SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Total Cervical Disc Replacement
Device Trade Name:	ProDisc™-C Total Disc Replacement
Applicant's Name and Address:	Synthes Spine 1302 Wrights Lane E. West Chester, PA 19380
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P070001
Date of Notice of Approval of Application:	December 17, 2007

II. INDICATIONS FOR USE

The ProDisc™-C Total Disc Replacement is indicated in skeletally mature patients for reconstruction of the disc from C3-C7 following single-level discectomy for intractable symptomatic cervical disc disease (SCDD). Symptomatic cervical disc disease is defined as neck or arm (radicular) pain and/or a functional/neurological deficit with at least one of the following conditions confirmed by imaging (CT, MRI, or X-rays): herniated nucleus pulposus, spondylosis (defined by the presence of osteophytes), and/or loss of disc height. The ProDisc™-C Total Disc Replacement is implanted via an open anterior approach. Patients receiving the ProDisc™-C Total Disc Replacement should have failed at least six weeks of non-operative treatment prior to implantation of the ProDisc™-C Total Disc Replacement.

III. CONTRAINDICATIONS

The ProDisc™-C Total Disc Replacement should not be implanted in patients with the following conditions:

- Active systemic infection or infection localized to the site of implantation
- Osteoporosis defined as DEXA bone density measured T-score $\leq$ -2.5
- Marked cervical instability on neutral resting lateral or flexion/extension radiographs; translation > 3mm and/or > 11° of rotational difference to either adjacent level
- Allergy or sensitivity to the implant materials (cobalt, chromium, molybdenum, polyethylene, titanium)
- Severe spondylosis characterized by bridging osteophytes or a loss of disc height > 50% or an absence of motion (<2°), as this may lead to limited range of motion and may encourage bone formation (e.g., heterotopic ossification, fusion)

- Clinically compromised vertebral bodies at the affected level due to current or past trauma (e.g., by radiographic appearance of fracture callus, malunion, or nonunion)
- Patients with SCDD at more than one level

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the ProDisc™-C Total Disc Replacement labeling.

V. DEVICE DESCRIPTION

The ProDisc™-C Total Disc Replacement is made up of three components:

- an inferior CoCrMo (cobalt chromium molybdenum) alloy plate with a midline keel orientated anterior-posterior that is anchored into the endplate of the inferior vertebral body
- an Ultra High Molecular Weight Polyethylene (UHMWPE) insert that is pre-assembled snap-locked into a tray detail in the inferior CoCrMo alloy plate and provides the inferior convex bearing surface
- a CoCrMo alloy plate with a midline keel that anchors to the superior vertebral body and has a highly polished concave bearing surface that articulates with the convex UHMWPE spherical dome.

The endplate footprints range from 15-19 mm wide (medial-lateral) x 12-18 mm deep (anterior-posterior). Each endplate size is available in three disc heights (5, 6, and 7 mm) to accommodate a range of vertebral sizes.

The bone contacting surfaces of the inferior and superior plates as well as both keels are titanium plasma spray coated.

The maximum range of motion allowed by the ProDisc™-C Total Disc Replacement device design is 20° in flexion/extension (17.5° for the 5mm Large, Large Deep, Extra Large, and Extra Large Deep implants), 20° in lateral bending (17.5° for the 5mm Large, Large Deep, Extra Large, and Extra Large Deep implants), and the device is unconstrained in axial rotation as measured through *in vitro* testing.

The plates are manufactured from CoCrMo alloy conforming to ISO 5832-12 "Implants for surgery -- Metallic Materials – Part 12: Wrought cobalt-chromium-molybdenum alloy". The insert is manufactured from ultra-high molecular weight Polyethylene (UHMWPE) conforming to ISO 5834-2 "Implants for surgery -- Ultra-high molecular weight polyethylene – Part 2: Molded forms". The surfaces of both inferior and superior plates that abut the bone are plasma sprayed with Titanium CP conforming to ISO/DIS 5832 -2 "Implants for surgery – Metallic materials -- Part 2: Unalloyed titanium".

Table 1: Implant Components

Catalog Number	Component Description	A/P (mm)	Lateral (mm)	Disc Height (mm)
09.820.025S	ProDisc-C Implant, medium 5mm, sterile	12	15	5, 6, 7
09.820.026S	ProDisc-C Implant, medium 6mm, sterile	12	15	5, 6, 7
09.820.027S	ProDisc-C Implant, medium 7mm, sterile	12	15	5, 6, 7
09.820.035S	ProDisc-C Implant, medium Deep 5mm, sterile	14	15	5, 6, 7
09.820.036S	ProDisc-C Implant, medium Deep 6mm, sterile	14	15	5, 6, 7
09.820.037S	ProDisc-C Implant, medium Deep 7mm, sterile	14	15	5, 6, 7
09.820.045S	ProDisc-C Implant, large 5mm, sterile	14	17	5, 6, 7
09.820.046S	ProDisc-C Implant, large 6mm, sterile	14	17	5, 6, 7
09.820.047S	ProDisc-C Implant, large 7mm, sterile	14	17	5, 6, 7
09.820.055S	ProDisc-C Implant, large deep 5mm, sterile	16	17	5, 6, 7
09.820.056S	ProDisc-C Implant, large deep 6mm, sterile	16	17	5, 6, 7
09.820.057S	ProDisc-C Implant, large deep 7mm, sterile	16	17	5, 6, 7
09.820.065S	ProDisc-C Implant, extra large 5mm, sterile	16	19	5, 6, 7
09.820.066S	ProDisc-C Implant, extra large 6mm, sterile	16	19	5, 6, 7
09.820.067S	ProDisc-C Implant, extra large 7mm, sterile	16	19	5, 6, 7
09.820.075S	ProDisc-C Implant, extra large Deep 5mm, sterile	18	19	5, 6, 7
09.820.076S	ProDisc-C Implant, extra large Deep 6mm, sterile	18	19	5, 6, 7
09.820.077S	ProDisc-C Implant, extra large Deep 7mm, sterile	18	19	5, 6, 7

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Non-operative alternative treatments for SCDD include, but are not limited to, physical therapy, medications, braces, chiropractic care, bed rest, spinal injections, or exercise programs.

When conservative attempts fail to alleviate the pain and/or neurological deficits caused by SCDD, the most common treatment is decompression of the affected nerves and spinal cord. Surgical decompression of the affected nerves and spinal cord is most often accomplished by removal of the diseased cervical disc, known as cervical discectomy, and associated osteophytes.

Most cervical decompressions are followed by the insertion of a bone graft into the space after the disc is removed to maintain intervertebral height and facilitate fusion of the adjacent vertebrae. This is most commonly accompanied by the placement of an anatomical plate anterior to the bone graft to immobilize the vertebral segment and provide stability. This procedure is known as an anterior cervical discectomy and fusion (ACDF).

SCDD may also be treated surgically using another approved artificial cervical disc.

VII. MARKETING HISTORY

The ProDisc™-C Total Disc Replacement has been commercially available in markets outside of the United States since December, 2002. The device has not been withdrawn from the market for any reason relating to the safety and effectiveness of the device. The countries in which ProDisc™-C Total Disc Replacement is available are provided in the table below.

Table 2: Global Distribution

Argentina	Czech Republic	Greece	Mexico	Saudi Arabia	Switzerland
Australia	Denmark	Hong Kong	Netherlands	Singapore	Thailand
Austria	Ecuador	Hungary	New Zealand	Slovakia	Turkey
Belgium	Egypt	Iran	Norway	Slovenia	Venezuela
Brazil	Finland	Israel	Panama	South Africa	
Chile	France	Italy	Poland	South Korea	
China	Germany	Luxembourg	Portugal	Spain	
Colombia	Great Britain	Malaysia	Russia	Sweden	

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The following adverse events were reported during a multi-center, prospective, randomized, non-inferiority clinical study comparing 103 patients implanted with the ProDisc™-C Total Disc Replacement to 106 control patients who received an anterior cervical discectomy and fusion (ACDF).

Table 3: All Adverse Events

Adverse Event	Intra-Op (0-2 days)		Peri-Op (>2 - 42 days)		Short Term (>42-210 days)		Long Term (>210 days)		ACDF (N=106)		ProDisc-C (N=103)	
	ACDF	PRC	ACDF	PRC	ACDF	PRC	ACDF	PRC	Patients (%)	Events (E/Pt)	Patients (%)	Events (E/Pt)
ALL ADVERSE EVENTS									86 (81.1%)	254 (2.40)	84 (81.6%)	237 (2.30)
Adjacent Level DDD or DJD	0	0	0	0	1	0	3	0	4 (3.8%)	4 (0.04)	0 (0.0%)	0 (0.00)
Burning or Dysesthetic Pain	0	0	0	1	0	0	0	0	0 (0.0%)	0 (0.00)	1 (1.0%)	1 (0.01)
Cancer	0	0	0	0	0	0	0	1	0 (0.0%)	0 (0.00)	1 (1.0%)	1 (0.01)
Cardiovascular	2	2	0	1	3	1	2	1	7 (6.6%)	7 (0.07)	5 (4.9%)	5 (0.05)
DDD Progression, Non-Cervical	0	0	0	0	1	0	0	1	1 (0.9%)	1 (0.01)	1 (1.0%)	1 (0.01)
Dermatological	0	0	1	0	0	0	0	1	1 (0.9%)	1 (0.01)	1 (1.0%)	1 (0.01)
Dizziness	0	0	0	1	0	0	0	0	0 (0.0%)	0 (0.00)	1 (1.0%)	1 (0.01)
Dural Tear	0	1	0	0	0	0	0	0	0 (0.0%)	0 (0.00)	1 (1.0%)	1 (0.01)
Dysphagia	3	2	5	3	0	0	1	1	9 (8.5%)	9 (0.08)	6 (5.8%)	6 (0.06)
Dysphonia	1	0	0	0	0	0	0	0	1 (0.9%)	1 (0.01)	0 (0.0%)	0 (0.00)
Edema	1	2	0	0	0	0	0	0	1 (0.9%)	1 (0.01)	2 (1.9%)	2 (0.02)
Fatigue	0	1	0	0	0	0	0	0	0 (0.0%)	0 (0.00)	1 (1.0%)	1 (0.01)
Fracture - Vertebral	0	0	0	0	0	0	1	0	1 (0.9%)	1 (0.01)	0 (0.0%)	0 (0.00)
Gastrointestinal	11	15	1	1	2	1	2	2	15 (14.2%)	16 (0.15)	16 (15.5%)	19 (0.18)
Genitourinary	2	4	0	1	0	0	1	0	3 (2.8%)	3 (0.03)	5 (4.9%)	5 (0.05)
Headache	1	3	2	4	3	4	8	9	12 (11.3%)	14 (0.13)	18 (17.5%)	20 (0.19)
Infection - Non-Wound	0	1	0	0	2	2	4	0	6 (5.7%)	6 (0.06)	2 (1.9%)	3 (0.03)
Infection - Superficial Wound	0	0	1	0	0	0	0	0	1 (0.9%)	1 (0.01)	0 (0.0%)	0 (0.00)
Insomnia	3	4	0	1	0	0	0	1	3 (2.8%)	3 (0.03)	6 (5.8%)	6 (0.06)
Musculoskeletal	0	1	4	3	2	10	15	7	16 (15.1%)	21 (0.20)	18 (17.5%)	21 (0.20)
Musculoskeletal (Spasms - Back)	0	0	1	0	0	0	0	1	1 (0.9%)	1 (0.01)	1 (1.0%)	1 (0.01)
Musculoskeletal (Spasms - Neck)	1	0	2	0	1	2	1	1	5 (4.7%)	5 (0.05)	3 (2.9%)	3 (0.03)
Musculoskeletal (Spasms - Non-Specific)	2	2	0	0	2	0	0	1	4 (3.8%)	4 (0.04)	3 (2.9%)	3 (0.03)
Narcotics Use	0	0	0	1	0	0	0	0	0 (0.0%)	0 (0.00)	1 (1.0%)	1 (0.01)
Neurological	0	1	0	0	0	1	1	2	1 (0.9%)	1 (0.01)	4 (3.9%)	4 (0.04)
Numbness Index Level	0	0	0	0	0	0	2	0	2 (1.9%)	2 (0.02)	0 (0.0%)	0 (0.00)
Numbness Non-Index Level	0	2	0	1	3	2	4	8	7 (6.6%)	7 (0.07)	11 (10.7%)	13 (0.13)
Ossification	0	0	0	0	0	0	0	1	0 (0.0%)	0 (0.00)	1 (1.0%)	1 (0.01)
Other	1	1	0	2	2	1	4	1	6 (5.7%)	7 (0.07)	4 (3.9%)	5 (0.05)
Pain - Back	0	0	1	2	4	3	3	6	8 (7.5%)	8 (0.08)	11 (10.7%)	11 (0.11)
Pain - Back and Lower Extremeties	0	0	0	1	0	1	2	3	2 (1.9%)	2 (0.02)	4 (3.9%)	5 (0.05)
Pain - Incision Site	0	1	0	0	0	0	1	0	1 (0.9%)	1 (0.01)	1 (1.0%)	1 (0.01)
Pain - Neck	2	1	2	2	10	7	11	6	22 (20.8%)	25 (0.25)	16 (15.5%)	16 (0.16)
Pain - Neck and Other	0	0	0	0	0	0	0	1	0 (0.0%)	0 (0.00)	1 (1.0%)	1 (0.01)
Pain - Neck and Shoulder	0	2	0	1	2	1	4	4	6 (5.7%)	6 (0.06)	7 (6.8%)	8 (0.08)
Pain - Neck and Upper Extremeties	0	0	0	0	1	2	6	1	6 (5.7%)	7 (0.07)	3 (2.9%)	3 (0.03)
Pain - Neck and Upper Ext. with Numbness	0	0	0	1	5	2	2	3	6 (5.7%)	7 (0.07)	6 (5.8%)	6 (0.06)
Pain - Other	6	0	0	0	0	0	3	5	7 (6.6%)	9 (0.09)	5 (4.9%)	5 (0.05)
Pain - Shoulder	0	0	1	1	2	4	6	5	9 (8.5%)	9 (0.08)	9 (8.7%)	10 (0.10)
Pain - Upper Extremeties	0	2	0	0	2	3	3	4	5 (4.7%)	5 (0.05)	8 (7.8%)	9 (0.09)
Pain - Upper Extremeties with Numbness	0	0	1	0	1	1	3	3	5 (4.7%)	5 (0.05)	4 (3.9%)	4 (0.04)
Pseudoarthrosis	0	0	0	0	0	0	2	0	2 (1.9%)	2 (0.02)	0 (0.0%)	0 (0.00)
Psychological	3	3	0	0	0	0	2	1	5 (4.7%)	5 (0.05)	4 (3.9%)	4 (0.04)
Pulmonary Infection	0	0	0	0	0	1	0	0	0 (0.0%)	0 (0.00)	1 (1.0%)	1 (0.01)
Puritis	1	0	1	0	0	0	0	0	2 (1.9%)	2 (0.02)	0 (0.0%)	0 (0.00)
Reflex Change	0	0	0	1	0	0	0	0	0 (0.0%)	0 (0.00)	1 (1.0%)	1 (0.01)
Respiratory	0	2	0	1	2	0	1	1	3 (2.8%)	3 (0.03)	4 (3.9%)	4 (0.04)
Seizures	1	0	0	0	1	0	0	0	2 (1.9%)	2 (0.02)	0 (0.0%)	0 (0.00)
Sore Throat	0	1	0	0	1	0	0	0	1 (0.9%)	1 (0.01)	1 (1.0%)	1 (0.01)
Surgery - Index Level	1	0	1	0	2	1	6	1	10 (9.4%)	10 (0.09)	2 (1.9%)	2 (0.02)
Surgery - Other	0	0	3	3	7	1	17	12	21 (19.8%)	27 (0.25)	12 (11.7%)	16 (0.16)
Wound Issues, Other	0	3	1	1	1	0	0	0	2 (1.9%)	2 (0.02)	3 (2.9%)	4 (0.04)

Patients experiencing adverse events in more than one category are represented in each category in which they experienced an adverse event.

Adverse event categories identified as Musculoskeletal are further defined as:

- Musculoskeletal (spasms – back): any event involving muscular spasms in the lumbar spine region
- Musculoskeletal (spasms – neck): any event involving muscular spasms in the cervical spine region
- Musculoskeletal (spasms – non-specific): any event involving general complaints of muscular spasms not related to the lumbar or cervical spine
- Musculoskeletal: classifies all events related to muscles, tendons, ligaments, cartilage, bones, joints and surrounding tissues that do not fall into one of the categories above.

Adverse event category "Neurological" broadly includes AEs related to the nervous system. Any specific episodes of numbness or reflex changes are further classified in the following categories: Numbness Index Level, Numbness Non-Index Level, and Reflex Change.

*Other – the following 5 adverse events in 4 ProDisc™-C patients: Keratitis, diagnosed with Dry Eye Syndrome, IV Infiltrated, Left leg weakness and heavy, and Horner's Syndrome as well as the following 7 adverse events in 6 ACDF patients: diagnosed with early Diabetes, Radiographic films show no evidence of a solid fusion, worsening of Diabetes, Wegener's disease, Polycythemia, Ringing bilateral ears, and Ringing ears.

Death, a potential adverse event, did not occur during the randomized clinical trial. There was one death reported in the continued access cohort of the study that was due to a methadone overdose approximately one and a half weeks postoperatively and was not considered to be associated with the implant or the implantation procedure.

Of note, unintended fusion (i.e., heterotopic ossification resulting in bridging trabecular bone and a loss of motion (<2°)), occurred in three ProDisc-C patients in the randomized clinical trial.

Adverse events were further subdivided into several categories for further analysis: those thought to be related to the implant or procedure, and secondary interventions at the index surgical level.

The table below shows those adverse events that were considered implant-related with the time-course of their occurrence:

Table 4: Implant Related Adverse Events

Adverse Event	Intra-Op (0-2 days)		Peri-Op (>2 - 42 days)		Short Term (>42-210 days)		Long Term (>210 days)		Total	
	ACDF	PRC	ACDF	PRC	ACDF	PRC	ACDF	PRC	ACDF	PRC
Dysphagia	0	0	1	0	0	0	0	0	1	0
Infection - Superficial Wound	0	0	1	0	0	0	0	0	1	0
Musculoskeletal	0	0	1	0	0	0	0	0	1	0
Pain - Neck	0	0	1	0	0	0	0	0	1	0
Surgery - Index Level	1	0	1	0	2	0	1	2	5	2

There were nine (9) implant related AEs in seven (7) ACDF patients and two (2) implant related AEs in two (2) ProDisc-C patients. All "Surgery – Index Level" AEs were considered severe or life threatening as well as the "Infection – Superficial Wound" AE in the ACDF group. The relationship of an adverse event to the implant was determined by the treating physician.

There were no statistically significant differences between the ProDisc™-C and ACDF treatment groups for the percentage of patients experiencing at least one adverse event in the following analysis categories at 24 months:

- All Adverse Events (p=1.0000)
- Device-related Adverse Events (p=0.1706)
- Surgery-related Adverse Events (p=0.4113)

A statistically significant difference in favor of ProDisc™-C was detected for the percentage of patients experiencing at least one severe or life-threatening adverse event (p=0.0137).

The number of secondary surgical procedures defined as revisions, removals, re-operations or supplemental fixation, was significantly higher (p=0.0335) in the ACDF group (10/106) compared to the ProDisc™-C Total Disc Replacement group (2/103). Tables 5 and 6 provide additional information about the secondary surgeries at the index level reported in the pivotal clinical trial.

Table 5: Secondary Surgical Procedures – Index Level

Tx Group	Cause	Action	Days Post-op
ACDF	Worsening Cervical Radiculopathy	Plate Removal - (C5-6), ACDF (C6-7)	1079
ACDF	MVA	Supplemental Fixation C6-7 and L4-5 PSF	420
ACDF	Adjecent Level Disease	Plate Removal - (C5-6), ACDF (C6-7)	732
ACDF	C5-6 Pseudoarthrosis;	C5-6 Supplemental Fixation	377
ACDF	Allograft Subsidence At C6-7	Revision C6-7 ACDF	296
ACDF	Dysphagia	Revision C6-7 ACDF	14
ACDF	Neck Pain	Revision C6-7 ACDF	425
ACDF	Adjecent Level Disease	Plate Removal - (C5-6), ACDF (C6-7)	826
ACDF	Neck Pain	Revision C4-5 ACDF	644
ACDF	Non Union C6-7	Supplemental Fixation C6-7	637
ACDF	Stenosis C6-7, Subsidence C6-7	Re-operation C6-7, Bone Fortification	300
PRC	Pt Had Worsening Pain	Removal of TDR with Fusion	499
PRC	Neck Pain	Removal of TDR with Fusion	492

One ACDF patient underwent a second revision surgery at the index level at 917 days post-op in response to ongoing pain and weakness.

Table 6: Secondary Surgical Procedures – Index Level – Time Course (Randomized)

	Prior to Discharge		6 wks		3 mo		6 mo		12 mo		18 mo		24 mo		>24 mo		Total	
	ACDF	ProDisc-C	ACDF	ProDisc-C	ACDF	ProDisc-C	ACDF	ProDisc-C	ACDF	ProDisc-C	ACDF	ProDisc-C	ACDF	ProDisc-C	ACDF	ProDisc-C	ACDF	ProDisc-C
Removals	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	2
Reoperations	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0
Revisions	0	0	1	0	0	0	1	0	1	0	1	0	1	0	3	0	8	0
Supplemental Fixation	0	0	0	0	0	0	0	0	1	0	1	0	1	0	0	0	3	0

The rate of re-operations, removals, revisions and supplemental fixation at 24 months was statistically different between the two groups in favor of ProDisc-C (p=0.0327).

IX. POTENTIAL RISKS

Potential risks associated with the use of ProDisc-C™ Total Disc Replacement 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 ProDisc-C™ Total Disc Replacement. 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 were observed in the clinical study and therefore 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; gastrointestinal compromise; 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 chord, 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 the total disc implant in the cervical spine are: early or late loosening of the components; disassembly; bending or breakage of any or all of the components; implant migration; malpositioning of the 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; 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; 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; and interference with radiographic imaging because of the presence of the implant;

4. Wound, local and/or systemic infections;

5. Inability to resume activities of normal daily living;

6. Death

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

X. SUMMARY OF NONCLINICAL LABORATORY STUDIES

A series of mechanical tests and animal studies were performed to characterize the properties and function of ProDisc™-C Total Disc Replacement. The tests conducted were:

- Dynamic Creep Relaxation Test
- Static Compression Shear Test
- Compression Shear Fatigue Test
- Subluxation Test
- Impingement Test
- UHMWPE Inlay Push-out Test
- Expulsion Test

- Wear Test
- Wear Particulate Analysis
- Wear Debris Particulate Animal Test
- Shelf Life and Packaging Validation Tests

Dynamic Creep Relaxation Test
The purposes of this test were to examine the creep relaxation characteristics of the ProDisc™-C in a worst case configuration, and to evaluate the deformation that occurs under extreme loading over time.

Six (6) gamma-sterilized device samples of the Size M, 9mm were selected for testing. This represents the implant with the smallest-cross sectional area, leading to the greatest stresses, and the tallest UHWMPE inlay, which is prone to the greater amount of deformation due its height and greater volume of material. The implant assembly incorporated a total shear angle of 18° to the horizontal. The test was carried out in Ringer's solution at a constant 37°C. The test actuator applied a dynamic axial compressive creep load at three levels. A low static relaxation load immediately followed each of these three dynamic loads. The following loading sequence was intended to model the *in vivo* disc loads experienced in the C3-C7 cervical spine during a 24 hour period.

Test results showed that the polyethylene inlays exhibited a permanent deformation of 0.469mm. The magnitude and duration of the dynamic loads employed are representative of what would be expected *in vivo*; the results suggest that failure due to creep is unlikely.

Static Compression Shear Test
The purpose of this test is to characterize the performance of the device in static compressive shear loading under worst case conditions.

Five (5) gamma-sterilized device samples of the Size M, 9mm were selected for testing. This represents the implant with the smallest-cross sectional area, leading to the greatest stresses, and the tallest UHWMPE inlay, which is prone to the greater amount of deformation due its height and greater volume of material. This test setup was identical to the setup used for the dynamic creep relaxation test, except the test was conducted in ambient air (20°C). Specimens were loaded at a rate of 10mm/minute until failure.

The mean 2% offset yield load was 1,589.13N ± 62.68N, with a mean displacement of 0.75mm ± 0.01mm. The results suggest that the ProDisc™-C can withstand loads above the expected *in vivo* loads of the cervical spine.

Compression Shear Fatigue Test
The purpose of this test is to characterize the performance of the device in dynamic compressive shear loading under worse case conditions.

Six (6) gamma-sterilized device samples of the Size M, 9mm were selected for testing. This represents the implant with the smallest-cross sectional area, leading to the greatest stresses, and the tallest UHWMPE inlay, which is prone to the greater amount of deformation due its height

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and greater volume of material. This test setup was identical to the setup used for the dynamic creep relaxation test. Specimens were loaded to 10 million cycles. Specimens were subjected to loads using an R=10 at various frequencies.

Two specimens were subjected to a maximum load of 1300N out to 10 million cycles. The results suggest that the ProDisc™-C can withstand dynamic loads above the expected *in vivo* loads of the cervical spine.

Subluxation Test
The purpose of the test is to measure the shear force required to subluxate the device.

Five (5) gamma-sterilized device samples of the Size M, 9mm were selected for testing. This represents the implant with the smallest-cross sectional area, leading to the smallest area to resist shear. A dead weight actuator applied a compressive force of 50N between the superior and inferior endplates to represent the head weight. Specimens were loaded at a rate of 10mm/minute until 5.0mm displacement was reached.

The mean maximum subluxation resistance force was 62.52N ± 0.602N with a mean displacement of 0.84mm ± 0.024mm at the maximum force. The results suggest that the amount of force required to dislocate the superior endplate from the UHMWPE inlay is above the expected *in vivo* shear loads of the cervical spine.

Impingement Tests
The purpose of this test was to evaluate the impact of high loads occurring at extreme flexion/extension angles exceeding the physiologic range of motion.

Two (2) gamma-sterilized device samples of the Size M, 5mm were selected for testing. This represents the implant with the smallest-cross sectional area, leading to the greatest stresses on the implant, as well as the smallest UHMWPE inlay height, which will more likely see impingement than the other sizes offered. The superior plate was angled in flexion and extension until it contacted the inferior plate. The tests were carried out in ambient air (20°C).

The test actuator applied a single cycle axial load at a rate of 10mm/minute until the desired load level is reached. One specimen was subjected to various loads representing the range of forces expected *in vivo*. In order to assess the effects of multiple cycles of impingement following the static tests, the other specimen was dynamically loaded for 1,000 cycles at 50-150 N.

Both specimens (static and dynamic) showed no fractures of the UHMWPE inlay or metal plates at any load. Small surface indentations of the UHMWPE inlay were found at the point of contact of the superior plate for all load steps. No effect on the UHMWPE inlay locking mechanism was observed. No signs of wear or wear debris were observed. Even in the instance of extreme flexion/extension, the devices showed no signs of failure or major deformation.

UHMWPE Inlay Push-out Test
The purpose of this test is to examine the force required to overcome the snap-lock fixation UHMWPE inlay within the inferior endplate of the implant.

Five (5) gamma-sterilized device samples of the Size M, 9mm were selected for testing (only the inferior endplate and UHMWPE inlay). This represents the implant with the smallest-cross sectional area, leading to the smallest area to resist shear and the least amount of UHMWPE material necessary to cause failure. A single cycle axial load was applied to each test specimen at the posterior face of the inlay at a rate of 5mm/minute until failure.

The mean force required to disengage the UHMWPE inlay step from the inferior endplate was 351.8N ± 10.2N with a mean displacement of 1.75mm ± 0.06mm. The results suggest that the amount of force required to dislocate the UHMWPE inlay from the inferior endplate is above the expected *in vivo* shear loads of the cervical spine.

Expulsion Test
The purpose of this test is to evaluate the strength of the implant's initial fixation while implanted onto a block of synthetic foam under a single cycle shear force.

Four (4) gamma-sterilized device samples of the Size M inferior endplate were selected for testing. This represents the implant with the smallest-cross sectional area, leading to the smallest area to resist shear. Polyurethane foam blocks were used to simulate compressed cancellous bone. An applied compressive force of 45N was used between the endplate and the polyurethane foam. The test was carried out at room temperature (20° C) in ambient air. Specimens were subjected to a pure single-cycle shear load to the posterior aspect of the implant at a rate of 5mm/min until failure.

The mean ultimate force was 303.9N ± 29.6N with a mean displacement of 1.54mm ± 0.25mm. The results suggest that the amount of force required to dislocate the UHMWPE inlay from the inferior endplate is above the expected *in vivo* shear loads of the cervical spine.

Wear Test
The purposes of this test are to quantify the wear debris generated as a function of time and to evaluate the bearing surfaces for changes under worst-case 3-axis loading conditions.

Six (6) gamma-sterilized device samples of Size Extra Large Deep, 6mm were tested under simulated *in vivo* conditions over 10 million cycles at a frequency of 1 Hz using combined flexion/extension (±7.5°), lateral bending (±6°), and axial rotation (±4°). Two loaded soak controls served as a reference. All specimens were subjected to a constant load of 150N and placed in 37° ± 2° C bovine calf serum baths.

Linear wear was observed up to 10 million cycles with no visible run-in wear. The mean total weight loss was 25.6 ± 3.8 mg with a mean wear rate over 10 million cycles of 2.59 ± 0.36 mg/million cycles.

Wear Particulate Analysis
The sponsor also conducted an analysis of the particles generated during the wear test.

Particle analysis was performed using a scanning electron microscope (SEM) at magnifications of 4,000x. At least 100 particles were analyzed for every coupling. The shape of the particles was measured according to the procedure described by Wirth using image analysis software. The mean particle sizes are presented in the table below.

Table 7: Wear Debris Mean Particle Size (µm)

Cycles (million)	Machine No.	Test Report 46.070502.30.508-part 1 (46.060622.30.402)		Test Report 46.070502.30.508-part 2 (46.060622.30.403)	
		Mean (µm)	Range (µm)	Mean (µm)	Range (µm)
0.0 to 0.5	251	0.21 ± 0.14	0.08 to 0.90	0.27 ± 0.22	0.08 to 1.58
	258	0.26 ± 0.14	0.08 to 0.85	0.22 ± 0.11	0.09 to 0.64
0.5 to 1.0	251	0.21 ± 0.13	0.07 to 0.65	0.23 ± 0.13	0.08 to 1.06
	258	0.28 ± 0.18	0.09 to 1.24	0.27 ± 0.25	0.08 to 2.26
1.0 to 2.0	251	0.17 ± 0.09	0.08 to 0.64	0.25 ± 0.12	0.08 to 0.72
	258	0.21 ± 0.13	0.08 to 1.13	0.26 ± 0.14	0.08 to 0.87
2.0 to 3.0	251	0.26 ± 0.14	0.08 to 0.82	0.30 ± 0.16	0.08 to 0.82
	258	0.20 ± 0.10	0.08 to 0.69	0.28 ± 0.17	0.08 to 0.95
3.0 to 4.0	251	0.24 ± 0.14	0.08 to 1.15	0.27 ± 0.15	0.08 to 0.99
	258	0.22 ± 0.11	0.08 to 0.55	0.25 ± 0.19	0.08 to 1.65
4.0 to 5.0	251	0.22 ± 0.11	0.13 to 1.23	0.26 ± 0.13	0.13 to 0.80
	258	0.28 ± 0.13	0.13 to 0.70	0.25 ± 0.15	0.13 to 0.94
5.0 to 6.0	251	0.18 ± 0.09	0.08 to 0.66	0.35 ± 0.20	0.08 to 0.89
	258	0.25 ± 0.12	0.09 to 0.71	0.30 ± 0.20	0.08 to 1.32
6.0 to 7.0	251	0.20 ± 0.10	0.08 to 0.72	0.33 ± 0.19	0.08 to 0.97
	258	0.22 ± 0.10	0.08 to 0.51	0.20 ± 0.14	0.08 to 1.09
7.0 to 8.0	251	0.33 ± 0.18	0.08 to 0.72	0.18 ± 0.07	0.04 to 0.46
	258	0.31 ± 0.16	0.09 to 0.82	0.28 ± 0.14	0.09 to 0.80
8.0 to 9.0	251	0.24 ± 0.14	0.08 to 0.76	0.19 ± 0.09	0.09 to 0.68
	258	0.20 ± 0.10	0.08 to 0.60	0.17 ± 0.08	0.08 to 0.43
9.0 to 10.0	251	0.21 ± 0.13	0.08 to 1.00	0.28 ± 0.17	0.09 to 1.16
	258	0.22 ± 0.14	0.09 to 1.53	0.19 ± 0.08	0.08 to 0.44

Wear Debris Particulate Animal Test

The purpose of this study was to evaluate the local and systemic response to various sizes and doses of UHMWPE particulates implanted into the epidural space of New Zealand White rabbits.

A total of 54 adult rabbits were used for this study. Under direct visualization, the animals had 0.3 ml of one of four sizes (range of all sizes 0.023 – 13.351 µm) of UHMWPE particulates in saline or 0.3 ml of the saline carrier alone injected into the epidural space. Animals were monitored post-injection for standard evaluations of neurotoxicity and pain. Subjects were euthanized and necropsied on Day 89/91/92 or 169/171/172 post-injection. Incision sites were evaluated on Days 2-10.

At necropsy, gross anatomic, histological and systemic analyses were performed. The systemic response was evaluated by examining the heart, lung, liver, spleen, kidneys, brain, spinal cord, and the tracheobronchial lymph nodes.

Gross analysis showed no clinical signs of neurotoxicity. The spine and adjacent neural tissue appeared normal. For all animals, the tracheobronchial lymph nodes and all other organs appeared normal. Histopathologic analysis indicated that for all time points, there were no changes in tissues. The results of this study indicate that there were no local or systemic reactions in the axial skeleton or central nervous system following exposure to a worse case dose of UHMWPE wear debris that could be generated from the ProDisc™-C. Additionally, there

was no evidence of any particulate migration from the axial skeleton into any of the major organs.

Shelf Life and Packaging Validation Tests
The sponsor conducted shelf life and packaging validation studies to demonstrate that the device packaging can maintain a sterile barrier under worst case conditions. These data support a shelf life of 6 months.

XI. SUMMARY OF CLINICAL STUDIES

Clinical data were collected to evaluate the safety and effectiveness of the ProDisc™-C Total Disc Replacement as compared to the control device, an anterior cervical discectomy and fusion (ACDF) surgery with the use of allograft bone (cortical ring) and an anteriorly applied plating system in patients undergoing single-level discectomy for intractable SCDD. The purpose of the study was to determine whether the ProDisc™-C Total Disc Replacement was non-inferior to ACDF. A total of 209 subjects were enrolled, randomized and treated (103 patients in the investigational ProDisc™-C treatment group and 106 patients in the control group) at 13 investigational sites. To qualify for enrollment in the study, patients met all the inclusion criteria and none of the exclusion criteria listed in the following table:

Inclusion

1. Symptomatic cervical disc disease (SCDD) in only one vertebral level between C3-C7 defined as:
   - Neck or arm (radicular) pain; and/or a functional / neurological deficit with at least one of the following conditions confirmed by imaging (CT, MRI or X-rays)
   - Herniated nucleus pulposus;
   - Spondylosis (defined by the presence of osteophytes); and/or
   - Loss of disc height
2. Age between 18 and 60 years.
3. Unresponsive to non-operative treatment for approximately six weeks or has the presence of progressive symptoms or signs of nerve root/spinal cord compression in the face of conservative treatment.
4. Neck Disability Index (NDI) score greater than or equal to 15/50 (30%) (Considered moderate disability).
5. Psychosocially, mentally and physically able to fully comply with this protocol including adhering to follow-up schedule and requirements and filling out forms.
6. Signed informed consent.

Exclusion

1. More than one vertebral level requiring treatment.
2. Marked cervical instability on resting lateral or flexion/extension radiographs:
   a. translation greater than 3 mm and/or
   b. greater than 11 degrees of rotational difference to that of either adjacent level .
3. Has a fused level adjacent to the level to be treated.
4. Radiographic confirmation of severe facet joint disease or degeneration.
5. Known allergy to cobalt, chromium, molybdenum, titanium or polyethylene.
6. Clinically compromised vertebral bodies at the affected level(s) due to current or past trauma, e.g., by the radiographic appearance of fracture callus, malunion or nonunion.
7. Prior surgery at the level to be treated.
8. Severe spondylosis at the level to be treated as characterized by any of the following:
   a. Bridging osteophytes;
   b. A loss of disc height greater than 50%; or
   c. Absence of motion (<2°).
9. Neck or arm pain of unknown etiology.
10. Osteoporosis: A screening questionnaire for osteoporosis, SCORE[1] (Simple Calculated Osteoporosis Risk Estimation), will be used to screen patients who require a DEXA bone mineral density measurement. If DEXA is

Inclusion	Exclusion
	required, exclusion will be defined as a DEXA bone density measured T score ≤ -2.5 (The World Health Organization definition of osteoporosis.[2])
	11. Paget's disease, osteomalacia or any other metabolic bone disease (excluding osteoporosis which is addressed above).
	12. Severe diabetes mellitus requiring daily insulin management
	13. Pregnant or interested in becoming pregnant in the next 3 years.
	14. Active infection - systemic or local.
	15. Taking medications or any drug known to potentially interfere with bone/soft tissue healing (e.g., steroids).
	16. Rheumatoid arthritis or other autoimmune disease.
	17. Systemic disease including AIDS, HIV, hepatitis.
	18. Active malignancy: A patient with a history of any invasive malignancy (except non-melanoma skin cancer), unless he/she has been treated with curative intent and there have been no clinical signs or symptoms of the malignancy for at least 5 years.

Following surgery, while investigators were advised to prescribe the appropriate rehabilitation program and manage patient progress on an individual basis, they were given certain guidelines to follow irrespective of the subject's treatment group. The guidelines included a hard or soft collar at the surgeon's discretion. Direction was given to the patient regarding standard wound care procedures. Limitations were placed on patients in regard to prolonged or strenuous activity initially and for a period of weeks to months depending on the individual patient's progress. The patients were instructed not to resume heavy physical activity until the surgeon had reviewed postoperative radiographs and was confident that the implant was stable and functioning. In addition, patients were instructed to immediately report any change in their pain or neurologic status to their doctor.

Patients were not treated with NSAIDs postoperatively in either treatment group despite some reports in the literature that short-term postoperative use of NSAIDs may reduce the incidence of heterotopic ossification in total disc replacement patients.

Subjects were evaluated pre-operatively, intra-operatively, and immediately post-operatively followed by evaluations at 6 weeks, 3 months, 6 months, 12 months, 18 months and 24 months. Complications and adverse events, device-related or not, 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.

The safety of the ProDisc™-C Total Disc Replacement was assessed by monitoring intra-operative and post-operative adverse events. Radiographs were used to monitor the occurrence of some of the adverse events, including device subsidence, migration, and breakage as well as heterotopic ossification and unintended fusion in the investigational group.

All radiographic endpoints were evaluated independently by a core laboratory (Medical Metrics, Inc., Houston, TX) and reviewed by an independent radiologist.

The Overall Success analysis using the composite primary endpoint (Overall Success),, is presented in Table 8. FDA requested that an additional analysis of the Overall Success (Additional Analysis) be presented, using an improvement in Neck Disability Index (NDI) of ≥15 points relative to the pre-operative baseline. FDA also requested that a non-inferiority delta of 10% be applied to the analyses. Sensitivity analyses for both definitions used a non-inferiority delta of 10%.

Table 8: Overall Success Definitions

Overall Success	Additional Analysis
The patient's NDI score improves by at least 20% over baseline value	The patient's NDI score improves by at least 15 points over baseline value
The patient's neurologic parameters, i.e. motor sensory, and relexes are maintained or improved	The patient's neurologic parameters, i.e. motor sensory, and relexes are maintained or improved
No removals, revisions, re-operations or additional fixation were required to modify any implant	No removals, revisions, re-operations or additional fixation were required to modify any implant
No adverse events occur which are related to the treatment, ProDisc-C or its implantation or ACDF surgery or its associated implants or graft material	No adverse events occur which are related to the treatment, ProDisc-C or its implantation or ACDF surgery or its associated implants or graft material

A patient was considered a neurological success only if their neurologic status was maintained or improved for all three success criteria (motor status, sensory deficit, and reflexes).

The secondary endpoints assessed were quality of life measured with the SF-36 questionnaire, improvement on a Visual Analog Scale (VAS) for neck and arm pain intensity and frequency, and several radiographic assessments (device migration, subsidence, disc height, range of motion, heterotopic ossification, fusion status). Other outcomes measured included VAS, subject satisfaction, willingness to have the same surgery again, employment status, and medication use.

Results

Subject Demographics

The table below shows select demographics and baseline characteristics of the investigational and control groups.

Table 9: Demographic and Baseline Characteristics

	ProDisc-C (N Trtd=103)	ACDF (N Trtd=106)	Two-Sided p-value
Implant Level			**0.4764**
C3-C4	3 (2.9%)	1 (0.9%)	
C4-C5	10 (9.7%)	6 (5.7%)	
C5-C6	58 (56.3%)	61 (57.5%)	
C6-C7	32 (31.1%)	38 (35.8%)	
Age at Surgery (years)			**0.2025**
Mean	42.1	43.5	
STD	8.42	7.15	
Age Group [N (%)]			**0.5810**
<=42 years	52 (50.5%)	49 (46.2%)	
>42 years	51 (49.5%)	57 (53.8%)	
Gender [N (%)]			**0.8897**
Female	57 (55.3%)	57 (53.8%)	
Male	46 (44.7%)	49 (46.2%)	
Race [N (%)]			**0.1000**
Caucasian	88 (85.4%)	97 (91.5%)	
African-American	4 (3.9%)	1 (0.9%)	
Hispanic	3 (2.9%)	5 (4.7%)	
Asian American	5 (4.9%)	0 (0.0%)	
Other	3 (2.9%)	3 (2.8%)	
Smoking Status			**0.9159**
Never	51 (49.5%)	49 (46.2%)	
Former	18 (17.5%)	20 (18.9%)	
Current	34 (33.0%)	37 (34.9%)	
Height (in)			**0.2839**
Mean	67.23	67.77	
STD	3.703	4.106	
Weight (lbs)			**0.0943**
Mean	171.04	180.27	
STD	41.797	47.331	
Body Mass Index (kg/m^2)			**0.0896**
Mean	26.44	27.34	
STD	5.319	5.54	
NDI Score (%)			**0.4560**
Mean	53.93	52.28	
STD	15.096	14.544	
Duration of Neck/Arm Pain			**0.9645**
<6 weeks	3 (2.9%)	3 (2.8%)	
6 weeks to a year	44 (42.7%)	44 (41.5%)	
>1 year	56 (54.4%)	59 (55.7%)	

Surgical and Hospitalization Information

The mean intra-operative time in the ProDisc™-C Total Disc Replacement group was 107.2 minutes whereas it was 98.7 minutes in the ACDF group ($p<0.0078$). The mean estimated blood loss (EBL) in the ProDisc™-C Total Disc Replacement group was 83.5cc whereas it was 63.5cc in the ACDF group ($p<0.0094$). The length of hospital stay was analogous in both groups; 1.4 days ProDisc™-C and 1.3 days ACDF, $p<0.7882$. While the differences in the means for estimated blood loss and operative time were statistically significant, in each case the ranges were similar so the statistical significance may not be clinically significant.

Table 10 describes the implant sizes used in the ProDisc-C patients:

Table 10: Implant Sizes Used

Inlay	Medium	Medium Deep	Large	Large Deep	Extra Large	Extra Large Deep
5 mm	23 (22.3%)	16 (15.5%)	25 (24.3%)	6 (5.8%)	1 (1.0%)	0 (0.0%)
6 mm	7 (6.8%)	6 (5.8%)	14 (13.6%)	4 (3.9%)	0 (0.0%)	0 (0.0%)
7 mm	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)

Clinical Effectiveness Evaluation

The analyses of overall success are presented below for Overall Success and Additional Analysis. These analyses reflect the composite primary endpoint as described in the IDE protocol (Overall Success) and FDA's requested additional analysis (Additional Analysis) respectively. In order to be considered an overall success, the patient must have been successful in each of the criteria at Month 24. The primary effectiveness endpoint of this study was the difference in proportion of Overall Success between the two treatment groups at 24 months post-operatively. The success status of subjects was summarized by treatment group.

The population which was used to assess these endpoints consisted of all randomized subjects who completed all evaluations at the 24-month time point, regardless of when the 24-month measurements occurred.

Table 11: Overall Success (IDE)

Visit	ACDF (N Trtd=106)	ProDisc-C (N Trtd=103)	Difference (ACDF - ProC)	Non-inferiority p-value (15% margin)
Week 6	65/ 97 (67.0%)	66/ 96 (68.8%)	-1.80%	0.0068
Month 3	60/ 91 (65.9%)	79/ 95 (83.2%)	-17.30%	<0.0001
Month 6	60/ 86 (69.8%)	73/ 90 (81.1%)	-11.30%	<0.0001
Month 12	46/ 74 (62.2%)	68/ 87 (78.2%)	-16.00%	<0.0001
Month 18	55/ 80 (68.8%)	65/ 87 (74.7%)	-5.90%	0.0014
Month 24	**75/101 (74.3%)**	**78/101 (77.2%)**	**-2.90%**	**0.0017**

Table 12: Overall Success (Additional Analysis)

Visit	ACDF (N Trtd=106)	ProDisc-C (N Trtd=103)	Difference (ACDF - ProC)	Non-inferiority p-value (10% margin)
Week 6	55/ 97 (56.7%)	60/ 96 (62.5%)	-5.8%	0.0132
Month 3	52/ 91 (57.1%)	75/ 95 (78.9%)	-21.8%	<0.0001
Month 6	55/ 86 (64.0%)	68/ 90 (75.6%)	-11.6%	0.0011
Month 12	46/ 74 (62.2%)	63/ 87 (72.4%)	-10.2%	0.0039
Month 18	54/ 80 (67.5%)	63/ 87 (72.4%)	-4.9%	0.0192
Month 24	**69/101 (68.3%)**	**73/101 (72.3%)**	**-4.0%**	**0.0159**

Table 13: Components of Overall Success at Month 24

Component of Overall Success	ProDisc-C	ACDF	Fisher's Exact Test p-value (One Sided)
NDI Success (IDE)* (≥20% Improvement from Baseline)	84/ 99 (84.9%)	79/ 92 (85.9%)	0.6561
NDI Success (FDA)* (≥15 Point Improvement from Baseline)	79/ 99 (79.8%)	72/ 92 (78.3%)	0.4665
Neurological Success* (Maintenance or Improvement from Baseline)	90/ 99 (90.9%)	81/ 92 (88.0%)	0.3407
Absence of Revisions, Removals, Re-operations or Supplemental Fixation at the Index Level	101/103 (98.1%)	97/106 (91.5%)	0.0327
Absence of Adverse Events Related to the Implant or Implantation	100/103 (97.1%)	99/106 (93.4%)	0.1779
Analysis	**ProDisc-C**	**ACDF**	
Overall Success (IDE) (20% NDI)	78/101 (77.2%)	75/101 (74.3%)	0.3715
Additional Analysis (FDA) (15 point NDI)	73/101 (72.3%)	69/101 (68.3%)	0.3222

* Denominators for NDI and Neurological Success (92 ACDF, 99 ProDisc™-C) reflect only patients that completed the study. Denominators for Re-operations and Adverse Events (106 ACDF, 103 ProDisc™-C) include all patients treated in the study. Denominators for Overall Success reflect all patients with known outcomes at month 24. The relationship of adverse events to the implant or its implantation was determined by the treating physician.

In the IDE protocol, the test of the sole, primary hypothesis that ProDisc™-C Total Disc Replacement is non-inferior to ACDF is based on an exact 95% one-sided, upper confidence bound for the difference in success probabilities, P_A-P_B, where A denotes the fusion (ACDF) arm and B denotes the ProDisc™-C Total Disc Replacement arm. If the upper bound is delta = 0.15 or less, then ProDisc™-C Total Disc Replacement will be considered non-inferior to ACDF." The Overall Success upper bound of the exact 95% one-sided confidence interval is 7.10%. This result is below the 15% delta needed to establish non-inferiority under the IDE protocol and below the 10% delta needed to establish non-inferiority under the FDA's requested analysis. Using the Additional Analysis criteria for overall success, the upper bound of the exact 95% one-sided confidence interval was 7.0%. This result is below the 10% delta needed to establish non-inferiority. The results of both overall success analyses indicate that the ProDisc™-C Total Disc Replacement is statistically non-inferior to the ACDF control group.

Sensitivity Analyses for Overall Success at Month 24

To assess the impact on the conclusion of non-inferiority of patients with unknown outcomes at Month 24 (5 ACDF, 2 ProDisc™-C) a number of sensitivity analyses were conducted. The following conditions were applied for all patients with unknown outcomes at Month 24 for both Overall Success and the Additional Analysis:

- All Failures (all designated as failure regardless of treatment group)
- All Success (all designated as success regardless of treatment group)
- Last observation carried forward (LOCF), if there were no outcomes for a patient for any post-operative time-point the patient was removed from analysis
- Modified LOCF using only Month 12 or Month 18 results, if a patients had no known outcomes at Month 12 or beyond they were designated as success if ACDF and failure if ProDisc™-C Total Disc Replacement
- Worst Case (all ACDF designated as success, all ProDisc™-C Total Disc Replacement designated as failure)

Under all sensitivity analyses the ProDisc™-C Total Disc Replacement remained non-inferior, with the upper bound of the exact 95% one-sided confidence intervals under worst case analysis falling below the 15% non-inferiority delta for Overall Success and below the 10% non-inferiority delta for FDA's requested Additional Analysis.

Safety Analysis and Conclusions
The safety population consisted of all treated patients in the ACDF (n = 106) and ProDisc™-C Total Disc Replacement (n = 103) groups.

Adverse Events
There were no statistically significant differences between the ProDisc™-C Total Disc Replacement and ACDF treatment groups for the percentage of patients experiencing at least one adverse event in the following categories:

- All Adverse Events (p=1.0000)
- Device-related Adverse Events (p=0.1706)
- Surgery-related Adverse Events (p=0.4113)

A statistically significant difference in favor of ProDisc™-C was detected for the percentage of patients experiencing at least one severe or life-threatening adverse event (p=0.0137).

Table 14: Summary: Adverse Events (Patients)

	ProDisc-C (n = 103) Patients (%)	ACDF (n = 106) Patients (%)	Difference (ACDF-PRC)	95% One-Sided CI Upper Bound	95% Two-Sided CI Lower Bound	95% Two-Sided CI Upper Bound	Fishers Exact p-value (two-sided)
All Adverse Events	84 (81.6%)	86 (81.1%)	-0.5%	8.7%	-11.3%	10.4%	**1.0000**
Implant Related Adverse Events	2 (1.9%)	7 (6.6%)	4.7%	10.1%	-1.1%	11.3%	**0.1706**
Surgery Related Adverse Events	11 (10.7%)	16 (15.1%)	4.4%	12.3%	-5.0%	14.0%	**0.4113**
Severe or Life-Threatening Adverse Events	16 (15.5%)	32 (30.2%)	14.7%	24.3%	3.1%	26.0%	**0.0137**

A summary of the incidence of all adverse events, implant-related, surgery-related, and severe or life-threatening, in the treatment groups is presented in the table below. There were no

statistically significant differences between the ProDisc™-C Total Disc Replacement and ACDF treatment groups for event frequency for:

- All Adverse Events (p=0.6533)
- Device-related Adverse Events (p=0.0591)
- Surgery-related Adverse Events (p=0.4322)

A statistically significant difference in favor of ProDisc™-C Total Disc Replacement was detected for event frequency for Severe or Life-Threatening Adverse Events (p=0.0129).

Table 15: Summary: Adverse Events (Events)

	ProDisc-C (n = 103) Events (E/Pt)	ACDF (n = 106) Events (E/Pt)	Difference (ACDF-PRC)	95% One-Sided CI Upper Bound	95% Two-Sided CI Lower Bound	95% Two-Sided CI Upper Bound	Chi-square p-value (two-sided)
All Adverse Events	237 (2.30)	254 (2.40)	0.10	0.444	-0.320	0.511	**0.6533**
Implant Related Adverse Events	2 (0.02)	9 (0.08)	0.06	0.117	0.004	0.127	**0.0591**
Surgery Related Adverse Events	14 (0.14)	19 (0.18)	0.04	0.134	-0.064	0.151	**0.4322**
Severe or Life-Threatening Adverse Events	21 (0.20)	42 (0.40)	0.20	0.317	0.044	0.341	**0.0129**

Implant Related Adverse Events

The table below presents the number and percentage of patients who experienced an implant-related adverse event. The relationship of an adverse event to the implant was determined by the treating physician. All adverse events identified by investigators as probably or definitely related to the implant are presented. The overall device-related adverse event profile is similar between the ProDisc™-C Total Disc Replacement (1.0%) and ACDF (1.9%) treatment groups (patients p=0.1706, events p=0.0591).

Table 16: Implant Related Adverse Events

Adverse Event	ProDisc-C (N=103)		ACDF (N=106)		p-value	p-value
	Patients (%)	Events (E/Pt)	Patients (%)	Events (E/Pt)	Patients	Events
Any Adverse Event	2 (1.9%)	2 (0.02)	7 (6.6%)	9 (0.08)	0.1706	0.0591
Dysphagia	0 (0.0%)	0 (0.00)	1 (0.9%)	1 (0.01)		
Infection - Superficial Wound	0 (0.0%)	0 (0.00)	1 (0.9%)	1 (0.01)		
Musculoskeletal	0 (0.0%)	0 (0.00)	1 (0.9%)	1 (0.01)		
Pain - Neck	0 (0.0%)	0 (0.00)	1 (0.9%)	1 (0.01)		
Surgery - Index Level	2 (1.9%)	2 (0.02)	5 (4.7%)	5 (0.05)		

There were nine (9) implant related AEs in seven (7) ACDF patients and two (2) implant related AEs in two (2) ProDisc-C patients. All "Surgery – Index Level" AEs were considered severe or life threatening as well as the "Infection – Superficial Wound" AE in the ACDF group. The relationship of an adverse event to the implant was determined by the treating physician.

Surgery Related Adverse Events

The table below presents the number and percentage of patients who experienced a surgery-related adverse event. The overall surgery-related adverse event rate is similar between the

ProDisc™-C Total Disc Replacement and ACDF groups (10.7%, 15.1%). The relationship of an adverse event to the surgical procedure was determined by the treating physician. All adverse events identified by investigators as definitely related to the surgery are presented. The overall surgery-related adverse event profile is similar between the ProDisc™-C Total Disc Replacement and ACDF treatment groups (patients p=0.4113, events p=0.4322). The dural tear and surgery index level were determined to be clinically significant.

Table 17: Surgery Related Adverse Events

Adverse Event	ProDisc-C (N=103)		ACDF (N=106)		p-value	p-value
	Patients (%)	Events (E/Pt)	Patients (%)	Events (E/Pt)	Patients	Events
Any Adverse Event	11 (10.7%)	14 (0.14)	16 (15.1%)	19 (0.18)	0.4113	0.4322
DDD Progression, Other Cervical	0 (0.0%)	0 (0.00)	1 (0.9%)	1 (0.01)		
Dural Tear	1 (1.0%)	1 (0.01)	0 (0.0%)	0 (0.00)		
Dysphagia	2 (1.9%)	2 (0.02)	4 (3.8%)	4 (0.04)		
Edema	1 (1.0%)	1 (0.01)	0 (0.0%)	0 (0.00)		
Gastrointestinal	6 (5.8%)	6 (0.06)	4 (3.8%)	5 (0.05)		
Genitourinary	1 (1.0%)	1 (0.01)	0 (0.0%)	0 (0.00)		
Pain - Back	1 (1.0%)	1 (0.01)	0 (0.0%)	0 (0.00)		
Pain - Neck	0 (0.0%)	0 (0.00)	1 (0.9%)	1 (0.01)		
Pain - Neck and Upper Extremeties	0 (0.0%)	0 (0.00)	2 (1.9%)	2 (0.02)		
Pain - Upper Extremities	2 (1.9%)	2 (0.02)	0 (0.0%)	0 (0.00)		
Pseudoarthrosis	0 (0.0%)	0 (0.00)	2 (1.9%)	2 (0.02)		
Surgery - Index Level	0 (0.0%)	0 (0.00)	2 (1.9%)	2 (0.02)		
Wound Issues, Other	0 (0.0%)	0 (0.00)	2 (1.9%)	2 (0.02)		

Severe or Life-Threatening Adverse Events

The table below presents the number and percentage of patients who experienced a severe or life-threatening event in each treatment group. A severe or life-threatening adverse event was defined as any adverse event that required hospitalization or surgery. The overall rate of severe or life-threatening adverse events was lower in the ProDisc™-C Total Disc Replacement group compared with ACDF (15.5%, 30.2%). The difference between the treatment groups was statistically significant for patients and events (patients p=0.0137, events p=0.0189). The most notable difference was in the event category Surgery – Index Level, which occurred in 10 (9.4%) ACDF patients compared to 2 (1.9%) ProDisc™-C Total Disc Replacement patients.

Table 18: Severe or Life Threatening Adverse Events

Adverse Event	ProDisc-C (N=103)		ACDF (N=106)		p-value	p-value
	Patients (%)	Events (E/Pt)	Patients (%)	Events (E/Pt)	Patients	Events
Any Adverse Event	16 (15.5%)	21 (0.20)	32 (30.2%)	42 (0.40)	0.0137	0.0129
Cardiovascular	0 (0.0%)	0 (0.00)	1 (0.9%)	1 (0.01)		
Dermatological	1 (1.0%)	1 (0.01)	0 (0.0%)	0 (0.00)		
Dural Tear	1 (1.0%)	1 (0.01)	0 (0.0%)	0 (0.00)		
Gastrointestinal	0 (0.0%)	0 (0.00)	1 (0.9%)	1 (0.01)		
Infection - Non-Wound	0 (0.0%)	0 (0.00)	1 (0.9%)	1 (0.01)		
Infection - Superficial Wound	0 (0.0%)	0 (0.00)	1 (0.9%)	1 (0.01)		
Other	0 (0.0%)	0 (0.00)	1 (0.9%)	1 (0.01)		
Surgery - Index Level	2 (1.9%)	2 (0.02)	10 (9.4%)	10 (0.09)		
Surgery - Other	13 (12.6%)	17 (0.17)	21 (19.8%)	27 (0.25)		

Primary Efficacy Parameters

Neck Disability Index (NDI)

Summaries of success distribution and of descriptive statistics for the NDI and change in NDI by evaluation interval are presented below. Tables 14 and 15 below represent the time-course analysis of NDI improvement for the study, based on two definitions of successful improvement.

Table 19: NDI Success (≥20% Improvement from Baseline)

Visit	ACDF	ProDisc-C	p-value (One-Sided)
Week 6	69/ 96 (71.9%)	71/ 97 (73.2%)	0.4823
Month 3	67/ 90 (74.4%)	86/ 95 (90.5%)	0.0033
Month 6	69/ 85 (81.2%)	77/ 90 (85.6%)	0.2825
Month 12	55/ 71 (77.5%)	75/ 89 (84.3%)	0.1861
Month 18	61/ 74 (82.4%)	74/ 85 (87.1%)	0.2769
Month 24	79/ 92 (85.9%)	84/ 99 (84.9%)	0.6561

Table 20: NDI Success (≥15 point Improvement from Baseline)

Visit	ACDF	ProDisc-C	p-value (One-Sided)
Week 6	57/ 96 (59.4%)	65/ 97 (67.0%)	0.1709
Month 3	57/ 90 (63.3%)	81/ 95 (85.3%)	0.0005
Month 6	61/ 85 (71.8%)	72/ 90 (80.0%)	0.1361
Month 12	53/ 71 (74.7%)	70/ 89 (78.7%)	0.3406
Month 18	59/ 74 (79.7%)	72/ 85 (84.7%)	0.2696
Month 24	72/ 92 (78.3%)	79/ 99 (79.8%)	0.4665

The table below summarizes the distribution of improvement in NDI outcomes at 24 months post-operative. This analysis demonstrates significant achievement in pain reduction across treatment groups.

Table 21: Distribution of Change in NDI at 24 Months

	ProDisc-C	ACDF
No. Evaluated	99	92
Deteriorated	5 (5.1%)	4 (4.3%)
No Change	1 (1.0%)	1 (1.1%)
>0 - 4.9 Point Improvement	2 (2.0%)	2 (2.2%)
5 - 9.9 Point Improvement	3 (3.0%)	4 (4.3%)
10 - 14.9 Point Improvement	9 (9.1%)	9 (9.8%)
>= 15 Point Improvement	79 (79.8%)	72 (78.3%)

Neurological Status

A patient was considered a neurological success only if their neurologic status was maintained or improved for all three success criteria (motor status, sensory deficit, and reflexes). The number and proportion of patients who were neurologic successes at each visit are presented in the table below.

Table 22: Overall Neurological Success

Group	Week 6	Month 3	Month 6	Month 12	Month 18	Month 24
ProDisc-C	88/ 97 (90.7%)	88/ 95 (92.6%)	87/ 92 (94.6%)	81/ 88 (92.0%)	74/ 85 (87.1%)	90/ 99 (90.9%)
ACDF	89/ 98 (90.8%)	80/ 90 (88.9%)	74/ 87 (85.1%)	59/ 72 (81.9%)	63/ 73 (86.3%)	81/ 92 (88.0%)
p-value	1.0000	0.4498	0.0460	0.0907	1.0000	0.6377

Secondary Endpoints

SF-36

A positive change from baseline indicates an improvement in the outcome measure, as a higher score indicates a better health state.

Table 23: PCS/MCS Changes from Baseline to 24 months

	ProDisc-C	ACDF
PCS		
# evaluated	99	90
Improvement ≥15 points	51/99 (51.5%)	31/90 (34.4%)
Improvement to <15 points	29/99 (29.3%)	36/90 (40.0%)
No change	8/99 (8.1%)	8/90 (8.9%)
Any deterioration	11/99 (11.1%)	15/90 (16.7%)
MCS		
# evaluated	99	90
Improvement ≥15 points	36/99 (36.4%)	38/90 (42.2%)
Improvement to <15 points	35/99 (35.4%)	24/90 (26.7%)
No change	6/99 (6.1%)	8/90 (8.9%)
Any deterioration	22/99 (22.2%)	20/90 (22.2%)

Radiological Assessments

Radiographic evaluation for device migration, subsidence, loss of disc height, presence of visible gaps (ACDF only), bridging bone and the presence of radiolucencies appears in table 19 below.

Table 24: Radiographic Evaluation: Time Course

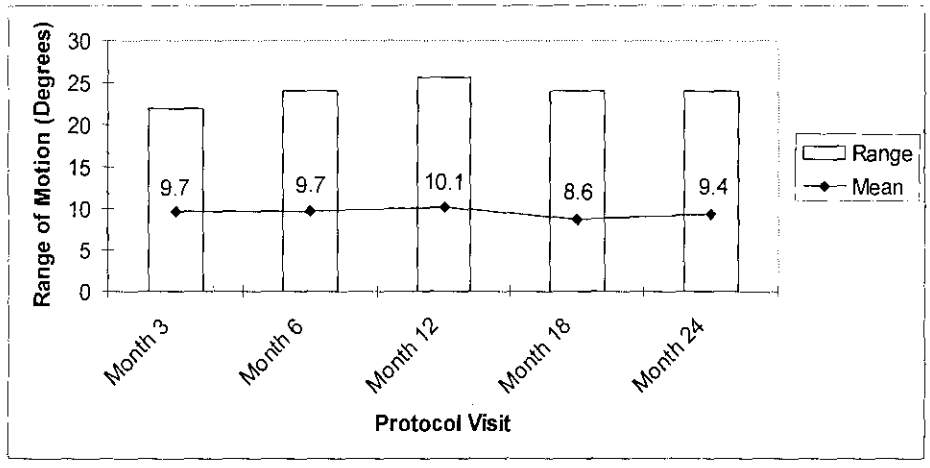
	Treatment	Month 3	Month 6	Month 12	Month 18	Month 24
Device Migration (>3mm)	ProDisc-C	0/95 (0.0%)	0/93 (0.0%)	0/86 (0.0%)	0/86 (0.0%)	0/98 (0.0%)
	ACDF	0/89 (0.0%)	0/83 (0.0%)	0/72 (0.0%)	0/71 (0.0%)	0/92 (0.0%)
Device Subsidence (>3mm)	ProDisc-C	0/95 (0.0%)	0/93 (0.0%)	0/86 (0.0%)	0/86 (0.0%)	0/98 (0.0%)
	ACDF	0/89 (0.0%)	0/83 (0.0%)	0/72 (0.0%)	0/71 (0.0%)	0/92 (0.0%)
Disc Height: Decrease (>3mm)	ProDisc-C		0/88 (0.0%)	0/83 (0.0%)	0/86 (0.0%)	0/98 (0.0%)
	ACDF		0/82 (0.0%)	0/69 (0.0%)	0/69 (0.0%)	0/89 (0.0%)
Presence of Gaps	ACDF			2/72 (2.8%)	1/71 (1.4%)	0/92 (0.0%)
Bridging Bone	ProDisc-C			0/86 (0.0%)	3/86 (3.5%)	3/98 (3.0%)
	ACDF			19/72 (26.4%)	4/71 (5.6%)	8/92 (8.7%)
Radiolucency	ProDisc-C	0/95 (0.0%)	0/93 (0.0%)	0/86 (0.0%)	0/86 (0.0%)	0/98 (0.0%)
	ACDF	3/89 (3.4%)	4/83 (4.8%)	4/72 (5.6%)	2/71 (2.8%)	1/92 (1.1%)
Range of Motion	ACDF	32/65 (49.2%)	47/80 (58.8%)	49/68 (72.1%)	64/68 (94.1%)	83/91 (91.2%)

Note: Unintended fusion (i.e., heterotopic ossification resulting in bridging trabecular bone and a loss of motion (<2°)), occurred in three ProDisc-C patients in the randomized clinical trial. The bridging bone category represents number of ProDisc-C subjects with presence of bridging bone and the number of ACDF subjects without bridging bone. The radiolucency category represents the number of ProDisc-C subjects with >25% radiolucency at the superior or inferior components and the number of ACDF subjects with >25% radiolucency at the fusion mass.

Flexion/extension range of motion (ROM) in degrees at the operative level, determined as the difference in Cobb measurements between dynamic flexion/extension lateral radiographs, was determined at pre-op, 3, 6, 12, 18 and 24 months for ProDisc™-C Total Disc Replacement.

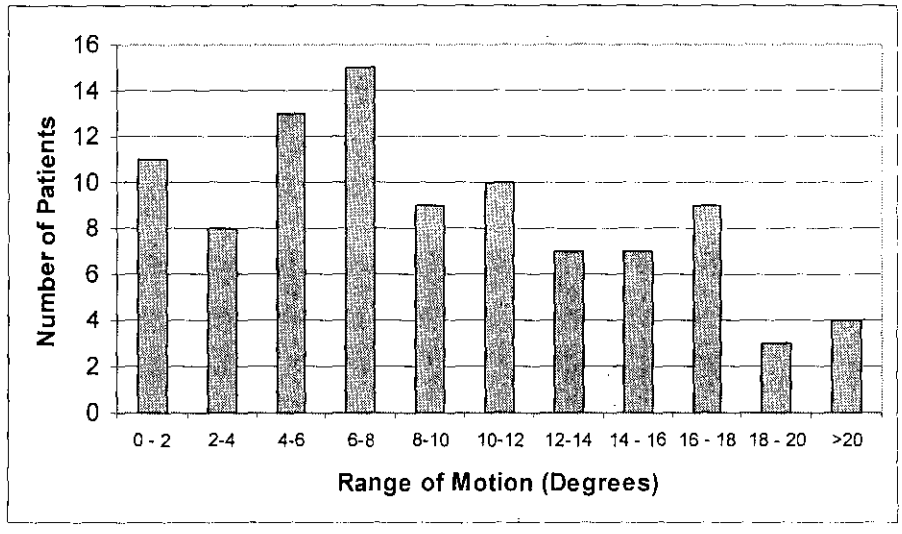
The figure below summarizes the results for mean Flexion/Extension (F/E) Range of Motion over time for ProDisc™-C Total Disc Replacement.

Figure 1: ProDisc™-C Total Disc Replacement Time Course of Mean Flexion/Extension Range of Motion



A histogram is provided showing the range of motion values recorded for all ProDisc™-C Total Disc Replacement subjects at 24 months. This histogram used values obtained by rounding recorded range of motion for each subject to the nearest integer.

Figure 2: Histogram of ProDisc™-C Total Disc Replacement Flexion/Extension ROM at 24 Months (N=96 subjects)



Range of motion success for the ProDisc-C cohort was defined as ≥4° of motion of flexion/extension or maintenance of motion relative to pre-operative baseline. Of the 81/96 (84.4%) ProDisc-C patients who were considered range of motion "successes", 77/81 (95.1%) achieved ≥4° of motion of flexion/extension at Month 24, 53/81 (65.4%) maintained motion from pre-operative baseline, and 49/81 (60.5%) were successes under both criteria.

The overall success rates at month 24 of subjects with ≥4° of motion were compared to subjects with <4° of motion using both the IDE Overall Success analysis as well as the Additional Analysis (FDA) success criteria. Neither analysis demonstrated a statistically significant difference (p=0.7439, p=0.7587 respectively) between the groups.

Additional Data

Visual Analogue Scale (VAS) Neck Pain Intensity

The Neck Pain Intensity score, the ratio of the patient response to the total length of the VAS scale, is demonstrated in Table 20.

Table 25: VAS Neck Pain Intensity Changes from Baseline to 24 months

	ProDisc™-C	ACDF	p-value (2-sided)
# evaluated	98	90	0.7285
Significant improvement (≤-20mm)	77 (78.6%)	68 (75.6%)	
Some improvement (>20 to -3mm)	7 (7.1%)	7 (7.8%)	
No change (>-3 to <3mm)	5 (5.1%)	5 (5.6%)	
Deterioration (≥3mm)	9 (9.2%)	10 (11.1%)	

VAS Neck Pain Frequency

Results of the Neck Pain Frequency score, the ratio of the patient response to the total length of the VAS scale, appear in Table 21.

Table 26: VAS Neck Pain Intensity Changes from Baseline to 24 months

	ProDisc™-C	ACDF	p-value (2-sided)
# evaluated	98	90	0.7289
Significant improvement (≤-20mm)	75 (76.5%)	71 (78.9%)	
Some improvement (>20 to -3mm)	9 (9.2%)	3 (3.3%)	
No change (>-3 to <3mm)	8 (8.2%)	5 (5.6%)	
Deterioration (≥3mm)	6 (6.1%)	11 (12.2%)	

VAS Arm Pain Intensity

VAS Arm Pain Intensity score, the ratio of the patient response to the total length of the VAS scale, is shown in Table 22.

Table 27: VAS Arm Pain Intensity Changes from Baseline to 24 months

	ProDisc™-C	ACDF	p-value (2-sided)
# evaluated	98	90	0.5063
Significant improvement (≤-20mm)	70 (71.4%)	69 (76.7%)	
Some improvement (>20 to -3mm)	15 (15.3%)	10 (11.1%)	
No change (>-3 to <3mm)	5 (5.1%)	2 (2.2%)	
Deterioration (≥3mm)	8 (8.2%)	9 (10.0%)	

VAS Arm Pain Frequency

Arm Pain Frequency score, the ratio of the patient response to the total length of the VAS scale, is demonstrated in Table 23.

Table 28: VAS Arm Pain Frequency Changes from Baseline to 24 months

	ProDisc™-C	ACDF	p-value (2-sided)
# evaluated	98	89	0.5065
Significant improvement (≤-20mm)	70 (71.4%)	68 (76.4%)	
Some improvement (>20 to -3mm)	17 (17.3%)	11 (12.4%)	
No change (>-3 to <3mm)	4 (4.1%)	5 (5.6%)	
Deterioration (≥3mm)	7 (7.1%)	5 (5.6%)	

VAS Patient Satisfaction Scores

Patient satisfaction after surgery at the final evaluation timepoint is presented in Table 24.

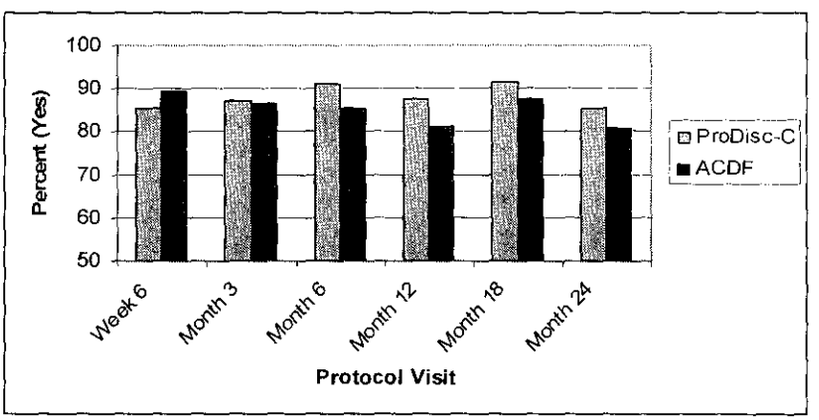
Table 29: Distribution of VAS satisfaction at 24 months

	ProDisc™-C	ACDF
# evaluated	95	88
Less than 20mm	5 (5.3%)	6 (6.8%)
20 - <40mm	3 (3.2%)	3 (3.4%)
40 - <60mm	5 (5.3%)	6 (6.8%)
60 - <80mm	15 (15.8%)	13 (14.8%)
80 – 100mm	67 (70.5%)	60 (68.2%)

Surgery Again

Patients were asked at each time-point whether they would have the same surgery again. At all time-points there was no statistically significant difference in the percentage of ProDisc™-C Total Disc Replacement patients indicating that they would have the surgery again relative to ACDF. The percentage of patients responding that they would elect to have the same surgery again is presented graphically below.

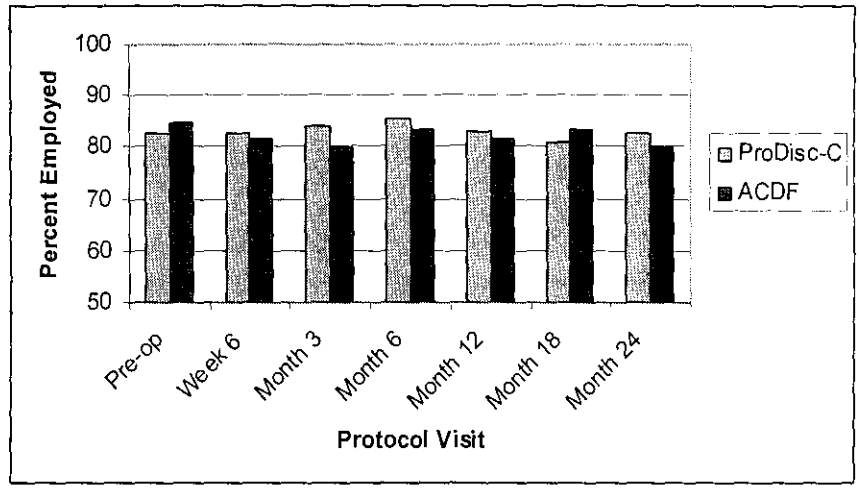
Figure 3: Surgery Again



Employment Status

At all time-points there was no statistically significant difference in the percentage of ProDisc™-C Total Disc Replacement patients indicating that they were employed relative to ACDF. The percentage of patients responding that they were employed is presented graphically below.

Figure 4: Employment Status



Medication Use

In patients that were considered overall study successes, the percentage of patients using strong narcotics, weak narcotics, and muscle relaxants decreased considerably in both treatment groups relative to baseline. In patients considered overall study failures, the use of strong and weak narcotics decreased in both treatment groups. The table below shows the percentage decrease in the number of patients using medications at month 24 relative to pre-operative baseline.

Table 30: Percentage Decrease in Medication Use: Pre-operative Baseline to Month 24

	Strong Narcotics	Weak Narcotics	Non-Narcotics	Muscle Relaxants
ProDisc-C (Success)	93.8%	90.0%	22.7%	90.9%
ACDF (Success)	76.9%	87.5%	31.6%	70.6%
ProDisc-C (Failure)	35.1%	37.7%	-3.8%	9.1%
ACDF (Failure)	53.6%	40.4%	-78.9%	-62.3%

Efficacy Conclusion

The objective of this clinical investigation was to compare the safety and effectiveness of ProDisc™-C Total Disc Replacement to anterior cervical discectomy and fusion (ACDF) surgery in the treatment of discogenic pain associated with SCDD in the cervical spine.

The primary hypothesis of this study is the ProDisc™-C Total Disc Replacement implant is non-inferior to ACDF surgery at 24 months. To evaluate this hypothesis, patients were assigned a treatment, either ProDisc™-C Total Disc Replacement or ACDF surgery, according to a blocked randomization schedule stratified by center at 13 sites.

In this study, 209 patients were enrolled and treated (106 ACDF, 103 ProDisc™-C) in accordance with the protocol. All 209 patients had reached the 24 month study endpoint as of the date of database closure on November 27, 2006.

Overall, there was an high follow-up rate of 96.5%. Adequate power was achieved. Statistical analysis concludes that the results from all sites are poolable to determine safety and effectiveness.

Analysis of all patient demographic data showed no statistically significant difference between the treatment groups. There was a statistically significant difference in intra-operative data (operative time and estimated blood loss) between the ProDisc™-C Total Disc Replacement and ACDF groups in favor of the ACDF group, though the magnitude of the difference may not be clinically significant.

Results were analyzed using the IDE success criteria (Overall Success) as well as an additional analysis using modified success criteria requested by FDA (Additional Analysis). The results of overall success, using both sets of success criteria, indicate that the ProDisc™-C Total Disc Replacement, is non-inferior to the ACDF control group. To assess the impact of patients with unknown outcomes at 24 months, sensitivity analyses were conducted. The results of all sensitivity analyses indicate that the ProDisc™-C Total Disc Replacement is non-inferior to ACDF.

In addition to the analyses of overall success, additional exploratory analyses were conducted. The secondary exploratory analyses support the conclusions of the primary analysis.

At all follow-up time-points greater than 85% of all ProDisc™-C Total Disc Replacement patients indicated that they would have the surgery again. This is consistent with the NDI scores that show pain relief and increased function in the ProDisc™-C Total Disc Replacement patients.

Results show that the mean range of motion at Month 24 was 9.4° with 81/96 (84.4%) of all ProDisc-C patients achieving range of motion success as defined in the IDE protocol. However, range of motion was not correlated with overall success by comparative statistical analysis.

It is the outcomes of this analysis that the null hypothesis must be rejected. This study indicates that the ProDisc™-C Total Disc Replacement is non-inferior to ACDF.

XII. CONCLUSIONS DRAWN FROM THE STUDIES

The valid scientific evidence presented in the preceding sections provides reasonable assurance that the ProDisc™-C Total Disc Replacement is safe and effective for reconstruction of the disc from C3-C7 following single-level discectomy for intractable symptomatic cervical disc disease (SCDD); and the device is non-inferior when comparing Overall Success rates to the ACDF control for the studied indication.

XIII. PANEL RECOMMENDATION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Orthopaedic and Rehabilitation Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIV. CDRH DECISION

CDRH approved the ProDisc™-C Total Disc Replacement based on the following:

- The overall incidence of adverse events occurring in the ProDisc™-C group was non-inferior to the control group.
- The number of adverse events considered to be device-related in the ProDisc™-C group was non-inferior to the control group.
- The Overall Success rate of the ProDisc™-C group was non-inferior to the Overall Success rate of the control group, with a non-inferiority margin of 10%, using FDA's criteria for Overall Success.

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

FDA issued an approval order on December 17, 2007. The conditions of approval cited in the approval order are described below.

1. The sponsor has agreed to conduct a post-approval study (PAS) to evaluate the long-term safety and effectiveness of the ProDisc™-C Total Disc Replacement. This study will involve investigational and control patients from the pivotal investigational device exemption (IDE) study, as well as patients who received the ProDisc™-C as part of the Continued Access arm. This PAS will evaluate the long-term safety and effectiveness of the ProDisc™-C Total Disc Replacement by following 209 subjects from the randomized clinical trial (103 ProDisc™-C patients, and 106 control subjects) out to 7 years (i.e., 84 months). All 99 Continued Access subjects will also be evaluated through 7 years (i.e., 84 months) post-surgery.

   The PAS will evaluate Overall Success, defined as:

   - improvement in the Neck Disability Index (NDI) $\geq$ 20% at 84 months compared to the score at pre-operative baseline
   - neurological status improved or maintained (motor, sensory, reflexes) as compared to the pre-operative baseline
   - no removals, revisions, re-operations or additional fixation were required to modify any implant
   - no adverse events occur which are related to the treatment, ProDisc™-C, or its implantation or anterior cervical discectomy and fusion (ACDF) surgery, or its associated implants or graft material

   This analysis will utilize a non-inferiority margin of 10%

   The sponsor has agreed to conduct an additional analysis evaluating Overall Success with NDI success defined as an improvement in the NDI score $\geq$ 15 points at 84 months compared to the score at pre-operative baseline (instead of an improvement of $\geq$ 20%). This analysis will use a non-inferiority margin of 10%.

   The PAS will also evaluate all adverse events as well as adjacent segment degeneration both symptomatically and using radiographs; radiographic parameters including implant migration, subsidence, radiolucency, disc height, motion/fusion status patient satisfaction and

quality of life (SF-36), and heterotopic ossification; neck and arm pain on a Visual Analog Scale (VAS); and the correlations of range of motion (ROM) with NDI and VAS scores.

PAS reports will be submitted every six months for the first two years and then annually until the study is completed.

2. The sponsor has agreed to perform a 5-year enhanced surveillance study of the ProDisc™-C Total Disc Replacement to more fully characterize adverse events when the device is used in the intended patient population under general conditions of use. The sponsor will collect, analyze, and submit all adverse events and complaints received by the company for the ProDisc™-C Total Disc Replacement, as well as information on the total number of devices shipped and implanted. The study will commence at the time of PMA approval. The Enhanced Surveillance Study reports will be submitted every six months for the first two years and then annually through the fifth year after approval.

3. The sponsor has agreed to submit amended labeling (via a PMA supplement) with the results of the PAS and enhanced surveillance study outlined in items 1-2 above upon completion of the studies , and/or at earlier timepoints, as needed.

XV. APPROVAL SPECIFICATIONS

Directions for Use: See product labeling

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

Post Approval Requirements and Restrictions: See the Approval Order.

XVI. REFERENCES

1. Lydick E, Cook K, Turpin J, et al. Development and validation of a simple questionnaire to facilitate identification of women likely to have low bone density. *American Journal of Managed Care*, 4:37-48, 1998.
2. The WHO Study Group: Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Geneva, World Health Organization, 1994.