

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Artificial Cervical Disc

Device Trade Name: BRYAN® Cervical Disc

Applicant's Name and Address: Medtronic Sofamor Danek
1800 Pyramid Place
Memphis, TN 38132

Date of Panel Recommendation: July 17, 2007

Premarket Approval Application (PMA) Number: P060023

Date of FDA Notice of Approval: May 12, 2009

II. INDICATIONS FOR USE

The BRYAN® 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 BRYAN® device is implanted via an open anterior approach. Intractable radiculopathy and/or myelopathy is defined as any combination of the following: disc herniation with radiculopathy, spondylotic radiculopathy, disc herniation with myelopathy, or spondylotic myelopathy resulting in impaired function and at least one clinical neurological sign associated with the cervical level to be treated, and necessitating surgery as demonstrated using computed tomography (CT), myelography and CT, and/or magnetic resonance imaging (MRI). Patients receiving the BRYAN® Cervical Disc should have failed at least six weeks of non-operative treatment prior to implantation of the BRYAN® Cervical Disc.

III. CONTRAINDICATIONS

The BRYAN® Cervical Disc should not be implanted in patients with the following conditions:

- Active systemic infection or infection at the operating site;
- Allergy to titanium, polyurethane, or ethylene oxide residues;
- Osteoporosis defined as a DEXA bone mineral density T-score equal to or worse than -2.5;
- Moderate to advanced spondylosis characterized by bridging osteophytes, marked reduction or absence of motion, or collapse of the intervertebral disc space of greater than 50% of its normal height;

- Marked cervical instability on radiographs (e.g., radiographic signs of subluxation greater than 3.5 mm or angulation of the disc space more than 11 degrees greater than adjacent segments);
- Significant cervical anatomical deformity or compromised vertebral bodies at the index level (e.g., ankylosing spondylitis, rheumatoid arthritis, or compromise due to current or past trauma);
- Significant kyphotic deformity or significant reversal of lordosis; or
- Symptoms necessitating surgical treatment at more than one cervical level.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the BRYAN® Cervical Disc Physician labeling.

V. DEVICE DESCRIPTION

The BRYAN Cervical Disc is a non-fusion artificial disc prosthesis. It is implanted between two vertebrae in the neck matching the depth of the endplate in a pocket milled into the bone. Two wings extend up and down on the anterior edge. The BRYAN Cervical Disc is not fastened to the vertebrae with screws.

The BRYAN® Cervical Disc is comprised of the following components: two titanium alloy shells (Ti-6Al-4V per ASTM F136), two titanium retaining wires (commercially pure per ASTM F67), a polycarbonate polyurethane nucleus (Bionate –S), a polyether polyurethane sheath (BioSpan-S), and two titanium alloy seal plugs (ASTM F136). The articulating surfaces of the device are polyurethane and titanium.

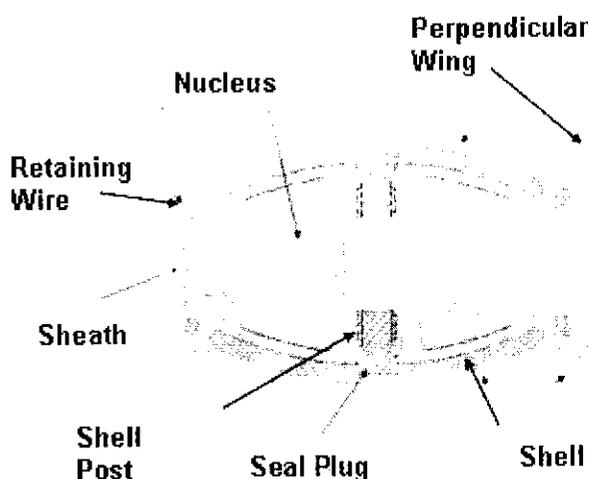


Figure 1: BRYAN Cervical Disc Cross Section

The polyurethane nucleus component fits between and moves with respect to the two shells. The titanium alloy shells have inward facing shell posts that fit into flared holes in the nucleus for a controlled range of motion and for soft stops at the extremes of the full flexion/extension, full lateral bending and maximum translation. During normal motion

(approximately $\pm 4.9^\circ$ flexion/extension, $\pm 4.0^\circ$ lateral bending) the shell posts do not contact the nucleus. The full range of motion is shown below.

Table 1. Full range of motion *ex-vivo* for all prosthesis sizes

Flexion/Extension	Lateral Bending	Rotation	Translation
$\pm 10^\circ$	$\pm 11^\circ$	$\pm 7^\circ$	± 1 mm

The outer sides of the shells, which sit in the pockets which are milled into the vertebral bodies, have a beaded, vacuum-sintered commercially-pure titanium coating (CP Ti B.I. Thortex K-coat). Beaded coatings are used in orthopedic implants to encourage bone growth into the fixed part of the prosthesis. On the anterior ends of the shells there is a perpendicular wing with through holes. These holes are not intended for screw fixation. There are also holes through the shell posts. Prior to implantation, saline is injected through a hole in the shell post. The titanium alloy seal plugs are screwed into the shell posts to retain the saline. The polyurethane sheath forms a compartment to contain the saline and to restrict tissue growth into the moving parts of the prosthesis. Retaining wires clasp the sheath to the shells.

The available components are shown in Table 2 below.

Table 2. BRYAN® Cervical Disc Device Sizes

Catalog Number	Diameter (mm)
6470314	14
6470315	15
6470316	16
6470317	17
6470318	18

After implantation of the device, the resultant interbody height is approximately 6mm.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Nonoperative alternative treatments for intractable radiculopathy and/or myelopathy 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 patient's pain and/or neurological deficits, surgery is an alternative. The most common surgical treatment is anterior cervical discectomy and fusion (ACDF) which includes decompression of the affected nerves and spinal cord (cervical discectomy) and is typically followed by placement of bone graft in the intervertebral space to maintain height and accomplish fusion as well as an anterior plate to provide immobilization and stability. Another surgical alternative is the use of a different approved artificial cervical disc replacement device. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with their physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The device has a marketing history outside the United States that began in 2000. The device has not been withdrawn from marketing for any reason. The countries in which the BRYAN Disc is available are provided in Table 3 below.

Table 3. BRYAN Disc Availability

Argentina	Greece	Portugal
Australia	Hong Kong	Qatar
Austria	Hungary	Russia
Belgium	Iceland	Saudi Arabia
Brazil	India	South Africa
Canada	Italy	South Korea
Chile	Jordan	Spain
China	Lebanon	Sweden
Costa Rica	Mexico	Switzerland
Croatia	Netherlands	Turkey
Denmark	New Zealand	Taiwan
France	Pakistan	United Kingdom
Germany	Poland	

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Risks associated with the use of the BRYAN® 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 BRYAN® 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 were observed in the clinical study and are subsequently reported in the adverse events tables in Section X below.

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; gastrointestinal 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 BRYAN® 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; 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. 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.

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

The engineering testing done on the BRYAN™ Total Cervical Disc Prosthesis is grouped by concerns that the testing addresses. The motion and load justification is relevant to multiple tests. After the load justification, the tests addressing wear, expulsion, constraint, joint encapsulation and materials concerns are listed.

1. Motion and Load Justification

Medtronic provided justifications based on literature for the cervical range of motion and loads in the cervical spine. Table 4 below shows flexion/extension, lateral bending and axial rotation for C4-C5. The BRYAN Cervical Disc Prosthesis motion is designed to be the same as that reported for C4-C5.

Table 4. Range of Motion Justification

Reference	C4-C5 flexion/ extension	C4-C5 Lateral Bending	C4-C5 Axial Rotation
Representative Angle ¹	±10°	±11°	±7°
Average Neutral zone ²	±4.9°	±4.0°	±3.8°
ASTM F2423-05 Standard Guide for Functional, Kinematic, and Wear Assessment of Total Disc Prostheses (test profile)	±7.5°	±6°	±6°
ISO 18192-1 Implants for surgery - Wear of total intervertebral spinal disc prostheses	±7.5°	±6°	±4°
Flexion/extension from observed motions ³ C4-C5 Level motion defined with White and Punjabi	±3.58°	n/a	n/a
Flexion/extension from observed motions ⁴ C4-C5 Level motion defined with Medical Metrics	±3.96°	n/a	n/a
Flexion/ extension angle ⁵	±0.4 to 5.85°	n/a	n/a
BRYAN Cervical Disc Prosthesis Designed Range of Motion	±10°	±11°	±7°
BRYAN Cervical Disc Prosthesis Tested Motion for wear testing	±4.9°	n/a	±3.8°

Maximum Compressive Load

The maximum physiologic compressive load on the cervical intervertebral disc was determined by Moroney et al. in a biomechanical model.⁶ The calculated compression forces based on this model for the C4-5 motion segment were as high as 1164 N. The 1164 N C4-C5 compressive load is used in Static testing of the nucleus in axial compression.

Average Compressive Load

The average compressive loads on the cervical intervertebral discs during activities of daily living were defined by Snijders.⁷ Using the load profile established by this study, the sponsor states that the average compressive load in the cervical spine is 130 N. Since the load in the cervical spine is borne by facet joints as well as the disc, 130 N is a conservative value for load on the device. The average compressive load is used in tests for static and fatigue testing of the shell, Friction testing of the shell on bone, the effect of frequency on material characteristics, Creep testing of the nucleus, Wear simulator testing, Evaluation of load, lubricant, and frequency effects on durability and Shear testing of the prosthesis in a cadaveric model.

Maximum Shear Load

The maximum physiologic shear load on the cervical intervertebral disc during activities of daily living was calculated by Moroney et.al.⁸ The calculated C4-C5 joint shear load was 135 N for anterior/posterior exertions. The maximum shear load is used in Static and Fatigue testing of the shell post, Shell stability in antepulsion and retropulsion and Shear testing of the prosthesis in a cadaveric model.

2. Tests and Analysis Related to Wear

To address the novel articulation material combination (polyurethane on titanium) and to evaluate the long-term functionality and durability of the BRYAN® Cervical Disc prosthesis following 10,000,000 cycles simulating normal activities of daily living, Medtronic performed the following series of tests to characterize the wear behavior of the device.

- Wear simulator testing of the prosthesis (4 Hz, bovine serum wear test)
- Evaluation of load, lubricant, and frequency effects on durability in the absence of a sheath (4 and 6 Hz, saline and bovine serum, 130 and 300N wear test)
- Evaluation of BRYAN Cervical Disc Prosthesis wear tested at 2 Hz and in the absence of a sheath
- The influence of frequency and load level on the mandrel temperature during durability tests
- Lifetime durability testing

The first four tests were conducted in cervical spine durability machines that simulate flexion/extension and axial rotation movements simultaneously under a constant axial compressive load. The table below shows the test parameters reported in wear tests.

Table 5. Wear Test Parameters

<u>Parameter</u>	<u>Values tested</u>
Flexion/ extension	±4.9°
Axial Rotation	±3.8°
Axial Compressive Load	130 and 300N
Test Cycle Frequency	2, 4 and 6 Hz
Test media	Saline, Bovine Serum

The most physiologically relevant loads and motions are the average compressive load (130 N axial), and 10 million cycle, neutral zone motion (±4.9° flexion/extension and ±3.8° axial rotation) at 2 Hz. The device is axi-symmetric; flexion/extension motion can be used to model lateral bending. The bearing surfaces are spherical; larger motions (short of the soft stop) would not change the surface contact geometry. Since the moving parts of this device are encapsulated by a polyurethane sheath and the device is initially saline filled, Medtronic conducted wear testing both in saline and in serum as shown in Table 5 above. Over time the sheath sealing may fail and the saline may be replaced with other

fluids. To characterize device behavior at the ends of range of motion, shell post fatigue was tested separately (described in Section 4 below).

After 10 million cycles of wear testing the device met the acceptance criteria as follows:

- No fracture or dislodgment of the retaining wire, lips of the mandrels, or posts of the mandrels.
- No nucleus surface cracks longer and deeper than 2 mm (no cracks were visible).
- No large pieces of polyurethane broke off the nucleus (no particles generated larger than 315 μm)
- Minimal wear on the nucleus (no contact between the shells for full range of motion)
- Less than 15 mg of wear debris generated (at 4 Hz in saline)
- More than 90% of the particles generated were smaller than 1 μm
- No leaks, after completion of 10,000,000 cycles, under a 1 atmosphere internal pressure held for 15 seconds.
- No tearing or rupturing of the sheath, or separating of the sheath from the mandrels.

The amount of wear generated in the 4 Hz saline test in 10 million cycles was used to develop the dosing for the rabbit particulate response test. The particulate characterization and biological response to particles are described in the rabbit particulate response test. Refer to Section B Animal Studies below.

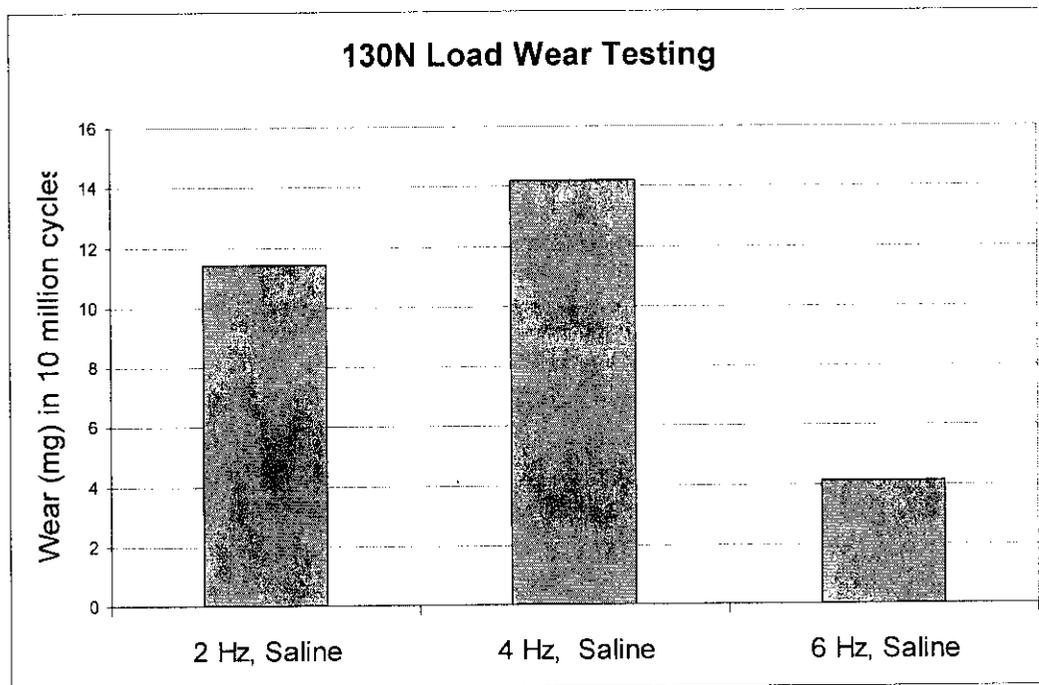


Figure 2. Wear Test Debris Generation

The fifth test related to wear was Lifetime durability testing. This test continued the 4 Hz, 130 N load wear test until device failure. The devices failed with a hole through the rim of the nucleus at almost 40 million cycles. Medtronic estimates that this is equivalent to 295 yrs of in vivo use.

For a description of the biological reaction to wear particles in a rabbit model, see rabbit study under Section B, Animal Studies, below.

For a description of the functional animal study in a goat model supporting bench top wear testing, see Section B, Animal Studies, below.

For a description of the Human Explant analysis, see Section C, Additional Studies, below.

3. Tests and Analysis Related to Migration or Expulsion

The BRYAN™ Total Cervical Disc Prosthesis is designed with a unique method of fixation to bone. BRYAN sits in a pocket milled into the vertebral endplate and is not screwed or secured by teeth to the vertebra. To address fixation concerns, Medtronic conducted the following tests:

- Shell stability in antepulsion and retropulsion
- Friction testing of shell on bone and shell on nucleus in axial rotation
- Shear testing of the prosthesis in a cadaveric model
- BRYAN Cervical Disc Stability in Antepulsion using a Minimally loaded and extended cervical spine model
- Mechanical testing of the shell surface coating
- Microstructural analysis of the shell surface coating

These tests assessed the ability of the BRYAN™ Total Cervical Disc Prosthesis to resist expulsion, to articulate on the nucleus shell interface instead of the shell bone interface and to resist shear forces. Expulsion testing was conducted at low load and high load in a neutral orientation and at low load at maximum device extension.

Table 6. Expulsion force data

Axial Compressive Load -» Antepulsion Retropulsion	<u>Expulsion Force at a low load</u>	<u>Expulsion Force at a high load</u>	<u>Expulsion Force at a low load with extension</u>
Test Parameter- Compressive Load	40N	130N	50 N
Test Parameter- Extension Angle	0°	0°	11°
Antepulsion (N)	120	270	113
Retropulsion (N)	309	429	

Expulsing the disc from the milled spherical cavity takes significant force even with no bone ingrowth into the sintered porous coating on the shell.

The friction testing and the cadaver testing show that the shell does not move easily on the bone. There is less friction at the nucleus shell interface than the bone shell interface. In the worst case anatomic direction (retropulsion) the BRYAN™ Total Cervical Disc Prosthesis resists shear forces.

4. Tests Related to Device Design

The BRYAN™ Total Cervical Disc Prosthesis includes a new type of constraint (flat on flat, ball joint, etc.) for a cervical disc prosthesis. The BRYAN cervical disc has a novel post in a flared hole constraint. To address concerns about the new joint geometry, Medtronic has provided the following test reports:

- Static and fatigue testing of the shell post
- Static and fatigue testing of the shell in bending

The shell tests demonstrated sufficient strength and fatigue resistance for expected physiologic loads.

The BRYAN™ Cervical Disc includes a polyurethane nucleus. Polyurethane is not typically used in joints or load bearing surfaces. To alleviate issues about the polyurethane strength and fatigue properties, Medtronic has provided the following tests:

- Static testing of the nucleus in axial compression
- Fatigue testing of the nucleus in axial compression
- Creep testing of the nucleus
- Saturation testing of the nucleus
- The effect of frequency on the material characteristics of the nucleus

The nucleus tests showed that the polyurethane nucleus met the acceptance criteria as designed. A maximum physiologic load of 1164 N would not compress the nucleus to the point that the shells contacted each other. In fatigue, the nucleus withstood more than twenty times the average physiologic load for 10 million cycles without compression leading to shell to shell contact. The creep test demonstrated that the nucleus did not compress significantly over time. The saturation test showed that the outer dimensions of the nucleus remained essentially unchanged after 31 day soak in saline.

At the advisory meeting held on July 17, 2007, the Orthopedic and Rehabilitation Devices Panel had the following concerns about the characterization of the polyurethane.

- No chemical analysis of in vivo tested samples was performed.
- Volatile gasses were not measured.
- No measurement of molecular weight of surface layer was taken.
- Coefficient of friction between polyurethane nucleus and titanium shell was not specified.

In response to these concerns Medtronic provided a chemical analysis of the *in vivo* tested samples with FTIR spectra and molecular weights. The FTIR spectra of the explants correlated with that of the controls; degradation products were not observed in the explants. GPC results showed that the molecular weight of the 10 month explant, 8 month explant, and control were 159 ± 27 , 172 ± 7 , and 170 ± 15 kD, respectively for the sheaths and 124 ± 3 , 124 ± 2 , and 116 ± 2 kD, respectively, for the nuclei. Over the short period of time studied there was no significant decrease in molecular weight of the polyurethane. To characterize the surface layer of the material Medtronic looked for adhesive and abrasive wear with SEM and interferometry. Although microscopic evidence of wear was seen, even after 6.1 years *in vivo* there was no evidence of cracking or stress degradation.

A high coefficient of friction would contribute to polyurethane delamination and device wear. Medtronic provided a study that showed that the coefficient of friction values for PCU-metal and UHMWPE-metal articulations were 0.015 and 0.035, respectively. No delamination or significant device wear was seen in any of the explanted samples.

FDA agrees that Medtronic has shown that the BRYAN cervical disc does not degrade in the 2 year clinical trial period. Because the specific polyurethanes used have not been exhaustively studied for use as sheaths or nuclei in a cervical disc prosthesis, FDA recommends that the sponsor continue to evaluate explanted devices in a 10 year post approval study.

5. Tests to address joint encapsulation

The BRYAN™ Total Cervical Disc Prosthesis includes a new design feature, a sheath which covers the nucleus and attaches to the shell. The following testing was completed to characterize the sheath:

- Tensile testing
- Torsion testing
- Seal Plug Pressurization testing

Medtronic conducted tensile and torsion testing of the sheath in which integrity was assessed after 3 tension or torsion cycles by inflating the sheath and checking for leakage. These tests were not comprehensive fatigue tests of the sheath and retaining ring. Medtronic states that the sheath has only three purposes:

1. to hold the 3 piece implant together during insertion
2. to temporarily contain lubricating saline of initial friction reduction between the nucleus and shells
3. to prevent acute tissue growth

The sheath and shell plug air pressure test evaluated the sheath and retaining ring integrity. The enclosed joint design met the acceptance criteria by holding 1 atm.

pressure. Medtronic makes no claims regarding the ability of the sheath to retain particles. The ability of the sheath to retain saline or prevent tissue ingrowth was not assessed in the animal model or confirmed with the human explant analysis.

6. Biocompatibility

To address concerns about biocompatibility of the implant the sponsor defined the materials used, provided a materials characterization and tested to the recognized biocompatibility standard, ISO 10993

The materials used in the BRYAN™ Total Cervical Disc™ Prosthesis are:

- Nucleus: Bionate –S (99% polycarbonate-urethane, 1% silicone)
- Sheath: BioSpan-S polyether segment polyurethane (94% polyurethaneurea, 6% silicone)
- Shell: Titanium alloy (Ti-6Al-4V) with beaded, vacuum sintered porous coating of pure titanium
- Retaining wire: Titanium (commercially pure)

The biocompatibility testing is shown in the table below.

Table 7. Biocompatibility Testing

<u>Test</u>	<u>Title</u>	<u>Result</u>
ISO 10993-5	Cytotoxicity Study using the ISO Elution Method	“0” not cytotoxic
ISO 10993-10	ISO Maximization Sensitization study (Manusson Kligman)	Not significantly higher than control, not a contact sensitizer
ISO 10993-10	ISO Intracutaneous Study	“0” in SCI extraction, 0.3 in oil Negligible primary irritation
ISO 10993-11	ISO Material Mediated Pyrogen Study	No temperature rise >0.5°C, no material mediated pyrogenicity
ISO 10993-6	ISO Implantation Study (Goat and Chimpanzee)	Raised particulate questions
	Particulate Injection Study (Rabbit)	Resolved particulate questions

Titanium alloy (Ti-6Al-4V) and commercially pure titanium are common implant materials with a long history of biocompatibility.

7. Shelf Life testing

Shelf life testing involved 2X EtO sterilization of 60 double (inner and outer) packages that contained product. These underwent ASTM D4169:2005 protocols. This was the previously agreed upon test schedule and challenge level; both are worst

case. Of these 50 inner and 50 outer packages (total 100 data points) underwent Dye Penetration testing per ASTM F1929: 1998, and all 4 sides of 10 inner and 10 outer packages (total 80 data points) underwent Seal Strength testing per ASTM F 88:2006. All products passed in both categories: no dye leakage, and all peel strength values were 1.71 lbs or higher (averages of each sub-group of 10 ranged from 1.94 to 2.14).

This data is adequate for distribution simulation. The aging data justified the requested 5 year shelf life claim requested.

B. Animal Studies

The sponsor conducted the following animal testing of the BRYAN™ Total Cervical Disc™ Prosthesis.

1. Chimpanzee Study

The Six Month Chimpanzee Study used a "previous" device design in 6 animals. The devices were explanted after six months and fusion was performed. The study was conducted to evaluate the instrumentation and the surgical technique for proper placement of the Bryan device. Safety was assessed in terms of the need for re-operation, neurological damage, subluxation, subsidence, and bone and soft tissue damage. Efficacy endpoints included evaluation of the surgical instrumentation functionality during the implant procedure and chronic device performance, including continued range of motion, maintenance of disc space height, bone ingrowth into the shell, degree of wear of the components of the prosthesis, and debris generation from the disc. This study identified certain issues with the device design (wear debris at the anchor/screw/wing interface, angulated anchors, lack of bony ingrowth into the porous surfaces, seal plug dislocation, lack of desired range of the cervical motion).

The Three Month Chimpanzee Study used a current device in 2 animals and a previous design in 2 additional animals. The devices were explanted after three months and fusion was performed. According to the sponsor, based on results of the six month study, the prosthesis design was modified and the current design implanted into two animals. The design modifications included wing/shell interface, shell coating and rim, elimination of the anterior tension band, modifications of the seal plug, elimination of anchor, screw and biodegradable washer.

2. Goat Study

To support the bench top engineering testing, Medtronic provided functional animal testing in a goat model and assessed the biologic response to the shards of urethane and particulates. Polarizable material was seen in tissue samples taken from around the implant and in the spinal cord in 2 of the 3 goats. In Goat 006, there was no reaction to the small particulates in the adjacent tissue but there was hemorrhage in the tissue that contained 10 to 40 by 150 micron shards. In Goat 007, one section of the cephalic spinal cord contained shards with no inflammatory reaction. Other tissue sections included macrophages and

particulates. In Goat 008, no particulate material was identified in the sampled tissue. The goats studied had normal blood chemistry and histology. The gross review of periprosthetic tissue, draining lymph nodes, spinal cord, dura mater, spleen, liver, heart and kidneys showed no abnormalities.

3. **Rabbit Particulate Test:**

To address issues of biological reaction to particulates Medtronic provided the Rabbit Particulate test. Based on the 4 Hz, saline wear test of the BRYAN Cervical Disc , 190 to 230 µL of solution with urethane particles were injected per rabbit. The solution was injected into the epidural space of lumbar spine.

Table 8. Particle Reaction Doses

	Sheath – Biospan Polyurethane (mg/ml)	Total Biospan injected mg	Nucleus – Bionate Polyurethane (mg/ml)	Total Bionate injected mg
Low Dose	0.08	0.018	2.67	0.61
High Dose	0.23	0.053	8.02	1.84

If the rabbit mass of 4 kg is scaled to an adult male 75 kg, then the high dose urethane injection approximates the amount of wear generated in the 10⁷ cycle wear test.

The particle sizes ranged from <0.5 to 20 µm and the distribution is shown in the graph below. The particle size distribution of particles injected in the rabbit is similar to the particle size distribution generated in the wear test.

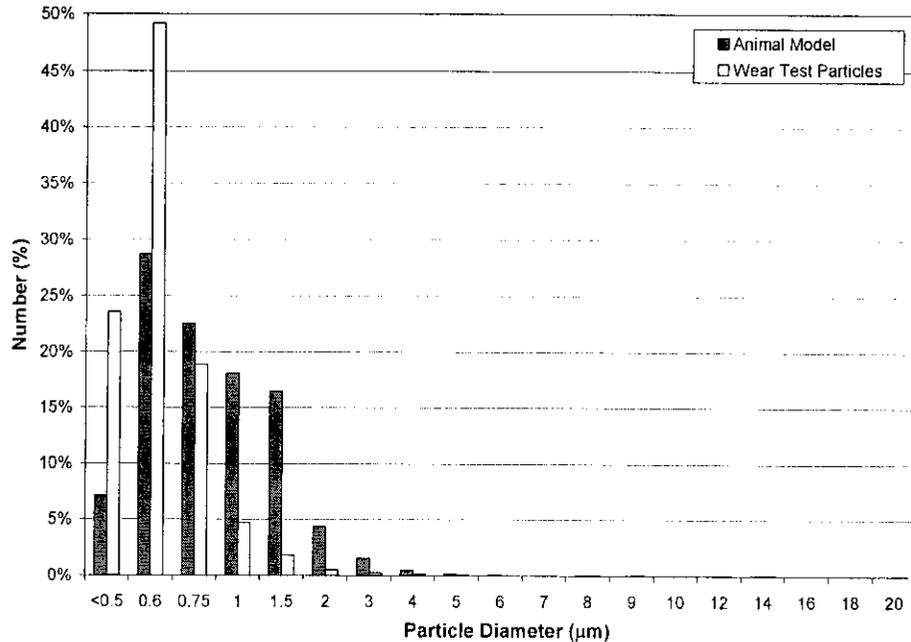


Figure 3. Particle Characterization

More than 50% of the particles injected were less than 1 µm. Particles were only observed in the spine tissue of one animal. No particles were found in the target organs sampled for analysis.

Hematology and gross and microscopic histology data was analyzed. In some cases there are statistically different differences between the investigational and control groups for hematology, chemistry or organ weight but the values were always within normal limits. A few exceptions include:

- At three months the control group kidneys were normal and the treatment group kidneys showed tubular basophilia (2 of 3 rabbits), tubular ectasia (2 of 3 rabbits), and chronic kidney infarcts (1 of 3 rabbits).
- Hematology data from 5 of 16 investigational animals (at 6 months) is missing due to clotting of the test samples.
- The thoracic lymph nodes analysis is missing from the high dose sheath particle treatment group at 6 months.

The particulate injection study in the rabbit does not show aggregation of particles in distal organs or significant biological response to wear debris.

The results of the rabbit particulate study raised several Panel concerns including:

- Particle size and distribution
- Kidney effects

To resolve these concerns Medtronic provided a retrospective microscopic evaluation of the rabbit brain tissue which identified *E. cuniculi* protozoa which

causes Encephalitozoonosis. Encephalitozoonosis is a common disease in rabbits. Lesions commonly occur in the brain and kidney tubules. The course of the illness is usually 5–12 days.

Based on the identification of *E. cuniculi* and analysis of the 6 month data, FDA determined the kidney abnormalities were likely not linked to the particle injection.

C. Additional Studies

Over 240 devices were implanted for the US IDE trial. 3 devices were explanted - 2 due to residual pain and 1 secondary to trauma. 2 explanted devices were available for analysis. The histological analyses of surrounding tissues showed macrophages, foreign body giant cells, and fibrous tissues surrounding some metallic and polymeric debris.

Explant analysis showed:

- limited wear with no adverse reactions,
- consistent ingrowth,
- biomechanical stability.
- No osteoclastic resorption,
- No osteolysis, and
- No evidence of infection

D. Laboratory Studies Conclusion

FDA determined that the preclinical animal and mechanical bench testing support the approval of the BRYAN® Cervical Disc.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to evaluate the safety and effectiveness of the BRYAN Cervical Disc for the treatment of patients with intractable radiculopathy and/or myelopathy in the U.S. under IDE #G000123. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

A multi-center, prospective, randomized, non-inferiority clinical trial of the BRYAN® Cervical Disc was conducted in the United States comparing the anterior spinal use of the BRYAN® device to anterior cervical discectomy and fusion (ACDF) using allograft and plating stabilization, the control, for reconstruction of the disc from C3-C7 following single-level discectomy for intractable radiculopathy and/or myelopathy.

Clinical study surgeries were performed during a period from May 28, 2002, to October 8, 2004. A total of 463 patients were treated at 30 investigational centers in

the clinical trial: 242 patients in the investigational BRYAN® device treatment group and 221 patients in the control group. The results and conclusions in the PMA are based upon an interim analysis of 300 patients with 2 year follow-up as pre-defined in the protocol. The data presented below represents data from 160 investigational patients and 140 control patients as of June 5, 2006. Enrollment is completed, and follow up on all enrolled patients is ongoing. This document will be updated to reflect the results of these patients.

The control group received a standard anterior cervical discectomy and fusion procedure (ACDF) which is standard of care for most forms of cervical degenerative spondylotic disease that results in radiculopathy and/or myelopathy. An ACDF procedure involves a lateral incision in the neck followed by a dissection to the anterior cervical spine. The control treatment was commercially available allograft (without bone matrix paste) used in conjunction with the Medtronic Sofamor Danek ATLANTIS™ Cervical Plate System, a legally marketed alternative.

The study was approved to enroll up to 470 patients (245 investigational, 225 control). Simulations were provided to justify both the total sample size and the number of patients to be included in the interim analysis. The simulations also showed that the proposed Bayesian analysis plan had acceptable frequentist operating characteristics (type I error and power).

Bayesian statistical methods were planned to determine whether the investigational device is non-inferior to the control with respect to the overall success rate at 24 months. A non-inferiority margin of 10% was selected. Non-inferiority can be claimed if the posterior probability that the success rate of the BRYAN group was not lower than the control group by more than 10% is greater than 95%.

If non-inferiority is claimed, then the posterior probability of superiority is also computed. If this probability is greater than 95%, then superiority can be claimed.

Similar Bayesian analyses (i.e., posterior probabilities of non-inferiority, along with 95% HPD intervals) are provided for all other endpoints in the trial. Non-informative priors are used for all prior distributions.

Two analyses were planned: one interim analysis when 300 patients have valid outcomes for the overall success endpoint at 24 months and a final analysis when all enrolled patients have reached the 24-month evaluation. The analysis of overall success incorporates all available 12- and 24-month data, including the available 12-month data for those patients who have not yet reached the 24-month evaluation period. However, the focus of the analysis remains on the 24-month overall success rates in each treatment group.

A data safety monitoring committee was used for periodic review of safety information or on an as-needed basis. The study was not stopped for safety issues during the course of the trial.

Radiographs were evaluated by an independent evaluator.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the BRYAN® Cervical Disc study was limited to patients who met the following inclusion criteria

- Requires surgical treatment at any one level (C3-4, C4-5, C5-6, or C6-7) that has failed conservative treatment (by the investigator or referring physician) lasting at least six weeks; for any combination of the following: disc herniation with radiculopathy, spondylotic radiculopathy, disc herniation with myelopathy, or spondylotic myelopathy. The six-week conservative treatment period may be waived in cases of myelopathy requiring immediate treatment (e.g., acute onset of clinically significant signs);
- The requirement for surgical treatment must be demonstrated using computed tomography (CT), or myelography and CT, and/or magnetic resonance imaging (MRI);
- Patient must score 30 or more points on the NDI questionnaire and exhibit at least one clinical sign associated with the cervical level to be treated (i.e., abnormal reflex, decreased motor strength, or abnormal dermatome sensitivity);
- Skeletally mature (at least 21 years old);
- Willing and likely to follow the requirements of the protocol; and.
- Voluntarily signs the Patient Informed Consent.

Patients were not permitted to enroll in the BRYAN® Cervical Disc study if they met any of the following exclusion criteria:

- Active systemic infection or infection at the operating site
- Metabolic bone disease, such as osteoporosis, which is defined as a bone mineral density T-score equal to or worse than -2.5;
Note: If the investigator detects the presence of significant radiolucence, bone mineral density (BMD) scan in the spine, wrist, and femoral neck must be obtained to verify the absence of osteoporosis
- Known allergy to titanium, polyurethane, or ethylene oxide residuals;
- Concomitant conditions requiring steroid treatment.
- Diabetes mellitus requiring daily insulin management;
- Extreme obesity, as defined by NIH Clinical Guidelines Body Mass Index;
- Pregnancy;
- Axial neck pain as the solitary symptom;

- Previous cervical spine surgery;
- A medical condition that may interfere with the postoperative management program, such as advanced emphysema, or Alzheimer's disease;
- A medical condition that may result in patient death prior to study completion;
 - Unstable cardiac disease
 - Active malignancy
- Current or recent history of substance abuse (alcoholism and/or narcotic addiction) requiring intervention;
- Signs of being geographically unstable, such as recent or pending divorce, or high level of job dissatisfaction.

Patients with the following radiographic features at the symptomatic level were excluded from the study. These features at adjacent levels did not disqualify the patient from the study.

- Significant cervical anatomical deformity; e.g., ankylosing spondylitis, rheumatoid arthritis, etc.
- Moderate to advanced spondylosis. Patients who demonstrate advanced degenerative changes. Such advanced changes are characterized by any one or combination of the following:
 - Bridging osteophytes
 - Marked reduction or absence of motion
 - Collapse of the intervertebral disc space of greater than 50% of its normal height
- Radiographic signs of subluxation greater than 3.5 mm
- Angulation of the disc space more than 11 degrees greater than adjacent segments; and
- Significant kyphotic deformity or significant reversal of lordosis.

The recommended post-operative care included avoidance of heavy physical activity and limitations on extended automobile rides, working, lifting, bending and twisting. The recommended post-operative regimen also included avoidance of physically demanding sports or recreational activities for 3 months post-operatively. The decision whether to use a post-operative orthosis was left to the discretion of the investigator. Investigational patients were instructed to use NSAIDs for the first two weeks postoperatively.

2. Follow-up Schedule

All patients were evaluated preoperatively (within 2 months of surgery), intraoperatively, and postoperatively at 6 weeks, 3, 6, 12, and 24 months, and biennially thereafter until the last subject enrolled in the study had been seen for their 24-month evaluation. Complications and adverse events, device-related or not, were evaluated over the course of the clinical trial. 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.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

Clinical outcome parameters assessed at each time point were pain/disability, neck and arm pain, general health, neurological status, patient global perceived effect, and doctor's perception of results. Additional measures included gait, patient satisfaction, and work status. The radiographic outcome parameters consisted of functional spinal unit height as well as evaluations of motion and fusion at the treated level for the investigational and control group, respectively. Implant position and adjacent level motion were also evaluated.

Primary Assessments:

- Pain/disability status was measured using the Neck Disability Index Questionnaire. Success was defined as a 15-point improvement in the NDI score from the preoperative 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 baseline score for each parameter. Overall neurological status success required that each individual parameter be a success for that subject to be counted as a success.

Secondary Assessments:

Clinical outcome parameters included:

- Neck/Arm Pain: Numerical rating scales were used to specifically evaluate pain intensity and duration in both the neck and arm. The scales for each parameter ranged from 0 to 10, with a lower score representing a better condition. A composite pain score was derived by summing the numeral rating scores from the intensity and duration scales. Neck pain success was determined by comparing the postoperative composite neck pain score to the preoperative score on a patient basis.
- SF-36: The Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) was used to assess general health status of all study patients. The 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.

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. Implant position and adjacent

level motion were also evaluated. For all radiographic evaluations, if the two primary radiographic reviewers yielded conflicting success outcomes for a patient, a third reviewer was used for adjudication.

- The FSU height was determined from lateral neutral radiographs of the treated spinal area and was expressed in millimeters. The anterior FSU height was obtained by measuring from the anterior-most point of the endplate on the superior ventral cortical margin of the cephalic vertebral body to the anterior-most point on the inferior ventral cortical margin of the caudal vertebral body of the treated segment. The posterior FSU height was determined similarly from the posterior aspect. By comparing the magnification-corrected measurements over time, one could determine if the FSU height had changed. FSU height was considered to be maintained or improved, i.e., considered success, if either the anterior or posterior postoperative measurement was no more than 2 mm less than the 3-month postoperative measurement.
- Subsidence was assessed by measuring the distance, in millimeters, through the vertebral midline from the apex of the superior metallic shell to the outermost margin of the cortical endplate of the superior vertebra. The same measurement was then repeated from the inferior metallic shell to the cortical endplate of the vertebra caudad to the target disc space. A successful outcome was defined as no more than a 2-mm decrease from the 3-month measurement. Overall subsidence success required successful outcomes for both the superior and inferior observations.
- Further, FSU and subsidence information was combined at each timepoint beginning at the 6-month evaluation. FSU/subsidence success was based on a patient not having a surgical intervention related to a failure finding for either FSU or subsidence.
- Radiographic success for control patients was evaluated by the presence of fusion of the treated spinal segment. To be considered fused, radiographic evidence of bone spanning the two vertebral bodies in the treated segment must be present. Additional criteria for fusion included flexion/extension angular motion stability ($\leq 4^\circ$) and no radiolucent lines covering more than 50% of the graft surface. Fusion observations were performed by two radiographic reviewers.
- In order to determine the effect, if any, of the study treatment on adjacent levels, the stability of the cervical segments above and below the treated level was assessed. Motion at these levels was measured on flexion/extension films preoperatively and postoperatively beginning at 3 months through the timepoints in the study.

3. Clinical Endpoints and Overall Success Criteria

The IDE study was designed to demonstrate non-inferiority of the investigational device compared to standard anterior cervical fusion. The primary endpoint for the clinical investigation was a composite variable termed “overall success.”

Investigational treatment success was based on the 24-month overall success rate being statistically non-inferior to the control group rate. The primary composite endpoint (“overall success”) included:

1. An improvement 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; and
4. No additional surgical procedure classified as “Failure.”

The proportions of patients meeting all 4 of these endpoints for the investigational and control groups were calculated. The non-inferiority hypothesis is that the overall success rate for the investigational device is not more than 10% worse than the overall success rate for the control

B. Accountability of PMA Cohort

At the time of database lock, 463 subjects were enrolled in the PMA study (242 investigational, 221 control). Follow-up at the 24 month interim analysis was 95.2% for the investigational group and 85.4% for the control group. The 24 month cohort consisted of 300 subjects (160 investigational and 140 control) with complete Overall Success Outcomes.

Table 9. Patient Accountability

	6 Months		12 Months		24 Months	
	BRYAN	Contr	BRYAN	Contr	BRYAN	Contr
Enrolled Patients	242	221	242	221	242	221
Theoretical Follow-up	242	221	242	221	168	165
Deaths (Cumulative)	-	-	-	-	-	1(1)
Deaths not Due	-	-	-	-	-	0
Expected	242	221	242	221	168	164
Number of Patients who had Overall Success Outcomes	227	196	235	196	160	140
Percent of Patients who had	93.8%	88.7%	97.1%	88.7%	95.2%	85.4%

Overall Success Outcomes						
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C. Study Population Demographics and Baseline Parameters

Table 10 contains the patient demographic information obtained prior to surgery. Treatment group comparisons were made using ANOVA for continuous variables and using Fisher’s exact test for categorical variables. There were no statistically significant differences between the two groups.

Table 10. Study Patient Demographics and Baseline Characteristics

Variables	Investigational (N=242)	Control (N=221)	p-value
Age (years)	44.4 ± 7.9	44.7 ± 8.6	0.723
Height (inches)	67.6 ± 3.8	67.6 ± 3.8	0.991
Weight (lbs.)	173.3 ± 37.7	180.0 ± 38.9	0.061
BMI	26.6 ± 4.8	27.6 ± 5.0	0.027
Sex (% male)	45.5%	51.1%	0.228
Race			
Caucasian	231	204	0.527
Black	3	5	
Asian	1	2	
Hispanic	3	7	
Other	4	3	
Marital Status			
Single	29	29	0.437
Married	184	169	
Divorced	19	20	
Separated	6	1	
Widowed	4	2	
Education Level			
< High School	16	15	0.743
High School	63	65	
> High School	161	141	
Worker’s Compensation	6.2%	5.0%	0.687
Unresolved Spinal Litigation	2.5%	2.7%	1.000
Current Tobacco Use	25.5%	24.0%	0.746
Current Alcohol Use	8.4%	4.1%	0.083
Preoperative Work Status	64.5%	65.0%	0.923
Preoperative NDI Score	51.4 ± 15.3	50.2 ± 15.9	0.392
Duration of Symptoms			
< 6 wks.	10	13	0.180
6 wks. – 3 mos.	36	52	
3 – 6 mos	47	39	
6 mos – 1 yr.	52	37	
1 – 2 yrs.	38	28	
> 2 yrs.	59	52	

In addition to the study patients described above, 117 patients were randomized but declined participation in the study prior to receiving the assigned treatment. Of these patients, 37 would have received the BRYAN disc treatment, while 80 were potential

control patients. The demographic and preoperative characteristics of the patients who declined to participate were comparable to the study patients.

There were 12 patients in this study who were randomized to the investigational treatment but received the control treatment, and one patient who was randomized to the control treatment but received the investigational treatment. Most of these were intraoperative conversions due to sizing issues or difficulty visualizing the target disc space.

Table 11 summarizes the surgical and hospitalization information.

Table 11. Surgical Information

	Investigational	Control	Probability that the surgical measurements of the investigational group are less than that of the control group (%)
Mean operative time (hrs)	2.2 (n=241)	1.4 (n=221)	0.0
Mean EBL (ml)	91.5 (n=240)	59.6 (n=221)	0.0
Hospitalization (days)	1.1 (n=242)	1.0 (n=221)	4.7
Spinal level treated			
C ₃₄ (%)	3 (1.2)	0 (0.0)	N/A
C ₄₅ (%)	12 (5.0)	17 (7.7)	N/A
C ₅₆ (%)	140 (57.9)	110 (49.8)	N/A
C ₆₇ (%)	87 (36.0)	94 (42.5)	N/A
BRYAN® Cervical Disc Size Used			
14mm (%)	55 (22.7)	N/A	N/A
15mm (%)	66 (27.3)	N/A	N/A
16mm (%)	57 (23.6)	N/A	N/A
17mm (%)	36 (14.8)	N/A	N/A
18mm (%)	28 (11.6)	N/A	N/A

Only 3 investigational patients and zero control patients were implanted at C3-C4. However the Panel determined this level is similar enough to adjacent levels to allow inclusion of C3-4 in the indications.

It should be noted that while the operative time for the investigational group was longer than in the control group, there was a learning curve effect in that subsequent surgeries by the same investigator took less time than the original surgery. The mean implant time for the first five investigational procedures for each investigator was 2.4 hours. The subsequent cases had a mean operative time of 1.9 hours. This difference was statistically significant ($p < 0.001$). The operative time in the control groups also decreased significant after the first five cases from 1.5 to 1.3 hours ($p = 0.003$).

In addition to this analysis, the sponsor has provided an analysis of adverse event

rates associated with operative time. In particular, the rate of wound infections was not increased with increased operative time.

Table 12 below summarizes the baseline values of the clinical effectiveness endpoints. Treatment comparisons for each endpoint were made using ANOVA. No statistically significant differences between the treatment groups were found, except for the mental component summary (MCS) of the SF-36 questionnaire (p-value = 0.041). The investigational mean score was 2.3 points lower than the control mean score.

Table 12. Baseline evaluations for clinical effectiveness endpoints, by treatment group

Variable	Investigational (n = 242)	Control (n = 221)	p-value
NDI Pain Score Mean +/- stdev (min, max)	51.4 +/- 15.3 (12.0, 90.0)	50.2 +/- 15.9 (4.0, 90.0)	0.392
SF-36 PCS Mean +/- stdev (min, max)	32.6 +/- 6.7 (16.9, 51.7)	31.8 +/- 7.2* (15.4, 55.8)	0.208
SF-36 MCS Mean +/- stdev (min, max)	42.3 +/- 12.5 (16.8, 72.8)	44.6 +/- 11.6* (16.7, 72.5)	0.041
Neck Pain Score Mean +/- stdev (min, max)	75.4 +/- 19.9** (0.0, 100.0)	74.8 +/- 23.0 (0.0, 100.0)	0.765
Arm Pain Score Mean +/- stdev (min, max)	71.2 +/- 19.5 (0.0, 100.0)	71.2 +/- 25.1 (0.0, 100.0)	0.976

* Based on n = 220 ** Based on n = 241

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the 242 BRYAN® cervical disc patients and 221 control patients enrolled in the multi-center clinical study of the BRYAN® cervical disc. Adverse events are reported in Tables 13, 13b, and 14, below.

Adverse effects that occurred in the PMA clinical study:

A multi-center, prospective, randomized, non-inferiority clinical trial of the BRYAN® Cervical Disc was conducted in the United States comparing the anterior spinal use of the BRYAN® device to anterior cervical discectomy and fusion (ACDF) using allograft and plating stabilization, the control, for reconstruction of the disc from C3-C7 following single-level discectomy for intractable radiculopathy and/or myelopathy. The adverse effects, as shown in Table 13 below, were reported from the 242 BRYAN® disc patients and 221 control patients enrolled in the multi-center clinical study. 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. The rate of investigational patients having at least one of any type of adverse event was 83.5% (202/242) and the rate of control group patients having at least one of any type of adverse event was 78.7% (174/221). These rates were not statistically different. Patients experiencing adverse events in more than one category are represented in each category in which they experienced an adverse event. At the time Tables 13 and 13b below were compiled, all patients had reached the 12-month follow-up visit, and 207 investigational and 175 control patients had 24-month follow-up information. As shown in Table 13b, a minority of the adverse events were deemed related to the study treatment. Relationship determinations were approved by a physician reviewer.

The following tables summarize the adverse events recorded for the investigational device group and control group:

Table 13. Adverse Events in US IDE Study¹

Complication	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	
	Inves.	Control	Inves.	Control	Inves.	Control	Inves.	Control	Inves.	Control	Inves.	Control	Inves.	Control	Investig. # Patients (% of 242) Total # Events	Control # Patients (% of 221) Total # Events
Anatomical/Technical Difficulty	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0 (0.0) 0	1 (0.5) 1
Cancer	0	0	0	0	1	0	0	0	1	0	0	0	0	0	2 (0.8) 2	0 (0.0) 0
Cardiovascular	0	0	1	0	0	0	1	1	0	0	0	1	2	0	4 (1.7) 4	2 (0.9) 2
Carpal Tunnel Syndrome	0	0	0	1	3	0	2	1	3	1	2	1	2	0	12 (5.0) 12	4 (1.8) 4
Death	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0 (0.0) 0	1 (0.5) 1
Dysphagia/Dysphonia	10	1	15	15	3	3	0	1	0	0	0	0	0	0	26 (10.7) 28	19 (8.6) 20
Dysphagia	9	1	5	12	1	2	0	1	0	0	0	0	0	0	15 (6.2) 15	16 (7.2) 16
Dysphonia	1	0	10	3	2	1	0	0	0	0	0	0	0	0	13 (5.4) 13	4 (1.8) 4
Gastrointestinal	0	2	2	0	0	1	1	1	4	1	0	1	5	0	9 (3.7) 12	6 (2.7) 6
Infection	0	0	8	2	4	1	1	0	2	1	2	2	1	4	17 (7.0) 18	10 (4.5) 10
Superficial	0	0	5	1	2	0	0	0	0	0	0	0	0	0	7 (2.9) 7	1 (0.5) 1
Deep Wound	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0 (0.0) 0	0 (0.0) 0
Other Non-Wound related	0	0	3	1	2	1	1	0	2	1	2	2	1	4	10 (4.1) 11	9 (4.1) 9
Malpositioned Implant	1	0	0	0	0	0	0	0	1	0	0	0	0	0	2 (0.8) 2	0 (0.0) 0
Neck and/or Arm Pain	1	0	20	14	31	23	23	28	29	20	28	22	8	21	115 (47.5) 140	96 (43.4) 128
Neck Pain	0	0	10	7	13	14	6	17	16	7	12	9	2	8	59 (24.3) 59	60 (27.1) 62
Arm Pain	1	0	8	5	11	4	8	5	11	6	11	9	4	8	54 (22.3) 54	37 (16.7) 37
Neck and Arm Pain	0	0	2	2	7	5	9	6	2	7	5	4	2	5	27 (11.2) 27	29 (13.1) 29
Neurological	0	1	8	5	5	9	16	8	8	10	16	12	7	5	48 (19.8) 60	46 (20.8) 50
Upper Extremity	0	1	5	5	4	9	13	7	7	9	15	10	6	5	50 (20.7) 50	46 (20.8) 46
Lower Extremity	0	0	3	0	1	0	2	1	1	1	0	1	1	0	8 (3.3) 8	3 (1.4) 3
Neurological (both)	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1 (0.4) 1	0 (0.0) 0
Neurological (non-specific)	0	0	0	0	0	0	0	0	0	0	1	1	0	0	1 (0.4) 1	1 (0.5) 1
Non-Union	0	0	0	0	0	0	0	1	0	2	0	1	0	1	0 (0.0) 0	5 (2.3) 5
Other ³	7	6	19	7	11	5	7	5	11	10	15	5	14	9	59 (24.4) 84	39 (17.6) 47
Other Pain ⁴	0	0	7	4	6	7	11	13	10	7	9	8	13	8	49 (20.2) 56	44 (19.9) 47
Pending Non-Union	0	0	0	0	0	1	0	1	0	1	0	1	0	1	0 (0.0) 0	5 (2.3) 5
Respiratory	0	0	3	4	1	0	0	2	0	0	0	0	0	0	4 (1.7) 4	6 (2.7) 6

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 rash, depression, or hypertension. This category also consists of three events related to an investigator's report of lack of motion of the prosthesis.

4 Other Pain consists of non-neck and/or arm pain events such as headache, lower back pain, or leg pain.

Complication	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	
	Inves.	Control	Inves.	Control	Inves.	Control	Inves.	Control	Inves.	Control	Inves.	Control	Inves.	Control	Investig. # Patients (% of 242) Total # Events	Control # Patients (% of 221) Total # Events
Spinal Event ⁵	1	0	1	1	2	4	6	2	1	5	6	7	6	6	4	6
Cervical	1	0	0	1	1	2	2	2	0	2	4	1	3	4	21 (8.7) 23	20 (9.0) 25
Non-Cervical	0	0	1	0	1	2	4	0	1	3	2	6	3	2	11 (4.5) 11	12 (5.4) 12
Trauma	1	0	2	2	2	2	5	4	10	5	14	7	8	7	12 (5.0) 12	13 (5.9) 13
Urogenital	0	0	0	0	0	0	0	1	2	0	4	2	2	0	34 (14.0) 42	22 (10.0) 27
Vascular Intra-Op	0	0	0	0	0	0	0	1	2	0	4	2	2	0	6 (2.5) 8	3 (1.4) 3
Any Adverse Event	2	1	0	2	0	0	0	0	0	0	0	0	0	0	2 (0.8) 2	3 (1.4) 3
															202 (83.5)	174 (78.7)

Table 13b. Adverse Events Classified as Device-Related or Device/Surgical Procedure-Related in US IDE Study¹

Complication	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	
	Invest.	Control	Invest.	Control	Invest.	Control	Invest.	Control	Invest.	Control	Invest.	Control	Invest.	Control	Invest. # Patients (% of 242) Total # Events	Control # Patients (% of 221) Total # Events
Malpositioned Implant	1*	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.4) 1	0 (0.0) 0
Neck and/or Arm Pain	0	0	0	0	1*	1*	1*	0	0	0	0	0	0	0	2 (0.8) 2	1 (0.5) 1
Neck Pain	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0 (0.0) 0	1 (0.5) 1
Neck and Arm Pain	0	0	0	0	1	0	1	0	0	0	0	0	0	0	2 (0.8) 2	0 (0.0) 0
Non-Union	0	0	0	0	0	0	0	1*	0	2*	0	1*	0	1*	0 (0.0) 0	5 (2.3) 5
Other	0	0	0	0	0	0	0	0	1	0	1	0	1	0	3 (1.2) 3	0 (0.0) 0
Pending Non-Union	0	0	0	0	0	1	0	1	0	1	0	1	0	1	0 (0.0) 0	5 (2.3) 5
Spinal Event	0	0	0	0	0	0	0	0	0	0	0	0	0	1*	0 (0.0) 0	1 (0.5) 1
Cervical	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0 (0.0) 0	1 (0.5) 1
Trauma	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															7 (2.9)	12 (5.4)

* denotes WHO Grade 3 or 4 serious adverse events.

¹ Based on 24-month cohort at time of interim analysis as pre-specified in IDE protocol.

⁵ Spinal event consists of events reported as a spinal diagnosis/disorder, e.g., degenerative disc disease, disc herniation, stenosis, scoliosis.

One death occurred in a control group patient. The reported death was due to injuries sustained in a motor vehicle crash approximately 17 months postoperatively and was not considered to be associated with the control group implant or implantation procedure.

A Bayesian analysis was conducted on adverse events using non-informative priors. The results are presented in Table 14.

Table 14. Bayesian Comparison of Adverse Events

Adverse Event	Posterior Adverse Event Rate		There is a 95% probability that adverse event rates will fall within the following range		Probability that the adverse event rate of investigational group is lower than that of the control group (%)
	Inves.	Control	Inves.	Control	
Anatomical/Technical Difficulty	0.000	0.005	0.0% to 1.2%	0.0% to 2.1%	77.3
Cancer	0.008	0.000	0.1% to 2.6%	0.0% to 1.3%	14.2
Cardiovascular	0.017	0.009	0.5% to 3.8%	0.1% to 2.9%	26.4
Carpal Tunnel Syndrome	0.050	0.018	2.7% to 8.2%	0.6% to 4.2%	3.5
Death	0.000	0.005	0.0% to 1.2%	0.0% to 2.1%	77.3
Dysphagia/Dysphonia	0.107	0.086	7.3% to 15.0%	5.4% to 12.8%	22.2
Gastrointestinal	0.037	0.027	1.8% to 6.6%	1.1% to 5.5%	28.3
Infection	0.070	0.045	4.3% to 10.7%	2.2% to 7.8%	13.1
Malpositioned Implant	0.008	0.000	0.1% to 2.6%	0.0% to 1.3%	14.2
Neck and/or Arm Pain	0.475	0.434	41.4% to 53.9%	37.2% to 50.1%	19.0
Neurological	0.198	0.208	15.2% to 25.2%	15.8% to 26.4%	60.4
Non-Union	0.000	0.023	0.0% to 1.2%	0.8% to 4.8%	98.9
Other	0.244	0.176	19.3% to 30.1%	13.1% to 23.0%	3.9
Other Pain	0.202	0.199	15.5% to 25.5%	15.1% to 25.5%	46.6
Pending Non-Union	0.000	0.023	0.0% to 1.2%	0.8% to 4.9%	98.9
Respiratory	0.017	0.027	0.5% to 3.8%	1.1% to 5.4%	77.7
Spinal Event	0.087	0.090	5.5% to 12.6%	5.7% to 13.3%	55.8
Trauma	0.140	0.100	10.0% to 18.8%	6.6% to 14.4%	9.1
Urogenital	0.025	0.022	1.0% to 5.0%	0.3% to 3.5%	20.9
Vascular Intra-Op	0.008	0.014	0.1% to 2.6%	0.3% to 3.6%	69.9
Any adverse Event	0.835	0.787	78.4% to 87.7%	72.9% to 83.6%	9.7

Table 15 summarizes the secondary interventions in the BRYAN® device and control treatment groups that occurred at or before the 24-month post-operative interval. Revisions, removals, and supplemental fixations were considered second surgery failures in the clinical study. Reoperations were not considered second surgery failures in the study. Table 15 also presents the Bayesian statistical comparison of secondary surgeries between the BRYAN® device and control treatment groups.

For these safety comparisons, probabilities exceeding 97.5% are considered statistically significant.

Table 15. Secondary Interventions and Surgical Procedures

	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)		36 Months (≥30 Mos- <40 Months)		Total ≤ 24 Months		Probability that the second surgery rate of investigational group is lower than that of the control group (%)
	Invest.	Control	Invest.	Control	Invest.	Control	Invest.	Control	Invest.	Control	Invest.	Control	Invest.	Control	Invest.	Control	Invest. # Patients (% of 242) Total # Events	Control # Patients (% of 221) Total # Events	
Revisions	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1* (0.4) 1	0 (0.0) 0	27.3
Removals	0	0	0	0	0	0	1	0	1	1	1	0	0	1	0	0	3** (1.2) 3	2*** (0.9) 2	38.6
Reoperations	0	0	0	0	0	0	0	0	0	0	2	1	0	0	0	0	2**** (0.8) 2	1 (0.5) 1	34.6
Supplemental Fixations	0	0	0	0	0	0	0	1	0	1	0	1	0	3	0	1	0 (0.0) 0	5 (2.3%) 6	98.9
Other –Cervical Adjacent Level	0	0	0	0	0	0	2	0	0	0	3	1	1	4	1	0	7 (2.9) 7	4 (1.8) 5	N/A
Other – Cervical Non- Adjacent Level	0	0	0	0	0	0	0	0	0	0	1	1	0	2	0	1	1 (0.4) 1	4 (1.8) 4	N/A

* Revision procedure due to malpositioned implant after wound closure at surgery.
 ** Removals attributed to residual pain (2) and trauma (1).
 *** Removals attributed to non-unions.
 **** Both of the two reoperations occurred within 1 month of the 12-month postoperative timepoint. One of these reoperations was due to stenosis with radiculopathy, and the other resulted from pain and numbness following a motor vehicle accident.

2. Effectiveness Results

Primary analyses:

Study success was expressed as the number of individual subjects categorized as a success divided by the total number of subjects evaluated. The table below describes the success rates and Bayesian predictions for individual outcome parameters and overall success. Observed success rates are the 24-month outcomes of the clinical trial. Posterior means can be interpreted as the chance of success at 24 months. When a patient receives the BRYAN device, the chance of overall success as defined in the clinical study at 24 months is 80.4%. Given the results of the trial, there is a 95% probability that the chance of success ranges from 74.3% to 85.8%. When a patient receives the control treatment, the chance of overall success at 24 months is 71.8%. Given the results of the trial, there is a 95% probability that the chance of success ranges from 65.0% to 78.9%. The conclusions were based on the interim analysis which was pre-defined in the protocol. The Bayesian interim analysis considered all available data for 12 months and data for the first 300 patients at 24 months.

Table 16. Observed Success Rates at 12 and 24 Months and Posterior Probabilities of Success at 24 Months

Primary Outcome Variable	12-Month Observed Success Rate		24-Month Observed Success Rate		24-Month Posterior Mean (95% HPD Credible Interval)		24-Month Posterior Probabilities	
	Inv	Ctrl	Inv	Ctrl	Inv	Ctrl	Non-Inferiority	Superiority
NDI	207/234 (88.5%)	153/197 (77.7%)	134/159 (84.3%)	106/140 (75.7%)	85.0% (79.7%, 89.9%)	76.2% (69.7%, 82.6%)	~100%	98.0%
Neurological	220/234 (94.0%)	184/196 (93.9%)	149/159 (93.7%)	128/140 (91.4%)	92.4% (88.4%, 96.1%)	90.9% (86.4%, 95.3%)	~100%	69.2%
Free from Serious, Related Adverse Event Failure*	238/242 (98.4%)	216/221 (97.7%)	158/160 (98.7%)	133/140 (95.0%)	97.6% (95.5%, 99.4%)	95.2% (92.1%, 98.1%)	~100%	89.8%
Free from 2 nd Intervention Failure*	239/242 (98.8%)	218/221 (98.6%)	158/160 (98.7%)	135/140 (96.5%)	97.9% (95.9%, 99.5%)	96.1% (93.2%, 98.7%)	~100%	85.1%
Overall Success	198/235 (84.3%)	144/196 (73.5%)	129/160 (80.6%)	99/140 (70.7%)	80.4% (74.3%, 85.8%)	71.8% (65.0%, 78.9%)	~100%	96.9%

* The denominators for the rates at 12 months are given as the total number of patients due to the cumulative nature of these events. In this table, the clinical evaluation visit dates were used as the back end of the windows, whereas Tables 14 and 15 utilized wider, continuous time windows. Therefore, the events included in this table may appear to differ from those in Tables 14 and 15.

Non-inferiority of the BRYAN® disc group to the control group was demonstrated for all endpoints listed in Table 15 above.

Statistical superiority of the BRYAN® disc group to the control group was demonstrated for overall success and the NDI variable for the specifically defined population studied in the clinical trial at 24 months postoperatively. The neurological component was not found to be statistically superior in the BRYAN® group.

Additional Analyses:

Per-protocol dataset

The per-protocol dataset is a subset of the primary analysis dataset and was constructed only for overall success and its component variables. Patients with major protocol violations, such as not meeting inclusion/exclusion criteria, receiving the wrong device, etc., were excluded from this dataset. All available 12- and 24-month data contributed to this analysis of the overall success rates at 24 months. The following table shows the observed results (in **bold italics**) that contribute to the likelihood used in the analysis.

Table 17. Data contributing to per-protocol analysis of 24-month overall success rate

	Investigational 24 months				Control 24 months			
	Success	Failure	Not obs	Total	Success	Failure	Not obs	Total
12 months								
Success	<i>105</i>	<i>11</i>	<i>64</i>	180	<i>63</i>	<i>10</i>	<i>45</i>	118
Failure	<i>8</i>	<i>11</i>	<i>9</i>	28	<i>9</i>	<i>15</i>	<i>11</i>	35
Not obs	<i>1</i>	<i>1</i>	<i>5</i>	7	<i>6</i>	<i>1</i>	13	20
Total	114	23	78	215	78	26	69	173

Based on the per-protocol dataset, the posterior mean probability of success p_c in the control group is 75.0% (95% HPD: 67.2%, 82.6%), the posterior mean probability of success p_t in the investigational group is 82.7% (76.7%, 88.3%), and the posterior mean of the difference $p_c - p_t$ is -7.8% (-17.8%, 1.6%). The posterior probability of non-inferiority $P(p_c - p_t < 0.10 \mid \text{Data})$ is greater than 99%, which supports a claim of non-inferiority. The sponsor also calculated the posterior probability of superiority $P(p_c - p_t < 0 \mid \text{Data})$, which is found to be 94.4%. This probability does not reach the superiority threshold of 95%.

Missing-equals-failure dataset

A Bayesian analysis was not performed for the missing-equals-failure dataset. Instead, the sponsor provided the following table showing the cross-classification of overall success outcome by treatment group for the first 333 patients to reach the 24-month evaluation period. Thirty-three (33) of these patients had missing outcomes (8 investigational, 25 control). For this analysis, all missing outcomes are assumed to be failures. Based on this dataset, the observed success rates are 76.8% (129/168) in the investigational group and 60.0% (99/165) in the control group.

Furthermore, we calculated the 95% confidence interval for the difference between the investigational and control success rates. The observed difference is 16.8%, and the 95% CI for the difference is (6.4%, 27.2%). These results favor the investigational device, although it is important to note that these results may be biased against the control since there were more missing observations in the control group.

Table 18. Summary of overall success by treatment group for the missing-equals-failure dataset

Overall Success	Treatment Group		Total
	Investigational	Control	
Success	129	99	228
Failure	39	66	105
Total	168	165	333

Sensitivity analyses

As mentioned above, 333 patients have reached the 24-month evaluation period, but 33 patients have missing outcomes for overall success. These missing values were ignored in the analysis of overall success based on the primary dataset. In order to investigate the impact these missing data might have on the study conclusions, some sensitivity analyses have been performed. The sponsor considered several outcome scenarios. For the 8 missing outcomes in the investigational group, the sponsor made two assumptions: (i) half (i.e., 50%) of the missing outcomes were successes, and (ii) none (i.e., 0%) of the missing outcomes were successes. For each of the assumptions (i) and (ii), the success rate for the 25 missing outcomes in the control group was assumed to be 50%, 60%, 70%, 80%, 90%, and over 99%. The results obtained from four of these scenarios (assumption (i) together with control success rates 50% and over 99%, and assumption (ii) together with control success rates 50% and over 99%) are presented in the table below.

Table 19. Partial summary of the sensitivity analyses for overall success at 24 months

Imputation Scenarios		Success rates		95% CI for $p_i - p_c$	p-value for non-inferiority hypothesis
Investigational (8 missing values)	Control (25 missing values)	Investigational	Control		
50% Success (S = 4, F = 4)	50% Success (S = 13, F = 12)	79.2% (133/168)	67.9% (112/165)	(1.9%, 20.7%)	<0.0001
50% Success (S = 4, F = 4)	100% Success (S = 25, F = 0)	79.2% (133/168)	75.2% (124/165)	(-5.0%, 13.0%)	0.0011
0% Success (S = 0, F = 8)	50% Success (S = 13, F = 12)	76.8% (129/168)	67.9% (112/165)	(-0.7%, 18.5%)	<0.0001
0% Success (S = 0, F = 8)	100% Success (S = 25, F = 0)	76.8% (129/168)	75.2% (124/165)	(-7.5%, 10.8%)	0.0065

The confidence intervals and p-values presented in Table 19 were obtained using conventional frequentist methods. Note that the last row represents a worst-case scenario in which all missing outcomes in the investigational group are assumed to be failures, while all missing outcomes in the control group are assumed to be successes. Even in this worst-case scenario, it appears that a non-inferiority claim is still supported. Superiority is marginally supported by the first and third analyses shown in Table 19.

Radiographic Analyses:

Radiographic endpoints included FSU height/implant subsidence; anteroposterior implant migration; treated level angular motion in flexion, extension, and side bending; translational motion. Fusion measurements replaced motion measurements in control patients

Bayesian analyses comparing the investigational FSU success rate to that for the control group demonstrated a posterior probability of non-inferiority value of over 99%, thereby demonstrating statistical non-inferiority.

For patients receiving the BRYAN® device, the mean angular range of motion values at 12 and 24 months postoperative, respectively, were 7.77° (n=226) and 7.74° (n=154) as compared to a preoperative value of 6.43° (n=214). Based on the interim analysis cohort, the range of motion values measured from flexion/extension radiographs at 24 months for the BRYAN® device patients are presented in Figure 4. This histogram used values obtained by rounding recorded range of motion for each subject to the nearest integer.

Table 20. Motion at the Treated Level

	Investigational group n=154
Angular motion success	79.6%
Right and left bending success	49.7%
Bridging bone	100% (not bridged)
Radiolucency	100% (Not radiolucent)
Radiographic success	79.6%

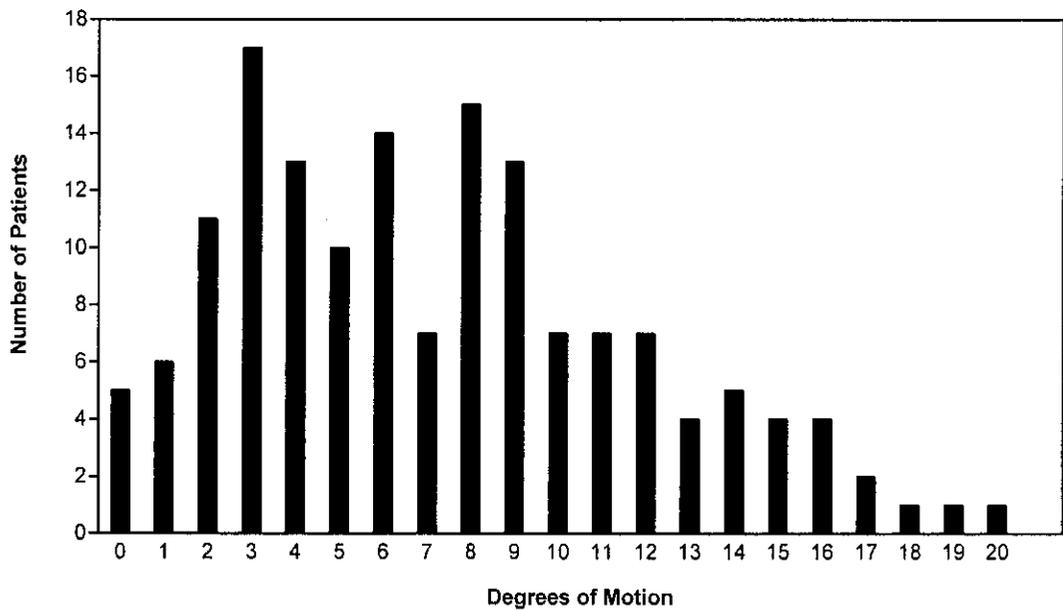


Figure 4. Histogram of BRYAN® Cervical Disc Angular Range of Motion at 24 Months.

An analysis of the correlation between the degree of segmental motion and pain was also performed, and no statistically significant correlations were noted.

Table 21 summarizes the effect of the BRYAN® Cervical Disc on adjacent levels.

Table 21. Angular Motion at Adjacent Levels

	Preoperative		12 Months		24 Months	
	Invest	Contr	Inves.	Contr	Inves	Contr
Above Treated Segment	8.3°	7.8°	9.8°	8.7°	9.1°	8.9°
Below Treated Segment	5.0°	5.2°	6.2°	5.8°	6.4°	6.2°

The Panel recommended that adjacent level motion and maintenance of motion in the treated level be measured in the post-approval study. No claims relating preservation of motion and clinical success will be made.

Secondary Endpoint Analyses:

Table 22 describes the results of the secondary effectiveness endpoints at the interim analysis.

Table 22. Secondary Endpoints

Variable	BRYAN® Disc	Control	Posterior Probability of Non-Inferiority	Posterior Probability of Superiority
Neck pain				
Success	151 (95.6)	130 (92.9)	100.0%	75.1%
Failure	7 (4.4)	10 (7.1)		
Arm pain				
Success	150 (94.3)	125 (89.3)	100.0%	93.8%
Failure	9 (5.7)	15 (10.7)		
SF-36 PCS				
Success	136 (85.5)	125 (90.6)	94.3%	14.1%
Failure	23 (14.5)	13 (9.4)		
SF-36 MCS				
Success	111 (69.8)	100 (72.5)	87.2%	19.0%
Failure	48 (30.2)	38 (27.5)		
Patient Perceived Effect				
Complete recovery	82 (51.9)	63 (45.0)	Not Available*	Not Available
Much improved	64 (40.5)	58 (41.4)		
Doctor Perception				
Excellent			Not Available*	Not Available

Good	109 (68.6) 40 (25.2)	80 (57.6) 44 (31.7)		
Gait				
Success	157 (98.7)	138 (98.6)	Not Available*	Not Available
Failure	2 (1.3)	2 (1.4)		
Work Status				
Median days until return to work	48	61	Not Available*	Not Available

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

The secondary effectiveness results support the conclusion that the BRYAN Cervical Disc is non-inferior to the control.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

A. Panel Meeting Recommendation

At an advisory meeting held on July 17, 2007 the Orthopedic and Rehabilitation Devices Panel recommended that Medtronic Sofamor Danek's PMA for the Bryan® Artificial Cervical Disc be conditionally approved.

For the complete panel transcript visit <http://www.fda.gov/ohrms/dockets/ac/cdrh07.htm#orthopaedic> and choose one of the transcript options.

The following questions were asked of the Panel:

1. The sponsor has provided a combination of engineering testing, biocompatibility testing, functional animal studies, device retrievals and analysis, radiographic follow up and clinical observations to address the degree of constraint, materials of articulation, and other design features of the Bryan Cervical Disc Prosthesis. Please discuss the testing, the data and the clinical observations regarding:
 - device wear
 - material and particulate reaction
 - device expulsion or migration
 - implant durability and reliability and
 - sheath purpose and function
2. The sponsor has presented radiographic data to demonstrate preservation of motion at the index level in the patients receiving the investigational device. Motion at the index level did not correlate with clinical success. Further analysis has demonstrated that the motion, as measured by dynamic radiographs, was not significantly different at adjacent levels for the investigational device and for controls. Please discuss how index level and adjacent level motion contribute to the effectiveness of the investigational device.

3. Please discuss the adequacy of the device labeling. What information related to mean operative time should be included in the labeling? What information related to cervical levels should be included?
4. Under CFR 860.7(d)(1) , safety is defined as reasonable assurance, based on valid scientific evidence, that the probable benefits to health under conditions of the intended use, when accompanied by adequate directions for use and warnings against unsafe use, outweigh any probable risks. Considering the adverse event rates for the subject device, please discuss whether the clinical data in the PMA provide reasonable assurance that the device is safe.
5. Please discuss whether the clinical data in the PMA provide reasonable assurance that the proposed device is effective.

The Panel made a recommendation of Approval subject to the resolution of the following concerns:

- The sponsor should provide additional information in response to concerns regarding kidney effects in the rabbit study and materials characterization of the polyurethane.
- Adjacent level motion, maintenance of motion at the treated level, and heterotopic ossification will be measured in a post approval study
- No claims can be made relating the preservation of motion with clinical success
- No mention can be made of preventing adjacent level disease
- The sponsor should continue to monitor long term safety and effectiveness in a post-approval study and post-market adverse event analysis.
- The sponsor will be limited to claims of non-inferiority and statistical superiority in the specifically defined patient population studied in the clinical trial at 24 months.

B. FDA's Post-Panel Action

All pre-clinical issues were resolved following the Panel meeting and a post-approval study was developed to satisfy the remaining concerns. CDRH concurred with the Panel recommendation of July 17, 2007 that there is a reasonable assurance of safety and effectiveness of the BRYAN® Cervical Disc based on the results of the preclinical testing and the results of the clinical study.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

The adverse effects of the device are based on data collected in a clinical study conducted to support PMA approval as described above (in Tables 13 and 13b) and on supplemental data provided to support the PMA. In summary, the investigational

device was found to be at least as safe as the control treatment. The rate of investigational patients having at least one adverse event was not statistically different from the control group rate. The rates of adverse events that were classified as implant- or implant/surgical procedure-associated, both serious and non-serious, were lower for investigational patients. The investigational group had statistically lower rates of second surgical procedures related to supplemental fixations. These findings resulted in a lower second surgery failure rate for investigational patients. Lastly, the investigational group's neurological success rate was statistically non-inferior to that of the control.

B. Effectiveness Conclusions

The 24-month NDI, neurological and overall success rates for the investigational group were found to be statistically non-inferior to the control group rates. A secondary analysis suggested statistical superiority for NDI and overall success rate. Therefore, the clinical study objective was met, indicating that the BRYAN® Cervical Disc System is as safe and effective as the control for treating cervical disc disease.

C. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

XIII. CDRH DECISION

CDRH issued an approval order on May 12, 2009. The final conditions of approval cited in the approval order are described below.

1. A 10-year post-approval study (PAS) will be performed to evaluate the longer term safety and effectiveness of the BRYAN® Cervical Disc as provided in Amendment 14 dated April 25, 2008. 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 5 years, 7 years and 10 years. At each timepoint, the following data will be collected: Neck Disability Index score; radiographic information; neurological status, heterotopic ossification, disc orientation, and adjacent-level disease as well as other outcomes measured in the IDE study. In addition, data will be collected for explanted devices and 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. This information will be provided in PAS reports submitted every six months for the first two years and then annually through the end of PAS.
2. A 5-year enhanced surveillance study of the BRYAN® Cervical Disc will be performed as provided in Amendment 14 dated April 25, 2008. This study will more fully

characterize adverse events when the device is used in a broader patient population. All adverse events and complaints received by the company for the BRYAN[®] Cervical Disc will be collected, analyzed, and submitted 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.

3. Revised labeling (via a PMA supplement) will be submitted to reflect the results of the PAS and enhanced surveillance study when the studies are completed, as well as at any other timepoint deemed necessary by FDA if significantly new information from this study becomes available.

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

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

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