Long-term clinical and radiographic outcomes of the Prestige LP artificial cervical disc replacement at 2 levels: results from a prospective randomized controlled clinical trial

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OBJECTIVE The aim of this study was to assess long-term clinical safety and effectiveness in patients undergoing anterior cervical surgery using the Prestige LP artificial disc replacement (ADR) prosthesis to treat degenerative cervical spine disease at 2 adjacent levels compared with anterior cervical discectomy and fusion (ACDF).

METHODS A prospective, randomized, controlled, multicenter FDA-approved clinical trial was conducted at 30 US centers, comparing the low-profile titanium ceramic composite-based Prestige LP ADR (n = 209) at 2 levels with ACDF (n = 188). Clinical and radiographic evaluations were completed preoperatively, intraoperatively, and at regular postoperative intervals to 84 months. The primary end point was overall success, a composite variable that included key safety and efficacy considerations.

RESULTS At 84 months, the Prestige LP ADR demonstrated statistical superiority over fusion for overall success (observed rate 78.6% vs 62.7%; posterior probability of superiority [PPS] = 99.8%), Neck Disability Index success (87.0% vs 75.6%; PPS = 99.3%), and neurological success (91.6% vs 82.1%; PPS = 99.0%). All other study effectiveness measures were at least noninferior for ADR compared with ACDF. There was no statistically significant difference in the overall rate of implant-related or implant/surgical procedure–related adverse events up to 84 months (26.6% and 27.7%, respectively). However, the Prestige LP group had fewer serious (Grade 3 or 4) implant- or implant/surgical procedure–related adverse events (3.2% vs 7.2%, log hazard ratio [LHR] and 95% Bayesian credible interval [95% BCI] –1.19 [–2.29 to –0.15]). Patients in the Prestige LP group also underwent statistically significantly fewer second surgical procedures at the index levels (4.2%) than the fusion group (14.7%) (LHR –1.29 [95% BCI –2.12 to –0.46]). Angular range of motion at superior- and inferior-treated levels on average was maintained in the Prestige LP ADR group to 84 months.

CONCLUSIONS The low-profile artificial cervical disc in this study, Prestige LP, implanted at 2 adjacent levels, maintains improved clinical outcomes and segmental motion 84 months after surgery and is a safe and effective alternative to fusion.

Clinical trial registration no.: NCT00637156 (clinicaltrials.gov)

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KEY WORDS cervical degenerative disc disease; cervical disc arthroplasty; Prestige LP disc replacement; artificial cervical disc; 2-level disc disease

ABBREVIATIONS ACDF = anterior cervical discectomy and fusion; ADR = artificial disc replacement; AE = adverse event; BCI = Bayesian credible interval; DDD = degenerative disc disease; FSU = functional spinal unit; HO = heterotopic ossification; LHR = log hazard ratio; MCS = Mental Component Summary; NDI = Neck Disability Index; PCS = Physical Component Summary; PPS = posterior probability of superiority; TDR = total disc replacement.

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ANTERIOR cervical discectomy and fusion (ACDF) is a standard surgical procedure for treating cervical degenerative disc disease (DDD) associated with intractable radiculopathy or myelopathy. However, ACDF significantly limits the segmental motion at adjacent vertebrae, altering the biomechanics of the spine and creating abnormal loads,^{5,22} which may place additional stress on the adjacent discs, possibly resulting in accelerated degeneration of those discs.^{8,17,22} Recent studies have demonstrated that cervical total disc replacement (TDR) is a safe and effective alternative to ACDF for treatment at a single level of the cervical spine, and that cervical TDR preserves segmental motion and maintains normal intervertebral disc space height at the treated level.^{2-4,6,11,14,15,18}

Many patients have multilevel disease, and 2-level ACDF procedures may result in even greater stresses to the adjacent discs, potentially accelerating adjacent-level disc degeneration.¹² Furthermore, pseudarthrosis in multilevel ACDF is considerably higher than single-level ACDF, as are revisions, complications, and reoperations.^{19,20} For these reasons, TDR may represent an effective alternative to ACDF for treating multilevel degenerative disc disease.

The Prestige LP cervical disc (Medtronic, Inc.), an artificial disc replacement (ADR) device, was approved by the FDA for treating single-level DDD and intractable radiculopathy or myelopathy.⁹ A clinical trial was initiated in 2006 to evaluate the safety and effectiveness of Prestige LP cervical discs at 2 adjacent levels compared with ACDF. The primary outcome measure was overall success at 24 months after surgery. The overall study success rates were 81.4% and 69.4% for the Prestige LP ADR and ACDF groups, respectively.¹⁰ Both noninferiority and superiority in overall success, the primary study end point, were established for ADR compared with ACDF. Overall, the findings indicate that Prestige LP ADR at 2 levels is at least as safe and effective as ACDF, up to 24 months after surgery, and it was granted marketing approval by the FDA for treating 2-level DDD and intractable radiculopathy or myelopathy in 2016.

The present study assessed the long-term effectiveness and safety of the Prestige LP ADR at 2 contiguous levels by comparing outcomes up to 84 months postoperatively with those for the ACDF treatment group.

Methods

The FDA granted final approval of an IDE application (G050202) for this study in January 2006, and surgeries occurred between June 2006 and November 2007 (clinical trial registration no.: NCT00637156 [clinicaltrials.gov]). The study protocol and informed consent form were reviewed by independent IRBs at each investigational site (30 sites) and received IRB approval before the study began (*Appendix*). The prospective, randomized, multicenter, controlled study was designed to assess the safety and effectiveness of the investigational treatment (2-level Prestige LP artificial cervical disc replacement) compared with the control treatment (2-level ACDF procedure involving a cortical ring allograft and the Atlantis Cervical Plate System, Medtronic, Inc.) in patients with

intractable radiculopathy and/or myelopathy at 2 adjacent levels of the cervical spine. Blinding of patients and surgeon investigators was not feasible or considered appropriate beyond the screening and informed consent process. Informed consent was obtained from all patients. The specific methods and procedures for the clinical trial have been described in detail elsewhere¹⁰ and are similar to those reported for the single-level study,⁹ but are summarized here.

Patients

A sample size calculation for the primary study hypothesis of noninferiority in overall success of the Prestige LP ADR compared with ACDF at 24 months—based on assumed success rates of 72% and 70% in the investigational and control groups, respectively, a noninferiority margin (delta) of 10%, an alpha level of 0.05, and power of 80%—yielded a requirement for 177 patients in each group (354 patients). Allowing for a possible 15% loss to follow-up, the enrollment goal was 420 ± 10 patients at a maximum of 30 sites. Inclusion and exclusion criteria are listed in Table 1. Whether patients met the few subjective criteria was left to the judgment of the surgeons based on their clinical expertise. Patients were randomized in a 1:1 ratio to receive either the investigational device (Prestige LP ADR) or fusion control treatment (ACDF). The randomization schedule was centrally generated by the sponsor's statistician.

A total of 456 patients signed the informed consent forms and were randomized into the 2 treatment groups. However, 42 patients assigned to the ACDF group and 17 patients assigned to the Prestige LP group did not complete the study treatment for reasons including deciding not to have surgery or a change in condition, not wanting randomized treatment (9 of the ACDF patients), insurance issues, or other reasons. In total, 397 patients (209 in the ADR group and 188 in the ACDF group) were treated with the assigned treatment. Patient enrollment and follow-up information are provided in the CONSORT flow diagram (Fig. 1). At 60 months postoperatively, 167 patients in the Prestige LP ADR group and 138 in the ACDF group completed all evaluations required to assess overall success; at 84 months, 154 and 126, respectively, did so, yielding follow-up rates of 76.2% for the ADR group and 74.1% for the ACDF group after excluding deaths and withdrawals. All but 3 withdrawals were initiated by the patients after surgery, most commonly because they found the study requirements too demanding (e.g., too much time involved, too many visits), they were feeling better and did not feel they needed to see the doctor, or they were moving from the area. Other patients were lost to follow-up over time, most frequently because of lack of contact information after moving out of the area or unwillingness to undergo further evaluations.

The treatment groups were similar demographically (Table 2), with no statistically significant differences ($p \leq 0.05$) except preoperative work status, which was not considered to be a clinically important difference. Preoperative medical history was similar in the 2 treatment groups, and the patients did not differ in any relevant preoperative medical conditions or medication usage, including time

TABLE 1. Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Cervical DDD at 2 adjacent cervical levels (from C-3 to C-7) requiring surgical treatment & involving intractable radiculopathy, myelopathy, or both	Cervical spinal condition other than symptomatic cervical DDD requiring surgical treatment at the involved levels
Herniated disc &/or osteophyte formation at each level to be treated, producing symptomatic nerve root &/or spinal cord compression. The condition documented by patient history (e.g., neck &/or arm pain, functional deficit &/or neurological deficit), & the requirement for surgical treatment evidenced by radiographic studies (e.g., CT, MRI, radiographs)	Documented or diagnosed cervical instability relative to adjacent segments at either level, defined by dynamic (flexion/extension) radiographs showing sagittal plane translation >3.5 mm or sagittal plane angulation >20°
Unresponsive to nonoperative treatment for ≥6 wks or presence of progressive symptoms or signs of nerve root/spinal cord compression in the face of continued nonoperative management	>2 cervical levels requiring surgical treatment
No previous surgical intervention at the involved levels or any subsequent planned/staged surgical procedure at the involved or adjacent level(s)	A fused level adjacent to the levels to be treated
≥18 yrs old & skeletally mature at the time of surgery	Severe pathology of the facet joints of the involved VBs
Preop NDI score ≥30	Previous surgical intervention at either 1 or both of the involved levels or at adjacent levels
Preop neck pain score ≥8 based on the preop neck & arm pain questionnaire	Previously diagnosed w/ osteopenia or osteomalacia
If a female of childbearing potential, nonpregnant, non-nursing, and agreed not to become pregnant during the study period	If risk factor for osteoporosis, a DEXA scan was required to determine eligibility; a T score of -3.5 or lower (e.g., -3.6, -3.7) or a T score of -2.5 or lower (e.g., -2.6, -2.7) w/ vertebral crush fracture, excluded the patient from the study
Willing to comply w/ the study plan & sign the patient informed consent form	Presence of spinal metastases
	Overt or active bacterial infection, either local or systemic
	Insulin-dependent diabetes
	Tobacco user who did not agree to suspend smoking prior to surgery
	Chronic or acute renal failure or prior history of renal disease
	Documented allergy or intolerance to stainless steel, titanium, or a titanium alloy
	Belonged to a vulnerable population (e.g., mentally incompetent, prisoner, pregnant)
	Alcohol &/or drug abuser as defined by undergoing treatment for alcohol &/or drug abuse
	Involved w/ current or pending litigation regarding a spinal condition
	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

DEXA = dual-energy x-ray absorptiometry; VB = vertebral body.

from symptom onset to surgery, previous neck surgery, or pain medication usage. Table 3 shows the distribution of presenting complaints for the 2 groups. Finally, there were no significant preoperative differences between groups in any of the clinical measures.

Materials

Investigational Device

The Prestige LP Cervical Disc is a dynamic device made of a titanium alloy/titanium carbide composite (also referred to as a titanium ceramic composite) (Fig. 2). The devices are implanted through an anterior approach after a discectomy and are available in various sizes to accommodate the intervertebral disc space and to engage the adjacent vertebral bodies. Device components are placed into the vertebral bodies through impaction at surgery and maintained via bony ingrowth over time.

Outcome Measures

The primary end point was overall success, a composite of both safety and efficacy end points. A patient was considered to have attained overall success if postoperative improvement in the Neck Disability Index (NDI)²¹ score was at least 15 points, neurological status did not worsen, and no serious implant-associated or implant/surgical procedure-associated adverse event (AE) occurred, including a second surgery at the treatment level classified as a supplemental fixation, revision, or nonelective removal.

al. Definitions of success for individual efficacy measures are shown in Table 4.

Other efficacy and safety outcome measures included neck and arm pain rating scales adapted from a previously defined scale,¹³ which produced a total pain score based on both intensity and frequency, the Medical Outcomes Study SF-36²³ Physical Component Summary (PCS) and Mental Component Summary (MCS), gait assessment (Nurick's Classification¹⁶), radiographic assessments (disc height measurement, or functional spinal unit [FSU], heterotopic ossification [HO] in the ADR group graded from 0 to IV, implant condition), patient satisfaction (3 questions, 5-point scale ranging from "definitely true" to "definitely false"), patient global perceived effect (7-point scale from "completely recovered" to "vastly worsened"), foraminal compression test, work status including time to return to work after surgery, physician's perception of results ("excellent," "good," "fair," or "poor"), AE including severity (Grades 1–4) and possible association with the implant and/or surgical procedure assessed by an independent Clinical Adjudication Committee, neurological status, and second surgical procedures that were classified as revision, removal, supplemental fixation, reoperation, or other.

Procedures

Baseline evaluations, including basic demographics; medical history; assessments of pain, disability, and

FIG. 1. CONSORT flowchart of participants throughout the 84-month study. Numbers shown in each box are cumulative through the time period.

neurological status; and radiographic evaluation, were conducted before surgery. Additional radiographs of the treated area were obtained before patients left the facility; surgical data were also collected.

Patient evaluations were scheduled to occur preoperatively (within 6 months of surgery), at surgery, and postoperatively at 6 weeks (± 2 weeks), 3 months (± 2 weeks), 6 months (± 1 month), 12 months (± 2 months), 24 months (± 2 months), 36 months (± 2 months), 60 months (± 3

months), 84 months (± 3 months), and 120 months (± 3 months). At this time, follow-ups through 84 months have been completed, and those findings are reported here.

Radiographic Measurements

Images obtained at study sites were sent to a central core laboratory (Biomedical Systems) for independent review by 2 primary reviewers using a proprietary imaging archival system and software-based measurement tools

TABLE 2. Demographic characteristics of the Prestige LP ADR and the fusion treatment ACDF groups at baseline

Variable	Prestige LP ADR (n = 209)	ACDF (n = 188)	p Value
Age (yrs)			0.84 (NS)
Mean (SD)	47.1 (8.3)	47.3 (7.7)	
Min–max	22.0–75.0	25.0–69.0	
Height (inches)			0.28 (NS)
Mean (SD)	67.2 (3.9)	67.6 (4.0)	
Min–max	59.0–77.0	60.0–78.0	
Weight (lbs)			0.30 (NS)
Mean (SD)	182.1 (42.6)	186.3 (37.2)	
Min–max	105.0–360.0	106.0–300.0	
Body mass index			0.48 (NS)
Mean (SD)	28.2 (5.6)	28.6 (4.9)	
Min–max	16.4–46.1	18.0–43.4	
Sex, n (%)			0.48 (NS)
Male	92 (44.0)	90 (47.9)	
Female	117 (56.0)	98 (52.1)	
Race, n (%)			0.88 (NS)
Caucasian	195 (93.3)	172 (91.5)	
Black	8 (3.8)	8 (4.3)	
Asian	1 (0.5)	3 (1.6)	
Hispanic	4 (1.9)	4 (2.1)	
Other	1 (0.5)	1 (0.5)	
Marital status, n (%)			0.70 (NS)
Single	25 (12.0)	29 (15.4)	
Married	146 (69.9)	133 (70.7)	
Divorced	32 (15.3)	23 (12.2)	
Separated	4 (1.9)	2 (1.1)	
Widowed	2 (1.0)	1 (0.5)	
Education level, n (%)			0.65 (NS)
< High school	21 (10.0)	20 (10.6)	
High school	63 (30.1)	64 (34.0)	
> High school	125 (59.8)	104 (55.3)	
Workers' compensation, n (%)	26 (12.4)	19 (10.1)	0.53 (NS)
Alcohol used, n (%)	116 (55.5)	88 (46.8)	0.09 (NS)
Preop work, n (%)	146 (69.9)	113 (60.1)	0.045

NS = not significant.

for quantitative measurements (e.g., intervertebral angle, horizontal translation, FSU height). A third reviewer was used for adjudications.

Statistical Methods

The primary objective of the IDE clinical study was to demonstrate that the overall success rate in the Prestige LP ADR group was statistically noninferior to the overall success rate in the ACDF control group at 24 months after surgery, with a prespecified noninferiority margin of 0.10. If noninferiority in overall success was established with respect to the control treatment, the investigational

TABLE 3. Preoperative presenting complaints for the Prestige LP ADR and ACDF groups

Presenting Complaint	Prestige LP ADR (n = 209)	ACDF (n = 188)	Significance
Radiculopathy	71.8%	72.9%	NS
Myelopathy	2.4%	3.2%	NS
Radiculopathy & myelopathy	25.8%	23.9%	NS

ADR treatment was considered to be safe and effective. For the purposes of this long-term follow-up, the primary end point, overall success, was evaluated at 36, 60, and 84 months. If noninferiority of the ADR treatment compared with the ACDF treatment in overall success was established, superiority in overall success at 36, 60, and 84 months was evaluated. Success rates for the individual effectiveness end points were also compared between the 2 treatment groups; when noninferiority of the investigational treatment was established, superiority was evaluated.

Bayesian statistical methods using noninformative priors in the Bayesian models were used for comparing differences in success rates between groups. When the posterior probability of noninferiority was at least 95%, noninferiority of the Prestige LP ADR investigational device compared with the control was considered established. If noninferiority was found, superiority of the ADR group to the ACDF group was assessed in a similar fashion using the criterion of a posterior probability of superiority (PPS) of at least 95.0%. Continuous measures, such as NDI score, SF-36 scores, and neck and arm pain scores, were also assessed using paired t-tests for improvement from pre- to postoperatively for each treatment group and were compared between the treatment groups using Bayesian methods. For all AEs and second surgical procedures, the log hazard ratio (LHR) of rates of occurrence between groups and the 95% Bayesian credible interval (BCI) of highest posterior density were computed to determine whether the rates differed statistically between groups.

The outcomes of patients who underwent additional

FIG. 2. The Prestige LP cervical disc. Courtesy of Medtronic.

TABLE 4. Definitions of success

Measure	Definition of Success
NDI	Improvement of ≥ 15 points
Neck & arm pain	Any improvement in score
SF-36 PCS & MCS	Any improvement in score
Gait assessment (Nurick's classification)	Maintenance or improvement on preoperative score
Radiographic measurements	Maintenance of motion for the ADR group at both treated levels (angulation of target level $>4^\circ$ but $\leq 20^\circ$ of angular motion, based on lateral flexion/extension radiographs & no radiographic evidence of bridging bone forming a continuous bony connection w/ the adjacent VBs) & by evidence of fusion for the ACDF group at both treated levels (angulation of target level $\leq 4^\circ$ of angular motion, based on lateral flexion/extension radiographs & evidence of bridging bone, based on the evidence of a continuous bony connection w/ VBs above & below in at least 1 of the following areas: lateral, anterior, posterior, &/or through the allograft ring, & no evidence of radiolucency covering $>50\%$ of either the superior or inferior surface of the graft)
Disc height (FSU)	Postop follow-up FSU height minus 6-wk postop FSU ≥ -2 mm for both treated levels at either the anterior or posterior measurement
Patient satisfaction	Responses of "Definitely true" or "Mostly true"
Patient global perceived effect	1 of the 3 responses on the "Improved" end of the 7-point scale
Foraminal compression test	Postop maintenance or improvement of preop status
Physician's perception of results	An "excellent" or "good" response
AEs	No Grade 3 or 4 implant/surgical procedure-associated AE
Neurological status for motor function, sensory function, & reflexes	Maintenance or improvement in all 3 functions
2nd surgery	None

surgical procedures/interventions were deemed failures for overall success, and since these additional surgical procedures/interventions had potential to alter the original study treatment's outcomes, for all neurological status and all individual effectiveness variables, the last observation obtained before the additional surgery occurred was carried forward for all subsequent observation periods. For comparison of preoperative measures, ANOVA was performed for continuous variables and Fisher's exact test for the categorical variables.

An independent statistical analysis using the same protocol approved by the FDA was performed for the 24-month and 60-month data by the Vanderbilt University Medical Center Biostatistics Collaboration Center. Results for both intervals were consistent with Medtronic's analyses and thus were not performed for other intervals.

Results

Efficacy Success Rates

Figure 3 shows the success rates and posterior probabilities of superiority for overall success, NDI, and neurological success over time. Superiority was established for ADR compared with ACDF for overall success rate and NDI at all postoperative intervals. The observed overall success rates for the ADR and ACDF groups were 81.6% and 70.5% at 36 months postoperatively, respectively, 79.6% and 65.9% at 60 months, and 78.6% and 62.7% at 84 months. By 84 months, 87.0% of ADR patients met criteria for NDI success compared with 75.6% of the ACDF group. A similar difference was shown at 84 months for neurological success (91.6% vs 82.1%, PPS = 99.0%).

Individual Effectiveness Variables

Observed mean scores over time for a number of the individual effectiveness variables, including NDI, neck pain, arm pain, and SF-36 PCS, are shown in Fig. 4. Both groups improved significantly over baseline on all of these measures (all p values ≤ 0.001), with the ADR group showing superiority at all intervals for NDI score and neck pain score. SF-36 PCS showed superiority for the ADR group at long-term follow-up of 60 and 84 months, while arm pain score showed superiority for the ADR group at 24 and 60 months. Foraminal compression test results were negative in 98.0% and 94.2%, of the ADR and ACDF groups, respectively.

Bayesian Analyses

Table 5 presents a summary of the Bayesian analysis to establish posterior probabilities of noninferiority and superiority and 95% BCI of success for all of the effectiveness variables at 36, 60, and 84 months postoperatively. A probability of noninferiority of $\geq 95\%$, allowing a claim of noninferiority of ADR compared with ACDF, was found for all efficacy variables at all test intervals. A posterior probability of at least 95.0%, suggesting superiority of Prestige LP ADR, was found for overall success and NDI success at all time points, and for neurological success, neck pain success, and SF-36 PCS success at 1 or more intervals. Table 5 also shows the mean success probabilities for each efficacy variable based on the Bayesian analyses, as well as the lower and upper bounds of the 95% BCI and the difference in probabilities between the two groups.

FIG. 3. Success rates over time for efficacy measures overall success (A), NDI success (B), and neurological success (C). pps = posterior probability of superiority; pps > 95% considered as being statistically superior.

Patient and Physician Perceptions

At 84 months postoperatively, based on responses to the nonvalidated questionnaire, 94.8% of patients in the Prestige LP ADR group and 92.6% of the patients in the ACDF group reported that they were “definitely” or “mostly” satisfied, and 94.8% and 89.4%, respectively, said they would undergo the surgery again for the same condition. The rates of physicians’ perceptions of results as successful, also based on a nonvalidated questionnaire, were 95.4% and 78.9% for the 2 treatments, respectively. Preoperatively, 69.9% and 60.1% of the original study groups reported

that they were employed, respectively. At 84 months, the percentages of patients working were 66.7% and 59.3%, respectively.

Radiographic Measurements

FSU height was maintained in both groups, with overall success rates at 84 months of 90.6% and 92.7% for the 2 groups, respectively (Fig. 5). Angular range of motion (ROM) at superior and inferior target levels on average was maintained in the ADR group, with no statistically significant changes from preoperative to 84 months (Fig. 6). Fig-

FIG. 4. Mean scores over time for efficacy measures NDI (A), neck (B) and arm (C) pain, and SF-36 PCS (D). For NDI, neck pain, and arm pain, a lower score indicates less disability or pain. For SF-36 PCS, a higher score means better functioning. pps = posterior probability of superiority; pps > 95% is considered as being statistically superior.

ure 7 is a radiograph showing a 2-level arthroplasty ROM at long-term follow-up (84 months). The fusion success rates for the ACDF group at 36 months, 60 months, and 84 months were 83.3%, 94.0%, and 92.0%, respectively. Some of the differences in fusion rates between intervals are likely due to the slightly different samples of patients over time because of death, withdrawal, being lost to follow-up (Fig. 1), and the independent radiological review, which was blinded to fusion status of each patient at previous intervals.

Safety

Table 6 summarizes the percentage of patients having

any type of AE, cumulative through 84 months postoperatively. The ADR group had a statistically lower rate of any type of serious AEs and a lower rate of possibly device-related AEs. The rate of serious AEs (Grade 3 or 4) classified as implant or implant/surgical procedure associated was 3.2% in the ADR group and 7.2% in the ACDF group cumulatively through 84 months postoperatively (LHR -1.19 [95% BCI -2.29 to -0.15]), and the prevalence of specific serious implant- or implant/surgical procedure-associated AEs is detailed in Table 7. All statistically significantly different comparison results favored the ADR group. Nearly all of the device- or procedure-related neurological AEs occurred within the first 6 months after

FIG. 5. FSU success rates for the Prestige LP ADR and ACDF groups over time. pps > 95% considered as being statistically superior.

TABLE 5. Summary of posterior probabilities of noninferiority and superiority and 95% BCI of success for effectiveness variables at 36, 60, and 84 months postoperatively

Variable	Probability of Noninferiority (delta = 0.10) (%)	Probability of Superiority (%)	Posterior Mean & 95% BCI								
			ACDF			Prestige LP ADR			ACDF – ADR*		
			Mean	LB	UB	Mean	LB	UB	Mean	LB	UB
Overall success											
36 mos	~100.0	99.2	0.702	0.629	0.774	0.813	0.756	0.867	-0.111	-0.203	-0.020
60 mos	~100.0	99.6	0.657	0.578	0.734	0.793	0.731	0.853	-0.136	-0.234	-0.036
84 mos	100.0	99.8	0.625	0.541	0.708	0.782	0.717	0.845	-0.157	-0.263	-0.052
NDI success											
36 mos	~100.0	97.5	0.819	0.757	0.879	0.893	0.848	0.935	-0.074	-0.151	0.001
60 mos	~100.0	99.6	0.774	0.703	0.842	0.888	0.839	0.933	-0.114	-0.199	-0.030
84 mos	100.0	99.3	0.752	0.676	0.826	0.865	0.811	0.917	-0.113	-0.206	-0.021
Neurological success											
36 mos	~100.0	96.1	0.833	0.773	0.891	0.898	0.855	0.94	-0.065	-0.139	0.008
60 mos	~100.0	79.3	0.870	0.813	0.923	0.899	0.853	0.942	-0.030	-0.103	0.041
84 mos	100.0	99.0	0.816	0.748	0.882	0.91	0.865	0.953	-0.094	-0.176	-0.014
FSU success											
36 mos	98.7	13.2	0.946	0.906	0.981	0.913	0.869	0.954	0.033	-0.026	0.091
60 mos	99.8	47.2	0.924	0.877	0.969	0.923	0.878	0.964	0.002	-0.064	0.066
84 mos	98.4	28.4	0.92	0.869	0.966	0.899	0.847	0.948	0.02	-0.053	0.092
Neck pain success											
36 mos	~100.0	96.4	0.933	0.892	0.97	0.973	0.95	0.993	-0.040	-0.088	0.005
60 mos	~100.0	97.4	0.912	0.865	0.957	0.964	0.936	0.989	-0.052	-0.108	0.001
84 mos	100.0	65.7	0.944	0.903	0.98	0.955	0.922	0.984	-0.011	-0.064	0.040
Arm pain success											
36 mos	99.3	29.8	0.899	0.851	0.945	0.882	0.835	0.927	0.018	-0.049	0.085
60 mos	99.7	44.7	0.898	0.847	0.946	0.894	0.846	0.938	0.004	-0.065	0.073
84 mos	96.1	18.1	0.904	0.852	0.953	0.87	0.817	0.921	0.034	-0.04	0.108
SF-36 PCS success											
36 mos	99.8	57.9	0.856	0.799	0.911	0.864	0.814	0.911	-0.008	-0.084	0.067
60 mos	~100.0	98.1	0.797	0.728	0.864	0.884	0.835	0.931	-0.087	-0.171	-0.004
84 mos	100.0	93.2	0.795	0.723	0.865	0.863	0.808	0.915	-0.068	-0.158	0.021
SF-36 MCS success											
36 mos	99.8	77.2	0.719	0.646	0.791	0.756	0.693	0.816	-0.036	-0.132	0.058
60 mos	99.4	70.8	0.722	0.645	0.796	0.750	0.683	0.814	-0.028	-0.129	0.072
84 mos	99.5	76.3	0.713	0.632	0.791	0.752	0.682	0.818	-0.039	-0.145	0.066
Gait success											
36 mos	~100.0	93.5	0.967	0.938	0.992	0.989	0.975	1.000	-0.023	-0.057	0.008
60 mos	~100.0	93.3	0.964	0.932	0.991	0.988	0.972	1.000	-0.024	-0.061	0.009
84 mos	100.0	60.4	0.976	0.949	0.997	0.981	0.959	0.998	-0.005	-0.041	0.029

LB = lower bound; UB = upper bound.

* A negative mean difference indicates that the Prestige LP ADR treatment group had a higher success rate than the ACDF control treatment group.

the study surgery, and none of the neurological AEs in the ADR group were Grade 3 or 4. The great majority of all other types of AEs occurred within the first 24 months postoperatively.

The presence of any Grade III or IV HO in the ADR group is summarized in Table 8, although no Grade III or IV HO AEs considered likely to be device related or clinically significant were reported (Table 7). Grade IV HO was observed on radiographs at either or both of the superior and inferior treatment levels in 11.5% and 11.9% of patients at 60 and 84 months, respectively.

The rates of a second surgery at the treated levels through 84 months were 4.2% and 14.7% for the ADR

and ACDF groups, respectively, a statistically significant difference (LHR -1.29 [95% BCI -2.12 to -0.46]) favoring the ADR group (Table 9). The ACDF group had statistically significant higher rates of elective removals and supplemental fixations. An elective removal in this trial was one in which the device was removed at the discretion of the investigator and/or the patient and was not the result of an AE. In the ACDF group, elective removals were typically performed at the discretion of the investigator during a surgical procedure on adjacent or other cervical levels requiring removal of the plate and placement of a new plate. In the ADR patients, one removal occurred at 40 days postoperatively because of radicular arm pain and a

FIG. 6. Angular range of motion (ROM) for the Prestige LP ADR group over time at both the target and adjacent levels. Both superior and inferior levels are shown.

positive foraminal compression test, and another occurred at 1.3 years because of postsurgical cervical kyphosis and sagittal imbalance. The other removals occurred between 1.7 and 4.5 years postoperatively because of foraminal stenosis and other degenerative changes (2 cases), failed arthroplasty (1 case), and loosening of hardware with exacerbation of symptoms by a motor vehicle accident (1 case).

The cumulative rates of second surgeries that involved adjacent levels through 84 months after the clinical study treatment were 6.5% and 12.5% for the ADR and ACDF groups, respectively. Figure 8 demonstrates how the difference in rates of second surgeries between groups, although not significant, continued to increase over time, with a PPS at 84 months, falling just short of significance (PPS = 94.2%).

Discussion

The primary objective for the original FDA-approved clinical study was to demonstrate noninferiority of investigational treatment (Prestige LP artificial cervical disc) over control treatment (ACDF) at 2 levels for symptomatic cervical DDD. At 60 months and 84 months postop-

eratively, the Prestige LP ADR group had superior results compared with the ACDF group in terms of overall success and NDI success and was noninferior on all of the effectiveness outcome measures. At 60 months, the Prestige LP group also showed superiority in SF-36 PCS success, while at 84 months it did so for neurological success. By 84 months, the vast majority of patients in both groups reported satisfaction with their surgery (> 92% in both groups). FSU height was maintained in both groups. The device served in the ADR group to maintain distraction of the disc space. Clinically significant AEs (Grade 3 or 4) that were considered to possibly be associated with the implant or implant/surgical procedure occurred significantly less frequently in the ADR group (3.2% vs 7.2%), as was the rate of second surgeries (4.2% vs 14.7%). Finally, the rates of adjacent-level surgery up to 84 months after the clinical study treatment were higher in the ACDF group. Although this difference did not achieve statistical significance (PPS = 94.2%), the trend appears clear, and the rates continue to diverge over time (Fig. 8).

A recent meta-analysis reviewing 19 randomized controlled trials involving 4516 cases demonstrated better outcomes for TDR compared with ACDF on a wide variety of measures.²⁴ The potential benefits of 2-level TDR for intractable radiculopathy or myelopathy of the cervical spine are similar to those of single-level TDR: motion preservation and diminished stress on adjacent levels. Maintaining mobility at the 2 surgically treated segments better preserves the normal cervical spine biomechanics, protecting the integrity of adjacent segments, and possibly resulting in better patient outcomes for TDR than ACDF patients at 2 levels. One meta-analysis has suggested that outcomes for patients undergoing single-level or multilevel TDR were equally favorable,²⁵ as did a recent individual study.¹ And, as in the current study, others have found that outcomes after 2-level TDR were superior to outcomes after 2-level ACDF.⁷ However, we believe that this is the first study to report results through 84 months postoperatively

FIG. 7. Flexion (left) and extension (right) radiographs obtained in a patient in whom a Prestige LP ADR was placed, showing ROM at 84 months postoperatively.

TABLE 6. Percentage of patients who reported AEs cumulative through 84 months postoperatively

Variable	Prestige LP ADR (n = 209)	ACDF (n = 188)	Log Hazard Ratio (95% BCI)
≥1 of any AEs	99.1	98.2	0.019 (−0.18 to 0.21), NS
Any serious AEs*	56.7	68.2	−0.38 (−0.65 to −0.11)
Possibly device-related AEs†	26.6	27.7	−0.13 (−0.55 to 0.26), NS
Serious, possibly device-related AEs	3.2	7.2	−1.19 (−2.29 to −0.15)

* WHO Grade 3 or 4 adverse events are considered as serious.

† Those deemed to be associated with device or device/surgical procedure.

for an ADR device used at 2 levels, showing the long-term maintenance of results with the Prestige LP and its continued superiority over time to ACDF.

A possible source of bias in this study that might favor an investigational device is the lack of blinding, which is just not possible in this type of study. However, a number of measures were taken to preclude bias: radiological assessments were made by independent reviewers, AEs were evaluated by an independent committee, and statistical analyses were confirmed by statisticians independent of the study sponsor for the 24-month and 60-month data. Patient bias in reporting satisfaction, pain, and so on, could occur, but it seems unlikely that any such bias would sustain itself over long-term follow-up—in this study, 84 months. Not unexpectedly, we were unable to obtain follow-up on all patients through 84 months (7 years). However, the loss to follow-up rates were similar between the groups and results were consistent with those found for earlier intervals so this likely did not produce selection bias that would affect the comparison between groups.

Conclusions

The low-profile artificial cervical disc in this study,

Prestige LP, implanted at 2 adjacent levels, maintains improved clinical outcomes and segmental motion 84 months after surgery. It was statistically noninferior to ACDF in every outcome measure and was statistically superior in overall success rate as well as other measures at 60 months and 84 months after surgery, while having a significantly lower rate of serious adverse effects possibly related to the procedure or device and a lower rate of second surgeries. This makes the Prestige LP artificial cervical disc an effective alternative to standard fusion treatment in patients with DDD associated with intractable radiculopathy or myelopathy at 2 adjacent levels of the cervical spine.

Appendix

The following is a list of other principal investigators who participated in the clinical trial: Mark Adams, MD, Adams Neurosurgery, Saginaw, MI; Carter Beck, MD, Montana Neuroscience Institute, Missoula, MT; Gary Bloomgarden, MD, Orchard Medical Center, New Haven, CT; Isa Canavati, MD, NeuroSpine & Pain Center, Fort Wayne, IN; James Chaddock, MD, Virginia Brain and Spine, Winchester, VA; Wayne Cheng, MD, LLU Orthopedic Group, Loma Linda, CA; Frank J. Coufal, MD, La Jolla Neurosurgical Associates, La Jolla, CA; Doug Ehrler, MD, Crystal Clinic, Inc., Akron, OH; Sanford Emery, MD, MBA, West Virginia University Department of Orthopaedics, Morgantown, WV; Mokbel Chedid, MD, Henry Ford Health System, West Bloomfield, MI; Kevin Gibbons, MD, University at Buffalo Neurosurgery and Kaleida Health—Buffalo General Medical Center/Global Vascu-

TABLE 7. Percentage of patients with Grade 3 or 4 implant or implant/surgical procedure–associated AE cumulative through 84 months

AE	Prestige LP ADR	ACDF	LHR (95% BCI)
Grade 3 or 4 AEs	3.2%	7.2%	−1.19 (−2.29 to −0.15)
Dysphagia/dysphonia	1.3%	0.0%	796.21 (−2.32 to 1961.21), NS
HO	0.0%	1.6%	−798.33 (−1957.40 to −0.77)
Implant events	1.0%	1.6%	−0.6601 (−2.68 to 1.36), NS
Neck &/or arm pain	0.5%	3.1%	−2.24 (−4.94 to 0.15), NS
Neurological	0.0%	1.9%	−796.16 (−1955.69 to −0.49)
Nonunion	0.0%	5.6%	−802.05 (−1969.11 to −1.43)
Other	0.5%	0.6%	−0.17 (−3.77 to 3.44), NS
Spinal event	1.5%	3.3%	−0.94 (−2.46 to 0.52), NS
Trauma	0.0%	0.6%	−797.62 (−1958.28 to 1.34), NS
Vascular	0.5%	0.0%	795.87 (−1.45 to 1953.08), NS
Wound (noninfectious)	0.0%	0.5%	−795.68 (−1959.00 to 1.30), NS

TABLE 8. Percentage of patients with Grade III and IV HO for superior and inferior levels over time for the Prestige LP ADR group

Follow-Up Period & HO Grade	Superior Level	Inferior Level	Either or Both Levels
36 mos (n = 184)			
III	14.1%	21.2%	
IV	4.9%	4.9%	7.6%
III or IV	19.0%	26.1%	32.1%
60 mos (n = 165)			
III	19.4%	20.0%	
IV	8.5%	8.5%	11.5%
III or IV	27.9%	28.5%	38.8%
84 mos (n = 151)			
III	25.8%	25.2%	
IV	8.6%	7.3%	11.9%
III or IV	34.4%	32.5%	42.4%

TABLE 9. Second surgeries, including number of events and number and percentage of patients cumulative through 84 months postoperatively, based on the life-table method

Variable	Prestige LP ADR		ACDF		LHR (95% BCI)
	Events	Patients	Events	Patients	
2nd op at index level*	10	8 (4.2%)	27	22 (14.7%)	-1.29 (-2.12 to -0.46)
Revision	0	0 (0.0%)	1	1 (0.5%)	-795.68 (-1958.99 to 1.29), NS
Removal	6	6 (3.2%)	6	6 (3.4%)	-0.18 (-1.36 to 1.01), NS
Elective	0	0 (0.0%)	6	6 (4.3%)	-798.67 (-1963.72 to -1.32)
Supplemental fixation	1	1 (0.5%)	7	7 (5.5%)	-2.64 (-5.34 to -0.36)
Reop	3	3 (1.6%)	7	5 (3.1%)	-0.7861 (-2.36 to 0.71), NS
Supplemental fixation BGS†	0	0 (0.0%)	5	5 (2.8%)	-799.25 (-1962.07 to -1.76)
2nd op at adjacent level	12	12 (6.5%)	22	17 (12.5%)	-0.5937 (-1.35 to 0.156), NS

BGS = external bone growth stimulator.

* Some patients had more than 1 second surgery.

† Not included in the total number of second surgeries at the treated level.

FIG. 8. Rates of second surgeries at an adjacent level over time for the Prestige LP ADR and ACDF groups. pps > 95% is considered as being statistically superior.

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Disclosures

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