

FDA Executive Summary
P060023
BRYAN Cervical Disc
from Medtronic Sofamor Danek

July 17, 2007 Panel Meeting

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Introduction

This executive summary provides an overview of the information provided by Medtronic Sofamor Danek in the PMA submission P060023 for the BRYAN Cervical Disc. The summary includes the rationale for bringing the device to panel as well as issues for panel consideration. The indications for use and device description tell you what the device is intended to do and what it is. The engineering test section describes the tests used to characterize the performance and to verify the safety of the device. The animal testing investigates the biocompatibility of the materials, the response to the wear particles and the function of the device. IDE- ----- gathered clinical data on BRYAN Cervical Disc for patients with cervical degenerative disc disease (DDD). The clinical results are reported and the statistical analysis is provided. The manufacturing, sterility, packaging, labeling and post-market study reviews are all summarized. Throughout this executive summary, we have provided references to the PMA submission P060023. All sections of the PMA are available to the panel members upon request.

Rationale for Bringing the BRYAN Cervical Disc to panel

FDA is bringing the BRYAN Cervical Disc to panel for deliberation on the safety and efficacy of this novel cervical disc prosthesis. Novel features of this device design include:

1. Degree or Type of constraint (flat on flat, ball joint, etc.)-- The BRYAN Cervical Disc has a novel joint design. This device is the first disc design to use a post on the shell to fit into a flared hole in the nucleus to limit joint movement providing a unique degree of constraint.
2. Type of articulation (material combination) -- The articulation surfaces for the BRYAN Cervical Disc are polyurethane on titanium. This is the first use of polyurethane moving and potentially wearing against titanium in a joint prosthesis.
3. Fixation to bone-- The BRYAN Cervical Disc sits in a pocket milled into the bone, and has a beaded porous coating intended for biological fixation instead of fixation using screws into the vertebrae or fixation by use of stabilizing keels.
4. Novel encapsulated joint design—The BRYAN Cervical Disc includes a sheath to prevent tissue ingrowth into the articulating surfaces.

Indication for Use

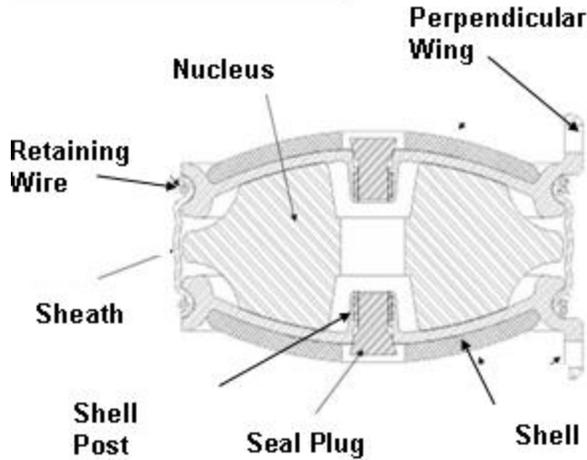
The BRYAN Cervical Disc is indicated in skeletally mature patients with cervical degenerative disc disease (DDD) at one level from C3-C7. DDD is defined as any combination of the following: disc herniation with radiculopathy, spondylotic radiculopathy, disc herniation with myelopathy, or spondylotic myelopathy. The BRYAN® device is to be implanted via an open anterior approach.

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 made up of: two titanium shells, two titanium retaining wires, polyurethane nucleus, polyurethane sheath, and two titanium seal plugs. It is available in 5 diameters – 14mm, 15mm, 16mm, 17mm, and 18mm.

Figure 1. BRYAN Cervical Disc – cross section



The polyurethane nucleus component fits between and moves with respect to the two shells. The titanium alloy (ASTM F136) shells have inward facing shell posts that fit into a 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 for all prosthesis sizes

<u>Flexion/Extension</u>	<u>Lateral Bending</u>	<u>Rotation</u>	<u>Translation</u>
$\pm 10^\circ$	$\pm 11^\circ$	$\pm 7^\circ$	$\pm 1 \text{ mm}$

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 (-----) Beaded coatings are used in orthopedic implants to encourage bone growth into-----sis. 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 (ASTM F136) 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.

Engineering Testing with supporting Animal Study, Cadaver and Human Clinical Data

In considering the safety and efficacy of novel orthopedic device designs, we use a combination of engineering test data, animal study information, cadaver research results and the data from clinical trials. This section of the executive summary provides a brief review of the engineering tests. To describe how the bench top engineering data relates to clinical use of the device, we also include a brief description of the animal, cadaver or clinical results that are relevant to the test issue. Other sections of the executive summary provide a full description of animal testing and of the clinical study. A discussion of the motion and load justification is presented first as these test parameters are considered relevant to multiple tests. This section continues with a brief review of the engineering tests. The engineering tests are grouped by

issues that the testing addresses. The issues include wear, response to wear debris, expulsion, device durability and joint encapsulation.

Motion and Load Justification

Medtronic has provided justifications for the motion and loads in the cervical spine based on literature with testing and modeling.

Range of Motion

The table below shows flexion/extension, lateral bending and axial rotation for C4-C5. The BRYAN Cervical Disc full range of motion is designed to be the same as the maximum motion reported for C4-C5. One of the expulsion tests used the full extension motion. The wear tests were conducted over the neutral zone.

Table 2. Cervical Spine Motion at C4-C5 Level

	<u>Flexion/ Extension</u>	<u>Lateral Bending</u>	<u>Axial Rotation</u>
Reference Representative Angle from White A, Panjabi M Clinical Biomechanics of the Spine	±10°	±11°	±7°
Average Neutral zone from White A, Panjabi M. Clinical Biomechanics of the Spine	±4.9°	±4.0°	±3.8°
ISO F2423-05 Standard Guide for Functional, Kinematic, and Wear Assessment of Disc Prostheses (test profile)	±7.5°		±6 °
Flexion/extension observed motions* C4-C5 Level motion defined with White and Panjabi	±3.58°		
Flexion/extension observed motions* C4-C5 Level motion defined with Medical Metrics	±3.96°		
Flexion/ extension angle from “Active range of motion utilized in the cervical spine to perform daily functional tasks” Bennett, J Spinal Disord Tech 2002	±0.4 to 5.85°		
BRYAN Cervical Disc Designed Range of Motion	±10°	±11°	±7°
BRYAN Cervical Disc Tested Motion for wear testing	±4.9°		±3.8°

*Flexion/extension from global motions: Ariens GAM, et al, Are neck flexion, neck rotation, and sitting at work risk factors for neck pain? Results of a prospective cohort study. Occup Environ Med 2001; 58:200-7

Maximum Compressive Load

The sponsor references “Analysis and Measurement of Neck Loads” from Journal of Orthopedic Research 1988; by Moroney S. P, Schultz A B, and Miller J. A. to determine the maximum physiologic compressive load on the cervical intervertebral disc. Moroney et al. constructed a biomechanical model. 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 test #7, Static testing of the nucleus in axial compression.

Average Compressive Load

To determine the average compressive loads on the cervical intervertebral discs during activities of daily living the sponsor references “A Biomechanical Model for the analysis of the Cervical Spine in Static Postures” from Journal of Biomechanics 1991 by Snijders, CJ, Hoek Van Duke GA and Roosch ER. Using the load profile defined by Snijders, 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, we believe that 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 (Test #2), Friction testing of the shell on bone (Test #3), the effect of frequency on material characteristics (Test #9), Creep testing of the nucleus (Test #11), Wear simulator testing (Test #16), Evaluation of load, lubricant, and frequency effects on durability (Test #19) and Shear testing of the prosthesis in a cadaveric model (Test #20).

Maximum Shear Load

The sponsor references “Analysis and Measurement of Neck Loads” by Moroney to determine the maximum physiologic shear load on the cervical intervertebral disc during activities of daily living. As for the compressive load Moroney calculated forces at the C4-C5 joint and validated the calculations with measurements of muscle myoelectric activity. 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 (Test #1), Shell stability in antepulsion and retropulsion (Test #6) and Shear testing of the prosthesis in a cadaveric model (Test #20).

Tests and Analysis related to Wear

The articulation surfaces on the BRYAN Cervical Disc are polyurethane on titanium. Medtronic has provided a combination of engineering testing, functional animal studies, device retrievals and analysis, and clinical observations to address issues about device wear. The wear tests and analysis are presented in this section. The animal and human responses to the wear particulates are presented in the next section.

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

- Wear simulator testing of the prosthesis (4 Hz, bovine serum wear test) (Test #16, Module 1 pg. 341)
- 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) (Test #19, Module 1 pg. 377)
- Evaluation of BRYAN Cervical Disc Prosthesis Wear Tested at 2 Hz and in the Absence of a Sheath, TR07-207 (A004 pages 93-151)
- The influence of frequency and load level on the mandrel temperature during durability tests (Test #17, Module 1 pg. 365)
- Lifetime durability testing (Test #18, Module 1 pg. 370)
- The effect of frequency on the material characteristics of the nucleus (Test #9, Module 1 pg. 177)

The first three tests were conducted simulating flexion/extension and axial rotation movements simultaneously for 10 million cycles under a constant axial compressive load. Multiple durability assemblies were tested for each axial compressive load and test frequency. Additional durability assemblies were used as load soak controls. The table below shows the test parameters reported in wear tests (#16, #19 and TR07)

Table 3 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

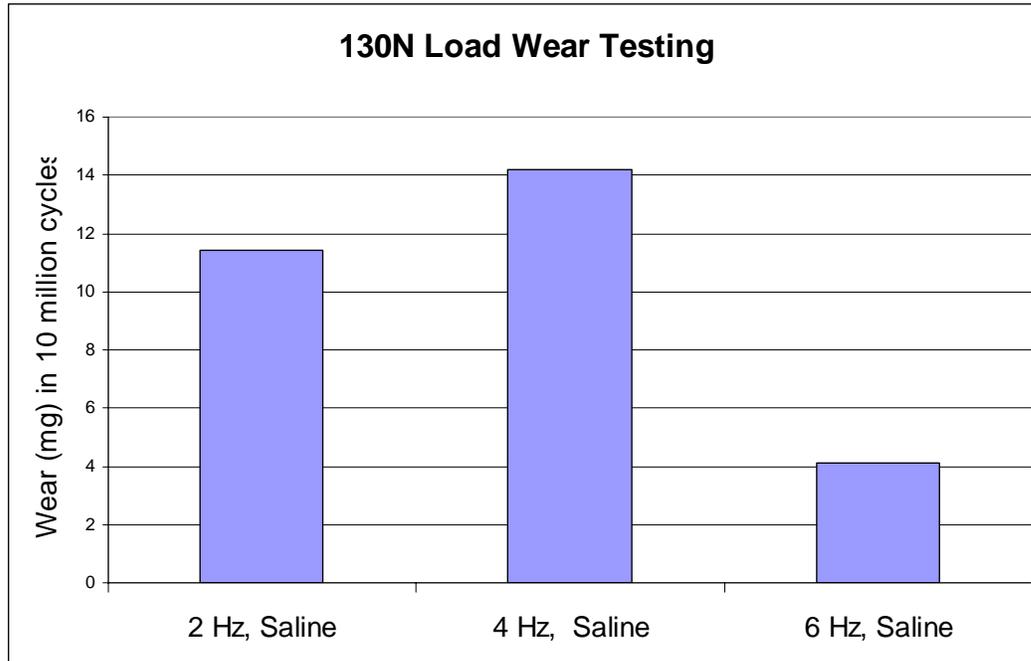
The most physiologically relevant loads and motions are the average compressive load (130 N axial), and 10 million cycle, neutral zone motion (±4.9° flexion/extension and ±3.8° axial rotation) at 2 Hz. The device is axi-symmetric; flexion/extension motion can be used to model lateral bending. The bearing surfaces are spherical; larger motions (short of the soft stop) would not change the surface contact geometry. For the soft stop situation, shell post fatigue was tested separately. ISO and ASTM standards recommend testing in serum¹. Since the moving parts of this device are encapsulated by a polyurethane sheath and the device is

¹ F2423-05 Standard Guide for Functional, Kinematic, and Wear Assessment of Total DISC PROSTHESES

initially saline filled, Medtronic conducted wear testing both in saline and in serum as shown in the table above. Over time the sheath sealing may fail and the saline may be replaced with other fluids.

The wear data is graphed below for the 130 N axial compressive load tests in saline. The 4 Hz test generated the greatest mass of wear particulates. The amount of wear generated in the 4 Hz saline test in 10 million cycles was used for the rabbit particulate response test. The particulate characterization is described in the rabbit particulate response test.

Figure 2 Wear Test Debris Generation



After 10 million cycles, the wear test showed:

- 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)
- Testing in bovine serum yielded comparable results (18 mg of wear debris at 4 Hz) and
- More than 90% of the particles generated were smaller than 1 μm (see particle characterization in figure 3)

Medtronic conducted the fourth test, #17, the influence of frequency and load level on the mandrel (test fixture) temperature during durability test (Module 1 pg. 365), to show that the 2 Hz (or physiologically relevant movement rate) test should not be necessary. The temperature at the mandrel may not correlate to wear generated. At FDA's request for a physiologically relevant wear test, Medtronic conducted the 2 Hz wear test in saline and the results are included above.

The final bench top mechanical test related to wear was #18, 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 number of cycles is equivalent to the number of motions that would be encountered through 295 years of in vivo use.

To support the bench top engineering testing, Medtronic also provided functional animal testing in a goat model. (Goat Test VR-01110-023D, Module 4 vol 5 pg 1355 and response to def #2 A004). In retrospect, the goat may not be an ideal animal model for this device. The anatomy and kinematics of the goat cervical

spine are different from the anatomy and kinematics of the human cervical spine. The center of rotation of the device as implanted in the goat was far from the center of the prosthesis. In addition, the device was implanted so that the BRYAN Cervical Disc was in full extension (the full range of motion in extension is 11°) while the animals were in their neutral position. The goat model may replicate an error in implantation and is a challenging functional animal model.

The wear debris generated in the goat model included both particles (both urethane and titanium) and shards (probably urethane nucleus material). In Goat 006, the tissue around the implant contained 10 to 40 by 150 micron shards as well as particles. In Goat 007, one section of the cephalic spinal cord contained shards. In Goat 008, no particulate material was identified in the sampled tissue. The response to the particulates is discussed in the section below.

To further support the bench top wear testing, Medtronic has provided wear information on human explant analysis for IDE and outside US (OUS) patients (P060023 pg 0879). The information on wear and particulates are shown in the table below.

Table 4. Human Explant Observations

Study	Observations
-----	metallic debris, polymeric debris
-----	polymeric debris
-----	no tissue samples
OUS	no tissue samples
OUS	polymeric debris
OUS	polymeric debris

As shown in the table above, small particles of polymeric debris were found in samples of the surrounding tissue. One explanted device was observed to have some abrasive wear on the anterior aspect of the shells, but this was attributed to the device having been implanted in an anterior closed-shell alignment rather than with the shells parallel. This patient was found to have metallic particles in samples of the surrounding tissue.

During the panel meeting, FDA may ask the panel a question about device wear.

In the BRYAN Cervical Disc the titanium shells move with respect to the polyurethane nucleus. Please consider whether the combination of engineering testing, functional animal studies, device retrievals and analysis, radiographic follow up and clinical observations are sufficient to address issues about device wear.

Tests and Analysis related to Response to Generated Particulates

Urethane is a novel material for use in a cervical disc prosthesis. As shown in the testing above, the urethane nucleus generates wear particles. The sheath does not ensure that the particles will be trapped for the life of the device. This section reviews the animal tests related to biologic response to the wear debris or particulates and then provides the relevant clinical observations. The tests provided to address material reaction are:

- Rabbit Particulate P/N 6470116, Module 4 pg 2220
- Goat Test VR-01110-023D, Module 4 vol 5 pg 1355
- Human Explant Analysis , P060023 pg 0879

To address issues of biological reaction to particulates Medtronic has 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.

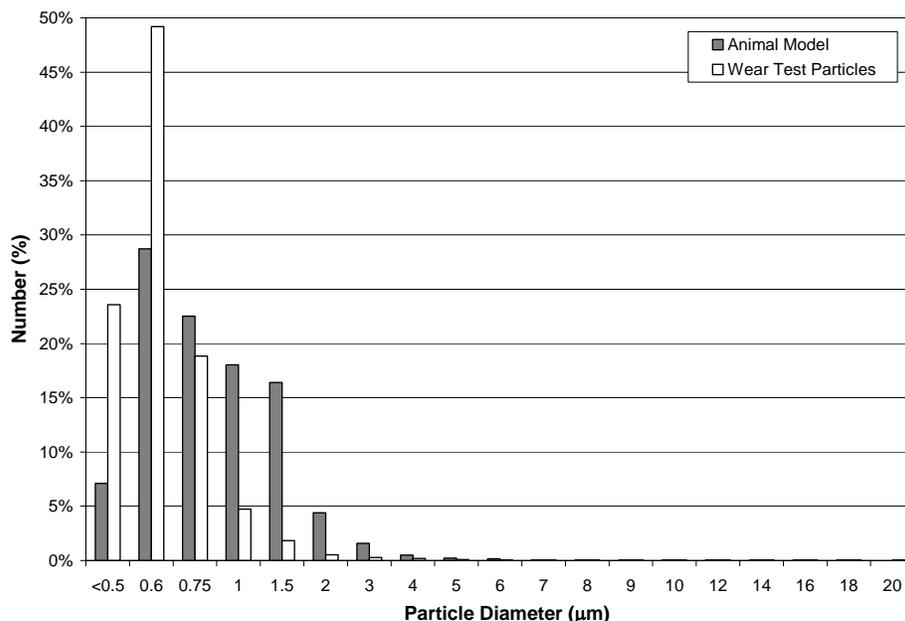
Table 5. Particle Reaction Doses

	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 we scale the rabbit mass 4 kg to an adult male 75 kg, then the high dose urethane injection was scaled to approximate wear generated in the 10^7 cycle wear test.

The particle sizes range from 1 to 200 μm as 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



Particles less than 1 μm are difficult to see with optical microscopes at 400x. Polarized light microscopy increases contrast of polarized particles but does not increase resolution. More than 50% of the particles injected were less than 1 μm . Particles were only observed in the spine tissue of one animal. A few thin (5-10 μm) slices of organs were taken to look for particles but no particles were found in these slides.

Since it was unlikely that particles would be observed through direct observation, Medtronic also looked for indirect evidence of wear debris. Hematology and gross and microscopic histology data was submitted for review. 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 first bullet raises the question of potential kidney reaction to the polyurethane particles. The histologic analysis of the kidneys of the animals sacrificed at 6 months (normal and treatment) show none of these abnormalities. The second and third bullets are examples of errors made while gathering large amounts of data from the animal study. The particulate injection study in the rabbit does not show aggregation of particles in distal organs or significant biological response to wear debris.

In the goat study, Medtronic 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.

To further show biocompatibility of the wear debris, Medtronic has provided histologic observations of the reactions to particles from the human explant analysis which discussed in the wear test section. The histological analyses showed macrophages, foreign body giant cells, and fibrous tissues surrounding the metallic and polymeric debris. Osteoclastic resorption, osteolysis and evidence of infection were not observed in peri-prosthetic tissues. The tissue responses were consistent with those typically seen in proximity to metallic and polymeric implants. There were no adverse reactions to the implant materials reported in the clinical study.

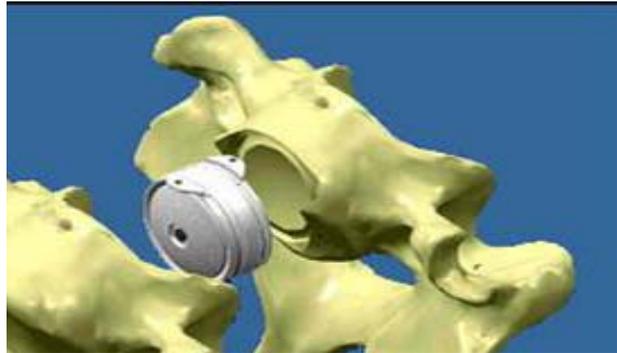
During the panel meeting, FDA may ask the panel a question about the biocompatibility of the materials and of the wear debris.

Urethane is a novel material for use in a cervical disc prosthesis. Please reflect on whether the biocompatibility testing, the particulate injection studies in rabbits, the human tissue analysis and clinical observations are sufficient to address material reaction issues?

Tests and Analysis related to Migration or Expulsion

The BRYAN Cervical Disc sits in a pocket milled into the vertebral endplate and is not screwed to the vertebra and not secured by teeth in the shell fixing into the bone. The drawing below shows the milled pocket and device with anterior flanges.

Figure 4. Milled Pocket and BRYAN Cervical Disc



To address fixation issues, Medtronic conducted the following tests:

- Shell stability in antepulsion and retropulsion (Test #6, Module 1 pg. 148)
- Friction testing of shell on bone and shell on nucleus in axial rotation (Test #3, Module 1 pg. 119)
- Shear testing of the prosthesis in a cadaveric model (Test # 20, Module 1 pg. 385)
- BRYAN Cervical Disc Stability in Antepulsion using a Minimally loaded and extended cervical spine model (A001 pg 309)
- Mechanical testing of the shell surface coating (Test #4, Module 1 pg. 135)
- Microstructural analysis of the shell surface coating (Test #5, Module 1 pg. 141)

To describe how the bench top engineering expulsion data and cadaver testing relates to clinical use of the device, we also include a brief description clinical results that are relevant to the expulsion.

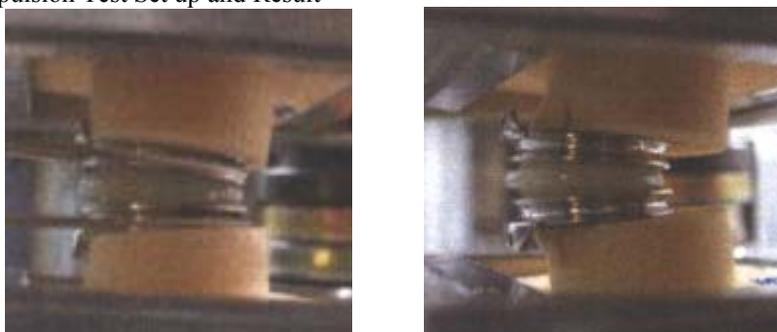
The tests assessed the ability of the BRYAN Cervical Disc to resist expulsion, to articulate on the nucleus shell interface instead of the shell bone interface and to resist shear forces. Expulsion testing was conducted at low loads and high loads with a neutral orientation and at a low load with maximum cervical extension. The expulsion force data are shown in the table below:

Table 6. Expulsion Test Parameters and Failure Forces

	<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>
Axial Compressive Load -> Antepulsion Retropulsion			
Test Parameter- Compressive Load	40N	130N	50 N
Test Parameter- Extension Angle	0°	0°	11°
Antepulsion (N)	120	270	113
Retropulsion (N)	309	429	

At FDA’s request the sponsor performed worst case testing, with the lowest compressive load and maximum cervical extension. The photograph below shows the expulsion test setup for the 11° extension angle. Note that the vertebral body mock ups cracked before the device expelled from the milled pocket. The device did not move out of the pocket with 113 N of force applied. Expulsing the disc from the milled spherical cavity takes significant force even with no bone ingrowth into the sintered porous coating on the shell.

Figure 5. 11° Expulsion Test Set up and Result



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 Cervical Disc resists shear forces.

The shell surface coating is a porous beaded titanium coating. As discussed in FDA Guidance Document For Testing Orthopedic Implants With Modified Metallic Surfaces Adjoining Bone or Bone Cement², surface treatment of orthopedic devices is an attempt to improve implant fixation. Published literature³ indicates that porous coatings may increase the shear strength of the device/bone interface in animal models. No bone ingrowth testing of this porous coating in the spine was provided.

During the clinical study, no patients were reoperated on due to device migrations or expulsions. Radiographic evaluations showed no anterior or posterior migration of the device greater 3.5 mm. As described below radiographic reviewers made unconfirmed observations of implant movement or separation but these observations were not confirmed and did not result in clinical failures.

One patient was noted by a single radiographic reviewer to have a migrated implant at the 3-month evaluation; this observation was not confirmed by other reviewers. The patient did not have an additional surgical procedure, and was an overall success at 24 months. A single reviewer noted that another patient may have had separated implant components at the 3- and 6-month evaluations. This patient had an adjacent-level fusion at the 12-month time period. During the fusion surgery, the surgeon did not report a BRYAN device failure. There was no second surgical procedure at the treated level in this patient, and this

² <http://www.fda.gov/cdrh/ode/827.html>

³ Melican, M., Zimmerman, M., Dhillon, M., Ponnambalam, A., Curodeau, A., Parsons, R., Three-dimensional printing and porous metallic surfaces: A new orthopedic application, Journal of Biomedical Materials Research, VL: 55, NO: 2, pg 194-202, 2001

patient was an overall success at 24 months.

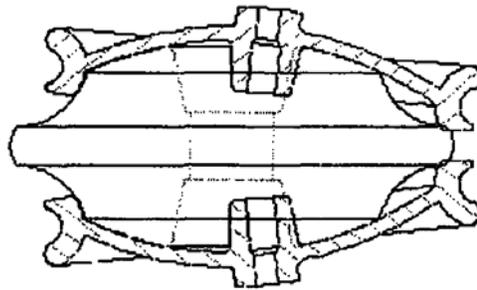
There was one reported revision procedure in the investigational group. The revision of the investigational patient was described as being due to an incorrectly implanted device. The device was implanted in an anterior closed-shell alignment rather than with the shells parallel. This was a surgical error and not a device migration. This patient was revised by repositioning the implant without additional complications related to the implant.

During the panel meeting, FDA may ask the panel a question about device fixation, expulsion or migration. The BRYAN Cervical Disc is set in a milled spherical pocket in the vertebrae above and below the affected disc space. The shell porous coating may encourage bone ingrowth. Flanges extend up and down to prevent posterior motion. Please consider whether the engineering testing, radiographic evaluations and clinical observations are adequate to address issues of device expulsion or migration.

Tests and Analysis related to Device Design

The BRYAN Cervical Disc design includes a new type of constraint (spherical bearing with the shell post in the nucleus hole) and a new material (polyurethane) used as the nucleus. The figure below shows the device at the extreme range of motion with the post contacting the nucleus. The issues with this new design include shell fracture and bending as well as nucleus compression and failure. Medtronic has addressed these issues through a series of shell tests, nucleus tests, functional animal testing and clinical observations which are described below.

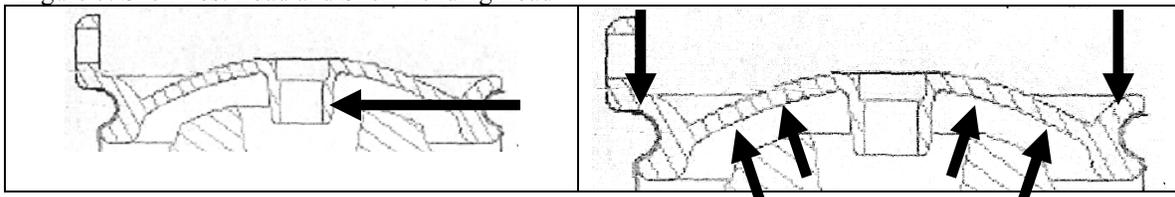
Figure 6. Device Motion with New Constraint Design



The BRYAN cervical disc has a novel shell post in a flared hole in the nucleus design which is intended to limit the motion. To address issues about the new joint geometry, Medtronic has provided the following test reports:

- Static and fatigue testing of the shell post (Test #1, Module 1 pg. 100)
- Static and fatigue testing of the shell in bending (Test #2, Module 1 pg. 109)

Figure 7. Shell Post Load and Shell Bending Load



The figures above show the loading for the shell post and shell bending tests. 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 (Test #7, Module 1 pg. 160)
- Fatigue testing of the nucleus in axial compression (Test #8, Module 1 pg. 169)
- Creep testing of the nucleus (Test #11, Module 1 pg. 185)

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 mechanical testing of the nucleus showed that the component performed adequately.

The adequate performance of the titanium shell and the polyurethane nucleus in the engineering testing is further supported by clinical observations. In the clinical study, one investigational patient was noted by a single reviewer to have a bent, fractured shell, as well as separated implant components at the surgery/discharge timepoint but this was not seen by reader 2, and was not adjudicated as a device failure. This patient did not have an additional surgical procedure, and was an overall success at 24 months.

During the clinical study two BRYAN Cervical Discs were removed due to residual pain and a third was removed subsequent to trauma. After the investigational removal procedures, the devices were in good condition. There were no observations of bent or cracked shells. The explanted polyurethane nuclei were not crushed, permanently compressed or fractured.

During the panel meeting, FDA may ask the panel a question about design validation.

The design of the BRYAN Cervical Disc includes a spherical bearing surface and also a post integrated in the shell which extends into the polyurethane nucleus. The sponsor has provided engineering testing of the shell and nucleus, radiographic evaluations, retrieved devices and clinical observations on implant durability.

Tests to address joint encapsulation

The BRYAN™ Cervical Disc includes a new design feature, a sheath which covers nucleus and attaches to shell.

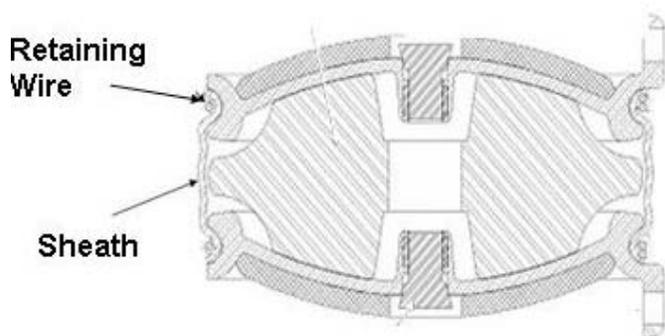
- Tensile testing (Test #13, Module 1 pg. 198)
- Torsion testing (Test #14, Module 1 pg. 204)
- Seal Plug Pressurization testing (Test #15, Module 1 pg. 210)

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. The sheath was not designed to contain wear particles.

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

Figure 8. BRYAN™ Cervical Disc with Sheath and Retaining Wire



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

During the panel meeting, FDA may ask the panel a question about the polyurethane sheath testing. The BRYAN Cervical Disc includes a polyurethane sheath which provides some joint encapsulation. Are there additional issues to consider in the sheath testing?

Biocompatibility

To address issues about biocompatibility of the implant the sponsor defined the materials used, provided a materials characterization (Module 1 pg. 394), and tested to the recognized biocompatibility standard, ISO 10993 (Module 2).

The materials used in the BRYAN Cervical Disc are:

Bionate –S (99% polycarbonate-urethane, 1% silicone)- nucleus

BioSpan-S polyether segment polyurethane (94% polyurethaneurea, 6% silicone) – sheath

Titanium alloy (Ti-6Al-4V) with beaded, vacuum sintered porous coating of pure titanium – shell

Titanium (commercially pure) – retaining wire

The biocompatibility tests are 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) Particulate Injection Study (Rabbit)	Raised particulate questions Resolved particulate questions

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

Clinical Study

The clinical study section includes the study design, patient description and the study results with the statistical analysis. The clinical study safety results are followed by the primary endpoint efficacy results and the secondary endpoint results.

Study Design

The sponsor conducted a prospective, randomized multicenter, controlled clinical trial comparing the outcomes for patients with cervical degenerative disc disease treated with the BRYAN Cervical Disc to those receiving a standard anterior surgical fusion using bone graft and plate stabilization. A total of 463 patients participated, with 242 receiving the BRYAN (investigational) device and 221 having the control fusion treatment. Clinical study surgeries were performed during a period from May 28, 2002, to October 8, 2004. The results and conclusions in the PMA are based upon a pre-specified interim analysis of 300 patients with 2 year follow-up as pre-defined in the protocol.

The study design is defined by the study type, sample size, endpoints, statistical analysis plan and control. This section also includes the patient population definition with the inclusion and exclusion criteria. Post operative care and follow up are specified.

Endpoints

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 secondary endpoints included

Operative time	AP Implant Migration
Blood Loss	Change in Angular Motion
Hospital Stay	Translation
Treatment levels	Summary of Radiographic Success
External Orthosis	Bending at Target level
Overall Neuro Status	Fusion Status
NDI Score	Angular Motion at Adjacent levels – above
Neck Pain Score	Angular Motion at Adjacent levels – below
Arm Pain Score	Gait
SF-36 Health Survey	Patient Satisfaction
FSU Height/Implant Subsidence	

Note that functional spinal unit (FSU) height is not part of the primary endpoint. It is not clear how maintaining FSU height correlates to successful treatment of cervical degenerative disc disease.

The investigational device may restore, or provide, motion at the affected level; in contrast to the standard of care which traditionally causes loss of motion due to fusion of the vertebral bodies. The study included radiographic measurements of mean angular motion at the treated level or adjacent levels. Again the relationship between motion and successful treatment of cervical degenerative disc disease is unclear.

Control Group and ACDF procedure

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. 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.

Statistical Analysis Plan

Bayesian statistical methods were planned (p. 229-243, Vol 1) to determine whether the investigational device is non-inferior to the control with respect to the overall success rate at 24 months. A fixed non-inferiority margin of 10% was agreed upon by FDA and the sponsor. The non-inferiority hypothesis is that

the overall success rate p_t for the investigational device is not more than 10% worse than the overall success rate p_c for the control, i.e., $p_t > p_c - 0.10$. In other words, the success rate for the investigational device is allowed to be a little lower than the success rate for the control, but not by more than 10%. Non-inferiority can be claimed if the posterior probability of non-inferiority, $P(p_t > p_c - 0.10 \mid \text{Data})$, is greater than 95%. The 95% Highest Posterior Density (HPD) interval is also provided for each posterior distribution of interest (in particular, for each success rate p_t and p_c , and for the difference $p_t - p_c$ in success rates between the two groups).

If non-inferiority is claimed, then the posterior probability of superiority, $P(p_t > p_c \mid \text{Data})$, 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 pre-specified interim analysis when 300 patients have sufficient data to evaluate 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 the 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. Details of the analysis method can be found on pp. 236-239 (Attachment A, Vol 1) and in Lipscomb, Ma, & Berry (Clinical Trials, 2005).

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).

Inclusion Criteria

The population studied was those with degenerative disc disease (DDD) at a single level between C3 and C7 with any combination of disc herniation with radiculopathy, spondylotic radiculopathy, disc herniation with myelopathy, or spondylotic myelopathy. The study inclusion criteria were:

- At least 6 weeks unsuccessful conservative treatment, except in cases of myelopathy requiring immediate treatment (e.g., acute onset of clinically significant signs);
- Requirement for surgical treatment demonstrated by CT, myelography and CT, and/or MRI;
- Skeletally mature (≥ 21 years of age);
- Preoperative Neck Disability Index score of ≥ 30 and at least one clinical sign associated with level to be treated;
- Willing to sign informed consent and comply with protocol.

Exclusion Criteria

Patients were excluded from the study if they had any of the following at the involved level:

- Significant cervical anatomical deformity; e.g., ankylosing spondylitis, rheumatoid arthritis, etc.
- Moderate to advanced spondylosis.

Patients were also excluded who demonstrated advanced degenerative changes 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;
- Significant kyphotic deformity or significant reversal of lordosis;

Other exclusion criteria included:

- Axial neck pain as the solitary symptom;

- Previous cervical spine surgery;
- Metabolic bone disease, such as osteoporosis, defined as a BMD T-score equal to or worse than -2.5. If significant radiolucence is detected, a BMD scan in the spine, wrist, and femoral neck must be obtained.
- Active systemic infection or infection at the operative site;
- Known allergy or 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;
- 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;
- Pregnant;
- Current or recent alcohol and/or drug abuser requiring intervention;
- Signs of being geographically unstable, such as recent or pending divorce, or high level of job dissatisfaction;

Postoperative Care

The recommended postoperative care for the first two weeks postoperative included avoidance of heavy physical activity as well as limiting extended automobile rides, lifting, bending, and twisting. The recommended postoperative regimen also included avoidance of physically demanding sports or recreational activities for up to 3 months postoperatively. The use of post-operative orthoses was left to the individual investigators in this study.

Clinical Follow-up

Patients were evaluated preoperatively (within 2 months of surgery), intraoperatively, and postoperatively at 6 weeks, 3, 6, 12, and 24 months. Patients were followed biennially thereafter until the last subject enrolled in the study has been seen for his/her 24-month evaluation. At each evaluation timepoint, clinical and/or radiographic outcome parameters were evaluated. Success was determined from data collected during the initial 24 months of follow-up.

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.

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.

The sponsor used their own pre-specified algorithm to transform the scores for each parameter into an overall classification representing a maintenance or improvement in neurological status at a given postoperative time as compared to their preoperative neurological status. The values were totaled for each neurological subsection, i.e., motor, sensory, and reflexes, and then expressed as a percent of the maximum possible score for that subsection. After determining the percentage scores, the postoperative subsection scores were then compared to the preoperative scores and a successful outcome was declared if the postoperative score was greater than or equal to the preoperative score, i.e. maintenance or improvement in condition. Overall neurological success was based on demonstrating maintenance or improvement, i.e., success, in all three neurological parameters

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. 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

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.

Description of Patients

Patient demographics, patient accounting and an analysis of the involved cervical level show that the study results are likely to reflect device performance and that the results are not likely to be confounded by these variables.

Patient Demographics

The study was approved for up to 35 investigational sites and up to 470 total subjects. A total of 242 investigational and 221 control patients had surgeries in the study. Demographics are outlined below.

Table 8. Patient Demographics

	<u>Investigational</u>	<u>Control</u>
n	242	221
men/women	110/132	113/108
mean age (range)	44.4 (25.0-78.0)	44.7 (27.0-68.0)
mean weight (lbs) (range)	173 (108-312)	180 (100-285)
worker's comp (%)	15 (6.2)	11 (5.0)
tobacco user (%)	61 (25.5)	53 (24.0)

A statistical analysis of patient characteristics between the two groups demonstrated no statistically significant differences.

Patient Accounting

The accountability of patients in the investigational and control groups at the different clinical study

periods is provided in Tables 1, 2, and 3 in the sponsors application. These tables also provide patient evaluation distributions as a function of time within each study period. A total of 242 patients received the investigational device, and the control group had a total of 221 patients. The date of database closure for analyses was June 5, 2006.

The composite follow-up rate for the two treatment groups was approximately 90% (300 of 332 expected) at 24 months. As of the cutoff date, June 5, 2006., there were 168 patients in the investigational group and 164 in the control group with 24 month evaluations. The 24-month follow-up rate for the investigational group was 95.2% (160 patients), compared to a control group rate of 85.4% (140 patients).

Table 9. Patient accountability based on availability of overall success outcomes (from p. 85, Vol 1).

	3 Months		6 Months		12 Months		24 Months	
	Invest	Contr	Invest	Contr	Inves.	Contr	Inves	Contr
Enrolled Patients	242	221	242	221	242	221	242	221
Theoretical Follow-up	242	221	242	221	242	221	168	165
Deaths (Cumulative)	-	-	-	-	-	-	-	1(1)
Deaths not Due	-	-	-	-	-	-	-	0
Expected	242	221	242	221	242	221	168	164
Number of Patients who had Overall Success Outcomes	234	205	227	196	235	196	160	140
Percent of Patients who had Overall Success Outcomes	96.7	92.8	93.8	88.7	97.1	88.7	95.2	85.4

In the table above, enrolled patients include all who signed consent and received a device. The theoretical number of patients are those who have met or passed anniversary date for a particular follow-up visit. The number of expected patients is equal to the number of theoretical patients minus the number of cumulative deaths plus the number of deaths of patients who are not due for that particular follow-up time point. The patients were considered to have data to determine the overall success outcome if any data was available for that patient at given study period. The percent follow-up is based on expected number of patients.

Randomization Issues

There were two issues with patient randomization. Some patients were enrolled and declined participation and some patients were enrolled and treated with the wrong device.

One hundred seventeen (117) patients were randomized but declined participation in the study prior to receiving the assigned treatment. Thirty-seven (37) of these patients would have received the investigational treatment, while 80 were randomized to control. The reasons for declination prior to surgery have been are listed below.

Table 10 Reasons for Declination Prior to Surgery

	<u>Investigational</u>	<u>Control</u>
Insurance Denied	7	1
Condition Improved	7	11
Dissatisfied with randomization	0	32
Inclusion/Exclusion Criteria Not Met	3	5
Decided not to participate	6	7
Combination of Condition Improved and Unhappy with Randomization	0	2
Other	11	18
Unknown	3	4
Total	37	80

The demographic and baseline status data were collected for these randomized but not enrolled patients, and statistical comparisons were made to compare these patients to those who did receive study treatments. The non-study patients appear similar to those who underwent a study surgery. There were three

comparisons made between study and non-study patients for which statistical differences were found ($p < 0.05$). For investigational patients, the non-study patient cohort had a higher frequency of tobacco users. For control patients, a higher rate of alcohol usage and a higher mean SF-36 PCS score was noted in non-study patients.

There were twelve (12) patients in this study who were randomized to the investigational group but received the control treatment and one patient (1) who was randomized to the control group but received the investigational treatment.

Procedure Level

Statistical analyses were not performed, regarding the distribution of the treatment level for the two groups, though, on observation, the distribution of patients across level were similar and reflect the typical distribution for cervical spondylotic disease and those undergoing ACDF procedures. Over 92% of the patients in both treatment groups had procedures at either C5-C6 or C6-C7. There was a small number of patients ($n=3$) who had the investigational device implanted at C3-4, while no control patients had the device implanted at this level.

Table 11. Procedure Level

<u>Treatment Level</u>	<u>Investigational (n=242)</u>	<u>Control (n=221)</u>
C3-4	3 (1.2%)	0
C4-5	12 (5.0%)	17 (7.7%)
C5-6	140 (57.9%)	110 (49.8%)
C6-7	87 (36.0%)	94 (42.5%)

During the panel meeting, FDA may ask the panel a question about labeling for the C3-4 level and other levels. In the US IDE study only 3 patients were treated with the investigational device at the C3-4 level; no patients in the control group were treated at this level.

Safety Results

The sponsor compared the adverse event rate of the investigational device to the control treatment. The rate of investigational patients having at least one of any type of adverse event was very similar to the control group rate. The adverse event rate was also similar for serious adverse events. 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. Investigational patients had similar rates of revisions and removals to control patients. The investigational group had statistically lower rates of second surgical procedures related to supplemental fixations. The table on the following page summarizes the adverse events recorded for the investigational device group and control group:

Total Numbers of Adverse Events

A total of 202 (83.5%) investigational patients had at least one adverse event. Similarly, the number of patients in the control group with any adverse event was 174 (78.7%). These rates were not statistically different.

Death

There was one death in the control group unrelated to the procedure. One patient (a 37 year old male) underwent an anterior cervical fusion procedure at C6-7 with the control treatment. Approximately 17 months postoperatively, the patient died as a result of injuries sustained in a motor vehicle crash.

Table 11. Safety Results

ADVERSE EVENTS																		
Complication	Surgery		Postoperative (1 day - <4 Wks)		6 Weeks (≥4 Wks – <9 Wks)		3 Months (≥9 Wks – <5 Mon)		6 Months (≥5 Mon- <9 Mon)		12 Months (≥9 Mon- <19 Mon)		24 Months (≥19 Mon- <30 Mon)		Total adverse events		# of Patients Reporting*	
	Invest	Contr	Invest	Contr	Invest	Contr	Invest	Contr	Invest	Contr	Inves.	Contr	Inves	Contr	Inves	Contr	Investig (% of 242)	Control (% of 221)
Anatomical/Technical Difficulty	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0 (0.0)	1 (0.5)
Cancer	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	2	2 (0.8)	0 (0.0)
Cardiovascular	0	0	1	0	0	0	1	1	0	0	0	1	2	0	4	2	4 (1.7)	2 (0.9)
Carpal Tunnel Syndrome	0	0	0	1	3	0	2	1	3	1	2	1	2	0	12	4	12 (5.0)	4 (1.8)
Death	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0 (0.0)	1 (0.5)
Dysphagia/Dysphonia	10	1	14	14	3	3	0	1	0	0	0	0	0	0	28	20	26 (10.7)	19 (8.6)
Gastrointestinal	0	2	2	0	0	1	1	1	3	1	0	1	3	0	12	6	9 (3.7)	6 (2.7)
Infection	0	0	8	2	4	1	1	0	2	1	1	2	1	4	18	10	17 (7.0)	10 (4.5)
Malpositioned Implant	1	0	0	0	0	0	0	0	1	0	0	0	0	0	2	0	2 (0.8)	0 (0.0)
Neck and/or Arm Pain	1	0	20	14	30	23	22	28	29	19	28	20	7	18	140	128	115 (47.5)	96 (43.4)
Neurological	1	0	8	5	5	9	16	8	8	10	16	12	7	5	60	50	48 (19.8)	46 (20.8)
Non-Union	0	0	0	0	0	0	0	1	0	2	0	1	0	1	0	5	0 (0.0)	5 (2.3)
Other	7	6	17	6	11	5	7	5	10	10	13	5	11	7	84	47	59 (24.4)	39 (17.6)
Other Pain	0	0	6	4	6	7	11	13	10	7	9	8	12	7	56	47	49 (20.2)	44 (19.9)
Pending Non-Union	0	0	0	0	0	1	0	1	0	1	0	1	0	1	0	5	0 (0.0)	5 (2.3)
Respiratory	0	0	3	4	1	0	0	2	0	0	0	0	0	0	4	6	4 (1.7)	6 (2.7)
Spinal Event	1	0	1	1	2	4	6	2	1	5	6	7	6	6	23	25	21 (8.7)	20 (9.0)
Trauma	1	0	2	2	2	2	5	3	10	5	11	6	7	7	42	27	34 (14.0)	22 (10.0)
Urogenital	0	0	0	0	0	0	0	1	2	0	4	2	2	0	8	3	6 (2.5)	3 (1.4)
Vascular Intra-Op	2	1	0	2	0	0	0	0	0	0	0	0	0	0	2	3	2 (0.8)	3 (1.4)
Any Adverse Event																	202 (83.5)	174 (78.7)

*None of the differences in complication rates was statistically significant (i.e., no p-value was less than 0.05).

The safety results were analyzed for number of serious adverse events, neck and/or arm pain, neurological events, and implant or procedure related events as repeated in the table below. The details of these complications are described in the paragraphs following the table.

Table 12 Safety results discussed in detail in this section

Complication	Percent of Patients Reporting		p Value
	Investigative (% of 242)	Control (% of 221)	
Serious Adverse Event (WHO grade 3 or 4)	26.4	24.9	0.802
Neck and/or Arm Pain	47.5	43.4	0.431
Neurological	19.8	20.8	0.884
Implant or surgical procedure related Serious Adverse Events	1.7	3.2	0.299
Implant or surgical procedure related Adverse Events	2.9	5.4	0.254
Subsequent Surgical Interventions	2.5	4.1	0.481
Implant migration or failure related adverse events	2.9	5.4	0.254

Serious Adverse Events

The number of patients having serious adverse events, i.e., those with a WHO grade of 3 or 4, in the investigational group was very similar to that found in the control group (26.4% vs. 24.9%, p value non-significant). The treatment group rates for the various categories were fairly similar. There were only six categories in which the rates differed by one percentage point or more. For these, the investigational group had lower rates of grade 3 or 4 adverse events classified as neck and/or arm pain, non-unions, and respiratory. Similarly, the control group had lower incidences of adverse events classified as other, trauma, and urogenital. For the latter finding, there were five investigational patients who had grade 3 urogenital adverse events as compared to one in the control group. In the investigational patients, these five events were due to hematuria, pelvic pain from a benign dermoid tumor, ureteropelvic junction stone, bladder stones, and dysmenorrhea. The one urogenital event in a control patient was due to kidney stones. None of these were considered related to the treatments.

Neck and/or Arm Pain

A total of 140 events classified as neck and/or arm pain occurred in 115 patients in the investigational device group (47.5%). The events included the following: 34 neck pain; 18 shoulder pain; 16 arm pain; seven neck and arm pain; seven neck and shoulder pain; seven neck spasms; four arm and shoulder pain; four rotator cuff events; four trapezius pain; three neck and scapular pain; three neck and trapezius pain; three scapular pain; two neck and scapular pain with neck spasms; two neck and shoulder pain with spasms; two neck pain with headache; two neck pain with spasms; two rotator cuff tendonitis; two tightness at incision site; two trapezius spasm; and two shoulder, scapular, and arm pain.

By comparison, a total of 128 events classified as neck and/or arm pain occurred in 96 patients (43.4%) in the control group. The events included the following: 36 neck pain; 12 neck and arm pain; 11 shoulder pain; eight arm pain; eight trapezius pain; five scapular pain; five neck and shoulder pain; five neck spasms; four rotator cuff events; three neck pain with headache; three neck pain with muscle spasms; three neck, shoulder, and arm pain; two arm and shoulder pain; two elbow pain; and two neck, trapezius, and arm pain.

These rates of neck and/or arm pain were not significantly different.

Neurological Events

A total of 60 neurological events occurred in 48 patients in the investigational group (19.8%). The most commonly reported event among investigational patients was numbness (26 events). Of these 26 events, 15 involved the upper extremities (arms, hands and fingers). There were two reports of numbness in the C6 distribution. There was one report each of general numbness, numbness in the C7 distribution, numbness in the C8 distribution, and numbness in the face and extremities. In addition, there were five numbness events that occurred in the lower extremities.

The next most frequently reported neurological events in investigational patients involved paresthesia, tingling, numbness and tingling, numbness and pain, neuropathy, and radiculopathy. There were two events of paresthesia affecting the arm and one event of nonspecific paresthesia. There was one report each of tingling affecting the hands, the feet, the fingers, left upper extremity, and the left shoulder and fingertips. There were two events of numbness and tingling affecting the fingers, and one report each of numbness and tingling affecting the hands and numbness and tingling affecting the toes and knees. There were four events of numbness and pain affecting the neck, and one event of numbness in the neck accompanied by intrascapular pain.

There were two events of neuropathy affecting the upper extremities and two events of neuropathy affecting the lower extremities. There were four events of nonspecific radiculopathy.

There were two events of weakness reported. One event of weakness affected the left upper extremities (one event), and the other affected the left side (one event). There were two reports of dysesthesia. One event of dysesthesias affected the fourth and fifth digits of the left hand, and the other event was a nonspecific report of dysesthesias. Additionally, there were two instances of tremors (one event was nonspecific, and the other event affected the right hand).

A total of 50 neurological events occurred in 46 patients in the control group (20.8%). 20 reports of numbness are included in the 50 control group neurological events: 18 reports of numbness in the upper extremities, one report of numbness in the leg and one report of general numbness. The next most reported neurological event for the control group was numbness accompanied by tingling, pain and/or burning (11 events). As in the investigation group, there were also reports of radiculopathy (2 events). Myelopathy (2 events, dysthesias (2 events), tingling (2 events) and weakness (3 events) were also reported. All of these events are not unexpected for anterior cervical procedures.

Implant and/or Procedure related Serious Adverse Events and Other Adverse Events

The adverse events that were both serious and classified as implant- or implant/surgical procedure-related are also summarized below. Four such events occurred in investigational patients (1.7%). One of these was a malpositioned implant at the time of surgery, two were neck and/or arm pain events (one at 6 weeks and one at 3 months postoperative), and one was a trauma (work injury) at 6 months postoperative.

Seven events classified as serious and implant- or implant/surgical procedure-related occurred in control patients (3.2%). One of these was neck and/or arm pain at 6 weeks, and one was a spinal event at 24 months. The other five events, which were all due to non-unions, occurred at 3 months, 6 months (2 events), 12 months, and 24 months postoperative.

The total number of adverse events that were classified as implant or implant/surgical procedure associated was 2.9% (n=7) for the investigational group and 5.4% (n=12) in the control group. These event rates were fairly similar for both treatment groups in most of the specific categories. The main exceptions were the non-union and pending non-union categories, where the control group rates were 2.3% and 2.3%, respectively, as compared to 0.0% rates for investigational patients. There were no unanticipated adverse device effects (UADE) reported in this study

Subsequent Surgical Interventions

Some of the reported adverse events required surgical interventions subsequent to the initial surgery. The number of subjects requiring a second surgical intervention classified as a revision, removal, reoperation, or supplemental fixation was 2.5% (6/242) in the investigational group and 4.1% (9/221) in the control group. The investigational group had a statistically lower rate of supplemental fixations than the control group.

There was one reported revision procedure (0.4%) in the investigational group and none in the control group. The revision of the investigational patient was due to a malpositioned implant after wound closure at surgery, and this patient was revised by repositioning the implant without additional complications related to the implant. There was no statistical difference in revision rates between control and investigational groups.

There were no supplemental fixations performed on investigational patients, as compared to seven procedures on six (2.7%) control patients. These rates were statistically different. The supplemental fixation procedures were all related to suspected non-unions in the control patients. A non-union alone would not be classified as a reoperation or removal unless it resulted in a reoperation or removal. Non-unions were not a consideration for investigational patients, because they did not receive a fusion procedure. Two of the seven reported supplemental fixations were attributed to the use of bone growth stimulators.

Implant removals occurred in both treatment groups. The investigational group removal rate was similar to that of the control group (1.2% vs. 0.9%). There were three removals in the investigational group. Two of them were due to residual pain, and the third was secondary to trauma. Fusion procedures followed these removals. Both of the control implant removals were non-elective and followed non-unions.

Investigational patients experienced higher rates of reoperations and surgical procedures classified as “other” (0.8% vs. 0.4% and 17.8% vs. 15.4%, respectively) when compared to the control patients. In neither comparison was the difference in rates found to be statistically different.

If a study patient had a revision, removal, or supplemental fixation procedure, he/she was then classified as a second surgery “failure”. These events are considered in the calculations of “overall success” rate for the study. Cumulatively, the investigational group had five second surgery “failures”, as compared to six for the control group. Two of the “failures” in the control group occurred within 24 hours of the procedure.

Implant migration or failure related adverse events

In the investigational group, one patient was noted by a single reviewer to have a bent, fractured shell, as well as separated implant components at the surgery/discharge timepoint. Another patient was noted by a single reviewer to have a migrated implant at the 3-month evaluation. Neither patient had an additional surgical procedure, and both were overall successes at 24 months. Finally, a single reviewer noted a third patient to have separated implant components at the 3- and 6-month evaluations. This patient did have a second surgical procedure classified as “other”, which was an adjacent-level fusion at the 12-month time period. However, there was no second surgical procedure at the treated level in this patient, and this patient was an overall success at 24 months.

Radiographic observations were also used to evaluate implant migration. Anteroposterior position of the prosthesis and cervical plate was measured at each of the postoperative radiographic timepoints, and success was defined as no anterior or posterior migration of the device >3.5 mm. At 24 months postoperative, the AP implant migration position success rates was 100.0% in the investigational device group, and 86.8% in the control group.

Effectiveness Results – Primary Endpoint

The primary endpoint was the composite endpoint including improvement in Neck Disability Index score, maintenance or improvement in neurological status, no serious implant related adverse event and no additional surgical procedures classified as “Failure”. The 24 month success rates for the Interim Analysis cohort are provided in the table below.

Table 13. Effectiveness Results

	<u>Investigational</u>	<u>Control</u>
Primary Composite endpoint Variable		
An improvement of at least 15 points from the baseline Neck Disability Index score	84.3%	75.7%
Maintenance or improvement in neurological status	93.7%	91.4%
No serious adverse event classified as implant-associated or implant/surgical procedure-associated	98.3%	96.8%
No additional surgical procedure classified as “Failure.”	97.5%	95.9%
Overall Success	80.6%	70.7%

Overall Success

Overall success at 24 months is the primary endpoint for the clinical study and it is the parameter on which the success of the clinical study is determined. Overall success is based on a patient demonstrating successful outcomes for NDI and neurological status. Also, to be considered an overall success, a patient could not have had a serious implant-associated or implant/surgical procedure-associated adverse event or have undergone a second surgery classified as a “failure”. Therefore, this parameter encompasses both important safety and effectiveness aspects of the treatment.

The sponsor has used Bayesian statistics to determine a posterior probability of non-inferiority. Based upon the success outcome measures in the primary analysis dataset (defined below) the posterior probability of non-inferiority was over 99%. The posterior probability of superiority was found to be 96.9%.

Following implantation of the BRYAN Cervical Disc, the chance (posterior probability) of overall success at 24 months was 80.4%. There was 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 was 71.8% and there was a 95% probability that the chance of success ranges from 65.0% to 78.9%. The results for the primary effectiveness outcome parameters for the investigational group were non-inferior to the control group.

Neurological Success

Success rates of neurological status at all timepoints were nearly identical for the control and investigational groups for each of the individual parameters (motor, sensory, reflexes). This was also true of overall neurological success. Overall success rates at 24 months were 93.7% and 91.4% for the investigational groups and control groups, respectively. Tabulated below are the success rates for the different neurological outcomes and overall neurological success at 24 months.

Table 14. Neurologic Results (reference Table 14 Interim Analysis Tables)

<u>Neurologic Parameter</u>	<u>Investigational</u>	<u>Control</u>
<u>At 24 months</u>	<u>Success rate (%)</u>	<u>Success rate (%)</u>
Motor	98.7	97.1
Sensory	96.9	96.4
Reflexes	97.5	97.1
Overall	93.7	91.4

Success -- NDI

Success based upon NDI were similar for almost all time points between the control and investigational groups. At 24 months there was a higher success rate based upon NDI for the investigational group (84.3%) than the control group (75.7%). Success based upon neck pain score at 24 months were more similar; this rate was 95.6% in the investigational group and 92.9% in the control group.

Table 15. NDI scores at 24 months for the investigational and control groups (reference Table 16 Interim Analysis Tables)

<u>Pain Score (NDI)</u>	<u>Investigational</u>	<u>Control</u>
<u>At 24 months</u>	<u>(n=159)</u>	<u>(n=140)</u>
Mean	16.4	20.0
Change from Pre-op		
Mean	-32.1	-28.7
Min/Max	-84/+14	-80/+36
P	<0.001	<0.001
Success Rate (NDI)	84.3%	75.7%
Success Rate (Neck Pain)	95.6%	92.9%

Statistical Analysis of the Primary Effectiveness Results

The sponsor constructed three analysis datasets (pp. 44-45, Vol 1). A brief description of each dataset follows:

- Primary analysis dataset – Consists of patients who received a study device and completed surgical procedures. Patients were analyzed according to treatment received, rather than according to randomization (12 patients were randomized to the investigational group but received the control device instead, and one patient was randomized to the control group but received the investigational device instead). Only patients with observed data were included; missing data were not imputed.
- Per-protocol dataset – This 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, did not meet inclusion/exclusion criteria, received wrong device, etc., were excluded from this dataset.
- Missing-equals-failure dataset – In this dataset, missing responses are assumed to be failures. The primary dataset is a subset of this dataset. Success rates based on this dataset are given for each treatment group, but no formal statistical comparisons were performed.

Note that the sponsor did not include an intent-to-treat analysis, in which patients would be analyzed as-randomized. However, in PMA amendment 4, an ITT analysis was presented. The results of the ITT analysis are qualitatively similar to the results obtained based on the primary analysis dataset (presented below).

The results of the effectiveness endpoints are given below. The results are given for each of the datasets described above.

Primary 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. (p. 1154, Attachment K, Vol 4)

Table 16. Data contributing to primary analysis of 24-month overall success rate (p. 1264, Attach S, Vol 4).

12 months	Investigational 24 months				Control 24 months			
	Success	Failure	Not obs	Total	Success	Failure	Not obs	Total
<i>Success</i>	<i>119</i>	<i>13</i>	<i>66</i>	198	<i>78</i>	<i>14</i>	<i>52</i>	144
<i>Failure</i>	<i>9</i>	<i>17</i>	<i>11</i>	37	<i>14</i>	<i>26</i>	<i>12</i>	52
<i>Not obs</i>	<i>1</i>	<i>1</i>	5	7	<i>7</i>	<i>1</i>	17	25
Total	129	31	82	242	99	41	81	221

Based on the primary dataset, the posterior mean probability of success p_c in the control group is 71.8% (95% HPD: 65.0%, 78.9%), the posterior mean probability of success p_t in the investigational group is 80.4% (74.3%, 85.8%), and the posterior mean of the difference $p_c - p_t$ is -8.6% (-18.1%, 0.2%). The posterior probability of non-inferiority $P(p_c - p_t < 0.10 | \text{Data})$ is greater than 99%. Since the probability of non-inferiority is greater than 95%, the sponsor claims non-inferiority. Since non-inferiority can be claimed, the sponsor calculated the posterior probability of superiority $P(p_c - p_t < 0 | \text{Data})$, which is found to be 96.9%. Since this probability is greater than 95%, the sponsor further claims superiority of the investigational device with respect to the overall success rate.

Per-protocol 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. (pp. 1249-1251, Attachment P, Vol 4)

Table 17. Data contributing to per-protocol analysis of 24-month overall success rate (p. 1265, Attach S, Vol 4).

12 months	Investigational 24 months			Total	Control 24 months			Total
	Success	Failure	Not obs		Success	Failure	Not obs	
Success	105	11	64	180	63	10	45	118
Failure	8	11	9	28	9	15	11	35
Not obs	1	1	5	7	6	1	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 (p. 1262, Attachment Q, Vol 4). Instead, the sponsor simply presents 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 (p. 1263, Attachment R, Vol 4). 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			
Investigational (8 missing values)	Control (25 missing values)	Investigational	Control	95% CI for $p_t - p_c$	p-value for non-inferiority hypothesis
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.

During the panel meeting, FDA may ask the panel a question about superiority of the device. The sponsor has presented comparisons of the investigational and control procedures based on a variety of datasets. Please consider whether these analyses support the sponsor's claim that the investigational device is superior to the control procedure with respect to the overall success endpoint.

Results -- Secondary Endpoints

Success -- Arm Pain Scores

Arm pain scores were similar in the investigational and control groups at almost all time points. At 24 months, the mean arm pain scores for the investigational group was 19.3, while it was slightly higher 22.5 in the control group. However, the mean improvement in the arm pain scores was identical in both groups at 24 months: -50. Success rates for improvement in arm pain scores were 94.3% in the investigational group and 89.3% in the control group. Tabulated below are Arm Pain scores at 24 months for the investigational and control group.

Table 20. Arm Pain Scores

<u>Arm Pain Score</u>	<u>Investigational</u>	<u>Control</u>
<u>At 24 months</u>	<u>(n=159)</u>	<u>(n=140)</u>
Mean	19.3	22.5
Change from Pre-op		
Mean	-50.1	-50
Min/Max	-100/+60	-100/+50
P	<0.001	<0.001
Success Rate	94.3%	89.3%

Success QOL 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 physical component summary (PCS) is based primarily on the physical functioning, role-physical, bodily pain, and general health scales of the SF-36 survey. The mental

component summary (MCS) is comprised primarily of the vitality, social functioning, role-emotional, and mental health scales. In terms of the mean PCS and MCS results, all mean postoperative scores were higher than preoperative scores for both treatment groups. The mean improvement in PCS scores from preoperative to 12 and 24 months following surgery for the investigational group (15.7 and 14.4) compared favorably to those values for the control group (13.9 and 14.5, respectively). The mean improvements in MCS scores from preoperative to 12 and 24 months postoperative for the investigational patients (9.9 and 8.1) were also comparable, if not higher, to those values for the control group (6.9 and 7.3).

At 12 months following surgery, the PCS and MCS success rates for the investigational group were higher than those of the control (93.1% vs. 88.2% and 77.3% vs. 72.8%, respectively). However, at 24 months postoperative, the findings changed. For both the PCS and MCS, the control group success rates bettered the investigational rates (90.6% vs. 85.5% and 72.5% vs. 69.8%, respectively).

Patient Global Assessment

At each postoperative time period, patients were asked to evaluate their overall impression of their study treatment effectiveness as a function of pain. The seven possible answers ranged from “completely recovered” to “vastly worsened”. At 12 and 24 months following surgery, respectively, 91.0% and 92.4% of the investigational patients indicated that they had either “completely recovered” or were “much improved”. These rates were higher than the 81.7% and 86.4% rates for the control group at 12 and 24 months, respectively.

Investigator Global Assessment

At each postoperative visit, the patient’s physicians were asked to provide their perceptions of the patients’ conditions. The responses could be “excellent”, “good”, “fair”, or “poor”. At 12 months following surgery, 93.6% of the doctors responded that investigational patients were in “excellent” or “good” condition. This rate is higher than the 89.8% value for the control group. At 24 months postoperative, 93.8% of the investigational device and 89.3% of the control responses were either “excellent” or “good”.

Return to Work

Investigational patients returned to work more quickly than control patients. The median time to return to work for investigational patients was 48 days, which was 13 days shorter than the time for control patients. This difference was statistically significant.

Operative Time and Intraoperative Blood Loss

Investigational device patients had statistically longer operative times and higher blood losses as compared to control patients. Length of hospital stay was similar between the investigational and control groups.

Table 21. Operative Time and Intraoperative Blood Loss

	<u>Investigational</u>	<u>Control</u>
mean operative time (hrs)	2.2	1.4
mean EBL (ml)	91.5	59.6
hospitalization (days)	1.1	1.0
spinal level treated		
C ₃₄ (%)	1.2	0.0
C ₄₅ (%)	5.0	7.7
C ₅₆ (%)	57.9	49.8
C ₆₇ (%)	36.0	42.5

During the panel meeting, FDA may ask the panel a question about including operative time in the device labeling. The mean operative time for the investigational procedure was significantly higher than that of the control procedure. In addition, the operative time required for the investigational procedure decreased with surgeon experience.

Motion at Target Level for Investigational group

Radiographic success for the investigational group was based on 1) the existence of flexion/extension angular motion >4°, 2) no evidence of bridging trabecular bone forming a continuous connection between vertebral bodies, and 3) no radiolucency >50% of the convex surface of either the superior or inferior shell

of the device. The success rates at all time periods were similar. At 12 and 24 months following surgery, the success rates were 81.8% and 79.6%, respectively. Bridging bone and radiolucency were not observed in any patients.

The investigational device is designed to preserve some motion at the level of insertion. The sponsors compared angulation, translation and right to left bending on dynamic radiographs for those patients in the investigational group. The motion at these levels was also compared to the motion observed pre-operatively. Tabulated below are Angulation, translation and right-left bending measurements for patients in the investigational group.

Table 22. Motion at the Treated Level

	<u>Investigational group n=154</u>
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%

Angular motion in the sagittal plane was measured at each study period by comparing lateral flexion and extension radiographs. The mean angular motion value prior to surgery was 6.4°. At both 12 and 24 months postoperative, the mean angular motion values were 7.8° and 7.7°, respectively. The angular motion component yielded success rates between 78.0% and 81.8% at all measured postoperative time periods.

Lateral bending was evaluated by comparing the angular movements from left and right neck bending films. Lateral bending success was defined as motion $\geq 4^\circ$. Throughout the postoperative course, the mean results were very consistent in a range of 4.0° to 4.4°. Success rates for this measurement were 54.0% and 49.7% at 12 and 24 months postoperative, respectively.

Translational motion was also measured throughout the course of the study by comparing lateral flexion and extension radiographs. Again, the postoperative values approximated the preoperative determinations. The mean values at every study period were very low, at less than 0.4 mm.

Motion at adjacent levels was also analyzed in these radiographs for patients in both groups and compared. These results did not demonstrate any appreciable differences in adjacent level motion between those undergoing intended fusion with ACDF and those receiving the investigational device.

The sponsor attempted to correlate amount of segmental motion with pain relief. No statistically significant correlations were noted at any time period.

During the panel meeting, FDA may ask the panel a question about motion preservation and effectiveness. The sponsor has presented radiographic data to demonstrate preservation of motion at the index level in the patients receiving the investigational device. 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 and that motion at the index level did not correlate with clinical success. Please consider how index level and adjacent level motion contribute to the effectiveness of the investigational device.

Functional Spinal Unit (FSU) Height

Measurements pertaining to the FSU height and implant subsidence were made to evaluate whether the disc space had been maintained during the postoperative course. 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

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.

The FSU, subsidence, and FSU/subsidence success rates at all time points were high, exceeding 99%, for the investigational treatment group at the three postoperative periods. These success rates for the control group were likewise high, but at 6 and 12 months, there were a few failure reports in the FSU and subsidence categories. At 6, 12, and 24 months, both treatment groups experienced over 99% success rates for FSU/subsidence. 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.

Angular Motion Measurements at Adjacent Levels

In order to determine the effect of the study treatment on adjacent levels, the motion of the cervical segments above and below the treated level was assessed. For the level above the treated segment, the mean preoperative values for the investigational and control treatments were similar at 8.3° and 7.8°, respectively as shown in the table below. The mean 24-month angular motion value for the level above in investigational device patients was 9.1°, as compared to 8.9° for control patients.

Table 23 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°			6.4°	6.2°

The mean preoperative angular motion values at the level below the treated segment were consistently less than those above the segment. The preoperative values for the investigational and control groups were 5.0° and 5.2°, respectively. At 24 months following surgery, the angular motion levels had increased from preoperative, with mean values of 6.4° and 6.2° for the two respective treatment groups.

Radiographic Fusion rates for control group

Radiographic success for control patients was based on the presence of fusion of the treated spinal segment. To be considered fused, there had to be radiographic evidence of bone spanning the two vertebral bodies in the treated segment, flexion/extension angular motion stability ($\leq 4^\circ$) and no radiolucent lines covering more than 50% of the graft surface. Radiographic evidence of fusion occurred in 93% of the control patients at 24 months.

Heterotopic Ossification

Heterotopic Ossification was not included in the original study endpoints and the IDE investigational protocol did not call for assessments of heterotopic ossification in the cervical spine. A recent report in the literature demonstrated that the rate of heterotopic ossification (HO) may be as high as 18% following BRYAN cervical disc replacement in Europe¹. Since this information is important for understanding the risks associated with cervical disc replacement, including loss of motion due to HO and rate of progression of HO, Medtronic analyzed the radiographic results to detect clinically significant HO and searched for

¹Leung C, et al. Clinical significance of heterotopic ossification in cervical disc replacement: a prospective multicenter clinical trial. *Neurosurgery* 57(4):759-63,2005.

comments on bone demineralization or osteophytes on the radiographic case report forms. Over the course of the IDE study, there were 196 of these additional comments recorded by the reviewers. Of these, 42 pertained to the BRYAN investigational group and 154 to the fusion control group. In the investigational group, there were six patients (2.5%) who had “osteophytes” mentioned in the radiologist’s comments:

Table 24. Analysis of Range of Motion (ROM) for Patients with Radiographic Comments on Osteophytes -

<u>Sagittal ROM</u>	<u>Lateral bending ROM</u>
3.19	2.4
12.03	6.29
3.56	4.08
7.99	4.96
4.26	6.31
0.70	0.54

For these six patients, only one was a clinical failure by success criteria. In the clinical US IDE study, patients were treated with NSAIDs for 14 days post-operatively, and there is some evidence to suggest that NSAIDs decrease the rate of HO formation and spontaneous fusion at the index level.

During the panel meeting, FDA may ask the panel a question about heterotopic ossification. Prior reports in the literature have describe heterotopic ossification (HO) following implantation of cervical disc arthroplasty devices. HO was not specifically studied as a radiographic outcome measure in the US IDE study. Only six patients who were implanted with the investigational device had osteophytes observed on follow-up radiographs. The sponsor has suggested that their study protocol, which included 14 days of treatment with NSAIDs, may have been responsible for this low rate of HO.

Sterility and Packaging

The BRYAN Cervical Disc is ethylene oxide sterilized and a sterilization validation report has been provided. A comparative resistance study was conducted to evaluate the subject device and resistance to the sterilization process in comparison to process challenge devices. Bioburden on the BRYAN Cervical Disc were presented and the “Alert” and “Action” limits are defined. The final sterilization report is under review.

Bacterial Endotoxin/Pyrogenicity testing has not been provided. FDA suggests that endotoxin testing be performed on, and a labeling claim of “non-pyrogenic” should be placed on, all medical devices that are direct blood contacting devices or are permanent implants.

The primary packaging for the BRYAN Cervical Disc is a double barrier Tyvek/Poly pouch. This is packed in an SBS Carton which is placed in a corrugated shipper. The packaging was tested and found to be adequate.

Compliance (Quality Systems Review)

Office of Compliance reviewed the manufacturing information in the PMA. The manufacturing review includes design control information including design input, design output, design review, verification, validation, design transfer, changes, and the design history file. The Office of Compliance also reviewed the Quality Systems procedures, production flow, purchasing controls, production and processing controls, inspection, measuring and test equipment, process validation, receiving acceptance, nonconforming products, corrective and preventive action, and customer complaint files.

Bioresearch Monitoring (BIMO)

The Division of Bioresearch monitoring reported that the FDA conducted eight audits during the IDE. No significant investigational findings were noted. ODE review of the data raised no cause for concern about the investigational data.

Patient Labeling

The proposed patient labeling is included in the panel pack for your review. OCER reviewed of the original patient labeling provided by the sponsor. The labeling review was based on FDA guidance www.fda.gov/ohip/guidance/1128.html.

As mentioned in other sections, FDA may ask the panel series of question about device labeling. Please consider whether the labeling provided is adequate related to the presentation of the Bayesian analyses; the superiority claims; operative time for the investigational procedure was significantly higher than that of the control procedure; and indicated levels of use as only 3 patients were treated with the investigational device at the C3-4 level; and no patients in the control group were treated at this C3-4 level.

Post Market Study

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

Cervical arthroplasty has a very short history. Compared with anterior cervical discectomy and fusion (ACDF), cervical disc replacement for the treatment of cervical disc disease may preserve segmental motion at index disc level and decrease rate of progression of adjacent segment degeneration thus improving the treatment of adjacent segment disease. Cervical arthroplasty may also reduce the intraoperative and postoperative morbidity and allow an earlier return to activity. The BRYAN Cervical Disc was developed in 2000 and its first reported use was in 2002 for the management of cervical spondylotic disease. Based on the results of the IDE study and literature published to date, a few issues remain to be addressed regarding the BRYAN Cervical Disc, which include:

- 1) the survival of the implant;
- 2) whether particle and wear debris will trigger new complications during longer-term use of the device;
- 3) the protective effect for adjacent levels which is not yet known because of the short period of follow-up (≤ 2 years) to date; and
- 4) other complications that have been reported and may affect the longer-term use of the device: anterior-to-posterior disc migration; heterotopic ossification after BRYAN Cervical Disc implantation and subsequent loss of movement; and the occurrence of kyphosis of the functional spinal unit after implantation.

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

The sponsor did not provide a post-approval study plan in the original PMA but has submitted a post-approval study outline. The full PAS protocol has not been developed. The primary objective of the post-approval study is to assess long-term performance of the BRYAN Cervical Disc in the treatment of patients with cervical degenerative disc disease. The sponsor proposes to recruit subjects for the PAS from the 431 persons in the IDE study cohort and the 18 subjects in the continued access study and to follow and evaluate them at 4, 5 and 7 years post-operation to measure the composite overall success outcome of the device and other endpoints used in PMA study, in comparison with the concurrent fusion control group.

Since the current proposal includes no new patients recruited for PAS study, one will need consider whether this may limit the assessment of device performance under actual condition of use after approval as the patients, physicians, and clinical sites who utilize the device in the post-market environment may differ in significant ways from the relatively select patients, physicians, and clinical sites that participated in the pre-market trial. One will need to consider potential compensatory measures that the sponsor may take if the number of subjects falls below 200 during follow-up. One of parameters in the composite overall

success outcome is Neck Disability Index improvement. The criteria to determine improvement is unclear. One will need to consider identifying appropriate criteria to define the improvement. One will need to consider secondary endpoints such as radiographic success and adjacent segment disease considered necessary to be tracked and analyzed as well to contribute to our understanding of the long-term safety and effectiveness of the BRYAN Cervical Disc Prosthesis.

During the panel meeting, FDA may ask the panel a series of questions about a possible Post-Approval Study. Our discussion of a post-approval study plan does not in any way alter the requirements for pre-market approval. Please remember that recommendations from the Panel on whether to approve a device or not must be based on the premarket data. Please consider the following Post-Approval Study issues:

- *Assessment of treated level and adjacent level motion and the occurrence or progression of adjacent-segment disease in both groups*
- *Evaluation of the rate of heterotopic ossification (HO) and kyphosis*
- *Patient recruitment beyond the PMA cohort*