

P060023

BRYAN Cervical Disc

FDA Presenters:

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Orthopedic and Rehabilitation Devices Panel Meeting

July 17, 2007



1 of 101



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FDA Presentation

- Introduction
- Pre-Clinical Issues
- Clinical Study
- Statistical Analysis
- Post-Approval Study
- Panel Questions



Rationale for Bringing to Panel

- Polyurethane-on-Titanium articulation
- Fixation to Bone
- Type of Constraint
- Novel encapsulated joint design



Indications 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.

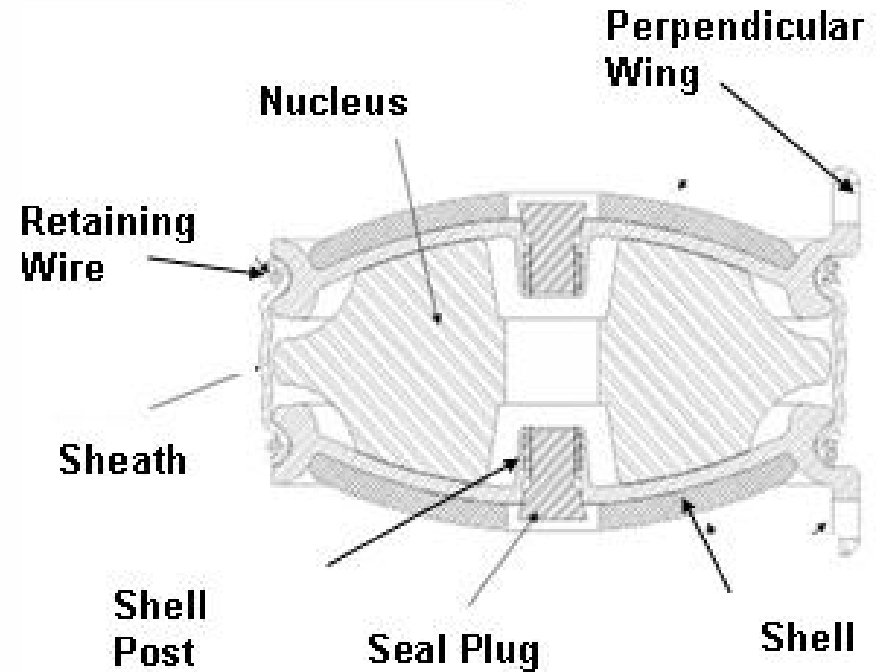


Device Description

Polyurethane Nucleus

Polyurethane Sheath

Titanium shell, with porous, beaded coating and shell post



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Pre-Clinical Issues

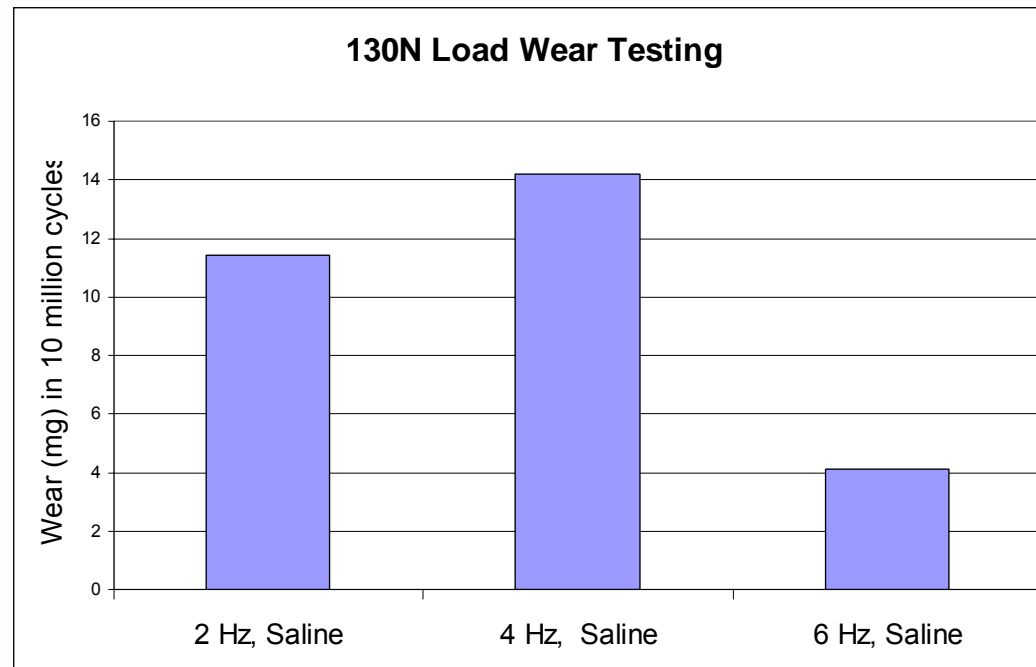
- Device Wear
- Response to Generated Particulates
- Device Migration or Expulsion
- Device Reliability
- Joint Encapsulation

Wear Test Parameters

<u>Parameter</u>	<u>Values Tested</u>
Flexion/Extension	$\pm 4.9^\circ$
Axial Rotation	$\pm 3.8^\circ$
Axial Compressive Load	130 and 300N
Test Cycle Frequency	2, 4 and 6 Hz
Test media	Saline, Bovine Serum

Wear Test Results

- No nucleus cracking or large particles generated
- Bovine serum generated comparable results



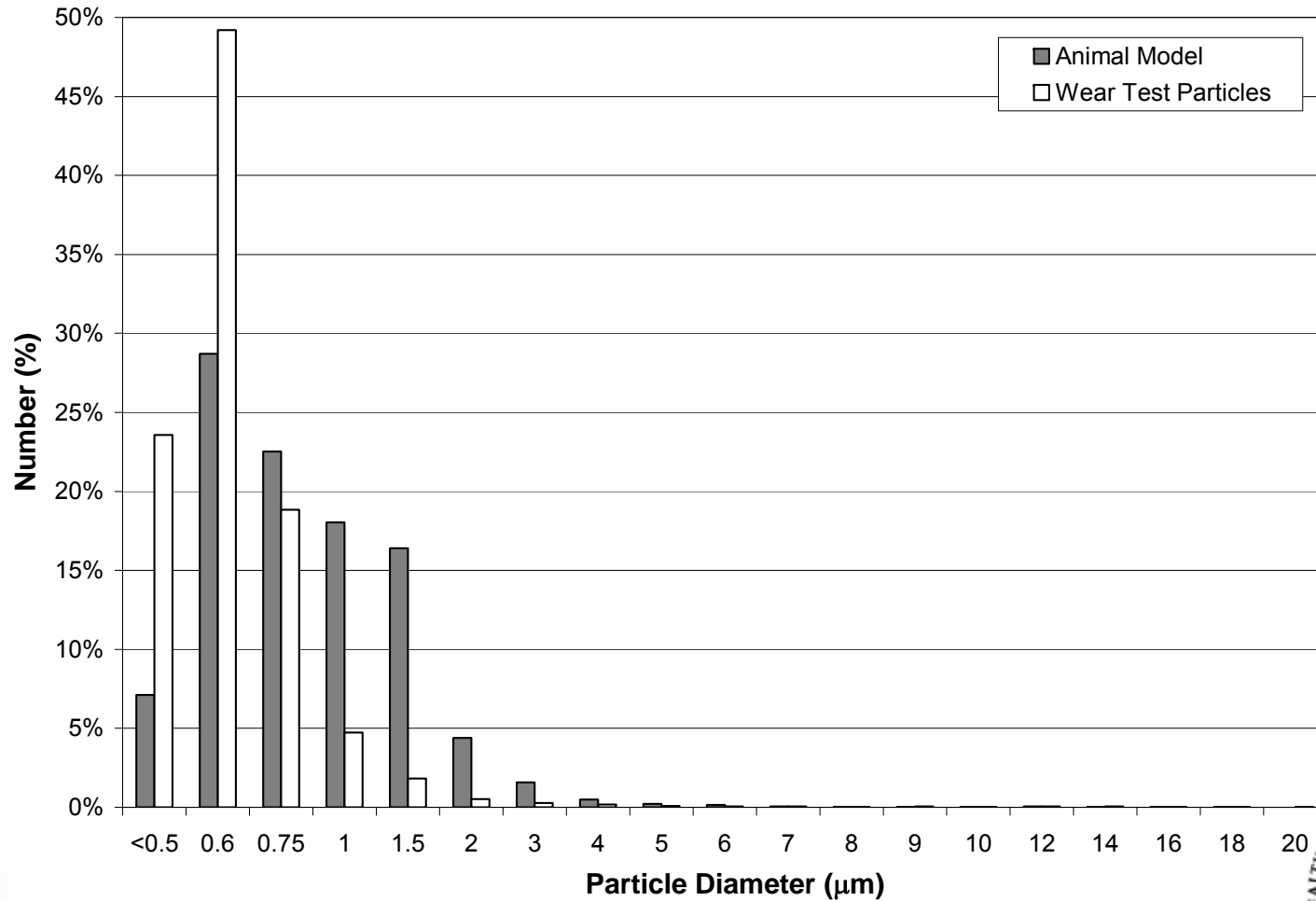
Wear Observations

- Clinical Trial
 - Explanted devices had minimal wear
 - Wear not observed clinically
- Goat study
 - 10-150 μm urethane particles

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.*

Wear Particle Characterization



Particulate Response

Rabbit Particulate Injection Study

- Nucleus and Sheath materials tested
- Low and High particulate concentration doses
- 3 month and 6 month sacrifices
- Particle shape and size were tailored to match bench test particles

- Sponsor's Conclusions: Materials are non-irritant and non-toxic



Explant Information

- Polymer particles observed
- Metal particles observed in a single patient
- Adverse Reaction to particles was not observed
 - No osteoclastic resorption,
 - No osteolysis and
 - No evidence of infection

Particulate Response

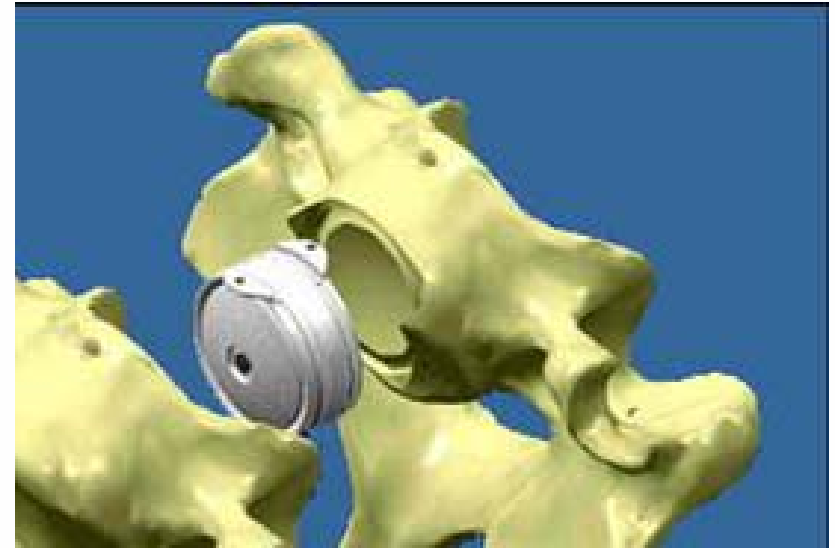
Urethane is a novel material for use in a cervical disc prosthesis. Please reflect on whether the biocompatibility testing, the particulate injection studies in rabbits, the human tissue analysis and clinical observations are sufficient to address material reaction issues?



Device Expulsion or Migration

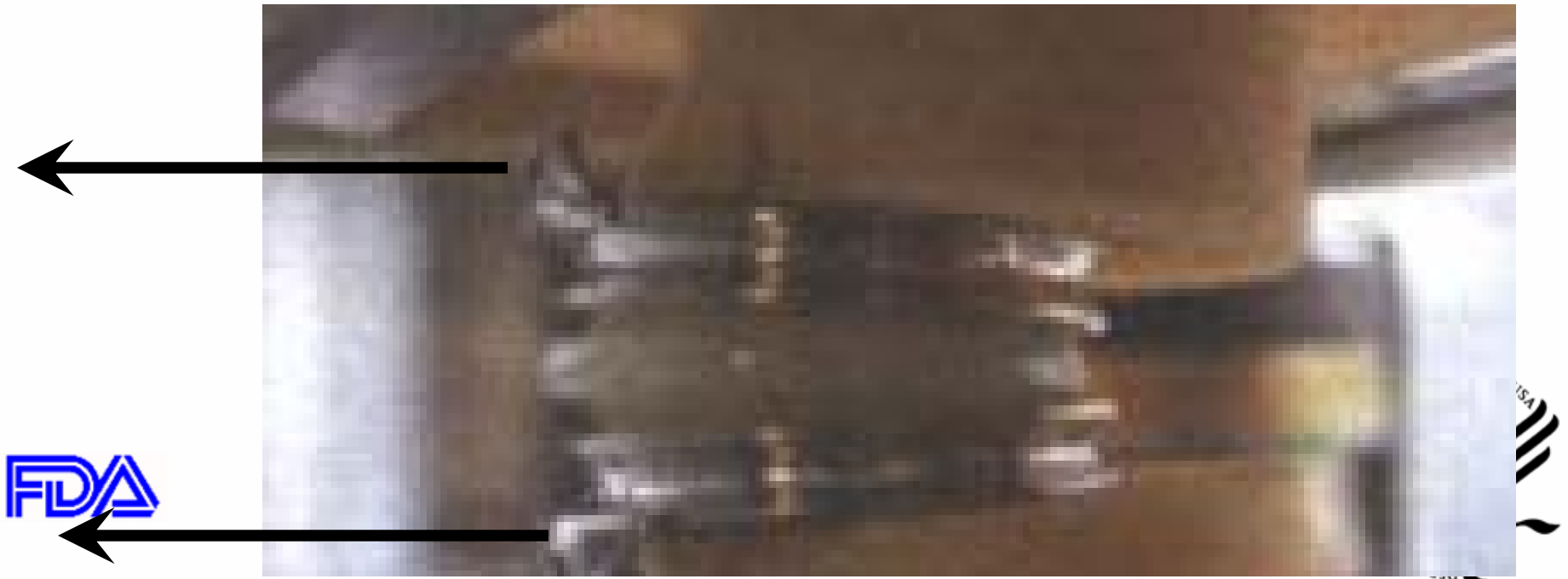
Device Fixation

- Fits into spherical milled pocket
- Anterior wings resist posterior migration
- Beaded coating for bone ingrowth



Expulsion Test Results

	Low Load	High Load	Low load with Extension
Test Parameter- Compressive Load	40N	130N	50N
Test Parameter- Extension Angle	0°	0°	11°
Antepulsion (N)	120	270	113
Retropulsion (N)	309	429	



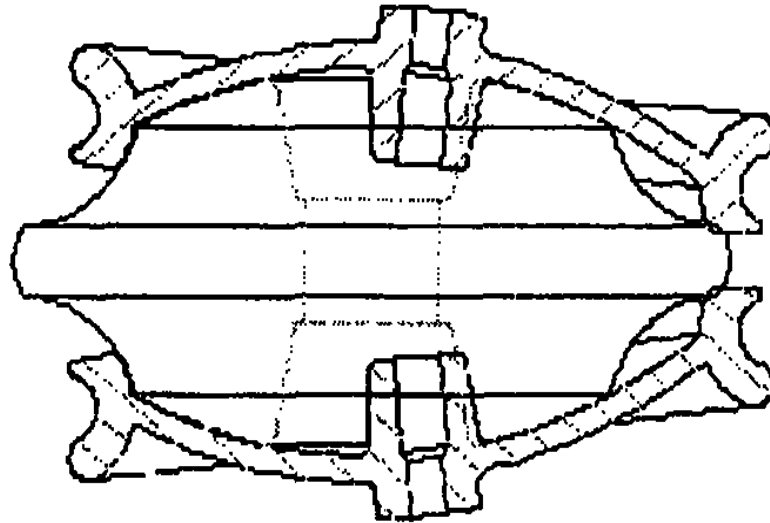
Expulsion Observations

- No patients re-operated for migration or expulsion
- No device migration >3.5 mm
- No clinical study failures due to device expulsion or migration

Expulsion and 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.*

Device Reliability



Static and fatigue testing of the shell post
Static and fatigue testing of the shell in bending
Static testing of the nucleus in axial compression
Fatigue testing of the nucleus in axial compression
Creep testing of the nucleus

Test Results, Radiographic Data and Explant Analysis

- Shells and Nucleus met test acceptance criteria
- No radiographic device failures
- No observations of shell or nucleus failures on explant



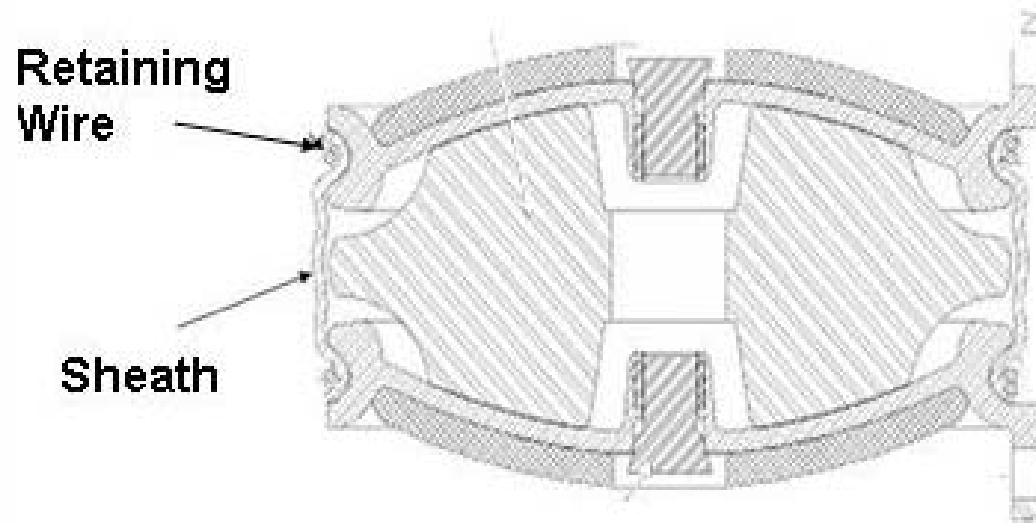
Implant Reliability

- *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.*



Joint Encapsulation

- Sheath Tensile testing
- Sheath Torsion testing
- Seal Plug Pressurization testing



Joint Encapsulation Results

- Bench testing
- Animal testing
- Clinical Observations



Joint Encapsulation

The BRYAN Cervical Disc includes a polyurethane sheath which provides some joint encapsulation. Are there additional issues to consider in the sheath testing?



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Clinical Trial Design

- Randomized (1:1), multicenter, prospective, unblinded trial
- 463 patients (242 BRYAN, 221 Control) at 30 centers
- Follow-up at 6 weeks, and 3, 6, 12, and 24 months



Primary Endpoint

- Overall Success Components:
 - 1) At least 15 point improvement on NDI
 - 2) Maintained/improved neurological status
 - 3) No serious AEs that were implant/surgery related
 - 4) No additional surgery classified as “failure”



Safety Endpoints

- Adverse events (AEs)
- Serious AEs (WHO grade 3 or 4)
- AEs classified as implant/surgery related
- Radiological findings
- Secondary surgical procedures (revisions, removals, supplemental fixations, reoperations)
- Neurological status



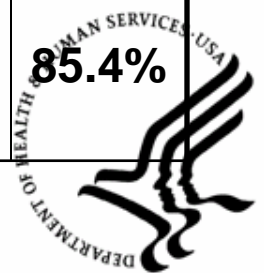
Secondary Endpoints

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




Patient Accounting

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



Patient Demographics

Variable	BRYAN (n = 242)	Control (n = 221)	Unadjusted P-value
Age (years)*	44.4	44.7	0.723
Height (in)*	67.6	67.6	0.991
Weight (lb)*	173.3	180.0	0.061
Sex (% male)	45.5	51.1	0.228
% Worker's compensation	6.2	5.0	0.687
% Tobacco use	25.5	24.0	0.746
% Preop work status	64.5	65.0	0.923

 *Average values are reported.



Baseline Clinical Assessments

Variable*	BRYAN (n = 242)	Control (n = 221)	Unadjusted P-value
NDI Pain Score	51.4	50.2	0.392
SF-36 PCS	32.6	31.8	0.208
SF-36 MCS	42.3	44.6	0.041
Neck pain	75.4	74.8	0.765
Arm Pain	71.2	71.2	0.976



*Average values are reported.



Cervical Levels Treated

Treatment levels	BRYAN n (% of 242)	Control n (% of 221)
C3-C4	3 (1.2)	0 (0)
C4-C5	12 (4.9)	17 (7.7)
C5-C6	140 (57.9)	110 (49.8)
C6-C7	87 (36.0)	94 (42.5)



Treated 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.



Misrandomized Patients

Reason	# of Patients
Disc space smaller than 14 mm	5
Poor intraoperative visualization of C6-7	4
Prominent clavicle preventing device placement	1
Retraction of airway at C4-5 leading to airway obstruction	1
Inadequate fit of prosthesis at C6-7	1



Surgical and Hospitalization Assessments

Variable	Posterior mean BRYAN	Posterior mean Control	BRYAN – Control (95% HPD)
Operative time (hrs)	2.2	1.4	0.8 (0.7, 0.9)
Blood loss (mls)	91.5	59.6	31.9 (20.7, 43.1)
Hospital stay (days)	1.1	1.0	0.1 (-0.02, 0.22)

Operative Time

The mean operative time for the investigational procedure was higher than that of the control procedure. The operative time required for the investigational procedure decreased with surgeon experience.



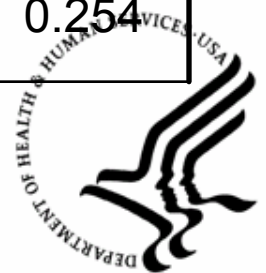
Primary Composite Endpoint

Components	<u>Investigational</u>	<u>Control</u>
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%



Results – Safety Endpoints

Complication	BRYAN (% of 242)	Control (% of 221)	p-value
Serious AE (WHO grade 3 or 4)	26.4	24.9	0.782
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	0.445
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



Results – Secondary Surgical Procedures

Procedure	BRYAN n (% of 242)	Control n (% of 221)
Revision	1 (0.4)	0 (0)
Removal	3 (1.2)	2 (0.9)
Supplemental fixation	0 (0)	6 (2.7)
Reoperation	2 (0.8)	1 (0.5)

Results – Motion at Treated Level

- Evaluated in n=154 BRYAN patients
- Mean angular motion values:
- Preoperative – 6.4°
- 12 months – 7.8°
- 24 months – 7.7°
- Angular motion success = 79.6%



Results – Motion at Adjacent Levels

	Preoperative		12 Months		24 Months	
	BRYAN	Contr	BRYAN	Contr	BRYAN	Contr
Mean Angular Motion (Above)	8.3°	7.8°	9.8°	8.7°	9.1°	8.9°
Mean Angular Motion (Below)	5.0°	5.2°	6.2°	5.8°	6.4°	6.2°



Preservation of Motion

The sponsor has presented radiographic data to demonstrate preservation of motion at the index level in the patients receiving the investigational device. Motion at the index level did not correlate with clinical success.

Further analysis has demonstrated that the motion, as measured by dynamic radiographs, was not significantly different at adjacent levels for the investigational device and for controls.

Please consider how index level and adjacent level motion contribute to the effectiveness of the



Heterotopic Ossification

- Not included among study endpoints and assessments were not planned
- Recent report suggests rate may be as high as 18% following treatment with BRYAN in Europe
- Six BRYAN patients had osteophytes observed on follow-up radiographs.
- US IDE protocol included 14 days of treatment with NSAIDs



Heterotopic Ossification

FDA will ask the panel a question about heterotopic ossification. Prior reports in the literature have described a high rate of 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.



Summary of Clinical Study

- Non-inferiority study → Superiority Study
- Effectiveness
 - Overall success based on 300 implanted patients followed for 24 months
- Safety based on 463 implanted patients



FDA Presentation

- Introduction
- Pre-Clinical Issues
- Clinical Study
- **Statistical Analysis**
- Post-Approval Study
- Panel Questions



P060023

BRYAN Cervical Disc

Statistical Analysis

Jason Schroeder, PhD
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Orthopedic and Rehabilitation Devices Panel Meeting
July 17, 2007



Clinical Trial Overview

- Randomized, controlled, multicenter trial
- 463 patients (242 BRYAN, 221 Control) treated at 30 centers
- Follow-up evaluations at 6 weeks, and 3, 6, 12, and 24 months
- Pre-planned Bayesian interim analysis when 300 patients had 24-month data



Trial Objectives

- Assess whether overall success rate at 24 months for BRYAN is non-inferior to Control
- Determine whether BRYAN is superior to Control with respect to overall success rate
- Determine whether BRYAN is non-inferior (or superior) to Control with respect to individual effectiveness and radiographic variables
- Compare adverse event rates between BRYAN and Control



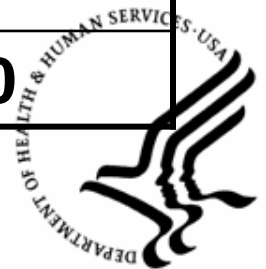
Randomization

- 1:1 randomization, stratified by center, fixed block size of 4
- 463 patients randomized and received treatment
 - 12 patients randomized to BRYAN, but received Control instead
 - 1 patient randomized to Control, but received BRYAN instead
- An additional 117 patients (37 BRYAN, 80 Control) were randomized, but never received treatment



Randomization, continued

Reason	BRYAN	Control
Insurance denied	7	1
Condition improved	7	11
Dissatisfied w/ randomization	0	32
Inclusion/exclusion criteria not met	3	5
Decided not to participate	6	7
Combination	0	2
Other	11	18
Unknown	3	4
TOTAL	37	80



Randomization, continued

- Imbalance between randomized Control (80) and BRYAN (37) patients dropping out prior to receiving treatment
- In particular,
 - Control: 40% (32/80) dissatisfied w/ randomization
 - BRYAN: None (0/37) dissatisfied w/ randomization
- Comparisons between the 463 study and 117 non-study patients with respect to demographics and baseline variables
 - No clinically relevant differences found

Primary Endpoint

- Was the patient an “Overall Success” at 24 months?
- Overall Success is a composite endpoint with both effectiveness and safety components:
 - 1) At least 15 point improvement on NDI
 - 2) Maintained/improved neurological status
 - 3) No serious AEs that were implant/surgery related
 - 4) No additional surgery classified as “failure”
- Patient must succeed on all 4 parts to be considered an overall success

Study Hypotheses

- Non-inferiority hypothesis (with non-inferiority delta = 10%):
 - Overall success rate for BRYAN (p_B) is not lower than Control (p_C) by more than 10%:

$$\text{Non-inferiority: } p_B > p_C - 0.10$$

- BRYAN non-inferior to Control if posterior probability of Non-inferiority is at least 95%:

$$\text{Pr(Non-inferiority | Data)} > 0.95$$



Study Hypotheses, continued

- If non-inferiority claimed, follow with test of superiority hypothesis:
 - Overall success rate for BRYAN (p_B) is greater than Control (p_C):
Superiority: $p_B > p_C$
- BRYAN superior to Control if posterior probability of Superiority is at least 95%:
 $\Pr(\text{Superiority} \mid \text{Data}) > 0.95$

Interim Analysis Plan

- PMA based on results of pre-specified Bayesian interim analysis of primary endpoint
- Non-informative priors were used
- Interim analysis was scheduled to occur when 300 patients had 24-month overall success evaluated
- At time of interim analysis, 333 patients (168 BRYAN, 165 Control) had reached 24-month evaluation window, but only 300 (160 BRYAN, 140 Control) with outcomes evaluated



Interim Analysis, continued

- Bayesian interim analysis method:
 - Since 12-month outcomes may carry information about 24-month outcomes, use ***all available*** 12- and 24-month data
 - Any patient with at least 12-month data contributes to analysis, but focus is on overall success rate at 24 months
 - Using all available 12- and 24-month data, posterior probability of non-inferiority:

$$\begin{aligned} & \Pr(\text{Non-inferiority} \mid \text{Data}) \\ &= \Pr(p_B > p_C - 0.10 \mid \text{Data}) \end{aligned}$$

Analysis Datasets

- Primary analysis dataset
 - All patients receiving a device; analyzed according to treatment received
- Per-protocol dataset
 - Excludes patients with major protocol violations (e.g., not meeting entry criteria, received wrong device)



Primary Analysis Dataset

- Of 242 BRYAN patients, 5 (2.1%) have neither 12- nor 24-month data – these 5 do not contribute to analysis
- Of 221 Control patients, 17 (7.7%) have neither 12- nor 24-month data – these 17 do not contribute to analysis
- All other treated patients contribute to the Bayesian interim analysis



Results – Overall Success

Primary analysis dataset

	Estimated 24-mo success rate*	95% HPD
BRYAN, p_B	80.4%	(74.3%, 85.8%)
Control, p_C	71.8%	(65.0%, 78.9%)
$\Pr(p_B > p_C - 0.10 \mid \text{Data}) > 99.9\%$ → Non-inferiority criterion met		

*Posterior means.



Per-Protocol Dataset

- Of 242 BRYAN patients, 27 (11.2%) excluded for per-protocol analysis
- Of 221 Control patients, 48 (21.7%) excluded for per-protocol analysis
- There appears to be an imbalance in number of patients excluded due to major protocol violations

Per-Protocol Dataset, continued

- Of 215 BRYAN patients, 5 (2.3%) have neither 12- nor 24-month data – these 5 do not contribute to analysis
- Of 173 Control patients, 13 (7.5%) have neither 12- nor 24-month data – these 13 do not contribute to analysis
- Remaining patients contribute to Bayesian interim analysis

Results – Overall Success

Per-protocol dataset

	Estimated 24-mo success rate*	95% HPD
BRYAN, p_B	82.7%	(76.7%, 88.3%)
Control, p_C	75.0%	(67.2%, 82.6%)
$\Pr(p_B > p_C - 0.10 \mid \text{Data}) > 99.9\%$ → Non-inferiority criterion met		

*Posterior means.



Results – Overall Success

Sensitivity Analyses

- Sensitivity analyses conducted to assess impact of the 33 patients (8 BRYAN, 25 Control) missing 24-month data
- Non-inferiority claim supported by all sensitivity analyses...
- ...even in worst-case scenario:
 - Any missing BRYAN = failure
 - Any missing Control = success
 - Estimated difference $p_B - p_C = 1.6\%$ (95% CI: -7.5%, 10.8%)
 - Test for non-inferiority yielded p-value = 0.0065



Results – Overall Success

Sensitivity Analyses

- If all missing outcomes are counted as failures:
 - Estimated BRYAN success rate $p_B = 76.8\%$ (129/168)
 - Estimated Control success rate $p_C = 60.0\%$ (99/165)
- But, this analysis may be biased against Control group due to its higher rate of missingness



Results – Overall Success

- Sponsor tested for superiority after meeting non-inferiority criterion
- Primary analysis dataset
 - $\text{Pr}(\text{ Superiority } | \text{ Data}) = 96.9\%$
 - *Superiority criterion met*
- Per-protocol dataset
 - $\text{Pr}(\text{ Superiority } | \text{ Data}) = 94.4\%$
 - *Superiority criterion not met*



Labeling – Superiority Claim

FDA will 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.



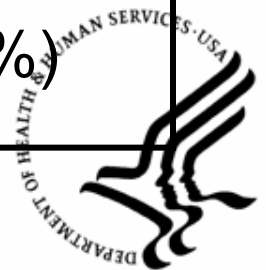
Results – Neck Disability Index (24-month interim results)

	BRYAN (n=159)	Control (n=140)
Mean NDI (min, max)	16.4 (0, 74.0)	20.0 (0, 78.0)
Mean change from baseline	-32.1	-28.7
NDI success: > 15 points improvement?	84.3% (134/159)	75.7% (106/140)



Results – Neurological Status (24-month interim results)

	BRYAN (N=159)	Control (N=140)
Overall: n (%)	149 (93.7%)	128 (91.4%)
Motor: n (%)	157 (98.7%)	136 (97.1%)
Sensory: n (%)	154 (96.9%)	135 (96.4%)
Reflexes: n (%)	155 (97.5%)	136 (97.1%)



Results – Secondary Effectiveness

Primary analysis dataset

Variable	BRYAN p_B (%)	Control p_C (%)	$p_B - p_C$ (95% HPD)
NDI	85.0	76.2	8.8 (0.2, 16.9)
Neuro	92.4	90.9	1.5 (-4.5, 7.5)
FSU	97.9	97.1	0.8 (-3.2, 5.1)
Neck pain	93.6	91.6	2.0 (-3.9, 8.0)
Arm pain	93.3	88.3	4.9 (-1.7, 11.1)
SF-36 PCS	84.9	88.9	-4.0 (-11.8, 3.0)
SF-36 MCS	68.4	72.8	-4.3 (-14.1, 5.4)

Summary

- Sponsor conducted a randomized, controlled, multicenter trial, with 463 patients at 30 centers
- All analyses support claim that BRYAN Cervical Disc is non-inferior to the Control with respect to Overall Success rate at 24-months
- Results are inconclusive regarding claim of superiority of BRYAN Cervical Disc compared to Control



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P060023

BRYAN Cervical Disc

Post-Approval Study (PAS)

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Outline

- General Principles/Rationale for PAS
- Postmarket Questions
- Proposed PAS Outline
- Discussion of PAS Outline
- PAS Issues for Panel Discussion



Reminder

- The discussion of a Post-Approval Study (PAS) prior to a formal recommendation on the approvability of this PMA should not be interpreted to mean that FDA is suggesting the Panel find the device approvable
- The plan to conduct a PAS does not decrease the threshold of evidence required to find the device approvable
- The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness in order for the device to be found approvable



PAS General Principles

- Objective is to evaluate device performance and potential device-related problems in a broader population over an extended period of time after premarket establishment of reasonable device safety and effectiveness
- Post-approval studies **should not** be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of a reasonable assurance of device safety and effectiveness.



Post-Approval Study Uses

- Gather postmarket information
 - Longer-term device performance
 - Community performance (clinicians & patients)
 - Effectiveness of training programs
 - Sub-group performance
 - Real world experience & rare adverse events
- Address Panel recommendations



Long-Term Issues for BRYAN Cervical Disc

- Survival of the implant
- Overall success of the device, compared to Arthrodesis
- Effect on adjacent levels
- New complications from particle and wear debris
- Reported complications that may affect the longer-term use of the device:
 - anterior-posterior disc migration
 - heterotopic ossification
 - kyphosis of the functional spinal unit



Overview of Sponsor's PAS Outline

Study Design	Prospective Cohort, non-inferiority design, with Arthrodesis patients as concurrent controls
Population	Patients from IDE and CAS, minimum 200 (100 each from control and investigational arms)
Data Collection	4, 5, 7 years post-operation
Primary Outcome	A composite success outcome: NDI, Neurological status, no serious adverse event, no device failure
Secondary Outcomes	All other effectiveness and safety outcomes in IDE study

Discussion of Sponsor's PAS Study Design

- Study is hypothesis-driven with non-inferiority design
- Delta level to be defined



Discussion of Sponsor's PAS (cont.) Success Outcome

- Primary outcome is a composite success outcome, including NDI improvement, neurological status, no serious adverse event, and no device failure
- Criteria for NDI improvement
- Radiographic measurements



Discussion of Sponsor's PAS (cont.)

Study Population

- Consists of patients from PMA cohort.
- Data on representativeness of patients and physicians in PMA study are needed
- Inclusion of new patients:
 - the generalizability of the study results
 - device performance under actual conditions of use
 - sample size requirements



Discussion of Sponsor's PAS (cont.)

Sample Size

- A minimum of 200 patients from PMA cohort
- To be clarified/developed:
 - how the patients will be selected
 - whether this will provide sufficient power for statistical analysis
 - plan to minimize loss to follow-up
 - measures to be taken if the number falls below 200 during follow-up



PAS Issues for Panel Discussion

1) Adjacent Segment Degeneration:

- *Cervical disc replacement may preserve segmental motion and reduce the progression of adjacent segment degeneration ¹*
- *The effect of BRYAN Cervical Disc prosthesis on adjacent levels is not yet known*

1. Acosta, et al. Neurosurg Clin N Am, 2005 (16) 603-07



PAS Issues for Panel Discussion

2) Other Complications:

- *Heterotopic ossification (HO), which may result in subsequent loss of movement of the implanted disc*²
- *Post-operative Kyphotic change of the Functional Spinal Unit (4-6°) and overall cervical spine (4°) has been reported and clinical significance is unclear*³

2. Leung C, et al. *Neurosurgery* 2005; 57(4):759-63

3. Sears W, et al. *J Spinal Disord Tech* 2007; 20: 1-6



PAS Issues for Panel Discussion

3) “Real-World” Performance

- *The current PAS outline only includes patients from the PMA cohort*
- *Patients selection on the effects of BRYAN Cervical Disc implantation has been noted ⁴*

4. Pickett, GE, et al. *J Neurosurg Spine* 2006;4: 98–105



PAS Issues for Panel Discussion

4) Length of Follow-up

- *The current PAS outline proposes to follow patients up to 7 years post-operation*
- *The design features and materials used on this device are unique*



THANK YOU !



FDA Presentation

- Introduction
- Pre-Clinical Issues
- Clinical Study
- Statistical Analysis
- Post-Approval Study
- Panel Questions



Pre-Clinical Issues

1. The sponsor has provided a combination of engineering testing, biocompatibility testing, functional animal studies, device retrievals and analysis, radiographic follow up and clinical observations to address the degree of constraint, materials of articulation, and other design features of the Bryan Cervical Disc Prosthesis. Please discuss the testing, the data and the clinical observations regarding:

- device wear
- material and particulate reaction
- device expulsion or migration
- implant durability and reliability and
- sheath purpose and function.



Preservation of Motion

2. The sponsor has presented radiographic data to demonstrate preservation of motion at the index level in the patients receiving the investigational device. Motion at the index level did not correlate with clinical success

Further analysis has demonstrated that the motion, as measured by dynamic radiographs, was not significantly different at adjacent levels for the investigational device and for controls.

Please discuss how index level and adjacent level motion contribute to the effectiveness of the investigational device.



Labeling

3. Please discuss the adequacy of the device labeling.

What information related to mean operative time should be included in the labeling?

What information related to cervical levels should be included?



Safety

4. Under CFR 860.7(d)(1) , safety is defined as reasonable assurance, based on valid scientific evidence, that the probable benefits to health under conditions of the intended use, when accompanied by adequate directions for use and warnings against unsafe use, outweigh any probable risks.

Considering the adverse event rates for the subject device, please discuss whether the clinical data in the PMA provide reasonable assurance that the device is safe.



Efficacy

5. Please discuss whether the clinical data in the PMA provide reasonable assurance that the proposed device is effective.



Superiority

6. The sponsor has presented comparisons of the investigational and control procedures based on a variety of datasets (e.g., as randomized, as implanted). Please discuss whether these prespecified secondary analyses support the sponsor's claim that the investigational device is superior to the control procedure with respect to the overall success endpoint



NOTE TO PANELISTS: *FDA's inclusion of a question regarding a Post approval study 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 premarket approval and a recommendation from the Panel on whether or not to approve a device must be based on the pre-market data. The pre-market 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.*



Post-Approval Study

7. Please discuss the following issues related to a potential post-approval study (PAS):

Is it necessary to recruit new patients/physicians in the PAS or to use an alternative approach to evaluate the device's "real-world" performance after approval?

Is 7 year follow up appropriate for this device?



Post-Approval Study

Question continued from previous slide

7 . Please discuss the following issues related to a potential post-approval study (PAS):

Should treated level and adjacent level motion and the occurrence or progression of adjacent-segment disease be assessed in both groups in the PAS?

Should the rate of HO and kyphosis after Bryan Cervical Disc implantation be investigated in the PAS?

