant levels observed by autoradiography in bladder, tooth root & stomach, & small intestine at early time points
	0.35	773 ^a	.025	8.5	6193	0.082	-	-	
	3.5	6500 ^a	.08	7.5	47620	0.093	-	-	
04-008 Rabbit Implantation OP-1 Putty	0.54	239	24	-	26400 ^b	-	-	-	Radioactivity in circulation low: ≤2% radioactivity dose. Surgical site retained most of radioactivity. Little accumulation in other areas/tissues. Radioactivity excretion mainly via urine. Fusion rate 100% in 35-day group.

07-012 Rabbit Implanta- tion OP-1 Putty	1	16	420		8015				Release of OP-1 from collagen/CMC carrier was slow and not dose dependant. ALL animals treated with OP-1 Putty, regardless of dose, were fused by day 35
	2	17	840		7817				
	3	19	638		8748	-	-	-	

Note: For comparison, all data are from male animals.

^aexpressed as ng/gm blood

^bexpressed as AUC_{+last}·+last = 840 hours

Pharmacokinetic Conclusions

OP-1[®] Putty has nearly ideal PK characteristics for a device intended for local use. Systemic PK studies demonstrated that OP-1 is rapidly cleared from the blood after systemic injection. Its PK characteristics were very similar in nonhuman primates and rats. In addition, there were no significant differences in PK based on the sex of the animals (in rats). The clearance rate of OP-1 approximates the glomerular filtration rate, indicating it is cleared by the kidneys. Moreover, its volume of distribution was similar to the volume of whole body water suggesting that OP-1 was not distributed into the deep tissue compartment. OP-1 did not accumulate in any tissue for a long period of time after either IV injection or implantation, except for the desired persistence at the surgical site in rabbits. The minimal exposure of OP-1 away from the surgical site correlates well with the lack of adverse systemic effects observed in toxicology studies.

9. SUMMARY OF CLINICAL STUDIES

9.1 Overview

The primary source of clinical data supporting this PMA is pivotal study S01-01US in conjunction with its extension study 06-UPLF-01, both of which were conducted under Investigational Device Exemption #G990028. Pivotal study S01-01US followed all study patients until the last patient enrolled had completed a minimum of 2-years follow-up. Extension study 06-UPLF-01 brought back as many patients as possible from pivotal study S01-01US for a single longer-term follow-up visit at 36+ months to collect additional radiographic and clinical outcomes data.

9.2 Study Design

Pivotal Study S01-01US

Pivotal study S01-01US was a controlled, open-label (with blinded radiographic assessment), randomized, prospective, multicenter, multinational pivotal study in which patients with single level (L3-S1) degenerative lumbar spondylolisthesis (Grade 1 or 2) and spinal stenosis underwent decompression and posterolateral spinal fusion. Patients were randomized to treatment in a 2:1 ratio to either OP-1 Putty or the control arm, in which autogenous bone graft harvested from the iliac crest (autograft) was used.

Patients underwent standard surgical procedures for lumbar spinal posterior decompression with concomitant posterolateral intertransverse process arthrodesis using OP-1 Putty or autograft, as determined by randomization. Patients were evaluated postoperatively at 6 weeks, and 3, 6, 9, 12, and 24 months, and annually thereafter, until the last patient achieved 2 years of follow-up.

The study was conducted by 25 clinical sites in the US and Canada (although only 24 sites actually treated patients). A total of 336 patients were enrolled and randomized, and 295 were treated: 208 received OP-1 Putty and 87 received autograft. The remaining 41 enrolled patients withdrew prior to study treatment.

Follow-up Study 06-UPLF-01 (Extension to S01-01US)

Follow-up study 06-UPLF-01 was a prospective collection of longer-term data on the patient population from pivotal study S01-01US, and was conducted to expand the information regarding efficacy, particularly with regard to radiographic assessment of fusion, as well as the longer-term safety of OP-1 Putty in uninstrumented posterolateral fusion (PLF) as compared to autograft. All data that were previously evaluated in the patients in S01-01US were collected again at a single, longer-term follow-up, 36+ month evaluation, with the exception of most laboratory assessments and anteroposterior (AP) and lateral plain films. In addition, all patients were requested to undergo a CT scan. Review of the 36+ month radiographic assessment data was conducted according to a prospective, independent, blinded, multi-reviewer evaluation protocol.

Stryker Biotech attempted to enroll into 06-UPLF-01 all treated patients from pivotal study S01-01US who had not been failures due to retreatment in pivotal study S01-01US and had not died. Of the 257 patients from S01-01US who met these criteria, 5 patients were found to have died prior to initiation of study 06-UPLF-01, and 202 of the remaining 252 (80%) enrolled in study 06-UPLF-01: 144 patients in the OP-1 Putty group, and 58 in the autograft group. Twenty three of the sites from study S01-01US participated in 06-UPLF-01. (One site that had enrolled only 3 patients in study S01-01US did not participate in the follow-up study 06-UPLF-01).

9.3 Inclusion/Exclusion Criteria

Pivotal Study S01-01US

Patients were included in study S01-01US only if they met all of the following criteria:

1. The patient or legal guardian was willing and able to understand, sign and date the study specific Patient Informed Consent, which was approved by the Institutional Review Board.
2. The patient was a skeletally mature male or female less than 85 years of age.
3. The patient had a diagnosis of degenerative lumbar spondylolisthesis of Grade 1 or 2 with spinal stenosis demonstrated by medical history, physical examination, and radiographic imaging. Radiographic diagnosis was 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 patient had 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 > 0% and < 50% translation of the vertebrae and/or > 10 degrees and < 20 degrees angular motion) measured on flexion/extension radiographs
 - osteophyte formation or hypertrophy of the facet joint
4. The patient was a candidate for decompression and spinal fusion with the use of autograft from the iliac crest.
5. The patient required one level lumbar fusion (L-3 to S-1).
6. The patient agreed to participate in post-operative clinical and radiographic evaluations and required rehabilitation regimen.

7. The patient had no history of previous fusion attempt(s) to the affected spinal level.
8. The patient was non-responsive to at least 6 months of non-operative treatment prior to study enrollment.
9. The patient had a preoperative Oswestry Disability Index (ODI) of 30-100.

Patients were excluded from study S01-01US if they met any of the following criteria:

1. The patient had non-degenerative spondylolisthesis of any grade at the affected level.
2. The patient had degenerative spondylolisthesis of Grade 3 or 4.
3. The patient had active spinal and/or systemic infection.
4. The patient had a systemic disease or condition, which affected 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 patient was a prisoner, a transient, or had been treated for alcohol and/or drug abuse in an inpatient substance abuse program within 6 months prior to proposed study enrollment.
6. The patient had participated in clinical trials evaluating investigational devices, pharmaceuticals, or biologics within 3 months of enrollment in the study.
7. The patient was a woman able to bear children, e.g., not post-menopausal, had not had a hysterectomy, etc.
8. The patient was morbidly obese (defined as weight \geq 60% over the recommended ideal weight as described in the 1996 Metropolitan Height and Weight Tables for Men and Women).
9. The patient had a known sensitivity to any component of OP-1[®] Putty.
10. The patient was known to require at the time of treatment, additional surgery to the lumbar spinal region within the next 6 months.
11. The patient had spinal instability measured on flexion/extension radiographs of \geq 50% translation of the vertebrae or \geq 20 degrees of angular motion.
12. The patient used tobacco or nicotine or was prescribed steroids such as cortisone.

Follow-up Study 06-UPLF-01 (Extension to S01-01US)

To be eligible for participation in study 06-UPLF-01, patients met all of the following criteria:

1. The patient was treated in Stryker Biotech clinical protocol S01-01US (Pivotal IDE study) and was not a failure due to retreatment at the time of study completion.
2. The patient or legal guardian was willing and able to understand, sign and date the study-specific Patient Informed Consent, which had been approved by the Institutional Review Board (IRB).
3. The patient agreed to complete the necessary clinical and radiographic evaluations. Radiographic evaluations were not required if the patient was pregnant.

There were no exclusion criteria for participation in study 06-UPLF-01.

9.4 Safety and Efficacy Measures

Pivotal Study S01-01US

Patients were evaluated preoperatively, intraoperatively, postoperative (within 72 hours of operative), and postoperatively at 6 weeks (± 14 days), 3 months (± 14 days), 6 months (± 30 days), 9 months (± 30 days), 1 year (± 60 days), 2 years (± 60 days), and annually thereafter until the last patient achieved the 2-year follow-up (± 60 days).

Efficacy was measured by calculating the overall success rates in the OP-1[®] Putty and the autograft groups. To be an “overall success” a patient had to achieve each of the following:

- Improvement of at least 20% in the ODI from baseline
- Absence of retreatment
- Absence of treatment-related serious adverse events (SAEs)
- Absence of a decrease in neurological status (assessing muscle strength, reflexes, sensory and straight leg raise), unless attributable to a concurrent medical condition or to the surgical procedure by a blinded Independent Neurological Reviewer.
- Radiographic Success, which was also a composite measure comprising all of the following:
 - Presence of bone formation assessed by plain films
 - Angulation of $\leq 5^\circ$ on flexion/extension plain film radiographs of the affected level
 - Translational movement of ≤ 3 mm on flexion/extension plain film radiographs of the affected level

Safety was assessed principally by AEs, clinical laboratory evaluations (including immunologic evaluations), and neurological status.

The following additional information was also collected for each patient:

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

Follow-up Study 06-UPLF-01 (Extension to S01-01US)

Patients were evaluated at a single, longer-term follow-up visit (called 36+ months). The mean time from the study S01-01US surgical procedure for the study 06-UPLF-01 follow-up visit was 4.4 years (range 3.7 years to 5.5 years).

The key clinical outcomes parameters collected at 36+ months were the same as those collected during study S01-01US: Oswestry Disability Index, incidence of retreatment, incidence of treatment-related serious adverse events, and assessment of neurological status. Overall radiographic success was also evaluated at 36+ months; however, in study 06-UPLF-01, the assessment of presence of bone was done by using CT scans, a more accurate technique than the plain film technique used in study S01-01US.

Safety was assessed in study 06-UPLF-01 by reviewing the adverse events that were ongoing as of the close of study S01-01US, any new serious adverse events, and any new medical history and physical findings. Incidence of retreatments and evaluation of neurological status were both safety and effectiveness measures.

Additional evaluations for VAS, donor site pain (for autograft patients only), and general health (SF-36) were also conducted at 36+ months.

The primary success endpoint for study 06-UPLF-01 was a comparison of Overall Success rates for the OP-1 Putty and autograft groups, with overall success for a patient defined as meeting each of the following criteria:

- Improvement of at least 20% in the ODI from baseline at 24 months
- Absence of retreatment at any time up to and including 36+ months
- Absence of treatment-related serious adverse events (SAEs) at 24 months
- Absence of a decrease in neurological status at 24 months (assessing muscle strength, reflexes, sensory and straight leg raise), unless attributable to a concurrent medical condition or to the surgical procedure by a blinded Independent Neurological Reviewer.
- Radiographic success at 36+ months, which was also a composite measure comprising all of the following:
 - Presence of bone formation assessed by CT scan at 36+ months

- Angulation of $\leq 5^\circ$ on flexion/extension plain film radiographs of the affected level at 36+ months
- Translational movement of ≤ 3 mm on flexion/extension plain film radiographs of the affected level at 36+ months

9.5 Demographics and Accountability

Baseline demographics for patients who enrolled in S01-01US were similar between the OP-1 Putty and autograft treatment groups. Overall mean age was 68 years, with the range among groups of 36 to 84 years. The groups were similar in age distribution, with a majority of patients in each group aged >65 years. More of the patients (approximately two-thirds) were women, which is expected because the diagnosis of degenerative spondylolisthesis is more prevalent in women. Weight and height were similar across both treatment groups. Ninety-three percent of patients in the OP-1 Putty group and 92% of patients in the autograft group had lumbar spinal stenosis with a definitive diagnosis of Grade 1 degenerative lumbar spondylolisthesis. Selected baseline demographic variables are presented in Table 2 below.

Table 2: Pivotal Study S01-01US: Key Baseline Demographics

Parameter			OP-1® Putty	Autograft
Age (years)		Mean (Std. Dev.)	68 (9.8)	69 (8.3)
Sex:	Male	N (%)	71 (34.3)	26 (30.2)
	Female	N (%)	136 (65.7)	60 (69.8)
Level Fused:	L3-L4	n (%)	21 (10.1)	10 (11.6)
	L4-L5	n (%)	178 (86.0)	74 (86.0)
	L5-S1	n (%)	8 (3.9)	2 (2.3)
ODI		Mean (Std. Dev.)	48.8 (11.60)	48.8 (13.59)
Degree of Angular Motion (degrees)		Mean (Std. Dev.)	3.9 (3.40)	4.7 (3.20)
Translational Movement (mm)		Mean (Std. Dev.)	1.7 (1.44)	1.6 (1.49)

Of all patients from S01-01US who were eligible for participation in 06-UPLF-01 (n=257, 183 for OP-1 Putty group and 74 for autograft group), the key demographics and baseline characteristics (including key clinical outcomes as measured in pivotal study S01-01US) between study groups for the patients who enrolled in 06-UPLF-01 (n=202, 144 for the OP-1 Putty group, and 58 for the autograft group) versus the patients who were eligible for 06-UPLF-01 were maintained. This provides reasonable assurance that the results of the 36+ month data analyses are representative of the entire study population, and that 36+ month data from follow-up study 06-UPLF-01 does not appear to be biased by disproportionately representing those patients pre-disposed to success or failure in either treatment group.

Table 3: Summary of Key Demographic Parameters and S01-01US Success Outcomes for Extension Study 06-UPLF-06

Parameter	Statistic	OP-1 Putty		Autograft	
		Eligible for 06-UPLF-01	Enrolled in 06-UPLF-01	Eligible for 06-UPLF-01	Enrolled in 06-UPLF-01
Age (years)	Mean	67.6	66.8	69.3	68.7
	Std. Dev.	9.54	9.25	8.72	8.66
Sex: Male	N (%)	64 (35.0)	50 (34.7)	19 (25.7)	16 (27.6)
Female	N (%)	119 (65.0)	94 (65.3)	55 (74.3)	42 (72.4)
Level Fused: L3-L4	n (%)	19 (10.4)	17 (11.8)	10 (13.5)	9 (15.5)
L4-L5	n (%)	156 (85.2)	124 (86.1)	62 (83.8)	48 (82.8)
L5-S1	n (%)	8 (4.4)	3 (2.1)	2 (2.7)	1 (1.7)
ODI	Mean	48.5	48.2	50.1	50.7
	Std. Dev.	11.11	10.74	13.48	12.47
Degree of Angular Motion (degrees)	Mean	4.0	4.1	4.7	4.3
	Std. Dev.	3.42	3.53	3.24	3.03
Translational Movement (mm)	Mean	1.7	1.8	1.6	1.5
	Std. Dev.	1.48	1.55	1.52	1.42
Prior overall success at 24 months as determined in pivotal study S01-01US*	%	42.9	43.8	57.6	60.0
Prior success in presence of bone assessment by 9 month CT scan in pivotal study S01-01US*	%	91.2	89.7	98.4	100.0

* Prior overall success at 24 months was calculated using the plain films assessment for presence of bone, which was later found to be inadequate for assessing the type of medial bone formation more common for OP-1 Putty than for autograft. The 9-month presence of bone assessment does not represent peak bone formation in OP-1 Putty group. These measures are presented only to demonstrate that the patients who returned for 36+ month assessments in study 06-UPLF-01 were not predisposed to success or failure as compared with all patients eligible to return for 36+ month assessments, based on potential key success/failure predictors from study S01-01US.

The disposition of all patients through study S01-01US and extension study 06-UPLF-01 is summarized in Table 4.

Table 4: Disposition of Patients in S01-01US and 06-UPLF-01

Parameter	Overall N (%)	OP-1 Putty N (%)	Autograft N (%)
All patients enrolled and treated in S01-01US	295 (100)	208 (100)	87 (100)
Disposition of patients during S01-01US			
Died during S01-01US	11 (3.7)	7 (3.4)	4 (4.6)
Retreatment failure during S01-01US	26 (8.8)	18 (8.7)	8 (9.2)
No post-baseline visit during S01-01US	1 (0.3)	0 (0.0)	1 (1.1)
Patients Eligible for 06-UPLF-01	257 (87.1)	183 (88.0)	74 (85.1)
Disposition of patients eligible for 06-UPLF-01	257	183	74
Patients Enrolled in 06-UPLF-01	202	144	58
Patients not enrolled in 06-UPLF-01	55	39	16
Reasons not enrolled in 06-UPLF-01			
Died subsequent to S01-01US	5 (1.7)	4 (1.9)	1 (1.1)
Refused to participate in 06-UPLF-01	23 (7.8)	16 (7.7)	7 (8.0)
Unable to locate	15 (5.1)	10 (4.8)	5 (5.7)
Site refused to participate in 06-UPLF-01	3 (1.0)	2 (1.0)	1 (1.1)
Other	9 (3.1)	7 (3.4)	2 (2.3)

An accounting of patients by interval through 36+ months is provided in [Table 5](#). Follow-up at the 24 month interval was 93% overall (237/255). The follow-up rate for visits at 36+ months is 79% (195/247) overall; however, the follow-up rate for status assessments at 36+ months is 80% overall (represented by the number of patients who enrolled in 06-UPLF-01 divided by the number of patients eligible to enroll in 06-UPLF-01 who had not dies subsequent to S01-01US: 202/252).

Table 5: Patient accounting through 36+ Months, S01-01US and 06-UPLF-01 (Safety Population)

	Operative^a (<28 Days)	6 Weeks (28-77 Days)	3 Months (78-152 Days)	6 Months (153-605 Days)	12 Months (306-670 Days)	24 Months (671-1035 Days)	36+ Months (>=1036 Days)
OP-1 Putty							
Theoretical	208	208	208	208	208	208	208
Deaths (cumulative) ^b	1	1	2	5	5	9	11
Failures (cumulative)	0	0	2	5	12	17	21
Expected	207	207	204	198	191	182	176
Actual ^c	23	201	195	195	187	176	140
% Follow-up ^d	11	97	96	99	98	97	80
Autograft							
Theoretical	87	87	87	87	87	87	87
Deaths (cumulative) ^b	0	0	0	0	2	4	5
Failures (cumulative)	0	0	0	0	8	10	11
Expected	87	87	87	87	77	73	71
Actual ^c	10	83	79	83	72	61	55
% Follow-up ^d	12	95	91	95	94	84	78

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

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

(c) Patients with any assessment or visit data occurring within the window time frame. Patient 1210 was flagged as enrolled at 36+ month (based on inclusion/exclusion criteria), but was excluded in actual counts because there were no assessments in 06-UPLF-001.

(d) Percent follow-up rates are not the same as the percentage of patients for whom follow-up assessments were collected, because retreatment failures were subtracted from follow-up rates.

9.6 Surgical Procedure and Hospitalization

Table 6 presents surgical procedure characteristics as collected in study S01-01US. Mean operative time was 20 minutes shorter for the OP-1 Putty. Longer mean operative time in the autograft group is presumed to be attributed to additional operative time required to harvest autograft from the iliac crest. Mean estimated blood loss was also statistically lower for the OP-1 Putty group. Mean length of stay post surgery was comparable for the two treatment groups. The shorter operative time and reduced blood loss experienced in the OP-1 Putty group are important clinical benefits. A 20 minute reduction in operative time provides benefit for the patient (reduced risk associated with prolonged general

anaesthesia in this elderly population) and the hospital (reduced costs associated with operating room time).

Table 6: Surgical Procedure Characteristics (Safety Population)

	Statistic	OP-1 Putty	Autograft	P value for difference
Operative Time (min)	Mean	144	164	P=.006
	Std. Dev.	53.3	62.4	
Estimated Blood Loss (cc)	Mean	309	471	P=.0004
	Std. Dev.	244.5	379.7	
Length of Stay Post Surgery (Days)	Mean	4.5	4.4	P=.529
	Std. Dev.	2.9	1.7	

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

9.7 Clinical and Radiographic Outcomes

The primary efficacy endpoint is the Overall Success rate for the mITT population, in which missing data were imputed. Overall Success is a composite endpoint consisting of radiographic success, improvement in Oswestry Disability Index, absence of retreatment, absence of neurological compromise, and absence of serious treatment-related adverse events. Success regarding the improvement of ODI, absence of neurological compromise, and absence of serious treatment-related adverse events is determined at 24 months from the data collected in the original pivotal study, S01-01US. Success regarding radiographic evidence of fusion (presence of bone by CT scan, angular motion success and translational movement success by plain films) is based on the 36+ months data collected in study 06-UPLF-01 (because CT scans were not taken at 24 months, and because plain films such as those taken at 24 months are now known to be inadequate for assessing medial bone formation). Success regarding retreatment is based on retreatment at any time up to and including 36+ months. Results for the primary endpoint of Overall Success are presented in [Table 7](#).

Table 7: Overall Success at 24 months (with Radiographic and Retreatment subcomponents at 36+ months): mITT Population

Outcome	OP-1 Putty		Autograft		p-value Non-inferiority
	Number of Patients	N (%) Successes	Number of Patients	N (%) Successes	
Overall Success ¹	207	97.75 (47.2)	86	40.25 (46.8)	0.025 ²

¹ Missing values were imputed.

² p-value is based on one-sided 2-sample test for non-inferiority in the angular scale with a non-inferiority margin of 0.14 (radians); estimates and standard errors are based on logistic regression and multiple imputation.

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

⁴ Missing data are not imputed.

In this analysis using retreatment and radiographic data collected at the 36+ month interval (where presence of bone was assessed using CT scan rather than plain films), OP-1 Putty demonstrated non-inferiority to autograft with regard to the pre-specified primary composite endpoint Overall Success. OP-1 Putty achieved 47.2% success and autograft achieved 46.8% success (p=0.025).

**Table 8: Overall Radiographic Success and Overall Success Subcomponents
 mITT Population**

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

¹ Missing values were imputed.

² p-value is based on one-sided 2-sample test for non-inferiority in the angular scale with a non-inferiority margin of 0.14 (radians); estimates and standard errors are based on logistic regression and multiple imputation.

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

⁴ Missing data are not imputed.

Sources: Statistical Tables S.4.A, S.7.A, 5.2.2 ADHOC, 5.4.2.ADHOC, 5.5.2.ADHOC, S.4.3.A in Section 14.1 of CSR 06-UPLF-01 (Appendix B, Section V, PMA Amendment)

While OP-1 Putty did not demonstrate non-inferiority to autograft with regard to the secondary endpoint, Overall Radiographic Success (imputed) at 36+ months, the results were clinically comparable, and the differences between OP-1 Putty and autograft in radiographic success (non-imputed) and all subcomponents of overall success (non imputed) were not statistically significant or clinically relevant (Table 8). In addition, there were no statistically significant differences between the OP-1 Putty and autograft groups with regard to the three subcomponents of Overall Radiographic Success at 36+ Months: Presence of Bone, Angular Motion, and Translational Movement (as shown in Table 9).

Table 9: Subcomponents of Radiographic Success at 36+ Months (mITT Population)

Radiographic Measure	OP-1 Putty		Autograft		p-value ^a For Difference
	Number of Patients	Number (%) of Successes	Number of Patients	Number (%) of Successes	
• Presence of Bone by 36+ month CT	143	107 (74.8)	53	41 (77.4)	0.852
• Angular Motion $\leq 5^\circ$, 36+ months	137	95 (69.3)	57	39 (68.4)	1.000
• Translational Movement ≤ 3 mm, 36+ months	136	103 (75.7)	57	43 (75.4)	1.000

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

(a) p-value is based on Fisher's Exact test.

9.8 Discussion of Primary Endpoint Definition

In the original study, S01-01US, OP-1 Putty failed to demonstrate non-inferiority to autograft according to the composite overall success endpoint with all subcomponents measured at 24 months. Failure to demonstrate non-inferiority of OP-1 compared with autograft was primarily attributable to one component of one parameter: the presence of bone as assessed by plain films. The OP-1 Putty group achieved clinically comparable improvements in all other key clinical outcomes at 24 months post surgery including Oswestry Disability Index (ODI), absence of retreatment, absence of treatment-related serious adverse effects and absence of decrease in neurological status. Comparable success in the other radiographic parameters measuring stability of the fused level (angulation and translation) at 24 months was also observed.

Given that clinical experience and the literature demonstrate a high correlation between fusion and positive clinical outcomes in patients undergoing decompression with laminectomy, these results were unexpected^{1,2} Because the OP-1 Putty patients had comparable clinical outcomes to the autograft patients and demonstrated comparable segmental stability, they should also have shown comparable results for the radiographic assessment of the presence of bone. That is, the OP-1 patients would not be expected to demonstrate improved and durable clinical outcomes at 24 months and beyond if fusion had not occurred. In addition it would stand to reason in the absence of a bone fusion, the OP-1 patients would have been expected to demonstrate increased angular and translational instability.

Since the patients in the OP-1 Putty group achieved clinical improvements and radiographic stability comparable to the autograft group, it was reasonable to question whether the radiographic assessments performed at 24 months accurately assessed the

presence of bone. In order to better understand these anomalous results, Stryker Biotech brought together two nationally recognized spine surgeons and one academic musculoskeletal radiologist who were not previously involved with the study and who were blinded to the study data, to examine the 24-month plain films as well as the CT scans (which had only been taken at 9 months post surgery in S01-01US) in a subset of study patients. CT scans were selected from both the autograft and OP-1 group for this exploratory assessment, and selection was heavily weighted towards patients who were failures for presence of bone by plain film. The independent expert assessment revealed that in many cases, bone was not seen on the 24-month plain films, but *was* seen on the 9-month CT scan medial to the transverse processes and along the lateral border of the facet joints. These findings suggested that the plain film technique used to assess fusion at 24 months was inadequate for assessing medial bone formation, which is now known to be more commonly associated with OP-1 Putty than with autograft.

The finding of bone formation medial to the transverse processes was unexpected, because it had been assumed that OP-1 Putty-directed new bone formation would occur as it does for autograft—laterally, along the transverse processes. Stryker Biotech believes that the difference in the observed pattern of bone formation may relate to the physical properties of the graft materials studied; OP-1 Putty is a compressible, moldable material that does not harden, whereas autograft is not malleable and has a non-compressible physical structure. During the spinal fusion procedure used in the clinical study, the surgeon retracts the paraspinal muscles to lay down the OP-1 Putty or autograft material. When the retractors are removed and the muscles are released, the OP-1 Putty product may be compressed medially, leading to more medial bone formation. This is not easily detected by plain x-ray because the lumbar vertebrae are retroperitoneal structures for which overlying abdominal organs, bowel, bowel contents, and bowel gas can easily obscure new bone formation. In addition, the medial location of the OP-1 putty-directed bone formation may be obscured by the lateral border of the vertebral body and hypertrophied facet joints.

Therefore, to resolve the apparent disparity in outcomes and adequately investigate whether patients in the OP-1 Putty group experienced fusion rates comparable to the autograft group, a radiographic assessment tool more sensitive than the plain films used at 24 months was needed. Stryker Biotech designed and conducted the prospective follow-up study, 06-UPLF-01, to collect additional radiographic and clinical data on all available study patients at the longer-term follow-up interval of 36+ months. Considerable effort was expended to locate and evaluate as many patients as possible in both the autograft and OP-1 Putty groups.

Eighty percent (80%) of eligible patients from S01-01US returned (or had died since S01-01US) and were therefore accounted for in follow-up study 06-UPLF-01. The mean time from surgery was 4.4 years in the OP-1 arm and 4.5 years in the autograft group. The overall range from surgery in both groups was between 3.7 and 5.5 years. All key demographic characteristics and 24 month outcome variables (as assessed in S01-01US) of the patients who participated in the extension study, compared to those eligible to participate, were similar.

Patients received CT scans to assess for the presence of bone, and repeat flexion/extension films to provide measurements of angulation and translation at the same time point. All key clinical outcome measures collected in the original study S01-01US were also collected at the 36+ month interval in 06-UPLF-01. Great care was taken to standardize the prospective CT scan including the imaging algorithm and the imaging protocol that was prospectively developed. Each CT scan was read by two blinded orthopedic spine surgeons according to a standardized protocol that was prospectively defined. In case of discrepant readings, the scan was read by a third blinded orthopedic spine surgeon who determined the final assessment.

The CT scan analysis conducted under the follow-up study, in addition to the accompanying assessments of angulation and translation by flexion/extension films, demonstrated that radiographic success did occur at comparable rates between the OP-1 Putty and autograft groups at 36+ months. In support of the original hypothesis that led to collection of additional data in study 06-UPLF-01, of the OP-1 Putty subjects who were judged negative for the presence of bone based on plain films at 24 months, 71% (27/38) were judged positive for presence of bone based on CT scans at 36+ months, with 81% (22/27) of those patients showing presence of medial bone formation.

The results from the more accurate 36+ month radiographic assessment were therefore combined with the original 24 month clinical outcome assessments to develop a modified Overall Success assessment. The 36+ month radiographic assessment is an accurate representation of the expected results at 24 months because radiographic results would be expected to remain constant between 24 months and 36 months.³ One additional change that was made from S01-01US to the overall success composite was to update the retreatment analysis. Retreatment failures were included in the analysis of overall success up to and including the 36+ month follow-up visit due to the critical importance of this outcome to both patients and physicians and because other components are meaningless as measures of the treatment effect if there has been an intervening surgery to promote fusion.

In summary, the Overall Success composite as defined in study 06-UPLF-01 is an appropriate measure to assess the safety and effectiveness of OP-1 Putty for the proposed indication. The composite includes assessments of key parameters that are important to patients undergoing fusion surgery, including radiographic success, clinical success, neurological success and freedom from reoperation and device related serious adverse events. The modified composite includes data collected at both 24 months and 36+ months. This provides important additional long-term follow-up information in the analysis without introducing bias. Patients who have undergone decompression with arthrodesis for degenerative spondylolisthesis may exhibit similar clinical improvements at early time points regardless of whether they have achieved definitive fusion or pseudarthrosis⁴; however, significant differences in clinical outcomes have become apparent between these two groups with longer-term follow-up⁵. Therefore, while twenty-four months post surgery is the earliest time point at which comparisons of radiographic and clinical outcomes are generally considered sufficient proof of safety and efficacy for a spinal fusion procedure, data from later time points are more valid, and in addition provide important insight into the durability of the clinical results. Evaluation of

the radiographic and clinical data through the 24-month interval collected in pivotal study S01-01US along with the radiographic and clinical data collected through the 36+ month interval in study 06-UPLF-01 provides a reliable comparison of the critical factors relevant to an assessment of both the early and longer-term safety and effectiveness of OP-1 Putty as compared to autograft, and demonstrates that OP-1 Putty has equivalent clinical and radiographic outcomes to autograft without the additional comorbidities associated with autograft harvest.

9.9 Safety and Immune Response Evaluation

Immune Response Evaluation

In the OP-1 Putty group, 93.7% of patients were antibody positive at any time point versus 20.9% of patients in the autograft group. In the OP-1 Putty group 25.6% of patients had evidence of anti-OP-1 neutralizing antibodies versus 1.2% of autograft patients. The peak presence of neutralizing antibodies was observed at 3 months and declined thereafter. By 24 months, none of the patients had neutralizing antibodies present. In follow-up study 06-UPLF-01, all patients who had been antibody positive at 24 months (or, if they did not have a 24-month visit, were positive at their last visit in S01-01US) had serum samples analyzed at the 36+ month visit. Using a more sensitive assay than was available in S01-01US, none of the patients in either treatment group were positive for neutralizing antibodies at the 36+ month interval.

Individual profiles of patients who had neutralizing antibodies at any time point were assessed in S01-01US. No significant patterns emerge from these profiles except that the peak presence of antibody titers was observed between 6 weeks and 3 months and declined thereafter. The presence of neutralizing antibodies was not statistically correlated with clinical success outcomes (Overall Success and its subcomponents) based on data from clinical success outcomes at the 24-month interval (with radiographic success and overall success calculated with 36+ month radiographic success) from extension study 06-UPLF-01.

Safety Evaluations

A presentation of adverse events reported in study S01-01US and serious adverse events reported in study 06-UPLF-01 is provided in Section 5 of this document.

Safety of OP-1 Putty treatment in PLF is similar to that of autograft treatment with respect to the proportion of patients experiencing Treatment-emergent AEs, Severe AEs, Treatment-related AEs, SAEs, Unanticipated AEs, Neoplasm, and Death in pivotal study S01-01US, as shown in [Table 10](#).

Table 10: Number of Patients with Treatment -Emergent Adverse Events in Pivotal Study S01-01US (Safety Population)

Parameter	OP-1 Putty (N=208)		Autograft (N=87)	
	Number (%) of Patients with Events	95% CI	Number (%) of Patients with Events	95% CI
Any AE	201 (96.6)	(93.2, 98.6)	82 (94.3)	(87.1, 98.1)
Severe AE	43 (20.7)	(15.4, 26.8)	17 (19.5)	(11.8, 29.4)
Treatment-related AE	54 (26.0)	(20.1, 32.5)	23 (26.4)	(17.6, 37.0)
Unanticipated AE	6 (2.9)	(1.1, 6.2)	0 (0.0)	(0.0, 4.2)
Serious AE	104 (50.0)	(43.0, 57.0)	43 (49.4)	(38.5, 60.4)
Serious and Unanticipated AE	5 (2.4)	(0.8, 5.5)	0 (0.0)	(0.0, 4.2)
Treatment-related Serious AE	25 (12.0)	(7.9, 17.2)	6 (6.9)	(2.6, 14.4)
Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps)	12 (5.8)	(3.0, 9.9)	8 (9.2)	(4.1, 17.3)
Death	7 (3.4)	(1.4, 6.8)	4 (4.6)	(1.3, 11.4)

The safety data from pivotal study S01-01US, supported by the additional safety data from extension study 06-UPLF-01, support the following conclusions:

- No pattern of clinically relevant laboratory changes was associated with OP-1 Putty treatment.
- There does not appear to be any association of neutralizing antibodies and the development of potentially immunologically-related AEs or SAEs of any kind based on the data. The presence of neutralizing antibodies was not statistically correlated with clinical success outcomes. There were no patients who had neutralizing antibodies at 24 months or at 36+ months.
- The risk of post-operative AEs related to the lumbar spine is clinically equivalent for OP-1 Putty and autograft treatments as demonstrated in pivotal study S01-01US. This conclusion is supported by the additional data on ongoing adverse events, new serious adverse events, and new medical conditions and physical findings collected at the 36+ month visit in extension study 06-UPLF-01.
- There was a slightly higher reported rate of AEs in the cardiac SOC in the OP-1 Putty treated group during pivotal study S01-01US (using a very conservative test for significance of $p \leq 0.2$). Review of medical history of OP-1 patients who had a cardiac related adverse event revealed that a substantial majority 25/27 had clinically significant risk factors for cardiac disease or underlying cardiac disease at baseline. No difference between treatment groups with regard to the proportion of patients with new serious adverse events or new medical conditions or physical

- findings in this SOC was seen at the 36+ month interval in extension study 06-UPLF-01.
- There was a higher reported rate of AEs in the infections and infestations SOC in the OP-1 Putty treated groups during pivotal study S01-01US (using a very conservative test for significance of $p \leq 0.2$); however, no patterns of particular types of infections emerged (infections were disparate), and there was no evidence of an increased incidence of surgically-related wound infections in the OP-1 Putty group compared to autograft. No difference between treatment groups with regard to the proportion of patients with new serious adverse events or new medical conditions or physical findings in the infections and infestations SOC was seen at the 36+ month interval in extension study 06-UPLF-01.
 - There was a higher reported rate of AEs in the blood and lymphatic system disorders SOC in the autograft group during pivotal study S01-01US (using a very conservative test of statistical significance of $p \leq 0.2$). The difference in blood and lymphatic system disorders, which was largely related to donor site complications and anemia in study S01-01US, did not persist at 36+ months based on data from study 06-UPLF-01.
 - Although respiratory and gastrointestinal SOC categories were identified (using a very conservative test of statistical significance at $p \leq 0.2$) as having a higher rate of AEs in the OP-1 Putty group compared to autograft in study S01-01US, there were no clinically relevant patterns of AEs that emerged in these areas. At the 36+ month evaluation in study 06-UPLF-01, there were no apparent differences between groups in the proportion of patients who had new SAEs or new medical conditions/physical findings in these SOC categories.
 - There was a higher reported rate of AEs in the injury, poisoning and procedural complications SOC in the autograft group during pivotal study S01-01US (using a very conservative test of statistical significance of $p \leq 0.2$). At the 36+ month visit for 06-UPLF-01, there was still a higher percentage of patients in the autograft group than in the OP-1 Putty group with new serious AEs and new medical conditions and physical findings for this SOC, although the difference between groups was not statistically significant. The higher incidence of patients with events in this SOC at 36+ months with regard to new medical conditions and physical findings appeared to be related primarily to the preferred term, “fall.”
 - At the 36+ month visit for 06-UPLF-01, the nervous systems disorders SOC was identified (using a very conservative test of statistical significance at $p \leq 0.2$) as having a higher percentage of patients reporting new medical conditions and physical findings in the autograft group as compared to OP-1 Putty (10.0% of

patients in the OP-1 Putty group and 16.1% in the autograft group, $p=0.167$). The difference between groups was not associated with any particular preferred term within this SOC.

- There were no SOC categories for new serious adverse events or new medical history and physical findings at 36+ months that were identified (using a very conservative test of statistical significance at $p \leq 0.2$, and calculating p-values for any SOC terms reported by $\geq 5\%$ of patients in at least one treatment group) as having higher rates in the OP-1 Putty group as compared to autograft.
- Of adverse events that were ongoing at the time of the last patient visit for study S01-01US, the percentage of events that had become serious adverse events since study S01-01US or that had resulted in spine surgery since study S01-01US was no higher in the OP-1 Putty group than in the autograft group. The system organ class General Disorders and Administration Site Conditions was the only SOC category where the difference between treatment groups was statistically significant at $p \leq 0.2$: events were reported in 2.9% of OP-1 Putty patients and 6.9% of autograft patients ($p=0.191$). The most frequently occurring preferred term within this SOC was asthenia: 1.0% for OP-1 Putty group, and 3.4% for the autograft group.
- In study S01-01US, 10.5% of patients across both treatment groups reported 44 SAEs that were either determined to be “suspected related” to study treatment, or were assessed as “relationship unknown” by the Principal Investigator. For the purposes of this analysis, events assessed as “suspected related” or “relationship unknown” were considered to be treatment-related. In the OP-1 Putty treatment group, 25 (12.0%) patients experienced 38 treatment-related SAEs, and in the autograft group, 6 (6.9%) patients experienced 6 treatment-related SAEs. It should be noted, however, that of the 25 patients in the OP-1 Putty group with treatment-related SAEs, only 10 patients (4.8%) experienced SAEs (13) that were assessed as “suspected related” by the Investigator, and the other 15 patients (7.2%) experienced SAEs (25) that were assessed as “relationship unknown.” By comparison, all 6 patients (6.9%) in the autograft group with treatment-related SAEs (6) had events that were reported as “suspected related.” The percentage of patients with “suspected related” SAEs was comparable between study groups (4.8% for OP-1 Putty and 6.9% for autograft). (Source: Table 45 in CSR S01-01US, Appendix B, Section V, original PMA.) The percentage of patients with SAEs ruled as “relationship unknown” was higher in the OP-1 Putty group; however, this difference is assumed to be attributable to the open-label study design. (Because the OP-1 Putty device was investigational and autograft was not, and because Investigators knew the treatment group assignment of all patients, they may have been more likely to assign SAEs as relationship “unknown” for the investigational device than for the autograft.) This assumption is supported by considering that the percentages of patients reporting SAEs and severe SAEs in

- study S01-01US were no different between treatment groups (SAEs: 50.0% for OP-1 Putty and 49.4% for autograft; severe AEs: 20.7% for OP-1 Putty and 19.5% for autograft). Furthermore, in follow-up study 06-UPLF-01, the percentage of patients with new serious adverse events that were treatment-related (suspected related or relationship unknown) was no higher for OP-1 Putty (1.0%) than for autograft (5.7%), and the percentage of patients with new medical history and physical findings that were treatment-related (suspected related or relationship unknown) was no higher for OP-1 Putty (5.8%) than for autograft (12.6%).
- In study S01-01US, there were 5 patients (2.4%) in the OP-1 Putty treatment group who reported 7 SAEs that were determined to be Unanticipated by the Principal Investigator. The SAEs were thyroid gland cancer (patient 1320), atrial fibrillation and transient ischemic attack (patient 1507), extradural haematoma (Patient 2405), lumbar spinal stenosis (patient 2514), and pulmonary oedema and hypotension (patient 3008). No patients (0.0%) in the OP-1 Putty group had unanticipated SAEs that were ruled “suspected related” to treatment, and only one patient (0.5%), patient 3008, had unanticipated SAEs that were treatment related (ruled “relationship unknown” by the Investigator). (Source: page 103 and Table 45 of CSR S01-01US, Appendix B, Section V, original PMA.)
 - Regarding events reported in the Neoplasms, benign or malignant SOC, there were no patterns or specific events of concern identified in either study with respect to type of cancer, time to onset post surgery, or distribution between treatment groups. Twenty-four patients across both treatment groups reported events in the SOC Neoplasms, Benign and Malignant (including cysts and polyps) over the course of this study: 14 (6.7%) in the OP-1 Putty group (12 from S01-01US, and 2 from 06-UPLF-01), and 10 (11.5%) in the autograft group (8 from S01-01US, and 2 from 06-UPLF-01).
 - There were 11 patients who died in the OP-1 Putty group: 7 during study S01-01US, and 4 subsequent to S01-01US and prior to study 06-UPLF-01. There were 5 patients who died in the autograft group: 4 during study S01-01US, and 1 subsequent to S01-01US and prior to study 06-UPLF-01. No patterns of concern emerged with respect to etiology of death, or the time to occurrence post surgery.

10. CONCLUSIONS

In patients undergoing lumbar PLF with use of OP-1 Putty, pain is relieved, function is improved, few additional procedures were needed for relief of pain or treatment of complications, and AE rates are generally low and clinically acceptable. OP-1 Putty was successful in meeting the primary endpoint by demonstrating non-inferiority to autograft with regard to the composite safety and effectiveness primary endpoint of Overall

Success (47.23% for OP-1 Putty and 46.8% for autograft, p=0.025). OP-1 Putty treatment is generally safe and well-tolerated in the PLF population, and offers a favorable risk/benefit ratio when compared with the potential pain and co-morbidities associated with autograft harvest.

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