

Artificial Intervertebral Disc Arthroplasty for Treatment of Degenerative Disc Disease of the Cervical Spine



Assessment
Program
Volume 22, No. 12
February 2008

Executive Summary

Background

An estimated 60% of individuals older than 40 years have radiographic evidence of cervical degenerative disc disease (DDD) secondary to spondylosis. Symptoms of DDD include neck and arm pain associated with radiculopathy or myelopathy, respectively. Untreated, the signs and symptoms of cervical DDD may decrease or stabilize, but may worsen. Initial conservative, noninvasive therapies aim to relieve pain and prevent permanent injury to the spinal cord and nerve roots. Typically, if at least 2 to 6 months of conservative treatment is ineffective, or the patient becomes unable to perform activities of daily living, surgical intervention is indicated.

Anterior cervical discectomy and fusion (ACDF) using autologous or allogeneic bone has long been considered the definitive surgical treatment for symptomatic DDD of the cervical spine. More recently, artificial intervertebral disc arthroplasty (AIDA) has been proposed as an alternative procedure in patients for whom ACDF is indicated. AIDA uses virtually the same surgical approach as ACDF, but differs in that an artificial disc device is secured in the intervertebral space, rather than bone. It has been hypothesized that properly performed AIDA maintains anatomical disk space height, normal segmental lordosis, and physiological motion patterns at the index and adjacent cervical levels. Furthermore, maintenance of physiological spinal motion patterns has been proposed to reduce risk for subsequent development of adjacent-level DDD secondary to altered kinematics at segments above or below the fusion site. These hypotheses have been used as rationale for the development and use of artificial disc devices.

Objective

The objective of this Assessment is to determine whether AIDA improves health outcomes when used as an alternative to anterior-plated ACDF for patients with DDD of the cervical spine.

Search Strategy

MEDLINE[®] was searched (via PubMed) using the terms “cervical disc” and “replacement” or “prosthesis” and also with the term “cervical arthroplasty.” The search was performed through August 2007, limited to English-language articles on human subjects.

Selection Criteria

The central focus of the Assessment is the randomized, investigational device exemption (IDE) clinical trial of the Prestige ST artificial disc, which was approved (via premarketing application [PMA] approval) by the U.S. Food and Drug Administration (FDA) in July 2007. Other studies were not included as they used a precursor device to the Prestige disc and presented preliminary data.



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Clinical results for the Bryan disc are available from the FDA, and are summarized in the Appendix of this Assessment, even though the device has not received final approval.

Main Results

The available evidence for the Prestige ST disc consists of one unblinded, randomized, controlled trial (RCT) in which disc arthroplasty (n=276) was compared to anterior-plated ACDF using allograft bone (n=265). The trial was a noninferiority design ($\delta=0.1$), that used Bayesian analysis of 12- and 24-month data with noninformative or uniform priors to calculate the posterior probabilities of noninferiority. A secondary analysis to assess statistical superiority was performed for all investigational group outcomes that were shown noninferior to corresponding control group outcomes.

Patients (mean age 43–44 years, 46% males) had neck and arm pain secondary to DDD at a single level between C3 and C7 with documented presence of a herniated disc or osteophyte formation. Prior to surgery, all had received conservative therapy for a period of less than 6 weeks (4–6% of cases), from 6 weeks to 6 months (29–34%), and for more than 6 months (60–63%).

In this study, AIDA with the Prestige disc was shown to be statistically noninferior to ACDF in all three primary outcome variables (Neck Disability Index [NDI], neurological status, and functional spinal unit [FSU] height). The neurological status outcome reached the prespecified level for statistical superiority, but neither the NDI nor the FSU did so. The primary composite endpoint of the trial (“overall success”) was defined as attainment of all of the following: success as defined for the three primary outcome variables, plus a requirement for no serious implant- or procedure-associated adverse event and no additional surgical procedure classified as a failure. Because of difficulty in evaluating FSU height, due to anatomical interference with the radiographic image, an alternate overall success determination was also made based on the criteria without the FSU height. Both overall success composite endpoints for AIDA were found to be statistically noninferior, as well as superior to ACDF. However, it appears that the neurological status outcome was the main driver of superiority in overall success for AIDA in this trial, given the lack of statistical superiority for the NDI and FSU outcomes.

Perioperative and surgical outcomes were similar between groups. Radiographic fusion was shown for 97.5% of ACDF patients at 24-month follow-up. Cervical neck angular motion was maintained at preoperative levels at the surgical level in arthroplasty patients and restricted, as expected, in ACDF patients. Radiographic evidence of adjacent-segment degeneration was not assessed, nor is information available from the clinical study on wear debris in the disc space. Secondary surgical procedures, classified as revisions, hardware removals, and supplemental fixations were reported, but their clinical relevance is not clear.

Author’s Comments and Conclusions

Analysis of the results of the Prestige ST disc IDE pivotal trial data raises a number of concerns. In particular, the 24-month follow-up period does not permit conclusions about long-term device performance, durability, and potential need for revision. These are key considerations for the young (mid-40s) patients who underwent arthroplasty in the Prestige study and for those likely to undergo AIDA in clinical practice. This concern is underscored by the FDA approval conditions that the Prestige device manufacturer continue the IDE study for 7 years to evaluate the safety and function of the device, and perform a 5-year, enhanced surveillance study to more fully characterize adverse events associated with AIDA in a broader patient population.

A second concern with the Prestige trial is that the noninferiority study design makes it difficult to discern whether or not AIDA produces a net health benefit compared to ACDF. Thus, the statistical superiority (benefit) of the overall success outcome for AIDA compared to ACDF appears to have been driven solely by the reported statistical superiority of the neurological status variable, which was only one of three components of that composite endpoint. However, the investigators provided no details on how the neurological status itself was measured and evaluated, thus precluding analysis of its three subcomponents, their clinical relevance, and their relative contribution to the overall success rate. Thirdly, failure to blind physician outcome assessors and patients to study

treatments could have biased results toward favoring disc arthroplasty (“new” treatment) over ACDF (“old” treatment). Finally, the Prestige disc trial provides no direct evidence on subsequent adjacent-level DDD in control or investigational group patients.

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether artificial intervertebral disc arthroplasty as a treatment for DDD of the cervical spine meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

1. The technology must have final approval from the appropriate governmental regulatory bodies.

One cervical disc arthroplasty product (Prestige ST Cervical Disc) received FDA marketing approval July 16, 2007. The Prestige ST Cervical Disc is indicated in skeletally mature patients for reconstruction of the disc from C3-C7 following single-level discectomy for intractable radiculopathy and/or myelopathy. The device is implanted via an open anterior approach. Intractable radiculopathy and/or myelopathy should present with at least one of the following items producing symptomatic nerve root and/or spinal cord compression which is documented by patient history (e.g., pain [neck and/or arm pain], functional deficit, and/or neurological deficit), and radiographic studies (e.g., CT, MRI, X-rays, etc.): 1) herniated disc, and/or 2) osteophyte formation.

A second product (Bryan Cervical Disc) received an approvable decision by an FDA advisory panel July 17, 2007, but had not received final marketing approval at the time this Assessment was prepared. The Bryan disc is indicated for use in patients similar to those for whom the Prestige device is indicated.¹

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

One noninferiority design RCT is available that compares AIDA (n=276) with anterior plated ACDF using allograft bone (n=265). For several reasons, this evidence is insufficient to support conclusions concerning the effect of AIDA on health outcomes.

First, the evidence from the IDE trial does not permit conclusions on the long-term performance of AIDA and adverse events. Device performance, durability, and revisability are key considerations for the relatively young population enrolled in the pivotal trial. The available evidence also is insufficient to permit conclusions as to whether or not AIDA affects the postsurgical development of adjacent-level DDD. By contrast, conclusions on the relative safety of cervical disc arthroplasty appear sufficiently supported in the short term.

Second, although the study results consistently demonstrated statistical noninferiority for AIDA versus ACDF in all three primary outcome variables, and for the overall success composite outcome, the neurological status was the only primary outcome variable for which statistical superiority was shown. It thus appears to be the primary determinant of statistical superiority for the overall success of the disc versus ACDF. However, quantitative data on the neurological status are not available, which precludes analysis of its clinical meaning and relevance. Further, the study failed to demonstrate statistical superiority for AIDA in terms of the NDI, which is a clinically validated, multidimensional outcome measure of neck pain and disability caused by cervical DDD. Taken together, these uncertainties make it difficult to determine the effect of AIDA on health outcomes in more specific, validated terms than the ill-defined neurological status variable and by extension the overall success rate. Finally, failure to blind patients and physician outcomes assessors to the study treatment allocation could have biased study results, favoring disc arthroplasty over ACDF.

¹ As this Assessment was in press, the ProDisc™-C Total Disc Replacement received premarketing application (PMA) approval on December 17, 2007 (<http://www.fda.gov/cdrh/pdf7/p070001.html>).

3. The technology must improve the net health outcome; and
 4. The technology must be as beneficial as any established alternatives.

The evidence does not permit conclusions as to whether artificial intervertebral disc arthroplasty for the cervical spine improves the net health outcome or is as beneficial as established alternatives.

5. The improvement must be attainable outside the investigational settings.

Whether artificial disc arthroplasty for the cervical spine improves the net health outcome has not been established in the investigational setting.

Based on the above, artificial intervertebral disc arthroplasty for the treatment of patients with cervical degenerative disc disease does not meet the TEC criteria.

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Published in cooperation with Kaiser Foundation Health Plan and Southern California Permanente Medical Group.

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Assessment Objective

The objective of this Assessment is to determine whether AIDA improves health outcomes when used as an alternative to anterior plated ACDF for patients with DDD of the cervical spine.

Background

Cervical Degenerative Disc Disease

Cervical degenerative disc disease (DDD) is a manifestation of spinal spondylosis that causes deterioration of the intervertebral discs of the cervical spine (Emery 2001). Intervertebral discs are soft, spongy pads of tissue located between individual vertebrae, and act to absorb shock and stress of motion. While the exact causes of DDD are unclear, it is associated with aging, during which discs begin to lose proteoglycans, particularly chondroitin sulfate, leading to moisture loss. Dessicated discs become inelastic, with development of small microfissures and herniation of the nucleus pulposus. This is followed by settling and collapse of the index level segment, which affects the structure of the spinal column, causes abnormal spinal motion patterns and eventually results in the formation of spurs where the annular fibers insert near the end plate, in the facet joints, and at the uncovertebral joints. Bone spurs at the uncovertebral regions narrow the foramen and may impinge nerve roots, resulting in pain and, ultimately, disability. Symptoms of cervical DDD include arm pain, weakness, and paresthesias associated with cervical radiculopathy. Disc herniation, osteophytes, kyphosis or instability that compress the spinal cord result in myelopathy, which is manifested by subtle changes in gait or balance, weakness in the arms or legs and numbness of the arms or hands, in severe cases.

The prevalence of DDD secondary to cervical spondylosis increases with age. An estimated 60% of individuals older than 40 years have radiographic evidence of cervical DDD. By age 65, some 95% of men and 70% of women have at least one degenerative change evident at radiographic examination. It is estimated that some 5 million adults in the U.S. are disabled to an extent by spine-related disorders, although only a small fraction of those are clear candidates for spinal surgery.

The Nationwide Inpatient Sample (NIS) is a database maintained by the Agency for Healthcare Research and Quality that represents a 20% random sample of all discharges from nonfederal hospitals within the U.S., based on ICD-9-CM procedure codes. A study of NIS data for the years 1995 through 2003 shows that overall utilization of cervical spinal fusion in the U.S. increased from 26 per 100,000 to 50 per 100,000, with symptomatic DDD the primary diagnosis, representing about 85% of cervical DDD cases in 2003 (Cowan et al. 2006).

Treatment of Cervical DDD

Conservative Therapy. If untreated, the signs and symptoms of cervical DDD may decrease or stabilize, but may worsen (Emery 2001). Initial conservative, noninvasive therapies are aimed to relieve pain and prevent permanent injury to the spinal cord and nerves. These include rest; application of ice or heat; anti-inflammatory or analgesic agents; exercise; physical therapy; or support appliances such as a cervical collar or pillow. Typically, if 6 months of conservative treatment is ineffective, or the patient becomes unable to perform activities of daily living due to progression of pain or neurological symptoms in a shorter time frame, surgical intervention is indicated. Both radiculopathy and myelopathy are manifestations of cervical DDD that warrant consideration for surgical intervention. Axial neck pain alone from cervical spondylosis is typically treated conservatively. However, certain patients without radiculopathy or myelopathy but with significant, intractable neck pain have cervical stenosis that requires surgical intervention if conservative treatments fail.

Surgical Fusion. Numerous surgical methods, instrumentation, and bone graft sources for spinal fusion have been investigated over the past several decades. Anterior cervical discectomy and fusion (ACDF) is currently considered definitive surgical treatment for symptomatic single-level DDD of the cervical spine (Irwin et al. 2005). The goals of ACDF are to relieve pressure on the spinal nerves (decompression) and to restore spinal column alignment and stability. Resolution of pain and neurological symptoms may be expected in more than 80% to 100% of ACDF patients (Xie and Hurlbert 2007; Yue et al. 2005). The current procedure involves an anterolateral surgical approach, decompression of the affected spinal level,

discectomy, and emplacement of either autograft or allograft bone in the prepared intervertebral space to stimulate healing and eventual fusion between the vertebral endplates. A metal anterior cervical plate is attached to the adjoining vertebral bodies to stabilize the fusion site, maintain neck lordosis, and reduce the need for prolonged postoperative brace application that is needed following ACDF without an anterior plate.

The choice of bone material for interbody fusion in ACDF has important clinical implications. Allograft bone has several drawbacks, including a minute (albeit unproven) risk of infectious disease transmission; possible immunological reaction to the allograft; and, possible limited commercial availability of appropriate graft material (Malloy and Hilibrand 2002). In contrast, the use of autograft bone in ACDF has potentially substantial morbidities at the harvest site, generally the iliac crest (Galler and Sonntag 2003). These include moderate-to-severe, sometimes prolonged pain; deep infection; adjacent nerve and artery damage; and, increased risk of stress fracture. Although there may be slight differences between autograft and allograft sources in the postoperative rate of union, clinical studies demonstrate similar rates of postoperative fusion (90–100%) and satisfactory outcomes for single-level, anterior plated ACDF using either bone source (Fraser and Hartl 2007; Samartzis et al. 2005; Yue et al. 2005; Suchomel et al. 2004). Thus, the choice of graft material involves a trade-off between the risks specific to autograft harvest versus those specific to use of allograft material. This choice is usually left to the patient, based on thorough explanation of the relative risks and benefits by the surgeon.

Artificial Intervertebral Disc Arthroplasty.

Artificial intervertebral disc arthroplasty (AIDA) is proposed as an alternative to ACDF for patients with symptomatic cervical DDD (Anderson et al. 2007; Smucker and Sasso 2006; Phillips and Garfin 2005; Anderson and Rouleau 2004). Disc arthroplasty and ACDF for single-level disease have very similar surgical indications, primarily unremitting pain due to radiculopathy or myelopathy, weakness in the extremities, or paresthesia (Brown and Heller 2006; McAfee 2004). However, the chief complaint in AIDA candidates should be radicular or myelopathic symptoms in the absence of significant spondylosis. Patients with advanced spondylosis or hard disc herniations have a

separate pathology and require a different surgical approach (Brown and Heller 2006).

In AIDA, an artificial disc device is secured in the prepared intervertebral space rather than bone. An anterior plate is not placed to stabilize the adjacent vertebrae and a postsurgical external orthosis is usually not required. The surgical procedure and perioperative complications of AIDA are nearly identical to those of anterior fusion (Goffin 2006). It is suggested that AIDA maintains anatomical disk space height, normal segmental lordosis, and physiological motion patterns at the index and adjacent cervical levels (Sears et al. 2006). This has been proposed to reduce the risk of adjacent-level DDD above or below a fusion site, and has been the major rationale driving device development and use. However, while biomechanical modeling studies have suggested that altered adjacent segment kinematics following fusion may lead to adjacent-level DDD, the clinical relevance of these changes has not been established (Anderson et al. 2007; Phillips and Garfin 2005; Wigfield et al. 2002).

The Table in Appendix A summarizes information on 7 artificial cervical discs. One (Prestige ST) has received FDA marketing approval, one (Bryan) received an “approvable” decision in July 2007, and the others are in various stages of development in the U.S. The Prestige and Bryan discs are completely different in structure and composition; the former is a metal-on-metal ball and trough device while the latter is a metal-on-polymer biarticulating sandwich model. Both are characterized as semi-constrained but utilize different primary fixation methods. This Assessment found no direct comparative data on any of these discs to base selection of one over another.

Outcome Measures

Various outcome measures have been used for AIDA studies. Three primary outcome variables in the Prestige trial were the Neck Disability Index (NDI), neurological status, and functional spinal unit height (FSU). The NDI is a validated multidimensional instrument that measures the effects of pain and disability on a patient’s ability to manage everyday life (Vernon and Mior 1991). It is a modification of the Oswestry Low Back Pain Index, based on the response to 10 questions that focus on neck pain intensity, personal care, lifting, reading, headaches, concentration, work, driving, sleeping, and recreation. The response to each question ranges

from 1 to 5, with a lower numeric score representing a better pain and disability status for that variable. A total NDI score is obtained by adding individual question scores and dividing by the maximum total of 50 if all questions are answered. Therefore, NDI scores range from 0% to 100%, with a lower percentage indicating less pain and disability.

The neurological status is a composite measure of motor function, sensory function, and deep tendon reflexes. It is used to judge if patients are within normal parameters for those categories based on physiological measurement. Neurological success in the Prestige trial was based on postoperative maintenance or improvement of condition as compared to preoperative status for each component.

The anterior FSU height is a radiographic measure of interdiscal space. Comparison of the immediate postoperative FSU height with the 6-week postoperative value shows whether or not the disc space has decreased, which indicates graft or device subsidence has occurred.

Secondary outcome measures include the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) mental (MCS) and physical (PCS) component summaries, neck and arm pain status, patient satisfaction, patient global perceived effect, gait assessment, foraminal compression test, adjacent level stability and measurements, return to work, and physician's perception.

FDA Status. One cervical disc arthroplasty product (Prestige ST Cervical Disc) received FDA premarket application (PMA) approval as a Class III device on July 16, 2007. The Prestige ST Cervical Disc is indicated in skeletally mature patients for reconstruction of the disc from C3-C7 following single-level discectomy for intractable radiculopathy and/or myelopathy. The device is implanted via an open anterior approach. Intractable radiculopathy and/or myelopathy should present with at least one of the following items producing symptomatic nerve root and/or spinal cord compression which is documented by patient history (e.g., pain [neck and/or arm pain], functional deficit, and/or neurological deficit), and radiographic studies (e.g., CT, MRI, X-rays, etc.): 1) herniated disc, and/or 2) osteophyte formation.

A second disc (Bryan® Cervical Disc, Medtronic) was deemed “approvable” by an FDA advisory committee on July 17, 2007, for treatment using an anterior approach of single-level cervical DDD defined as any combination of the following: disc herniation with radiculopathy; spondylotic radiculopathy; disc herniation with myelopathy, or spondylotic myelopathy. Final approval is expected in late 2007.

Several other devices are under study in FDA IDE trials in the U.S., but final approval of those is not expected for several years (see Appendix A).²

Methods

Search Strategy

MEDLINE® was searched (via PubMed) using the terms “cervical disc” and “replacement” or “prosthesis” and also with the term “cervical arthroplasty.” The search was performed with no time limitation through August 2007, but limited to English-language articles on human subjects. Review articles and meta-analyses provided background information. The bibliographies of retrieved articles were consulted to identify references that may have been overlooked by the electronic search. The “related articles” function was used in conjunction with key articles to identify other papers that may have been missed by the search process. Manufacturers and other vendor websites were consulted for information on commercial products.

Study Selection

The central focus of the Assessment is the randomized IDE clinical trial of the Prestige ST artificial disc. Clinical results for the Bryan disc are not considered in detail in the Review of Evidence as the device has not received final FDA approval. Data from the Bryan IDE PMA submission are compiled in the Appendix of this Assessment. Other studies were not included as they either used a precursor device to the current approved iteration (Prestige ST) or presented preliminary or incomplete data (Bryan).

Medical Advisory Panel Review

This Assessment was reviewed by the Blue Cross and Blue Shield Association's Medical Advisory Panel (MAP) on October 17, 2007.

² As this Assessment was in press, the ProDisc™-C Total Disc Replacement received premarketing application (PMA) approval on December 17, 2007 (<http://www.fda.gov/cdrh/pdf7/p070001.html>)

To maintain the timeliness of the scientific information in this Assessment, literature search updates were performed subsequent to the Panel's review (see "Search Methods"). If the search updates identified any additional studies that met the criteria for detailed review, the results of these studies were included in the text where appropriate. There were no studies that would change the conclusions of the Assessment.

Formulation of the Assessment

Patient Indications

Candidates for surgical intervention have chronic pain or neurologic symptoms secondary to cervical DDD at a single level between C3 and C7, lack of improvement with at least 6 weeks of nonoperative treatment, and no contraindications for the procedure. The indications and contraindications for cervical AIDA are fundamentally the same as those for ACDF, thus making artificial cervical disc arthroplasty an option in patients for whom ACDF is indicated.

Specific contraindications for AIDA include the presence of an active infection and allergy to stainless steel. Other contraindications include cervical instability; more than one cervical level requiring surgical treatment; fused level adjacent to the treatment level; severe facet joint pathology; osteopenia, osteomalacia, or spinal metastases; and presence of osteoporosis.

Technologies to be Compared

Artificial intervertebral disc arthroplasty will be compared to single-level ACDF utilizing anterior plate fixation and an interbody allograft bone disc. However, the only available complete data are for the Prestige disc.

Health Outcomes

Benefits. Potential benefits of AIDA for treatment of cervical spine DDD include pain relief; amelioration of neurologic symptoms; maintenance of index level motion and function; and prevention of adjacent-level DDD.

Harms. Potential harms of AIDA include worsened pain and symptoms; perioperative complications; and, device- and procedure-specific complications, for example, revision to ACDF.

Specific Assessment Question

Does AIDA improve health outcomes in terms of pain relief, amelioration of neurologic

symptoms, and restoration of function among patients with chronic pain and neurologic symptoms caused by radiculopathy or myelopathy secondary to single-level DDD of the cervical spine, as compared to ACDF utilizing anterior fixation and allograft bone interbody graft?

Review of Evidence

Prestige ST Disc IDE Clinical Trial

Methods. Information on the pivotal IDE trial submitted in support of the Medtronic PMA application for the Prestige ST artificial disc is available in the peer-reviewed literature (Mummaneni et al. 2007) and in the PMA Summary of Safety and Effectiveness submitted to the FDA (<http://www.fda.gov/cdrh/pdf6/p060018.html>). Both data sources were used in this analysis. The IDE trial was a multicenter (34 sites), nonblinded, randomized, controlled study of 541 patients (276 investigational and 265 control patients) that compared ACDF using allograft bone and anterior cervical plate fixation with the Prestige ST artificial disc to treat DDD. Inclusion criteria comprised DDD accompanied by neck pain at a single level between C3 and C7 confirmed by history and radiographic studies; presence of a herniated disc and/or osteophyte formation; at least 6 weeks of unsuccessful conservative treatment or signs of progression or spinal cord/nerve root compression with continued nonoperative care; no previous surgical intervention at involved level or planned procedures at involved or adjacent level; older than 18 years of age; preoperative NDI score greater than 30; preoperative neck pain score of greater than 20 on Neck and Arm Pain Questionnaire; and not pregnant.

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

Adjacent level motion was also evaluated. At each evaluation timepoint, the primary and secondary clinical and radiographic outcome parameters were evaluated.

Primary Study Endpoints and Success Criteria

The primary composite endpoint, termed “overall success,” was a composite of the following parameters: pain and functional disability using the NDI; neurological status; implant- or surgery-associated adverse events; secondary surgical interventions; and, a radiographic spinal unit height determination. Overall success was defined as attainment of all of the following:

1. An improvement (reduction) of at least 15 points from the baseline NDI score. Details on the NDI are presented in the Background of this Assessment.
2. Maintenance or improvement in neurological status based on 3 parameters (sensory, motor, reflex). No detail was provided on how these were measured.
3. No serious adverse event classified as implant-associated or implant/surgical procedure associated.
4. No additional surgical procedure, for example revision to ACDF or removal of the device, that would be classified as “failure.”
5. FSU height maintenance. FSU height was considered maintained if it did not decrease more than 2 mm after 6 weeks following surgery.

Because of the difficulty in evaluating FSU, due to anatomical interference with the radiographic image, an alternate overall success determination was also made based on the above criteria without the addition of FSU height maintenance. This was not prespecified in the trial protocol.

Statistical Analysis Plan

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

24-month visit. However, the main focus of the analysis is success rates at 24 months. The comparability of the two groups was demonstrated using a logistic regression which included the preoperative medical conditions and preoperative measurements of effectiveness variables on the overall success results.

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

Prestige ST Study Results Preoperative Characteristics

As shown in Table 1, demographic and clinical characteristics of the control and experimental group were well-matched. The average age approximated 43 years (46% male). A significant proportion (34%) of patients used tobacco at the time of enrollment, and 45-53% reported alcohol use. The data sources do not provide details about preoperative neurological findings, such as weakness or reflex changes. Thirty-six investigational patients and 48 control patients declined participation after randomization; two investigational patients and 11 control patients declined participation because of “dissatisfaction” with their randomization status.

Surgical Results

Surgical results are shown in Table 2. Although there were statistically significant differences between the intervention and control groups in mean operative time and the use of an external orthosis, these were not deemed clinically significant.

Clinical Outcomes

Table 3 summarizes the clinical outcomes of the Prestige IDE trial. As shown by the Bayesian posterior probabilities, all primary outcome variables were shown to be statistically noninferior to ACDF, but statistical superiority was shown only for the neurological status. Around

Table 1. Prestige ST Cervical Disc IDE Clinical Trial: Preoperative Characteristics

Demographic Characteristics	Prestige Disc (%)	ACDF (%)	p value
Enrolled and randomized	276 (100)	265 (100)	NA
Dissatisfied with randomization	2 (1)	11 (4)	0.009
Age (years, mean \pm SD)	43 \pm 8	44 \pm 9	0.43
Males	46	46	0.77
Tobacco use	34	35	1.00
Alcohol use	43	53	0.02
Work status	66	63	0.47
Symptom duration			
<6 weeks	21 (8)	15 (6)	0.43
6 weeks to 6 months	81 (29)	89 (34)	
>6 months	174 (63)	161 (60)	
Spinal level treated			
C3-C4	7 (2)	10 (4)	0.41
C4-C5	14 (5)	15 (6)	
C5-C6	143 (52)	149 (56)	
C6-C7	112 (41)	91 (34)	
Outcomes Scores (mean \pm SD)			
NDI	56 \pm 15	56 \pm 16	0.63
Neck Pain Score	68 \pm 23	69 \pm 22	0.55
Arm Pain score	59 \pm 29	62 \pm 28	0.19
SF-36 PCS	32 \pm 7	32 \pm 8	0.76
SF-36 MCS	42 \pm 12	43 \pm 12	0.79
FSU: functional spinal unit; MCS: Mental Component Summary; NDI: Neck Disability Index; PCS: Physical Component Summary; SD: standard deviation; SF-36: 36-Item Short Form Health Survey			

Table 2. Prestige ST Cervical Disc IDE Clinical Trial: Surgical Results

Surgical Results	Prestige Disc	ACDF	p value
Mean operative time (hours)	1.6	1.4	<0.001
Mean blood loss (mL)	60	58	0.64
Mean hospitalization (days)	1.1	1.0	0.041
External orthosis (%)	31	59	<0.009

Table 3. Prestige ST Cervical Disc IDE Clinical Trial: Clinical Outcomes

	Posterior Mean Probabilities of Success at 24 Months (95% HPD credible interval) ^a			Prestige Disc vs. ACDF	
	Prestige Disc [p(t)]	ACDF [p(c)]	Difference [p(t) – p(c)]	Statistically noninferior by study criteria?	Statistically superior by study criteria?
Primary Composite Endpoint^b					
Overall Success (without FSU)	78.8% (72.1–85.0) n=128	70.0% (62.7–77.4) n=122	8.8% (0.9–18.7)	Yes	Yes
Overall Success (with FSU)	80.1% (73.1–87.4) n=95	64.0% (55.3–72.8) n=90	16.0% (4.9–27.9)	Yes	Yes
Primary Outcome Variables					
Neck Disability Index (>15 point decrease)	80.8% (74.7–87.0) n=128	80.8% (74.1–86.7) n=122	0.0% (-8.9–9.7)	Yes	No
Maintenance or improvement in neurological status (required in all three measures of motor, sensory, reflexes)	92.1% (87.6–96.2) n=128	84.7% (78.6–90.5) n=122	7.3% (-0.1–15.0)	Yes	Yes
Functional Spinal Unit (FSU) Height (must be within 2 mm of 6 weeks postop height)	95.4% (91.5–98.7) n=128	93.7% (89.2–97.8) n=122	1.7% (-4.3–7.4)	Yes	No
Secondary Outcome Variables					
Neck Pain	93.6% (89.9–97.2) n=128	97.7% (95.1–99.8) n=121	- 4.0% (- 8.5–0.5)	Yes	No
Arm Pain	90.0% (85.2–94.6) n=225	93.0% (88.8–96.9) n=197	- 3.0% (- 9.7–3.2)	Yes	No
SF-36 Physical Component Summary	82.8% (76.5– 88.9) n=127	83.8% (77.2–89.9) n=119	0.9% (-7.8–9.9)	Yes	No
SF-36 Mental Component Summary	66.9% (59.6–73.9) n=127	70.8% (63.7–78.4) n=119	3.9% (-6.6–13.9)	No	No

^a Data from preplanned interim analysis of first 250 evaluable patients; HPD = highest posterior density;

^b Overall success was defined as attainment of all of the following: an improvement (reduction) of at least 15 points from the baseline NDI score; maintenance or improvement in neurological status based on 3 parameters (sensory, motor, reflex); no serious adverse event classified as implant-associated or implant/surgical procedure associated; no additional surgical procedure, for example revision to ACDF or removal of the device, that would be classified as “failure”; and, FSU height maintenance. FSU height was considered maintained if it did not decrease more than 2 mm after 6 weeks following surgery.

80% of Prestige recipients versus 64–70% of ACDF patients achieved the primary composite endpoint, overall success with or without the FSU height measurement also reaching the level of statistical superiority. The study also considered a number of secondary endpoints at 24 months, although detailed statistical analysis was not done for all of them. Neck pain worsened (failure) in 6.2% of investigational patients versus 0.8% of controls. Failure on the arm pain scores were 9.4% and 5.8%, respectively. Also, while success for the PCS (Physical Health Summary Score) was equivalent (86%) success in the experimental group was lower than the control group for role-physical (92.1% and 97.5%) and pain (92.2% and 95.8%). None of the secondary outcome variables for AIDA reached statistical superiority compared to fusion. Furthermore, at 24 months, there were no intergroup differences in the patient's global perceived effect, with 85% of interventional patients reporting they had completely recovered or were much improved, compared to 81% of ACDF patients. Similarly, the doctor's perception of results at 24 months was either good or excellent in 94.5% of device recipients versus 91.7% of ACDF patients.

Device-Related Adverse Events and Functional Measures

As shown in Table 4, few cases of implant failures, migrations, or subsidence were found in the interventional group. Device-related adverse events of any type were reported in 9 (3.3%) AIDA patients and 29 (10.9%) ACDF cases ($p=0.0005$). This difference was due primarily to the rates of nonunion ($n=6$) and pending nonunion ($n=16$) in ACDF patients, which are irrelevant to AIDA. Secondary surgical procedures, classified as revisions, hardware removals, reoperations, or supplemental fixations, were performed on both groups subsequent to the initial operation (Table 4). Revisions, removals, and supplemental fixations were considered second surgery failures in the study. A revision was defined as any procedure in which the original implant configuration was adjusted or modified. There were no revision surgeries in the AIDA group but there were 5 (1.9%) in the ACDF group ($p=0.02$).

Nearly all ACDF patients (97.5%) experienced radiographic fusion at 24-month follow-up. Mean cervical neck angular motion (7.87 degrees) was maintained at preoperative levels (mean 7.55 degrees) at the surgical level in arthroplasty patients and restricted as expected

in ACDF patients. In the AIDA group, mean adjacent-level angular motion measurements for the level above and below the treated level were higher than those for the treated segment at 24 months (12.05 degrees vs. 9.47 degrees vs. 7.87 degrees, respectively). Radiographic evidence of adjacent-segment degeneration was not assessed, nor is information available from the clinical study on wear debris in the disc space. Similar proportions (66% disc, 63% ACDF) of patients were actively working prior to surgery and 24 months postsurgery (75.4% and 74.7%, respectively). Kaplan-Meier analysis showed a median return-to-work time of 45 days for arthroplasty patients and 61 days for ACDF patients, a 16 day difference which approached statistical significance ($p=0.094$ log-rank test).

Discussion

The Prestige disc IDE RCT had several strengths. It was powered sufficiently for its design, the patient groups were well-matched, and they appear representative of the population for whom surgical fusion is indicated (Brown and Heller 2006). Achievement of complete fusion in 98% of ACDF control cases is well within the historical range for this procedure (Malloy and Hilibrand 2002). The high fusion success rate could be inferred to reflect the internal validity of the study results, and presents a difficult efficacy endpoint for disc arthroplasty to exceed. This implicitly supports the rationale for a noninferiority study design rather than a traditional superiority frequentist design (Pocock 2003). Finally, the rigor of the trial was theoretically enhanced by the use of allograft rather than autograft bone in ACDF. This choice would permit assessors (patients and physicians) to focus on the clinical outcomes of the fusion procedure, free from external influences such as pain or other discomfort typically associated with an iliac crest bone harvest procedure, confident that there is little difference in the ultimate success of fusion based on graft source (Galler and Sonntag 2003).

Despite the positive aspects of the Prestige trial, several issues provide cause for skepticism toward the results. In particular, the 24-month follow-up interval precludes conclusions about long-term in vivo device performance, durability, and revisability. Performance and durability are key considerations given the relatively young age (mid-40s) of the patients in the

Table 4. Prestige ST Cervical Disc IDE Clinical Trial: Device-Related Adverse Events and Secondary Surgical Procedures at 24 Months

Adverse Event	Prestige n=276 (%)	ACDF n=265 (%)
Anatomical/technical difficulty	1 (0.4)	0 (0.0)
Implant displacement/loosening	2 (0.7)	3 (1.1)
Infection	0 (0.0)	1 (0.4)
Neck and/or arm pain	1 (0.4)	2 (0.8)
Neurological	4 (1.4)	1 (0.4)
Nonunion	N/A	6 (2.3)
Pending nonunion	N/A	16 (6.0)
Subsidence	1 (0.4)	0 (0.0)
Any adverse device-related event	9 (3.3)	29 (10.9); p=0.0005
Secondary Surgical Procedures		
Revisions	0 (0.0)	5 (1.9); p=0.02
Hardware removals (elective and nonelective)	5 a (1.8)	9 b (3.5)
Reoperations	4 c (1.4)	2 (0.8)
Supplemental fixations	0 (0.0)	8 (3.0); p=0.004
Total secondary surgical procedures	9 (3.2)	24 (9.2); p = 0.005

^a One of these followed complaints for unresolved neck pain, one followed unresolved arm pain, the others were related to neck and arm pain
^b Two were elective, 7 were non-elective
^c Two followed unresolved neck pain, one followed unresolved arm pain, one was related to both neck and arm pain

trial, who conceivably could outlive the disc lifespan. This point is underscored by the FDA approval condition that the manufacturer of the Prestige ST disc continue to follow the patients in the IDE trial for 7 years total and in addition, perform a 5-year enhanced surveillance study to evaluate adverse events in a broader patient population. The 7-year follow-up period mandated by FDA is likely sufficient to evaluate device durability and adjacent-level DDD, which has been estimated to occur at a rate of about 3% annually during the first 10 years following anterior cervical fusion (Hilibrand et al. 1999). Another significant concern with the Prestige trial, and current and future disc trials approved by FDA, is that the potential difficulty of revising a failed implant is not addressed (McAfee 2006). This is a critical issue given the potentially serious effects of device slippage or failure that would require revision surgery.

For several reasons related to the primary composite endpoint (overall success rate) and the overall Prestige disc study design, it is difficult to discern a real health benefit from disc arthroplasty compared to ACDF. Thus, even though the overall success rate for AIDA was statistically noninferior to that obtained in the ACDF group, it is evident that the superiority of this endpoint was driven by the neurological status variable alone. However, the investigators provide no detail on how the neurological status was measured and evaluated, which precludes analysis of its components and their relative contribution to the overall success rate. Furthermore, the study failed to demonstrate statistical superiority for the NDI, which is a clinically validated, multidimensional outcome measure of pain and disability caused by cervical DDD. This makes it difficult to ascribe a health benefit to AIDA in more specific

terms than the ill-defined neurological status variable, and by extension the overall success rate. Finally, failure to mask patients and physicians to the study treatments could have biased results in favor of disc arthroplasty (“new” treatment) over ACDF (“old” treatment), a possibility suggested editorially by others (Benzel 2007). The potential for bias inherent to the unmasked study design is underscored by the report of a small (4%) but statistically significant proportion of patients who were randomized to undergo ACDF and who withdrew prior to surgery because they were dissatisfied with their treatment group.

It has been suggested that perturbations in physiological spinal motion patterns above or below the index level in patients who undergo ACDF cause disc pathologies at those levels that ultimately lead to adjacent-level DDD (Durbhakula and Ghiselli 2005). One hypothesis driving the use of artificial cervical discs is that recipients maintain normal spinal motion patterns and posture at the index level, which reduces their risk for adjacent-level disc pathology and subsequent DDD (Phillips and Garfin 2005). While this is an attractive hypothesis on which to base disc implantation, given the relative noninferiority and safety of AIDA compared to ACDF, the Prestige disc trial provides no direct evidence on subsequent adjacent-level DDD in control or investigational group patients. Furthermore, no study has definitively established that adjacent-level DDD subsequent to fusion is a consequence of altered spinal motion patterns, rather than just due to the natural progression of DDD (Anderson et al. 2007; Levin et al. 2007). Therefore, assertion that AIDA will reduce the risk for adjacent-level DDD is unsupported by firm clinical evidence, including the Prestige trial.

Summary of Application of the Technology Evaluation Criteria

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether artificial intervertebral disc arthroplasty as a treatment for DDD of the cervical spine meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

1. The technology must have final approval from the appropriate governmental regulatory bodies.

One cervical disc arthroplasty product (Prestige ST Cervical Disc) received FDA marketing approval July 16, 2007. The Prestige ST Cervical Disc is indicated in skeletally mature patients for reconstruction of the disc from C5-C7 following single-level discectomy for intractable radiculopathy and/or myelopathy. The device is implanted via an open anterior approach. Intractable radiculopathy and/or myelopathy should present with at least one of the following items producing symptomatic nerve root and/or spinal cord compression which is documented by patient history (e.g., pain [neck and/or arm pain], functional deficit, and/or neurological deficit), and radiographic studies (e.g., CT, MRI, X-rays, etc.): 1) herniated disc, and/or 2) osteophyte formation.

A second product (Bryan Cervical Disc) received an approvable decision by an FDA advisory panel July 17, 2007, but had not received final marketing approval at the time this Assessment was prepared. The Bryan disc is indicated for use in patients similar to those for whom the Prestige device is indicated.⁵

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

One noninferiority design RCT is available that compares AIDA (n=276) with anterior plated ACDF using allograft bone (n=265). For several reasons, this evidence is insufficient to support conclusions concerning the effect of AIDA on health outcomes.

First, the evidence from the IDE trial does not permit conclusions on the long-term performance of AIDA and adverse events. Device performance, durability, and revisability are key considerations for the relatively young population enrolled in the pivotal trial. The available evidence also is insufficient to permit conclusions as to whether or not AIDA affects the postsurgical development of adjacent-level DDD. By contrast, conclusions on the relative safety of cervical disc arthroplasty appear sufficiently supported in the short term.

⁵ As this Assessment was in press, the ProDisc™-C Total Disc Replacement received premarketing application (PMA) approval on December 17, 2007 (<http://www.fda.gov/cdrh/pdf7/p070001.html>).

Second, although the study results consistently demonstrated statistical noninferiority for AIDA versus ACDF in all three primary outcome variables, and for the overall success composite outcome, the neurological status was the only primary outcome variable for which statistical superiority was shown. It thus appears to be the primary determinant of statistical superiority for the overall success of the disc versus ACDF. However, quantitative data on the neurological status are not available, which precludes analysis of its clinical meaning and relevance. Further, the study failed to demonstrate statistical superiority for AIDA in terms of the NDI, which is a clinically validated, multidimensional outcome measure of neck pain and disability caused by cervical DDD. Taken together, these uncertainties make it difficult to determine the effect of AIDA on health outcomes in more specific, validated terms than the ill-defined neurological status variable and by extension the overall success rate. Finally, failure to blind patients and physician outcomes assessors to the study treatment allocation could have biased study results, favoring disc arthroplasty over ACDF.

3. The technology must improve

the net health outcome; and

4. The technology must be as beneficial as any established alternatives.

The evidence does not permit conclusions as to whether artificial intervertebral disc arthroplasty for the cervical spine improves the net health outcome or is as beneficial as established alternatives.

5. The improvement must be attainable outside the investigational settings.

Whether artificial disc arthroplasty for the cervical spine improves the net health outcome has not been established in the investigational setting.

Based on the above, artificial intervertebral disc arthroplasty for the treatment of patients with cervical degenerative disc disease does not meet the TEC criteria.

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Appendix A

Table. Cervical Disc Prostheses Available or Under Investigation in the U.S.

Prosthesis (Manufacturer)	Implant Composition	Articulation Design	Bearing Surface	Bearing Constraint	Fixation	FDA Status
Prestige ST® (Medtronic)	316L SS	Ball and trough	MoM	Semi-constrained	Primary – locked vertebral body screws Secondary – same	FDA advisory panel recommended approval by vote of 7-0 (9/19/06) Received final FDA approval (#P060018) on 7/16/07
Bryan® (Medtronic)	Titanium alloy Polyurethane	Biarticulating contained bearing	MoP	Semi-constrained	Primary – milled vertebral endplates Secondary – endplate ingrowth	FDA advisory panel recommended approval by vote of 7-1 (7/16/07) Final FDA approval pending (#P060023) and expected by early 2008.
Prestige® LP (Medtronic)	Titanium-ceramic composite	Ellipsoid saucer	MoM	Semi-constrained	Primary – dual rails Secondary – endplate ingrowth	FDA IDE clinical trial enrollment complete
ProDisc-C® (Synthes Spine Solutions)	Cobalt-chromium- molybdenum UHMWPE	Ball and socket	MoP	Constrained	Primary – central keel Secondary – endplate ingrowth	FDA IDE clinical study enrollment complete. Approved 12/17/07
Porous Coated Motion (PCM®) (Cervitech)	Cobalt-chromium- molybdenum UHMWPE	Ball and socket	MoP	Semi-constrained	Primary – ridged metallic endplates Secondary – endplate ingrowth	In FDA IDE clinical trial enrollment
Kineflex C® Cervical Artificial Disc Implant (Spinal Motion)	Cobalt-chromium- molybdenum	Three piece, metal core	MoM	Unconstrained	Primary – central keel Secondary – endplate ingrowth	In FDA IDE clinical trial enrollment
CerviCore™ Intervertebral Disc (Stryker)	Cobalt-chromium- molybdenum	Saddle	MoM	Unconstrained	Primary – dual rails Secondary – endplate ingrowth	In FDA IDE clinical trial enrollment

IDE: investigational device exemption; MoM: metal-on-metal; MoP: metal-on-polyethylene; PMA: premarket approval; SS: stainless steel; UHMWPE: ultra-high molecular weight polyethylene

Appendix B

Bryan Cervical Disc IDE Clinical Trial

Methods. 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 cervical discectomy and fusion procedure (ACDF) using commercially available allograft (without bone matrix paste) used in conjunction with the Medtronic Sofamor Danek ATLANTIS™ Cervical Plate System. 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.

Patients had 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. 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); and, moderate to advanced spondylosis.

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.

Primary Study Endpoints and Success

Criteria. The IDE study was designed to demonstrate noninferiority 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 noninferior 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.”

Note that unlike the Prestige disc trial, the functional spinal unit (FSU) height was not part of the primary endpoint in the Bryan disc study. It was not clear how maintaining FSU height correlates to successful treatment of cervical degenerative disc disease

Statistical Analysis Plan. Bayesian statistical methods were planned to determine whether the investigational device is noninferior to the control with respect to the overall success rate at 24 months. A fixed noninferiority margin of 10% was agreed upon by FDA and the sponsor. The noninferiority hypothesis was that the overall success rate for the investigational device was not more than 10% worse than the overall success rate for the control. Noninferiority was if the posterior probability of noninferiority was greater than 95%. The 95% Highest Posterior Density (HPD) interval was also provided for each posterior distribution of interest. If noninferiority was claimed, then the posterior probability of superiority was also computed. If this probability was greater than

95%, then superiority was claimed. Similar Bayesian analyses (i.e., posterior probabilities of noninferiority, along with 95% HPD intervals) were provided for all other endpoints in the trial. Noninformative priors were used for all prior distributions.

Results

Preoperative Characteristics

Table A summarizes the patient demographics for the Bryan Cervical Disc IDE clinical trial. Patients were very similar to those enrolled in the Prestige ST disc trial, with no significant differences between treatment groups except for patients who were dissatisfied with their randomization status. Thirty-two (14%) of patients randomly assigned to ACDF expressed dissatisfaction with their treatment and withdrew prior to undergoing surgery.

Surgical Results

Although differences were reported in surgical results, none was deemed clinically relevant to the study outcomes (Table B).

Clinical Outcomes

Table C summarizes the clinical outcomes of the Bryan disc IDE trial. As shown by the Bayesian posterior probabilities, all primary outcome variables were shown to be statistically noninferior to ACDF, but statistical superiority was shown only for the NDI. Around 80% of Bryan disc recipients versus 72% of ACDF patients achieved the primary composite endpoint, overall success, which also reached the level of statistical superiority. The study also considered a number of secondary endpoints at 24 months, although detailed statistical analysis was not done for all of them. All reached the

Table A. Bryan Cervical Disc IDE Clinical Trial: Preoperative Characteristics

Demographic Characteristics	Bryan Disc (%)	ACDF (%)	p value
Enrolled and randomized	242 (100)	221 (100)	NA
Age (yrs, mean \pm SD)	44 + 8	45 + 9	0.72
Dissatisfied with randomization	0 (0.0)	32 (14)	<0.0001
Males	46	51	0.23
Tobacco use	26	24	0.75
Alcohol use	8	4	0.08
Work status	64	65	0.92
Symptom duration			
<6 weeks	NR	NR	NR
6 weeks to 6 months			
>6 months			
Spinal level treated			
C3-C4	3 (1)	0 (0)	NR
C4-C5	12 (5)	17 (8)	
C5-C6	140 (58)	110 (50)	
C6-C7	87 (36)	94 (42)	
Outcomes Scores (mean \pm SD)			
NDI	51	50	
Neck Pain Score	NR	NR	NR
Arm Pain score	NR	NR	NR
SF-36 PCS	NR	NR	NR
SF-36 MCS	NR	NR	NR

FSU: functional spinal unit; NDI: Neck Disability Index; MCS: Mental Component Summary; NR: not reported; PCS: Physical Component Summary; SD: standard deviation; SF-36: 36-Item Short Form Health Survey

Table B. Bryan Cervical Disc IDE Clinical Trial: Surgical Results

Surgical Results	Bryan Disc	ACDF	p-value
Mean operative time (hrs)	2.2	1.4	NR
Mean blood loss (mL)	92	60	NR
Mean hospitalization (days)	1.1	1.0	NR
External orthosis (%)	NR	NR	NR

Table C. Bryan Cervical Disc IDE Clinical Trial: Clinical Outcomes

Primary Outcome Variable	Posterior Mean Probabilities at 24 Months (95% HPD credible interval)*				
	Bryan Disc	ACDF	Difference	Noninferiority	Superiority
Neck Disability Index (>15 point decrease)	85.0% (79.7–89.9) n=159	76.2% (69.7–82.6) n=140	8.8 (NR)	100%	98%
Maintenance or improvement in neurological status (required in all three measures of motor, sensory, reflexes)	92.4% (88.4–96.1) n=159	90.9% (86.4–95.3) n=140	1.5% (NR)	100%	69.2%
Functional Spinal Unit (FSU) Height (within 2 mm of 6 weeks postop height)	99% (NR)	99% (NR)	0%	100%	0%
Primary Composite Endpoint					
Overall success without FSU	80.4% (74.3–85.8)	71.8% (65.0–78.9)	8.6% (NR)	100%	96.9%
Overall success with FSU	NR	NR	NR	NR	NR
Secondary Outcome Variables					
Neck Pain	95.6% (NR)	92.9% (NR)	2.7% (NR)	Yes	NR
Arm Pain	94.3% (NR)	89.3% (NR)	5.0% (NR)	Yes	NR
SF-36 PCS	90.6% (NR)	85.5% (NR)	5.1% (NR)	Yes	NR
SF-36 MCS	72.5% (NR)	69.8% (NR)	2.7% (NR)	Yes	NR

* Data from preplanned interim analysis of first 300 evaluable patients in PMA submission to FDA

level of statistical inferiority, but superiority compared to fusion was not reported.

Device-Related Adverse Events and Functional Measures

A total of 9 (3.7%) adverse events were classified as implant or implant/surgical procedure associated for the investigational group versus 29 (13.1%) in the control group ($p=0.004$) (Table D). Event rates were similar for both treatment groups in most of the specific categories, except the non-union and pending non-union categories, where the control group rates were 2.3% and 6.0%, respectively but not applicable for the investigational patients.

Discussion

It is evident that the results of the Bryan disc trial mirror those of the Prestige ST study. The Bryan disc was noninferior in all primary and secondary outcome variables to ACDF using

allograft bone and anterior fixation as well as in overall success. The latter also was found to be statistically superior for AIDA compared to ACDF, driven primarily by the NDI rather than the neurological status or FSU height. This differs from the Prestige disc results, in which superiority of the overall success was driven by the neurological status and not by the NDI. Device-related adverse events were similar between groups in the Bryan disc study, with no clinically significant differences between the interventions. Similar to the Prestige trial, a number of caveats arise in the Bryan disc study relating to a lack of evidence that does not permit conclusions on long-term device performance, durability, and revision. No data are available to draw conclusions on adjacent-level DDD in this study. Overall, the conclusions for the Prestige ST disc are generally applicable to the Bryan disc based on the evidence presented in the pivotal trial of the latter.

Table D. Bryan Cervical Disc IDE Clinical Trial: Device-Related Adverse Events and Secondary Surgical Procedures at 24 Months

Adverse Event	Bryan Disc n=242 (%)	ACDF n=221 (%)
Anatomical/technical difficulty	1 (0.4)	0 (0.0)
Implant displacement/loosening	2 (0.7)	3 (1.1)
Infection	0 (0.0)	1 (0.4)
Neck and/or arm pain	1 (0.4)	2 (0.8)
Neurological	4 (1.4)	1 (0.4)
Nonunion	N/A	6 (2.3)
Pending nonunion	N/A	16 (6.0)
Subsidence	1 (0.4)	0 (0.0)
Any adverse device-related event	9 (3.7)	29 (13.1); $p=0.0004$
Secondary Surgical Procedures		
Revisions	1 (0.4)	0 (0.0)
Removals (elective and non-elective)	3 (1.2)	2 (0.9)
Re-operations	2 (0.8)	1 (0.5)
Supplemental fixations	0 (0.0)	5 (2.3)



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