SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Artificial Cervical Disc System
Device Trade Name:	PRESTIGE® Cervical Disc System
Applicant's Name and Address:	Medtronic Sofamor Danek 1800 Pyramid Place Memphis, TN 38132
Date of Panel Recommendation:	September 19, 2006
Premarket Approval Application (PMA) Number:	P060018
Date of Notice of Approval to Applicant:	July 16, 2007

II. INDICATIONS FOR USE

The PRESTIGE® Cervical Disc is indicated in skeletally mature patients for reconstruction of the disc from C3-C7 following single-level discectomy for intractable radiculopathy and/or myelopathy. Intractable radiculopathy and/or myelopathy should present with at least one of the following items producing symptomatic nerve root and/or spinal cord compression which is documented by patient history (e.g., pain [neck and/or arm pain], functional deficit, and/or neurological deficit), and radiographic studies (e.g., CT, MRI, x-rays, etc.): 1) herniated disc, and/or 2) osteophyte formation. The PRESTIGE® device is implanted via an open anterior approach.

III. CONTRAINDICATIONS

The PRESTIGE® Cervical Disc should not be implanted in patients with an active infection or with an allergy to stainless steel.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the PRESTIGE® Cervical Disc physician labeling.

V. DEVICE DESCRIPTION

The PRESTIGE® Cervical Disc system is a two-piece articulating metal device that is inserted into the intervertebral disc space at a single cervical level using an open anterior approach. The device is manufactured from wrought type 316 stainless steel (ASTM F-138) and consists of two metal plates which interact via a ball and trough mechanism. The superior component of the implant contains the ball portion of the mechanism, and the inferior component incorporates the trough portion. The flat portion of each component, which contacts the vertebral endplate, is aluminum oxide grit blasted.

Each component is affixed to the vertebral body by two bone screws through an anterior flange. The bone screws are held in place by a lock screw mechanism. In the implanted disc, the bone screws are divergent in the cephalic/caudal direction and convergent in the medial/lateral direction.

The device assembly was designed to allow the following motions *ex-vivo*: a minimum of 10° motion off the neutral position in flexion/extension and lateral bending, unconstrained axial rotation, and 2mm of anterior/posterior translation.

Table 1: PRESTIGE® Cervical Disc Configurations.

Catalog Number	Component Description
6961260	6 mm x 12 mm Disc Assembly
6961460	6 mm x 14 mm Disc Assembly
6961660	6 mm x 16 mm Disc Assembly
6961270	7 mm x 12 mm Disc Assembly
6961470	7 mm x 14 mm Disc Assembly
6961670	7 mm x 16 mm Disc Assembly
6961870	7 mm x 18 mm Disc Assembly
6961480	8 mm x 14 mm Disc Assembly
6961680	8 mm x 16 mm Disc Assembly
6961880	8 mm x 18 mm Disc Assembly
6960013/6961340*	Self-Tap Bone Screw 4.0 mm x 13 mm
6960015/6961540*	Self-Tap Bone Screw 4.0 mm x 15 mm
6960113/6961345*	Self-Tap Bone Screw 4.5 mm x 13 mm
6960115/6961545*	Self-Tap Bone Screw 4.5 mm x 15 mm
6960120/6961120*	Lock Screw

* Catalog number for screws in implant box / catalog number for separately packaged extra screws, if needed.

Device Modification:

Six new device sizes were added after the completion of the clinical trial based on surgeon feedback. The new sizes include: 6x14mm, 6x16mm, 7x16mm, 7x18mm, 8x16mm and 8x18mm. In order to accommodate the new sizes a modification was made to the device design. The anterior cut angle on the superior component was modified from 10° to 3°, thus strengthening the anterior flange. This change was made in all sizes. FDA determined that the new sizes were adequately characterized by preclinical bench testing and that, given the modifications made, collection of additional clinical data on the new device sizes was not necessary.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

Nonoperative alternative treatments for symptomatic cervical degenerative disc disease include, but are not limited to, physical therapy, medications, braces, chiropractic care, bed rest, spinal injections, or exercise programs. In addition, there are alternative surgical techniques which include, but are not limited to, surgical decompression, or fusion using various bone grafting techniques (e.g., Cloward bone dowels, Smith Robinson tri-cortical wedges, and keystone grafts) sometimes used in conjunction with anterior/anterolateral spinal systems (e.g., plate and screw systems), posterior spinal systems (e.g., screw/rod, plate systems, posterior wiring systems), or cage devices.

VII. MARKETING HISTORY

Since 2003, a small number of devices have been sold in England, Australia, France, and Switzerland. The device has not been withdrawn from marketing for any reason.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The sponsor conducted a randomized, prospective, multicenter trial to assess the safety and effectiveness of the PRESTIGE® Cervical Disc compared to a single level surgical fusion utilizing bone graft and plate stabilization. This study is described in more detail beginning in Section X. This section discusses the adverse events observed in the study.

The adverse effects, as shown in the table below, were reported from the 276 PRESTIGE® device patients and 265 control patients enrolled in the multi-center clinical study of the PRESTIGE® Cervical Disc. The control treatment was a single level anterior interbody fusion procedure with allograft and plate stabilization. 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; events are listed in alphabetical order. In the PRESTIGE® group, the most common adverse events were neck and/or arm pain, neurological, other pain, and trauma. At the time Tables 2 and 2b below were compiled, all patients had reached the 12-month follow-up visit, and 223 investigational and 198 control patients had completed 24-month follow-up visits. As shown in Table 2b, a minority of the adverse events reported were related to the study treatment.

Table 2: Adverse Events in US IDE Study.

ADVERSE EVENTS[1]

	Surgery		Postoperative (1 day - <4 Weeks)		6 Weeks (≥4 Wks - <9 Weeks)		3 Months (≥9 Wks - <5 Months)		6 Months (≥5 Mos - <9 Months)		12 Months ≥9 Mos - <19 Months		24 Months ≥19 Mos - <30 Months		# of Patients Reporting & Total adverse events	
Complication	Invest.	Control[2]	Invest.	Control	Invest.	Control	Invest.	Control	Invest.	Control	Invest.	Control	Invest.	Control	**Invest. # Patients (% of 276) Total # Events**	**Control # Patients (% of 265) Total # Events**
Anatomical/Technical Difficulty	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.4) 1	0 (0.0) 0
Cancer	0	0	0	1	0	0	0	0	0	0	2	0	3	1	5 (1.8) 5	2 (0.8) 2
Cardiovascular	0	0	2	1	0	1	2	2	1	0	7	2	3	3	14 (5.1) 15	8 (3.0) 9
Carpal Tunnel Syndrome	0	0	1	1	1	1	3	1	0	0	8	2	1	2	12 (4.3) 14	7 (2.6) 7
Death	0	0	0	0	0	0	0	1	0	0	0	1	0	1	0 (0.0) 0	3 (1.1) 3
Dysphagia/Dysphonia	2	3	16	12	3	3	0	3	1	0	1	1	0	0	23 (8.3) 23	22 (8.3) 22
Gastrointestinal	0	2	4	3	1	1	3	2	4	2	11	11	3	5	25 (9.1) 26	24 (9.1) 26
Implant Displacement/ Loosening	0	0	0	0	0	2	1	0	0	0	0	1	1	1	2 (0.7) 2	4 (1.5) 4
Infection	2	0	6	3	2	4	6	2	3	2	8	4	3	7	27 (9.8) 30	20 (7.5) 22
Neck and/or Arm Pain	1	0	25	17	32	17	27	34	48	38	34	42	23	25	138 (50.0) 190	127 (47.9) 173
Neurological	4	1	8	9	12	5	14	10	14	8	19	18	7	14	66 (23.9) 78	55 (20.8) 65
Non-Union	0	0	0	0	0	1	0	2	0	2	0	1	0	0	0 (0.0) 0	6 (2.3) 6
[3]	2	2	18	18	14	12	9	9	19	6	32	18	15	17	70 (25.4) 109	66 (24.9) 82
Other Pain[4]	2	2	4	4	10	5	13	13	14	15	28	18	17	11	69 (25.0) 88	56 (21.1) 68
Pending Non-Union	0	0	0	0	0	0	0	1	0	5	0	7	0	3	0 (0.0) 0	16 (6.0) 16
Respiratory	1	0	1	2	0	1	1	0	1	1	2	3	2	2	8 (2.9) 8	8 (3.0) 9
Spinal Event	0	0	2	2	1	3	6	9	3	9	6	5	0	4	17 (6.2) 18	30 (11.3) 32
Subsidence	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1 (0.4) 1	0 (0.0) 0
Trauma	0	0	4	2	7	8	13	11	17	10	20	6	8	10	59 (21.4) 69	40 (15.1) 47
Urogenital	0	0	0	0	0	0	3	4	2	1	8	1	3	0	15 (5.4) 16	5 (1.9) 6
Vascular Intra-Op	2	1	2	1	1	0	0	0	0	0	0	0	0	0	5 (1.8) 5	2 (0.8) 2
Any Adverse Event															226 (81.9)	212 (80.0)

[1] Based on 24-month cohort at time of interim analysis as pre-specified in IDE protocol.
[2] Control=Single level anterior interbody fusion procedure with allograft and plate stabilization.
[3] Other consists of various events that do not fit into another category, such as allergic reaction, depression, or insomnia.
[4] Other Pain consists of non-neck and/or arm pain events such as headache, lower back pain, or leg pain.

Table 2b: Adverse Events Classified as Device-Related or Device/Surgical Procedure Related in US IDE Study.

POSSIBLY RELATED ADVERSE EVENTS[5]																
	Surgery		Postoperative (1 day - <4 Weeks)		6 Weeks (≥4 Wks - <9 Weeks)		3 Months (≥9 Wks - <5 Months)		6 Months (≥5 Mos- <9 Months)		12 Months (≥9 Mos- <19 Months)		24 Months (≥19 Mos- <30 Months)		# of Patients Reporting & Total adverse events	
Complication	Invest.	Control[6]	Invest.	Control	Invest.	Control	Invest.	Control	Invest.	Control	Invest.	Control	Invest.	Control	Invest. # Patients (% of 276) Total # Events	Control # Patients (% of 265) Total # Events
Anatomical/ Technical Difficulty	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.4) 1	0 (0.0) 0
Implant Displacement/ Loosening	0	0	0	0	0	1	1	0	0	0	0	1	1	1	2 (0.7) 2	3 (1.1) 3
Infection	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0 (0.0) 0	1 (0.4) 1
Neck and/or Arm Pain	0	0	0	0	1	0	0	0	0	2	0	0	0	0	1 (0.4) 1	2 (0.8) 2
Neurological	0	0	0	0	1	0	1	1	0	0	2	0	0	0	4 (1.4) 4	1 (0.4) 1
Non-Union	0	0	0	0	0	1	0	2	0	2	0	1	0	0	0 (0.0) 0	6 (2.3) 6
Pending Non-Union	0	0	0	0	0	0	0	1	0	5	0	7	0	3	0 (0.0) 0	16 (6.0) 16
'ence	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1 (0.4) 1	0 (0.0) 0
Any Adverse Event															9 (3.3)	26 (9.8)

There were five neoplastic events in the PRESTIGE® group and two in the control group. The five events in the PRESTIGE® group included breast cancer, colon cancer, basal cell cancer, thyroid cancer and Non-Hodgkin's lymphoma. The two events in the control group were astrocytoma and a skin cancer recurrence.

No deaths were reported among investigational patients. Three control group deaths were reported, all of which were due to myocardial infarction or cardiac arrest.

The study was designed to use Bayesian methods with non-informative or uniform priors to analyze the primary endpoint. To be consistent, the sponsor conducted a Bayesian analysis on the adverse events using non-informative priors. The results are presented in Table 3.

[5]Based on 24-month cohort at time of interim analysis as pre-specified in IDE protocol.
[6]Control=Single level anterior interbody fusion procedure with allograft and plate stabilization.

Table 3: Bayesian Comparison of Adverse Events.

Adverse Event	Posterior Adverse Event Rate		95% probability that adverse event rates will fall within the following range		Probability that adverse event rate of investigational group is lower than that of the control group (%)
	Invest.	Control	Invest.	Control	
Anatomical/Technical Difficulty	0.007	0.004	0.0% to 1.7%	0.0% to 1.1%	26.0
Cancer	0.022	0.011	0.6% to 3.9%	0.1% to 2.4%	15.6
Cardiovascular	0.054	0.034	2.8% to 8.1%	1.4% to 5.6%	11.9
Carpal Tunnel Syndrome	0.047	0.030	2.4% to 7.2%	1.1% to 5.1%	14.7
Death	0.004	0.015	0.0% to 1.1%	0.3% to 3.0%	94.3
Dysphagia/Dysphonia	0.086	0.086	5.5% to 12.0%	5.4% to 12.1%	49.6
Gastrointestinal	0.094	0.094	6.0% to 12.8%	6.1% to 12.9%	50.1
Implant Displacement/Loosening	0.011	0.019	0.1% to 2.3%	0.5% to 3.5%	79.1
Infection	0.101	0.079	6.6% to 13.6%	4.8% to 11.2%	18.1
Neck and/or Arm Pain	0.500	0.479	44.1% to 55.9%	42.1% to 54.0%	31.5
Neurological	0.241	0.210	19.1% to 29.2%	16.2% to 25.9%	19.0
Non-Union	0.004	0.026	0.0% to 1.1%	0.9% to 4.5%	99.4
Other	0.255	0.251	20.6% to 30.8%	20.0% to 30.4%	45.2
Other Pain	0.252	0.213	20.2% to 30.4%	16.4% to 26.2%	14.4
Pending Non-Union	0.004	0.064	0.0% to 1.1%	3.6% to 9.3%	100.0
Respiratory	0.032	0.034	1.3% to 5.4%	1.4% to 5.6%	53.4
Spinal Event	0.065	0.116	3.6% to 9.3%	7.9% to 15.4%	98.3
Subsidence	0.007	0.004	0.0% to 1.7%	0.0% to 1.1%	26.0
Trauma	0.216	0.154	16.7% to 26.4%	11.2% to 19.8%	3.0
Urogenital	0.058	0.022	3.1% to 8.5%	0.6% to 4.0%	1.5
Vascular Intra-Op	0.022	0.011	0.6% to 3.9%	0.1% to 2.4%	15.6
Any adverse Event	0.817	0.798	77.1% to 86.1%	74.9% to 84.5%	28.9

Some of the reported adverse events required surgical interventions subsequent to the initial surgery. These secondary surgical interventions can be classified as revisions, removals, reoperations, or supplemental fixations. Revisions, removals, and supplemental fixations were considered second surgery failures in the clinical study. Table 4 summarizes the secondary surgical interventions in the PRESTIGE® and control treatment groups that occurred through the 24-month post-operative interval. Table 4 also presents the Bayesian statistical comparison of secondary surgeries between the PRESTIGE® and control treatment groups. Probabilities exceeding 97.5% are considered statistically significant.

Table 4: Secondary Surgical Procedures.

	# Pts ≤24 Months		Probability that the second surgery rate of investigational group is lower than that of the control group (%)
	Invest. (N=276)	Control (N=265)	
Revisions	0	5 (1.9)	98.7
Removals	5* (1.8)	9** (3.5)	87.0
Supplemental Fixations	0	8 (3.0)	99.8
Reoperations	4*** (1.4)	2 (0.8)	24.2

*One of these removals occurred following complaints for unresolved neck pain, one occurred following unresolved arm pain, and the other three were related to both neck and arm pain.
**Control removals include both elective (2) and non-elective (7) removals.
***Of the four subjects who had re-operations, two occurred prior to 12 months and two occurred after 12 months postoperative. Two of these re-operations followed unresolved neck pain, one followed unresolved arm pain, and one was related to both neck and arm pain.

Potential Adverse Events:
Potential risks associated with the use of the PRESTIGE® Cervical Disc include: 1) those commonly associated with any surgery; 2) those specifically associated with cervical spinal surgery using an anterior approach; and 3) those associated with a spinal implant, as well as those pertaining to the PRESTIGE® Cervical Disc. However, the causality of these adverse events is not exclusive to these categories. There is also the risk that this surgical procedure will not be effective, and may not relieve or may cause worsening of preoperative symptoms. Some of these effects may have been previously reported in the adverse events table.

1. Risks associated with any surgical procedure are those such as: abscess; cellulitis; wound dehiscence; wound necrosis; edema; hematoma; heart and vascular complications; hypertension; thrombosis; ischemia; embolism; thromboembolism; hemorrhage; thrombophlebitis; adverse reactions to anesthesia; pulmonary complications; organ, nerve or muscular damage; seizure, convulsion, or changes to mental status; and complications of pregnancy including miscarriage and fetal birth defects.

2. Risks associated with anterior interbody surgery of the cervical spine include: dysphagia; dysphasia; dysphonia; hoarseness; vocal cord paralysis; laryngeal palsy; sore throat; recurring aspirations; nerve deficits or damage; tracheal, esophageal, and pharyngeal perforation; airway obstruction; external chylorrhea; warmth or tingling in the extremities; deficit or damage to the spinal cord, nerve roots, or nerves possibly resulting in paralysis or pain; dural tears or leaking; cerebrospinal fistula; discitis, arachnoiditis, and/or other types of inflammation; loss of disc height; loss of proper curvature, correction, height or reduction of the spine; vertebral slipping; scarring, herniation or degeneration of adjacent discs; surrounding soft tissue damage, spinal stenosis; spondylolysis; otitis media; fistula; vascular damage and/or rupture; and headache.

3. Risks associated with implants in the spine, including the PRESTIGE® device, are: early or late loosening of the components; disassembly; bending or breakage of any or all of the components; implant migration; malpositioning of implant; loss of purchase; sizing issues with components; anatomical or technical difficulties; implant fracture; bone fracture; skin penetration, irritation, pain, bursitis resulting from pressure on the skin from component parts in patients with inadequate tissue coverage over the implant; foreign body reaction to the implants including possible tumor formation, autoimmune disease, metallosis, and/or

scarring; possible tissue reaction; bone resorption; bone formation that may reduce spinal motion or result in a fusion, either at the treated level or at adjacent levels; development of new radiculopathy; myelopathy or pain; cessation of bone growth of the operated portion of the spine; tissue or nerve damage caused by improper positioning and placement of implants or instruments; loss of neurological function; decreased strength of extremities; decreased reflexes; appearance of cord or nerve root injury; loss of bowel and/or bladder control or other types of urological system compromise; gastrointestinal and/or reproductive system compromise; and interference with radiographic imaging because of the presence of the implant.

4. Wound, local, and/or systemic infections.

5. Surgical instrument bending or breakage, as well as the possibility of a fragment of a broken instrument remaining in the patient.

6. Inability to resume activities of normal daily living, including loss of consortium.

7. Death.

NOTE: Additional surgery may be necessary to correct some of the adverse effects.

IX. SUMMARY OF PRECLINICAL STUDIES

Mechanical (Bench) Tests:
The biomechanical properties of the PRESTIGE® Cervical Disc prosthesis were assessed in a series of preclinical experiments. When applicable, all tests were performed on the worst-case device for the given test. As described above in Section V, six new device sizes were added since the completion of the clinical trial. If a new size represented a new worst-case for any of the tests below, the new size was tested. This is reflected in the testing reported below.

The following bench tests were performed on the PRESTIGE® Cervical Disc: Static Compression, Compression Fatigue, Subluxation, Subsidence, Push-out, Pull-out and Wear Testing.

Static Compression:
Purpose:
Testing was done to determine the static compressive loads that the device can withstand.

Worst Case Design:
The sponsor determined the 6mm x 16mm device to be the worst case design for compression *fatigue* testing. However, the 8mm x 12mm device and the 8mm x 14mm device were utilized for static testing. Although the worst case device was not used for this testing, results were far in excess of in vivo loads and indicate that the worst case (6mm x 16mm) device would perform adequately as well.

Acceptance Criteria:
The fatigue load must be greater than the compressive load on the cervical spine (74N) as reported by White and Panjabi.[1]

Methods:
Testing was performed on both the 8mm x 12mm and the 8mm x 14mm device sizes. Three discs of each size were tested. Loading was applied at 0.1mm per second. Testing was performed with UHMWPE test blocks in order to utilize the bone screws.

Results:
Results are given in terms of a force at a given displacement into the polyethylene blocks. The 8mm x 12mm specimens had an average load of 1,343 ± 191N at 2mm of displacement and 6,279 ± 173N at 5mm of displacement. The 8mm x 14mm specimens had an average load of 1,709 ± 245N at 2mm of displacement and 5,664 ± 210N at 5mm of displacement.

Compression Fatigue:
Purpose:
Testing was done to determine the fatigue loads the device can withstand.

Worst Case Design:
The 6mm x 16mm disc size, which has the shortest height and longest depth, was determined by the sponsor to be the worst case in compression fatigue.

Acceptance Criteria:
The fatigue load must be greater than the compressive load on the cervical spine (74N) as reported by White and Panjabi[1].

Methods:
Three 6mm x 16mm discs were tested under a load of 225N. Loading was performed in sinusoidal load amplitude control at 10 Hz with an R value of 10. UHMWPE test blocks were used.

Results:
The three devices each experienced run-out without failure to 10 million cycles under a 225N cyclic load.

Compression fatigue testing was also performed on the 6mm x 12mm disc, 6 x 14mm disc, 8mm x 12mm disc, 8mm x 14mm disc. All of the device sizes had 10 million cycle run-outs to under at least a 225N cyclic load except for the 8mm x 12mm discs which were only tested under a 150N cyclic.

Subsidence Testing:
Purpose:
Testing was done to determine the amount of force necessary to subside the device into a cancellous bone model.

Worst case:
The worst case device chosen was 8mm x 12mm because this device has the smallest footprint (area contacting vertebral endplates) offered.

Acceptance Criteria:
The subsidence force must be greater than the maximum *in vivo* compressive load in the cervical spine (74N) as reported by White and Panjabi[1].

Methods:
Subsidence testing was performed five times on one 8mm x 12mm device. Grade 15 foam test blocks were used to simulated bone. Axial compressive loading was applied at 0.1mm/second until the foam blocks touched, which was a distance of ~8mm.

Results:
Table 5: Subsidence Test Results.

Specimen	Yield Strength (N)	Yield Displacement (mm)	Ultimate Strength (N)	Ultimate Displacement (mm)	Stiffness (N/mm)
Mean ± SD	550 ± 20	3.05 ± 0.20	718 ± 62	8.0	363.1 ± 37.0

Subluxation Testing:
Purpose:
Testing was done to determine the amount of force required to dislocate the upper component of the disc assembly from the lower component when the disc is in the neutral position and at extreme angles of flexion, extension, and lateral bending.

Worst Case:
No worst case device was identified for this testing because all devices share the same articulation.

Acceptance Criteria:
The subluxation force must be greater than maximum *in vivo* shear load in the cervical spine (20N) as reported by White and Panjabi[1].

Methods:
Testing was conducted using five 7mm x 14mm discs. Polyethylene test blocks were used. A 100N compressive preload was used during all testing. Shear loads were applied to the inferior test block in displacement control at a rate of 0.1mm/sec. Each of the five discs was subject to each of the loadings below (in random order to capture possible effects from previous tests).

Results:
Table 6: Subluxation Test Results.

Angle	Direction of Shear Force	Average Peak Shear Load (N) (n=5)
0° (neutral)	-Y (medial to lateral)	111.5 ± 31.5
10° Lateral Bend	-Y (medial to lateral	108.1 ± 9.5
10° Lateral Bend	+Y (medial to lateral)	86.8 ± 25.9
10° Flexion	-X (anterior to posterior)	104.7 ± 6.7
10° Flexion	+X (posterior to anterior)	77.1 ± 9.3

Other Subluxation Tests:
The sponsor performed two other subluxation tests. However, results were far more variable potentially due to the fact that the same device was used for all tests. Therefore, at the request of FDA, the above test was performed.

Push-out:
Purpose:
Testing was done to determine the push-out load of the device in the absence of screw fixation.

Worst Case:
The 8mm x 12mm disc was used for this testing as it has the smallest footprint available and therefore the minimum surface area in contact with bone.

Acceptance Criteria:
The push-out force must be greater than maximum in vivo shear load in the cervical spine (20N) as reported by White and Panjabi.[1]

Methods:
Testing was completed on five 8mm x 12mm specimens. Specimens were loaded between pieces of grade 15 foam bone with 100N of preload while an axial force was applied to the posterior portion of the disc at 25mm/min until 10mm was reached. Grade 15 foam is used to mimic the physical properties of natural bone.

Results:
The average push-out load for the five samples was 129 ± 9.6N.

Pull-out:
Purpose:
Determine the pullout load of the PRESTIGE® disc with bone screw fixation.

Worst Case:
The 8mm x 12mm disc was used for this testing as it has the smallest footprint and therefore the minimum surface area in contact with bone.

Acceptance Criteria:
The pull-out force must be greater than maximum *in vivo* shear load in the cervical spine (20N) as reported by White and Panjabi[1].

Methods:
Each test article consisted of one male component or one female component attached to a foam block with bone screws. Specimens were subjected to static axial pullout in accordance with ASTM F1691-96. Load was applied by a cable that is loops through the screw holes of the device. Load was applied at a rate of 25mm/min. The male and female components were tested separately. The metal components were reused because they were not damaged during the test; however, the foam blocks were replaced for each run.

Results:
After five runs, the male components had an average pull-out strength of 200 ± 24N and the female components had an average pull-out strength of 251 ± 36N.

This same testing was also performed on the 8mm x 14mm disc. After five runs, the male components had an average pull-out strength of 191 ± 35N and the female components had an average pull-out strength of 225 ± 50N.

Wear Testing
Purpose:
Testing was done to determine the long term functionality and wear production of the PRESTIGE® device.

Worst Case Device:
Test articles consisted of an upper and lower test coupon. Because all implant sizes have identical articulating geometry, there is not a worst-case size for this test. Furthermore, this test required the use of a testing coupon in lieu of a standard device to facilitate attachment to the machines and to ensure proper measurement of the weight change of the articles. The testing coupon was a disc with the same articulating geometry and surface finish as the standard parts. The coupon does not include the bone interface geometry that is part of the standard device because the test machine does not readily allow the use of these features. However, these bone interface features were determined to be irrelevant for wear testing.

Acceptance Criteria:
This testing was performed to establish the wear characteristics of this device. The wear data that were generated were used to establish the parameters for the particulate injection study in rabbits. However, the components could not show any cracks as a result of the testing.

Methods:
Two groups of three specimens each were tested in a simulator to evaluate the wear. The first group was tested in coupled lateral bending/axial rotation (LB/AR) motion followed by flexion/extension (FE). The second group was tested in the reverse order to determine the effect of motion sequence on wear. The parameters for each test are in Table 7 below.

Table 7: Wear Test Parameters.

Motion Type	Motion/Frequency	Compressive Load	Number of Cycles
Lateral Bending/ Axial Rotation	± 4.7° LB @ 2Hz coupled with ± 3.8° AR at 2Hz	49N	5 million
Flexion/Extension	± 9.7° FE at 2Hz	148N	10 million

The ranges of motion (ROM) represent the total ROM of adult function spine segments measured with simulated in vivo loading due to head weight.

The simulated motions were conducted in a 25% bovine serum bath of approximately 800 ml maintained at 37°C. The test was stopped at 0.5 million cycles (Mc) at 1.0 Mc and then at a minimum of once every seven days (At 2Hz, stopping every 7 days works out to stopping about

every 1.2Mc) for device cleaning, weighing and photographing. The serum was changed at each stoppage and the used serum was stored.

Results:

Table 8: Volumetric wear after 15Mc.

LB/AR then FE		FE then LB/AR	
Specimen	**Volumetric Wear (mm^3)**	**Specimen**	**Volumetric Wear (mm^3)**
SS-1	4.481	SS-4	5.152
SS-2	2.201	SS-5	2.609
SS-3	4.416	SS-6	3.804
Mean	3.699 ± 1.298	**Mean**	3.855 ± 1.272

The average volumetric wear rate for devices tested in 5 million cycles of LB/AR followed by 10 million cycles of FE (n=3) was 0.533 ± 0.208mm^3/million cycles (for the 5 million cycles of LB/AR) and 0.067 ± 0.015mm^3/million cycles (for the 10 million cycles of FE).

The average volumetric wear rate for devices tested in 10 million cycles of FE followed by 5 million cycles of LB/AR (n=3) was 0.006 ± 0.005mm^3/million cycles (for the 10 million cycles of FE) and 0.733 ± 0.252mm^3/million cycles (for the 5 million cycles of LB/AR).

Additional Wear Testing:

This was a preliminary wear test done using two discs (specimen 1 and specimen 2). Similar loads were used to the above test. The flexion and extension testing was performed with a 20° of motion to 10 million cycles under a 148N load. The coupled motion testing was done with a 10.4° of lateral bending and 7.6° of axial rotation to 5 million cycles under a 49N load.

Results:

Total weight loss for specimen 1 was 0.00050g in flexion extension and 0.43888g in lateral bending/axial rotation. Volumetric wear was 0.063mm^3 and 5.520mm^3, respectively. Total weight loss for specimen 2 was 0.00050g in flexion/extension and 0.04998g in lateral bending/axial rotation. Volumetric wear was 0.063mm^3 and 6.287mm^3, respectively.

Particle Characterization:

Three samples of bovine serum containing wear debris from two wear test specimens were centrifuged, ashed, and imaged on a scanning electron microscope at magnifications as high as 20,000X. In this analysis, a range of particle sizes was found with particle dimensions as small as 0.13 microns and as large as 1.58 microns. Five sets of particle measurements were made at 10,000X and an additional five sets of particle measurements were made at 20,000X from unique samples. Results are tabulated below. The majority of the particles were granular in shape.

Table 9: Particulate Mean Size.

Magnification	Mean Particle Size ± SD (nanometers)
10,000X	554 ± 183
10,000X	550 ± 218
10,000X	429 ± 146
10,000X	570 ± 379
10,000X	595 ± 287
20,000X	364 ± 146
20,000X	296 ± 112
20,000X	362 ± 126
20,000X	399 ± 254
20,000X	302 ± 162

The particulate characterization was used to develop the dosing for the animal study described below.

Animal Study

The local effects of the particulate form of the stainless steel material on periprosthetic tissues were evaluated in a rabbit model.

Rabbit Model:

The particle chemistry, shape, and size were tailored to be as close to that observed in wear tests as technically possible. The resultant metal wear debris was injected into the intervertebral space for direct contact with the spinal column. Thus, the implant site selected for this procedure was intended to mimic clinical use.

One key difference between this animal model and the clinical scenario in humans was that the dose of particles was high and intended to be representative of many years of clinical use, even for the low dose animals. Clinically, the particles would be generated gradually, whereas in this model the particles are delivered as a bolus. The particle size distribution included particles of the size range observed in previous bench testing.

Rabbit Model Methods:

This animal model was used to investigate the local and distant response to a 20-million cycle equivalent does and a 60-million cycle equivalent does of particles. The equivalent dose was determined by linearly scaling the worst-case human dose determined in the custom spine simulators to a rabbit dose based on body weight. The representative human body weight was assumed to be 75kg. This selection of human body weight is more worst-case than the body weight for an obese patient since the rabbit would receive more particles.

Clean particles of ASTM F138 material were obtained with a size distribution that matched the characterized spine simulator particles as closely as technically possible. The particles ranged in size from less than one micron in diameter to 44 microns in diameter.

One of three doses (control, low, and high) was injected into the epidural space of each of twenty New Zealand White rabbits in a carrier of contrast media (ISOVUE M-300). Dynamic fluoroscopic video was obtained at the time of injection to confirm that the particles were delivered to the intended tissue space. The animals were euthanized at 3-months (n=9) and 6-

months (n=11) time points to assess the biologic response to the particles at sites both near and distant from the site of injection.

Rabbit Model Results:
Overall animal health was good. One three-month high dose rabbit suffered a traumatic injury during a routine cage change and was euthanized 20 days following injection of the particles. The fracture was deemed to be unrelated to the test article.

There was no evidence of neurotoxicity, systemic toxicity, or local spinal effects associated with treatment with the stainless steel particles. Microscopic examination of tissues at three and six months post-epidural injection did not reveal any evidence of local or systemic lesions that were thought to be attributable to the presence of the particles. Both the low and high doses of particles were considered to be non-irritants.

Clinical Observations:
There were no observations that were considered to reflect evidence of systemic or neurotoxicity or other adverse effects directly associated with the test control article.

Necropsy and Macroscopic Observations:
There were no findings that were considered to be related to presence of the test or control material.

Clinical Pathology:
There were no changes in clinical pathology parameters in either interval for both test groups that were considered suggestive of systemic toxicity or an inflammatory response. Several parameters were noted to be statistically different from the respective control. However, the occurrences were considered spurious and due to the small group sizes for comparison rather than biological significant differences.

Histopathology:
3 months: The low- and high-dose wear debris test article did not cause any microscopic findings indicating any systemic or local toxicity three months after spinal implantation. Additional evaluation of the vertebral canal sections using an Oil-red-O stain and polarized light microscopy did not reveal any apparent wear debris. Vertebral muscle/canal and spinal cord lesions noted in one high dose rabbit were likely traumatic in nature and not test article related.

6 months: Microscopically, there were no findings indicating systemic or local toxicity by the low- and high-dose wear debris six months after spinal implantation. Additional evaluation of the vertebral canal sections using polarized light microscopy did not reveal any apparent wear debris.

The 3 and 6-month study intervals demonstrate that the low- and high-dose wear debris are nonirritant.

Preclinical Studies Conclusion:
FDA determined that the preclinical animal and mechanical bench testing support the approval of the PRESTIGE® Cervical Disc.

X. SUMMARY OF CLINICAL STUDIES

Objective:
The objective of the IDE clinical study was to evaluate the safety and effectiveness of the PRESTIGE® Cervical Disc for the treatment of patients with symptomatic cervical disc disease.

Study Synopsis:
The clinical study was designed as a randomized, prospective, multicenter trial to assess the safety and effectiveness of the PRESTIGE® Cervical Disc compared to a single level surgical fusion utilizing bone graft and plate stabilization (the control treatment). Subjects were randomized at each site to either the PRESTIGE® or control treatment; the groups were randomized in a 1:1 manner.

The effectiveness of the PRESTIGE® device was based on an improvement in the Neck Disability Index (NDI) and maintenance of disc height, i.e. functional spinal unit or FSU. Safety was based primarily on improvement or maintenance of neurological status as well as the nature and frequency of adverse events and second surgeries.

Overall, the clinical trial enrolled 541 subjects at 32 sites; 276 subjects received the PRESTIGE® Disc and 265 received the control treatment. An interim analysis was done once 250 patients (128 investigational and 122 control) reached the two-year time point.

Inclusion and Exclusion Criteria:
Subjects were enrolled in this study according to the following inclusion/exclusion criteria.

Inclusion Criteria

- Degenerative disc disease (DDD) accompanied by neck pain of discogenic origin at a single level between C3 and C7 confirmed by history and radiographic studies. DDD was determined to be present if a herniated disc and/or osteophyte formation were noted.
- At least 6 weeks unsuccessful conservative treatment or signs of progression or spinal cord/nerve root compression with continued non-operative care;
- No previous surgical intervention at involved level or planned procedures at involved or adjacent levels;
- ≥ 18 years of age;
- Preoperative Neck Disability Index score of ≥ 30;
- Preoperative neck pain score of ≥ 20 on Neck and Arm Pain Questionnaire;
- Not pregnant.

Exclusion Criteria

- Cervical spinal condition other than symptomatic cervical disc disease requiring surgical treatment at the involved level;
- Documented or diagnosed cervical instability defined by dynamic (flexion/extension) radiographs showing sagittal plane translation > 3.5 mm or sagittal plane angulation > 20°;
- More than one cervical level requiring surgical treatment;
- Fused level adjacent to the level to be treated;

- Severe pathology of the facet joints of the involved vertebral bodies;
- Previous surgical intervention at the involved level;
- Previous diagnosis of osteopenia or osteomalacia;
- Has any of the following that may be associated with a diagnosis of osteoporosis (if Yes to any of the below risk factors, a DEXA Scan will be required to determine eligibility):
  - Postmenopausal Non-Black female over 60 years of age and weighs less than 140 pounds.
  - Postmenopausal female that has sustained a non-traumatic hip, spine, or wrist fracture.
  - Male over the age of 70.
  - Male over the age of 60 that has sustained a non-traumatic hip or spine fracture.
  - If the level of BMD is a T score of -3.5 or a T score of -2.5 with vertebral crush fracture, then the patient is excluded from the study.
- Spinal metastases;
- Overt or active bacterial infection, either local or systemic;
- Severe insulin dependent diabetes;
- Chronic or acute renal failure or prior history of renal disease;
- Fever (temperature > 101°F oral) at the time of surgery;
- Documented allergy or intolerance to stainless steel, titanium, or a titanium alloy;
- Mental incompetence;
- Prisoner;
- Pregnant;
- Alcohol and/or drug abuser currently undergoing treatment;
- Received drugs which may interfere with bone metabolism within two weeks prior to the planned date of spinal surgery;
- History of an endocrine or metabolic disorder known to affect osteogenesis;
- Condition that requires postoperative medications that interfere with the stability of the implant;
- Treatment with an investigational therapy within 28 days prior to implantation surgery or such treatment is planned during the 16 weeks following implantation with the PRESTIGE® Cervical Disc.

Post-Operative Care:
The recommended post-operative care included avoidance of heavy lifting, repetitive bending, and high-impact exercise or athletic activity for 60 days postoperatively. Avoidance of prolonged NSAID use (beyond 2 weeks postop) was also specified in the postoperative regimen, although the use of NSAIDs was recommended for the first two weeks postoperatively. The use of electrical bone growth stimulators was prohibited during the 24-month follow-up period. Patients who smoked were also encouraged to discontinue smoking.

Assessments:
Subjects were evaluated preoperatively (within 6 months of surgery), intraoperatively, and postoperatively at 6 weeks ± 2 weeks, 3 months ± 2 weeks, 6 months ± 1 month, 12 months ± 2 months, 24 months ± 2 months, and annually thereafter. The effectiveness variables included the NDI (which assesses pain/disability), neck pain, arm pain, patient gait, foraminal compression, general health status, patient global perceived effect, doctor's perception of results, radiographic parameters and overall success. The radiographic outcome parameters consisted of functional spinal unit (FSU) height as well as evaluations of motion and fusion at

the treated level for the investigational and control group, respectively. Adjacent level motion was also evaluated. At each evaluation timepoint, 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.

Outcomes Assessed and Success Criteria:

Primary Study Assessments:

- Pain/disability status was measured using the Neck Disability Index Questionnaire. Success was defined as a 15-point improvement (reduction) in the NDI score from the pre-op baseline score.

- Neurological status was based on motor function, sensory function, and reflexes. Neurological status success was defined as maintenance or improvement of the pre-op status for each element. Overall neurological status success required that each individual parameter be a success.

- Functional spinal unit height measurements were based on the radiographs. This parameter was considered to be a success if either the anterior or posterior postoperative height was no more than 2 mm less than the 6-week postoperative height.

Secondary Study Assessments:

- Neck pain was assessed on a numerical rating scale ranging from 0 to 10, with a lower score representing a better condition. Neck pain was a composite of intensity and duration scales. Neck pain success was determined by comparing the postoperative composite neck score to the preoperative score on a subject basis.

- Arm pain was assessed on a numerical rating scale ranging from 0 to 10, with a lower score representing a better condition. Arm pain was a composite of intensity and duration scales. Arm pain success was determined by comparing the postoperative composite neck score to the preoperative score on a subject basis.

- General health was assessed with the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36-36). This questionnaire consists of eight subscales that are summarized into two measures, i.e. the physical health summary (PCS) and the mental health summary (MCS). Success was defined as the proportion of subjects who demonstrated maintenance or improvement in the SF-36 subscores.

- Global perceived effect was assessed by asking subjects to evaluate their overall impression of their study treatment effectiveness as a function of pain. Success was defined as the proportion of subjects who rated their treatment as "completely recovered" or "much improved."

- Doctor's perception of results was assessed by asking the doctors to provide their perceptions of the subjects' conditions. Success was defined as the proportion of subjects who were rated as "excellent" or "good" by their doctor.

- Gait was assessed using Nurick's classification. Success was defined as the proportion of subjects whose gait was rated as normal.

- Foraminal compression was assessed by applying a force to the top of the head while the patient laterally flexes their head. Success was defined as a subject having no pain upon compression.

- Work status was examined. Success was defined as the proportion of subjects who were working.

- Radiographic success was defined according to the treatment.
    - For the PRESTIGE® group, radiographic success was based on 1) the existence of flexion/extension angular motion in a range of >4° to ≤20° and 2) no evidence of bridging trabecular bone forming a continuous connection between vertebral bodies.
    - Angular motion was measured by comparing lateral flexion and extension radiographs. Translational motion was also measured by comparing lateral flexion and extension radiographs.
    - For the control group, radiographic success was based on 1) radiographic evidence of bone spanning the two vertebral bodies, 2) the existence of angular motion stability <4° and 3) no radiolucent lines covering more than 50% of the implant surface.

Primary Study Endpoints/Success Criteria

The primary endpoint was determined at 24 months as a composite of the following parameters: pain and functional disability, neurological status, adverse events, secondary surgical interventions, and a radiographic spinal unit height determination. This was termed overall success.

In the approved protocol, individual subject success (i.e. overall success) was defined as attainment of all of the following:

1. An improvement (reduction) of at least 15 points from the baseline Neck Disability Index score;
2. Maintenance or improvement in neurological status;
3. No serious adverse event classified as implant-associated or implant/surgical procedure-associated;
4. No additional surgical procedure classified as "Failure"; and
5. Functional spinal unit (FSU) height maintenance. FSU height was considered maintained if it did not decrease more than 2 mm after 6 weeks following surgery.

As a note, because of the difficulty in evaluating FSU, due to anatomical interference with the radiographic image, an alternate overall success determination was also made based on the above criteria without the addition of FSU height maintenance.

Statistical Analysis Plan:

The study was designed as a non-inferiority trial with a margin of 10%. Bayesian methods with non-informative or uniform priors were used to obtain the posterior probabilities of non-inferiority and superiority. The Bayesian model incorporates data from both the 24-month follow-up visit and 12-month follow-up visit, including those from only the 12-month visit or

only the 24-month visit. However, the main focus of the analysis is the success rates at 24 months.

The study hypothesis was that the success rate of the PRESTIGE® group was not lower than that of the control group by more than 10%. The primary endpoint was deemed successful, i.e., the PRESTIGE® is not inferior to the control, if the posterior probability that the success rate of PRESTIGE® group was not lower than control group by more than 10% was greater than 95%. If non-inferiority was demonstrated, analyses were also defined in the statistical plan to determine whether the investigational group had statistically superior outcomes as compared to the control group. An interim analysis was planned when a total of approximately 250 patients had follow-up visits at 24 months.

Data Analyses and Results:
The results of the clinical study were evaluated using Bayesian statistical methods. The study was designed to use Bayesian methods with non-informative or uniform priors to analyze the primary endpoint.

To demonstrate the comparability of the two groups a logistic regression (covariate) analysis was performed which examined the relationship of all demographic, preoperative medical conditions and preoperative measurements of effectiveness variables on the overall success results. The primary results are similar when statistically significant variables were included in the analysis.

Study Results:
Patient Demographics and Preoperative Data
The clinical trial enrolled 541 subjects at 32 sites; 276 subjects received the PRESTIGE® system and 265 were controls. Demographic data for these subjects are presented in Table 10.

Table 10: Study Patient Demographics.

Variables	Investigational (N=276)	Control (N=265)	p-value
Age (years)	43.3 ± 7.6	43.9 ± 8.8	0.435
Height (inches)	67.4 ± 3.9	67.5 ± 4.2	0.767
Weight (lbs.)	181.7 ± 39.7	184.7 ± 41.5	0.389
Sex (% male)	46.4%	46.0%	1.000
Race			
Caucasian	260	243	0.448
Black	6	13	
Asian	1	2	
Hispanic	7	6	
Other	2	1	
Marital Status			
Single	44	32	0.240
Married	188	204	
Divorced	36	24	
Separated	5	3	
Widowed	3	2	
Education Level			
< High School	10	14	0.458
High School	73	77	
> High School	193	173	
Worker's Compensation	11.6%	13.2%	0.603
Unresolved Spinal Litigation	10.9%	12.1%	0.687
Tobacco Used	34.4%	34.7%	1.000
Alcohol Used	43.5%	53.2%	0.025
Preoperative Work Status	65.9%	62.6%	0.473

There were no statistically significant differences between the two groups in terms of the demographic parameters presented in Table 10.

Table 11 shows the preoperative evaluations for the two groups and that there were no statistically significant differences between the two groups.

Table 11: Preoperative Evaluation of Clinical Endpoints.

Variables	Investigational (N=276)	Control (N=265)	p-value
NDI	55.7 ± 14.8	56.4 ± 15.9	0.632
SF-36 PCS	31.9 ± 7.0	32.0 ± 7.5	0.760
SF-36 MCS	42.4 ± 12.1	42.7 ± 12.4	0.795
Neck Pain Score	68.2 ± 22.7	69.3 ± 21.5	0.553
Arm Pain Score	59.1 ± 29.4	62.4 ± 28.5	0.191

Table 12 summarizes other preoperative considerations and medication use.

Table 12: Preoperative Medical Condition and Medication Usage.

Variables	Investigational (N=276)	Control (N=265)	p-value
Time to have symptoms leading to planned surgery < 6 weeks 6 weeks to 6 months > 6 months	 21 81 174	 15 89 161	 0.435
Number of previous neck surgeries 0 1 2	 275 1 0	 263 1 1	 0.745
Non-Narcotic medications	197 (71.9%)	187 (71.1%)	0.849
Weak Narcotic medications	130 (47.3%)	127 (48.3%)	0.863
Strong Narcotic medications	57 (20.9%)	58 (22.0%)	0.833
Muscle Relaxant medications	119 (43.4%)	114 (43.2%)	1.000

Patient Accountability

The clinical study was powered statistically for 550 patients. At the time of the IDE the sponsor planned to perform an interim analysis when 250 implanted subjects had completed their 24-month follow-up visit. At this time all enrolled subjects, i.e. 541 implanted subjects would have reached their 12 month follow-up window. If the results of this interim analysis demonstrated statistical non-inferiority of the subjects receiving the PRESTIGE® device compared to controls, the sponsor would submit a PMA application. The sponsor submitted data after 128 in the investigational group and 122 patients in the control reached the 24-month follow-up time point with overall success outcome data (without functional spinal unit height). The subject accountability data are summarized in Table 13.

Table 13: Patient Accountability

Number of Patients:	12 Months (±2 Months)		24 Months (±2 Months)	
	Invest.	Control	Invest.	Control
Enrolled	276	265	276	265
Theoretical FU	276	265	137	148
Expected	276	263	137	148
Evaluable for Overall Success w/o FSU (% of Total Expected)	263 (95.3%)	223 (84.8%)	128 (93.4%)	122 (82.4%)
Evaluable for Overall Success w/ FSU (% of Total Expected)	205 (74.3%)	173 (65.8%)	95 (69.3%)	90 (60.8%)

Surgical Results and Hospitalization

The mean operative times and mean hospitalization times were similar between the two groups, as shown in Table 14.

Table 14: Surgical Results

	Investigational	Control
Mean operative time (hrs)	1.6	1.4
Mean EBL (ml)	60.1	57.5
Hospitalization (days)	1.1	1.0
Spinal level treated		
C_{3-4} (%)	7 (2.5)	10 (3.8)
C_{4-5} (%)	14 (5.1)	15 (5.7)
C_{5-6} (%)	142 (51.4)	149 (56.2)
C_{6-7} (%)	113 (40.9)	91 (34.3)

Results of Primary Effectiveness Analysis

Study success was expressed as the number of individual subjects categorized as a success divided by the total number of subjects evaluated. Table 15 describes the success rates for the individual outcome parameters and overall success. All success rates were based on the data from the 24-month follow-up evaluation and posterior probabilities of success were calculated using Bayesian statistical methods. The conclusions were based on an interim analysis which was pre-defined in the protocol.

FDA approved overall success endpoint included the evaluation of FSU. Because of the difficulty in evaluating FSU, due to anatomical interference with the radiographic image, an alternate overall success determination was also made based on the above criteria without the addition of FSU height maintenance.

In some cases, not all data was available, i.e. FSU height. Therefore the number of subjects included in each of the assessments varies (See Table 16).

Table 15: Posterior Probabilities of Success at 24 Months.

Primary Outcome Variable	Investigational Posterior Mean (95% HPD Credible Interval)	Control Posterior Mean (95% HPD Credible Interval)	Posterior Probabilities Non-Inferiority	Superiority
NDI	80.8% (74.7%, 87.0%)	80.8% (74.1%, 86.7%)	98.5%	50.0%
Neurological	92.1% (87.6%, 96.2%)	84.7% (78.6%, 90.5%)	~100%	97.1%
FSU Height	95.4% (91.5%, 98.7%)	93.7% (89.2%, 97.8%)	~100%	71.7%
Overall Success (without FSU)	78.8% (72.1%, 85.0%)	70.0% (62.7%, 77.4%)	~100%	95.9%
Overall Success (with FSU)	80.1% (73.1%, 87.4%)	64.0% (55.3%, 72.8%)	~100%	99.7%

Bayesian analysis was performed utilizing both 12-month and 24-month data to calculate the posterior probabilities in Table 15 above. The number of patients with the primary outcome variable data at 12 and 24-months are listed in Table 16 below.

Table 16: Patient Data Available for Bayesian Calculations

Primary Outcome Variable	12 Months (±2 Months)		24 Months (±2 Months)	
	Inv	Ctrl	Inv	Ctrl
NDI	263	222	128	121
Neurological	264	226	128	121
FSU Height	205	171	94	88
Overall Success* (without FSU)	263	223	128	122
Overall Success* (with FSU)	205	173	95	90

*If a patient failed based on either a second surgery or serious, possibly implant- or implant/surgical procedure-associated adverse event, the patient was counted as an Overall Success failure and included in the analysis, regardless of whether or not they had the FSU measurement, NDI score, or neurological outcome.

Non-inferiority of the PRESTIGE® group to the control group was demonstrated for all endpoints listed in Table 15 above. Superiority of the PRESTIGE® group to the control group was demonstrated for overall success (both with and without FSU) and the neurological variable. The NDI and FSU components were not found to be statistically superior in the PRESTIGE® group.

Results of Radiographic Analysis

Table 17 shows radiographic success rates for the 123 PRESTIGE® subjects with evaluable radiographic data. Not all of these 123 patients, however, had data for each radiographic item (e.g., 116 of 123 patients had angular motion data). Data on the control devices are not presented because of the differences in radiographic success criteria between the investigational and control groups.

Table 17: Radiographic Success

Investigational Patients	Angular Motion >4° to ≤20°	No Bridging Bone	Overall Radiographic Success
24 Months			
Success (%)	85 (73.3)	122 (99.2)	85 (72.6)
Failure (%)	31 (26.7)	1 (0.8)	32 (27.4)

Table 18 describes the results of the angular motion, translational motion and lateral bending.

Table 18: Treated Level Measurements

	Pre Operative	12 months	24 months
Angular motion (mean)	7.55°	7.59°	7.87°
Translational motion (mean)	0.26 mm	0.33 mm	0.28 mm
Lateral bending (mean)	ND	6.73°	6.39°

The histogram below shows the flexion/extension range of motion values for the cohort of patients that reached 24 months (n=116).

Histogram of PRESTIGE® Cervical Disc Angular Range of Motion at 24 Months

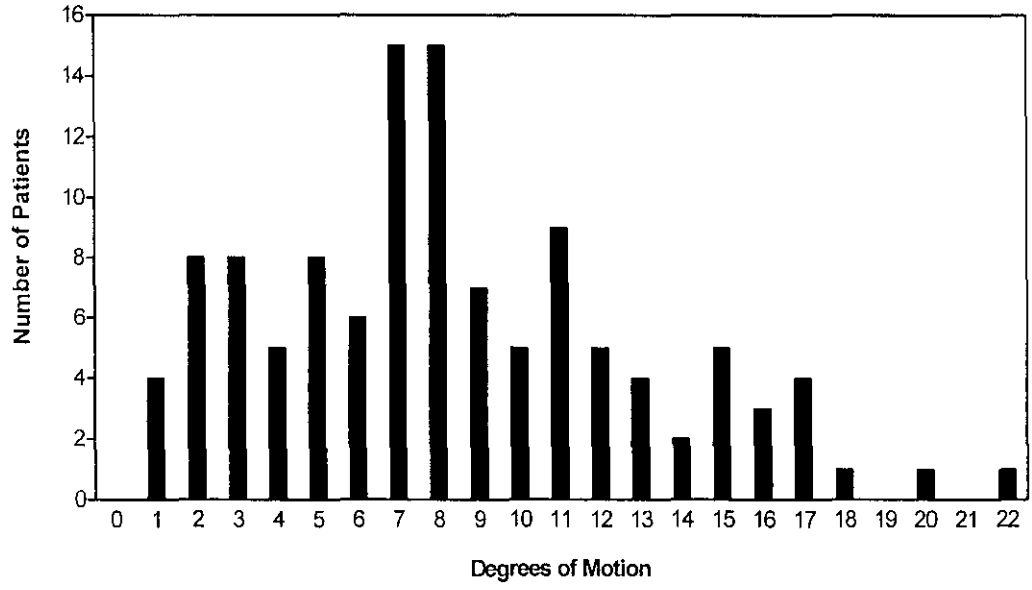

Table 19 summarizes the effect of the PRESTIGE® device on adjacent levels.

Table 19: Adjacent Level Measurements Angular Motion

	Pre-op		12 months		24 months	
	Invest.	**Control**	**Invest.**	**Control**	**Invest.**	**Control**
Level above treated segment (Mean)	11.17°	10.77°	11.94°	12.07°	12.05°	11.63°
Level below treated segment (Mean)	8.32°	7.77°	8.33°	9.53°	9.47°	9.07°

Results of Secondary Effectiveness Variables

Table 20 describes the results of the secondary effectiveness endpoints.

Table 20: Secondary Endpoints

Variable	PRESTIGE®	Control	Posterior Probability of Non-inferiority
Neck pain			
Success	120 (93.8)	99 (81.8)	99.2%
Failure	8 (6.2)	22 (18.2)	
Arm pain			
Success	116 (90.6)	114 (94.2)	98.1%
Failure	12 (9.4)	7 (5.8)	
SF-36 PCS			
Success	109 (85.8)	102 (85.7)	97.9%
Failure	18 (14.2)	17 (14.3)	
SF-36 MCS			
Success	84 (66.1)	88 (73.9)	87.5%
Failure	43 (33.9)	31 (26.1)	
Effect of Sx			
Complete Recovery	58 (45.7)	46 (38.0)	Not Available*
Much improved	50 (39.4)	52 (43.0)	
Doctor Perception			
Excellent	90 (70.9)	68 (56.2)	Not Available*
Good	30 (23.6)	43 (35.2)	
Gait			
Success	128 (100.0)	121 (100.0)	Not Available*
Failure	0 (0.0)	0 (0.0)	
Foraminal Compression			
Negative	121 (95.3)	116 (95.9)	Not Available*
Positive	6 (4.7)	5 (4.1)	
Work Status			
Working	100 (78.1)	87 (71.9)	Not Available*
Not working	4 (3.1)	4 (3.3)	
Others	24 (18.8)	30 (24.8)	

*Posterior probabilities were not supplied for these secondary endpoints because non-inferiority hypotheses were not pre-specified for these endpoints.

Additional Data Analyses

A per-protocol analysis and missing equals failure analysis were also performed. The "per protocol" dataset was a subset of patients who were included in the primary analysis dataset. Patients who were excluded from the "per protocol" analysis had major protocol deviations, i.e., did not meet the inclusion/exclusion criteria or received the wrong study treatment, or other major protocol deviations that could potentially affect clinical outcomes.

Table 21 summarizes the results at 24 months following surgery.

Table 21: Per-Protocol Analysis

"Per Protocol" Success Rates			
	Investigational	**Control**	**Post. Prob. of Non-inferiority**
NDI	82.5% (104/126)	83.0% (93/112)	97.1%
Neurological	93.7% (118/126)	86.6% (97/112)	100.0%
FSU Height	97.8% (90/92)	95.1% (78/82)	100.0%
Overall Success (without FSU)	80.2% (101/126)	72.6% (82/113*)	100.0%
Overall Success (with FSU)	81.7% (76/93*)	65.5% (55/84*)	100.0%

*If a patient failed based on either a second surgery or serious, possibly implant- or implant/surgical procedure-associated adverse event, the patient was counted as an Overall Success failure and included in the analysis, regardless of whether or not they had the FSU measurement, NDI score, or neurological outcome.

The statistical comparison for the "per protocol" dataset yielded a posterior probability of non-inferiority of $\geq 95\%$ for each of the individual components as well as the two overall success calculations.

For the "missing-equals-failure" data, secondary surgery failures, deaths, patients lost-to-follow-up, and missing observations due to other causes resulted in missing observations for the outcome variables and, therefore, were included in the denominators of the calculated rates, i.e., considered as "failures." By treating these patients as treatment failures, the clinical outcome rates in the "missing-equals-failure" analyses were lower than those observed in the clinical data. Refer to Table 22.

An analysis was performed to assess the ability to pool data across sites and to compare data between the study arms, using the Breslow-Day test. These analyses evaluated the primary clinical outcome variables, i.e. NDI, neurological status and FSU, as well as overall success. No heterogeneity was found that would prevent pooling of the data across the sites within a given group of subjects.

Table 22: Missing Equals Failure Analysis

Missing Equals Failure Success Rates			
Variable	**24 month outcome**	**Investigational (N=137)**	**Control (N=148)**
NDI	Success	106 (77.4)	99 (66.9)
	Failure	31 (22.6)	49 (33.1)
Neurological	Success	120 (87.6)	105 (70.9)
	Failure	17 (12.4)	43 (29.1)
FSU	Success	91 (66.4)	84 (56.8)
	Failure	46 (33.6)	64 (43.2)
Overall Success without FSU	Success	103 (75.2)	87 (58.8)
	Failure	34 (24.8)	61 (41.2)
Overall Success with FSU	Success	77 (56.2)	58 (39.2)
	Failure	60 (43.8)	90 (60.8)

Sensitivity Analysis for Assessing Missing Values

It was noted that there was a disparity in follow-up rates at 24 months between the investigational and control group. In the interim analysis cohort, nine (6.6%) of 137 investigational patients did not have overall success outcomes, as compared to 26 (17.6%) of 148 control patients. To assess the impact of lost-to-follow-up on study conclusions, a sensitivity analysis was performed of overall success at 24 months by various imputations for the missing outcomes. The analyses were focused on the 24-month data and used simple frequentist calculations.

The results show that in the worst case scenario (where all missing investigational outcomes are assumed to be failures and all missing control outcomes are assumed to be successes), statistical non-inferiority of the investigational treatment to the control ($p=0.0411$) was demonstrated. When 50% of missing investigational outcomes and 60% of the missing control outcomes are assumed to be successes (which favors the control group and could perhaps be closer to the actual situation), statistical superiority of the investigational treatment to the control is shown ($p=0.0363$).

Other Analyses

Analyses were performed to examine the relationships between certain key endpoints at 12 and 24 months postoperative. The results for the primary and "per protocol" dataset are presented in the table below.

Table 23: Percent Agreement Between 12- and 24-Month Data

	Primary Dataset		"Per Protocol" Dataset	
	Invest. (n=128)	Control (n=121)	Invest. (n=126)	Control (n=112)
NDI	88.1%	87.0%	88.7%	86.9%
Neurological	92.9%	88.8%	92.7%	88.0%
FSU Height	97.8%	97.5%	98.9%	98.7%
Overall Success (without FSU)	84.9%	83.6%	85.5%	83.3%
Overall Success (with FSU)	84.4%	80.7%	86.4%	80.8%

The agreement between the 12- and 24-month outcomes means that there is a likelihood of a patient in either treatment group having the same outcome at the two latter study periods.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

Overall success, i.e. an improvement in the pain and disability outcome scale, neurological success, maintenance of disc height, as well as no implant related serious adverse event or second surgical procedure, was the basis for demonstrating the effectiveness of the device. The overall success rate, with and without the disc height criteria, for the PRESTIGE® group was found to be statistically non-inferior to fusion with bone graft and plate stabilization for the treatment of cervical degenerative disc disease from C3 to C7. The primary efficacy endpoint was met at the time of interim analysis.

The safety profile demonstrated that the PRESTIGE® Cervical Disc was as safe as the control, in regards to adverse events and the need for second surgeries.

The results of the clinical study provide a reasonable assurance that the PRESTIGE® Cervical Disc is safe and effective for the indicated population.

The results from the pre-clinical studies (mechanical and animal) support the use of the device *in vivo.*

Thus, CDRH has determined that there is a reasonable assurance of safety and effectiveness of the PRESTIGE® Cervical Disc based on the results of the preclinical testing and the results of the clinical study.

XII. PANEL RECOMMENDATION

At an advisory meeting held on September 19, 2006, the Orthopedic and Rehabilitation Devices Panel recommended that Medtronic Sofamor Danek's PMA for the PRESTIGE® Cervical Disc be approved subject to submission to, and approval by, the Center for Devices and Radiological Health (CDRH) of the following:

- The indications should be altered to read: "Device is indicated for reconstruction of the disc following single-level anterior discectomy for decompression of intractable radiculopathy and/or myelopathy."
- The PMA approval should be limited to all claims of non-inferiority only.
- The sponsor should conduct a post-approval animal study to address particulate migration and the device/bone interface.
- The sponsor should conduct a post-approval study of the device that looks at the long term safety and function of the device.
- The sponsor should have no educational material that suggests that preserving motion at one segment preserves the adjacent segment from having disease.

XIII. CDRH DECISION

CDRH concurred with the Panel recommendation of September 19, 2006 that there is a reasonable assurance of safety and effectiveness of the PRESTIGE® Cervical Disc based on the results of the preclinical testing and the results of the clinical study. Accordingly, CDRH issued a letter to Medtronic Sofamor Danek on March 13, 2007, advising that its PMA was approvable subject to Medtronic Sofamor Danek addressing issues related to the postapproval conditions. Medtronic Sofamor Danek submitted a response on March 26, 2007.

Below is a discussion of FDA action on each of the Panel's recommendations:

(1) The indications should be altered to read: "Device is indicated for reconstruction of the disc following single-level anterior discectomy for decompression of intractable radiculopathy and/or myelopathy."

The sponsor agreed to alter the device indications to read, "The PRESTIGE® Cervical Disc is indicated in skeletally mature patients for reconstruction of the disc from C3-C7 following single-level discectomy for intractable radiculopathy and/or myelopathy. The PRESTIGE® device is implanted via an open anterior approach. Intractable radiculopathy and/or myelopathy must present with at least one of the following items producing symptomatic nerve root and/or spinal cord compression which is documented by patient history (e.g., pain [neck and/or arm pain], functional deficit, and/or neurological deficit), and radiographic studies (e.g., CT, MRI, x-rays, etc.): 1) herniated disc, and/or 2) osteophyte formation." This change has been reflected in the package labeling and all promotional materials.

(2) The PMA approval should be limited to all claims of non-inferiority only.

FDA permitted the sponsor to report the findings of their superiority analysis that was pre-specified at the time of IDE. Statistical superiority was demonstrated in the PRESTIGE® group for overall success (with and without the FSU height component) and the neurological component. Statistical superiority was not demonstrated in the PRESTIGE® group for the NDI (primary effectiveness variable that addresses pain and function) and FSU height components. Claims derived from these findings should take into account the fact that the superiority finding for overall success was driven primarily by superiority in the neurological component. Proportions for the NDI variable were nearly identical between the two groups.

(3) The sponsor should conduct a post-approval animal study to address particulate migration and the device/bone interface.

At the September 19, 2006 Advisory Panel Meeting, the panel requested a post-approval study to look at both the particulate migration and the device/bone interface. The panel noted that the injected particles could not be readily located in the animals at sacrifice. In addition, the panel wanted to look more closely at the long term fixation of the device. Hence, one of the conditions of approval from the panel for this PMA was a post-approval animal study to address particle migration and the longer term fixation of the device.

Given the long history of use of this stainless steel material in the spine and literature[2] showing similar results to the sponsor's study, FDA determined that another post-approval animal particulate study would not add value to this data set. In addition, an animal study of one or two years will not yield long term information on the device fixation. Because there were no incidences of device loosening that required re-operation among the cohort of implanted PRESTIGE® patients, FDA did not require an additional post-approval animal study.

(4) The sponsor should conduct a post-approval study of the device that looks at the long term safety and function of the device.

FDA agreed. See final conditions of approval below.

(5) The sponsor should have no educational material that suggests that preserving motion at one segment preserves the adjacent segment from having disease.

The sponsor agreed to remove any statement from their labeling or promotional materials that states or implies that motion retention preserves adjacent segments from having disease.

As part of the development of the final conditions of approval for this PMA, FDA considered not only the Panel input, but also the available data, issues that should be further evaluated, and our experience with postapproval studies for spinal implants.

FDA issued an approval order on July 16, 2007. The final conditions of approval cited in the approval order are described below.

1. The sponsor has agreed to perform a 7-year post-approval study to evaluate the longer term safety and effectiveness of the PRESTIGE® Cervical Disc. The study will involve the investigational and control patients from the pivotal investigational device exemption (IDE) study arm, as well as the patients who received the device as part of the continued access study arm. Data will be collected at 3 years, 5 years, and 7 years postoperatively for all patients. At each timepoint, the following data will be collected: Neck Disability Index score; radiographic information; and neurological status. In addition, the sponsor will collect all adverse events, including details of the nature, onset, duration, severity, relationship to the device, and relationship to the operative procedure and outcome, reported for these patients. Reports will be submitted annually until the completion of the study. The results of this long-term data must be reflected in the labeling (via supplement) when the post-approval study is completed, as well as any other timepoint deemed necessary by FDA if significantly new information from this study becomes available.

2. The sponsor has agreed to conduct a 5-year enhanced surveillance study of the PRESTIGE® Cervical Disc to more fully characterize adverse events when the device is used in a broader patient population. The sponsor will collect, analyze, and submit all adverse events and complaints received by the company for the PRESTIGE® Cervical Disc, as well as information on the total number of devices shipped. The study will commence at the time of PMA approval and reports will be submitted every six months for the first two years and then annually through the fifth year after approval.

The applicant's manufacturing facility was inspected and was found to be in compliance with the Quality System Regulation (21 CFR 820).

The PRESTIGE® Cervical Disc was granted expedited review status on May 19, 2006 because FDA believed that a cervical disc may offer an alternative to cervical fusion in some patients with cervical degenerative disc disease and that the application met the criteria for an expedited review.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.

XV. REFERENCES

1. White A, Panjabi M. *Clinical Biomechanics of the Spine* J.B. Lippincott Company. 1990.
2. Cunningham B.W. Basic scientific considerations in total disc arthroplasty. *The Spine Journal*, 4, 219S-230S, 2004.