

FDA Executive Summary for Zimmer Spine's Dynesys Spinal System

Orthopedic and Rehabilitation Devices Panel

November 4, 2009

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INTRODUCTION

The subject of this Executive Summary is Zimmer Spine's Dynesys Spinal System premarket approval (PMA, P070031) application, a pedicle screw-based, posterior dynamic stabilization system consisting of: titanium alloy pedicle screws, polycarbonate urethane (PCU) spacers, and polyethylene terephthalate (PET) cords. This application has been reviewed by the Center for Devices and Radiological Health of the Food and Drug Administration. Your time and effort in review of this application is greatly appreciated.

Rationale for Presentation to the Panel

This section describes the rationale for presentation of this PMA to the Orthopedic and Rehabilitation Devices Advisory Panel. This PMA application for Zimmer Spine's Dynesys Spinal System is the first pedicle screw-based, posterior dynamic stabilization system intended for the non-fusion treatment of spinal disorders that FDA has reviewed.

Since this is a first-of-a-kind system for non-fusion use, we will be informing the panel about the device and the patient outcomes related to the clinical data submitted in the PMA.

FDA Questions to the Panel

The questions FDA will be asking the panel are located in "FDA Questions" section of the panel pack.

BACKGROUND INFORMATION

Applicant Name and Address:

Zimmer Spine, Inc.
7375 Bush Lake Rd.
Minneapolis, Minnesota 55439

Indications for Use

The following Indications for Use were specified in the IDE for the Dynesys Spinal System:

The Dynesys Spinal System is indicated to provide spinal alignment and stabilization in skeletally mature patients at one or two contiguous levels from L1-S1. Patients may have radiculopathic symptoms including leg pain, muscle weakness, and/or sensation abnormality as evidenced by patient history and diagnostic studies. Patients may have a narrowing of the lateral or central canal and/or neurogenic claudication. These signs and symptoms are caused by:

- Degenerative spondylolisthesis or retrolisthesis (up to Grade I)
- Spinal stenosis or stenosing lesions.

Patients may require decompression at the levels considered for treatment. Dynesys is intended to be used without bone graft.

In a more recent PMA amendment, the applicant is now proposing the following Indications for Use:

The Dynesys Spinal System is indicated to provide spinal alignment and stabilization in skeletally mature patients at one or two contiguous levels from L1-S1. This includes patients who have been unresponsive for a minimum of 3 months of non-operative treatment, who would otherwise be indicated for spinal fusion and have the following radiculopathic symptoms:

- leg pain,
- muscle weakness, and/or
- sensation abnormality

as evidenced by patient history and diagnostic studies. This also includes narrowing of the lateral or central canal and/or neurogenic claudication. These signs and symptoms are caused by:

- Degenerative spondylolisthesis or retrolisthesis (up to Grade I)
- Spinal stenosis or other forms of encroachment on the spinal canal, including for example, such stenosing lesions as facet cysts, large central or lateral disc herniation or dynamic claudication.

Bony or soft tissue decompression is required at the levels considered for treatment. Dynesys is intended to be used without bone graft.

Based on the patient population studied in the IDE and their subsequent outcomes, FDA will be asking you to discuss the appropriate Indications for Use for the Dynesys device, and to specifically address whether the data presented supports the safety and effectiveness of the device for treating:

- *Patients with both one and contiguous two-level pathology.*
- *All proposed spinal levels (L1-S1).*
- *Patients who have undergone only a minimum of 3 months of non-operative treatment as opposed to 6 months which are typically required for lumbar devices.*
- *Patients with only leg pain versus those with only neurological symptoms (i.e., muscle weakness, sensation abnormality) versus those with both leg pain and neurological symptoms.*
- *Patients with the different primary radiographic indications that were studied.*

Also, we will ask you to comment on the following:

- *The reference to the device providing spinal alignment and stabilization considering that there was not a radiographic component in the primary study endpoint and there is a significant amount of missing radiographic data.*
- *The proposal to require that patients would otherwise be indicated for spinal fusion as opposed to the specification of more objective criteria.*

Contraindications

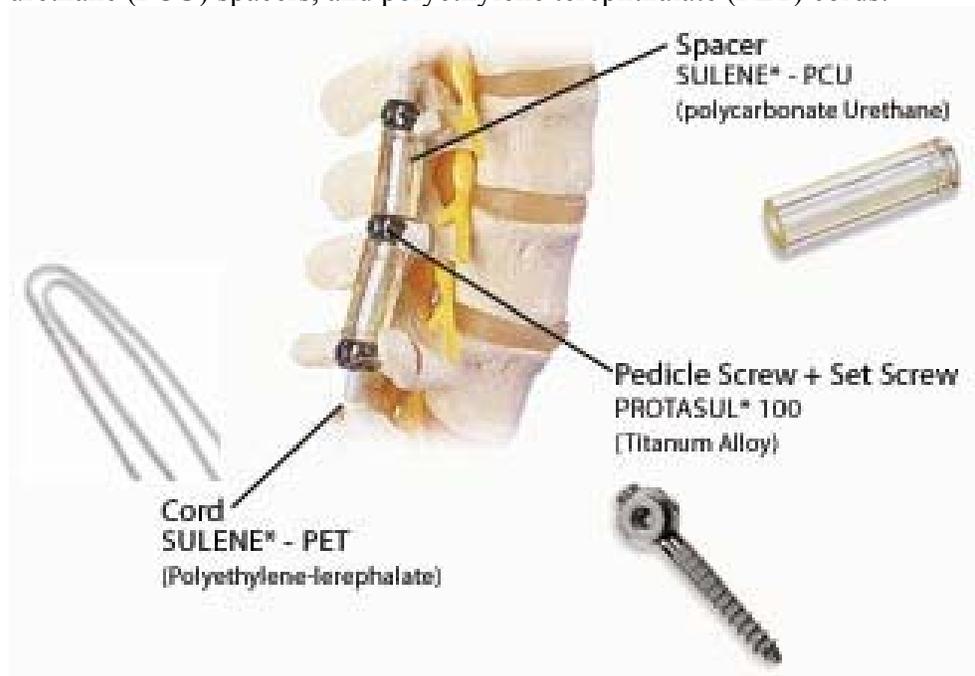
The sponsor proposes that use is contraindicated in cases with:

- Degenerative scoliosis > 10° at the affected level(s);
- Supplemental interbody column support (e.g., bone graft, spacers or fusion cages) is planned at the affected level(s);
- Greater than Grade I spondylolisthesis or retrolisthesis at the affected level(s);
- Radiculopathic signs from more than two contiguous or from two non-contiguous vertebral body segment(s);
- Previous lumbar fusion attempt(s), previous total facetectomy or trauma at the affected level(s);
- Gross obesity defined as exceeding ideal body weight by greater than 40%;
- Active local or systemic infection;
- Advanced osteoporosis;
- Receiving immunosuppressive or long-term steroid therapy;

- Allergy to polyethylene, polycarbonate urethane, polyethylene terephthalate or titanium;
- Current chemical dependency or significant emotional and/or psychosocial disturbance;
- Pregnancy;
- Severe muscular, neural or vascular diseases that endanger the spinal column;
- Missing bone structures due to severely deformed anatomy or congenital anomalies, that make good anchorage of the implant impossible;
- All concomitant diseases that can jeopardize the functioning and the success of the implant;
- Vertebral fractures;
- Treatment of the thoracic and cervical spine;
- Unilateral application of the Dynesys Spinal System.

Device Description

The Dynesys Spinal System consists of titanium alloy pedicle screws, polycarbonate urethane (PCU) spacers, and polyethylene terephthalate (PET) cords.



Pedicle Screws

The screws affix the system to the spine through pedicle attachment. They are manufactured from Ti-6Al-7Nb wrought alloy. They have self-tapping threads and a large “eye” with a set screw for attachment of the cord. The screws come in 20 sizes, and are placed lateral to the facet joints. Two or three screws are used on each side of the bilateral construct for one-level and two-level applications respectively.

Screw Sizes: Diameter x Length				
5.2mm x 35mm	6.0mm x 50mm	6.4mm x 50mm	7.2mm x 45mm	8.0mm x 40mm
6.0mm x 35mm	6.4mm x 35mm	6.4mm x 55mm	7.2mm x 50mm	8.0mm x 45mm
6.0mm x 40mm	6.4mm x 40mm	7.2mm x 35mm	7.2mm x 55mm	8.0mm x 50mm
6.0mm x 45mm	6.4mm x 45mm	7.2mm x 40mm	8.0mm x 35mm	8.0mm x 55mm

Note: Bolded sizes were used in the IDE study. Non-bolded sizes are newly proposed in this PMA.

Cords

The cord connects to the pedicle screws (by passing through the eyes of each screw) and runs through the center of the spacer component. The cord is locked and secured via set screws located in the heads of the pedicle screws. In addition to holding the components together, the cord is designed to provide tension to counteract flexion movement. The cords are manufactured from polyethylene-terephthalate (PET). Cords are available in lengths of 100mm and 200mm and are cut to the appropriate length. One cord is used on each side of the bilateral construct.

Spacers

The spacers are positioned between the heads of the pedicle screws to maintain the superior-inferior distance between the screws, and are designed to allow the cord to run through the center. The intended function of the spacer is to allow the construct to resist compressive loads while stabilizing the spinal segment without fusion. The spacers are manufactured from polycarbonate-urethane (PCU) and come in a 45mm length that is then cut by the surgeon to the appropriate size. One or two cords are used on each side of the bilateral construct for one-level and two-level applications, respectively.

Materials:

The spacers are manufactured from Corethane® 55D, which is a polycarbonate-urethane supplied by The Polymer Technology Group, Inc.

The cords are manufactured from polyethyleneterephthalate (PET).

The pedicle screws and set screws are manufactured from Ti-6Al-7Nb wrought alloy, Protasul 100® per ISO 5832:11¹.

Regulatory History:

The Dynesys Spinal System is also cleared for marketing in the United States when indicated for posterior fixation as an adjunct to fusion (through the 510(k) process in K031511, K045365, K060638, K071879, and K073347).

¹ ISO 5832:11 – Implants for Surgery-Metallic Materials-Part 11: Wrought Titanium 6-Aluminum 7-Niobium Alloy.

NON-CLINICAL DATA

Bench Testing:

The following mechanical bench tests were performed on the Dynesys Spinal System:

Construct Tests:

- Static Tension
- Static Torsion
- Static Shear
- Static Compression Bending
- Dynamic Compression-Tension
- Dynamic Torsion
- Dynamic Shear

Component Testing:

- Screw Fatigue Testing
- Static Cord-Screw Pullout Testing
- Dynamic Cord-Screw Pullout Testing
- Creep of PET Cord
- Cord Stress Relaxation
- Creep Behavior of PCU Spacer

Acceptance Criteria:

The sponsor outlined the following general acceptance criteria for the testing conducted:

- The static and dynamic strength of the cord and screws should exceed the strength of the facet capsular ligament: 250N².
- The static and dynamic compressive strength of the spacer and screws should exceed 300N, which are the worst case compressive loads reported in instrumented posterior fixation systems^{3, 4}.

Static Tension Testing

Static tension testing was performed on six bilateral constructs per ASTM F1717⁵. The test blocks were fixed to prevent bending (in flexion/extension). A spacer length of 22.5mm was used. Cords were cut with an overhang length of 10mm at each end. Testing was done in Ringer's solution at 37°C.

Results:

The mean failure load was 2090 ± 114.7N. The mean stiffness was 107.3 ± 14.1 N/mm.

² White AA, Panjabi MM. Clinical Biomechanical of the Spine, 1990, Second Edition, p. 22.

³ Rohlmann A, Bergmann G, Graichen F. Loads on internal spinal fixators measured in different body positions. *Eur Spine J.* 1999;8(5):354-9.

⁴ Rohlmann A, Bergmann G, Graichen F. Loads on an internal spinal fixation device during walking. *J. Biomechanics.* 1996: 30(1): 41-47.

⁵ ASTM F1717 – Standard test methods for spinal implant constructs in a vertebrectomy model

Static Torsion Testing

Static torsion testing was performed on six bilateral constructs per ASTM F1717. The test blocks were fixed to prevent bending (in flexion/extension). A spacer length of 22.5mm was used. Cords were cut with an overhang length of 10mm at each end. Testing was done in Ringer's solution at 37°C.

Results:

The mean failure torque was 62.97 ± 2.02 Nm. The mean stiffness was 2.10 ± 0.07 Nm/°.

Static Shear Testing

Static shear testing was performed on six bilateral constructs using a modified ASTM F1717 test setup. The test blocks were fixed to prevent bending (in flexion/extension). A spacer length of 22.5mm was used. Cords were cut with an over length of 10mm at each end. Testing was done in Ringer's solution at 37°C. Testing was conducted at 25mm/min.

Results:

The mean failure load was 2749 ± 131.1 N. The mean stiffness was 77.69 ± 6.23 N/mm.

Static Compression Bending Testing

Static compression bending testing was performed on six bilateral constructs per ASTM F1717. The spacer length used was 30mm. Specimens were preconditioned for 8 hours in Ringer's solution at 37°C. Testing was conducted at 25N/mm.

Results-

The average static compression yield load was 9.08 ± 0.73 N. The average stiffness was 1.10 ± 0.07 N/mm.

Compression-Tension Fatigue Testing

Seven constructs were tested using an ASTM F1717 test setup. Test blocks were not allowed to rotate (in flexion/extension). The spacer length used was 30mm. Testing was done at a frequency of 2Hz. Fixation torque was 4Nm. Spacers were pre-tensioned to 300N. Testing was done in Ringer's solution at 37°C. The system was fatigued in compression/tension under displacement control of ± 1.5 mm.

Results:

All constructs survived 10 million cycles of fatigue testing at ± 1.5 mm.

Average loads associated with the ± 1.5 mm of displacement at 5 million and 10 million cycles were +472/-396N and +236/-184N, respectively.

Shear Fatigue Testing

Ten assemblies were constructed consisting of two 5.2mm (diameter) screws, one 22.5mm spacer, and one cord tensioned approximately 300N and tightened with a 6Nm tightening torque trimmed at least 10mm from each screw. Five assemblies were tested

in distilled water at 37°C and five assemblies were tested in soybean oil at 37°C. Testing was conducted in displacement control ($\pm 5\text{mm}$) at a frequency of 2Hz.

Results:

Each specimen survived 10 million cycles of testing. No cord rupture or cord pullout was noted during testing. Minor screw indentations were observed in the ends of the spacers.

Average loads associated with the $\pm 5\text{mm}$ of displacement at 5 million and 10 million cycles were $+305\text{N}/-206\text{N}$ and $+281/-196\text{N}$, respectively.

Torsion Fatigue Testing

Six assemblies were tested that consisted of: two pedicle screws, one spacer (22.5mm long) and one cord. Set screws were tightened to 6.0Nm with a minimum of 5mm cord overhang on both sides. Assemblies were tested in soybean oil at 98°F. The assemblies were tested in rotation control of $\pm 3^\circ$ to 10 million cycles at 3Hz.

Results:

At the end of 10 million cycles, no devices had failed and all components were intact.

Average torques associated with the $\pm 3.0^\circ$ of angular displacement at 5 million cycles and 10 million cycles were $+4.09/-4.27\text{Nm}$ and $+3.25/-3.22\text{Nm}$, respectively.

Fatigue Testing of the Pedicle Screw:

The 5.2mm and 6.0mm diameter screws were tested in fatigue. The screws were inserted into test blocks consisting of an outer shell made of CEVOLIT (a duroplastic intended to mimic cortical bone) and a core made of EMA (a polyurethane foam meant to mimic cancellous bone). The screws were left proud 10mm (distance between the test block and the centerline of the eye of the screw head). Cyclic loading was applied down the centerline of the eye of the screw head between $F_{\text{max}} = 800\text{N}$ and $F_{\text{min}} = 100\text{N}$ at 6Hz. Testing was conducted in Ringer's solution at 37°C.

Results-

Both the 6.0mm and 5.2mm diameter pedicle screw passed 5 million cycles under the cyclic load applied.

Static Pullout Testing of Cord-Screw Connection:

Static pullout tests were conducted to determine the influence of the set screw tightening torque on the connection strength between the cord and the screw. Tests were carried out in two configurations: (1) with the cord cut flush above the pedicle screw and (2) with the cord cut with a 10mm overhang. The effective length of the cord was 40mm. Testing was conducted in Ringer's solution at room temperature. A total of 36 constructs were tested; three constructs were tested in each cord condition at each of the following tightening torques: 2Nm, 3Nm, 4Nm, 5Nm, 6Nm, 7Nm. Testing was conducted at 60mm/min.

Results-

The following table shows the mean pullout loads for each of the tightening torques in each cord configuration (overhang or flush).

Tightening Torque (Nm)	10mm Overhang Mean Pullout Load (N)	Flush Mean Pullout Load (N)
2Nm	650 ± 22	585 ± 69
3Nm	824 ± 43	772 ± 31
4Nm	1059 ± 101	1042 ± 35
5Nm	1197 ± 93	1222 ± 69
6Nm	1219 ± 78	1274 ± 41
7Nm	1312 ± 75	1424 ± 93

Test results from the static pullout testing were used to help formulate recommendations to the surgeon for set screw torque (4Nm) and cord configuration (overhang, 10mm).

Dynamic Pullout Testing of Cord-Screw Connection

Dynamic tension tests were performed under cyclic tensile loads between $F_{max} = 800N$ and $F_{min} = 100N$ at 6Hz. Testing was conducted in Ringer’s solution at 37°C. The effective length of the cord was 40mm. The set screw torque used was 4Nm (the set screw torque recommended in the surgical technique). Testing was run until pullout of the cord or until 5 million cycles was reached. If the construct ran out to 5 million cycles, the torque necessary to loosen the set screw was reported. A total of three constructs were tested.

Results-

All three constructs reached 5 million cycles without failure. The net displacement during the test stayed at approximately 1mm through the test, but the starting displacement shifted 0.29mm, 0.78mm and 0.49mm, respectively for each construct. These values indicate the amount the cord slipped in the screw during testing. Loosening torques were 1.7Nm, 1.5Nm, and 1.9Nm, respectively.

Creep Testing of the PET Cord

Six PET cords were mounted between clamps with a clamping torque of 6.75Nm. Testing was conducted in Ringer’s solution at 37°C. Cords were preconditioned for 8 hours and then pre-cycled for 10 cycles between 0N and 300N at a rate of 50N/s. Cords were then left under a 300N load for 20 hours. Time, displacement and load were measured and recorded.

Results-

The six cords exhibited an average viscoelastic elongation of $1.27 \pm 0.05\%$.

Stress Relaxation Testing of the PET Cord

Six PET cords were mounted between clamps with a clamping torque of 6.75Nm. Testing was conducted in Ringer’s solution at 37°C. Cords were preconditioned for 8 hours and then pre-cycled for 10 cycles between 0N and 300N at a rate of 50N/s. Cords

were then left in a displacement controlled environment under an initial load 380N load for 7 days (168 hours). Time, displacement and load were measured and recorded.

Results-

After 24 hours the average load was 53.9% of the initial load. After 168 hours the average load was 47.3% of the initial load. Therefore, 87% of the stress relaxation occurred within the first 24 hours.

Creep Testing of the PCU Spacer

A total of thirteen 28mm (length) PCU spacers were tested. Testing was performed under constant loads of 300N and 380N. Ten specimens were tested under a 380N load: four were tested in 37°C Ringer's solution, three were tested in 23°C Ringer's solution, and three were tested in air at 23°C. These ten specimens were tested out to 24 hours. Three specimens were tested under a 300N test and all were tested in 37°C Ringer's solution. These three specimens were tested out to seven days (168 hours).

Results of 380N test-

Results neared the asymptote by 24 hours. The specimens in the 37°C Ringer's solution group deformed between 6mm and 7mm (21% - 25%). The specimens in the 23°C Ringer's solution group deformed between 5mm and 5.5mm (17.5% - 19.5%). The specimens in the 23°C air group deformed between 4.5mm and 5.0mm (16% - 17.5%).

Results of 300N test-

All three devices appeared to reach an equilibrium value and deformed approximately 6mm (21%) in the seven days.

Deformation and Recovery Test of the PCU Spacers

The 45mm spacer was cut in half (22.5mm). Five 22.5mm (length) spacers were tested under a 450N load for seven days. Testing was conducted in Ringer's solution at 37°C. The samples were placed under a preload of 10N and displacement was set to zero. The specimens were placed under a 450N load for seven day (168 hours) while time, displacement and load were measured. The specimens were then relieved back to 10N for 24 hours. After 24 hours, the specimens were removed from the test machine and left in Ringer's solution for six additional days with length measurements taken every 24 hours.

Results-

The five specimens exhibited an average total creep of $33.9 \pm 0.8\%$ after seven days under the 450N load. After the specimens were unloaded to 10N they immediately recovered to an average creep of $15.8 \pm 0.5\%$. After 24 hours under a 10N load, the specimens continued to recover to an average creep of $11.6 \pm 1.0\%$. After an additional six days after removal from the test machine, specimens recovered to an average creep of $5.9 \pm 1.3\%$.

Wear Evaluations

The dynamic mechanical tests were not set up to evaluate wear debris. However, any obvious or significant wear debris would have been observed and noted during and after testing. Debris was noted in only the shear fatigue testing. The material was retrieved at the completion of the test and subjected to analysis. The results of the analysis indicated the material was composed of calcium, carbon and oxygen and was not associated with the test sample materials.

Biomechanical Evaluation Using Calf Spines:

Twelve fresh-frozen calf lumbar spines (L1-L5) were used. Spines were mounted on an MTS machine configured to allow six degree of freedom motion. Throughout testing, spines were kept between 35°C and 41°C. Intact spines were tested in flexion, extension, left and right lateral bending and axial rotation. Subsequently, six spines were instrumented with the Dynesys and six spines were instrumented with the Silhouette at L3-4. Instrumentation was applied using the manufacturer’s recommended techniques. Instrumented spines were then tested in flexion, extension, left and right lateral bending and axial rotation.

Results:

The following table shows the range of motion values observed in each motion type for each spine condition.

		Left/Right Axial Rotation	Flexion/Extension	Left/Right Lateral Bending
Dynesys	Intact ROM (degrees)	2.33 ± 0.50	3.93 ± 1.84	8.55 ± 1.43
	Instrumented ROM (degrees)	2.79 ± 0.82	2.06 ± 0.95	0.78 ± 0.22
	Intact Stiffness (Nm/degree)	5.47 ± 1.43	4.90 ± 2.84	1.54 ± 0.44
	Instrumented Stiffness (Nm/degree)	5.10 ± 2.97	9.80 ± 4.04	20.32 ± 6.68
Silhouette	Intact ROM (degrees)	1.56 ± 0.39	4.11 ± 0.45	8.11 ± 2.50
	Instrumented ROM (degrees)	1.83 ± 0.42	1.71 ± 1.33	0.98 ± 0.35
	Intact Stiffness (Nm/degree)	10.88 ± 8.52	3.45 ± 0.64	1.65 ± 0.47
	Instrumented Stiffness (Nm/degree)	7.10 ± 1.85	11.71 ± 4.31	16.50 ± 5.05

BIOCOMATIBILITY AND MATERIAL CHARACTERIZATION

Physicochemical Testing of PCU Spacers:

Physicochemical testing was performed on the PCU spacer to determine the presence of extractables using both pure water extract and isopropyl alcohol extract methods.

Purified Water:

Test samples were prepared with a ratio of 2g of sample to 10ml of Purified Water. The samples were extracted in 50°C for 72 hours. No significant extractables were noted for either the test articles. The infrared analysis results for the water extract samples exhibited a spectrum that was further characterized with the infrared isopropyl alcohol extract analysis.

Isopropyl Alcohol:

Test samples were prepared using a ratio of 2g of sample to 10ml of isopropyl alcohol. The samples were extracted at 50°C for 72 hours. The physicochemical attributes for the test samples are described as follows: NVR (13mg) and UV absorption (OD 3.335 at a maximum wavelength of 250nm). The higher absorbance, at the lower wavelength, indicated a non-volatile residue of 13mg. The non-volatile residue was further characterized, by conducting an infrared (FTIR) spectrum analysis, to be polyethylene carbonate.

Physicochemical Testing of PET Cords:

Physicochemical testing was performed on the PET cords to determine the presence of extractables using both pure water extract and isopropyl alcohol extract methods.

Purified Water:

Test samples were prepared with a ratio of 2g of sample to 10ml of Purified Water. The samples were extracted in 50°C for 72 hours. No significant extractables were noted through FTIR analysis. The infrared analysis of the Purified Water extract exhibited a spectrum that could not be identified. Additional infrared analysis was performed on the alcohol extract samples for further characterization.

Isopropyl Alcohol:

Test samples were prepared using a ratio of 2g of sample to 10ml of isopropyl alcohol. The samples were extracted at 50°C for 72 hours. The physicochemical attributes of the cord extract are described as follows: NVR (<1mg) and UV absorption (OD 1.151 maximum wavelength 240nm). The interim spectra results indicated the presence of a plasticizer. Follow-up analysis using gas chromatography and mass spectroscopy further characterized the plasticizer as a non-volatile residue butyl stearate. The amount extracted in the analysis was considered to be very low (0.9µg/mL).

The following table summarizes the biocompatibility testing performed on the PET and PCU materials per *ISO 10993 - Biological evaluation of medical devices*.

Biocompatibility Test	Applicable Standard	Acceptance Criteria	PET (Cord) Results	PCU (Spacer) Results
Cytotoxicity Testing: MEM Elution using L-929 mouse fibroblast cells Cultures evaluated at 24, 48 and 72 hours	ISO 10993-5 ⁶ :1999	Grade of 0, 1, or 2 (non-toxic)	Grade 0 for all samples. Non-toxic Pass	Grade 0 for all samples. Non-toxic Pass ⁷
Acute Systemic Toxicity Testing 0.9% Normal Saline (NS) and Cottonseed Oil Animals observed at 4, 24, 48, and 72 hours post injection	ISO 10993-11 ⁸ :1993 ISO 10993-12 ⁹ :1996	Test injected must show ≤ biological reaction than that of the control mice. Less than 2 mice show signs of toxicity. Less than 3 mice loose > 2 grams	Negative signs of toxicity and no weight loss of > 2 grams. Pass	Negative signs of toxicity. One mouse had > 2 gram weight loss. Pass
Irritation Testing Using 0.9% Normal Saline and Cottonseed Oil Injection sites examined at 24, 48 and 72 hours.	ISO 10993-10 ¹⁰ :1995 ISO 10993-12:1996	Mean Primary Irritation Index Score of 0 to 0.4 (Negligible) Non-Irritant	Primary irritation score for all animals equal to 0. Irritation Category Response equal to 0. Non-Irritant Pass	Primary irritation score for all animals equal to 0. Irritation Category Response equal to 0. Non-Irritant Pass

⁶ ISO 10993-5 – Biological evaluation of medical devices – Part 5: tests for in vitro cytotoxicity.

⁷ Cytotoxicity testing was also performed on the Titanium alloy material and was found to be non-toxic

⁸ ISO 10993-11 – Biological evaluation of medical devices – Part 11: tests for systemic toxicity

⁹ ISO 10993-12 – Biological evaluation of medical devices – Part 12: sample preparation and reference materials

¹⁰ ISO 10993-10 – Biological evaluation of medical devices – Part 10: tests for irritation and delayed-type hypersensitivity

Biocompatibility Test	Applicable Standard	Acceptance Criteria	PET (Cord) Results	PCU (Spacer) Results
<p>Mutagenicity Testing (Ames Assay)</p> <p>Five strains of Salmonella typhimurium (TA97a, TA98, TA100, TA102, TA1535)</p> <p>0.9% saline dimethylsulfoxide</p>	<p>ISO 10993-12:1996</p> <p>ISO 10993-3¹¹:1993</p>	<p>Less than a two-fold increase in the number of revertant colonies per plate over the mean vehicle for each strain.</p>	<p>Less than a two-fold increase for each strain.</p> <p>Non-mutagenic</p> <p>Pass</p>	<p>Less than a two-fold increase for each strain.</p> <p>Non-mutagenic</p> <p>Pass</p>
<p>Sensitization Testing (Guinea Pig)</p> <p>0.9% Normal Saline and Cottonseed Oil</p> <p>Dermal patch sites observed at 24, 48 and 72 hours post patch removal</p>	<p>ISO 1093-10:1995</p> <p>ISO 10993-12:1996</p>	<p>Grade less than 1 or no dermal inflammatory response greater control.</p> <p>Using the Magnusson-Klingman model, Grade 1, Class “Weak” allergenicity rating</p>	<p>None of the test articles exhibited a sensitization response greater than zero.</p> <p>Normal saline extracts of the test material overall showed a 0% sensitization response.</p> <p>Classified as a Grade 1 “Weak” sensitizer.</p> <p>Pass</p>	<p>None of the test articles exhibited a sensitization response greater than zero.</p> <p>Normal saline extracts of the test material overall showed a 0% sensitization response.</p> <p>Classified as a Grade 1 “Weak” sensitizer.</p> <p>Pass</p>
<p>Pyrogenicity Testing (Rabbit)</p> <p>0.9% Normal Saline</p>	<p>ISO 10993-11:1993</p> <p>ISO 10993-12:1996</p>	<p>No temperature difference less than or equal to 0.5°C from baseline 1-3 hours post injection.</p>	<p>No animals with the test article extract exhibited a temperature rise of more than 0.5°C during the three-hour period.</p> <p>Non-Pyrogenic</p> <p>Pass</p>	<p>No animals with the test article extract exhibited a temperature rise of more than 0.5°C during the three-hour period.</p> <p>Non-Pyrogenic</p> <p>Pass</p>
<p>Mammalian Cell Mutation Testing – Genotoxicity (Mouse Lymphoma Assay)</p> <p>0.9% Normal Saline and Dimethylsulfoxone</p>	<p>ISO 10993-3:1993</p> <p>ISO 10993-12:1996</p>	<p>Non-mutagenic if the test article dosed culture has a mutant frequency < two times that of the solvent control culture.</p>	<p>Each extract was determined to be non-mutagenic</p> <p>Non-mutagenic</p> <p>Pass</p>	<p>Each extract was determined to be non-mutagenic</p> <p>Non-mutagenic</p> <p>Pass</p>

¹¹ ISO 10993-3 – Biological evaluation of medical devices – Part 3: tests for genotoxicity, carcinogenicity and reproductive toxicity

Biocompatibility Test	Applicable Standard	Acceptance Criteria	PET (Cord) Results	PCU (Spacer) Results
Chromosome Aberration Analysis (Chinese Hamster Ovary) 0.9% Normal Saline and Dimethylsulfoxone	ISO 10993-3:1993 ISO 10993-12:1996	Non-mutagenic if the p value >0.05 for the test article as compared to the negative control for aberration rates.	For each extract no statistically significant increase in aberration rates were observed for both the test article and negative control. Non-Mutagenic Pass	For each extract no statistically significant increase in aberration rates were observed for both the test article and negative control. Non-Mutagenic Pass
Subcutaneous Implantation Test Observations at 56 Days and 84 Days	ISO 10993-6 ¹² :1995 ISO 10993-12:1996	The difference between the average test score minus the average control score equals the encapsulation score. Determine to be a non-irritant if the difference is equal to zero.	All animals exhibited overall histopathology score differences of zero. Based on these findings the material was considered a non-irritant. Non-Irritant Pass	All animals exhibited overall histopathology score differences of zero. Based on these findings the material was considered a non-irritant. Non-Irritant Pass

Particulate Testing in Rabbit Model (PCU, PET)

The purpose of this testing was to evaluate the local and systemic effects of PCU and PET particulate when implanted on the dura in a rabbit model. This testing was done by NAMSA Laboratories of Northwood, Ohio.

PET particulate was created using a combination of hammer and jet milling. Sizing characterization showed the PET particulate to be in the size range of 0.656µm to 22.83µm with 79% being less than 10µm. PCU particulate was created via cryogenic attrition milling. Sizing characterization showed the PCU particulate to be in the size range of 17.4µm to 1019.5µm with 90% less than 517µm.

A total of 68 rabbits were evaluated: 18 PET, 18 PCU and two 16 animal control groups. Animals were implanted with approximately 1 million particles (1mg) of either the PET or PCU particulate implanted on the dura at L2-L3. Animals were sacrificed at 48 hours, 2, 4, 8 and 12 weeks after implantation.

Heart, lungs, liver, spleen, thymus, kidneys, adrenal glands, mesenteric lymph nodes, submandibular lymph nodes, gonads, implantation sites, brains were weighed, and processed for histopathologic evaluations. Complete spinal segments and associated soft

¹² ISO 10993-6 – Biological evaluation of medical devices – Part 6: tests for local effects after implantation

tissues were excised from T10 to S1 and processed for evaluation. Polarized light microscopy was used to identify any polymer particles within a tissue slide. Inflammation scores and migration scores were established by the pathologist based on a numerical scale and toxicity index was calculated by adding the inflammation score to the migration score. A subjective analysis was done at the implant site for residual polymer debris and hemorrhage. The test article-tissue interface analysis was graded based on the ISO 10993-6 guidelines.

Results-

PET: The amount of tissue response did not change in severity throughout the study period. The response to the PET particles was a foreign body response that was limited, restricted and non-progressive. There was no evidence of local or systemic migration of PET particles during the study. The particles did not generate any immunological response such as the induction of osteolysis. In addition, no systemic toxicity was observed due to the PET particulate debris. The amount and quality of healing of the test and control animals were similar and appropriate for each study interval.

PCU: There was no tissue response to PCU wear particles at 48 hours. At 2 weeks post-implantation, a minor response was present. The PCU particle-tissue interface consisted of a very narrow rim of fibrous tissue that was indistinguishable from the appropriate healing process of the surgical site. The interface was infiltrated by low numbers of macrophages and very low numbers of giant cells. The response to the PCU particles resolved over time and was very minor at 12 weeks post-implantation. There was no progression of the response to the particles such as the presence of individual lymphocytes and plasma cells or the formation of lymphocytes and plasma cells aggregates as observed in periprosthetic tissues from failed hip or knee replacements. The stimulus for forming biologically relevant numbers of giant cells or aggregates of macrophages was not present in this study. Accordingly, the response to the PCU particles was classified as a very minor foreign body response that was limited, restricted, and nonprogressive. There were no biologically significant differences between the test and control laminectomy sites. There was no evidence of local migration of the particles at any of the study intervals. No test article particles were intracellular. The tissues peripheral to the test site including skeletal muscle, vertebral bone, bone marrow stromal elements, hematopoietic tissue, epidura, dura, spinal cord, and the interarcuate ligament failed to demonstrate any test related alterations. All alterations noted in these tissues were due to the surgical procedure.

There was no evidence of systemic migration of the test article particles in the soft tissues examined at any study interval evaluated. All spontaneous background lesions were evaluated with polarized light and all failed to reveal the presence of birefringent material (such as PCU particles). No alterations consistent with toxicity were observed in this study. There was no evidence of systemic toxicity in this study (overall toxicity score for test animals was 0). Also, there was no evidence of systemic distribution of PCU particles (systemic migration score of 0) and no evidence that the particles migrated from the surgical site (local migration score of 0). The test article was determined to be a non-irritant.

FDA will be asking you to discuss the adequacy of the preclinical testing as provided by the sponsor as an assessment of the long term function, biocompatibility and bio-durability of the Dynesys Spinal System and provide any additional testing recommendations.

STERILIZATION

The Dynesys Spinal System implants (screws, cords and spacers) are provided as sterile implants with a sterility assurance level (SAL) of 10^{-6} . Implants are sterilized using gamma irradiation at 25kGy. The sterilization technique is in accordance with the following standards:

- EN 552-Sterilization of medical devices-Routine control of sterilization by irradiation,
- EN 556-Sterilization of medical devices-Requirements for medical devices to be designated "STERILE".
- ISO11137 Sterilization of health care products-Requirements for validation and routine control-Radiation sterilization.
- ISO Technical Report 13409 - Sterilization of health care products radiation sterilization-substantiation of 25 kGy as a sterilization dose for small or infrequent production batches.

The sponsor is proposing a five year shelf life and has provided real time testing to support the requested shelf life.

EXPLANT EVALUATION

Explant analysis was performed on parts from four revision surgeries with *in vivo* durations ranging from nine to 19 months. The explanted parts included 17 pedicle screws, 10 PCU spacers and 14 PET cords. Analysis of the retrieved parts was performed using the following techniques/equipment:

- Visual inspection under light and low powered optical microscope
- Measurements taken using calipers
- Scanning electron microscopy (SEM)
- Attenuated total reflection Fourier transform infrared (ATR-FTIR)
- Gel permeation chromatography (GPC)

Results:

Screws: Visual inspection and SEM of the screws showed that all pedicle screws were scratched on the head and the threads of all set screws were slightly damaged. Attached residual bone tissues were also noted on the screws.

PCU Spacers: Visual inspection and SEM of the spacers showed that all spacers exhibited damages such as cuts and scratches. Imprints of the pedicle screws heads were present on the front surfaces with one spacer showing slight wear marks on the front surface instead of an imprint. Permanent bend along the longitudinal axis was evident in nine of ten spacers. Imprints of contacts with the cord were visible along the inner wall of the spacers. Small localized wear zones were found on the outer surfaces of eight out of ten spacers. All worn areas had primarily wavy surface features. ATR-FTIR showed very little change at the surfaces of the explanted spacers while nearly no change was observed at 100 μ m below the surface. The GPC analyses of the PCU spacer showed differences of molecular weights among ten retrievals and two references. This was hypothesized to be due to variability from lot to lot or within the same lot, in-vivo effects, or measurement error (5%).

PET Cords: Visual inspection and SEM of the cords showed that the connection site between screws and cords could not be identified clearly in all explanted cords. Damages such as broken single fibers or bundles of fibers were found in some cords. ATR-FTIR gave no indication of structural chemical changes due to biodegradation in the explanted cords. GPC results indicated no decrease in molecular weight at the outer surface and in the central fibers of the explanted cords.

Investigator's Conclusions:

The biostability of the PCU spacers and PET cords was supported by the findings of this evaluation.

CLINICAL STUDY DESCRIPTION

Purpose:

As stated in the IDE investigational plan, the purpose of this clinical study was to demonstrate the safety and effectiveness of the Dynesys Spinal System for patients requiring 1- or contiguous 2-level posterior spinal stabilization of the lumbar, and/or sacral spine following decompression. The ability for this implant to maintain spinal alignment and non-fusion of spinal segments, while positively affecting clinical outcomes, was assessed and compared to a posterior lateral spinal fusion (PLF) procedure using autogenous bone with a rigid, polyaxial posterior spinal fixation system (Silhouette Spinal Fixation System). The primary safety objectives were assessed by evaluating all patients for major complications and additional surgical intervention through 24 months, and neurological success based on the results from neurological assessments at 24 months. The primary efficacy objectives were assessed by evaluating all patients for leg pain success, based on patient pain reported on a 100 mm Visual Analog Scale (VAS) at 24 months and functional success based on results from the Oswestry Disability Index at 24 months. Note that although the IDE study purpose specified that the Dynesys was to be used following decompression, the Indications for Use and study inclusion/exclusion criteria specified that patients may require decompression at the levels considered for treatment and not all patients in the clinical study had a concomitant decompression.

Study Design:

The sponsor provided data from the multi-center, prospective, randomized, concurrently controlled, non-blinded, non-inferiority trial of the Dynesys Spinal System compared to posterolateral spinal fusion using autogenous bone with a posterior pedicle screw system (Silhouette Spinal Fixation System) in patients with radiculopathy and degenerative spondylolisthesis or retrolisthesis (up to Grade I), spinal stenosis or other stenosing lesion as defined in the study inclusion/exclusion criteria outlined below.

The original study design was approved for 399 patients at 30 sites (266 Dynesys, 133 Silhouette); however, the final study design sample size (after revisions to the statistical plan including specification of a 15% non-inferiority margin) was based on 184 Dynesys and 92 Silhouette patients.

368 patients were randomized and implanted at 26 clinical centers in the United States by 70 surgeons with 367 evaluated after 1 Dynesys patient was excluded for 3-level treatment for a total of 253 Dynesys and 114 Silhouette patients. An additional 28 non-randomized, Dynesys patients were studied as initial cases (one per active center) and are referred to as the Dynesys training cohort throughout this summary. The first surgery was performed on March 3, 2003.

Individual patient success (i.e., overall success) was determined at 24 months and was defined as a composite endpoint. A patient was considered a success if all of the following criteria were met:

- Leg Pain – improvement of at least 20mm on a 100mm Visual Analog Scale (VAS) from baseline level at 24 months
- Function – improvement of at least 15 points on the Oswestry Disability Index (ODI, version 2) graded on a 100 point scale at 24 months as compared to baseline;
- Maintenance or improvement in four neurological assessments (motor function, sensory function, reflexes, and straight leg raise) with no new permanent neurological deficits as compared to baseline at 24 months;
- Absence of major complications defined as major blood vessel injury, neurological damage, or nerve root injury over the first 24 postoperative months;
- Freedom from additional surgical intervention defined as revision, reoperation, removal or supplemental fixation/fusion at the affected level over the first 24 postoperative months.

There were no radiographic endpoints included in the evaluation of overall success.

The study was considered a success if the Overall Success Rate for Dynesys was determined to be non-inferior as compared to the Overall Success Rate for Silhouette.

Inclusion/Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> • Patients having degenerative spondylolisthesis or retrolisthesis (up to Grade I) <p>AND/OR</p> <ul style="list-style-type: none"> • Patients having lateral or central spinal stenosis or other stenosing lesion as diagnosed by radiculopathic signs, neurogenic claudication or imaging studies; • Candidate for single-level or contiguous two-level PLF between L1-S1; • Patients have a predominate component of leg rather than back symptoms; symptoms include pain, muscle weakness, and/or sensation abnormality as evidenced by patient history and diagnostic studies. • Patients may require decompression at the levels considered for treatment • Pre-operative leg pain score ≥ 40 mm on a 100 mm Visual Analog Scale (VAS); • Leg pain must be unresponsive to conservative (non-surgical) management for a minimum of 3 months; • Pre-operative Oswestry score ≥ 30 indicating at least moderate disability; • Skeletally mature individual between ages 20 and 80; • Must be willing and able to comply with study requirements; including willing and able to sign a study-specific, IRB-approved informed consent form, complete necessary study paperwork and return for required follow-up visits. 	<ul style="list-style-type: none"> • Primary diagnosis of discogenic back pain at affected levels as evidenced by a larger back than leg pain component. In the event of multi-level pathology a discogram should be considered; • Patients with leg pain due to etiologies other than those listed above, such as trauma, peripheral vascular disease and neuropathy should be excluded; • Degenerative scoliosis $>10^\circ$ at the affected motion segment; • Supplemental interbody column support (e.g., bone graft, spacers or fusion cages) is planned at the affected level(s); • Greater than Grade I spondylolisthesis or retrolisthesis at the affected level(s); • Radiculopathic signs from more than two contiguous or two noncontiguous vertebral body segment(s); • Previous lumbar fusion attempt(s), previous total facetectomy or trauma at the affected level(s); • Gross obesity defined as exceeding ideal weight by greater than 40%; • Active local or systemic infection; • Advanced osteoporosis as evidenced by plain film radiographs or history of fractures and confirmed by DEXA scan of $< -2t$ for age group. All women over 50 and men over 60 should have a DEXA scan to confirm adequate bone density; • Receiving immunosuppressive or long-term steroid therapy; • Active hepatitis (viral or serum) or HIV positive,

	<p>renal failure, systemic lupus erythematosus, or any other significant medical conditions which would substantially increase the risk of surgery;</p> <ul style="list-style-type: none">• Documented history of titanium alloy, PET or PCU allergy, or intolerance;• Active malignancy or other significant medical comorbidities;• Current chemical dependency or significant emotional and/or psychosocial disturbance that may impact treatment outcome or study participation as evidenced by three or more positive Waddell Signs;• Pregnancy;• Incarceration;• Severe muscular, neural or vascular diseases that endanger the spinal column;• Missing bone structures, due to severely deformed anatomy or congenital anomalies, which make good anchorage of the implant impossible;• All concomitant diseases that can jeopardize the functioning and success of the patient;• Vertebral fractures;• Treatment of the thoracic and cervical spine;• Severely deformed anatomy due to congenital anomalies.• Paralysis
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Post-Operative Care

There was no specific postoperative regimen stipulated in the protocol for the Dynesys Spinal System IDE, as pre-IDE discussions with the potential Investigators for this trial suggested that the subjects would be drawn from a population appropriate for fusion and that the standard of postoperative care was established for this procedure.

Evaluations

Patients were evaluated preoperatively (within 2 months of surgery), intra-operatively, and postoperatively at 3 weeks, 3, 6, 12, and 24 months, and annually until the last patient was seen for the 24 month evaluation. Complications and adverse events were evaluated over the course of the clinical trial. At each evaluation time-point, the primary and secondary clinical and radiographic outcome parameters were evaluated. Success was determined from data collected during the initial 24 months of follow-up.

Evaluation	Preoperative – 2 Months	Immediate Postoperative/ Discharge	3- Week ± 2 Weeks	3- Month ± 3 Weeks	6- Month ± 4 Weeks	12- Month ± 2 Months	24- Month ± 2 Months
Physician Evaluations							
Neuro Exam	X		X	X	X	X	X
PROLO Eval	X		X	X	X	X	X
Adverse Events		X	X	X	X	X	X
Subject Self Evaluations							
PROLO	X		X	X	X	X	X
ODI							
VAS Leg Pain							
VAS Back Pain							
VAS Iliac Crest							
Surgery Satisfaction							
Surgery Recommendation							
Radiographs							
Neutral Lateral	X	X	X	X	X	X	X
Anterior/Posterior	X	X	X	X	X	X	X
Flexion/Extension	X				X	X	X

Adverse Events:

An adverse event was defined as any undesirable deviation from a patient’s baseline condition, to include all new conditions or symptoms, or a worsening of a pre-existing condition or symptom regardless of etiology. Pain, neurological and functional symptoms were considered adverse events when a patient’s complaint for any of these symptoms resulted in an unscheduled visit or when a patient presented with new or worsening pain, neurological and/or functional symptoms as compared to the previous visit.

All adverse events reported in the original Clinical Summary Report dated December 21, 2007 underwent review and were classified by an independent Data Safety Monitoring Board (DSMB) with respect to the severity (complication or observation) and the relatedness of each event. A complication was defined as an adverse event that required invasive treatment or hospitalization, or resulted in death or serious injury, and any complication was then further classified as a Surgery-related complication, a Device-related complication, or Other. An observation was defined as an adverse event that resolved by non-invasive means, required minimal or no intervention, and observations were not classified by relatedness. In the submission, the sponsor describes that any incremental adverse events not included in the submission of the original Clinical Summary Report which were not adjudicated by the DSMB for severity and relatedness. 19.7% (323/1642) of the adverse events were reviewed and adjudicated by Shamiram R. Feinglass, M.D., MPH, Vice-President of Global Medical Affairs for Zimmer Inc. Dr. Feinglass has not been directly involved in the collection of the data for this project and was blinded to the treatment for this review.

For secondary surgical interventions, the protocol specified that removal would constitute patient failure unless the patient was asymptomatic and remained so for the remainder of the study, reoperation and supplemental fixation would constitute patient failure in all cases, and other surgical procedures would not constitute patient failure unless they can be directly related to the implant. Applying this in a conservative manner, the sponsor considered all additional surgical interventions (revisions, reoperations, removals, and supplemental fixation/fusion procedures at the affected level over the first 24 postoperative months) as clinical study failures. All patients who underwent secondary surgical procedures were followed for the duration of the study but data was censored at time of failure.

Primary Study Assessments:

VAS Leg Pain: The assessment of pre- and post-operative leg pain was performed using scores determined from measurements of responses to the leg pain question provided on a 100 millimeter (mm) Visual Analog Scale (VAS). The anchor points were “No Pain” (i.e. 0mm) and “Severe Pain” (i.e. 100mm). Patients were instructed to draw a single line across the scale at the point that best described their level of pain. The leg pain VAS assessment was administered preoperatively as well as at each postoperative visit. Individual patient success was based on a postoperative improvement at 24 months of at least 20/100mm from the baseline assessment.

ODI: The Oswestry Disability Index (ODI) was used to assess function. The ODI questionnaire is based on a patient’s response to ten questions, which focus on pain intensity, personal care, lifting, walking, sitting, standing, sleeping, sex life, social life, and traveling. The sponsor calculated a score for a given patient when at least eight questions had a response. The responses to each question range from zero to five. A lower numeric score represents a better pain and disability status regarding that variable. A total ODI score is determined by adding the scores of the individual questions and dividing that total by the maximum possible total score (50 if all questions are answered). This yields a percentage. Therefore, ODI scores are presented ranging from 0% to 100%, with a lower percentage indicating less pain and disability. The ODI questionnaire was administered preoperatively as well as at each postoperative visit. Individual patient success was based on a postoperative improvement at 24 months of at least 15 points from the baseline assessment.

Neurological Status: A comprehensive neurological examination was performed preoperatively and at all post-operative follow-up visits to assess neurological status. Each neurological examination included motor (10 evaluations), sensory (10 evaluations), reflex (four evaluations), and straight leg raising (2 evaluations). Each component was assessed separately on each anatomical side (left, right). Postoperative changes in neurological scores as compared to preoperative scores were assigned to categories representing worse, maintained or improved scores. Neurological success was defined as maintenance or improvement in the four neurological assessments (motor function, sensory function, reflexes, and straight leg raise) with no new permanent neurological deficits as compared to baseline at 24 months.

Major Complications: A major complication defined as major blood vessel injury, neurological damage, or nerve root injury over the first 24 postoperative months constituted failure.

Additional Surgical Intervention: Additional surgical intervention defined as revision, reoperation, removal or supplemental fixation/fusion at the affected level over the first 24 postoperative months constituted failure.

Secondary Study Assessments:

- **VAS Back Pain:** Back pain was measured on a 100 mm VAS. Patients were instructed to draw a single line across the scale at the point that best described their level of pain. Postoperative improvement in back pain was classified as a clinical success when there was a reduction in back pain scores of 20 millimeters or more as compared to the preoperative score.
- **SF-12 Health Survey:** Quality of life was assessed using the SF-12 which is a multipurpose short-form Quality of Life instrument with 12 questions selected from the SF-36 Health Survey. The SF-12 is a normative based instrument with higher scores indicative of higher functioning/better health. The Physical Component Summary Score is a composite of the Physical Functioning, Role Functioning, Bodily Pain and General Health Scales within the SF-12 instrument. The Mental Health Component Summary Score is a composite of the Vitality, Social Functioning, Role-Emotional and Mental Health Scales within the SF-12 instrument.
- **VAS Iliac Crest Pain:** Iliac pain scores were expressed in millimeters, where a rating of 0 mm represented no iliac crest pain and 100mm represented severe iliac crest pain. Patients were instructed to draw a single line across the scale at the point that best described their level of pain.
- **Patient Satisfaction:** Patient satisfaction was assessed three ways. First, the NASS MODEMS satisfaction item was completed by the patient at each postoperative clinical assessment. The question was used to gain an overall patient satisfaction rating for the spinal surgery by asking whether the surgery met expectations, improved the condition enough that the patient would go through it again for the same outcome, helped the patient but he/she would not go through it again for the same outcome, or left the patient the same or worse as before surgery. Second, the assessment of post-operative satisfaction using a 100mm VAS was completed by the patient. Satisfaction scores were obtain from patient responses, and were expressed in millimeters (mm). The anchor points were “Not Satisfied” (i.e. 0 mm) and “Completely Satisfied” (i.e. 100 mm). Patients were instructed to draw a single line across the scale at the point that best described their level of satisfaction. Third, the assessment of post-operative recommendation using a 100mm VAS was completed by the patient where patients were asked to rate how likely they would be to recommend this procedure to a loved one with the same condition. Recommendation scores were obtained from patient responses, and were expressed in millimeters

(mm). The patient recommendation score was based on a ranking of 0 to 100 millimeters with a rating of 0mm representing the lowest recommendation and 100 mm representing the highest.

- **PROLO Economic and Function assessment:** PROLO economic and function items were administered for both the patient and physician assessments. The assessment required the patient and the investigator to individually provide one economic and one function outcome which described the current status of the study patient. Each outcome was assigned a score which ranged from 1 to 5; where 5 was the most favorable and 1 was the least favorable score. The two scores were added to calculate an overall economic/function score, which could range between 2 and 10, inclusively. Scores of 9 and 10 were classified as excellent, 7 and 8 were classified as good, 5 and 6 were classified as fair, and below 5 were classified as poor.
- **Segmental Stability Without Fusion (Dynesys Group Only):** Radiographic success in the Dynesys group was defined as meeting the definition of segmental stability without meeting the definition of fusion.

Segmental Stability was defined as angular motion:

- $< 15^\circ$ at L1-L2, L2-L3, or L3-L4; or
- $< 20^\circ$ at L4-L5; or
- $< 25^\circ$ at L5-S1

and

- Translational motion < 4.5 mm.

Fusion was defined as:

- Clear evidence of bridging bone; and
- Translational motion < 3 mm; and
- Angular motion $< 5^\circ$.

The magnitude of angular and translational motion and the presence of clear evidence of bridging bone were separately determined from available radiographs by two independent primary radiologists (with a third to adjudicate in instances of disagreement regarding bridging bone, rotation and translation at the index level).

- **Fusion (Silhouette Group Only):** Radiographic success in the fusion group was defined as meeting the definition of fusion.

Fusion was defined as:

- Clear evidence of bridging bone; and
- Translational motion < 3 mm; and
- Angular motion $< 5^\circ$.

The magnitude of angular and translational motion and the presence of clear evidence of bridging bone were separately determined from available radiographs by two

independent primary radiologists (with a third to adjudicate in instances of disagreement regarding bridging bone, rotation and translation at the index level).

- **Other Radiographic Assessments:** Other radiographic assessments were completed based on the review of plain radiographs and consisted of evaluations of motion (rotational and translational) and fusion at the treated level for the Dynesys and Silhouette groups, respectively. Rotational and translational adjacent level motion, overall lumbar alignment (Cobb angle, loss of lordosis, flatback or kyphotic segment, disc angle in the sagittal plane), percent spondylolisthesis, and disc height (anterior, posterior) were also evaluated. These quantitative measures were assessed by Medical Metrics of Houston, Texas. The qualitative radiographic review was completed by two independent radiographic reviewers. If there was disagreement regarding radiographic findings between the two reviewers (for bridging bone, rotation, and translation at the index level only), a third independent reviewer adjudicated the results.
- **Postoperative Medication Use:** The use of narcotic analgesics, non-narcotic analgesics, non-steroidal anti-inflammatory, steroidal anti-inflammatory, and “other” medication within each time of postoperative clinical assessment was assessed.
- **Works Status:** The proportion of patients working, not working due to back disability, and not working for reasons other than back disability were evaluated at each postoperative timepoint for each treatment group.

Primary Study Endpoint / Success Criteria:

The primary study endpoint (individual patient success) was determined at 24 months and was defined as a composite endpoint. A patient was considered a success if all of the following criteria were met:

- Leg Pain – improvement of at least 20mm on a 100mm Visual Analog Scale (VAS) from baseline level at 24 months
- Function – improvement of at least 15 points on the Oswestry Disability Index (ODI version 2) graded on a 100 point scale at 24 months as compared to baseline;
- Maintenance or improvement in four neurological assessments (motor function, sensory function, reflexes, and straight leg raise) with no new permanent neurological deficits as compared to baseline at 24 months;
- Absence of major complications defined as major blood vessel injury, neurological damage, or nerve root injury over the first 24 postoperative months;
- Freedom from additional surgical intervention defined as revision, reoperation, removal or supplemental fixation/fusion at the affected level over the first 24 postoperative months.

There were no radiographic endpoints included in the evaluation of overall success for either Dynesys or Silhouette.

The study was considered a success if the Overall Success Rate for Dynesys was determined to be non-inferior as compared to the Overall Success Rate for Silhouette. The original protocol specified a 10% non-inferiority margin (delta) which was subsequently modified to 15% in a supplement to the IDE; however, the sponsor also included analyses using the 10% non-inferiority margin in their PMA based on an understanding that FDA would be using the 10% delta in the primary safety and effectiveness analyses.

Statistical Analysis Plan:

Randomization and Blinding:

The randomization was in a 2:1 ratio of investigational to control patients and was blocked by study center with an initial block of size 3, followed by 7 blocks of length 6, followed by a block of length 3, and finally a block size of 6.

The lack of patient and surgeon blinding in this study is an important limitation of the study design and an unaddressed source of bias, although blinding was not achievable in this study due to the nature of the two devices. Although the sponsor states that they attempted to keep patients blinded until after surgery, the lack of blinding for the remainder of the study could have led to reporting bias among patients and investigators, potentially in favor of the investigational treatment, or perhaps against the control treatment. This may have been particularly problematic for subjective assessments such as patient reported outcomes.

Hypotheses to be tested:

This was a non-inferiority trial and a fixed non-inferiority margin of 10% was required by FDA. The sponsor's ultimate sample size (after revisions to the statistical plan) was based on a 15% non-inferiority margin.

The sponsor states that, "The primary study hypothesis is the proportion of patients classified as a clinical success at 24 months implanted with a Dynesys device is not clinically worse than the corresponding proportion implanted with the Silhouette device" [Statistical Analysis Plan, p. 5]. They provided the following statistical hypotheses:

$$H_0: \Pi_{\text{Dynesys}} - \Pi_{\text{Silhouette}} \leq -0.15$$

$$H_A: \Pi_{\text{Dynesys}} - \Pi_{\text{Silhouette}} > -0.15$$

Superiority following successful non-inferiority was not tested by the sponsor.

Statistical Methodology:

The sponsor used 90% confidence intervals derived using large sample normal approximation for the purpose of assessing the primary non-inferiority outcome. The sponsor also made routine use of standard tests such as Student t-tests, Fisher's Exact test and likelihood ratio chi-square tests to test for significant differences between groups. Note in this regard that failure to establish a significant difference does not prove equivalence, particularly for small sample sizes.

CLINICAL STUDY RESULTS

Patient Accounting:

The IDE study database was initially closed on September 20, 2007, but was reopened for additional data entry on November 6, 2008 in order to respond to deficiencies from FDA. It was again closed on March 13, 2009.

The randomized controlled clinical trial generated study patients identifiers for 467 patients. Of these 368 were implanted with a study device; however, one patient in the Dynesys arm was a 3-level construct and therefore was excluded from analysis, resulting in a total of 367 randomized, treated patients (253 Dynesys, 114 Silhouette) at 26 sites. Additionally 28 patients were non-randomized and received the investigational device as the initial implant at 28 sites and are referred to as the Dynesys training cohort throughout this summary. Seventy-one (71) patients were assigned study IDs but not treated. Of these, twenty-four (24) patients were screen failures and were never randomized. Three (3) patients were eligible but withdrew prior to randomization. 1 patient was never randomized since the request for randomization occurred after enrollment in the trial was closed. Therefore, 411 patients were randomized (275 Dynesys, 136 Silhouette); however, forty-three (43) were not implanted (twenty-one (21) in the Dynesys arm and twenty-two (22) in the Silhouette arm).

The following table summarizes the reasons for the withdrawals after randomization in each treatment group:

Reason	Dynesys	Silhouette
Insurance Denial	5	1
Patient Decision	8	16
Physician Decision	5	3
Did not meet inclusion/exclusion criteria	2	2
Enrollment closed after randomization	1	0
Total	21	22

The following more specific reasons were listed for the physician decision category:

- Dynesys: during surgery old non-healing pars fracture with loose gill-fragment at L5 discovered so non-instrumented posterior spine fusion at 2 levels performed; during surgery joint appeared completely ankylosed on one side so physician did not feel it would be necessary to perform randomized procedure; patient already spontaneously fused from degenerative joint disease; no additional detail provided for one; one listed only as investigator discretion
- Silhouette: decided to implant patient with Dynesys 510(k) device; increased instability so anteroposterior fusion recommended; decided TLIF best option for patient

The sponsor was asked to evaluate these patients to determine whether they were different from the treated patients in a way that would have resulted in bias in the comparison of the treated cohorts (i.e., some form of selection bias). There were no statistically significant differences between Dynesys and Silhouette patients for the

baseline and demographic endpoints that were analyzed within this subgroup of patients randomized but not implanted; however, it should be noted that sample size in these comparisons was not large. Additional analyses were done to compare the demographic and baseline variables for the subgroup of patients randomized but not implanted to the remainder of the implanted patients in the Dynesys and Silhouette cohorts to assess for possible selection bias in the failure to implant some patients. No statistically significant differences were found. Therefore, from the data presented, it does not appear that a selection bias was associated with the failure to implant a study device in this set of patients.

The following table presents the patient accounting data for the 367 randomized, treated patients at 12 and 24 month follow-up:

	12 month			24 month		
	Dynesys	Silhouette	Training	Dynesys	Silhouette	Training
Theoretical	253	114	28	253	114	28
Cumulative Deaths ¹	1	1	0	1	1	0
Cumulative Failures ²	13	9	0	20	13	1
Expected	239	104	28	232	100	27
Any Data ³	207	92	26	191	78	23
% of expected	86.6	88.5	92.9	82.3	78.0	85.2
Any Data in Window ⁴	192	80	25	149	62	18
% of expected	80.0	76.9	89.3	64.2	62.0	66.7
Complete Data ³	183	84	275	173	70	22
% of expected	76.6	80.8	89.3	74.6	70.0	81.5
Complete Data in Window ⁴	169	69	21	133	56	16
% of expected	70.4	66.3	75.0	57.3	56.0	59.3

‘Any Data’ rows refer to patients with any evaluation data available for that visit window whereas ‘Complete Data’ rows refer to patients with complete primary endpoint data.

¹ In a given window, if a death occurs and there is any data in the window prior to the death, the patient is counted as present in that window for the purpose of study compliance. Conversely, if a death occurs and there is no other data in the window, the patient is counted as a death.

² In a given window if a failure occurs and there is any data in the window prior to the failure, the patient is counted as present in that window for the purpose of study compliance. If a failure occurs and there is no other data in the window, or if there is data present that occurs in the window but occurs after the failure, the patient is counted as a failure.

³ Refers to analysis windows (continuous windows used in all timecourse data tables in PMA):

- Pre-treat: days < -1
- Immediate post-op: days ≤ 6
- 3 wks: 6 < days ≤ 69
- 3 mo: 69 < days ≤ 154
- 6 mo: 154 < days ≤ 303
- 12 mo: 303 < days ≤ 669
- 24 mo: 669 < days < no upper limit

⁴ Refers to protocol-specified windows (discrete windows outlined in IDE protocol):

- Pre-treat: days ≤ -1
- 3 wks: 7 ≤ days ≤ 35

- 3 mo: $70 \leq \text{days} \leq 112$
- 6 mo: $155 \leq \text{days} \leq 211$
- 12 mo: $304 \leq \text{days} \leq 426$
- 24 mo: $669 \leq \text{days} \leq 791$

74.6% of Dynesys patients and 70% of Silhouette patients have complete 24 month primary endpoint data available with 57.3% and 56% within the protocol-defined study windows in each treatment group respectively. Considering all known data, there are a number of patients for whom primary endpoint success/failure can be determined even without complete primary endpoint data because they are a known failure for one of the required components. Specifically, primary endpoint determinations can be made for 217/252 (86.1%) of Dynesys patients and 89/113 (78.8%) of Silhouette patients with the denominators referring to the number of theoretical patients minus the 1 death prior to 24 months in each study group. Some radiographic data is available for 76.4% of Dynesys patients and 68% of Silhouette patients, and complete radiographic data is available for 73% of Dynesys patients and 67% of Silhouette patients.

FDA will be asking you to discuss the adequacy of the follow-up rates in each treatment group, as well as if the results of the sensitivity analyses provided by the sponsor adequately address the missing data.

Demographics and Preoperative Characteristics:

The following tables provide summary and comparisons of demographic variables, preoperative characteristics and evaluation of clinical endpoints, and surgery and discharge information between the Dynesys and Silhouette groups. Data on the non-randomized Dynesys training cohort is also provided. The investigational and control groups are comparable in demographic and baseline characteristics, except for history of smoking for which the average number of years is significantly less in the Dynesys group than in the Silhouette group.

Demographic Information

Variable	Dynesys (N=253)	Silhouette (N=114)	p-value	Dynesys Training (N=28)
Age (years)	56.9 ± 11.7	58.0 ± 11.5	0.38	56.7 ± 10.3
Gender (% male)	48%	41%	0.26	46%
Height (inches)	66.7 ± 3.9	66.5 ± 4.0	0.25	67.1 ± 3.8
Weight (lbs)	182.2 ± 36.8	178.4 ± 37.6	0.36	189.3 ± 35.8
BMI (kg/m ²)	28.5 ± 4.86	28.3 ± 4.32	0.70	29.4 ± 4.3
Race	Not provided	Not provided	--	Not provided
Compensation related injury (% yes)	11%	11%	0.86	11%
Presently smoking/chewing (% yes)	23%	25%	0.79	21%
# years	24.5 ± 11.6	23.7 ± 14.4	0.78	29.5 ± 3.0
History of smoking (% yes)	55%	54%	0.91	39%
# years	19.3 ± 12.1	23.2 ± 13.7	0.05	24.9 ± 14.6
Preoperative Work Status	Not provided	Not provided	--	Not provided

Preoperative Characteristics

Variable	Dynesys (N=253)	Silhouette (N=114)	p-value	Dynesys Training (N=28)
Length of back and/or leg symptoms (years)	5 ± 6.2	4.6 ± 5.7	0.59	4.6 ± 7.4
Length of prior conservative care	Not provided	Not provided	--	Not provided
Previous lumbar surgery (% yes)	31%	32%	0.90	29%
Pre-operative narcotic medication (% yes)	Not provided	Not provided	--	Not provided
Pre-operative non-narcotic analgesic (% yes)	Not provided	Not provided	--	Not provided
Pre-operative NSAIDs (% yes)	Not provided	Not provided	--	Not provided
Pre-operative steroid anti-inflammatory (% yes)	Not provided	Not provided	--	Not provided
Pre-operative muscle relaxant (% yes)	Not provided	Not provided	--	Not provided
Pre-operative other medication (% yes)	Not provided	Not provided	--	Not provided
Primary radiographic indication:				
• Central stenosis	26%	28%	0.59	31%
• Lateral stenosis	31%	25%		23%
• Spondylolisthesis	33%	40%		35%
• Retrolisthesis	4%	4%		4%
• Other	6%	4%		8%

Preoperative Evaluation of Clinical Endpoints

Variable	Dynesys (N=253)	Silhouette (N=114)	p-value	Dynesys Training (N=28)
Leg Pain VAS	79.1 ± 15.2	78.0 ± 16.0	0.55	72.7 ± 15.7
ODI	54.3 ± 14.1	52.6 ± 13.3	0.28	49.2 ± 14.5
Motor - % moderate/total impairment	2%	1%	0.68	0%
Sensory - % abnormal	41%	32%	0.13	42%
Straight Leg Raise - % positive	12%	10%	0.59	15%
Reflex Testing - % abnormal	55%	57%	0.91	56%
Back Pain VAS	56.7 ± 25.2	59.6 ± 24.4	0.31	54.4 ± 25.3
SF-12 PCS	27.5 ± 6.2	27.4 ± 12.9	0.84	31.04 ± 9.34
SF-12 MCS	43.7 ± 13.4	42.4 ± 12.5	0.36	45.78 ± 14.12

Surgical and Discharge Information:

The mean operative time, blood loss, and hospitalization times are not statistically different for the Dynesys and Silhouette groups. The majority of the patients in all groups underwent a concomitant decompression procedure which is now specified in the proposed Indications for Use statement. The majority of patients in both groups had procedures at L4-L5 or at L3-L5 or L4-S1. The distribution of treatment levels is comparable between the two treatment groups.

Surgical and Discharge Information

Variable	Dynesys (N=253)	Silhouette (N=114)	p-value	Dynesys Training (N=28)
Mean total anesthesia time (min)	183.6 ± 67.5	176.9 ± 61.6	0.37	209.6 ± 60.5
Mean EBL (cc)	413.9 ± 344.3	425.5 ± 367.8	0.77	445.5 ± 267.3
Mean hospitalization (days)	3.4 ± 2.0	3.7 ± 2.3	0.25	3.3 ± 1.5
Decompression done (% yes)	90%	96%	0.07	86%
Number instrumented levels			0.31	
• 1-level	137 (54%)	69 (61%)		14 (50%)
• 2-levels	116 (46%)	45 (39%)		14 (50%)
Instrumented Levels			0.51	
• L1-L2	0	1 (1%)		0
• L2-L3	2 (1%)	1 (1%)		2 (7%)
• L2-L3-L4	4 (2%)	4 (4%)		0
• L3-L4	17 (7%)	7 (6%)		3 (11%)
• L3-L4-L5	46 (18%)	20 (18%)		11 (39%)
• L4-L5	97 (38%)	50 (44%)		8 (29%)
• L4-L5-S1	66 (26%)	21 (18%)		3 (11%)
• L5-S1	21 (8%)	10 (9%)		1 (4%)
Number times implant used at:			--	
• L1-L2	0	1		0
• L2-L3	6	5		2
• L3-L4	67	31		14
• L4-L5	209	91		22
• L5-S1	87	31		4

EFFECTIVENESS EVALUATION

Primary Endpoint (Overall Clinical Success)

The primary endpoint for the clinical investigation is a composite variable termed “overall clinical success.” Study success is based on the Dynesys 24-month overall clinical success rate being statistically non-inferior to the Silhouette group rate.

The statistical data analysis demonstrates that the overall clinical success results for the Dynesys group are non-inferior to the Silhouette group (lower limit of the 90% confidence interval for the difference in Clinical Success rates between Dynesys and Silhouette is greater than the -10% or -15% non-inferiority margin). Overall clinical success is expressed as the number of individual patients categorized as a clinical success divided by the total number of patients evaluated. It should be noted that, in the primary analysis, outcomes for patients treated at one-level were pooled with outcomes for those treated at two-levels. Similarly, outcomes for the different radiographic indications for treatment (i.e., central stenosis, instability, lateral stenosis) and outcomes for those patients who were treated with a concomitant decompression and those who were not were also pooled in the primary analysis.

The following table describes the success rates in each treatment group for overall clinical success as well as the components of overall clinical success. Study success is evaluated based on data from the 24-month follow-up evaluation.

**Overall Clinical Success and Components of Overall Clinical Success at 24 Months
(Analysis Windows)**

Primary Outcome	Dynesys	Silhouette	Difference (90% confidence interval) ¹	Fisher’s Exact Test p-value (Left Tail)	Dynesys Training
VAS Leg Pain Success	151/173 (87%)	51/70 (73%)	N/A	0.01	19/22 (86%)
ODI Success	133/175 (76%)	49/70 (70%)	N/A	0.34	19/23 (83%)
Neurological Success (Maintain/Improve)	157/171 (92%)	58/69 (84%)	N/A	0.10	19/21 (90%)
No Major Complication	251/252 (99.6%)	112/113 (99.1%)	N/A	0.53	28/28 (100%)
No Secondary Surgery	231/253 (91%)	102/114 (89%)	N/A	0.56	27/28 (96%)
Overall Clinical Success	113/217 (52.1%)	36/89 (40.4%)	11.6% (1.4 – 21.8%)	0.98	15/24 (62.5%)

¹ The sponsor presents the 90% two-sided confidence limit as it provides the 95% one-sided lower limit when the upper bound is ignored to assess non-inferiority. Note that hypothesis testing only performed for overall clinical success, but not for components of overall clinical success.

The data in the above table presents outcomes based on the 24 month “analysis window” (22 months – no upper bound). The following table presents results if the data is analyzed based on the 24 month “protocol window” (22 months – 26 months):

Overall Clinical Success at 24 Months (Protocol Window)

Primary Outcome	Dynesys	Silhouette	Difference (90% confidence interval)¹	Fisher’s Exact Test p-value (Left Tail)	Dynesys Training
Overall Clinical Success based on 24 month “protocol window”	77/164 (47.0%)	27/72 (37.5%)	9.5% (1.9 – 20.8%)	0.93	Not provided

In summary, the results from this clinical study report a 52.1% overall clinical success rate in Dynesys patients as compared to a 40.4% overall clinical success rate in Silhouette patients and a 62.5% overall clinical success rate in Dynesys training patients. The overall clinical success rates drop to 47.0% for Dynesys and 37.5% for Silhouette if only patients in the protocol-defined windows are considered. In addition, only 74.6% of Silhouette patients are considered fused at 24 months.

FDA will be asking you to discuss the success rates (in both the Dynesys and Silhouette groups) in the context of expected clinical success rates for standard of care treatments for the patient population as defined in this study. In particular, we will be asking you to discuss the trend in outcomes from 12 to 24 months where the Dynesys success rates remained relatively constant (56.7% at 12 months, 52.1% at 24 months) whereas the Silhouette success rates decreased substantially (53.1% at 12 months to 40.4% at 24 months).

The following table compares the overall clinical success outcomes for the whole study cohort to overall success outcomes for the following subgroups of patients:

- Patients treated at one-level and patients treated at two-levels
- Patients with the different radiographic indications for treatment (i.e., central stenosis, instability, lateral stenosis)
- Patients who were treated with a concomitant decompression and those who were not.

Overall Clinical Success at 24 Months by Number of Levels Treated, Radiographic Indication, and Decompression or No Decompression

	Dynesys	Silhouette	Difference (90% confidence interval)¹	Fisher's Exact Test p-value (Left Tail)	Dynesys Training
Overall Clinical Success – ALL patients (from above)	113/217 (52.1%)	36/89 (40.4%)	11.6% (1.4-21.8%)	0.98	15/24 (62.5%)
Overall Clinical Success – 1-level patients	71/119 (59.7%)	26/57 (45.6%)	14.0% (0.9-27.2%)	0.97	7/12 (58.3%)
Overall Clinical Success – 2-level patients	42/98 (42.9%)	10/32 (31.3%)	11.6% (-4.2-27.4%)	0.92	8/12 (66.7%)
Overall Clinical Success – Central Stenosis	22/59 (37.3%)	12/22 (54.5%)	-17.3% (-37.6-3.0%)	0.13	Not provided
Overall Clinical Success – Instability	53/82 (64.6%)	17/41 (41.5%)	23.2% (7.8-38.5%)	>0.99	Not provided
Overall Clinical Success – Lateral Stenosis	36/71 (50.7%)	7/24 (29.2%)	21.5% (3.4-39.7%)	0.98	Not provided
Overall Clinical Success – Concomitant Decompression	104/197 (52.8%)	34/85 (40.0%)	12.8% (2.3% - 23.3%)	0.9824	13/21 (61.9%)
Overall Clinical Success – No Concomitant Decompression	9/19 (47.4%)	2/4 (50.0%)	-2.6% (-47.9% - 42.6%)	0.6708	2/3 (66.7%)

¹ The sponsor presents the 90% two-sided confidence limit as it provides the 95% one-sided lower limit when the upper bound is ignored to assess non-inferiority.

In summary, Dynesys and Silhouette patients experienced differential results depending on primary indication and whether treatment was at one or two-levels. For those patients with instability or lateral stenosis as the primary radiographic indication, Dynesys patients performed notably better, i.e. success rates for instability indication: 64.6% Dynesys, 41.5% Silhouette; success rates for lateral stenosis: 50.7% Dynesys, 29.2% Silhouette. However, for central stenosis the treatment difference was reversed, with Silhouette patients performing better than Dynesys patients, i.e. success rates for central stenosis: 37.3% Dynesys, 54.5% Silhouette. Although such an analysis was not pre-specified, there was a nominally statistically significant interaction for treatment-group-by-primary indication. This statistical result indicates that data should be considered separately for the subgroups defined by primary indication. While there was not a statistically significant interaction for treatment group by number of levels treated, as compared to the overall study results of 52.1% for Dynesys and 40.4% for Silhouette, the success rates in one-level procedures (59.7% for Dynesys and 45.6% for Silhouette) are higher and the success rates in two-level procedures (42.9% for Dynesys and 31.3% for Silhouette) are lower.

FDA will be asking you to discuss the differences in success rates for the different primary radiographic indications and for one-level versus two-level procedures for both treatment groups in the context of expected clinical success rates for standard of care treatments for the patient population as defined in this study.

The following table presents timecourse data for Overall Clinical Success. Analyses of the differences between Dynesys and Silhouette are all non-significant p-values, with all meeting a -10% non-inferiority margin except for the 6 month interval, where the lower bound of the 90% confidence interval is -12.2%.

Timecourse of Overall Clinical Success (Analysis Windows)

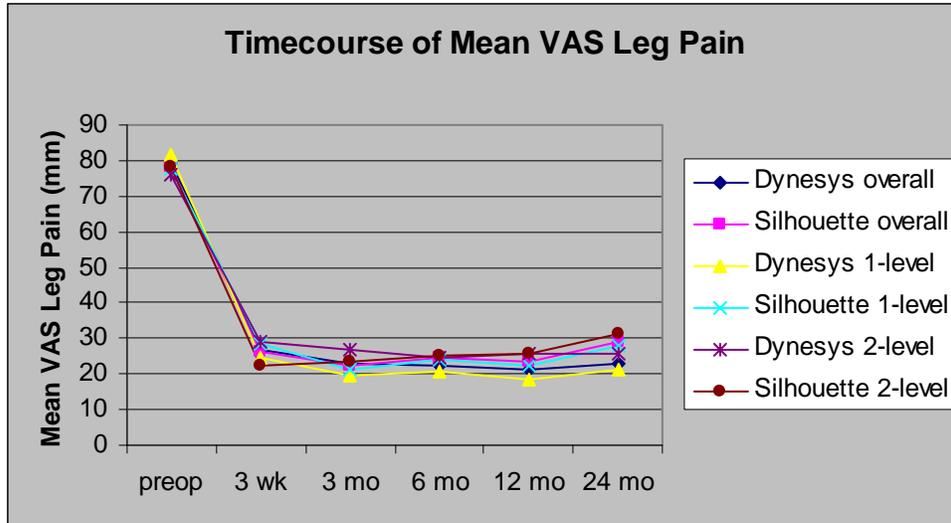
	Dynesys	Silhouette	Difference (90% confidence interval)¹	Fisher's Exact Test p-value (Left Tail)	Dynesys Training
3 Week Assessment	58/244 (23.8%)	18/105 (17.1%)	6.6% (-0.9-14.2%)	0.94	12/27 (44.4%)
3 Month Assessment	123/225 (54.7%)	53/96 (55.2%)	-0.5% (-10.5-9.4%)	0.51	18/25 (72.0%)
6 Month Assessment	132/220 (60.0%)	56/90 (62.2%)	-2.2% (-12.2-7.8%)	0.41	23/26 (88.5%)
12 Month Assessment	123/217 (56.7%)	51/96 (53.1%)	3.6% (-6.5-13.6%)	0.76	17/24 (70.8%)
24 Month Assessment	113/217 (52.1%)	36/89 (40.4%)	11.6% (1.4-21.8%)	0.98	15/24 (62.5%)

At 24 months following surgery, the overall clinical success rate for the Dynesys group is 52.1%, as compared to a 40.4% overall clinical success rate for the Silhouette group. The statistical data analysis demonstrates that the overall clinical success results for the Dynesys group are non-inferior to the Silhouette group (lower limit of 90% confidence interval for difference in Clinical Success rates between Dynesys and Silhouette (1.4%) is greater than the -10% or -15% non-inferiority margin).

Primary Effectiveness Components

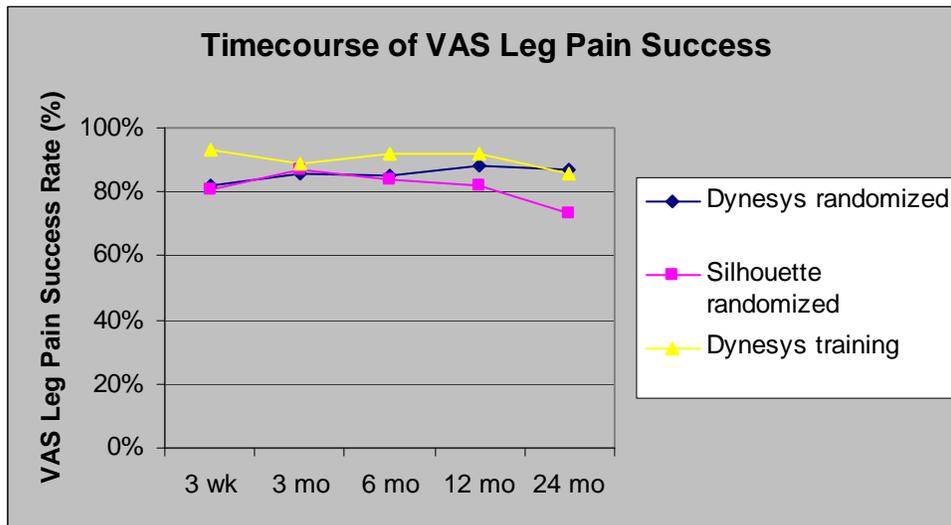
Leg Pain VAS

At all postoperative time periods for both treatment groups, the mean leg pain VAS scores improved when compared to the preoperative scores. The mean improvement for the Dynesys group at 24 months post-operative is 55.6mm which is greater than the mean improvement score of 46.8mm for the Silhouette group both of which are greater than the 20mm improvement which is considered clinically significant. At 24 months, the mean VAS leg pain is 23.1mm for all Dynesys patients as compared to 29mm for all Silhouette patients. On average, the results are slightly lower (indicative of less pain) than the overall means for 1-level patients (21.4mm for Dynesys as compared to 27.8mm for Silhouette) and slightly higher (indicative of more pain) than the overall means for 2-level patients (25.7mm for Dynesys as compared to 31.3mm for Silhouette).



Note: Based on data for all patients with available leg pain VAS data.

VAS leg pain success is a function of the preoperative VAS leg pain score. Postoperative improvement in leg pain is classified as a clinical success when a 20mm decrease in leg pain postoperatively is achieved as compared with the preoperative score. At 24 months, 87% of randomized Dynesys patients are considered a VAS leg pain success as compared to 73% of randomized Silhouette patients and 86% of Dynesys training patients.



Note: Based on data for all patients with available leg pain VAS data.

The sponsor performed an analysis to provide additional detail on the spectrum of clinically significant improvement from baseline. Specifically, the change from baseline scores are stratified as follows: greater than or equal to 20mm improvement = clinically meaningful improvement; between 3 and 20mm improvement = improvement but not clinically meaningful; less than or equal to 3mm improvement and less than or equal to 3mm deterioration = essentially the same; more than 3mm deterioration = deterioration.

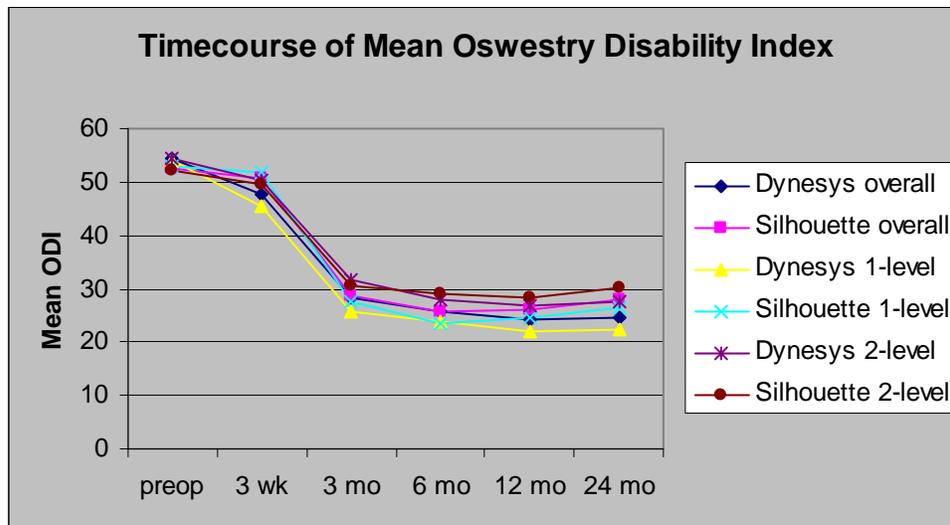
Stratification of VAS Leg Pain Outcomes at 24 Months

	Dynesys N=173	Silhouette N=70	Dynesys Training N=22
Clinically meaningful improvement	151 (87%)	51 (73%)	19 (86%)
Improvement but not clinically meaningful	11 (6%)	12 (17%)	0
Essentially the same	4 (2%)	1 (1%)	2 (9%)
Deterioration	7 (4%)	6 (9%)	1 (5%)

Seven patients (4%) in the Dynesys group and six (9%) in the Silhouette group have leg pain VAS scores at 24 months that are greater than their scores at baseline.

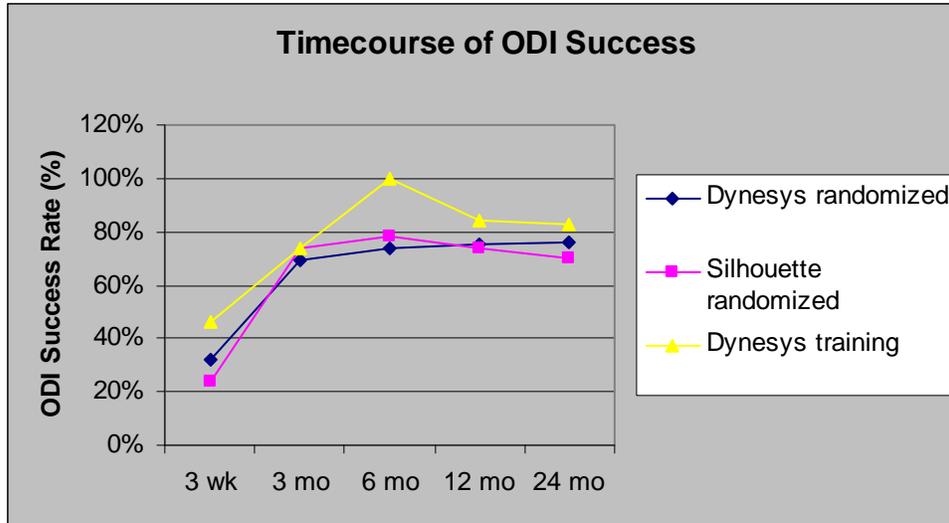
ODI

At all postoperative time periods for both treatment groups, the mean ODI scores improved when compared to the preoperative scores. The mean improvement in ODI scores for the Dynesys group at 24 months postoperative is 29.1 points which is greater than the mean improvement score of 24.5 for the Silhouette group, both of which are greater than the 15 point improvement which is considered clinically significant. At 24 months, the mean ODI is 24.5 points for all Dynesys patients as compared to 27.8 points for all Silhouette patients. On average, the results are slightly lower (indicative of less disability) than the overall means for 1-level patients (22.4 points for Dynesys as compared to 26.6 points for Silhouette) and slightly higher (indicative of more disability) than the overall means for 2-level patients (27.5 points for Dynesys as compared to 30.3 points for Silhouette).



Note: Based on data for all patients with available ODI data.

ODI success is a function of the preoperative ODI score. Postoperative improvement in ODI is classified as a clinical success when a 15 point decrease is achieved as compared with the preoperative score. At 24 months, 76% of randomized Dynesys patients are considered an ODI success as compared to 70% of randomized Silhouette patients and 83% of Dynesys training patients.



Note: Based on data for all patients with available ODI data.

The sponsor performed an analysis to provide additional detail on the spectrum of clinically significant improvement from baseline. Specifically, the change from baseline scores are stratified as follows: greater than or equal to 15 point improvement = clinically meaningful improvement; between 2 and 15 point improvement = improvement but not clinically meaningful; less than or equal to 2 point improvement and less than or equal to 2 point deterioration = essentially the same; more than 2 point deterioration = deterioration.

Stratification of ODI Outcomes at 24 Months

	Dynesys N=175	Silhouette N=70	Dynesys Training N=23
Clinically meaningful improvement	133 (76%)	49 (70%)	19 (83%)
Improvement but not clinically meaningful	23 (13%)	16 (23%)	1 (4%)
Essentially the same	8 (5%)	3 (4%)	3 (13%)
Deterioration	11 (6%)	2 (3%)	0 (0%)

Eleven patients (6%) in the Dynesys group and two (3%) in the Silhouette group have ODI scores at 24 months that are worse than their scores at baseline.

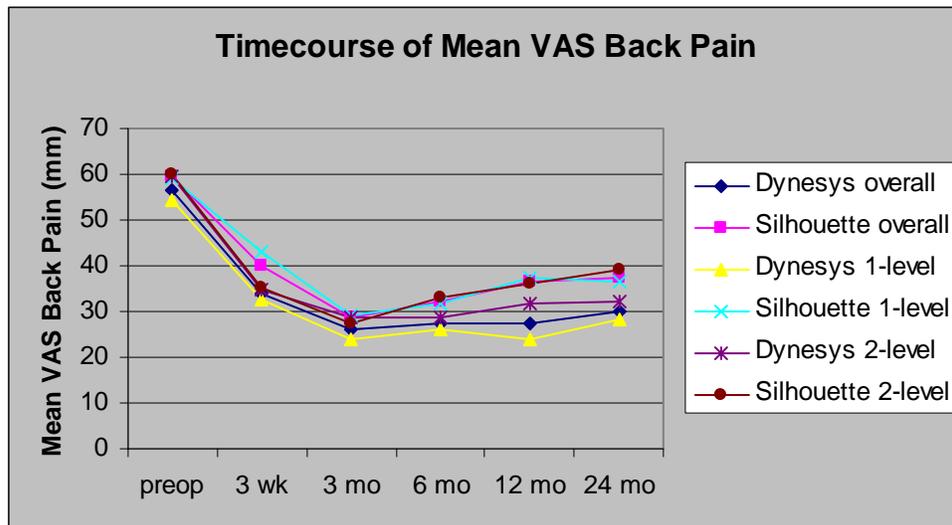
Secondary Effectiveness Endpoints:

Note: The sponsor's testing of the following secondary endpoints was not adjusted for multiplicity and were not submitted to the FDA in a priori order of importance. As a result, nominal p-values and confidence intervals are not directly interpretable and may indicate falsely significant results.

Back Pain VAS

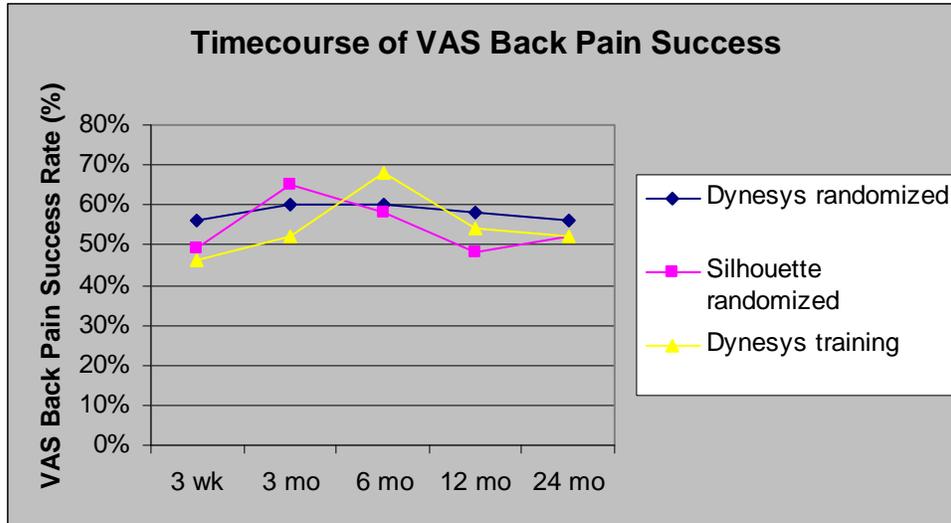
At all postoperative time periods for both treatment groups, the mean back pain VAS scores improved when compared to the preoperative scores. The mean improvement for

the Dynesys group at 24 months postoperative is 25mm which is slightly greater than the mean improvement score of 19.9mm for the Silhouette group. At 24 months, the mean VAS back pain is 30mm for all Dynesys patients as compared to 37.4mm for all Silhouette patients. On average, the results are slightly lower (indicative of less pain) than the overall means for 1-level patients (28.3mm for Dynesys as compared to 36.6mm for Silhouette) and slightly higher (indicative of more pain) than the overall means for 2-level patients (32.3mm for Dynesys as compared to 39mm for Silhouette).



Note: Based on data for all patients with available back pain VAS data.

VAS back pain success is a function of the preoperative VAS back pain score. Postoperative improvement in back pain is classified as a clinical success when a 20mm decrease in back pain postoperatively is achieved as compared with the preoperative score. At 24 months, 56% of randomized Dynesys patients are considered a VAS back pain success as compared to 52% of randomized Silhouette patients and 52% of Dynesys training patients.



Note: Based on data for all patients with available back pain VAS data.

The sponsor performed an analysis to provide additional detail on the spectrum of clinically significant improvement from baseline. Specifically, the change from baseline scores are stratified as follows: greater than or equal to 20mm improvement = clinically meaningful improvement; between 3 and 20mm improvement = improvement but not clinically meaningful; less than or equal to 3mm improvement and less than or equal to 3mm deterioration = essentially the same; more than 3mm deterioration = deterioration.

Stratification of VAS Back Pain Outcomes at 24 Months

	Dynesys N=175	Silhouette N=69	Dynesys Training N=23
Clinically meaningful improvement	98 (56%)	36 (52%)	12 (52%)
Improvement but not clinically meaningful	23 (13%)	10 (14%)	4 (17%)
Essentially the same	17 (10%)	6 (9%)	3 (13%)
Deterioration	37 (21%)	17 (25%)	4 (17%)

Thirty-seven patients (21%) in the Dynesys group and seventeen (25%) in the Silhouette group have VAS back pain scores at last follow-up that are greater than their scores at baseline.

SF-12

The SF-12 is a multipurpose short-form Quality of Life instrument, with 12 questions selected from the SF-36 Health Survey. The SF-12 is a normative based instrument with higher scores indicative of higher functioning/better health. The Physical Component Summary (PCS) Score is a composite of the Physical Functioning, Role Functioning, Bodily Pain and General Health Scales within the SF-12 instrument. In addition, the Mental Health Component Summary (MCS) Score is a composite of the Vitality, Social Functioning, Role- Emotional and Mental Health Scales within the SF-12 instrument.

The following table outlines mean PCS and MCS scores for each treatment group at 24 months as well as mean PCS and MCS change from baseline data at 24 months:

	Dynesys	Silhouette	p-value	Dynesys Training
Mean PCS	41.1 ± 12.3 N=170	37.4 ± 11.2 N=70	0.03	47.1 ± 10.9 N=22
Mean MCS	50.0 ± 11.2 N=170	51.0 ± 11.9 N=70	0.53	49.4 ± 9.4
Mean PCS change from baseline	13.4 ± 12.5 N=167	9.9 ± 10.8 N=68	0.04	Not provided
Mean MCS change from baseline	6.0 ± 14.1 N=167	7.2 ± 11.7 N=68	0.54	Not provided

The sponsor performed an analysis to provide additional detail on the spectrum of clinically significant improvement from baseline. Specifically, the change from baseline scores are stratified as follows: greater than or equal to 20 point improvement = very improved; between 10 and 20 point improvement = improving; less than or equal to 10 point improvement and less than or equal to 10 point deterioration = no change; more than 10 point deterioration = deterioration.

Stratification of SF-12 PCS and MCS Outcomes at 24 Months

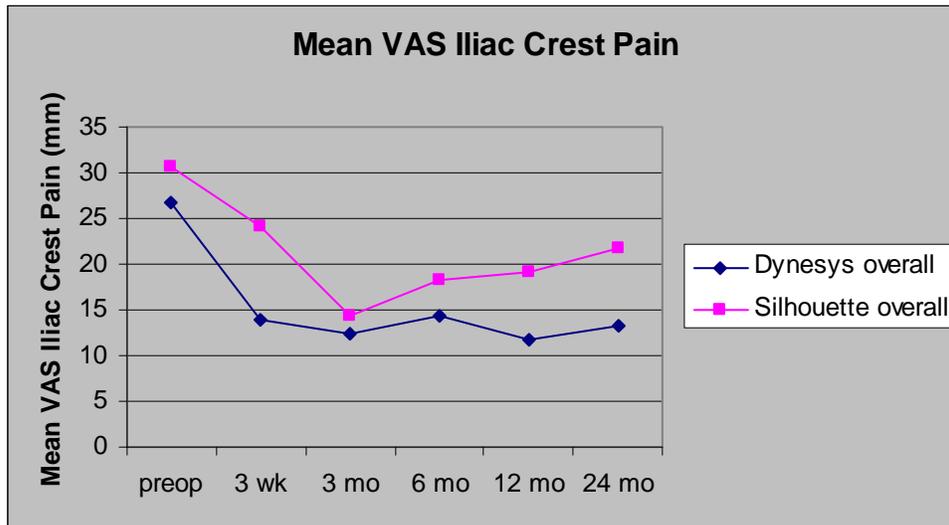
		Dynesys N=167	Silhouette N=68	Dynesys Training N=22
PCS	Very improved	51 (31%)	12 (18%)	8 (36%)
	Improving	55 (33%)	21 (31%)	7 (32%)
	No change	60 (36%)	34 (50%)	7 (32%)
	Deteriorated	1 (1%)	1 (1%)	0 (0%)
MCS	Very improved	28 (17%)	11 (16%)	2 (9%)
	Improving	32 (19%)	16 (24%)	7 (32%)
	No change	90 (54%)	39 (57%)	9 (41%)
	Deteriorated	17 (10%)	2 (3%)	4 (18%)

One patient (1%) in the Dynesys group and one (1%) in the Silhouette group have SF-12 PCS scores at 24 months that are worse than their scores at baseline. Seventeen patients (10%) in the Dynesys group and two (3%) in the Silhouette group have SF-12 MCS scores at 24 months that are worse than their scores at baseline.

VAS Iliac Crest

Iliac pain scores were expressed in millimeters, where a rating of 0 mm represented no iliac crest pain and 100mm represented severe iliac crest pain. Patients were instructed to draw a single line across the scale at the point that best described their level of pain. At all postoperative time periods for both treatment groups, the mean iliac crest pain VAS scores improved when compared to the preoperative scores. At 24 months, the mean VAS iliac crest pain is 13.3mm for all Dynesys patients as compared to 21.7mm for all Silhouette patients. On average, the results are slightly lower (indicative of less pain) than the overall means for 1-level patients (12.6mm for Dynesys as compared to 20.6mm

for Silhouette) and slightly higher (indicative of more pain) than the overall means for 2-level patients (14.4mm for Dynesys as compared to 23.9mm for Silhouette).



Note: Based on data for all patients with available VAS iliac crest pain data.

Patient Satisfaction

Patient satisfaction was evaluated in three ways:

- NASS MODEMS Satisfaction Item: This question was used to gain an overall patient satisfaction rating by asking whether the surgery met expectations, improved the condition enough that the patient would go through it again for the same outcome, helped the patient but he/she would not go through it again for the same outcome, or left the patient the same or worse as before surgery.

	Dynesys N=175	Silhouette N=69	p-value	Dynesys Training N=23
Surgery met my expectations	76 (43%)	17 (25%)	0.05	14 (61%)
Surgery Improved My Condition Enough So That I Would Go Through It Again For The Same Outcome	67 (38%)	36 (52%)		7 (30%)
Surgery Helped Me But I Would Not Go Through It Again For The Same Outcome	20 (11%)	9 (13%)		2 (9%)
I Am The Same Or Worse Compared To Before Surgery	12 (7%)	7 (10%)		0 (0%)

- VAS Satisfaction: The assessment of post-operative satisfaction using a 100mm VAS was completed by the patient. Satisfaction scores were obtained from patient responses, and were expressed in millimeters (mm). The anchor points were “Not Satisfied” (i.e. 0 mm) and “Completely Satisfied” (i.e. 100 mm). Patients were instructed to draw a single line across the scale at the point that best described their level of satisfaction. At 24 months, the mean VAS satisfaction score is statistically significantly different at 81.8mm for the Dynesys group as compared to 74.7mm for

the Silhouette group (p=0.05). At 24 months, the mean VAS satisfaction score is 87.1mm in the Dynesys training cohort.

- **VAS Recommendation:** The assessment of post-operative recommendation used a 100mm VAS which was completed by the patient where patients were asked to rate how likely they would be to recommend this procedure to a loved one with the same condition. Recommendation scores were obtained from patient responses, and were expressed in millimeters (mm). The patient recommendation score was based on a ranking of 0 to 100 millimeters with a rating of 0mm representing the lowest recommendation and 100 mm representing the highest. At 24 months, the mean VAS recommendation score is statistically significantly different at 84.0mm for the Dynesys group as compared to 73.7 mm for the Silhouette group (p<0.01). At 24 months, the mean VAS recommendation score is 87.9mm in the Dynesys training cohort.

PROLO Economic and Function Assessment

PROLO economic and function items were administered for both the patient and physician assessments. The assessment required the patient and the investigator to individually provide one economic and one function outcome which described the current status of the study patient. Each outcome was assigned a score which ranged from 1 to 5; where 5 was the most favorable and 1 being the least favorable score. The two scores were added to calculate an overall economic/function score, which could range between 2 and 10, inclusively. The following table presents the mean PROLO economic and function patient assessment and physician evaluation scores at 24 months:

	Dynesys	Silhouette	p-value	Dynesys Training
Mean PROLO patient assessment	6.8 ± 2.4 N=175	6.4 ± 2.1 N=69	0.24	Not provided
Mean PROLO physician assessment	7.1 ± 2.4 N=174	6.8 ± 2.0 N=69	0.33	Not provided

Scores of 9 and 10 were classified as excellent, 7 and 8 were classified as good, 5 and 6 were classified as fair, and below 5 were classified as poor. The following table presents the percentage of patients classified as excellent, good, fair, and poor for each study group at 24 months:

		Dynesys	Silhouette	p-value	Dynesys Training
PROLO patient assessment	N	175	69	0.01	22
	Excellent	59 (34%)	11 (16%)		9 (41%)
	Good	34 (19%)	23 (33%)		9 (41%)
	Fair	41 (23%)	20 (29%)		3 (14%)
	Poor	41 (23%)	15 (22%)		1 (5%)
PROLO physician evaluation	N	174	69	0.06	23
	Excellent	65 (37%)	16 (23%)		10 (43%)
	Good	40 (23%)	24 (35%)		9 (39%)
	Fair	36 (21%)	19 (28%)		4 (17%)
	Poor	33 (19%)	10 (14%)		0 (0%)

Radiographic Analyses:

Segmental Stability Without Fusion (Dynesys Group Only)

As outlined above, radiographic success in the Dynesys group was defined as meeting the definition of segmental stability without meeting the definition of fusion where segmental stability was defined as angular motion: < 15° at L1-L2, L2-L3, or L3-L4; or < 20° at L4-L5; or < 25° at L5-S1 and translational motion < 4.5 mm. Fusion was defined as: clear evidence of bridging bone; and translational motion < 3 mm; and angular motion < 5°. The following table outlines the radiographic success rates in the randomized Dynesys group and the Dynesys training group:

	Dynesys	Dynesys Training
Segmental Stability Without Fusion – ALL patients	166/168 (98.8%)	21/21 (100%)
Segmental Stability Without Fusion – 1-level patients	98/99 (99.0%)	Not presented
Segmental Stability Without Fusion – 2-level patients	68/69 (98.6%)	Not presented

Fusion (Silhouette Group Only): As outlined above, radiographic success in the Silhouette group was defined as meeting definition of fusion where fusion was defined as: clear evidence of bridging bone; and translational motion < 3 mm; and angular motion < 5°. Note that in the PMA, radiographic success rates for the investigational and control groups are statistically compared with significant differences favoring the Dynesys noted; however, FDA has presented the data separately without statistical comparison based on the different radiographic success rates for the Dynesys and Silhouette study groups.

	Silhouette
Fusion – ALL patients	50/67 (74.6%)
Fusion – 1-level patients	30/44 (68.2%)
Fusion – 2-level patients	20/23 (87.0%)

Range of Motion at Treated and Adjacent Level(s)

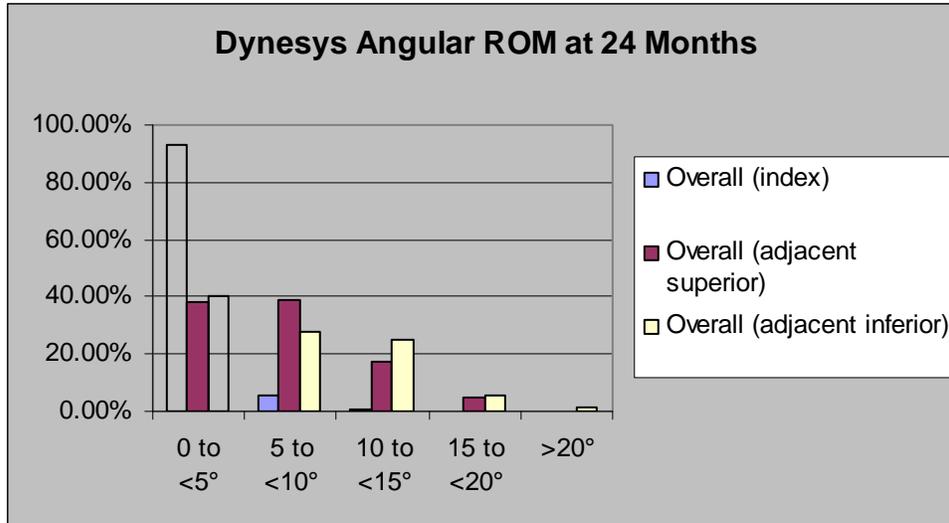
Angular and translational motion at both the treated and adjacent levels was measured at each study period by comparing lateral flexion and extension radiographs.

The following table presents mean timecourse angular and translational range of motion (ROM) data for the randomized Dynesys and Silhouette patients. Index and adjacent level data is presented:

		Pre Operative	6 months	12 months	24 months
Angular ROM (°)	Dynesys index level	5.8	2.1	1.8	1.8
	Silhouette index level	5.7	1.3	1.2	0.9
	<i>Dynesys adjacent superior</i>	5.2	6.8	6.6	7.3
	<i>Silhouette adjacent superior</i>	5.1	6.1	6.2	6.2
	<i>Dynesys adjacent inferior</i>	6.4	6.5	7.3	6.8
	<i>Silhouette adjacent inferior</i>	5.6	6.6	6.0	5.3
Translational ROM (mm)	Dynesys index level	1.0	0.4	0.3	0.4
	Silhouette index level	1.1	0.3	0.2	0.2
	<i>Dynesys adjacent superior</i>	1.1	1.4	1.4	1.3
	<i>Silhouette adjacent superior</i>	1.2	1.3	1.2	1.3
	<i>Dynesys adjacent inferior</i>	0.5	0.6	0.7	0.7
	<i>Silhouette adjacent inferior</i>	0.5	0.7	0.7	0.7

24 month angular range of motion outcomes are comparable between the Dynesys (a device intended to allow motion) and the Silhouette (a device intended for fusion). For both Dynesys and Silhouette patients, the mean angular range of motion values for the adjacent levels (both superior and inferior) are higher than the mean angular range of motion values for the treated level. Regarding translational motion, the mean values for both treatment groups are similar and remain fairly constant over time. The translational motion values for the level inferior to the treated segment are consistently lower than those for the level superior to the treated segment, but for both study groups, both the superior and inferior levels have higher translational motion than the treated segment.

The following figure presents data categorizing the 24 month Dynesys angular range of motion outcomes for both the index and adjacent levels. 93.3% of the evaluated index levels have 24 month angular range of motion outcomes less than 5° (the upper limit of the angular ROM cutoff for fusion as specified in the FDA guidance document).



Data evaluating the correlation (if any) between motion outcomes and pain/function (i.e., VAS, ODI) outcomes or overall clinical success outcomes were not provided.

In summary, 24 month angular range of motion outcomes are comparable between the Dynesys (a device intended to allow more motion than a traditional rigid pedicle screw system) and the Silhouette. Specifically, mean angular ROM for the Dynesys group is 1.8° at 24 months as compared to 0.9° for the Silhouette group at 24 months, and 93.3% of the evaluated Dynesys index levels have 24 month angular ROM outcomes less than 5°.

Given the statement within the proposed Indications for Use statement that the Dynesys Spinal System is indicated to provide spinal alignment and stabilization as well as the design rationale of the Dynesys device to allow more motion than a traditional rigid pedicle screw system, FDA will be asking you to discuss the radiographic stability and motion outcomes for the Dynesys group and in doing so, address the following points:

- The importance of motion in achieving a successful outcome after surgery with the Dynesys device both from the patient's perspective as well as the surgeon's perspective, and how radiographic success should be defined.*
- Whether the amount of motion afforded by the Dynesys device is clinically meaningful.*
- Any necessary analyses that should be provided to examine the relationship between radiographic success / motion and clinical outcomes.*
- The clinical interpretation of the increased adjacent level motion results for the Dynesys group as compared to the Silhouette group considering that nonfusion devices are hypothesized to potentially slow adjacent segment degeneration.*

Overall Lumbar Alignment

The sponsor reported several measures of overall lumbar alignment.

- The timecourse of Overall Cobb Angle (Global Lordosis), which measures L1-S1 lumbar alignment, is as follows:

	Pre Operative	6 months	12 months	24 months
Dynesys – ALL patients	53.4	51.4	52.3	52.5
Silhouette – ALL patients	49.8	51.4	49.7	49.4
p-value	0.04	0.97	0.17	0.11
Dynesys – 1-level patients	55.4	53.6	54.3	54.1
Silhouette – 1-level patients	50.2	52.6	52.2	51
Dynesys – 2-level patients	51.4	48.9	49.9	50.3
Silhouette – 2-level patients	49.1	49.3	45.4	45.8

- Loss of segmental lordosis which is defined as those patients whose intrasegmental disc angulation is less than their preoperative intrasegmental disc angulation assessment, for any instrumented level, given that the patient had a baseline disc angle greater than zero degrees preoperatively. In the case where a patient has two constructs, then loss of lordosis is determined for each construct and if either construct has loss of lordosis, the patient is considered to have loss of lordosis. There are a higher percentage of patients who experienced loss of lordosis in the Dynesys group than in the Silhouette group, at all time assessments, and those differences are statistically significant. That significant difference is also evident in the testing for the 1-level patients, but not for the 2-level patients where the loss of lordosis is proportionally greater but it was not statistically significant. Specifically, at 24 months 75.4% of Dynesys patients have loss of lordosis from baseline as compared to 56.4% of Silhouette patients (p=0.01). For 1-level patients, the percentages are 71.3% and 46.0% respectively for Dynesys and Silhouette (p=0.01), and for 2-level patients the percentages are 80.7% and 77.8% respectively for Dynesys and Silhouette (p=0.75).
- Global loss of lordosis is defined the same as loss of segmental lordosis but the summary was across all instrumented levels. There are no statistically significant differences in rates between Dynesys and Silhouette, for global loss of lordosis from baseline at any time period. At 24 months, 60.6% of Dynesys patients have global loss of lordosis as compared to 56.9% of Silhouette patients (p=0.74).
- Extreme loss of lordosis from baseline (flatback or kyphotic segment) is defined as patients whose postoperative assessment have a disc angle less than zero degrees for any instrumented level, given that the patient had a baseline disc angle greater than zero degrees preoperatively. There are no statistically significant differences in rates between Dynesys and Silhouette, for this more extreme condition of loss of lordosis at any time period. At 24 months, 10/202 (5.0%) of Dynesys segments have extreme loss of lordosis as compared to 3/73 (4.1%) of Silhouette segments.
- Disc angle in the sagittal plane is also summarized for both treatment groups at the preoperative, 6-month, 12-month and 24-month postoperative assessments. Results

for Dynesys patients exhibit a pattern of increasing average disc angle as the instrumented level goes from cephalad to caudal. At the 24 month assessment average disc angles of 1.1 degrees (L2-L3), 5.1 degrees (L3-L4), 6.9 degrees (L4-L5), and 9.0 degrees (L5-S1) are observed. Results for Silhouette patients also exhibit a pattern of increasing average disc angle as the instrumented level went from cephalad to caudal. At the 24-month assessment average disc angles of -2.7 degrees (L1-L2), 2.7 degrees (L2-L3), 4.1 degrees (L3-L4), 5.7 degrees (L4-L5), and 8.4 degrees (L5-S1) are observed.

In summary, the sponsor reports several measures of overall lumbar alignment. There is a statistically significant difference in overall Cobb angle between the two treatment groups preoperatively (Dynesys 53.4°, Silhouette 49.8°) but by 24 months there is no longer a statistically significant difference (Dynesys 52.5°, Silhouette 49.4°). For the evaluation of loss of lordosis, there are a statistically higher percentage of patients who experienced loss of lordosis in the Dynesys group than in the Silhouette group, at all time assessments including 24 months where 75.4% of Dynesys patients have loss of lordosis from baseline as compared to 56.4% of Silhouette patients. However, for global loss of lordosis across all instrumented levels and for extreme loss of lordosis from baseline there are no statistically significant differences in rates between Dynesys and Silhouette from baseline at any time period.

The FDA will be asking you to discuss the clinical significance of the results of these evaluations of overall lumbar alignment, and discuss whether any additional evaluations or analyses are necessary.

Percent Spondylolisthesis

Results from per-protocol patients indicate percent spondylolisthesis averages remain fairly constant over follow-up for *Dynesys* patients.

The following table presents data on the mean absolute value of percent spondylolisthesis at 24 months by treatment level:

	Dynesys (N=253)	Silhouette (N=114)		Dynesys Training (N=28)
L1-2	--	N=1 4.5%		--
L2-3	N=3 6.9%	N=4 4.0%		N=2 11.3%
L3-4	N=47 7.8%	N=16 9.2%		N=12 5.6%
L4-5	N=141 10.9%	N=54 10.1%		N=17 12.8%
L5-S1	N=52 8.0%	N=16 6.9%		N=3 10.0%

Disc Height

Anterior and posterior disc height were summarized at the preoperative, 6-month, 12-month and 24-month postoperative assessments. Dynesys and Silhouette patients exhibit

a pattern of an increasing average anterior disc height with the change in the location of the instrumented level going from cephalad to caudal. Dynesys and Silhouette patients exhibit a general pattern of the smallest average posterior disc height obtained at the most caudal instrumented level.

The following table presents mean anterior and posterior disc height data (mm) by treated level:

		Dynesys		Silhouette		Training	
		Pre-op	24 mo	Pre-op	24 mo	Pre-op	24 mo
L1-2	Anterior	--	--	8.0	4.2	--	--
	Posterior	--	--	4.7	5.8	--	--
L2-3	Anterior	8.5	5.2	9.3	7.3	9.6	9.5
	Posterior	4.6	4.5	5.9	5.6	4.6	2.6
L3-4	Anterior	9.0	8.0	9.2	7.3	10.5	9.9
	Posterior	5.0	4.9	5.3	4.8	4.9	4.5
L4-5	Anterior	10.3	9.7	9.5	8.6	10.7	9.7
	Posterior	5.5	5.6	5.3	5.3	5.0	5.2
L5-S1	Anterior	10.9	9.8	9.9	9.2	12.3	11.6
	Posterior	4.3	4.6	3.9	4.4	4.4	4.1

Medication Use

Narcotic analgesic use is prevalent but did not differ with statistical significance between Dynesys and Silhouette per-protocol procedures at any scheduled time of postoperative assessment. Narcotic analgesia in training procedures is less prevalent at each time of scheduled postoperative assessment than is seen in per-protocol procedures. Data on preoperative narcotic analgesic use was not provided. At 24 months, 24% of Dynesys patients and 30% of Silhouette patients were using narcotic analgesia (p=0.33).

Non-narcotic analgesia was infrequent, and in general observed differences between study device groups in the prevalence of postoperative nonnarcotic drug use are not statistically significant. However, non-narcotic analgesic use differs with statistical significance between Dynesys (9%) and Silhouette (18%) per-protocol procedures at the 6 month postoperative assessment (p=0.05). Data on preoperative non-narcotic analgesic use was not provided. At 24 months, 16% of Dynesys patients and 11% of Silhouette patients were using non-narcotic analgesia (p=0.43).

Non-steroidal anti-inflammatory (NSAID) use in per-protocol procedures did not significantly differ at any time. NSAID use is lowest at the 3 week postoperative assessment. NSAID use is more common and similar at all other subsequent periods of clinical assessment. Data on preoperative NSAID use was not provided. At 24 months, 28% of Dynesys patients and 26% of Silhouette patients were using NSAIDs (p=0.87).

In general, use of muscle relaxants decreased with time from surgery. Muscle relaxant use did not differ with statistical significance between Dynesys and Silhouette per-protocol procedures at any time. Data on preoperative muscle relaxant use was not provided. At 24 months, 12% of Dynesys patients and 7% of Silhouette patients were using muscle relaxants (p=0.51).

Work Status

Data on preoperative work status was not provided. At 24 months following surgery, the percent of working patients is 51% in the Dynesys group, 51% in the Silhouette group, and 65% in the Dynesys Training cohort. The percentages of patients not working due to back disability (15% Dynesys, 17% Silhouette) are comparable in the randomized study groups. No training patients are listed as not working at 24 months due to back disability.

Additional Data Presentations

Overall Clinical Success by Center and Justification for Pooling Data

Twenty-eight active centers participated in the IDE study and performed at least one surgical procedure. Twenty-six of those treated randomized patients. The other two only treated non-randomized, training patients. In evaluating overall clinical success outcomes by center, there is site variability, though not statistically significant. When looking at all centers, both treatment groups have some centers with 0% success rates and others with 100% success rates although most of the centers that fall at the extremes treated few patients. When looking at centers that treated more than 4 patients (to eliminate those with 0% or 100% success rates), success rates range from 16.7% to 87.5% in the Dynesys group and 28.6% to 85.7% in the Silhouette group. The sponsor performed several analyses to assess center poolability and to explore whether there are any significant center differences that might have an impact on the results of testing for differences between Dynesys and Silhouette using key baseline variables when all centers were pooled for analysis.

Statistical testing was performed to assess the (conditional) independence of the association between clinical success at 24 months and study device with study center using a Breslow-Day test of homogeneity of odds ratios. The sponsor was testing the null hypothesis that the odds ratios for all the levels of strata were equal, at a testing level of 0.10. The results from the testing do not indicate lack of homogeneity, with a p-value of 0.34. In addition, there is a similar lack of a site effect in most of the analyses of baseline and demographic characteristics by site. Some nominally significant differences were found when the data was stratified by 1 versus 2-level patients; however, these findings could be attributed to the large number of comparisons which were made. Based on this testing, the sponsor infers that overall there is not a center influence on the device differences between Dynesys and Silhouette.

Sensitivity Analyses

The primary analysis is an “as-treated” analysis among study completers which is the preferred analysis population for a non-inferiority study. However, it is still important to consider missing data. The sensitivity of the observed difference in primary comparisons of clinical success rates at the 24 month postoperative assessment between per-protocol procedures implanted with Dynesys and Silhouette devices for potentially influential factors was examined through multiple sensitivity analyses.

The following table presents several of the sensitivity analyses provided in the PMA including a missing equals failure analysis, worst case analyses where missing Dynesys patients are considered failures and missing Silhouette patients are considered successes, and best case analyses where missing Dynesys patients are considered successes and missing Silhouette patients are considered failures:

Analysis	Dynesys	Silhouette	Difference (90% confidence interval)¹	Fisher's Exact Test p-value (Left Tail)
Overall Clinical Success at 24 Months (FROM ABOVE)	113/217 (52.1%)	36/89 (40.4%)	11.6% (1.4-21.8%)	0.98
Missing equals failure	113/253 (44.7%)	36/114 (31.6%)	13.1% (4.3-21.9%)	0.99
Worst Case: ALL patients	113/252 (44.8%)	60/113 (53.1%)	-8.3% (-17.5-1.0%)	0.09
Worst Case: 1-level patients	71/136 (52.2%)	37/68 (54.4%)	-2.2% (-14.4-10.0%)	0.44
Worst Case: 2-level patients	42/116 (36.2%)	23/45 (51.1%)	-14.9% (-29.2 - -0.6%)	0.06
Best Case: ALL patients	148/252 (58.7%)	36/113 (31.9%)	26.9% (18-35.7%)	1.00
Best Case: 1-level patients	88/136 (64.7%)	26/68 (38.2%)	26.5% (14.7-38.3%)	1.00
Best Case: 2-level patients	60/116 (51.7%)	10/45 (22.2%)	29.5% (16.8-42.2%)	1.00

¹ The 90% two-sided confidence limit is presented as it provides the 95% one-sided lower limit when the upper bound is ignored to assess non-inferiority

In the worst case analysis (overall and stratified by 1- and 2-level patients), non-inferiority is not met; therefore, additional analyses to evaluate the impact of the missing data were completed. The sponsor is unable to determine 24 months outcomes for 35 Dynesys patients (32 missing neurological status, 1 missing leg pain VAS status, 1 missing ODI and leg pain VAS status, 1 missing ODI and leg pain VAS and neurological status) and 24 Silhouette patients (23 missing neurological status and 1 missing leg pain VAS and neurological status).

The following table presents data on overall clinical success rates for patients seen and evaluated at each study time point who ultimately went on to be study completers as compared to those who were ultimately missing at 24 months:

	Dynesys	Silhouette	Difference (90% confidence interval)¹	Fisher's Exact Test p-value (Left Tail)
3 Week Assessment – N (%)				
❖ Completers	58/244 (23.8%)	18/105 (17.1%)	6.6% (-0.9-14.2%)	0.94
❖ LTFU at 24 month	4/29 (13.8%)	4/19 (21.1%)	-7.3% (-25.9-11.4%)	0.39
3 Month Assessment – N (%)				
❖ Completers	123/225 (54.7%)	53/96 (55.2%)	-0.5% (-10.5-9.4%)	0.51
❖ LTFU at 24 month	8/20 (40.0%)	13/18 (72.2%)	-32.2% (-57.2 - -7.2%)	0.06
6 Month Assessment – N (%)				
❖ Completers	132/220 (60.0%)	56/90 (62.2%)	-2.2% (-12.2-7.8%)	0.41
❖ LTFU at 24 month	11/21 (52.4%)	14/19 (73.7%)	-21.3% (-45.7 - 3.1%)	0.14
12 Month Assessment – N (%)				
❖ Completers	123/217 (56.7%)	51/96 (53.1%)	3.6% (-6.5-13.6%)	0.76
❖ LTFU at 24 month	7/15 (46.7%)	9/17 (52.9%)	-6.3% (-35.4% - 22.8%)	0.50
24 Month Assessment – N (%)				
❖ Completers	113/217 (52.1%)	36/89 (40.4%)	11.6% (1.4-21.8%)	0.98

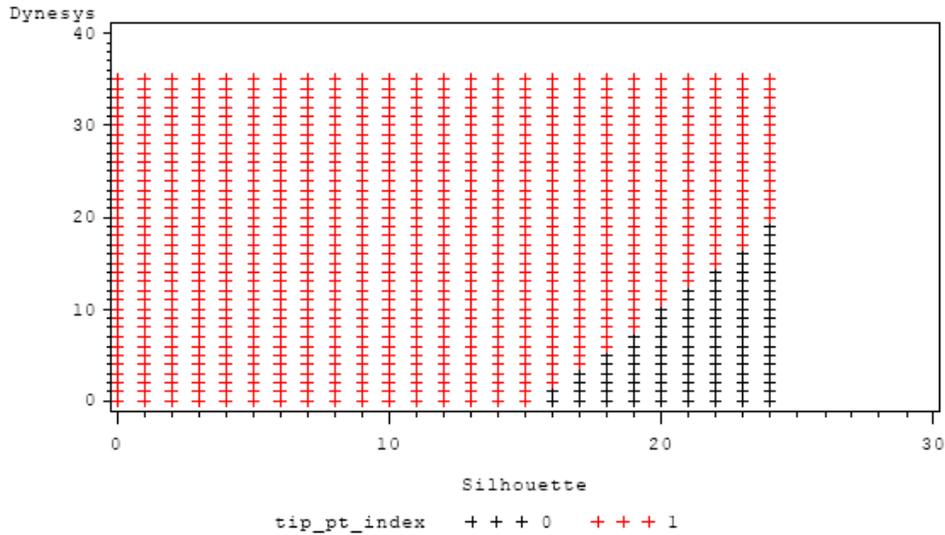
¹ The 90% two-sided confidence limit is presented as it provides the 95% one-sided lower limit when the upper bound is ignored to assess non-inferiority

Although the numbers are relatively small, there is a concerning trend (particularly at time points before 12 months) of lower success rates in Dynesys patients considered lost to follow-up as compared to completers and higher success rates in Silhouette patients considered lost to follow-up as compared to completers.

FDA requested the sponsor perform a tipping point sensitivity analysis of the missing primary endpoint data to assess the robustness of the observed results. Such an analysis involves imputing all possible combinations of success and failure in the missing data for the two groups, to determine the point at which the observed conclusion changes from primary endpoint success to primary endpoint failure.

The tipping point analysis involves the 35 missing Dynesys and 24 missing Silhouette patients. To summarize the findings, of the 900 possible outcome combinations for the missing data, 96 cases do not meet the 10% non-inferiority margin including the worst case scenario presented above. To highlight the most extreme cases that would have resulted in study failure, anything more than 15 out of 24 (62.5%) successes in the missing Silhouette data when there were 0 out of 35 (0%) successes in the Dynesys data would have resulted in a failure to show non-inferiority with a 10% delta. Similarly, if all (100%) of the missing Silhouette data were successes, anything less than 19 out of 35 (54.3%) successes in the missing Dynesys data would have resulted in not meeting the non-inferiority threshold. These results are depicted graphically in the following figure where the red plus signs indicate combinations that would meet the 10% delta whereas black plus signs indicate combinations that would not meet the 10% delta.

Tipping Point Analysis, Delta = -10



Learning Curve Analysis

The first patient at each site was not randomized and was treated with the Dynesys so there were 28 non-randomized patients considered Dynesys training patients. Otherwise, the training patients were treated and evaluated the same as the per-protocol randomized subjects. The sponsor compared demographic characteristics and outcomes between the training subjects and the per-protocol subjects. Outcome comparisons were used as an informal assessment to look for a potential learning curve. There are no substantial differences between the training subjects and the per-protocol randomized Dynesys subjects in terms of demographic and perioperative characteristics. In fact, based on 14 clinical endpoints that the sponsor evaluated, there is a suggestion that more favorable results were obtained for the training patients as compared to the randomized Dynesys patients for a number of clinical endpoints. Based on this data, the sponsor concludes that there is no learning curve.

Financial Disclosure Information and Analyses

The majority of patients treated in the study (in both treatment groups) were treated by financially interested investigators. Specifically, the sponsor requested that each investigator provide financial disclosure information by checking any of the four following statements if applicable:

- Neither I, my immediate family, nor the institution I represent are currently, or expect to be, paid more than \$25,000.00 by Zimmer Spine, Inc. during the course of the study and for 1 year following the completion of the study. Examples of payment requiring disclosure include grants to fund ongoing research, compensation in the form of equipment, retainers for ongoing consultation or honoraria that have a monetary value in excess of \$25,000.00. This excludes payments made to cover the costs of conducting the study.

- Neither I, nor my immediate family, own more than \$50,000.00 worth of Zimmer Holdings Inc. stock.
- Neither I, nor my immediate family, have a proprietary interest in a Zimmer Spine, Inc. product (including, but not limited to, a patent, trademark, copyright, or licensing agreement.) Product is defined as devices that have been or are presently commercialized by Zimmer Spine, Inc. and those which are under present or future evaluation by Zimmer Spine, Inc.
- Neither I, nor my immediate family, have any equity interest in the company in the way of stock options or other financial interest which value cannot be readily determined.

53 of the investigators checked all four statements, 8 checked three, 1 checked two, and 1 checked none. Ten of the twenty-six sites list a total compensation greater than \$100,000, and 53.8% of Dynesys patients and 53.5% of Silhouette patients were treated at those ten sites. Five of those ten sites list a total compensation greater than \$500,000, and 35.2% of Dynesys patients and 33.3% of Silhouette patients were treated at those five sites. Two of those five sites list a total compensation of almost \$1.5 million each, and 18.6% of Dynesys patients and 17.5% of Silhouette patients were treated at those two sites.

The sponsor provided several analyses to investigate the possibility that bias could have been introduced through the financial interests of investigators. One set of analyses used logistic regression to assess the possibility of an interaction between financial compensation and treatment group in predicting clinical success. No statistically significant treatment-by-compensation interaction was found. A second set of analyses examined the correlation between compensation and clinical success rates for the Dynesys treatment, Silhouette treatment and both cohorts combined. The correlation was positive for the Dynesys treatment and negative for the Silhouette, which are the anticipated directions if there were to be an effect of compensation. However, all correlations were far from being statistically significant. Therefore, there is only a trend which suggests the possibility of bias from compensation with no statistically significant evidence of such an effect.

FDA will be asking you to discuss whether the clinical data in the PMA provide reasonable assurance that the proposed device is effective for the specified indication and intended patient population and what additional data or analyses are needed.

SAFETY EVALUATION

The safety of the investigational device was assessed as part of the primary study endpoint by evaluating neurological status, major complications, and secondary surgical interventions. Safety was also evaluated based on the nature and frequency of adverse events which occurred in the Dynesys group, as compared to those that occurred in the Silhouette group.

Neurological Status

Neurological success was defined as maintenance or improvement in the four neurological assessments (motor function, sensory function, reflexes, and straight leg raise) with no new permanent neurological deficits as compared to baseline at 24 months. The following table outlines overall neurological status success rates and neurological component success rates at 24 months for all randomized patients, 1-level randomized patients, 2-level randomized patients, and the Dynesys training cohort. Qualitatively, higher neurological status success rates generally occurred in the Dynesys group as compared to the Silhouette group although the differences are not statistically significant.

Neurological Status Success at 24 Months

	All randomized		1-level randomized		2-level randomized		Training
	Dynesys	Silhouette	Dynesys	Silhouette	Dynesys	Silhouette	Dynesys
Neurological Success (Improve/Maintain)	157/171 (92%)	58/69 (84%)	93/100 (93%)	40/46 (87%)	64/71 (90%)	18/23 (78%)	19/21 (90%)
Fisher's Exact Test	0.10		0.35		0.16		--
Motor Success	167/174 (96%)	64/69 (93%)	Not provided	Not provided	Not provided	Not provided	19/22 (86%)
Reflex Success	156/177 (88%)	61/70 (87%)	Not provided	Not provided	Not provided	Not provided	21/23 (91%)
Sensory Success	165/173 (95%)	63/70 (90%)	Not provided	Not provided	Not provided	Not provided	20/22 (91%)
Straight Leg Raise Success	170/177 (96%)	69/70 (99%)	Not provided	Not provided	Not provided	Not provided	23/23 (100%)

Major Complications

Major complications were defined as blood vessel injury (e.g., great vessel damage, iliac vein laceration), neurological damage (e.g., nerve palsy, nerve trauma), or nerve root injury over the first 24 months. The sponsor's medical advisor, an investigator in the trial, determined nerve root injury status by reviewing the complete set of Case Report Forms (CRFs) for each patient with suspected nerve root injury. All study patients who had a motor score of "total paralysis" (0) or "palpable or visible contraction" (1) or a sensory score that was abnormal (0, 1 or 3) at any time during the investigation, for either side, at any lumbar spinal level, that did not return to a level above (1) for motor or return

to normal (2) for sensory by 24 months on the Neurological Assessments from the Physician Evaluation CRF were identified for further review. The DSMB then reviewed all adverse events for the patients that had a possible “Nerve Root Injury.”

Each randomized study group has one major complication. There are no major complications in the Dynesys training cohort.

- Dynesys: nerve trauma at 6 months in a two-level patient treated for lateral stenosis. Specifically, ~ 6 months post-operative the patient began experiencing right leg numbness which was radiographically diagnosed as a synovial cyst causing severe stenosis and nerve trauma. The cyst was surgically removed and the event resolved without sequelae.
- Silhouette: nerve root damage resulting in abnormal sensory function within the 12 month window in a two-level patient treated for lateral stenosis. Specifically, the patient reported radicular symptoms of numbness, cramping and jerking movement of the lower extremity starting at the 3 week follow-up which was managed by analgesics. Between the 6 and 12 month follow-up visits, the patient was involved in a Motor Vehicle Accident that resulted in low back and leg pain. Radiographically, the patient was diagnosed with a new Herniated Nucleus Pulposus and a dural tear at the index level resulting in a deficit of motor function (L5) or a severe deficit of sensory function in the lower extremity (right L2-L5, left L4-L5).

Secondary Surgical Interventions

Some of the adverse events reported during the study required a surgical intervention subsequent to the initial surgery. The percentage of patients requiring a second surgical intervention classified as a revision, removal, re-operation, or supplemental fixation in the first 24 months is 9% (22/252) in the Dynesys group and 11% (12/113) in the Silhouette group. Seven of the 22 Dynesys secondary surgeries occurred in 1-level patients (secondary surgery rate of 5%) whereas 15 of the 22 Dynesys secondary surgeries occurred in 2-level patients (secondary surgery rate of 13%). The difference is not statistically significant overall ($p=0.56$) or in the case of the 1-level or 2-level patients ($p=0.10$ and $p=0.59$ respectively). The percentage of patients requiring a second surgical intervention classified as a revision, removal, re-operation, or supplemental fixation in the Dynesys training cohort is 4% (1/28). Note that an additional 10 Dynesys subjects as compared to 1 Silhouette subject underwent a secondary surgical procedure after 24 months.

The following table presents timecourse data on secondary surgical interventions:

	Immediate y post-op		3 wks		3 mo		6 mo		12 mo		24 mo		>24 mo		TOTAL (0-24 mo)		TOTAL (incl >24 mo)	
	Dyn	Sil	Dyn	Sil	Dyn	Sil	Dyn	Sil	Dyn	Sil	Dyn	Sil	Dyn	Sil	Dyn	Sil	Dyn	Sil
Reoperation	0	0	6	4	1	1	0	0	1	0	1	0	2	0	9	5	11	5
Revision	0	1	0	0	0	1	0	0	1	1	0	0	1	0	1	3	2	3
Removal	0	0	0	1	0	0	1	0	1	0	0	0	1	1	2	1	3	2
Supplemental Fixation	0	0	0	0	0	0	1	0	1	1	2	0	3	0	4	1	7	1
Removal with Supplemental Fixation	0	0	0	0	2	0	0	0	3	2	1	0	3	0	6	2	9	2
TOTAL	0	1	6	5	3	2	2	0	7	4	4	0	10	1	22	12	32	13

The one secondary surgical intervention in the first 24 months in the Dynesys training cohort was a revision in the 12 month window. In addition, there were 2 additional interventions after 24 month follow-up in the training group (1 removal and 1 removal with supplemental fixation).

The following table summarizes the secondary surgical procedures for the Dynesys patients (randomized and training):

Subject ID	1- or 2-Level	Days from Index Surgery	Analysis Interval for Censoring	Intervention Classification	Brief Description
Dynesys Randomized Patients (Secondary Surgical Procedures Prior to 24 Months):					
1602006	1-Level	14	3-weeks	Reoperation	Decompressive laminectomy at L3-4 and L4-5 on 6/12/03; Hardware prophylactically removed on 6/16/03
1602016	1-Level	703	24-month	Suppl. Fixation	Laminectomy and fusion at L4-5 and L5-S1
1602046	2-Levels	499	12-month	Reoperation	Lumbar microdiscectomy at L4/5 and L5/S1
1603004	2-Levels	684	24-month	Reoperation	(R) L4-5 laminectomy; medial facetectomy; foraminotomy; L5 nerve root decompression, repair of dural tear; (R) L3-4 hemilaminectomy, medial facetectomy at non-investigative site
1603012	2-Levels	715	24-month	Removal/ Suppl. Fixation	Removal of device at L4-S1 with posterior fusion with instrumentation T9-S1 due to adjacent level degeneration and degenerative scoliosis with back pain
1604004	2-Levels	16	3-weeks	Reoperation	Removal of epidural hematoma at L2 to L4 on 11/26/03 and surgery repeated on 11/27/03
1604025	1-Level	663	24-month	Suppl. Fixation	Laminectomy and fusion at L3-4 due to disc degeneration disease diagnosis.
1606002	1-Level	145	3-month	Removal/ Suppl. Fixation	Exploration of lumbar incision and removal of pedicle screws (Dynesys) at L4-5 with reimplantation of pedicle screws and rods and posterior lateral fusion L4-5 with bilateral foraminotomies at L4 and L5
1608004	1-Level	349	12-month	Removal	Removal of device
1610007	2-Levels	17	3-weeks	Reoperation	Re-exploration of wound with lavage, culture and secondary closure due to wound dehiscence
1611012	2-Levels	393	12-month	Suppl. Fixation	(L) transforaminal interbody fusion (TLIF) at L5-S1

Subject ID	1- or 2-Level	Days from Index Surgery	Analysis Interval for Censoring	Intervention Classification	Brief Description
1612010	2-Levels	546	12-month	Removal/ Suppl. Fixation	Removal of device; fusion with instrumentation at L4-S1
1613004	2-Levels	151	3-month	Reoperation	Decompression of L4 and L5 nerve roots at the L4-5 level; re-instrumentation of the Dynesys system from L3 to L5 level
1614004	2-Levels	622	12-month	Revision	Revision of device and decompression at L2-3
1614007	1-Level	269	6-month	Removal	Removal of device L4-5, L5-S1
1614026	2-Levels	16	3-weeks	Reoperation	Wound drainage; Irrigation and Debridement
1615003	2-Levels	16	3-weeks	Reoperation	Irrigation and Debridement
1615015	2-Levels	7	3-weeks	Reoperation	Irrigation and Debridement
1620002	2-Levels	605	12-month	Removal/ Suppl. Fixation	Removal of device at L4-5, L5-S1 with lumbar fusion, pedicle instrumentation L4-5, L5-S1 with interbody fusion X 2 levels
1621014	2-Levels	438	12-month	Removal/ Suppl. Fixation	Removal of device at L4-5 to L5-S1 with posterolateral fusion at L4-5 to L5-S1 with ST360 instrumentation
1622004	1-Level	117	3-month	Removal/ Suppl. Fixation	Removal of device at L3-4; Fusion at L3-4
1627005	2-Levels	186	6-month	Suppl. Fixation	Anterior inner body fusion

Dynesys Randomized Patients (Secondary Surgical Procedures After 24 months)

1602013	1-Level	1167	24MOS2	Suppl Fixation	Revision – L4-5; Arthrodesis L3-4, L4-5, L3-4 laminectomy with medial facetectomy and foraminotomy
1602029	2-Level	1209	24MOS2	Reoperation	Laminectomy L2-3; Revision Laminectomy L3-L5
1605010	1-Level	937	24MOS2	Suppl Fixation	Segmental fixation bilateral L2, L3, L4, L5 and inter-transverse fusion bilateral L3, L4, L5
1605031	1-Level	1427	24MOS2	Removal/ Suppl. Fixation	Metal removal L3-4 and segmental fixation and fusion L2-L3-L4-L5
1605037	1-Level	854	24MOS2	Removal/ Suppl. Fixation	Revision laminectomy L3-4; Removal of Fixation L5-S1 and Segmental Fixation L3-4; L5-S1 and Fusion L5-S1
1605040	1-Level	1175	24MOS2	Suppl Fixation	Laminectomy L4-5 and fixation and fusion L2, L3, L4 for spinal stenosis and degenerative scoliosis
1609004	2-Level	1387	24MOS2	Removal	Removal of Dynesys and multiple I&D's Hemilaminectomy and decompression at L4-5
1611007	1-Level	747	24MOS2	Revision	Revision of Dynesys L4-5; Fusion L3-4; Stabilization L2-3; Central Laminectomy L2 and L3
1614006	1-Level	1208	24MOS2	Reoperation	Revision decompression of L3, L4-5 and L5-S1
1618005	1-Level	1355	24MOS2	Removal/ Suppl. Fixation	Removal of device and fusion of L3-4; L4-5

Dynesys Training Patients (Secondary Surgical Procedures Prior to 24 Months):

Subject ID	1- or 2-Level	Days from Index Surgery	Analysis Interval for Censoring	Intervention Classification	Brief Description
1616-001	2-Levels	631	12-month	Revision	Revision of device – removal of device at L3-4, L5-1 with reimplantation of device at L3-4 to L5-S1
<i>Dynesys Training Patients (Secondary Surgical Procedures After 24 Months):</i>					
1603001	2-Level	1200	24MOS2	Removal/ Suppl. Fixation	Removal of Dynesys instrumentation and fusion
1626001	1-Level	1175	24MOS2	Removal/ Suppl. Fixation	Hardware Removal with L3-4 and L4-5 decompression and circumferential fusion

The following table summarizes the secondary surgical procedures for the Silhouette patients:

Subject ID	1- or 2-Level	Days from Index Surgery	Analysis Interval for Censoring	Intervention Classification	Brief Description
<i>Silhouette Randomized Patients (Secondary Surgical Procedures Prior to 24 Months):</i>					
1602023	1-Level	14	3-week	Reoperation	Irrigation and Debridement
1605025	1-Level	82	3-month	Revision	Revision laminectomy (L) L4-5; partial pedicle resection (L) L5 (previously fractured during index surgery) and instrumentation removal on left side at L4-5
1605029	1-Level	379	12-month	Suppl. Fixation	Pars fracture repair; revision decompression; extend segmental fixation to inferior level - extend from L4-5 to L5-S1
1605046	1-Level	19	3-week	Reoperation	Irrigation and Drainage of site, dural tear repair and closure
1609007	1-Level	118	3-month	Reoperation	(L) hemilaminectomy, foraminotomy L3-4
1609010	1-Level	470	12-month	Removal/Suppl. Fixation	Removal of Silhouette instrumentation L5-S1, exploration of pseudoarthrosis at L5-S1; PLIF at L4-5 and L5-S1
1614032	2-Levels	360	12-month	Removal/ Suppl. Fixation	Removal of device, re-fusion with BMP, removal of lipoma, exploration of fusion (pseudoarthrosis)
1615007	2-Levels	9	3-week	Reoperation	Irrigation and Debridement
1615011	2-Levels	37	3-week	Reoperation	Irrigation and Debridement
1616007	2-Levels	5	Imm Postop	Revision	Re-exploration and reinstrumentation of the (R) L3 pedicle screw; reinstrumentation of L3-L5 PLF due to misplaced screw during index surgery
1620007	1-Level	621	12-month	Revision	Lumbar decompression at L4-5; bilateral posterolateral fusion L4-5; exploration of fusion (pseudoarthrosis) L5-S1; removal and replacement of hardware with extension of grafts L5-S1
1622007	1-Level	51	3-week	Removal	Exploratory surgery with unilateral removal of (L) implant at L4-5
<i>Silhouette Randomized Patients (Secondary Surgical Procedures After 24 Months):</i>					
1614036	1-Level	1149	24MOS2	Removal	Hardware removal

Eleven of the Dynesys patients had devices that were explanted. Explant analyses were performed on four of these cases and are discussed in the *Explant Evaluations* section above.

All Adverse Events

The adverse events, as shown in the table below, are reported from the randomized study which included 253 Dynesys patients and 114 Silhouette patients enrolled in the multi-center clinical study. Separate adverse event data is also presented for the 28 non-randomized Dynesys patients. Adverse event rates presented are based on the number of

patients having at least one occurrence for a particular adverse event divided by the total number of patients in that treatment group.

A total of 196/253 (77.5%) Dynesys patients had at least one adverse event, as compared to 77/114 (67.5%) Silhouette patients. The difference is statistically significant (p=0.05).

The following table presents a summary of the adverse event data by treatment group:

	Dynesys	Silhouette	Fisher's exact test	Dynesys Training
# patients with an AE	196/253 (77.5%)	77/114 (67.5%)	p=0.05	19/28 (67.9%)
Total # AEs	401	187	Not provided	40
% of total AEs ¹	727/784 (92.7%)	350/387 (90.4%)	p=0.21	76/85 (89.4%)
# patients with major complication	1/253 (0.4%)	1/114 (0.9%)	p=0.53	0/28 (0%)
# patients with device-related complication	8/253 (3%)	6/114 (5%)	0.38	Not provided
Total # device-related complications	11	12	Not provided	Not provided
# patients with surgery-related complication	55/253 (22%)	28/114 (25%)	0.59	Not provided
Total # surgery-related complications	82	47	Not provided	Not provided

¹ Percentages for adverse event totals were determined as the ratio of the total number of adverse events with onset during the first 24 postoperative months divided by the total plus the number of patients that did not experience an adverse event.
Note: AEs counted once per type within analysis window.

The following table presents a timecourse distribution of all adverse events that occurred during the clinical study by treatment group for the randomized subjects:

	Immediate Postop		3 Week		3 Month		6 Month		12 Month		24 Month ¹		24+ Month ²		Total Incidence (0-24 Months)		Dynesys (N=253)	Silhouette (N=114)	Fisher's Exact Test
	I ³	C ⁴	I	C	I	C	I	C	I	C	I	C	I	C	I	C			
Surgical/Post-Surgery																			
Allergic Reaction	2	0	3	0	0	0	0	0	0	0	0	0	0	0	5	0	5 (2.0%)	0 (0.0%)	P=0.33
Anesthetic	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1 (0.4%)	1 (0.9%)	P=0.53
Bladder Dysfunction	2	2	0	0	0	0	1	0	0	0	0	0	0	0	3	2	3 (1.2%)	2 (1.8%)	P=0.65
Dural Tear	24	9	1	0	0	0	0	0	0	1	1	0	0	0	26	10	25 (9.9%)	10 (8.8%)	P=0.85
Heart Attack (MI)/Cardiac Arrest	1	1	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1 (0.4%)	1 (0.9%)	P=0.53
Hematoma/Seroma (Implant Site)	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Ileus (Persistent)	6	2	0	0	0	0	0	0	0	0	0	0	0	0	6	2	6 (2.4%)	2 (1.8%)	P>0.99
Pneumonia/Atelectasis	1	1	0	0	1	0	0	1	1	1	0	0	1	0	3	3	3 (1.2%)	3 (2.6%)	P=0.38
Pulmonary Embolism	0	1	1	0	0	0	0	0	0	0	1	0	0	0	2	1	2 (0.8%)	1 (0.9%)	P>0.99
Infection (Urinary Tract)	3	1	0	0	0	0	0	0	0	0	0	0	0	0	3	1	3 (1.2%)	1 (0.9%)	P>0.99
Urinary Problems	1	2	1	0	0	0	0	0	0	0	0	0	1	0	2	2	2 (0.8%)	2 (1.8%)	P=0.59
Anemia*	2	1	0	0	0	0	0	0	0	0	0	0	0	1	2	1	2 (0.8%)	1 (0.9%)	P>0.99

	Immediate Postop		3 Week		3 Month		6 Month		12 Month		24 Month ¹		24+ Month ²		Total Incidence (0-24 Months)		Dynesys (N=253)	Silhouett e (N=114)	Fisher' s Exact Test
	I ³	C ⁴	I	C	I	C	I	C	I	C	I	C	I	C	I	C			
Bronchitis*	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Cardiac Palpitations*	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Dystonia*	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Fever*	5	3	0	0	0	0	0	0	0	0	0	0	0	0	5	3	5 (2.0%)	3 (2.6%)	P=0.71
Blood Loss*	1	3	0	0	0	0	0	0	0	0	0	0	0	0	1	3	1 (0.4%)	3 (2.6%)	P=0.09
Bleeding – Epidural*	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
CSF Leak*	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Chest Pain*	2	0	0	1	0	0	0	0	0	0	0	0	0	0	2	1	2 (0.8%)	1 (0.9%)	P>0.99
Dizziness*	1	0	0	0	0	0	0	0	2	0	0	0	1	0	3	0	3 (1.2%)	0 (0.0%)	P=0.56
Nausea*	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1 (0.4%)	1 (0.9%)	P=0.53
Nausea and Vomiting*	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Poor Pain Control*	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1 (0.4%)	1 (0.9%)	P=0.53
Respiratory Distress – Intraoperative*	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Shortness of Breath*	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Subdural Hematoma*	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Suture Reaction*	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Syncope*	1	0	0	1	0	0	1	0	1	0	0	0	1	0	3	1	3 (1.2%)	1 (0.9%)	P>0.99
Vomiting*	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0 (0.0%)	1 (0.9%)	P=0.31
Screw Integrity																			
Device Misplacement	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0 (0.0%)	1 (0.9%)	P=0.31
Implant Migration	0	0	0	0	0	0	0	0	1	0	0	0	1	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Screw Failure	1	1	1	0	1	0	0	0	0	0	1	0	0	0	4	1	4 (1.6%)	1 (0.9%)	P>0.99
Screw Misplacement	2	2	0	1	0	0	0	0	0	0	0	0	0	1	2	3	2 (0.8%)	3 (2.6%)	P=0.18
Screw Loosening*	0	0	0	0	0	0	0	2	0	0	0	1	1	0	0	3	0 (0.0%)	3 (2.6%)	P=0.03
Radiolucency –Screw*	0	0	0	0	1	0	1	0	3	0	0	2	3	0	5	2	5 (2.0%)	2 (1.8%)	P=0.99
Sensory Change*	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0 (0.0%)	1 (0.9%)	P=0.31
Instability/ Degeneration																			
Vertebral Fracture	2	0	0	1	1	0	0	0	1	0	0	0	0	0	4	1	4 (1.6%)	1 (0.9%)	P>0.99
Disc Herniation	0	0	0	0	0	0	1	0	1	0	2	0	1	1	4	0	4 (1.6%)	0 (0.0%)	P=0.31
Disc Degeneration	0	0	0	0	0	0	4	0	1	0	1	1	4	2	6	1	6 (2.4%)	1 (0.9%)	P=0.44
Stenosis (Central)	0	0	1	0	0	0	0	0	0	0	1	0	3	2	2	0	2 (0.8%)	0 (0.0%)	P>0.99
Foraminal Stenosis	0	0	0	1	0	0	0	0	1	0	0	0	1	1	1	1	1 (0.4%)	1 (0.9%)	P=0.53
Pseudoarthrosis/Non-union	0	0	0	0	0	0	0	1	0	1	0	1	1	0	0	3	0 (0.0%)	3 (2.6%)	P=0.03
Increased Instability	0	0	0	0	0	0	0	0	1	0	0	0	0	3	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Retrolisthesis-Superior*	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0			
Spondylolisthesis – Superior*	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	1	0 (0.0%)	1 (0.9%)	P=0.31
Hyperreflexia*	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0			
LE Instability*	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0			
Fusion - 360°*	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0 (0.0%)	1 (0.9%)	P=0.31
Fusion Superior Level*	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0 (0.0%)	1 (0.9%)	P=0.31
Laminectomy*	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Laminectomy and Fusion*	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99

	Immediate Postop		3 Week		3 Month		6 Month		12 Month		24 Month ¹		24+ Month ²		Total Incidence (0-24 Months)		Dynesys (N=253)	Silhouett e (N=114)	Fisher' s Exact Test		
	I ³	C ⁴	I	C	I	C	I	C	I	C	I	C	I	C	I	C				P- value	
Stroke	0	0	0	0	1	0	0	0	0	0	0	0	0	0	2	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Wound Infection																					
Infection (Graft Site)	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0 (0.0%)	1 (0.9%)	P=0.31
Infection (Implant Site)	0	0	4	3	0	0	0	0	0	0	0	0	0	0	0	4	3	4 (1.6%)	3 (2.6%)	P=0.68	
Wound Dehiscence (Implant Site)	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0	3	0	3 (1.2%)	0 (0.0%)	P=0.56	
Edematous Wound*	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99	
I & D*	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1	1 (0.4%)	1 (0.9%)	P=0.53		
Wound Drainage*	0	1	2	2	0	0	0	0	0	0	0	0	0	0	2	3	2 (0.8%)	3 (2.6%)	P=0.18		
Wound Infection*	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2	0	2 (0.8%)	0 (0.0%)	P>0.99		
Back Pain																					
Back Pain	5	2	4	9	17	2	5	4	12	8	5	0	16	10	48	25	47 (18.6%)	25 (21.9%)	P=0.48		
BP – Low*	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99		
Pain – Back*	0	0	0	0	0	0	2	0	1	0	1	1	2	0	4	1	4 (1.6%)	1 (0.9%)	P>0.99		
Pain - Back and Buttock*	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0					
Back and Leg Pain																					
Back And Leg Pain	4	1	9	1	10	2	9	2	13	3	4	0	15	6	49	9	47 (18.6%)	9 (7.9%)	P=<.01		
Pain – Back and Leg*	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99		
Pain – Buttock*	0	0	0	0	0	0	0	0	2	0	0	0	0	0	2	0	2 (0.8%)	0 (0.0%)	P>0.99		
Pain - Buttock and Hip*	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0					
Pain - Buttock and Thigh*	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99		
Leg Pain																					
Leg Pain	4	2	12	4	6	5	2	4	9	2	1	2	11	5	34	19	31 (12.3%)	19 (16.7%)	P=0.25		
Pain – Leg*	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0 (0.0%)	1 (0.9%)	P=0.31		
Pain – LE*	0	0	0	2	1	0	0	0	1	0	0	0	1	1	2	2	2 (0.8%)	2 (1.8%)	P=0.59		
Hip Related																					
Hip Pain	0	2	0	1	0	0	0	1	1	0	0	0	0	1	1	4	1 (0.4%)	3 (2.6%)	P=0.09		
AVN*	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99		
Pain – Hip*	3	0	2	0	2	0	1	1	4	0	0	0	2	0	12	1	12 (4.7%)	1 (0.9%)	P=0.07		
Pain - Hip and Buttock*	1	0	1	0	0	0	0	0	0	0	0	0	0	0	2	0	2 (0.8%)	0 (0.0%)	P>0.99		
Pain - Hip and Knee*	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99		
Pain - Hip and Leg*	0	0	0	0	1	0	0	0	0	0	0	0	0	1	1	0	1 (0.4%)	0 (0.0%)	P>0.99		
Pain - Hip and Neck*	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0 (0.0%)	1 (0.9%)	P=0.31		
Pain and Weakness - Hip and Leg*	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99		
Lower Extremity Issues																					
Burning Sensation – Feet*	0	0	0	0	0	1	0	0	1	0	0	0	0	0	1	1	1 (0.4%)	1 (0.9%)	P=0.53		

	Immediate Postop		3 Week		3 Month		6 Month		12 Month		24 Month ¹		24+ Month ²		Total Incidence (0-24 Months)		Dynesys (N=253)	Silhouett e (N=114)	Fisher' s Exact Test
	I ³	C ⁴	I	C	I	C	I	C	I	C	I	C	I	C	I	C			
Burning Sensation – LE*	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Burning Sensation – Thoracic*	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Sensation Decreased*	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0			
Claudication – LE*	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0			
Dyesthesia – LE*	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Numbness & Cramps – LE*	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0 (0.0%)	1 (0.9%)	P=0.31
Numbness & Tingling – LE*	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0 (0.0%)	1 (0.9%)	P=0.31
Numbness – LE*	0	0	1	1	0	1	1	0	1	1	0	0	1	0	3	3	3 (1.2%)	3 (2.6%)	P=0.38
Numbness – Thigh*	1	0	0	0	0	0	0	1	0	0	0	0	0	0	1	1	1 (0.4%)	1 (0.9%)	P=0.53
Pain & Numbness – LE*	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Pain – Feet*	0	0	0	0	1	0	0	0	0	0	0	0	1	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Pain - Great Right Toe*	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0			
Pain – Groin*	0	0	1	0	0	0	0	0	0	1	0	0	0	0	1	1	1 (0.4%)	1 (0.9%)	P=0.53
Pain – Knee*	0	0	0	0	0	0	1	1	1	1	0	0	6	1	2	2	2 (0.8%)	2 (1.8%)	P=0.59
Pain – Rib*	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	1	0 (0.0%)	1 (0.9%)	P=0.31
Pain – S.I. Joint*	0	0	0	0	2	0	0	1	0	0	1	0	1	0	3	1	3 (1.2%)	1 (0.9%)	P>0.99
Pain – Thigh*	0	0	0	1	0	0	0	0	0	0	1	0	0	0	1	1	1 (0.4%)	1 (0.9%)	P=0.53
Pain and Numbness - Back and LE*	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0			
Pain and Swelling – Ankle*	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0			
Pain and Swelling – Knee*	0	0	0	0	1	0	0	0	0	0	0	1	0	1	1	1	1 (0.4%)	1 (0.9%)	P=0.53
Pain and Swelling – LE*	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Paresthesia – LE*	1	0	0	0	0	0	0	0	1	0	0	0	0	0	2	0	2 (0.8%)	0 (0.0%)	P>0.99
Pars Fracture Repair*	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0 (0.0%)	1 (0.9%)	P=0.31
Peripheral Neuropathy – LE*	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0 (0.0%)	1 (0.9%)	P=0.31
Spasms - Back & Thighs*	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Weakness – LE*	1	0	0	0	2	1	0	1	0	1	1	0	1	1	4	3	4 (1.6%)	3 (2.6%)	P=0.68
Weakness and Numbness – LE*	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Cervical and Upper Extremity																			
ACDF*	0	0	0	0	0	0	0	0	1	0	0	0	1	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Cervical Disc Herniation and Myelopathy*	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0			
Cervical Myelopathy*	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0			
Cervical Radiculopathy*	0	0	0	0	0	0	0	0	1	1	0	0	0	0	1	1	1 (0.4%)	1 (0.9%)	P=0.53

	Immediate Postop		3 Week		3 Month		6 Month		12 Month		24 Month ¹		24+ Month ²		Total Incidence (0-24 Months)		Dynesys (N=253)	Silhouette (N=114)	Fisher's Exact Test
	I ³	C ⁴	I	C	I	C	I	C	I	C	I	C	I	C	I	C			
Cervical Spondylosis*	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Muscle Weakness – TA*	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0 (0.0%)	1 (0.9%)	P=0.31
Numbness & Tingling – UE*	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0			
Pain - Cervical Spine and Upper Trap*	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0			
Pain – Elbow* (Epicondylitis)	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Pain – Neck*	0	0	0	0	1	0	1	1	1	1	1	0	1	0	4	2	4 (1.6%)	2 (1.8%)	P>0.99
Pain – Neck and Arm*	0	0	0	0	0	0	1	0	0	1	0	0	0	1	1	1	1 (0.4%)	1 (0.9%)	P=0.53
Pain - Neck and Shoulder*	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Pain – Neck and UE*	0	0	0	0	1	0	0	0	0	0	0	0	1	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Pain – Occipital*	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0			
Pain – Shoulder*	0	0	0	1	0	1	0	0	1	0	0	0	1	0	1	2	1 (0.4%)	2 (1.8%)	P=0.23
Pain - Shoulder and Arm*	0	0	0	0	0	0	0	0	1	0	0	0	1	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Pain and Paresthesia – UE*	0	0	0	0	0	0	1	0	0	0	0	0	1	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Pain and Stiffness – Neck*	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0			
Pain and Stiffness – Shoulder*	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0			
Pain - Trapezius Muscle*	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0 (0.0%)	1 (0.9%)	P=0.31
Pain, Numbness and Weakness – Neck*	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Paresthesia and Pain – Hands*	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Partial Shoulder Replacement*	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0			
Shaky Dysfunction – UE*	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0 (0.0%)	1 (0.9%)	P=0.31
Tingling – UE*	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Weakness – UE*	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0			
Central Neurological Deficits*	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
Cancer																			
Cancer	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	1	0 (0.0%)	1 (0.9%)	P=0.31
Breast Cancer*	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0 (0.0%)	1 (0.9%)	P=0.31
Colon Cancer*	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0			
Degenerative Joint Disease																			
DJD – Knee*	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	1 (0.4%)	0 (0.0%)	P>0.99
DJD – Shoulder*	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0			
Other – Miscellaneous ⁵	11	6	5	3	6	4	17	5	26	10	3	3	38	20	68	31			

	Immediate Postop		3 Week		3 Month		6 Month		12 Month		24 Month ¹		24+ Month ²		Total Incidence (0-24 Months)		Dynesys (N=253)	Silhouette (N=114)	Fisher's Exact Test	
	I ³	C ⁴	I	C	I	C	I	C	I	C	I	C	I	C	I	C				P-value
Total	100	50	59	38	61	20	53	30	10	3	36	26	13	3	67	14	401	187		

1. The 24 Month assessment ends at the subjects' two-year anniversary from surgery.
2. The 24+ Month assessment is any assessment after the two-year anniversary from surgery. Please note: 24+ months is not included in the Fisher's exact test or total counts, and only ONE incidence per visit is counted (i.e., if more than one incidence is reported within the same window, only the first is counted).
3. I = Investigational (Dynesys Spinal System)
4. C = Control (Silhouette)
5. Other Miscellaneous Reported from 0-24 Months (Dynesys/Silhouette) - Adult Onset Diabetes (1/0); Anchory Procedure – Hand (1/0); Angina/SOB/HBP (0/1); Anxiety Attack (0/1); Arrhythmia (1/0); Arthritis – Knee (3/0); Arthritis – Thumb (1/0); Bleeding – Rectal (1/0); Bypass Surgery - Femoral Popliteal (1/0); Cellulitis – LE (1/0); Chest Pressure (1/0); Coccydynia (1/1); Colitis (0/1); Compartment Syndrome (0/1); Constipation (1/1); Depression (1/0); Dermatitis (1/0); Diarrhea (2/0); Edema – Leg (1/0); Effusion – Knee (1/0); Elevated RA Factor (0/1); Emphysema (0/1); Esophageal Spasm (0/1); Foreign Object Retrieval – Stomach (1/0); Fracture – Fibula (0/1); Fracture – Rib (1/0); Fracture - Stress, Foot (1/0); Gastric Dilatation (1/0); Gout (1/0); Head Cold (0/1); Headache (2/2); Hematuria (1/0); Hernia – Abdominal (0/1); Hernia – Inguinal (1/0); Hernia Repair - Umbilical and Abdominal (1/0); Hyperglycemia (1/0); Hypotensive Episode (1/0); Implant - Great Left Toe (1/0); Injury – Wrist (0/1); Intestinal Virus (0/1); Kidney Stone (2/0); Knee - Infection/Aspiration (1/0); Knee – Injury (0/1); Knee Surgery (1/0); Lyme Disease (1/0); Memory Loss (1/0); Meniscus Tear (0/1); Meralgia Paresthetica (1/0); Muscle Cramps (1/0); Orthostatic Hypotension (1/0); Osteoarthritis - End Stage (0/1); Osteoporosis (0/1); Pacemaker Lead Malposition (1/0); Pain with Sleep Disturbance (1/0); Pneumonia (0/1); Pulmonary Edema (0/1); Pulmonary Embolism (0/1); Respiratory Arrest (0/1); Respiratory Distress (0/1); Restless Leg Syndrome (0/2); Salivary Gland Aspiration (1/0); Shingles (2/0); Skin Discoloration (1/0); Small Bowel Obstruction (1/0); Surgery - Dequervain Release (Hand) (2/0); Surgery – Foot (1/0); Tachycardia (1/0); Tendonitis – Foot (1/0); Thumb Joint Dysfunction (1/0); Thumb Tendon Dysfunction (1/0); Tinnitus (1/0); Torn Meniscus (1/0); Trigger Thumb (1/0); Ulcer - Right Big Toe (1/0); Upper Respiratory Infection (2/0); Vascular Occlusion – Aortic (1/0); Vascular Occlusion – SVC (1/0); Voiding Difficulty (1/0); Weakness and Fatigue (1/0).

* All Other* AEs reported on this table were text reported on AE CRF under “Other, Specify”

The following table presents a time course distribution of all adverse events that occurred during the clinical study by treatment group for the Dynesys training subjects:

	Immediate Postop	3 Weeks	3 Month	6 Month	12 Month	24 Month ¹	24+ Month ²	Total Incidence (0-24 Months)	Dynesys (N=28)
	D ³	D	D	D	D	D	D		
Surgical/Post-Surgery									
Fall*	1	0	0	0	0	0	0	1	1 (3.6%)
Fever*	0	1	0	0	0	0	0	1	1 (3.6%)
Nausea and Vomiting*	1	0	0	0	0	0	0	1	1 (3.6%)
Numbness – Toe*	1	0	0	0	0	0	0	1	1 (3.6%)
CSF Leak*	0	0	0	0	0	0	1	0	
Bleeding - Excisional Wound*	0	0	0	0	0	0	1	0	
Dural Tear	1	1	0	0	0	0	0	2	1 (3.6%)
Skin Necrosis	0	1	0	0	0	0	0	1	1 (3.6%)

	Immediate Postop	3 Weeks	3 Month	6 Month	12 Month	24 Month ¹	24+ Month ²	Total Incidence (0-24 Months)	Dynesys (N=28)
	D ³	D	D	D	D	D	D		
Hematoma/Seroma (Implant Site)	0	1	0	0	0	0	0	1	1 (3.6%)
Instability/Degeneratons									
Disc Herniation	0	0	0	0	1	0	1	1	1 (3.6%)
Disc Degeneration	0	0	0	0	1	0	0	1	1 (3.6%)
Back Pain									
Back Pain	0	1	2	1	3	0	1	7	7 (25.0%)
Pain – Back*	0	0	0	0	0	0	2	0	
Pain - Back and Buttock*	0	0	0	0	1	0	1	1	1 (3.6%)
Pain - Buttock and Hip*	0	0	0	0	1	0	0	1	1 (3.6%)
Leg Pain									
Leg Pain	1	0	0	0	0	0	1	1	1 (3.6%)
Back And Leg Pain	0	0	0	0	1	0	3	1	1 (3.6%)
Hip and Lower Extremity									
Pain - Hip and Leg*	0	0	0	0	1	0	0	1	1 (3.6%)
Pain – LE*	0	0	0	0	0	1	0	1	1 (3.6%)
Pain – Sciatic*	0	0	0	1	0	0	0	1	1 (3.6%)
Peripheral Neuropathy – LE*	0	0	0	1	0	0	0	1	1 (3.6%)
Burning Sensation – LE*	0	0	0	0	0	0	1	0	
Claudication – LE*	0	0	0	0	0	0	1	0	
Dyesthesia – LE*	0	0	0	0	0	0	1	0	
Numbness & Tingling – LE*	0	0	0	0	1	0	0	1	1 (3.6%)
Dyesthesia - UE and LE*	0	0	0	0	0	0	1	0	
Pain – Groin*	0	0	0	0	1	0	0	1	1 (3.6%)
Pain – Hip*	0	0	0	1	0	0	0	1	1 (3.6%)
Pain – Knee*	0	0	0	0	1	0	1	1	1 (3.6%)
Pain – Perineal*	0	0	0	0	1	0	0	1	1 (3.6%)
Pain – Thigh*	0	0	1	0	0	0	0	1	1 (3.6%)
Stiffness – Back*	0	0	0	0	1	0	0	1	1 (3.6%)
Cervical and Upper Extremity									
Pain – Neck*	0	0	0	0	1	0	0	1	1 (3.6%)
Pain - Neck and Arm*	0	0	0	0	0	0	1	0	
Pain - Neck and Shoulder*	0	0	0	0	0	0	1	0	
Pain and Paresthesia – UE*	0	0	0	1	0	0	0	1	1 (3.6%)
Pain – Shoulder*	0	0	0	1	1	0	0	2	2 (7.1%)
Rotator Cuff Surgery*	0	0	0	1	0	0	0	1	1 (3.6%)
Screw Integrity									
Screw Misplacement	0	0	0	0	0	0	1	0	
Radiolucency – Screw*	0	0	0	0	1	0	1	1	1 (3.6%)
Screw Loosening*	1	0	0	0	0	0	0	1	1 (3.6%)
Cancer									
Cancer	0	0	0	0	0	0	1	0	
Breast Cancer*	0	0	0	1	0	0	0	1	1 (3.6%)
Breast Reconstruction*	0	0	0	0	0	0	1	0	
Other Miscellaneous ⁴	0	0	1	0	2	1	1		
Total	9	6	5	14	27	3	33		

1. The 24 Month assessment ends at the subjects two year anniversary from surgery.
2. The 24+ Month assessment is any assessment after the two year anniversary from surgery.
3. D = Dynesys Spinal System Training cohort

4. Other Miscellaneous Reported from 0-24 Months (Dynesys Training): Hernia Repair – Abdominal (1); Knee Replacement Surgery (1); Fracture – Hand (1); Headache and Diffuse Myalgia (1).

* All Other* AEs reported on this table were text reported on AE CRF under “Other, Specify”

Device-Related Complications

The number of patients who had adverse events classified as complications and further classified as device-related complications over the first 24 months in the Dynesys group is 8/253 (3%), as compared to 6/114 (5%) in the Silhouette group. This difference is not statistically significant (p=0.38). Looking separately at 1- and 2-level patients, the device-related adverse event rate is 4% in both study groups for 1-level patients (5/137 Dynesys patients and 3/69 Silhouette patients) but for 2-level patients is 3% (3/116) for Dynesys as compared to 7% (3/45) for Silhouette patients. Neither difference is statistically significant (p>0.99 and p=0.35 respectively).

The following table outlines the adverse events classified as device-related complications by category for each treatment group:

	Dynesys		Silhouette	
	# events	# subjects	# events	# subjects
Dural tear	0	0	1	1 (0.9%)
Implant migration	1	1 (0.4%)	0	0
Back pain	3	2 (0.8%)	0	0
Leg pain	0	0	2	1 (0.9%)
Pseudoarthrosis	0	0	1	1 (0.9%)
Back and leg pain	2	2 (0.8%)	0	0
Vertebral fracture	0	0	1	1 (0.9%)
Device misplacement	0	0	1	1 (0.9%)
Screw failure	3	3 (1.2%)	0	0
Screw misplacement	1	1 (0.4%)	2	2 (1.8%)
Other	1	1 (0.4%)	4	3 (2.6%)
Disc degeneration	0	0	0	0

Surgery-Related Complications

The number of patients who had adverse events classified as complications and further classified as surgery-related complications over the first 24 months in the Dynesys group is 55/253 (22%) as compared to 28/114 (25%) in the Silhouette group. This difference is not statistically significant (p=0.59). Looking separately at 1- and 2-level patients, the surgery-related adverse event rate for 1-level patients is 20% (27/137) in the Dynesys group as compared to 19% (13/69) in the Silhouette group. For 2-level patients, the corresponding rates are 24% (28/116) in the Dynesys group and 33% (15/45) in the Silhouette group. Neither difference is statistically significant (p>0.99 and p=0.24 respectively).

The following table outlines the adverse events classified as surgery-related complications by category for each treatment group:

	Dynesys		Silhouette	
	# events	# subjects	# events	# subjects
Bladder dysfxn	0	0	2 (0.9%)	1 (0.9%)
Disc herniation	2	2 (0.8%)	0	0
Dural tear	25	24 (9.5%)	10	9 (7.9%)
MI/cardiac arrest	1	2 (0.8%)	2	1 (0.9%)
Hematoma/seroma (implant site)	1	1 (0.4%)	0	0
Ileus (persistent)	2	2 (0.8%)	0	0
Infection (implant site)	2	2 (0.8%)	3	3 (2.6%)
Infection (UTI)	1	1 (0.4%)	0	0
Pneumonia/ atelectasis	1	1 (0.4%)	0	0
PE	1	1 (0.4%)	1	1 (0.9%)
Wound dehiscence (implant site)	2	2 (0.8%)	0	0
Back pain	2	4 (1.6%)	1	2 (1.8%)
Leg pain	2	2 (0.8%)	1	1 (0.9%)
Foraminal stenosis	0	0	1	1 (0.9%)
Pseudoarthrosis	0	0	1	1 (0.9%)
Hip pain	0	0	1	1 (0.9%)
Urinary problems	1	1 (0.4%)	0	0
Disc degeneration	2	1 (0.4%)	0	0
Stenosis (central)	2	2 (0.8%)	0	0
Back & leg pain	3	5 (2%)	1	0
Screw failure	0	0	1	1 (0.9%)
Screw misplacement	0	0	0	1 (0.9%)
Other	17	11 (4.3%)	15	9 (7.9%)

Detailed Information on Specific Adverse Event Categories:

Back and Leg Pain

There is a significant difference in “back and leg pain” adverse events with onset during the first 24 months with more patients experiencing events in Dynesys group (18.6%) as compared to the Silhouette group (7.9%). This difference is statistically significant ($p \leq 0.01$) overall and for the one-level patients. While there are still more “back and leg pain” adverse events in the two-level Dynesys patients as compared to the two-level Silhouette patients, the difference does not reach statistical significance. For the other adverse event categories related to back and leg pain, the Silhouette group generally has less adverse events than the Dynesys group although none of the other differences reach statistical significance.

	Dynesys	Silhouette	p-value
Leg Pain – all patients	31 (12.3%)	19 (16.7%)	P=0.25
1-level patients	17 (12.4%)	14 (20.3%)	P=0.15
2-level patients	14 (12.1%)	5 (11.1%)	P>0.99
Pain – LE - Other*	2 (0.8%)	2 (1.8%)	P=0.59
Pain – Leg - Other*	0 (0.0%)	1 (0.9%)	P=0.31
Back Pain	47 (18.6%)	25 (21.9%)	P=0.48
1-level	23 (16.8%)	18 (26.1%)	P=0.14
2-level	24 (20.7%)	7 (15.6%)	P=0.51
Pain - Low Back Pain - Other*	1 (0.4%)	0 (0.0%)	P>0.99
Pain - Back - Other*	4 (1.6%)	1 (0.9%)	P>0.99
Back And Leg Pain	47 (18.6%)	9 (7.9%)	P=<.01
1-level	26 (19.0%)	5 (7.2%)	P=0.04
2-level	21 (18.1%)	4 (8.9%)	P=0.22
Pain - Back and Leg - Other*	1 (0.4%)	0 (0.0%)	P>0.99
Spasms - Back & Thighs - Other*	1 (0.4%)	0 (0.0%)	P>0.99

* All Other* AEs reported on this table were text reported on AE CRF under “Other, Specify”

Screw/Device Related Adverse Events

There are 12 Dynesys adverse events related to the screw/device as compared to 11 Silhouette events listed in the adverse events time course table above. Events include screw failure, screw misplacement, screw loosening, screw radiolucency, device misplacement, and implant migration as outlined in the following table:

Screw Integrity	Dynesys	Silhouette	p-value
Device Misplacement	0 (0.0%)	1 (0.9%)	P=0.31
Implant Migration	1 (0.4%)	0 (0.0%)	P>0.99
Screw Failure	4 (1.6%)	1 (0.9%)	P>0.99
Screw Misplacement	2 (0.8%)	3 (2.6%)	P=0.18
Screw Loosening*	0 (0.0%)	3 (2.6%)	P=0.03
Radiolucency –Screw*	5 (2.0%)	2 (1.8%)	P=0.99
Sensory Change*	0 (0.0%)	1 (0.9%)	P=0.31

After submission of the original PMA and following discussions with the FDA, it was determined to count any screw failures, as defined by screw lucency, screw loosening, screw migration or screw misplacement, as a study failure and the patient was censored when the sponsor became aware of the failure. There are reported screw issues for 21 total patients, 16 Dynesys and 5 Silhouette. Of these 21 patients, 1 was a Dynesys training patient, 5 (3 Dynesys and 2 Silhouette) had an event prior to the screw integrity issue that censored their data from further analysis, and the remaining 15 were censored due to screw failure (12 Dynesys and 3 Silhouette). For the 15 subject censored for screw issues, a separate screw failure analysis was done to assess specifically the impact of screw failures on treatment differences; both overall and at the 1- level and 2-level instrumented levels. The table below contains the results of that analysis:

	Dynesys	Silhouette	Difference	90% 2-sided Confidence Interval	p-value
Overall	12/217 (5.5%)	3/89 (3.4%)	2.2%	(-1.9% to 6.2%)	0.86
1-level	4/119 (3.4%)	1/57 (1.8%)	1.6%	(-2.3% to 5.6%)	0.86
2-level	8/98 (8.2%)	2/32 (6.3%)	1.9%	(-6.5% to 10.3%)	0.76

Considering all screw failures, in the Dynesys group, 1 occurred at 3 weeks, 1 at 3 months, 1 at 6 months, 5 at 12 months (1 of which was not the reason for censoring), 3 at 24 months, 2 at 36 months, and 2 at other visits (both of which were not the reason for censoring). In the Silhouette group, 2 occurred at 6 months, 2 occurred at 24 months (1 of which was not the reason for censoring), and 1 occurred at another visit (and was not the reason for censoring). 10 of the 15 total Dynesys screw failures and 3 of the 5 total Silhouette screw failures occurred in 2-level patients.

The sponsor provided the following more detailed information about the 16 Dynesys, 5 Silhouette, and 1 Dynesys training patients with screw failures:

ID	Visit	Screw Issue Category/Visit	AE Report (Description and Date)	AE Comments	Additional AE Reporting
Dynesys Randomized					
1603004 (Reoperation, Censored)	Other	Loosening	"Other - screw loosening" on AE CRF 8/10/04 (Exam Date)	CT SCAN MYELO REVEALED LOOSENING OF S1 SCREW- RESULTING IN LEG AND BACK PAIN WITH FOOT DROP	"Other - Reoperation" on 7/6/05 (Exam Date) AE CRF
1604010 (3-level Subject, Censored)	12MOS	Fracture	"Screw Failure/Fracture Level L4 L5 (L)" on AE CRF 2/24/05 (Exam Date)	RADIOGRAPHS TAKEN ON 2/24/05 SHOW BOTH SCREWS ARE FRACTURED AS THEN PENETRATE THE POSTERIOR PLANE OF THE VERTEBRAL BODY - NO TREATMENT PLANNED	"Screw Failure/Fracture Level L4" - noted "occ Vicodin for pain" on 3/16/06, 5/15/07 and 3/18/08 (Exam Date) AE CRFs
1605006	24MOS	Lucency	"Other - screw radiolucency (L) L4" on AE CRF 6/17/05 (Exam Date)	RADIOLUCENCY NOTED ON AP XR OF LEFT L4 SCREW, PATIENT ASYMPTOMATIC	"Other- screw radiolucency (L) L4" on 7/14/06 (Exam Date) AE CRF
1605020	6MOS	Lucency	"Other - L3 screw lucency" on AE CRF 4/1/04 (Exam Date)	NEW LUCENCY SURROUNDING (R) L3 SCREW, NO ABNORMAL MOTION, ASYMPTOMATIC.	"Other- L3 screw lucency" noted "observation" on 9/10/04 and 3/01/07 (Exam Date) AE CRFs
1605022	36MOS	Migration	"Device Migration Level L4" on AE CRF 12/13/06 (Exam Date)	SET SCREW L4 SCREW LOOSENED, PATIENT DOING WELL	"Device Migration Level 4" noted "Pt complains of intermittent severe low back pain, MRI ordered" on 5/02/08 (Exam Date) AE CRF

ID	Visit	Screw Issue Category/Visit	AE Report (Description and Date)	AE Comments	Additional AE Reporting
1607004	12MOS	Lucency	"Other - (L) L4 Screw Lucency" on AE CRF 4/20/05 (Exam Date)	PT IS IN FOR 12 MOS. ROUTINE FOLLOW-UP. X-RAYS DEMONSTRATE LUCENCY AROUND LEFT L4 SCREW.	"Screw Failure/Fracture Level (R) L4" - noted "On X-ray the(R) L4 screw is fractured" on 4/19/06 and 4/19/07 Exam Dare AE CRFs; "Other - (L) L4 screw lucency"- noted "X-rays demonstrates persistent lucency around the (L) L4 screw" on 4/19/06, 4/19/07 and 5/29/08 (Exam Date) AE CRFs
1607005	3MOS	Lucency	"Other - (L) L4 Screw Lucency" on AE CRF 7/22/04 (Exam Date)	IT WAS NOTED ON X-RAYS DATED 7/22/04 THAT THERE APPEARS TO BE SOME LUCENCY AROUND HIS (L) L4 SCREW	"Other - (L) L4 Screw Lucency" on 10/21/04 - Noted "The lucency around the (L) L4 screw has resolved" on 10/21/04 (Exam Date) AE CRF
1608002	12MOS	Loosening	"Back Pain" on AE CRF 9/03/04 (Exam Date); "Other - Screw Loosening at L4 level" on AE CRF 9/03/04 (Exam Date)	SUBJECT C/O MID-LOW BACK PAIN AND BURNING OF LEGS AND FEET NOW. CT SCAN REVEALS LOOSENING SCREWS @L4-5. DR. WELCH ADVISES REMOVAL OF HARDWARE. HE ALSO FEELS THERE MAY BE A MILD NEUROPATHY - (TOO MILD TO DIAGNOSE); X-RAY ON 2/20/04 HALO WAS NOTED AROUND L4 SCREWS, CT SCAN OF 3/12/04 CONFIRMED THIS"	"Other - Screw loosening at L4 Level" - noted NO screw loosening or Halo on 9/7/07 X-rays"
1608004 (Partial removal, Censored)	Other	Loosening	"Other - Loosening of pedicle screw at L3" on AE CRF 7/4/04 (Exam Date)	PEDICLE SCREW LOOSE PER CT SCAN NOTED 7-8-04	"Other - Removal of Hardware"; "Note: Pedicle Screw Loose" on 3/31/05 (Exam Date) AE CRF
1609008	3WKS	Loosening	"Screw Failure/Fracture level L4 L5 (L)" on AE CRF 12/05/03 (Exam Date)	PATIENT COMPLAINS OF BACK AND LEFT LEG PAIN. X-RAY SHOWS L4-5 LOOSENING AT SCREW.	"Screw Failure/Fracture level L4 L5 (L)" noted - "X-ray views show Left L4 screw loose; 1/19/04 revision and reposition of L4-5 pedicle screw; (L) L4 screw removed and replaced and spacer was replaced" on 01/19/04 (Exam Date) CRF

ID	Visit	Screw Issue Category/Visit	AE Report (Description and Date)	AE Comments	Additional AE Reporting
1609015	24MOS	Lucency	"Back and Leg Pain" with crossed out "Other - MVA screw loosening" on AE CRF 3/14/06 (Exam Date)	PATIENT HAD MVA ON 6/18/04 AND SINCE THEN HE HAS BACK PAIN AND @ LE PAIN (NO NOTES OF SCREW ISSUES ON CRF WITH THE EXCEPTION OF CORRECTED/CROSSED OUT "SCREW LOOSENING" ON FRONT OF CRF	
1611003	36MOS	Lucency	"Other - Asymptomatic (L) L4 screw radiolucency" on AE CRF 4/27/07 (Exam Date)	NEW RADIOGRAPHIC LUCENCY AROUND LEFT L4 SCREW	
1611021	24MOS	Fracture	"Screw failure/Fracture level L5" on AE CRF 2/16/07 (Exam Date)	LEG AND BACK PAIN (NO NOTES ON SCREW FAILURE OR RADIOGRAPHIC ISSUES IN COMMENTS ON AE CRF)	
1612004	12MOS	Migration	"Device migration Level L2' on AE CRF 9/10/04 (Exam Date)	SCREW LOOSING WITH LATERAL MIGRATION LEFT L2 PEDICLE-BACK PAIN	"Device migration Level L2' with "L2 screw moving laterally" noted on 11/01/04 (Exam Date) AE CRF; "Device migration Level L2" with "Device Explanted" noted on 11/16/04 (Exam Date) CRF
1612012	12MOS	Loosening	"Other - loosening of upper screws at L4 and one of S1 screws" on AE CRF 6/9/05 (Exam Date)	X-RAYS AT 12 MOS VISIT SHOW EVIDENCE OF SOME LOOSENING OF THE UPPER SCREWS AT L4 AS WELL AS ONE OF THE S1 SCREWS. NONE ARE PULLED OUT. SUBJECT STATED SHE FELL ON SOME STEPS & STRUCK HER LOWER BACK.	"Other - L4 to S1 revision and fusion - removal of Dynesys due to loosening of screws" on 2/23/06 (Exam Date) AE CRF
<i>Silhouette Randomized</i>					
1609007 (Reoperation)	Other	Loosening	"Screw Failure/Fracture Level (L) L4" on AE CRF 6/17/04 (Exam Date)	AT RE-OP THE LEFT L4 SCREW WAS LOOSE AND WOBBLY (NOTED - THE SCREW WAS REMOVED.)	"Pseudoarthrosis" Note "Pseudoarthrosis was discovered during surgery posterior lateral fusion" on 10/21/04 (Exam Date) AE CRF
1611011 (Other - Discontinued)	24MOS	Loosening	"Other -radiographic loosening of screws" on AE CRF 7/11/06 (Exam Date)	RADIOGRAPHS LOOSEN NOTED ON FILM @ L3 & L5	
1614015	6MOS	Loosening	"Other - Asymptomatic screw loosening" on AE CRF 12/15/04 (Exam Date)	ASYMPTOMATIC SCREW LOOSENING L4 R	"Other - screw loosening" on 6/29/05 (Exam Date) CRF; "Other - asymptomatic screw loosening" on 6/5/06 (Exam Date) CRF

ID	Visit	Screw Issue Category/Visit	AE Report (Description and Date)	AE Comments	Additional AE Reporting
1614020	6MOS	Loosening	"Other - L4 screw loosening" on AE CRF 01/12/05 (Exam Date)	PEDICLE SCREW LOOSENING L4 ON RIGHT, (PSEUDOARTHROSIS, BONE GROWTH STIMULATOR ORDERED DUE TO CHEMOTHERAPY INFLUENCE)	Patient transferred to hospice care due to breast cancer; withdrawn from study 5/29/07
1627004	24MOS	Loosening	"Other - screw loosening" on AE CRF 9/13/06 (Exam Date)	SCREW LOOSENING (BILATERAL) AT S1	AE Comment on 9/13/06 - "Patient being forwarded to surgery on 01/30/07"+M46; Pt withdrew consent on 1/26/07 - transferred to new physician
<i>Dynesys Training</i>					
1607001	12MOS	Lucency	"Other - (R) L4 screw lucency" on AE CRF 2/07/05 (Exam Date)	PT. WAS IN FOR ROUTINE 12 MOS. FOLLOW UP X-RAYS OBTAINED SHOWED LUCENCY AROUND RIGHT L4 SCREW	

Neurological Adverse Events

There are 16 Dynesys adverse events and 11 Silhouette adverse events that describe a neurological symptom (e.g., weakness, numbness, tingling, sensory change, dysesthesia, burning sensation, paresthesia) in the lower extremity. For all categories, the event rate in the Dynesys group is not statistically different than the event rate in the Silhouette group.

	Dynesys	Silhouette	p-value
Sensory Change - Other*	0 (0.0%)	1 (0.9%)	P=0.31
Dysesthesia – LE - Other*	1 (0.4%)	0 (0.0%)	P>0.99
Weakness and Numbness – LE - Other*	1 (0.4%)	0 (0.0%)	P>0.99
Burning Sensation – Feet - Other*	1 (0.4%)	1 (0.9%)	P=0.53
Burning Sensation – LE - Other*	1 (0.4%)	0 (0.0%)	P>0.99
Numbness & Cramps – LE - Other*	0 (0.0%)	1 (0.9%)	P=0.31
Numbness & Tingling – LE - Other*	0 (0.0%)	1 (0.9%)	P=0.31
Numbness – LE - Other*	3 (1.2%)	3 (2.6%)	P=0.38
Numbness – Thigh - Other*	1 (0.4%)	1 (0.9%)	P=0.53
Pain & Numbness – LE - Other*	1 (0.4%)	0 (0.0%)	P>0.99
Paresthesia – LE - Other*	2 (0.8%)	0 (0.0%)	P>0.99
Weakness – LE – Other*	4 (1.6%)	3 (2.6%)	P=0.68
Pain and Weakness - Hip and Leg - Other*	1 (0.4%)	0 (0.0%)	P>0.99

* All Other* AEs reported on this table were text reported on AE CRF under “Other, Specify”

Wound Infection

The following information on wound infections was presented in the adverse event table above. Events include infection (graft site), infection (implant site), wound dehiscence (implant site), edematous wound, I&D, wound drainage – other, and wound infection – other as outlined in the following table:

Wound Infection	Dynesys	Silhouette	p-value
Infection (Graft Site)	0 (0.0%)	1 (0.9%)	P=0.31
Infection (Implant Site)	4 (1.6%)	3 (2.6%)	P=0.68
Wound Dehiscence (Implant Site)	3 (1.2%)	0 (0.0%)	P=0.56
Edematous Wound*	1 (0.4%)	0 (0.0%)	P>0.99
I & D*	1 (0.4%)	1 (0.9%)	P=0.53
Wound Drainage*	2 (0.8%)	3 (2.6%)	P=0.18
Wound Infection*	2 (0.8%)	0 (0.0%)	P>0.99

Elsewhere in the submission, the sponsor reports 17 incidences of adverse events that were classified as wound drainage/infection/dehiscence for a total of 14 patients (10 Dynesys, 4 Silhouette). Based on this cohort, they provide an analysis of treatment required including number of days of antibiotic therapy required. With the exception of one patient who was re-sutured, all of the patients implanted, independent of treatment arm, had their infection treated with irrigation and debridement or antibiotics or a combination of both. An analysis of the data for these 14 patients shows the mean days on oral antibiotic therapy is 21.0 days (15.2 day for the Dynesys group and 9.0 days for the Silhouette group). Of note, one Dynesys patient’s resolution post antibiotic treatment was reported at 74 days and was not included in the above average days. The average time from Index Surgery to onset of the Infection is 53.6 days for the Dynesys and 14.5 days for Silhouette. This reported result is skewed due to two of the ten Dynesys patients who presented with a deep wound infection after the performance of revision surgeries. There are no infections noted at any time after the Index Surgery for either of these patients. If these post-secondary surgery infections are removed from the analysis, the average time from Index Surgery to presentation of Infection is 12.73 days for the Dynesys arm and, as stated, 14.5 days for Silhouette.

The sponsor provided the following more detailed information about the 10 Dynesys patients with wound infections:

Patient ID	AE Field Description and Date of AE CRF	Date of Index Surgery	Date of Revision Surgery, If Applicable	Days of Exposure From Index Surgery to Onset	Duration	Clinical Narrative
1602-034	“Other – Wound drainage, minimal” AE CRF Date: 6/22/04	5/26/2004		15	74	At the 3-week visit, the subject presented on 6/22/04 with a shallow, superficial wound with a pale center and approximate measurement of 0.5 cm x 0.5 cm. The onset date of the adverse event was 6/11/04. Per the subject, the wound drainage continued; however, no spontaneous drainage was noted at the visit. The wound was treated with Keflex and follow-up recommended in 1 week. AE resolved on 8/24/04.

Patient ID	AE Field Description and Date of AE CRF	Date of Index Surgery	Date of Revision Surgery, If Applicable	Days of Exposure From Index Surgery to Onset	Duration	Clinical Narrative
1604-021	“Wound Dehiscence” AE CRF Date: 9/21/04	9/8/2004		8	1	At the 3 week visit, the subject presented on 9/21/04 (3 week visit) an adverse event of wound dehiscence at the implant site with an onset date of 9/16/04. The wound was sutured on 9/16/04 and the adverse event was resolved.
1606-035	“Allergic reaction” AE CRF Date: 4/22/05	1/26/2005		31	8	At the 3-month visit on 4/22/05, the subject reported minor wound drainage secondary to an allergic reaction to Vicryl suture. The onset date of the event was 2/27/05. As treatment, the wound was cleaned and the subject was prescribed antibiotics. The adverse event was resolved on 3/7/05 and at the 3-month visit, there was no evidence of drainage.
1608-004	“Infection – Wound” AE CRF Date: 4/13/05	4/2/2004	3/21/2005 (removal)	362	10	The subject had the original Dynesys implant explanted on 3/21/05. At the 12 month visit on 4/13/05 the subject reported having been seen on 4/4/05 for suture removal where a wound infection with onset date of 4/4/05 was noted. They were put on Keflex on 4/4/05, but the subject was seen in the ER on 4/7/05 for fever and chills and was advised to stay on Keflex. At the 12-month visit on 4/13/05, the wound was well healed with no signs and symptoms of infection.
1610-007	“Wound Dehiscence – Implant” AE CRF Date: 7/25/03	7/14/2003		10	18	At the 3 week visit on 7/25/03, the subject had wound drainage from the implant site with a possible subcutaneous hematoma - onset date 7/24/03. The subject was started on Cipro as treatment for the drainage. AE noted as resolved on 7/31/03.
1614-004	“Other – Superficial” AE CRF Date: 4/7/04	3/29/2004		8	7	At the 3-week visit on 4/7/04, the subject presented with slight drainage and erythema around the implant site. The onset date of the AE was 4/7/04. The subject was placed on oral antibiotics and followed up in 1 week (on 4/13/04), at which time the AE was noted as resolved
1614-004	“Other - Wound infection with wound dehiscence” AE CRF Date: 12/27/05	12/21/2005		2	33	The subject presented at an unscheduled visit on 12/27/05 with a possible wound infection with superficial dehiscence. The onset date of the AE was 12/23/05. As treatment, the subject received prescriptions for Keflex and Cipro. AE was noted as resolved on 1/25/06.
1614-026	“Other – Wound Infection” AE CRF Date: 10/20/04	10/4/2004		11	27	At the 3-week visit on 10/20/04, the subject presented at with a wound infection. The onset date of the infection was 10/15/04. The subject was hospitalized, at which time the wound was incised, drained, and debrided and the subject was given IV antibiotics. The AE was resolved on 11/11/04.
1615-003	“Infection – Implant” AE CRF Date: 10/17/03	9/29/2003		16	Ongoing	On 10/17/03, the subject reported being hospitalized for a deep wound infection that started and was treated with I & D on 10/15/03. The AE was not considered resolved

Patient ID	AE Field Description and Date of AE CRF	Date of Index Surgery	Date of Revision Surgery, If Applicable	Days of Exposure From Index Surgery to Onset	Duration	Clinical Narrative
1615-003	“Other-reoperations #1” AE CRF Date: 10/15/03	9/29/2003	10/17/2003 (revision)	16	Ongoing	On 10/17/03, the subject was still hospitalized and underwent a reoperation because of a continued post op wound infection with onset date of 10/17/03. The original Dynesys implant was removed and after irrigation and debridement, it was replaced with a second Dynesys. The AE was not considered resolved.
1615-003	“Other – reoperations #2” AE CRF Date: 10/17/03	9/29/2003	11/17/2003 (removal)	16	84	On 11/17/03, the subject was still hospitalized and underwent a reoperation because of a continued wound infection with onset date of 10/15/03. The Dynesys device was removed from the subject and a wound I&D was performed to resolve the AE.
1615-015	“Infection – Implant” AE CRF Date: 8/19/04	7/21/2004		7	42	At the 3-week visit, the subject reported on 7/28/04 there was continued drainage from the wound site. The patient was taken to the OR for I & D and suturing of the surgical wound. The patient was started on IV antibiotics and followed by Infectious Disease MD. AE resolved on 9/9/04.
1627-005	“Other-drainage from incision Site” AE CRF Date: 4/29/05	10/13/2004	4/19/2005 (suppl fixation)	195	29	On 4/29/05, the subject reported serous drainage from the umbilical portion of his wound that began on 4/28/05. This occurred after the subject underwent an ALIF procedure on 4/19/05. The subject received subcutaneous closure in several layers and was given Augmentin on 5/3/05. The drainage discontinued and the AE was resolved on 5/26/05.

The sponsor provided the following more detailed information about the 4 Silhouette patients with wound infections:

Patient ID	AE Field Description and Date of AE CRF	Date of Index Surgery	Date of Revision Surgery, If Applicable	Days of Exposure From Index Surgery to Onset	Duration	Clinical Narrative
1602-023	“Wound Dehiscence – Implant” AE CRF Date: 3/09/04	2/12/2004		6	91	At the 3-week visit on 3/9/04, the subject reported copious amounts of serosanguinous drainage from the implant site that started on 2/18/04. The subject underwent an I & D of the wound; oral antibiotics on 2/26/04 and home nursing care for the wound on 3/9/04. The AE was considered resolved on 5/18/2004. On 9/8/04, a revision laminectomy was performed to remove a retained sponge.
1607-006	“Other – Wound Drainage” AE CRF Date: 8/26/04	8/10/2004		8	9	At the 3-week visit on 8/26/04, the subject contacted the clinic to report drainage from her wound with onset date 8/18/04. The patient was placed on 500 MG of Cipro p.o., bid prophylactically for 10 days. She denied fever or chills. The subject’s incision is clean, dry and intact and no drainage noted. The AE was resolved on 8/26/04.
1615-007	“Infection – Implant” AE CRF Date: 4/13/05”	10/8/2003		8	46	At the 3-week visit on 11/11/03, the subject reported a draining lumbar wound at the implant site with onset date of 10/16/03. The subject underwent an I & D of the lumbar spine on 10/17/03 to resolve the AE and received 6 weeks of intravenous antibiotics. AE resolved on 12/1/03.
1615-011	“Infection – Implant” AE CRF Date: 12/18/03	11/12/2003		36	62	At the 3-week visit on 12/18/03, the subject presented with draining lumbar wound at the implant site, possibly due to an infection. The patient was initially treated with oral antibiotics, without resolution of the drainage. The subject received I & D and IV antibiotics on 12/19/03. AE resolved on 2/19/04.

In the Dynesys group, two of the reported wound infections occurred after secondary surgeries had been performed (1608-004 after an explant surgery and 1627-005 after supplemental fixation surgery). There were no reports of wound infections after secondary surgery for the Silhouette cohort or the Dynesys training cohort.

Two of the 14 patients required a reoperation or removal of the device to treat their wound infection, one each for Dynesys and Silhouette. In one Silhouette subject (1602-034), there was a revision laminectomy (considered a reoperation) to remove a retained sponge after resolution of the infection with antibiotic treatment. For the one Dynesys subject (1615-003), there were three Irrigation & Debridement (I&D) procedures performed: an original I&D; a secondary I&D with removal and immediate reimplantation of the Dynesys device and a third I&D with device removal. In addition, five subjects had an I&D (also considered a reoperation surgery) as part of their treatment for infection.

Cancer

In the Randomized subject cohort, there were three adverse events noted as cancer for this trial. Information on the cancer and resultant treatment provided for these subjects

was limited. Subject 1614-008 reported breast cancer at the 12-month interval and underwent surgery and chemotherapy as treatment. Subject 1614-020 reported breast cancer at the 6-month, with surgery reported for treatment. Subject 1617-003 reported colon cancer at the 36M visit, with chemo and radiation noted for treatment.

Deaths

There was 1 death in the investigational Dynesys group for a rate of 0.4% and 1 death in the Silhouette group for a rate of 0.9% prior to the 24 month follow-up. These rates are not statistically different. There were also 3 Dynesys patients who died after their 24 month follow-up visit. All 4 deaths were classified by the investigator as not related to the device.

The following table provides all known information on the 4 deaths:

Subject ID	Treatment Arm	Surgery Date	Date of Death	Cause of Death	Prior to or After 24 Month
1601006	Dynesys	2/18/04	12/10/05	Unknown	Prior
1603015	Dynesys	2/4/04	10/5/06	Heart attack	After
1610004	Dynesys	6/9/03	9/19/05	Blood clot	After
1604003	Dynesys	9/15/03	8/15/06	Lung Cancer	After
1615009	Silhouette	11/21/03	6/23/04	Liver and pancreatic disease	Prior

Safety Evaluation Summary:

The percentage of patients who had at least one adverse event is higher in the Dynesys group (77.5%) as compared to the Silhouette group (67.5%), and the difference is statistically significant (p=0.05); however, the rates of adverse events classified as device-related or surgery-related are not statistically different. The neurological status success rates are not statistically different between the two study groups, and the rates of secondary surgical procedures, while noteworthy (9% in the Dynesys group and 11% in the Silhouette group) are also not statistically different between the two study groups. There is a significant difference in “back and leg pain” adverse events with onset during the first 24 months with more patients experiencing events in Dynesys group (18.6%) as compared to the Silhouette group (7.9%); however, for the other adverse event categories related to back and leg pain, the Silhouette group generally has less adverse events than the Dynesys group although none of the other differences reach statistical significance. In addition, there are 12 Dynesys patients considered failures due to screw failure and an additional 3 who experienced screw failure but were already considered study failures for another reason. Also, while there was a slightly higher rate of secondary surgical intervention prior to 24 months in the Dynesys group (9%) as compared to the Silhouette group (11%), since the 24 month follow-up there has been a disproportionate number of secondary surgical procedures in the Dynesys group (10) as compared to the Silhouette group (1).

FDA will be asking you to discuss whether the clinical data in the PMA provide reasonable assurance that the proposed device is safe for the specified indications and intended patient population and whether any additional data or analyses that are needed.

POST APPROVAL STUDY

NOTE TO PANELISTS: *FDA's inclusion of a section/discussion on a Post-Approval study (PAS) in this memo should not be interpreted to mean that FDA has made a decision on the approvability of this PMA device. The presence of post-approval study plans or commitments does not in any way alter the requirements for pre-market approval and a recommendation from the Panel on whether to approve a device or not must be based on the premarket data. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study could be considered. The issues noted below are FDA's comments regarding potential post-approval studies should the panel find the device approvable following its discussion and deliberations of the premarket data.*

Compared with traditional rigid spine fusion, the main potential advantage of Dynesys Spinal System is to preserve motion at the treated segment, which may reduce the incidence of symptomatic adjacent-segment disease (ASD)¹³. In addition, implantation of Dynesys is intended to be a less invasive procedure than fusion procedures which require autograft harvest. Therefore, it may reduce the intra-operative and postoperative morbidity and may allow earlier return to activity¹⁴. Although the system was developed in 1994, there are issues that remain to be addressed, which include:

- The long-term survival of the Dynesys is unknown. As described in the literature, within a 2-year follow-up period, the rate of revision or secondary surgical intervention may be as high as 19%-27%^{15, 16} in comparison to the 9% secondary surgery rate reported in the IDE study.
- The long-term treatment effect of the device is not yet known based on the predominance of shorter term data (i.e., 2-4 years of follow-up) in the literature^{17, 18}.
- There is insufficient evidence in the literature regarding the effects of the Dynesys on the adjacent spinal levels. The most recent studies have reported that Dynesys has no

¹³ Cakir, B., et al., *Adjacent segment mobility after rigid and semirigid instrumentation of the lumbar spine*. Spine (Phila Pa 1976), 2009. **34**(12): p. 1287-91.

¹⁴ Stoll, T.M., G. Dubois, and O. Schwarzenbach, *The dynamic neutralization system for the spine: a multi-center study of a novel non-fusion system*. Eur Spine J, 2002. **11 Suppl 2**: p. S170-8.

¹⁵ Grob, D., et al., *Clinical experience with the Dynesys semirigid fixation system for the lumbar spine: surgical and patient-oriented outcome in 50 cases after an average of 2 years*. Spine (Phila Pa 1976), 2005. **30**(3): p. 324-31.

¹⁶ Bothmann, M., et al., *Dynesys fixation for lumbar spine degeneration*. Neurosurg Rev, 2008. **31**(2): p. 189-96.

¹⁷ Welch, W.C., et al., *Clinical outcomes of the Dynesys dynamic neutralization system: 1-year preliminary results*. Neurosurg Focus, 2007. **22**(1): p. E8.

¹⁸ Schaeren, S., I. Broger, and B. Jeanneret, *Minimum four-year follow-up of spinal stenosis with degenerative spondylolisthesis treated with decompression and dynamic stabilization*. Spine (Phila Pa 1976), 2008. **33**(18): p. E636-42.

effect with regard to adjacent segment mobility¹³. Disc degeneration at the bridged and adjacent segment seems to continue despite Dynesys dynamic stabilization¹⁹ and the rate of degeneration at adjacent motion segments is similar to the rate seen after fusion procedures¹⁸.

These issues are important in assessing the long-term safety and effectiveness of the device and could be addressed in a post-approval study (PAS).

The Sponsor submitted a PAS protocol to FDA on 05/22/09. The main objective of the PAS is to monitor the long-term safety and effectiveness of Dynesys® Spinal System in subjects requiring 1-level or contiguous 2-level posterior spinal stabilization of the lumbar and/or sacral spine with decompression. The study is a prospective, multi-center, controlled study comparing the long-term safety and effectiveness of the Dynesys® Spinal System with a Zimmer Spine rigid pedicle screw system (PSS). The primary study hypothesis is that the rate of clinical success of Dynesys subjects will not be less than the corresponding rate of clinical success for subjects implanted with a rigid PSS control device by more than the maximum clinically acceptable, non-inferiority margin of 10% at 10 years. The sponsor's proposed protocol for the post-approval study states that the other study objectives are "1) to replicate the short-term (2- year) safety and effectiveness of the Dynesys® Spinal System that was observed in the original IDE study population in a prospective observational cohort (Cohort 2) representing the continued use of Dynesys in routine clinical practice; 2) to demonstrate short-term (2 years) and mid-term (5 years) comparability of the Dynesys system to a rigid pedicle screw system in a secondary endpoint comparison of clinical success."

The study population of 323 subjects will be enrolled into two parallel cohorts, both of which will undergo long-term follow-up through 10 years. The first cohort (Cohort 1) will consist of subjects who participated in the original IDE study. This group will include eligible subjects that were both randomized and implanted with a study device Dynesys® Spinal System, or the control device *Silhouette Spinal System*®. Additionally, the roll-in training subjects (Dynesys) will be included. All subjects who participated in the original IDE study and who have not been discontinued or classified as a failure will be invited to enroll in the PAS. The second cohort (Cohort 2) will consist of newly enrolled subjects (who were not participants in the original Dynesys IDE study) from up to 20 clinical centers. The subjects in Cohort 2 will be implanted with either the Dynesys system or one of a number of rigid posterior pedicle screw system (PSS) control devices, all manufactured by Zimmer Spine. The sample size justification was based on the calculation that at the 10-year follow-up, the study requires 59 PSS control subjects and 118 Dynesys subjects to meet the statistical power requirements assuming a 45% attrition rate over 10 years.

In the pivotal study the primary endpoints was defined as a composite of assessment of function, leg pain, neurological status, absence of secondary surgery and absence of major complications. In the PAS, the sponsor proposes to incorporate radiographic

¹⁹ Kumar, A., et al., *Disc changes in the bridged and adjacent segments after Dynesys dynamic stabilization system after two years*. Spine (Phila Pa 1976), 2008. **33**(26): p. 2909-14.

segmental stability in the composite clinical success endpoint. Postoperative radiographic segmental stability will be evaluated at the treated level without fusion for Dynesys and with fusion for the Silhouette (control).

The study subjects in both cohorts will undergo long-term follow-up through 10 years. For Cohort 2, post-operative follow-up assessments will occur at 3 weeks, 3 and 6 months, and 1 and 2 years from the date of implantation of the study device. After completion of the 2-year study visit for both Cohorts 1 and 2, each subject will be required to complete an office visit at 5 and 10 years post-implantation. Follow-up telephone interviews will be conducted at 3, 4, 6, 7, 8, and 9 year intervals. The follow-up telephone interviews will only collect Adverse Event and Subject Assessment data, including: 1) patient-reported Medical History including any spine surgeries since last contact; 2) any Adverse Event occurrence since the last contact; and 3) appropriate outcomes measures. An independent Clinical Events Committee (CEC) will review all Adverse Events.

FDA would like the panel to comment on the following topics related to the proposed post approval study (PAS) design. Please note that the proposed PAS and the following topics related to the PAS will apply only if the device is recommended for approval.

- *The sufficiency of the proposed clinical follow-up schedule.*
- *Factors to consider in the enrollment of new sites/investigators so that the results are most representative of expected device performance in the real world practice.*
- *The validity of using six different rigid fusion systems as a combined control group.*
- *The importance of assessing adjacent segment degeneration.*