Cervical disc arthroplasty with PRESTIGE LP disc versus anterior cervical discectomy and fusion: a prospective, multicenter investigational device exemption study

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OBJECT This study compared the safety and efficacy of treatment with the PRESTIGE LP cervical disc versus a historical control anterior cervical discectomy and fusion (ACDF).

METHODS Prospectively collected PRESTIGE LP data from 20 investigational sites were compared with data from 265 historical control ACDF patients in the initial PRESTIGE Cervical Disc IDE study. The 280 investigational patients with single-level cervical disc disease with radiculopathy and/or myelopathy underwent arthroplasty with a low-profile artificial disc. Key safety/efficacy outcomes included Neck Disability Index (NDI), Neck and Arm Pain Numerical Rating Scale scores, 36-Item Short Form Health Survey (SF-36) score, work status, disc height, range of motion, adverse events (AEs), additional surgeries, and neurological status. Clinical and radiographic evaluations were completed preoperatively, intraoperatively, and at 1.5, 3, 6, 12, and 24 months postoperatively. Predefined Bayesian statistical methods with noninformative priors were used, along with the propensity score technique for controlling confounding factors. Analysis by independent statisticians confirmed initial statistical findings.

RESULTS The investigational and control groups were mostly similar demographically. There was no significant difference in blood loss (51.0 ml [investigational] vs 57.1 ml [control]) or hospital stay (0.98 days [investigational] vs 0.95 days [control]). The investigational group had a significantly longer operative time (1.49 hours vs 1.38 hours); 95% Bayesian credible interval of the difference was 0.01–0.21 hours. Significant improvements versus preoperative in NDI, neck/arm pain, SF-36, and neurological status were achieved by 1.5 months in both groups and were sustained at 24 months. Patient follow-up at 24 months was 97.1% for the investigational group and 84.0% for the control group. The mean NDI score improvements versus preoperative exceeded 30 points in both groups at 12 and 24 months. SF-36 Mental Component Summary superiority was established (Bayesian probability 0.993). The mean SF-36 PCS scores improved by 14.3 points in the investigational group and by 11.9 points in the control group from baseline to 24 months postoperatively. Neurological success at 24 months was 93.5% in the investigational group and 83.5% in the control group (probability of superiority ~ 1.00). At 24 months, 12.1% of investigational and 15.5% of control patients had an AE classified as device or device/surgical procedure related; 14 (5.0%) investigational and 21 (7.9%) control patients had a second surgery at the index level. The median return-to-work time for the investigational group was 40 days compared with 60 days for the control group ($p = 0.020$ after adjusting for preoperative work status and propensity score). Following implantation of the PRESTIGE LP device, the mean angular motion was maintained at 12 months (7.9°) and 24 months (7.5°). At 24 months, 90.0% of investigational and 87.7% of control patients were satisfied with the results of surgery. PRESTIGE LP superiority on overall success (without disc height success), a composite safety/efficacy end point, was strongly supported with 0.994 Bayesian probability.

ABBREVIATIONS ACDF = anterior cervical discectomy and fusion; AE = adverse event; ASD = adjacent-segment disease; CDA = cervical disc arthroplasty; DDD = degenerative disc disease; FSU = functional spinal unit; HPD = highest posterior density; IDE = investigational device exemption; MCS = Mental Component Summary; NDI = Neck Disability Index; PCS = Physical Component Summary; SF-36 = 36-Item Short Form Health Survey.

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CONCLUSIONS This device maintains mean postoperative segmental motion while providing the potential for biomechanical stability. Investigational patients reported significantly improved clinical outcomes compared with baseline, at least noninferior to ACDF, up to 24 months after surgery.

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KEY WORDS cervical disc arthroplasty; anterior cervical discectomy and fusion; artificial cervical disc; cervical radiculopathy; cervical myelopathy; adjacent level disease

PATIENTS with intractable neck pain or increasing neurological deficit due to cervical spondylosis or disc herniation with radiculopathy and/or myelopathy, in whom nonoperative treatment modalities and therapy have failed, are appropriate candidates for surgical decompressive surgery. Anterior cervical discectomy and fusion (ACDF) has been the standard of care for more than 50 years,^{2,4,10,27} providing effective relief of patient symptoms by decompressing the neural elements and permanently stabilizing the functional spinal unit (FSU). In recent years, anterior cervical decompression and fusion with allograft bone and anterior plate fixation has contributed to better outcomes due to improved lordosis and reduced pseudoarthrosis.^{4,6,10,14,32} However, complications including adjacent-segment degeneration (ASD), screw loosening, and plate-related complications have been widely reported.^{1,13,15,32}

In response to these concerns and a nascent body of evidence in support of lumbar total disc replacement,^{11,33} cervical disc arthroplasty (CDA) devices were developed and implanted beginning in the 1990s.⁷ In the United States, clinical trials of these cervical disc prostheses were initiated beginning in 2002,³ offering the potential to restore and/or maintain anatomical disc space height, normal lordosis, and physiological motion in the cervical spine with the theoretical benefit of decreased ASD and other fusion morbidities. The first of several large, randomized controlled trials comparing CDA with ACDF began in 2002. As of this writing, a total of 7 CDA devices have been approved by the FDA after demonstrating outcomes at least comparable to ACDF for treatment of symptomatic cervical degenerative disc disease (DDD).^{5,8,21–23,26,30}

This study reports 2-year results of the FDA-approved investigational device exemption (IDE) study for the PRESTIGE LP Cervical Disc (Medtronic). The device is an unconstrained ball-in-trough, metal-on-metal articulation manufactured from a titanium ceramic composite.

Methods

Study Design

The study was approved by the Hughston Sports Medicine Center Institutional Review Board on January 7, 2005. From January to November 2005, 280 nonrandomized patients at 20 investigational sites in this FDA IDE trial (clinicaltrials.gov: NCT00667459) received treat-

ment by 50 investigators and coinvestigators for single-level cervical degenerative disc disease using a low-profile CDA device. The safety and efficacy outcomes for these patients were compared with data from the 265 historical control patients from a previous FDA-approved IDE study (clinicaltrials.gov: NCT00642876) with identical inclusion and exclusion criteria²¹ who underwent ACDF with allograft bone and an anterior plate, utilizing a similar surgical approach. Patients were evaluated preoperatively, intraoperatively, and at routine postoperative intervals of 1.5, 3, 6, 12, and 24 months.

Independent Data Review

Consistent with an emerging trend^{9,16} but still rare for an FDA IDE study of a spinal implant device, the study sponsor delivered the entire raw data set to a team of independent statisticians at Vanderbilt University for analysis. Using the identical methods from the original FDA-approved statistical analysis plan in the study protocol, the independent analysis reached the same statistical conclusions as the study sponsor for all proposed comparisons. Whereas the sponsor statisticians used the statistical software SAS (SAS Institute) to generate the summary tables and WinBUGS to conduct the Bayesian analysis, the independent statisticians used R software to generate the summary tables and JAGS to conduct the Bayesian analysis.

Statistical Analysis

The results of FDA IDE studies for spinal devices have been almost exclusively reported using the Frequentist approach in the peer-reviewed literature. In the Frequentist approach, evidence for efficacy is generally thought to be provided by $p \leq 0.05$. This is the probability of observing, over repetitions of the same experiment, a test statistic as impressive as or more impressive than the observed statistic for comparing 2 groups if the null hypothesis is true. Bayesian results are “positive,” by comparison, when, for example, the posterior probability of efficacy is ≥ 0.95 . For assessing evidence, the Bayesian posterior probability of a statement such as “Treatment 1 tends to be better than Treatment 2” is the probability that the statement is true. In addition, the 95% Bayesian credible intervals are provided for parameters of interest. The primary objective in this study was to show that the overall success rate in the investigational group was statistically noninferior to

the rate in the historical control group. For deriving the overall success variable—the primary clinical trial end point—and for the purpose of statistical comparisons of secondary end points, the relevant variables were dichotomized as binary, that is, success or failure, using criteria described in the protocol for each specific endpoint. Generally, success was defined as maintenance or improvement compared with the preoperative measure, except for Neck Disability Index (NDI) success, which was defined as at least a 15-point improvement versus baseline.

The primary analysis data set consisted of all patients who received one of the study devices and completed surgical procedures. The outcomes of patients requiring an additional surgical procedure (removal, revision, or supplemental fixation) were recorded as a treatment failure for overall success, the primary study end point, and the last observations taken immediately before the additional surgical procedures/interventions were carried forward for all future evaluation periods. Descriptive statistics were provided for patient demographics, preoperative measures, and outcome measures using median, interquartile, mean, and standard deviation for continuous variables and frequencies for categorical variables. A 2-sample t-test or chi-square test was used to compare demographics and preoperative variables between the investigational and control groups. A paired t-test was used to compare pre- and postoperative changes in the outcomes within each group. Return to work was compared between the 2 groups using a log-rank test.

To adjust for any possible effects of demographic characteristics or preoperative measures on clinical outcomes, the propensity score technique was used. The propensity score was calculated based on a logistic regression model with the following covariates: age, height, weight, sex, race, marital status, education level, work status, workers' compensation, spinal litigation, tobacco use, alcohol use, nonnarcotic pain medication use, weak narcotic pain medication use, strong narcotic pain medication use, muscle relaxant medication use, time to onset of symptoms, and previous neck surgery, as well as treatment level and preoperative scores for NDI, 36-Item Short Form Health Survey (SF-36) Physical Component Summary (PCS), SF-36 Mental Component Summary (MCS), neck pain, arm pain, gait, foraminal compression test reaction, and neurological status (motor function, sensory, and reflex). Where an observation was missing for a given demographic/preoperative variable in a particular patient, the mean value of the corresponding treatment group was imputed for the missing data point. Covariate balance after propensity score adjustment was examined using ANCOVA or logistic regression.

Bayesian logistic regression models were fitted for primary outcomes (overall success, individual efficacy, and neurological status success at 24 months) with propensity score used as a covariate. Independent, “noninformative” priors were used for the parameters in the model. Markov chain Monte Carlo simulations were performed to obtain the posterior distributions of the control group success rate and the investigational group success rate, as well as the success rate difference between the treatment groups for an average patient with a propensity score set to be the

mean of all patients. The mean of the posterior distributions and 95% highest posterior density (HPD) were reported. The noninferiority of the investigational treatment to the control treatment was established by demonstrating at least a 0.95 posterior probability that the control success rate was no more than 10% greater than the investigational success rate. Once noninferiority was demonstrated, superiority was established if the posterior probability of the investigational success rate being greater than the control success rate was at least 0.95.

Similar models were used to assess adverse events (AEs) and additional surgical procedures or interventions. Bayesian normal linear regression models were fitted for surgery length, blood loss, and hospital stay, and the propensity score was included as a covariate. Independent, “noninformative” priors were used for the parameters in the models, and posterior distributions were calculated for the mean outcome of the control group and the investigational group, as well as the difference between the 2 groups. For these outcomes, superiority of the investigational treatment to the control treatment was established if the posterior probability that the investigational group outcome was better than the control group outcome was at least 0.975.

Sensitivity analyses were performed for primary outcomes by using “per protocol” and “per protocol, in window” data sets. In the “per protocol” data set, patients who had major protocol deviations were excluded. The “per protocol, in window” data set further excluded any “out of window” visits. We also fitted a Cox proportional hazards model to investigate the time to return to work between the 2 arms; propensity score and preoperative work status were included as covariates. All analyses by the independent statisticians were performed using the software R 3.0.2 (www.R-project.org) and the software JAGS 3.4.0 (Plummer, Martyn: JAGS: A Program for Analysis of Bayesian Graphical Models Using Gibbs Sampling, in Proceedings of the 3rd International Workshop on Distributed Statistical Computing [DSC 2003, Vienna, Austria, 2003]).

Inclusion and Exclusion Criteria

Study sites with institutional review board approvals consented and enrolled eligible patients (Table 1) with symptomatic cervical DDD requiring surgery at a single level from C-3 to C-7. All had intractable radiculopathy and/or myelopathy recalcitrant to nonoperative treatment modalities, such as reduction of painful activities and an integrated therapy program that may have included neck stabilization exercises, antiinflammatory medications, and other modalities such as traction, massage, and/or moist heat. All patients were considered candidates for a single-level standalone ACDF.

Device Design

The PRESTIGE LP Cervical Disc is a dynamic device made of a titanium ceramic composite that is inserted into the intervertebral disc space of the cervical spine. The device comprises 2 low-profile plates that interface through a ball-in-trough mechanism (Fig. 1), permitting segmental

TABLE 1. Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> • Cervical degenerative disc disease defined as: intractable radiculopathy &/or myelopathy w/ ≥ 1 of the following items producing symptomatic nerve root &/or spinal cord compression that is documented by patient history (e.g., pain, functional deficit, &/or neurological deficit radiological studies [e.g., CT, MRI, x-ray, etc.]): <ul style="list-style-type: none"> » Herniated disc » Osteophyte formation • One level requiring surgical treatment • C3–4 disc to C6–7 disc level of involvement • Unresponsive to nonoperative treatment for approximately 6 wks or presence of progressive symptoms or signs of nerve root/spinal cord compression in the face of continued nonoperative management • No previous surgical intervention at the involved level or any subsequent, planned/staged surgical procedure at the involved or adjacent level(s) • Is ≥ 18 yrs, inclusive, at the time of surgery • Preoperative NDI score ≥ 30 • Has a preoperative neck pain score ≥ 20 based on the Preoperative Neck and Arm Pain Questionnaire • If a female of child-bearing potential, patient is not pregnant at the time of surgery • Is willing to comply with the study plan & sign the patient informed consent form 	<ul style="list-style-type: none"> • Has a cervical spinal condition other than symptomatic cervical disc disease requiring surgical treatment at the involved level • Documented or diagnosed cervical instability defined by dynamic (flexion/extension) radiographs showing: <ul style="list-style-type: none"> » Sagittal plane translation >3.5 mm or » Sagittal plane angulation $>20^\circ$ • >1 cervical level requiring surgical treatment • Has a fused level adjacent to the level to be treated • Has severe pathology of the facet joints of the involved vertebral bodies • Previous surgical intervention at the involved level • Has been previously diagnosed w/ osteopenia or osteomalacia • Has any of the following that may be associated with a diagnosis of osteoporosis (if “yes” to any of the below risk factors, a DEXA scan will be required to determine eligibility): <ul style="list-style-type: none"> » Postmenopausal nonblack female >60 yrs & weighs <140 lbs » Postmenopausal female that has sustained a nontraumatic hip, spine, or wrist fracture » Male >70 yrs » Male >60 yrs who has sustained a nontraumatic hip or spine fracture • If the level of BMD is a T score of -3.5 or lower (i.e., -3.6, -3.7, etc.) or a T score of -2.5 or lower (i.e., -2.6, -2.7, etc.) w/ vertebral crush fracture, then the patient is excluded from the study • Has presence of spinal metastases • Has overt or active bacterial infection, either local or systemic • Has severe insulin-dependent diabetes • Has chronic or acute renal failure or prior history of renal disease • Has fever (temperature $>101^\circ\text{F}$ oral) at the time of surgery • Has a documented allergy to stainless steel, titanium, or a titanium alloy • Is mentally incompetent (if questionable, obtain psychiatric consult) • Is a prisoner • Is pregnant • Is an alcohol &/or drug abuser as defined by currently undergoing treatment for alcohol &/or drug abuse • Has received drugs that may interfere w/ bone metabolism w/in 2 wks prior to the planned date of spinal surgery (e.g., steroids or methotrexate), excluding routine perioperative antiinflammatory drugs • Has a history of endocrine or metabolic disorder known to affect osteogenesis (e.g., Paget's disease, renal osteodystrophy, Ehlers-Danlos syndrome, or osteogenesis imperfecta) • Has a condition that requires postoperative medications that interfere with the stability of the implant, such as steroids (does not include low-dose aspirin for prophylactic anticoagulation), excluding routine perioperative antiinflammatory drugs • Has received treatment with an investigational therapy w/in 28 days prior to implantation surgery or such treatment is planned during the 16 wks following Artificial Cervical Disc-LP implantation

BMD = bone mineral density; DEXA = dual-energy x-ray absorptiometry.

spinal motion. The device may also serve to maintain disc space height. Dual serrated keels on each endplate are attached to the vertebral bodies through impaction to stabilize the implant. A titanium plasma spray coating on the osseointegrating surfaces is intended to promote bony ingrowth. The device is available in various combinations of depth and height to accommodate the intervertebral disc space and to engage the adjacent vertebral bodies.

Surgical Procedure and Postoperative Care

Both the investigational and historical control groups underwent surgery using a similar standard anterior approach to the cervical spine. The level of the disc space was confirmed radiographically, and dissection was not carried out past the midportion of the vertebral bodies adjacent to the operative disc space. The anterior annulus, disc, and cartilaginous endplates were removed. Gentle

distraction was carried out, reestablishing the anatomical disc space height using either intradiscal distraction or Caspar vertebral body distraction pins.

The lateral margins of the disc space were exposed, extending superiorly off of the lateral margins of the inferior vertebral body. Hypertrophic uncovertebral joint spurs could be thinned with a high-speed bur; the neuroforamina could be enlarged with a fine curette or thin-footed Kerrison rongeur. The posterior annulus and posterior longitudinal ligament were partially or totally removed based on pathology and the central spinal canal was exposed and decompressed. The depth of the vertebral was precisely measured with a caliper.

In the investigational group, the endplates were preserved. The PRESTIGE LP implant that approximated the depth and height of the interspace was selected. Care was taken not to overdistract the interspace. The adjacent end-

FIG. 1. The PRESTIGE LP device.

plates were prepared utilizing a dual keel-cutting device. The implant was then impacted into the disc space.

In the control fusion group, the vertebral endplates were decorticated. An anterior plate was placed over the allograft (cortical ring) and secured to the adjacent vertebral bodies.

Patients were encouraged to ambulate immediately after surgery, and physical activities were advanced at the discretion of the attending surgeon. Smokers were encouraged to stop smoking. Use of nonsteroidal anti-inflammatory drugs was recommended for the first 2 weeks postoperatively, with avoidance thereafter. An external soft-sided orthosis was used at the preference of the attending surgeon.

Clinical Outcome Measurements

Clinical outcomes were measured by validated instruments: the NDI and the SF-36.¹⁹ Neck pain and arm pain numeric rating scales (adapted in part from McDowell and Newell¹⁸), neurological status, patient satisfaction, and work status were also assessed. Patients were examined preoperatively and immediately following surgery and completed self-reported outcomes questionnaires before surgery and at 1.5, 3, 6, 12, and 24 months after surgery.

The primary IDE clinical study end point, as required by FDA and defined in the protocol, was overall success at 24 months (Table 2), which required all of the following: NDI success, neurological success, disc height (FSU height) success, no serious AE classified as implant or implant/surgical procedure associated, and no secondary surgical procedure classified as a “failure.”

Radiographic Assessment

The objective of the radiographic analysis was to characterize the radiographic measurements of the investigational device, in particular disc space height and maintenance of motion. Two independent reviewers from the core laboratory performed radiographic assessment measurements utilizing an orthopedic reading system and digitized images of plain radiographs obtained at scheduled intervals to assess the patients’ progress. A third independent reviewer adjudicated conflicting findings.

Using FSU height (Fig. 2) was a surrogate for evaluating the maintenance of disc height or directly determining whether the implant had subsided. Using vertebral endplate distances in the conventional measurement of disc

TABLE 2. Overall success criteria

Condition*	Definition/Explanation
NDI success	At least 15-point improvement postoperatively compared to preoperative score
Neurological status success	Maintenance or improvement in postoperative neurological status (motor function, sensory function, and reflexes) compared w/ preoperative condition
Disc height success	Functional spinal unit anterior or posterior measurement height declined by no more than 2 mm compared w/ the 6-wk postoperative assessment
No serious adverse event classified as implant or implant/surgical procedure associated	Serious adverse event = Grade 3 or Grade 4 per WHO criteria (typically, resulting in ER visit or hospitalization)
No secondary surgical procedure classified as a “failure”	Supplemental fixation, removal, or revision = treatment failure; Reoperation or other surgical procedure ≠ treatment failure

ER = emergency room.
* A patient will be considered an overall success if all conditions are met.

height was thought to be problematic due to visualization challenges created by the investigational implant, despite its low profile. Likewise, formation of a solid fusion mass can potentially obscure 1 or more measurement landmarks in fusion patients. The determination of FSU height success was based on whether either the anterior or posterior measurement had declined by no more than 2 mm

FIG. 2. FSU height was measured anteriorly and posteriorly beginning 6 weeks after surgery. Any decline of more than 2 mm compared with the 6-week measurement indicated failure to maintain disc height. Copyright Matthew F. Gornet. Published with permission.

compared with the 6-week postoperative assessment. FSU height success, although potentially indicative of neither safety nor efficacy, was an FDA-required component of the overall success measurement. Results are given both with and without FSU height success in this report.

Device Safety Evaluation

The neurological status of the patients was evaluated preoperatively and postoperatively. Overall neurological status success was based on demonstrating maintenance or improvement in each test—motor function, sensory function, and reflexes—compared with the preoperative status.

In addition to neurological success, the safety of the patient's treatment with the investigational device was also evaluated based on the nature and frequency of AEs compared with those occurring in the control group. The primary AE summaries and statistical comparisons are based on a hybrid term/category mapping scheme proposed by the FDA, which draws on the study sponsor's internal process and the MeDRA (Medical Dictionary for Regulatory Activities) coding system to place each of 20 classifications of AEs under a broad body system (for example, neurological, cardiac disorders), incident (for example, trauma, infection), or other (associated conditions/systems with small numerical incidence). Adverse events were characterized by their nature into categories and graded according to WHO criteria as “non-serious” (Grade 1 or 2) or “serious” (Grade 3 or 4) events.³¹

These events were likewise classified according to their potential relation to the implant and/or surgical procedure. The AE relationship and severity determination were performed by an independent, external adjudication committee of 3 physicians, generating data for this publication and the sponsor's premarket application. An AE that resulted in a second surgical procedure would be classified as a “failure” if it required a supplemental fixation, implant removal, or a revision.

Results

Patient Accountability

Of the 280 investigational patients enrolled and treated with the PRESTIGE LP device in the study, information was received on 272 patients or 97.1% at 24 months compared with 84.0% of the 265 patients for whom any information was received in the control group. On the more conservative basis of counting only patients who had overall success outcomes (without FSU height) at 24 months, similar follow-up rates were achieved (96.8% and 83.0%, respectively). For overall success as defined by the FDA in the protocol (including FSU height), 80.7% of the investigational and 64.5% of the control patients had outcomes reported at 24 months.

Patient Demographics

As expected in light of the matching inclusion/exclusion criteria, the investigational and control groups were similar demographically, except for race and tobacco use. The historical control group had a higher percentage of patients using tobacco before their operation; however, fusion rates in the group were greater than 96%, indicating

that smoking did not have a significant impact on fusion in that study.

There were no statistically significant differences in terms of preoperative medical history, medical condition, or medication usage. Likewise, there were no statistically significant differences in preoperative status of key efficacy end points (NDI, SF-36, neck and arm pain) between the 2 treatment groups. With respect to neurological status, we found that there was no significant difference in normal reflexes between the groups and that the rates of normal motor function and sensory function were significantly higher in the investigational group. However, all were statistically well balanced after adjusting for propensity score, as indicated in the last 2 columns of Table 3. In summary, the investigational and historical control groups were comparable prior to surgery. Furthermore, potential confounding effects were statistically adjusted for by using the patient's propensity score as the covariate. This would support that conclusions drawn about safety and efficacy of the investigational device were based on treatment effect rather than confounding factors.

Surgical Data

All patients were treated using a standard extrapharyngeal anterolateral approach, and more than 90% of patients in each group were treated at the C5–6 or C6–7 level. Patients were classified as “inpatient” (hospitalization) in 66.4% of PRESTIGE LP and 69.1% of ACDF cases. Mean operative time was 1.49 hours in the investigational group and 1.38 hours in the control group, a difference of approximately 6.5 minutes, which was statistically significant (95% credible interval 0.01–0.21). Blood loss and hospital stay were similar between the groups (Table 4).

Safety Measurements

The safety of the investigational device was evaluated based on the nature and frequency of AEs compared with those occurring in the control group. Table 5 provides a time course summary of operative and postoperative AEs for both treatment groups. The total number of events per category and the number of patients involved are also reported. Statistical comparisons of the AE occurrence rates were made using predefined Bayesian methods (Table 6). Compared with the ACDF group, the investigational group had a higher rate of AEs categorized as anatomical difficulty, heterotopic ossification, implant event, neurological AE, spinal event, trauma, urogenital AE, vascular AE, and wound (noninfectious). As expected, the rate of nonunion events was significantly higher in the control group.

Adverse events that required a second surgery at the index level were classified as revisions, removals, supplemental fixations, or reoperations. A revision was defined as a procedure that adjusted or in any way modified the original implant configuration. A removal was defined as a procedure that removed 1 or more components of the original implant configuration without replacement with the same type of device. Supplemental fixation was defined as a procedure in which additional spinal devices not approved as part of the protocol were placed, including supplemental treatments such as bone growth stimulators. A reoperation was defined as any surgical procedure at the treated spinal

TABLE 3. Patient demographic and preoperative characteristics

Variable	Investigational (n = 280)*	Control (n = 265)*	p Value Before PS Adjustment†	p Value After PS Adjustment	
				PS as Continuous Covariate‡§	PS Stratification§¶
Age (yrs)			0.369	0.997	0.873
Median [IQR]	44 [39–49]	44 [38–49]			
Mean ± SD	44.5 ± 8.8	43.9 ± 8.8			
Height (in)			0.622	0.998	0.946
Median [IQR]	67 [64–71]	67 [64–71]			
Mean ± SD	67.7 ± 4.1	67.5 ± 4.2			
Weight (lbs)			0.565	0.998	0.962
Median [IQR]	180 [154–218]	181 [155–210]			
Mean ± SD	186.9 ± 45.0	184.7 ± 41.5			
NDI score			0.499	0.997	0.952
Median [IQR]	54 [44–66]	58 [44–68]			
Mean ± SD	55.5 ± 14.7	56.4 ± 15.9			
SF-36 PCS score			0.775	0.999	0.898
Median [IQR]	32.4 [27.4–36.7]	31.5 [27.1–36.6]			
Mean ± SD	32.2 ± 7.4	32.0 ± 7.5			
SF-36 MCS score			0.078	0.993	0.924
Median [IQR]	46.5 [34.9–53.6]	42.1 [33.1–53.0]			
Mean ± SD	44.5 ± 11.5	42.7 ± 12.4			
Neck pain score			0.190	0.995	0.987
Median [IQR]	70 [50–81]	72 [56–81]			
Mean ± SD	60.7 ± 20.8	69.3 ± 21.5			
Arm pain score			0.237	0.995	0.960
Median [IQR]	64 [40–80]	67 [42–83]			
Mean ± SD	59.6 ± 26.3	62.4 ± 28.5			
Female	151 (53.9)	143 (54.0)	1.000	1.000	0.881
Race			0.075	0.997	0.708
Caucasian	271 (96.8)	243 (91.7)			
Black	7 (2.5)	13 (4.9)			
Asian	0 (0.0)	2 (0.8)			
Hispanic	1 (0.4)	6 (2.3)			
Other	1 (0.4)	1 (0.4)			
Marital status			0.109	0.990	0.749
Single	40 (14.3)	32 (12.1)			
Married	189 (67.5)	204 (77.0)			
Divorced	42 (15.0)	24 (9.1)			
Separated	7 (2.5)	3 (1.1)			
Widowed	2 (0.7)	2 (0.8)			
Education level			0.063	0.991	0.877
<High school	15 (5.4)	14 (5.3)			
High school	57 (20.5)	77 (29.2)			
>High school	206 (74.1)	173 (65.5)			
Workers' compensation case	32 (11.4)	35 (13.2)	0.616	0.998	0.864
Unresolved spinal litigation case	34 (12.1)	32 (12.1)	1.000	1.000	0.928
Tobacco used	74 (26.4)	92 (34.7)	0.045	0.991	0.893
Alcohol used	150 (53.6)	141 (53.2)	1.000	1.000	0.900
Working before operation	188 (67.1)	166 (62.6)	0.312	0.996	0.968
Nonnarcotic relaxant medication use	208 (74.3)	187 (71.1)	0.462	0.997	0.836

(continued)

TABLE 3. Patient demographic and preoperative characteristics (continued)

Variable	Investigational (n = 280)*	Control (n = 265)*	p Value Before PS Adjustment†	p Value After PS Adjustment	
				PS as Continuous Covariate‡¶	PS Stratification§¶
Weak narcotic medication use	133 (47.7)	127 (48.3)	0.954	1.000	0.843
Strong narcotic medication use	62 (22.2)	58 (22.0)	1.000	1.000	0.995
Muscle relaxant medication use	100 (35.8)	114 (43.2)	0.097	0.993	0.977
Time to start of symptoms			0.488	0.999	0.992
<6 wks	22 (7.9)	15 (5.7)			
6 wks–6 mos	85 (30.4)	89 (33.6)			
>6 mos	173 (61.8)	161 (60.8)			
Normal motor functions	107 (38.2)	158 (59.6)	<0.001	0.979	0.751
Normal sensory functions	117 (41.8)	135 (50.9)	0.040	0.991	0.890
Normal reflexes	186 (66.4)	162 (61.1)	0.231	0.995	0.888
Normal gait score	262 (93.6)	204 (77.0)	<0.001	0.881	0.467
Positive foraminal compression test	120 (42.9)	144 (54.3)	0.009	0.989	0.875
Treatment level			0.201	0.989	0.981
C3–4	4 (1.4)	10 (3.8)			
C4–5	21 (7.5)	15 (5.7)			
C5–6	147 (52.5)	149 (56.2)			
C6–7	108 (38.6)	91 (34.3)			
C6–7	108 (38.6)	91 (34.3)			

PS = propensity score.

* Values are number of patients (%) unless stated otherwise.

† For continuous variables p values are from ANOVA, and for categorical variables they are from the chi-square test.

‡ For continuous variables p values are from ANCOVA, and for categorical variables they are from logistic regression, both with propensity score as a continuous covariate.

§ For categorical variables with multiple categories, they (except for treatment level) were dichotomized in the logistic regression models for calculating propensity scores in order to increase the model stability and for checking the covariate balance between treatment groups.

¶ For continuous variables p values are from ANCOVA, and for categorical variables they are from the Cochran-Mantel-Haenszel test.

level that did not remove, modify, or add any components. Examples of reoperations included procedures to remove disc materials and bone fragments, as well as decompression procedures. Secondary surgical interventions occurred in both treatment groups, and results at 24 months are compared in Table 7. The mean difference in the rate of supplemental fixation procedures between the investigational and the control group was -0.026 (95% credible interval -0.052 to -0.007). The posterior probability that the investigational group had a lower rate of supplemental fixation procedures was 0.995, demonstrating statistical superiority over the control group. Excluding external bone growth stimulators from supplemental fixation, rates were similar between the groups. The percentage of patients undergoing secondary surgeries at the adjacent level, cumulatively up to the 24-month follow up, was similar: 2.5% of investigational and 4.2% of control patients.

In this study, device- and device/surgical procedure–related AEs were reported in 12.1% of investigational and 15.5% of control patients, although the rates were very similar after factoring out the control group–specific non-union category. The incidence of AEs that were both serious and classified as device- and device/surgical procedure–related events was also similar in the investigational (5.0%) and control (4.9%) groups.

Radiographic Outcomes

Measurements pertaining to the FSU were made to evaluate maintenance of disc height during the postoperative period. Because of both visualization challenges and the requirement that both 1.5-month and 24-month measurements were needed to achieve FSU success, a success/failure determination could not be made for approximately 20% of patients in the investigational group. FSU height

TABLE 4. Comparisons of surgical data

Parameter	μ_1 (investigational)		μ_0 (control)		$\mu_1 - \mu_0$		Probability of Superiority
	Mean	95% HPD	Mean	95% HPD	Mean	95% HPD	
Operative time (hrs)	1.49	(1.43, 1.56)	1.38	(1.31, 1.45)	0.11	(0.01, 0.21)	0.015
Blood loss (ml)	51	(42.2, 60.0)	57.1	(48.2, 66.1)	-6.0	(-19.3, 7.2)	0.817
Hospital stay (days)	0.98	(0.92, 1.03)	0.95	(0.89, 1.01)	0.03	(-0.06, 0.11)	0.278

TABLE 5. Time course summary of adverse events

Adverse Event	Operative		1 Day–4 Wks		6 Wks ± 2 Wks		3 Mos ± 2 Wks		6 Mos ± 1 Mo		12 Mos ± 2 Mos		24 Mos ± 2 Mos		Total (%)	
	Events	Pts	Events	Pts	Events	Pts	Events	Pts	Events	Pts	Events	Pts	Events	Pts	Events	Pts
Investigational group (n = 280)																
Any adverse event	29	25	173	80	175	89	234	117	244	115	396	146	308	114	1559	257 (91.8)
Anatomical/technical difficulty	2	2	0	0	0	0	0	0	0	0	0	0	0	0	2	2 (0.7)
Cancer	0	0	1	1	0	0	0	0	1	1	3	2	0	0	5	3 (1.1)
Cardiac disorders	0	0	2	1	2	1	0	0	3	3	4	4	10	7	21	16 (5.7)
Death	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0 (0.0)
Dysphagia/dysphonia	1	1	16	12	4	4	5	5	5	4	0	0	2	2	33	26 (9.3)
Gastrointestinal	2	1	8	6	1	1	4	4	3	3	20	13	17	9	55	35 (12.5)
Heterotopic ossification	0	0	2	2	6	5	1	1	4	3	7	7	11	9	31	27 (9.6)
Implant events	6	6	1	1	2	2	3	2	1	1	0	0	4	4	17	16 (5.7)
Infection	1	1	5	4	6	5	6	5	11	10	16	11	12	11	57	34 (12.1)
Neck &/or arm pain	3	2	31	21	43	37	57	42	37	28	68	51	36	27	275	144 (51.4)
Neurological	2	2	18	13	34	25	47	35	31	26	73	51	37	23	242	136 (48.6)
Nonunion	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0 (0.0)
Other	5	5	19	15	12	10	24	14	29	22	55	40	33	23	177	93 (33.2)
Other pain	3	3	22	21	32	25	49	42	57	42	65	51	50	33	278	146 (52.1)
Respiratory	0	0	7	5	0	0	1	1	10	7	3	3	13	11	34	24 (8.6)
Spinal event	0	0	19	11	22	13	20	12	26	20	44	26	41	16	172	83 (29.6)
Trauma	0	0	6	6	5	5	12	11	11	11	19	19	18	16	71	61 (21.8)
Urogenital	1	1	1	1	2	2	1	1	9	6	12	8	16	12	42	26 (9.3)
Vascular	3	3	1	1	1	1	0	0	2	2	2	2	4	3	13	12 (4.3)
Wound (noninfection)	0	0	14	10	3	3	4	3	4	1	5	5	4	4	34	25 (8.9)
Control group (n = 265)																
Any adverse event	32	18	114	66	97	47	203	94	140	79	273	103	339	117	1198	219 (82.6)
Anatomical/technical difficulty	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0 (0.0)
Cancer	0	0	1	1	0	0	0	0	0	0	0	0	1	1	2	2 (0.8)
Cardiac disorders	0	0	2	2	1	1	2	2	3	2	3	3	9	9	20	18 (6.8)
Death	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0 (0.0)
Dysphagia/dysphonia	4	3	11	11	4	4	3	3	0	0	1	1	0	0	23	22 (8.3)
Gastrointestinal	7	4	7	5	3	2	4	4	2	2	21	12	24	13	68	38 (14.3)
Heterotopic ossification	0	0	1	1	4	1	2	2	1	1	2	2	11	8	21	15 (5.7)
Implant events	0	0	1	1	1	1	0	0	0	0	2	2	1	1	5	5 (1.9)
Infection	2	1	3	3	5	5	2	2	1	1	10	9	14	10	37	27 (10.2)
Neck &/or arm pain	1	1	16	13	19	15	49	37	40	32	50	42	38	27	213	124 (46.8)
Neurological	6	5	21	19	19	12	35	24	16	13	60	35	60	34	217	108 (40.8)

(continued)

TABLE 5. Time course summary of adverse events (continued)

Adverse Event	Operative		1 Day–4 Wks		6 Wks±2 Wks		3 Mos ± 2 Wks		6 Mos ± 1 Mo		12 Mos ± 2 Mos		24 Mos ± 2 Mos		Total (%)	
	Events	Pts	Events	Pts	Events	Pts	Events	Pts	Events	Pts	Events	Pts	Events	Pts	Events	Pts
Control group (n = 265) (continued)																
Nonunion	0	0	0	0	1	1	3	3	8	8	8	8	10	10	30	29 (10.9)
Other	3	2	14	12	13	10	16	12	9	9	21	15	57	32	133	81 (30.6)
Other pain	6	4	19	16	11	10	45	34	30	26	57	40	63	45	231	132 (49.8)
Respiratory	0	0	4	3	4	2	1	1	5	4	1	1	8	7	23	17 (6.4)
Spinal event	0	0	8	6	6	5	25	14	15	9	20	11	29	16	103	55 (20.8)
Trauma	0	0	2	2	4	4	12	11	5	5	9	8	12	10	44	35 (13.2)
Urogenital	0	0	0	0	0	0	1	1	3	3	5	4	2	2	11	9 (3.4)
Vascular	1	1	0	0	0	0	1	1	1	1	1	1	0	0	4	4 (1.5)
Wound (noninfection)	2	2	4	4	2	2	2	2	1	1	2	2	0	0	13	13 (4.9)

Pts = patients.

success rates were high for those patients for whom measurements were available, exceeding 90% for both treatment groups at all 4 postoperative evaluations. Statistical noninferiority was demonstrated with a posterior probability of 0.992.

Angular motion (Fig. 3) and translational motion at the index level were measured throughout the postoperative course. For the investigational group, mean angular motion was maintained postoperatively at 12 months (7.85°) and 24 months (7.51°), whereas mean translational motion for the postoperative period ranged from 0.90 mm to 1.03 mm. The independent radiologists at the core laboratory reported bridging bone in 5.95% of investigational patients.

Motion at levels adjacent to the surgery was also measured at planned postoperative intervals. Preoperatively and at all postoperative measurements, motion was greater in the control group at both the superior and inferior levels. Mean angular motion increased in both the investigational group and the control group at the superior level at 12 months and 24 months, whereas at the inferior level at 24 months, both groups declined compared with the mean motion measured at 12 months (Table 8).

Efficacy End Points

Compared with preoperative pain and disability assessments, highly significant improvements (all $p < 0.001$, paired t-tests) in NDI, SF-36 PCS and MCS, neck pain, and arm pain scores were achieved at 1.5 months and sustained through the patient assessments at 24 months for both the investigational and the control groups. Mean NDI improvements at 12 months and 24 months exceeded 30 points in both treatment groups (Fig. 4).

Success rates, with success generally defined in the protocol as maintenance or improvement compared with preoperative scores, were compared for the secondary end points (except NDI) using Bayesian methods (Table 9). Compared with the control group, the investigational group had a numerically higher rate of NDI success (≥ 15 -point improvement), of neurological status success, of arm pain success, and of MCS success. The success rates of FSU height, neck pain, and SF-36 PCS in the investigation group were numerically lower than those in the control group. The posterior probabilities (Fig. 5) that the success rate in the control group was less than 10% higher than in the investigational group were essentially 1.0 for all outcomes except SF-36 PCS, thus demonstrating statistical noninferiority of the investigational group to the control group for these outcomes. The posterior probabilities that the success rate in the investigational group was higher than control group were 1.000 (approximately), 0.993, and 0.994 for neurological status, SF-36 MCS, and overall success without FSU, respectively. These Bayesian probabilities exceeded the threshold of 0.95, providing for a conclusion of statistical superiority of the investigational group to the control group.

Treatment Effectiveness and Patient Satisfaction

Patients were asked to evaluate their overall impression of their treatment effectiveness as a function of pain at each postoperative follow-up interval. The 7 possible

TABLE 6. Comparisons of adverse events at 24 months*

Adverse Event	p_1 (investigational)		p_0 (control)		$p_1 - p_0$		Probability of Superiority
	Mean	95% HPD	Mean	95% HPD	Mean	95% HPD	
Anatomical/technical difficulty	0.005	(0.000, 0.017)	0.000	(0.000, 0.000)	0.005	(0.000, 0.017)	0.000
Cancer	0.011	(0.002, 0.026)	0.006	(0.001, 0.019)	0.004	(-0.012, 0.022)	0.270
Cardiac disorders	0.054	(0.030, 0.085)	0.070	(0.041, 0.105)	-0.016	(-0.061, 0.027)	0.771
Dysphagia/dysphonia	0.092	(0.060, 0.130)	0.082	(0.051, 0.120)	0.010	(-0.042, 0.061)	0.341
Gastrointestinal	0.129	(0.091, 0.172)	0.137	(0.096, 0.183)	-0.008	(-0.069, 0.054)	0.593
Heterotopic ossification	0.102	(0.068, 0.142)	0.050	(0.027, 0.080)	0.052	(0.005, 0.100)	0.014
Implant events	0.057	(0.032, 0.089)	0.018	(0.006, 0.038)	0.039	(0.006, 0.075)	0.011
Infection	0.119	(0.083, 0.162)	0.102	(0.068, 0.143)	0.017	(-0.039, 0.075)	0.278
Neck &/or arm pain	0.520	(0.457, 0.580)	0.463	(0.401, 0.527)	0.057	(-0.034, 0.148)	0.112
Neurological	0.495	(0.433, 0.556)	0.398	(0.336, 0.460)	0.097	(0.007, 0.190)	0.018
Nonunion	0.000	(0.000, 0.000)	0.114	(0.076, 0.159)	-0.114	(-0.159, -0.076)	~1.000
Other	0.337	(0.280, 0.396)	0.301	(0.245, 0.360)	0.036	(-0.050, 0.120)	0.201
Other pain	0.513	(0.451, 0.573)	0.507	(0.443, 0.570)	0.006	(-0.087, 0.096)	0.451
Respiratory	0.083	(0.053, 0.121)	0.065	(0.038, 0.099)	0.019	(-0.029, 0.067)	0.215
Spinal event	0.314	(0.258, 0.372)	0.189	(0.142, 0.241)	0.125	(0.045, 0.203)	0.001
Trauma	0.212	(0.163, 0.264)	0.135	(0.095, 0.181)	0.077	(0.007, 0.147)	0.016
Urogenital	0.087	(0.055, 0.127)	0.035	(0.016, 0.062)	0.052	(0.010, 0.098)	0.010
Vascular	0.046	(0.024, 0.075)	0.012	(0.003, 0.027)	0.034	(0.008, 0.066)	0.006
Wound (noninfection)	0.096	(0.062, 0.135)	0.042	(0.021, 0.071)	0.053	(0.008, 0.100)	0.010
Any adverse event	0.922	(0.887, 0.951)	0.820	(0.769, 0.867)	0.102	(0.041, 0.165)	0.001

* Compared with the control group, the investigational group had a significantly lower rate of nonunion adverse events, but the rates of anatomical difficulty, heterotopic ossification, implant events, neurological adverse event, spinal event, trauma, urogenital adverse event, vascular adverse event, and wound were greater in the investigational group than in the control group.

responses ranged from “completely recovered” to “vastly worsened.” At 12 months and 24 months following surgery, 86.1% and 86.6%, respectively, of the investigational patients indicated that they had either “completely recovered” or were “much improved.” In the control group, the rates were 74.9% and 80.8%, respectively.

At the same intervals, patients were asked to respond to 3 statements pertaining to their satisfaction with their treatment (Table 10). Patient responses at 12 months and 24 months after surgery indicated high satisfaction in both treatment groups, with rates of “definitely true” or “mostly true” responses ranging from 82.2% to 90.7%.

Overall Success

A patient was determined to be an overall success only if all 5 variables in the FDA-defined measure were successfully achieved: NDI success; neurological success; disc height (FSU height) success; no serious AE classified as implant or implant/surgical procedure associated; and no secondary surgical procedure classified as a “failure.” The rate of overall success in the investigational group exceeded the rate in the control group without FSU height success by 0.111 (95% credible interval 0.026–0.196), and with FSU 0.031 (95% credible interval -0.07 to 0.135), respectively (Table 9). The posterior probability that the overall success

TABLE 7. Comparisons of secondary surgical events at 24 months*

Surgical Event	p_1 (investigational)			p_0 (control)			$p_1 - p_0$		Probability of Superiority
	No. of Pts	Mean	95% HPD	No. of Pts	Mean	95% HPD	Mean	95% HPD	
Revisions	1	0.004	(0.000, 0.013)	5	0.016	(0.004, 0.037)	-0.013	(-0.034, 0.003)	0.950
Removals	10	0.037	(0.018, 0.063)	11	0.038	(0.018, 0.066)	-0.001	(-0.036, 0.033)	0.525
Supplemental fixation	2	0.005	(0.001, 0.015)	8	0.031	(0.014, 0.057)	-0.026	(-0.052, -0.007)	0.995
Reoperations	3	0.011	(0.002, 0.026)	2	0.006	(0.001, 0.019)	0.004	(-0.011, 0.021)	0.266
Others	62	0.219	(0.170, 0.272)	50	0.190	(0.144, 0.240)	0.030	(-0.043, 0.103)	0.211

* The mean difference in the rate of supplemental fixation procedures between the investigational group and the control group was -0.026 (95% credible interval was -0.052 to -0.007). The posterior probability that the investigational group had a lower rate of supplemental fixation procedures was 0.995, demonstrating a statistical superiority of the investigational group over the control group.

FIG. 3. Segmental motion was measured using the Cobb method (A) on lateral dynamic flexion (B) and extension (C) radiographs. Radiographic success required angular motion at the level of surgery to be $> 4^\circ$ but $< 20^\circ$ at each postoperative interval. Copyright Matthew F. Gornet. Published with permission.

rate (without FSU) in the investigational group was higher than the control group was 0.994, indicating a statistically significant superiority. Sensitivity analyses using the per protocol data set or the per protocol in-window data set produced similar results (data not shown).

Return to Work

Patient work status was recorded preoperatively and at each follow-up visit. Prior to surgery, 67.1% of investigational and 62.6% of control patients were reported to be working. At the 24-month follow-up, the percentage of patients working was similar in the investigational (73.4%) and control (75.9%) groups. However, a Kaplan-Meier time-to-event analysis demonstrated that PRESTIGE LP patients returned to work a median 20 days sooner than ACDF patients, and in the Cox regression analysis, the adjusted hazard ratio was 1.28 (95% CI 1.04–1.59, $p = 0.02$) in favor of investigational patients.

Discussion

Cervical disc arthroplasty was developed with the goal

of safely providing patients with comparable pain and disability improvement to ACDF while maintaining physiological global cervical motion and thereby potentially avoiding many of the reported complications of cervical arthrodesis for single-level disease. In this study, as with the other FDA-approved cervical disc prostheses, PRESTIGE LP was found to provide as good or better pain and disability outcomes compared with ACDF 24 months after surgery. The investigational devices were likewise found to be as safe as the control treatments, based on AEs, second surgeries, and neurological status. Patient satisfaction was high for both treatment groups in each study. The cumulative Level 1 evidence from thousands of patients in these very large clinical trials provides compelling support for surgical treatment of this cervical DDD patient population using either ACDF or CDA.

Using a historical cohort in this device study is admittedly subordinate in preference to a randomized trial. Nevertheless, the statistical analysis plan, as part of the entire protocol, was extensively reviewed with and approved by the FDA. Bayesian propensity score techniques (logistic regression model) used by the original designers of the

TABLE 8. Postoperative mean angular motion at adjacent levels

Time Point	Investigational (n = 280)			Control (n = 265)		
	No. of Pts	Mean $\pm$ SD	p Value	No. of Pts	Mean $\pm$ SD	p Value
6 wks						
Change in angulation at the segment above ($^\circ$)	266	-0.77 ± 3.61	<0.001	187	-1.13 ± 4.39	<0.001
Change in angulation at the segment below ($^\circ$)	172	-0.25 ± 3.17	0.298	86	0.70 ± 3.67	0.081
3 mos						
Change in angulation at the segment above ($^\circ$)	264	0.32 ± 3.85	0.175	194	0.06 ± 4.27	0.841
Change in angulation at the segment below ($^\circ$)	174	0.29 ± 3.48	0.266	91	1.21 ± 3.71	0.002
6 mos						
Change in angulation at the segment above ($^\circ$)	263	0.82 ± 3.84	<0.001	198	0.53 ± 4.26	0.084
Change in angulation at the segment below ($^\circ$)	166	0.65 ± 3.69	0.025	94	0.99 ± 3.93	0.017
12 mos						
Change in angulation at the segment above ($^\circ$)	267	1.27 ± 3.75	<0.001	188	1.32 ± 4.41	<0.001
Change in angulation at the segment below ($^\circ$)	166	1.11 ± 3.47	<0.001	95	1.89 ± 4.50	<0.001
24 mos						
Change in angulation at the segment above ($^\circ$)	262	1.88 ± 3.84	<0.001	187	1.04 ± 4.60	0.002
Change in angulation at the segment below ($^\circ$)	161	1.13 ± 3.75	<0.001	94	1.28 ± 4.28	0.005

FIG. 4. Mean NDI score, angular motion at target level, PCS, MCS, neck pain score, and arm pain score of the treatment groups at different time points. Vertical bars indicate 99% CIs of the means.

study—and again by the independent statisticians—balanced all covariates, removed the opportunity for variation caused by cofounders, and validated the statistical comparability of the 2 study groups.

Although the surgical approach is essentially the same for cervical arthroplasty or ACDF, there are subtle differences in the procedures that could lead to statistical differences in postoperative neurological test results. No statistical difference was reported at 24 months in at least 1 study, although most of the cervical arthroplasty IDE studies did report a difference at 24 months. The onset of adjacent-level changes in the fusion group may also have contributed to a decline in neurological outcome over time.

Safety assessments are a critical component of the FDA

approval process for investigational devices. In this study, overall AE rates were higher in the investigational group than in the historical control group; this may be attributable in part to the high follow-up rates in the investigational group.

One of the 8 AE categories in which the control group had statistically lower rates than the investigational group was heterotopic ossification, a finding reported by the investigator surgeons without third party review and without reference to grading or severity. A total of 31 heterotopic ossification AEs were reported in 27 investigational patients (9.6%) compared with 21 events in 15 patients (5.7%) in the control group. Despite the lack of formal grading, this compares favorably with risks of heterotopic ossification up to 24 months after CDA that were reported in other FDA studies of single-level CDA.^{23,29} The independent radiologist findings in this study, while not evaluating heterotopic ossification per se, did report on the incidence of bridging bone (5.95%) in investigational patients at 24 months, defined as evidence of a continuous connection of trabecular bone between vertebral bodies.

There was 1 revision procedure in the investigational group. After the device was reported to have migrated at approximately 2 months after the index surgery, the artificial disc device was removed and replaced with the same device in a different size. Thaler et al. reported high rates of undersizing of the most commonly used cervical disc implants, including the PRESTIGE LP, and warned of potential consequences, including subsidence, migration, heterotopic ossification, and biomechanical failure caused by incorrect center of rotation and load distribution.²⁸

As a general rule, patients tend to return to work when their pain has improved to the point that they are able to work. The patient in this study is asked at each follow-up after surgery if he/she is employed. If not, the patient is asked if this is because of neck pain. Following surgery, CDA patients report NDI improvement much more quickly than ACDF patients, particularly at 6 weeks and 3 months postoperatively. Although it is possible for surgeon preference to be a factor, pain and disability improvements track closely with return to work after surgery.

Adoption and utilization rates for CDA continued to lag behind ACDF following FDA approval in 2007 of the initial devices available in the US: PRESTIGE, BRYAN Cervical Disc, and ProDisc-C.¹⁷ Four- to 5-year data are now

TABLE 9. Comparisons of efficacy and neurological variables at 24 months

Variable	p _i (investigational)		p _o (control)		p _o - p _i		Probability of	
	Mean	95% HPD	Mean	95% HPD	Mean	95% HPD	Noninferiority	Superiority
NDI	0.872	(0.828, 0.911)	0.824	(0.768, 0.873)	-0.048	(-0.118, 0.019)	~1.000	0.916
Neurological status	0.935	(0.901, 0.961)	0.835	(0.780, 0.884)	-0.100	(-0.162, -0.039)	~1.000	~1.000
FSU	0.917	(0.876, 0.951)	0.951	(0.911, 0.979)	0.034	(-0.022, 0.086)	0.992	0.104
Neck pain	0.964	(0.937, 0.983)	0.974	(0.947, 0.991)	0.010	(-0.024, 0.043)	~1.000	0.269
Arm pain	0.967	(0.942, 0.985)	0.947	(0.912, 0.974)	-0.019	(-0.059, 0.018)	~1.000	0.843
SF-36 PCS	0.828	(0.778, 0.873)	0.875	(0.827, 0.917)	0.047	(-0.022, 0.115)	0.938	0.09
SF-36 MCS	0.786	(0.734, 0.834)	0.682	(0.614, 0.744)	-0.105	(-0.190, -0.020)	~1.000	0.993
Overall success (w/o FSU)	0.789	(0.736, 0.838)	0.678	(0.613, 0.741)	-0.111	(-0.196, -0.026)	~1.000	0.994
Overall success (w/ FSU)	0.688	(0.623, 0.749)	0.657	(0.579, 0.731)	-0.031	(-0.135, 0.070)	0.995	0.722

FIG. 5. Posterior distributions of differences in success rates of efficacy and neurological variables between the 2 treatment groups. *Horizontal bold lines* indicate 95% HPD, upper and lower limits of which are also labeled. The *dashed vertical line* is the upper limit of noninferiority, and the *dotted vertical line* is the upper limit of superiority.

published in the peer-reviewed literature for these devices, providing the first confirmatory Level 1 evidence that disc arthroplasty patients do at least as well as or better than ACDF control patients not just after 24 months, but also on a longer-term basis.^{5,25,34} For PRESTIGE LP and other more recently developed prostheses, if long-term results

TABLE 10. Patient satisfaction at 24 months

Level of Satisfaction	No. of Pts (%)	
	Investigational (n = 270)	Control (n = 219)
I am satisfied w/ the results of my surgery		
Definitely true	198 (73.3)	130 (59.4)
Mostly true	45 (16.7)	62 (28.3)
Do not know	18 (6.7)	11 (5.0)
Mostly false	5 (1.9)	5 (2.3)
Definitely false	4 (1.5)	11 (5.0)
I was helped as much as I thought I would be		
Definitely true	186 (68.9)	133 (60.7)
Mostly true	50 (18.5)	47 (21.5)
Do not know	21 (7.8)	11 (5.0)
Mostly false	10 (3.7)	14 (6.4)
Definitely false	3 (1.1)	14 (6.4)
All things considered I would have the surgery again		
Definitely true	216 (80.0)	154 (70.3)
Mostly true	29 (10.7)	29 (13.2)
Do not know	17 (6.3)	24 (11.0)
Mostly false	3 (1.1)	5 (2.3)
Definitely false	5 (1.9)	7 (3.2)

also confirm initial outcomes trends, this will offer the potential for additional support of CDA as a substitute for ACDF in appropriately selected patients with single-level degenerative disc disease. Meanwhile, debate continues regarding the benefits of CDA over ACDF, in particular the prospect of reduced adjacent segment degeneration and reoperation rates,^{3,12,20,24,35} as additional long-term evidence continues to be published.

Conclusions

The PRESTIGE LP Cervical Disc maintains mean postoperative segmental motion while providing the potential for biomechanical stability. Investigational patients reported significantly improved pain and disability outcomes, as good or better compared with ACDF, up to 24 months after surgery.

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