SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Artificial Cervical Disc
Device Trade Name:	PRESTIGE® LP Cervical Disc
Device Procode:	MJO
Applicant's Name and Address:	Medtronic Sofamor Danek 1800 Pyramid Place Memphis, TN 38132
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P090029
Date of FDA Notice of Approval:	July 24, 2014

II. INDICATIONS FOR USE

The PRESTIGE® LP Cervical Disc is indicated in skeletally mature patients for reconstruction of the disc at one level from C3-C7 following single-level discectomy for intractable radiculopathy (arm pain and/or a neurological deficit) with or without neck pain, or myelopathy due to a single-level abnormality localized to the level of the disc space and at least one of the following conditions confirmed by imaging (CT, MRI, X-rays): herniated nucleus pulposus, spondylosis (defined by the presence of osteophytes), and/or visible loss of disc height as compared to adjacent levels. The PRESTIGE® LP Cervical Disc is implanted using an anterior approach. Patients should have failed at least 6 weeks of non-operative treatment or have had the presence of progressive symptoms or signs of nerve root/spinal cord compression in the face of continued non-operative management prior to implantation of the PRESTIGE® LP Cervical Disc.

III. CONTRAINDICATIONS

The PRESTIGE® LP Cervical Disc should not be implanted in patients with the following conditions:

- Active systemic infection or localized infection at the surgical site
- Osteoporosis defined as a DEXA bone mineral density T-score equal to or worse than -3.5 or a T-score equal to or worse than -2.5 with vertebral compression fracture, or osteopenia defined as a DEXA bone mineral density T-score $\leq$ -1.0
- Allergy or sensitivity to titanium, aluminum or vanadium
- Marked cervical instability on neutral resting lateral or flexion/extension radiographs; translation >3.5mm and/or >11° rotational difference from that of either adjacent level

- Severe spondylosis at the level to be treated, characterized by bridging osteophytes, loss of disc height >50%, an absence of motion (<2°) as this may lead to a limited range of motion and may encourage bone formation (e.g. heterotopic ossification, fusion)
- Severe facet joint arthropathy
- Significant cervical anatomical deformity or clinically compromised vertebral bodies at the affected level due to current or past trauma (e.g., by radiographic appearance of fracture callus, malunion or nonunion) or disease (e.g., ankylosing spondylitis, rheumatoid arthritis)
- Significant kyphotic deformity or significant reversal of lordosis; or
- Symptoms attributed to more than one cervical level

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the PRESTIGE® LP Cervical Disc labeling.

V. DEVICE DESCRIPTION

The PRESTIGE® LP Cervical Disc is a two-piece articulating device that is inserted into the intervertebral disc space as a single unit at a single cervical level using an anterior approach. The device is manufactured from a titanium ceramic composite (Titanium-6Aluminum-4Vanadium with 10% Titanium Carbide) and consists of two metal plates which function via a ball and trough mechanism. The superior component of the implant contains the ball portion of the mechanism, and the inferior component contains the trough portion. These two features engage to create an interface designed to allow for motion after implantation. Each component is affixed to the adjacent vertebral body by two rail geometries incorporating anti-migration teeth which are press fit into two pre-drilled holes in the vertebral bone. The portion of the flat surface between the rails and contacting the vertebral endplate contains commercially pure titanium (CP Ti) plasma thermal sprayed coating designed to permit bony on-growth for additional device incorporation. The remaining portion of the flat surface is titanium ceramic roughened to enhance fixation.

PRESTIGE® LP implants are offered in a variety of configurations to accommodate varied patient anatomy. The available components are shown in **Table 1** below.

Table 1: PRESTIGE® LP Cervical Disc Device Sizes

Catalog Number	Size
6972260	6mm x 12mm
6972460	6mm x 14mm
6972660	6mm x 16mm
6972860	6mm x 18mm
6972470	7mm x 14mm
6972670	7mm x 16mm
6972870	7mm x 18mm
6972480	8mm x 14mm
6972680	8mm x 16mm
6972880	8mm x 18mm

PRESTIGE® LP devices are implanted using instruments specific to the device, as well as manual surgical instruments. Instruments specifically designed for implanting PRESTIGE® LP consist of trials, trial cutter guides, rail punches, and implant inserters. General purpose instruments include instruments for cervical distraction and discectomy preparation.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of intractable radiculopathy or myelopathy due to a single-level abnormality localized to the disc space.

- Nonoperative alternative treatments include, but are not limited to, physical therapy, medications, braces, chiropractic care, bed rest, spinal injections, or exercise programs.
- Surgical alternatives include, but are not limited to, surgical decompression and/or fusion using various bone grafting techniques (e.g., Cloward bone dowels, Smith Robinson tri-cortical wedges, and Keystone grafts) or interbody fusion devices, which may or may not be used in conjunction with anterior cervical plating (e.g., plate and screws), or posterior spinal systems (e.g., rods, hooks, wires). Anterior cervical discectomy and fusion (ACDF) with an interbody graft or spacer is the most commonly used method for decompression and fusion. Intractable radiculopathy or myelopathy due to a single-level abnormality localized to the disc space may also be treated surgically using another FDA approved artificial cervical disc.

Each alternative has advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician.

VII. MARKETING HISTORY

The device has a marketing history outside of the United States that began in 2004, and has not been withdrawn from marketing for any reason. The PRESTIGE® LP Cervical Disc device is marketed in:Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Chile, China, Costa Rica, Denmark, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Israel, Italy, Jamaica, Malaysia, Mexico, Netherlands, New Zealand, Norway, Pakistan, Poland,

Portugal, Saudi Arabia, Singapore, Slovakia, South Africa, South Korea, Spain, Sweden, Switzerland, Taiwan, Turkey and the United Kingdom.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the PRESTIGE® LP Cervical Disc.

1. Risks associated with any surgical procedure include: abscess; cellulitis; wound dehiscence; wound, local, and/or systemic infection; wound necrosis; edema; hematoma; heart and vascular complications; hypertension; thrombosis; ischemia; embolism; thromboembolism; hemorrhage; thrombophlebitis; adverse reactions to anesthesia; pulmonary complications; organ, nerve or muscular damage; gastrointestinal or genitourinary compromise; seizure, convulsion, or changes to mental status; complications of pregnancy including miscarriage and fetal birth defects; inability to resume activities of daily living including loss of consortium; and death.

2. Risks associated with anterior cervical spine surgery include: dysphagia; dysphonia; hoarseness; vocal cord paralysis; laryngeal palsy; sore throat; recurring aspirations; tracheal, esophageal, or pharyngeal perforation; airway obstruction; warmth or tingling in the extremities; neurologic complications including damage to nerve roots, other nerves, or the spinal cord possibly resulting in weakness, pain or even paralysis; dural tears or leaks; cerebrospinal fistula; discitis, arachnoiditis, and other types of inflammation; loss of disc height; loss of anatomic sagittal plane curvature or vertebral listhesis; scarring, herniation or degeneration of adjacent discs; surrounding soft tissue damage, spinal stenosis; spondylolysis; fistula; vascular damage and/or rupture; and headache.

3. Risks associated with a cervical artificial disc device, including the PRESTIGE® LP Cervical Disc, include: early or late loosening of the components; disassembly; bending or breakage of any or all of the components; implant migration; implant malpositioning; implant subsidence; loss of fixation; sizing issues with components; anatomical or technical difficulties; bone fracture; foreign body reaction to the implant including possible tumor formation, autoimmune disease, metallosis, and/or scarring; possible tissue reaction; bone resorption; bone formation (including heterotopic ossification) that may reduce spinal motion or result in a fusion, either at the treated level or at adjacent levels; development of new radiculopathy, myelopathy, or pain; tissue or nerve damage caused by improper positioning or placement of implants or instruments; bending or breakage of a surgical instrument, as well as the possibility of a fragment of a broken instrument remaining in the patient; loss of neurological function; decreased strength of extremities; decreased reflexes; cord or nerve root injury; loss of bowel and/or bladder control or other types of urological system compromise; interference with radiographic imaging because of the presence of the implant; and the need for subsequent surgical intervention.

For the specific adverse events that occurred in the clinical study of the PRESTIGE® LP Cervical Disc, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

A variety of testing was conducted to characterize the performance of the PRESTIGE® LP Cervical Disc, as follows:

A. Laboratory Studies

- Subluxation Testing
- Subsidence Testing
- Push-Out
- Static Compression
- Compression Fatigue
- Static Compression Shear
- Compression Shear Fatigue
- Durability and Wear Testing
- MRI Testing

B. Animal Testing

- Wear Particulate Injection Analysis

C. Additional Studies

- Biocompatibility
- Sterilization, Packaging, and Shelf Life Testing

A. Laboratory Studies

Table 2: Mechanical Testing

Test Description	Purpose	Methods	Medtronic's Acceptance Criteria	Results
Subluxation 1	To determine the amount of shear force applied to the inferior component required to dislocate (subluxate) the superior "ball" feature from the "trough" feature in multiple directions and lordotic angulations.	Under 100N preload, Components (n=1 assembly test puck) were tested in both the M-L and AP directions. M-L specimens were held in two relative positions 0° and 10°. A-P specimens were held in 10° flexion. In both configurations the inferior component of each specimen was displaced laterally in multiple directions until the superior component (ball) was displaced from the inferior component (trough).	The subluxation force must be greater than the maximum *in vivo* shear load in the cervical spine (20N).[1]	The mean maximum subluxation force was 357±8.3 N at 0º; 321±17.6 N at 10º positive lateral bending, and 769±82 N at 10 º negative lateral bending; 683±116.0 N at 10º flexion and 276±43.6 N at 10º extension. In all instances, the PRESTIGE® LP disc subluxation values exceeded the clinically acceptable value of 20 N. These results suggest that the device can resist subluxation loads that exceed anticipated physiologic loads on the cervical spine.
Subluxation 2	To determine what amount of shear force applied to the inferior component required to dislocate (subluxate) the superior "ball" feature from the "trough" feature in multiple directions and angulations.	Under 100N preload, n=6 (6mm x 16 mm) device assemblies were tested in both the M-L and AP directions. M-L specimens were held in two relative positions 0° and 10°. A-P specimens were held in 10° flexion. In both configurations the inferior component of each specimen was displaced laterally in positive and negative directions until the superior component (ball) was displaced from the inferior component (trough).	The medial-lateral and flexion-extension subluxation forces must exceed 20N.[1]	The mean maximum medial-lateral subluxation force was 246.2±16.0N at 0º; 360.5±21.0N at 10º positive lateral bending, and 73.7±4.5N at 10 º negative lateral bending; 406.9±37.9N at 10º flexion and 93.2±11.9N at 10º extension. In all instances, the PRESTIGE® LP disc subluxation values exceeded the clinically acceptable value of 20 N. These results suggest that the device can resist subluxation loads that exceed anticipated physiologic loads on the cervical spine.

[1] White A, Panjabi M. *Clinical Biomechanics of the Spine*. J.B Lippincott, Philadelphia. 2nd Edition, p. 9.

Test Description	Purpose	Methods	Medtronic's Acceptance Criteria	Results
Subsidence	To determine whether the PRESTIGE® LP implant can effectively withstand a static axial compressive load without subsiding (sinking) into the vertebral body endplates, which *in vivo* would potentially cause endplate fracture, instability, and/or pain at the implanted level.	n=1 (6mm x 12 mm) device assembly was assembled to mating foam blocks and axial load is applied at 0.1 mm/sec until the blocks contacted. Load/displacements were recorded for 5 repetitions of the test.	The subsidence force must be greater than the maximum *in vivo* compressive load in the cervical spine (74N) due to head weight[1] and equivalent to the stiffness of the previously approved PRESTIGE® Cervical Disc (363 N/mm).	The mean ultimate load was 513±28.6N with a stiffness value of 442± 19.1 N/mm. The average subsidence values were higher than the clinically acceptable value of 74N and PRESTIGE® Cervical Disc (363 N/mm). These results suggest that the device can resist subsidence loads that exceed anticipated physiologic loads on the cervical spine.
Push-Out	To determine overall resistance to push-out for the PRESTIGE® LP device	A 100 N preload was applied to n=1 (6mm x 12mm) device assembly while an axial force is applied in the anterior/posterior and medial lateral directions at 6 mm/min until failure is obtained.	The pushout force must be greater than the maximum *in vivo* intervertebral shear force in the cervical spine (20N).[1]	The mean ultimate load was 127.4±3.2N. The results exceeded the clinically acceptable load of 20N. These results suggest that the device can resist push-out loads that exceed anticipated physiologic loads on the cervical spine.
Static Compression 1	To characterize the PRESTIGE® LP device's ability to provide resistance to axial compressive loading	n=5 (7mm x 18 mm) device assemblies were placed between two unsupported stainless steel test blocks, and an axial compressive load was applied at 3mm/min until functional failure occurred.	The axial compressive failure load must exceed the clinically acceptable value of 74N.[1]	The mean failure load was 8808±2233N. The results of the static compression test far exceeded the clinically acceptable load of 74N. These results suggest that the device can resist compressive loading that exceeds anticipated physiologic loads on the cervical spine.

Test Description	Purpose	Methods	Medtronic's Acceptance Criteria	Results
Static Compression 2	To characterize the 6x18mm PRESTIGE® LP device's ability to withstand axial compressive loads by determining the ultimate failure load of the construct over multiple specimens	n=6 (6mm x 18mm) device assemblies were tested in accordance with ASTM Standard F2346 "Standard Test Method for Static and Dynamic Characterization of Spinal Artificial Discs"	The mean ultimate load for the 6x18mm PRESTIGE® LP implant was greater than or equal to 550N. This load is twice the acceptance criterion of the fatigue load and a factor of safety six times the compression load in the cervical spine due to the weight of the head (74N).[1]	The maximum load was 7992±748N and a stiffness of 21,096 N/mm. The results of the static compression test exceeded the clinically acceptable load of 74N as well as the 550N load. These results suggest that the device can resist compressive loading that exceeds anticipated physiologic loads on the cervical spine.
Compression Fatigue 1	To characterize the PRESTIGE® LP device's ability to provide resistance to axial compressive loading throughout the device's life cycle.	n=3 (7mm x 18mm) devices assemblies were placed between two polyethylene test blocks. They were then tested on an MTS machine in load control with an R value of 10 and a cyclical load of 225N until attainment of 5M cycles or failure of the component.	The compression fatigue force must exceed the clinically acceptable value of 74N.[1]	All three specimens ran out at 10 million cycles at an applied load of 225N. Results from the compression fatigue tests exceeded the clinically acceptable load of 74N. These results suggest that the device can resist dynamic compressive loading that exceeds anticipated physiologic loads on the cervical spine.

Test Description	Purpose	Methods	Medtronic's Acceptance Criteria	Results
Compression Fatigue 2	To characterize the 5x12mm and 5x16mm PRESTIGE® LP device's ability to provide resistance to axial compressive loading throughout a device's life cycle.	n=2 (5mm x 12mm) device assemblies were tested in accordance with ASTM Standard F2193 "Standard Specifications and Test Methods for Components Used in the Surgical Fixation of the Spinal Skeletal System."	The assemblies must attain two run outs at 10 million cycles at a compressive fatigue load of 225N without functional failure which represents a three times factor of safety of the compression load in the cervical spine due to the weight of the head (74N).[1]	All assemblies ran out at 10 million cycles at an applied load of 225N. Results from the compression fatigue tests far exceeded the clinically acceptable load of 74N and met the acceptance criterion as defined in the test protocol. These results suggest that the device can resist compressive loading that exceeds anticipated physiologic loads on the cervical spine.
Compression Fatigue 3	To characterize the 6x18mm PRESTIGE® LP device's ability to provide resistance to axial compressive loading throughout a device's life cycle.	n=2 (6mm x 18mm) device assemblies were tested in accordance with ASTM Standard F2346 "Standard Test Method for Static and Dynamic Characterization of Spinal Artificial Discs."	The assemblies must attain two run outs at 10 million cycles at a compressive fatigue load of 225N without functional failure which represents a three times factor of safety of the compression load in the cervical spine due to the weight of the head (74N).[1]	Both assemblies ran out at 10 million cycles at an applied load of 225N. Results from the compression fatigue tests far exceeded the clinically acceptable load of 74N and met the acceptance criterion as defined in the test protocol. These results suggest that the device can resist compressive loading that exceeds anticipated physiologic loads on the cervical spine.

Test Description	Purpose	Methods	Medtronic's Acceptance Criteria	Results
Static Compression Shear	To characterize the device's ability to resist shear compressive loads found during day-to-day physiologic loading of the cervical spine.	n=6 (5mm x 16mm) device assemblies were tested in accordance with ASTM Standard F2346 "Standard Test Method for Static and Dynamic Characterization of Spinal Artificial Discs."	The assemblies must attain at least a 550N compressive load prior to functional failure for all six samples which represents a six times factor of safety of the compression load in the cervical spine due to the weight of the head (74N).[1]	The mean maximum static compression shear load was 4962±674N with a mean stiffness of 6058±762N. The average ultimate load for all PRESTIGE® LP components exceeds the clinically acceptable load of 74N and the defined acceptance criteria of 550N. These results suggest that the device can resist compressive shear loading that exceeds anticipated physiologic loads on the cervical spine.
Compression Shear Fatigue	To characterize the device's ability to resist shear compressive loads found during day-to-day physiologic loading of the cervical spine.	n=2 (5mm x 12 mm) device assemblies were tested in accordance with ASTM Standard F2346 "Standard Test Method for Static and Dynamic Characterization of Spinal Artificial Discs."	The assemblies must attain two run outs at 10 million cycles without functional failure at a minimum compressive load of 225N which represents a three times factor of safety of the compression load in the cervical spine due to the weight of the head (74N).[1]	The assemblies ran out at 10 million cycles at a maximum compression shear axial load of 225N and maximum calculated shear load of 159N. Results from the compression fatigue tests far exceeded the clinically acceptable load of 74N and met the acceptance criterion as defined in the test protocol. These results suggest that the device can resist dynamic compressive shear loading that exceeds anticipated physiologic loads on the cervical spine.

Table 3: Wear Testing

Test Description	Purpose	Methods	Medtronic's Acceptance Criteria	Results
Wear Test 1 (Lateral bending coupled with axial rotation followed by flexion/extension)	To characterize the wear behavior for the PRESTIGE® LP family of implants.	n=6 (6mm x 16mm) device assemblies were tested in accordance with ASTM 2423 "Functional, Kinematic, and Wear Assessment of Total Disc Prostheses."	The wear rate under combined motion for the PRESTIGE® LP device must not be statistically higher than wear rate for hard bearing cervical disc replacements (1.10±0.09.mm^3/ MC).	The steady-state wear rate under combined motion for the PRESTIGE® LP Device was 0.35±0.03mm^3/MC with a mean particle diameter of <0.2µm. The total wear at 20MC was 4.22±0.21mm^3. The overall steady-state wear rate for the PRESTIGE® LP device was lower than that of other hard bearing cervical disc replacements, and met the acceptance criterion as defined in the test protocol. The wear rate and volume and size of particulate wear debris are similar to other legally-marketed hard bearing cervical disc replacements.
Wear Test 2 (Lateral bending combined with axial rotation and flexion/extension)	To characterize the wear behavior for the PRESTIGE® LP family of implants	n=6 (6mm x 16mm) device assemblies were tested in accordance with ISO 18192-1 "Implants for Surgery – Wear of Total Intervertebral Spinal Disc Prostheses – Part 1: Loading and Displacement Parameters for Wear Testing and Corresponding Environmental Conditions for Test.	This test was used to generate benchmark volumetric wear and wear rate data under the ISO standard, and there was no acceptance criteria quantified.	The steady-state wear rate was 0.25±0.04mm^3/MC The total accumulated wear was 2.74±0.38mm^3 Characterization only.

Test Description	Purpose	Methods	Medtronic's Acceptance Criteria	Results
Wear Test 3 (Lateral bending coupled with axial rotation followed by flexion/extension; Flexion/extension followed by lateral bending coupled with axial rotation)	To characterize the wear behavior for the PRESTIGE® LP family of implants under simulated loading of the cervical spine.	n=6 device test coupons (three in each sequence) were tested in coupled Lateral Bending and axial rotation followed by flexion/extension, and three were tested in reverse order with flexion/extension cycles first. Coupled motion was tested to 5.0 million cycles (MC) with a compressive load of 49N. Flexion/extension of 9.7° was tested to 10.0 MC with a compressive load of 148N. Combined motion testing was conducted in lateral bending at 4.7° and axial rotation at 3.8°. All specimen were tested in a temperature controlled both with a fluid medium of 25% alpha calf fraction.	All implants must be functional by allowing a total of ±4.7° lateral bending (LB) coupled with ±3.8° axial rotation (AR) followed by ±9.7° flexion/extension (FE). Furthermore, none of the inferior side components must wear through from the bottom of the trough feature to the test coupon.	All test components remained functional after 15.0 MC in all three motions. Therefore, the acceptance criteria were met. The total volumetric wear after 15 MC when testing first in lateral bending plus axial rotation and then flexion-extension was $1.25\pm0.89mm^3$. The total volumetric wear after 15 MC when testing in flexion-extension first and then lateral bending plus axial rotation was $1.32\pm0.71mm^3$. The mean steady-state wear rate when testing first in lateral bending plus axial rotation and then flexion-extension was $0.27\pm0.31mm^3$/MC for lateral bending plus axial rotation and was $0.01mm^3\pm0.00mm^3$/MC in flexion-extension. The mean steady-state wear rate when testing when testing in flexion-extension first and then lateral bending plus axial rotation was $0.21\pm0.18mm^3$/MC for lateral bending plus axial rotation and was $0.01mm^3\pm0.01mm^3$/MC in flexion-extension. These results suggest that the device will not wear through during expected physiological use.

Test Description	Purpose	Methods	Medtronic's Acceptance Criteria	Results
Wear Test 4 (Lateral bending coupled with axial rotation for high and low radial clearances)	To characterize the influence of radial clearance on the wear behavior of the PRESTIGE® LP Cervical Disc.	n=6 (n=3 high clearance; n=3 low clearance) device assemblies were tested in accordance with ASTM 2423 "Functional, Kinematic, and Wear Assessment of Total Disc Prostheses"	The steady-state wear rate for both the high and low clearances are statistically equivalent or lower than the specimen's nominal steady-state wear rate. (0.41±0.06.mm^3/ MC).	The steady-state wear rate at low clearance was 0.45±0.05 mm^3/MC and 0.28±0.17 mm^3/MC at high clearance. The volumetric wear for 5 MC at low clearance was 2.41±0.38 mm^3 and 1.52±0.92 mm^3 at high clearance. There was no statistically-significant difference between the steady-state wear rate of the low-clearance and the nominal specimens (p = 0.381) and between the high-clearance specimens and the nominal specimens (p = 0.107). These results suggest that the device has similar wear rates as other legally-marketed hard bearing cervical disc replacements.

Table 4: MRI Testing

Test Description	Purpose	Methods	Medtronic's Acceptance Criteria	Results
MRI Characterization	To evaluate the safety and compatibility of the PRESTIGE® LP Cervical Disc System in a 3 Tesla MRI environment	n=1 (8mm x 18mm) device assemblies were tested in accordance with ASTM F2052 "Standard Test Method for Measurement of Magnetically Induced Displacement Force on Medical Devices in the Magnetic Resonance Environment," ASTM F2182 "Standard Test Method for Measurement of Radio Frequency Induced Heating on or Near Passive Implants During Magnetic Resonance Imaging," and ASTM F2119, "Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants"	All tests were for characterization purposes and acceptance criteria were not established.	1.) Magnetic field interactions: Implant does not present an additional risk or hazard to the patient in a 3-tesla MRI environment with regard to translational attraction, migration, or torque. 2.) MRI-related heating: Highest temperature change recorded was not considered to be physiologically consequential for a human subject. 3.) Artifact test: Worst case artifacts that appeared on MR images were localized signal voids graded as "small" in comparison to the size and shape of the device.

B. Laboratory Studies

Two particulate injection studies were conducted in rabbit models to evaluate potential toxicity associated with debris and particulates obtained from Ti6Al4V/TiC particulates when placed in direct contact with the spinal column via epidural injection. Summary data for the studies are provided in the following table.

Table 5: Animal Testing

Test Description	Purpose	Methods	Medtronic's Acceptance Criteria	Results
Injection Study	To evaluate the host response to PRESTIGE® LP Cervical Disc's Ti6Al4V/TiC material	Rabbits were injected in the epidural space of the spinal canal with a control solution or a mixture of solution (contrast solution mixed wih 10% TiC/Ti-6Al-4V particulate injected into n=20 total rabbits) representative of wear debris. Test groups were divided into low and high doses and represented an equivalent dose of 18.9 and 57.7 million cycles of use based upon wear test data. Rabbits were terminated at 12 and 24 weeks. Local and distant tissues were harvested and examined for gross pathology (if present) and the tissue was analyzed histologically.	The test was for characterization purposes and acceptance criteria were not established.	Characterization of response to wear particles near the spine. The lungs, spleen, thymus, and lymph nodes were all observed to be unaffected by either the high or low dose. The particles generally elicited no tissue reaction or mild tissue reaction in both 12 and 24 week dose groups.

Test Description	Purpose	Methods	Medtronic's Acceptance Criteria	Results
Injection Study	To evaluate the potential toxicity associated with wear particulate generated from the Ti6Al4V/TiC material from which the PRESTIGE® LP Cervical Disc is manufactured	Rabbits were injected in the epidural space of the spinal canal with a control solution or a mixture of solution (contrast solution mixed wih 10% TiC/Ti-6Al-4V particulate injected into n=36 total rabbits) representative of wear debris. Test groups were divided into low and high doses representing an equivalent dose of 20 and 60 million cycles of use based upon wear test data. Rabbits were terminated at 3 and 6 months. Local and distant tissues were harvested and examined for gross pathology (if present) and the tissue was analyzed histologically.	The test was for characterization purposes and acceptance criteria were not established.	Characterization of response to wear near the spine. There were no adverse tissue effects such as necrosis or excessive inflammation.

C. Additional Studies

Biocompatibility Testing

Per the requirements of ISO 10993-1, PRESTIGE® LP Cervical Disc device is classified as a permanent contact, tissue/bone-contacting implant. The following biocompatibility tests were undertaken on the complete device (or extract, as required): Cytotoxicity, sensitization, intracutaneous reactivity, and systemic toxicity. Data are also available for genotoxicity and implantation. All standard acceptance criteria were met. The test results support the biocompatibility of the device materials. Therefore, the Ti-6Al-4V/TiC material is considered to be safe for use in the cervical spine.

Sterilization, Packaging and Shelf Life Validation

The PRESTIGE® LP Cervical Disc is provided in a sterile package ready for use. The PRESTIGE® LP Cervical Disc is sterilized using gamma radiation at a minimum dosage of 25 kGy, at a sterilization assurance level (SAL) of 10^{-6}. Sterilization validation according to ANSI/AAMI/ISO 11137-2:2006 was conducted to confirm that the sterility of the device is maintained through a sterile barrier. Shelf life and packaging validation studies, including packaging seal and integrity, accelerated aging, and real-time aging testing, were conducted to demonstrate the device packaging can maintain a sterile barrier with a shelf life of 8 years.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of reconstruction of the disc at one level from C3-C7 following single-level discectomy with the PRESTIGE® LP Cervical Disc for treatment of intractable radiculopathy or myelopathy due to a single-level abnormality localized to the level of the disc space in the United States under IDE #G040086. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Subjects were treated between January 13, 2005 and November 8, 2005. The database for this PMA reflected data collected through April 22, 2009 and included 280 subjects (termed "IDE Cohort") at 20 investigational sites. Fifty four additional subjects were enrolled at the same investigational sites, including: 30 subjects enrolled into a Metal Ion Cohort (MI) for which metal ion analysis was conducted based on blood draws at each follow-up time point; and, 24 Continued Access (CA) subjects.

The study was a prospective, multi-center, non-randomized, unmasked, non-inferiority clinical trial conducted in the United States to compare the safety and effectiveness of the PRESTIGE® LP Cervical Disc to the standard of care (a legally marketed alternative with similar indications for use) anterior cervical discectomy and fusion (ACDF) using structural allograft and stabilization using an Atlantis® anterior cervical plate. The control group consisted of a non-randomized historical control group that received treatment with ACDF for reconstruction of the disc from C3-C7 following single-level discectomy for intractable radiculopathy and/or myelopathy in the previous IDE randomized trial of the PRESTIGE® Cervical Disc (#G010188). To adjust possible effects on clinical outcomes caused by use of historical controls, the propensity score technique was utilized. The distribution of propensity scores revealed sufficient overlapping between the two groups with respect to subject demographic and baseline characteristics.

Subjects were evaluated pre-operatively, intra-operatively, immediately post-operatively and then at 6 weeks, 3 months, 6 months, 12 months, 24 months and annually thereafter. The recommended post-operative care included avoidance of overhead lifting, heavy lifting, repetitive bending, and high-impact exercise or athletic activity for 60 days postoperatively. Avoidance of prolonged (beyond 2 weeks post-op) non-steroidal anti-inflammatory drug (NSAID) use was specified in the postoperative regimen, although the use of NSAIDs was recommended for the first two weeks post-operatively. Post-operative bracing requirements were left to the discretion of the investigators and included the option for use of a soft collar as needed. The use of electrical bone growth stimulators was not recommended during the 24-month follow-up period. However, in a few cases where an electrical bone growth stimulator was utilized due to specific subject presentation, they were considered a supplemental form of therapy for spinal fusion surgery, and deemed failures included in the "Supplemental Fixation" Adverse Event category. Subjects who smoked were encouraged to discontinue smoking.

All adverse events (device-related or not) were monitored over the course of the study and radiographic assessments were done by an independent core laboratory. Overall success was determined by data collected during the initial 24 months of follow-up. All adverse events were independently adjudicated (for adverse event code, severity and relationship to the device and/or procedure) by a Clinical Adjudication Committee (CAC) composed of three independent spine surgeons.

Note that this was a Bayesian non-inferiority study with 280 PRESTIGE® LP IDE subjects and 265 subjects in the ACDF historical control. The pre-specified non-inferiority margin was 10% and the trial was adequately powered (83% power) based on an assumption of equal success rates of 75%. The statistical plan pre-defined that the data would initially be analyzed after approximately 125 PRESTIGE® LP IDE subjects had reached the 24-month evaluation time point. At that time point, all subjects were anticipated to reach 12-month follow-up time point. The sponsor also planned to analyze the data when the entire cohort reached the 24-month time point. Due to rapid study enrollment and timing considerations, the sponsor decided not to formally perform the pre-defined interim analysis.

1.Clinical Inclusion and Exclusion Criteria

Enrollment in the PRESTIGE® LP study was limited to subjects who met the following inclusion criteria:

- Cervical degenerative disc disease defined as: intractable radiculopathy and/or myelopathy with at least one of the following items producing symptomatic nerve root and/or spinal cord compression that is documented by subject history [(e.g., pain, functional deficit, and/or neurologic deficit and imaging studies (e.g., computed tomography (CT), magnetic resonance imaging (MRI), x-rays, etc.)]:
    - Herniated disc;
    - Osteophyte formation
- One level requiring surgical treatment;
- C3-C4 disc to C6-C7 disc level of involvement;
- Unresponsive to non-operative treatment for approximately six weeks or has the presence of progressive symptoms or signs of nerve root/spinal cord compression in the face of continued non-operative management;
- No previous surgical intervention at involved level or any subsequent, planned/staged surgical procedure at the involved or adjacent level(s);
- Is at least 18 years of age, inclusive, at the time of the surgery;
- Preoperative Neck Disability Index score of ≥ 30;
- Has a preoperative neck pain score of ≥ 20 on Preoperative Neck and Arm Pain Questionnaire;
- If a female of child-bearing potential, subject is not pregnant, at the time of surgery;
- Is willing to comply with the study plan and sign the Patient Informed Consent Form.

Subjects were <u>not</u> permitted to enroll in the PRESTIGE® LP study if any of the following exculsion criteria were present:

- 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 sagittal plane translation > 3.5 mm or sagittal plane angulation > 20°;
- More than one 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 previous diagnosis of 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):
    - Postmenopausal non-Black female over 60 years of age and weighs less than 140 pounds.
    - Postmenopausal female that has sustained a non-traumatic hip, spine, or wrist fracture.
    - Male over the age of 70;
    - Male over the age of 60 that has sustained a non-traumatic hip or spine fracture;

  If the level of bone mineral density (BMD) is a T score of -3.5 or a T score of -2.5 with vertebral crush fracture, then the subject 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°F oral) at the time of surgery;
- Has a documented allergy or intolerance to stainless steel, titanium, or a titanium alloy;
- Is mentally incompetent (If questionable, obtain psychiatric consult);
- Is a prisoner;
- Is pregnant;
- Is an alcohol and/or drug abuser currently undergoing treatment for alcohol and/or drug abuse;
- Has received drugs which may interfere with bone metabolism within two weeks prior to the planned date of spinal surgery (e.g. steroids or methotrexate) excluding routine perioperative anti-inflammatory drugs;
- Has a history of an 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. (This does not include low dose aspirin for prophylactic anticoagulation), excluding routine perioperative anti-inflammatory drugs;
- Has received treatment with an investigational therapy within 28 days prior to implantation surgery or such treatment is planned during the 16 weeks following implantation with the PRESTIGE® LP device.

2.Follow-up Schedule

Subjects were evaluated pre-operatively (within 6 months of surgery), intra-operatively, and post-operatively at 6 weeks (±2 weeks), 3 months (±2 weeks), 6 months (± one month), 12 months (± two months), 24 months (± two months), 36 months (± two months), 60 months (± two months) and 84 months (± two months), and annually thereafter until the last subject enrolled in the study had been seen for his or her 24-month evaluation. The following parameters were measured throughout the study:

Table 6: Schedule of Study Assessments

	Pre-/Peri-Operative		Postoperative				
Procedure	Pre-op	Surgery/ Hospital Discharge	6 wks	3 mo	6 mo	12 mo	24+ mo
Preoperative Information							
Confirm Patient Eligibility	X						
Obtain Informed Consent	X						
Obtain HIPAA Authorization	X						
Case Report Forms							
Patient Enrollment	X						
Patient Qualification	X						
Preoperative Data	X						
Prior History Questionnaire	X						
Neurological Status	X		X	X	X	X	X
Preoperative Gait Assessment and Foraminal Compression Test	X						
Preoperative Patient Survey	X						
Preoperative Neck Disability Index	X						
Preoperative Neck and Arm Pain Questionnaire	X						
Health Status Questionnaire (SF-36)	X				X	X	X
Surgery Data		X					
Hospital Discharge		X					
Postoperative Data			X	X	X	X	X
Postoperative Patient Survey			X	X	X	X	X
Neck Disability Index			X	X	X	X	X
Postoperative Neck and Arm Pain Questionnaire			X	X	X	X	X
Postoperative Gait Assessment and Foraminal Compression Test			X	X	X	X	X
Adverse Event Form (if any)		X	X	X	X	X	X
Outstanding (Unresolved) Adverse Event (if any)		X	X	X	X	X	X
Patient Disposition			X	X	X	X	X
Imaging – Radiographs and Scans*							
Anterior/Posterior X-ray	X	X	X	X	X	X	X
Lateral X-ray	X	X	X	X	X	X	X
Right/Left Lateral Bend X-rays	X		X	X	X	X	X
Flexion/Extension X-rays	X		X	X	X	X	X
CT and/or MRI	X						
DEXA Scan **	X						

* Patients who sign consent and are screened eligible, but who do not receive the PRESTIGE® LP device, were not required to have the preoperative radiographs obtained and forwarded to Medtronic.

** A DEXA Scan was only required if the patient had a risk factor that may be associated with a diagnosis of osteoporosis.

3.Clinical Endpoints

The safety of the PRESTIGE® LP was assessed by comparison to the historical control group with respect to the nature and frequency of adverse events, secondary surgical procedures, as well as maintenance or improvement in neurological status.

The effectiveness of the PRESTIGE® LP device was assessed using a composite definition of study success. The primary endpoint used for assessment of effectiveness was improvement in Neck Disability Index (NDI) pain/disability scores.

In addition, several radiograph-assisted assessments were considered in evaluating both safety and effectiveness including device subsidence, functional spinal unit (FSU) height maintenance, device migration, and device breakage.

According to the final IDE protocol, an individual subject in either treatment group was considered a success if the following criteria were met at 24 months :

1. An improvement (reduction) of at least 15 points from the baseline Neck Disability Index score;
2. Maintenance or improvement in neurological status;
3. Disc height (Functional Spinal Unit Height) success (FSU success)
4. No severe adverse event classified as implant-associated, surgical procedure-associated, or implant/surgical procedure-associated; and
5. No additional surgical procedure classified as "Failure"

An alternative analysis of the primary endpoint analysis was also conducted without the addition of FSU height as a success criterion. Disc height success was defined as the change in FSU height being less than or equal to 2mm between a measurement obtained at the six week post-operative timepoint to FSU height at the 24 month timepoint.

Secondary endpoints, measured in both treatment groups, included Radiographic Success, neck pain (VAS), arm pain (VAS), quality of life (SF-36 PCS and MCS scores), patient satisfaction, patient global perceived effort, gait assessment (Nurick's classification), and foraminal compression test. Additional measurements recorded were adjacent level stability, return to work, and doctor's perception of results. Radiographic Succcess for maintenance of motion is defined as >4° but <20° of angular motion based on lateral flexion/extension radiographs and no radiographic evidence of bridging trabecular bone that forms a continuous bony connection with the vertebral bodies (bridging bone). Criteria for the success of the control group was defined in a previous IDE study (G010188). Briefly, the same success criteria for the primary endpoints exist for the control group as the investigational group, with the exception that the secondary endpoint for radiographic success was defined by radiographic evidence of bone spanning the two vertebral bodies, existence of angular motion stability <4°, and no radiolucent lines covering more than 50% of the implant surface.

4.Statistical Analysis Plan

As stated previously, the study was designed as a non-inferiority trial with a margin of 10%. Bayesian statistical methods were predefined and used to determine non-inferiority and

superiority of the investigational device compared to the control device with respect to overall success, individual effectiveness and neurological status. A Bayesian logistic model was used to assess qualitative response outcomes, including success status, adverse event data, and additional surgical event data. A Bayesian linear model was used for assessment of surgery data, including operative time, blood loss, and hospital stay. The propensity score was used as the single covariate in the Bayesian models, mainly as a continuous independent variable, although as predefined, sensitivity analyses were also performed for the primary endpoint (overall success) and its components, in which the propensity score quantile class was used as the covariate.

The study hypothesis was that the success rate of the PRESTIGE® LP group was statistically non-inferior to the success rate in the control group by a margin of 10%. The primary endpoint was deemed successful, i.e., the PRESTIGE® LP is not inferior to the control, if the posterior probability that the success rate of PRESTIGE® LP group was not lower than control group by more than 10% was greater than 95%. If non-inferiority was demonstrated, analyses were also defined in the statistical plan to determine whether the investigational group had statistically superior outcomes as compared to the control group.

B.Accountability of PMA Cohort

The subject accountability data are summarized in **Table 7**. Please note that Continued Access Cohort (CA) and the Metal Ion Cohort (MI) were enrolled separately from the IDE Cohort at the same study sites. Safety and effectiveness data were collected for the IDE, Safety (IDE+CA+MI), and ACDF Control Cohorts while the statistical analyses were performed with the IDE Cohort in comparison to the control group.

Table 7: Subject Accountability

Number of Subjects:	**12 Months (±2 Months)**			**24 Months (±2 Months)**		
	PRESTIGE® LP IDE Cohort	**ACDF Control**	**PRESTIGE® LP Safety Cohort**	**PRESTIGE® LP IDE Cohort**	**ACDF Control**	**PRESTIGE® LP Safety Cohort**
Enrolled	280	265	333	280	265	333
Theoretical FU	280	265	333	280	265	333
Cumulative Deaths [2]	0	2	0	0	2	0
Subjects Evaluated Early [3]	0	0	0	0	0	0
Subjects Not Yet Overdue	0	0	0	0	0	0
Expected[4]	280	263	333	280	263	333
Evaluable for Overall Success (% of Total Expected)	274 (97.9%)	223 (84.8%)	326 (97.9%)	271 (96.8%)	220 (83.7%)	322 (96.7%)
Evaluable for Overall Success, In Window	271 (96.8%)	206 (78.3%)	321 (96.4%)	262 (93.6%)	201 (76.4%)	309 (92.8%)

[2] Cumulative deaths are the total number of deaths of study patients at the 12- and 24-month time points. However, none of the deaths were believed to be in any way related to the study treatment.
[3] Patients that completed follow-up visits early before the visit window
[4] Expected = Theoretical minus Cumulative Deaths minus Patients Not Yet Overdue plus Patients Evaluated Early for Visit

(% of Total Expected)						
Percent Follow-up	98.2%	87.1%	98.5%	97.1%	84.0%	97.3%

In addition to the study subjects described above, nineteen (19) subjects were consented but declined participation in the study prior to receiving the assigned treatment. The demographic and preoperative characteristics of the subjects who declined to participate in this study were comparable to the subjects included in this study.

A summary of accountability regarding data for specific study assessments at 24 months is provided in **Table 8** below.

Table 8: 24-Month Data Accounting For Specific Study Assessments

Variables	**PRESTIGE® LP IDE Cohort (N=280)**	**ACDF Control (N=265)**	**PRESTIGE® LP Safety Cohort (N=333)**
NDI	270 (96.4%)	219 (82.6%)	322 (96.7%)
Neurological	270 (96.4%)	220 (83.0%)	321 (96.4%)
SF-36 PCS	265 (94.6%)	218 (82.3%)	317 (95.2%)
SF-36 MCS	265 (94.6%)	218 (82.3%)	317 (95.2%)
Neck Pain	270 (96.4%)	220 (83.0%)	322 (96.7%)
Arm Pain	268 (95.7%)	220 (83.0%)	320 (96.1%)
Patient Perceived Effect	270 (96.4%)	219 (82.6%)	323 (97.0%)
Doctor's Perception	271 (96.8%)	220 (83.0%)	323 (97.0%)
Patient Satisfaction	270 (96.4%)	219 (82.6%)	323 (97.0%)
Gait	270 (96.4%)	220 (83.0%)	322 (96.7%)
Foraminal Compression	270 (96.4%)	220 (83.0%)	322 (96.7%)
Radiographic Assessment	264 (94.3%)	-	316 (94.9%)

C.Study Population Demographics and Baseline Parameters

Table 9 presents the summary statistics for demographic and baseline characteristics for the PRESTIGE® LP IDE Cohort, the ACDF Control, and PRESTIGE® LP Safety Cohort. The demographics of the study population are consistent with the demographics reported for prior cervical artificial disc studies conducted in the U.S.

The investigational and control treatment groups were very similar demographically, and there were no statistically significant differences ($p<0.05$) for any of the variables except for the use of tobacco and race. Current tobacco use was higher in the control group (34.7% versus 26.4%) as compared to the IDE Cohort. However, tobacco use was established through use of patient questionnaires which utilized a binary response (i.e., yes or no), and quantification of the extent or history of tobacco use was not established. Therefore, it is not possible to definitively ascertain whether there were any substantial confounding effects from tobacco use on subject outcomes. Regarding race differences among cohorts, there was a higher percentage of Caucasian subjects in the IDE Cohort compared to the control group (96.8% versus 91.7%).

Table 9: Study Population Demographics and Baseline Characteristics

Variables	PRESTIGE® LP IDE Cohort (N=280)	ACDF Control (N=265)	PRESTIGE® LP Safety Cohort (N=333)	p-value (IDE vs. Control)
Age (years)	44.5 ± 8.8 Range: 23 - 78	43.9 ± 8.8 Range: 22 - 73	43.8 ± 9.0 Range: 23 – 78	0.369
Height (inches)	67.7 ± 4.1 Range: 60.0 – 77.0	67.5 ± 4.2 Range: 58.0 – 80.0	67.7 ± 4.0 Range: 60.0 – 77.0	0.622
Weight (lbs.)	186.9 ± 45.0 Range: 100.0 – 340.0	184.7 ± 41.5 Range: 98.0 – 328.0	187.3 ± 45.2 Range: 100.0 – 340.0	0.567
BMI (kg/m^2)	28.5 ± 5.6 Range: 17.2 – 48.2	28.3 ± 5.1 Range: 19.0 – 53.6	28.5 ± 5.6 Range: 17.2 – 48.2	0.722
Sex Male (%) Female (%)	 129 (46.1%) 151 (53.9%)	 122 (46.0%) 143 (54.0%)	 155 (46.5%) 178 (53.5%)	1.000
Race Caucasian Black Asian Hispanic Other	 271 (96.8%) 7 (2.5%) 0 (0.0%) 1 (0.4%) 1 (0.4%)	 243 (91.7%) 13 (4.9%) 2 (0.8%) 6 (2.3%) 1 (0.4%)	 320 (96.1%) 10 (3.0%) 1 (0.3%) 1 (0.3%) 1 (0.3%)	**0.043**
Marital Status Single Married Divorced Separated Widowed	 40 (14.3%) 189 (67.5%) 42 (15.0%) 7 (2.5%) 2 (0.7%)	 32 (12.1%) 204 (77.0%) 24 (9.1%) 3 (1.1%) 2 (0.8%)	 47 (14.1%) 224 (67.3%) 51 (15.3%) 8 (2.4%) 3 (0.9%)	0.096
Education Level < High School High School > High School	 15 (5.4%) 57 (20.5%) 206 (74.1%)	 14 (5.3%) 77 (29.2%) 173 (65.5%)	 17 (5.1%) 78 (23.6%) 236 (71.3%)	0.062
Previous Neck Surgery Yes No	 3 (1.1%) 277 (98.9%)	 2 (0.8%) 263 (99.2%)	 3 (0.9%) 330 (99.1%)	1.000
Preoperative Medication use Non-Narcotics Weak Narcotics Strong Narcotics Muscle Relaxants	 208/280 (74.3%) 133/279 (47.7%) 62/279 (22.2%) 100/279 (35.8%)	 187/263 (71.1%) 127/263 (48.3%) 58/264 (22.0%) 114/264 (43.2%)	 246/333 (73.9%) 152/332 (45.8%) 68/332 (20.5%) 123/332 (37.0%)	 0.441 0.931 1.000 0.095

Variables	PRESTIGE® LP IDE Cohort (N=280)	ACDF Control (N=265)	PRESTIGE® LP Safety Cohort (N=333)	p-value (IDE vs. Control)
Preoperative Pain Status[5] Arm and Neck Pain Arm Pain Only Neck Pain Only	 255 (91.1%) 0 (0.0%) 25 (8.9%)	 238 (90.2%) 0 (0.0%) 26 (9.8%)	 299 (89.8%) 0 (0.0%) 34 (10.2%)	0.769
Worker's Compensation	32/280 (11.4%)	35/365 (13.2%)	54/333 (16.2%)	0.602
Unresolved Spinal Litigation	34/280 (12.1%)	32/265 (12.1%)	61/333 (18.3%)	1.000
Current Tobacco Use	74/280 (26.4%)	92/265 (34.7%)	94/333 (28.2%)	**0.041**
Current Alcohol Use	150/280 (53.6%)	141/265 (53.2%)	172/333 (51.7%)	1.000
Preoperative Work Status	188/280 (67.1%)	166/265 (62.6%)	217/333 (65.2%)	0.282
Duration of Symptoms < 6 wks. 6 wks. – 6 mos. > 6 mos.	 22 (7.9%) 85 (30.4%) 173 (61.8%)	 15 (5.7%) 89 (33.6%) 161 (60.8%)	 24 (7.2%) 97 (29.1%) 212 (63.7%)	0.494

The mean baseline pre-operative assessments for the PRESTIGE® LP IDE Cohort, Control Group, and PRESTIGE Safety Cohort are presented in **Table 10**. There were no statistical differences between the PRESTIGE® LP IDE Cohort and Control for NDI, SF-36 PCS, SF-36 MCS, neck pain, and arm pain. There were statistically significant differences in baseline motor neurologic status (38.2% - PRESTIGE® LP IDE Cohort; 59.5% - Control) and mean cervical range of motion (5.67º - PRESTIGE® LP IDE Cohort; 7.87º - Control). However, after propensity score adjustments, the variables appeared balanced between groups. Thus, differences in baseline symptoms were adjusted for in the analysis and are therefore unlikely to have led to significant bias in the reported results.

[5] Arm pain is defined as a subject having an arm pain score ≥20 and neck pain is defined as a subject having a neck pain score ≥20. If a subject has both an arm pain score ≥20 and a neck pain score ≥20, then this subject is considered as having "Arm and Neck Pain"; if a subject has a neck pain score ≥20 and an arm pain score < 20, then this subject is considered as having "Neck Pain Only"; if a subject has an arm pain score ≥20 and a neck pain score < 20, then this subject is considered as having "Arm Pain Only". Since neck pain score ≥20 is an inclusion criteria, there are no subjects with "Arm Pain Only". The PRESTIGE® LP Cervical Disc is indicated in skeletally mature patients for reconstruction of the disc at one level from C3-C7 following single-level discectomy for intractable radiculopathy (arm pain and/or a neurological deficit) with or without neck pain and is not indicated for treatment of isolated neck pain. No patients were included into the study with neck pain without any other symptoms.

Table 10: Preoperative Evaluation of Clinical Endpoints

Variables	PRESTIGE® LP IDE Cohort (N=280)	ACDF Control (N=265)	PRESTIGE® LP Safety Cohort (N=333)	p-value (IDE Cohort vs ACDF Control)
NDI	55.5 ± 14.7 Range: 30.0 – 98.0	56.4 ± 15.9 Range: 26.0 – 100.0	56.6 ± 15.0 Range: 30.0 – 98.0	0.498
SF-36 PCS	32.2 ± 7.4 Range: 14.3 – 57.9	32.0 ± 7.5 Range: 7.9 – 56.0	32.3 ± 7.1 Range: 14.3 – 57.9	0.777
SF-36 MCS	44.5 ± 11.5 Range: 16.5 – 68.3	42.7 ± 12.4 Range: 14.1 – 70.8	43.8 ± 11.9 Range: 16.5 – 68.3	0.079
Neck Pain Score	67.0 ± 20.8 Range: 20.0 – 100.0	69.3 ± 21.5 Range: 20.0 – 100.0	68.0 ± 20.8 Range: 20.0 – 100.0	0.191
Arm Pain Score	59.6 ± 26.3 Range: 0.0 – 100.0	62.4 ± 28.5 Range: 0.0 – 100.0	59.0 ± 27.1 Range: 0.0 – 100.0	0.236
Neurological Status (normal) • Motor • Sensory • Reflexes • Overall[6]	 107/280 (38.2%) 117/280 (41.8%) 186/280 (66.4%) 64/280 (22.9%)	 157/264 (59.5%) 134/264 (50.8%) 161/264 (61.0%) 79/264 (29.9%)	 135/333 (40.5%) 147/333 (44.1%) 200/333 (60.1%) 73/333 (21.9%)	 **< 0.001** 0.039 0.212 0.065
Baseline ROM angulation (°)	5.67 ± 3.69 Range: 0.27 – 18.10	7.87 ± 4.32 Range: 0.74 – 21.34	5.88 ± 3.78 Range: 0.27 – 19.47	**< 0.001**
Baseline ROM translation (mm)	N/A	0.26 ± 0.25 Range: 0.00 – 1.64	N/A	N/A

D.Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the as-treated cohort of 598 total subjects with surgery (333 PRESTIGE® LP "Safety" subjects consisting of 280 PRESTIGE® LP IDE Cohort subjects, as well as 54 subjects from the Continued Access(CA) and Metal Ion(MI) Cohorts; and 265 ACDF control subjects[7]). This was a non-randomized study and the ACDF group was a historical control.

Adverse events that occurred in the PMA clinical study

A summary of the total number of adverse events is shown in **Table 11**. Adverse events were classified by the independent Clinical Adjudication Committee (CAC) for severity and relationship to the device and/or surgical procedure. The overall adverse event rate was higher for subjects treated with the PRESTIGE® LP device (IDE Cohort, 91.8%; Safety Cohort, 91.9%) compared to the Control (82.6%) through 24 months. The adverse event rate between the PRESTIGE® LP IDE Cohort and the Control was statistically different with the 95% BCI for the difference of adverse events rates between the PRESTIGE® LP IDE Cohort and the ACDF Control Cohort being (4.1%, 16.2%), excluding 0. Although the rate of

[6] If at least one of the three components (motor, sensory, reflexes) is not normal, then overall is defined as "not normal", if all the components are normal, then overall is defined as "normal"

[7] One Metal Ion Cohort subject was also an IDE Cohort subject.

PRESTIGE® LP IDE subjects having at least one adverse event was statistically higher than the control group rate, the difference in adverse event rates was not considered to be clinically meaningful and this finding may be attributable to the higher follow-up rates (and potentially, higher reporting of events) for investigational subjects as compared to the ACDF control subjects. Specifically, note that the 24-month follow-up rates are 97.1% and 84.0% respectively for the PRESTIGE® LP IDE Cohort and ACDF Control Cohort.

Table 11: Summary of Adverse Events Up to the 24-Month Time Interval

Adverse Event Type	Measure	PRESTIGE® LP IDE Cohort (N=280)	ACDF Control (N=265)	PRESTIGE® LP Safety Cohort (N=333)	Posterior Mean and 95% BCI[8] of the Difference of Event Rate between IDE Cohort and ACDF Control[9]
All Adverse Events (AEs)	Subjects (%)	257 (91.8%)	219 (82.6%)	306 (91.9%)	10.2% (4.1%, 16.2%)
	Events (Events/Subject)	1559 (5.57)	1198 (4.52)	1863 (5.59)	
Device or Device/Surgical Procedure Related AEs	Subjects (%)	34 (12.1%)	41 (15.5%)	44 (13.2%)	-2.9% (-9.2%, 3.3%)
	Events (Events/Subject)	61 (0.22)	60 (0.23)	76 (0.23)	
Surgical Procedure Related AEs Only	Subjects (%)	72 (25.7%)	71 (26.8%)	78 (23.4%)	-0.5% (-8.6%, 7.4%)
	Events (Events/Subject)	132 (0.47)	121 (0.46)	140 (0.42)	
Severe AEs (Grade 3 or 4)	Subjects (%)	133 (47.5%)	98 (37.0%)	163 (48.9%)	13.3% (3.5%, 21.8%)
	Events (Events/Subject)	433 (1.55)	267 (1.01)	518 (1.56)	
Severe Device or Device/Procedure-Related AEs (Grade 3 or 4)	Subjects (%)	14 (5.0%)	13 (4.9%)	16 (4.8%)	0.7% (-3.0%, 4.6%)
	Events (Events/Subject)	33 (0.12)	22 (0.08)	40 (0.12)	

Adverse Events by Level of Treatment

Table 12 provides summary data on the number of adverse events in each treatment group by treatment level, including post-hoc statistical analysis and comparison between the PRESTIGE® LP IDE Cohort and the ACDF control group through the 24-month time point using Frequentist methods. The percentage of subjects with adverse events was not statistically different between the two groups for all levels except for C5-C6; however, this difference was not clinically meaningful.

[8] BCI = Bayesian HPD Credible Interval

[9] 95% BCI of the difference of the event rate between the investigational group and control group was only determined for the "All Adverse Events" category because the analysis was pre-defined. All other analyses were not pre-defined.

Table 12: Summary of Total Adverse Events by Level Treated through Month 24- IDE and Safety Population

Treatment Level	PRESTIGE® LP IDE Cohort (N=280)	ACDF Control (N=265)	PRESTIGE® LP Safety Cohort (N=333)	Point Estimate and 95% Confidence Interval[10] of Difference of Adverse Rate between IDE Cohort and ACDF Control Cohort
C3-C4	4/4 (100%)	9/10 (90.0%)	4/4 (100.0%)	10.0% (-19.9%, 39.9%)
C4-C5	20/21 (95.2%)	12/15 (80.0%)	27/28 (96.4%)	15.2% (-5.6%, 36.1%)
C5-C6	135/147 (91.8%)	124/149 (83.2%)	163/178 (91.6%)	8.6% (1.1%, 16.2%)
C6-C7	98/108 (90.7%)	74/91 (81.3%)	112/123 (91.1%)	9.4% (-0.1%, 19.0%)

All Adverse Events

The adverse events reported in the PMA from all 598 total subjects (333 PRESTIGE® LP Safety Cohort subjects, including the 280 PRESTIGE® LP IDE Cohort subject, and 265 ACDF Control subjects) are shown in **Table 13**. This table includes adverse events from all subjects to establish the safety profile of the device for the primary study endpoint (24 months). Adverse events are listed in alphabetical order according to adverse event categories. Definitions of the adverse event categories are provided in **Table 14**. **Table 15** is presented in a similar fashion as **Table 13** (using the categories as defined in **Table 14**). Adverse event rates are based on the number of subjects having at least one occurrence of an adverse event, divided by the number of subjects in that treatment group. Events per subject in **Table 11** are based on the number of adverse events, divided by the total number of subjects in each cohort. Subjects experiencing adverse events in more than one category are represented in each category in which they experienced an adverse event.

The most commonly reported categories of adverse events through 24 months were Neck and/or Arm Pain (in 55.3% of PRESTIGE® LP Safety Cohort subjects, 51.4% of PRESTIGE® LP IDE Cohort Subjects, and 46.8% of ACDF Control subjects), Other Pain (in 52.6% of PRESTIGE® LP Safety Cohort subjects, 52.1% of PRESTIGE® LP IDE Cohort Subjects, and 49.8% of ACDF Control subjects), Neurological (in 48.6% of PRESTIGE® LP Safety Cohort and IDE Cohort subjects and 40.8% of ACDF Control subjects), Other (in 33.0% of PRESTIGE® LP Safety Cohort subjects, 33.2% of PRESTIGE® LP IDE Cohort Subjects, and 30.6% of ACDF Control subjects), Spinal Event (in 31.8% of PRESTIGE® LP Safety Cohort subjects, 29.6% of PRESTIGE® LP IDE Cohort Subjects, and 20.8% of ACDF Control subjects), Trauma (in 20.7% of PRESTIGE® LP Safety Cohort subjects, 21.8% of PRESTIGE® LP IDE Cohort Subjects, and 13.2% of ACDF Control subjects), Gastrointestinal (in 12.9% of PRESTIGE® LP Safety Cohort subjects, 12.5% of PRESTIGE® LP IDE Cohort Subjects, and 14.3% of ACDF Control subjects), and Infection (in 12.0% of PRESTIGE® LP Safety Cohort subjects, 12.1% of PRESTIGE® LP IDE Cohort Subjects, and 10.2% of ACDF Control subjects). The non-union rate in ACDF control subjects was 10.9%.

[10] The 95% CI was provided using Frequentist Farrington and Manning methods

There were a total of three deaths in the investigational group and five deaths in the control group, of which two deaths occurred in the control group prior to 24 months (at the 12-month time point) and none in the investigational group prior to 24 months. Deaths were evaluated based upon available information and none of the deaths were believed to be in any way related to the study treatment.

Table 13: Adverse Events in Pivotal Study Through 24 Months[11, 12]

	Surgery			Postoperative (1 day - <4 Weeks)			6 Weeks (≥4 Wks - <9 Weeks)			3 Months (≥9 Wks - <5 Months)			6 Months (≥5 Mos-<9 Months)			12 Months (≥9 Mos- <19 Months)			24 Months (≥19 Mos- <30 Months)			Total (Up to 24 Month) # of Subjects Reporting & Total adverse events		
Adverse Events	PRESTIGE® LP IDE Cohort	ACDF Control[13]	PRESTIGE® LP Safety Cohort	PRESTIGE® LP IDE Cohort	ACDF Control	PRESTIGE® LP Safety Cohort	PRESTIGE® LP IDE Cohort	ACDF Control	PRESTIGE® LP Safety Cohort	PRESTIGE® LP IDE Cohort	ACDF Control	PRESTIGE® LP Safety Cohort	PRESTIGE® LP IDE Cohort	ACDF Control	PRESTIGE® LP Safety Cohort	PRESTIGE® LP IDE Cohort	ACDF Control	PRESTIGE® LP Safety Cohort	PRESTIGE® LP IDE Cohort	ACDF Control	PRESTIGE® LP Safety Cohort	**PRESTIGE® LP IDE Cohort # Subjects (% of 280) Total # Events**	**ACDF Control # Subjects (% of 265) Total # Events**	**PRESTIGE® LP Safety Cohort # Subjects (% of 333) Total # Events**
Anatomical / Technical Difficulty	2	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2 (0.7) 2	0 (0.0) 0	2 (0.6) 2
Cancer	0	0	0	1	1	1	0	0	0	0	0	0	1	0	1	3	0	3	0	1	2	3 (1.1) 5	2 (0.8) 2	5 (1.5) 7
Cardiac Disorders	0	0	0	2	2	2	2	1	3	0	2	0	3	3	3	4	3	5	10	9	11	16 (5.7) 21	18 (6.8) 20	19 (5.7) 24
Death	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Dysphagia / Dysphonia	1	4	1	16	11	17	4	4	6	5	3	5	5	0	5	0	1	1	2	0	3	26 (9.3) 33	22 (8.3) 23	30 (9.0) 38
Gastrointestinal	2	7	2	8	7	8	1	3	2	4	4	7	3	2	7	20	21	22	17	24	20	35 (12.5) 55	38 (14.3) 68	43 (12.9) 68
Heterotopic Ossification	0	0	0	2	1	2	6	4	6	1	2	1	4	1	5	7	2	9	11	11	12	27 (9.6) 31	15 (5.7) 21	31 (9.3) 35
Implant Events	6	0	6	1	1	1	2	1	3	3	0	3	1	0	3	0	2	1	4	1	5	16 (5.7) 17	5 (1.9) 5	21 (6.3) 22
Infection	1	2	1	5	3	5	6	5	7	6	2	9	11	1	12	16	10	16	12	14	13	34 (12.1) 57	27 (10.2) 37	40 (12.0) 63
Neck and / or Arm Pain	3	1	4	31	16	35	43	19	57	57	49	77	37	40	50	68	50	84	36	38	46	144 (51.4) 275	124 (46.8) 213	184 (55.3) 353
Neurological	2	6	2	18	21	20	34	19	42	47	35	55	31	16	39	73	60	88	37	60	43	136 (48.6) 242	108 (40.8) 217	162 (48.6) 289
Non-Union	0	0	0	0	0	0	0	1	0	0	3	0	0	8	0	0	8	0	0	10	0	0 (0.0) 0	29 (10.9) 30	0 (0.0) 0
Other	5	3	8	19	14	22	12	13	14	24	16	28	29	9	38	55	21	58	33	57	39	93 (33.2) 177	81 (30.6) 133	110 (33.0) 207
Other Pain[14]	3	6	3	22	19	23	32	11	39	49	45	65	57	30	69	65	57	71	50	63	58	146 (52.1) 278	132 (49.8) 231	175 (52.6) 328
Respiratory	0	0	0	7	4	7	0	4	1	1	1	1	10	5	10	3	1	6	13	8	14	24 (8.6) 34	17 (6.4) 23	27 (8.1) 39
Spinal Event	0	0	0	19	8	22	22	6	34	20	25	25	26	15	31	44	20	53	41	29	47	83 (29.6) 172	55 (20.8) 103	106 (31.8) 212
Trauma	0	0	0	6	2	7	5	4	6	12	12	13	11	5	12	19	9	20	18	12	21	61 (21.8) 71	35 (13.2) 44	69 (20.7) 79
Urogenital	1	0	1	1	0	1	2	0	2	1	1	1	9	3	9	12	5	13	16	2	20	26 (9.3) 42	9 (3.4) 11	31 (9.3) 47
Vascular	3	1	4	1	0	1	1	0	1	0	1	0	2	1	2	2	1	2	4	0	4	12 (4.3) 13	4 (1.5) 4	13 (3.9) 14
Wound (Non-Infectious)	0	2	1	14	4	15	3	2	3	4	2	4	4	1	4	5	2	5	4	0	4	25 (8.9) 34	13 (4.9) 13	27 (8.1) 36
Any Adverse Event																						257 (91.8) 1559	219 (82.6) 1198	306 (91.9) 1863

[11] Based on 24-month cohort.
[12] Some adverse events may lead to additional surgeries or interventions. Refer to Table 9 for more information.
[13] Control=Single-level anterior interbody fusion procedure with allograft and plate stabilization. Non-randomized control arm from IDE study of PRESTIGE® Cervical Disc.
[14] Back and/or lower extremity (LE) pain adverse events (AEs) and Headache AE's were classified as "Other Pain" AEs for the PRESTIGE® LP IDE study.

Table 14: Adverse Event Categories

Adverse Event Category	Definition
Anatomical/Technical Difficulty – Cervical Study Surgery	Anatomical or technical difficulty encountered during the original implantation of the PRESTIGE® device or control treatment device
Anatomical/Technical Difficulty – Cervical Non-Study Surgery	Anatomical or technical difficulty encountered during an additional surgery involving the cervical region, but did not involve the PRESTIGE® device or original control treatment device
Anatomical/ Technical Difficulty Non-Cervical	Technical problem encountered during an additional surgery that involved a region other than the cervical spine
Cancer	A malignancy or malignant tumor/neoplasm
Cardiac Disorders	Any condition of the heart
Death	Termination of life due to any cause
Dysphagia	Difficulty in swallowing
Dysphonia	Difficulty in speaking
Gastrointestinal	Any condition pertaining to the stomach and intestines
Heterotopic Ossification - Cervical	Event involving heterotopic ossification at any region of the cervical spine
Heterotopic Ossification - Non-Cervical	Event involving heterotopic ossification at any region of the spine that is not cervical or any other region of the body.
Implant Events - Malpositioning	Poor or inappropriate placement of the implant
Implant Events - Displacement	Incomplete or partial dislocation of the implant
Implant Events - Loosening	Wear around the implant and/or loosening of the implant surface
Implant Events - Breakage	Breakage of any implant or implant component
Implant Events - Other	Event that is implant-related, but does not meet the definition of malpositioned implant, implant displacement, implant loosening, or implant breaking
Infection - Superficial	An infection near the surface of the surgical incision
Infection - Deep	An infection below the fascia at the surgical incision
Infection - Other Wound	Infection occurring in other surgical wound not involving the study
Infection - Hematoma	Swelling or mass of blood that has become infected
Infection - CSF Leak	Infection resulting from the leakage of CSF
Inf ection - Systemic	Infection pertaining to the whole body
Infection - Urinary Tract	Infection of any part of the urinary system
Infection - Other	Any infection not listed above
Pain - Neck	Pain (including stiffness, strain, tightness) in the neck
Pain - Upper Extremities	Pain (including stiffness, strain, tightness) in the shoulder, arm, wrist or hand
Pain - Neck and Upper Extremities	Pain (including stiffness, strain, tightness) in the neck *and* shoulder, arm, wrist, or hand
Pain - Other	Pain (including stiffness, strain, tightness) in an area that is not of cervical spine etiology (e.g., abdominal pain of unknown etiology, headache, flank pain, bursitis).
Other	Event not associated with any other categories (e.g., weight loss, tinnitus, substance abuse, insomnia).
Respiratory	Ailments or symptoms associated with respiration or the respiratory system
Spinal Event – Cervical Study Surgery	Event involving the treated level of cervical spine
Spinal Event – Cervical Non-Study Surgery	Event involving one or more cervical spine level(s), with the exception of the treated level
Spinal Event - Non-Cervical	Event involving one or more spine levels other than cervical spine

Adverse Event Category	Definition
Trauma	Physical injury caused by a physical force or traumatic event (e.g. motor vehicle accident, fall, etc.)
Urogenital	Any condition of, relating to, affecting, treating, or being the organs or functions of excretion and reproduction
Vascular – injury (intraoperative)	Injury to a vascular structure that is sustained during the course of the operative procedure
Vascular – Vertebral artery	Injury to vertebral artery occurring at any time
Vascular - Other	Disorder or condition in which the vascular system is affected
Wound (Non-Infectious)	Any issue of surgical incision, such as hematoma, excluding infection

Bayesian analyses were conducted on all adverse events using non-informative priors. The results are presented in **Table 15** with 95% Bayesian Credible Intervals (BCI) for the difference in adverse event rates (PRESTIGE® LP IDE – ACDF). BCIs that exclude zero indicate statistical differences in the adverse event rates between the PRESTIGE® LP IDE cohort and the ACDF Control group while the BCIs that include zero fail to conclude that this is a statistical difference in the adverse event rates between the two groups. Based on the BCIs, statistical differences were noted between groups for the adverse event rates in the following categories: heterotopic ossification, implant events, neurological, non-union, spinal events, trauma, urogenital, vascular, and wound (non-infectious). All are statistically higher for the PRESTIGE® LP IDE Cohort except for non-union which was statistically higher for the control group.

Table 15: Bayesian Comparison of Posterior Probabilities of Adverse Events

Adverse Event	Subjects Experiencing Adverse Events (%)			Posterior Mean and 95% HPD of Adverse Event Rate		Posterior Mean and 95% BCI[15] of Difference of Adverse Event Rate between LP IDE Cohort and ACDF Control
	IDE Cohort	ACDF Control	Safety Cohort	IDE Cohort	ACDF Control	IDE - ACDF
Anatomical / Technical Difficulty	2 (0.7%)	0 (0.0%)	2 (0.6%)	0.5% (0.0%, 1.4%)	0.0% (0.0%, 0.1%)	0.5% (0.0%, 1.4%)
Cancer	3 (1.1%)	2 (0.8%)	5 (1.5%)	1.0 (0.1%, 2.3%)	0.6% (0.0%. 1.6%)	0.4% (-1.2%, 2.0%)
Cardiac Disorders	16 (5.7%)	18 (6.8%)	19 (5.7%)	5.4% (2.8%, 8.2%)	7.0% (4.0%, 10.4%)	-1.6% (-6.0%, 2.9%)
Dysphagia / Dysphonia	26 (9.3%)	22 (8.3%)	30 (9.0%)	9.3% (5.9%, 12.9%)	8.2% (4.8%, 11.6%)	1.0% (-4.2%, 6.1%)
Gastrointestinal	35 (12.5%)	38 (14.3%)	43 (12.9%)	12.9% (9.0%, 17.3%)	13.7% (9.3%, 17.9%)	-0.8% (-7.2%, 5.1%)
Heterotopic Ossification	27 (9.6%)	15 (5.7%)	31 (9.3%)	10.2% (6.7%, 14.0%)	5.0% (2.5%, 7.7%)	5.2% (0.5%, 10.1%)*
Implant Events	16 (5.7%)	5 (1.9%)	21 (6.3%)	5.7% (3.0%, 8.7%)	1.8% (0.4%, 3.4%)	3.9% (0.6%, 7.4%)*
Infection	34 (12.1%)	27 (10.2%)	40 (12.0%)	12.0% (8.2%. 16.1%)	10.3% (6.6%, 14.2%)	1.7% (-3.8%, 7.5%)
Neck and / or Arm Pain	144 (51.4%)	124 (46.8%)	184 (55.3%)	51.9% (45.9%, 57.9%)	46.2% (39.7%, 52.3%)	5.7% (-3.3%, 15.0%)
Neurological	136 (48.6%)	108 (40.8%)	162 (48.6%)	49.4% (43.2%, 55.6%)	39.8% (33.7%, 46.1%)	9.6% (0.6%, 18.9%)*
Non-Union	0 (0.0%)	29 (10.9%)	0 (0.0%)	0.0%	11.4% (7.3%, 15.4%)	-11.3% (-15.4%, -7.3%)*
Other	93 (33.2%)	81 (30.6%)	110 (33.0%)	33.6% (27.9%, 39.5%)	30.1% (24.4%, 36.0%)	3.5% (-4.9%, 12.1%)
Other Pain	146 (52.1%)	132 (49.8%)	175 (52.6%)	51.3% (45.3%, 57.4%)	50.7% (44.2%, 56.8%)	0.6% (-8.5%, 9.7%)
Respiratory	24 (8.6%)	17 (6.4%)	27 (8.1%)	8.3% (4.9%, 11.7%)	6.5% (3.6%, 9.7%)	1.9% (-2.9%, 6.7%)
Spinal Event	83 (29.6%)	55 (20.8%)	106 (31.8%)	31.4% (25.7%, 37.2%)	19.0% (13.8%, 23.8%)	12.4% (4.5%, 20.3%)*
Trauma	61 (21.8%)	35 (13.2%)	69 (20.7%)	21.2% (16.4%, 26.3%)	13.5% (9.4%, 17.9%)	7.6% (0.7%, 14.4%)*
Urogenital	26 (9.3%)	9 (3.4%)	31 (9.3%)	8.7% (5.2%, 12.2%)	3.5% (1.4%, 5.8%)	5.2% (1.1%, 9.9%)*
Vascular	12 (4.3%)	4 (1.5%)	13 (3.9%)	4.6% (2.3%, 7.3%)	1.2% (0.2%, 2.5%)	3.4% (0.6%, 6.5%)*
Wound (Non-Infectious)	25 (8.9%)	13 (4.9%)	27 (8.1%)	9.6% (6.0%, 13.1%)	4.2% (1.9%, 6.6%)	5.3% (0.7%, 9.7%)*
Any adverse Event	257 (91.8%)	219 (82.6%)	306 (91.9%)	92.3% (89.0%, 95.4%)	82.0% (77.2%, 86.9%)	10.2% (4.1%, 16.2%)*

*Asterisk denotes statistical difference.

Table 16 provides a higher level comparison of the pain adverse events that occurred in the study up to the 24-month visit. As shown in **Table 16**, there was a higher incidence of all pain adverse events in the PRESTIGE® LP IDE and Safety Cohorts as compared to the ACDF control group, but the adverse event rates were not statistically different between the IDE cohort and the ACDF control group (p-value = 0.304 using Fisher's exact test). There was a higher incidence of severe (grade III or IV) adverse pain events for subjects in the PRESTIGE® LP group.

[15] BCI = Bayesian HPD Credible Interval

Table 16: Pain Adverse Events up to 24 Months

Category	PRESTIGE® LP IDE Cohort (N = 280)	ACDF Control (N=265)	PRESTIGE® LP Safety Cohort (N = 333)
Subjects with ≥ 1 Pain AE	202 (72.1%)	180 (67.9%)	248 (74.5%)
Total Pain AEs	553	444	681
Pain AEs by Location:			
• Neck	138	110	174
• Arm	136	103	178
• Neck and Arm	1	0	1
• Back and/or LE Pain	44	53	50
• Headache	61	39	75
• Other Pain[16]	173	139	196

Adverse events were analyzed by subject gender (**Table 17**). Adverse event rates are comparable for all categories between the male and female cohorts except for "other pain" with a statistically higher rate of "other pain" adverse events through the 24 month time period was reported for female subjects (60.9% IDE Cohort and 60.7% Safety Cohort) compared to male subjects (41.9% IDE Cohort and 43.2% Safety Cohort, two sided p-value comparing the PRESTIGE® LP IDE Cohort and ACDF Cohort = 0.002 using Fisher's exact test). The male cohort also had a slightly higher incidence of decreased neck range of motion and bridging bone in any radiographic view compared to the female cohort (15% compared to 7.5%, respectively) up to the 24 month time period. However, the study was not appropriately powered to detect a difference between these cohorts and the clinical significance, if any, of these findings remains undetermined.

[16] Other pain in Table 17 consists of all AEs classified as "Other Pain" for the study except for the back and/or LE pain and headache AEs.

Table 17: Summary of All Adverse Events by Subject Gender

Adverse Event	PRESTIGE® LP IDE Cohort				PRESTIGE® LP Safety Cohort			
	Events		Subjects		Events		Subjects	
	Male (N=129)	Female (N=151)	Male (N=129)	Female (N=151)	Male (N=155)	Female (N=178)	Male (N=155)	Female (N=178)
Anatomical / Technical Difficulty	0	2	0 (0.0%)	2 (1.3%)	0	2	0 (0.0%)	2 (1.1%)
Cancer	4	1	2 (1.6%)	1 (0.7%)	5	2	3 (1.9%)	2 (1.1%)
Cardiac Disorders	12	9	9 (7.0%)	7 (4.6%)	13	11	10 (6.5%)	9 (5.1%)
Dysphagia / Dysphonia	13	20	9 (7.0%)	17 (11.3%)	14	24	10 (6.5%)	20 (11.2%)
Gastrointestinal	24	31	14 (10.9%)	21 (13.9%)	27	41	15 (9.7%)	28 (15.7%)
Heterotopic Ossification	22	9	19 (14.7%)	8 (5.3%)	25	10	22 (14.2%)	9 (5.1%)
Implant Events	5	12	5 (3.9%)	11 (7.3%)	8	14	8 (5.2%)	13 (7.3%)
Infection	22	35	16 (12.4%)	18 (11.9%)	23	40	17 (11.0%)	23 (12.9%)
Neck and / or Arm Pain	103	172	62 (48.1%)	82 (54.3%)	139	214	80 (51.6%)	104 (58.4%)
Neurological	102	140	60 (46.5%)	76 (50.3%)	120	169	72 (46.5%)	90 (50.6%)
Other	74	103	39 (30.2%)	54 (35.8%)	82	125	46 (29.7%)	64 (36.0%)
Other Pain	105	173	54 (41.9%)	92 (60.9%)	130	198	67 (43.2%)	108 (60.7%)
Respiratory	18	16	11 (8.5%)	13 (8.6%)	18	21	11 (7.1%)	16 (9.0%)
Spinal Event	85	87	40 (31.0%)	43 (28.5%)	113	99	55 (35.5%)	51 (28.7%)
Trauma	34	37	30 (23.3%)	31 (20.5%)	37	42	33 (21.3%)	36 (20.2%)
Urogenital	10	32	7 (5.4%)	19 (12.6%)	11	36	8 (5.2%)	23 (12.9%)
Vascular	5	8	4 (3.1%)	8 (5.3%)	5	9	4 (2.6%)	9 (5.1%)
Wound (Non-Infectious)	13	21	11 (8.5%)	14 (9.3%)	14	22	12 (7.7%)	15 (8.4%)
Any adverse Event	651	908	117 (90.7%)	140 (92.7%)	784	1079	140 (90.3%)	166 (93.3%)

Adverse Events Resulting in Secondary Surgical Interventions

Some adverse events resulted in surgical intervention at the index level, subsequent to the initial surgery. Secondary surgical interventions were classified as revisions, removals, reoperations or supplemental fixations at the index level. **Table 18** summarizes the secondary interventions in the PRESTIGE® LP device and control treatment groups that occurred at or before the 24-month post-operative interval. Revisions, removals, and supplemental fixations were considered as secondary surgery failures, while reoperations were not considered as secondary surgery failures according to the clinical study protocol. **Table 18** also presents the Bayesian statistical comparison of secondary surgeries between the PRESTIGE® LP IDE device and control treatment groups. Overall, there was a greater number of subjects undergoing secondary surgical procedures at the index level in the ACDF control group [21 (7.9 %)] compared to the PRESTIGE® LP IDE [14 (5.0%)] and Safety Cohorts [15 (4.5%)]. Bayesian statistical comparison of secondary surgeries between the PRESTIGE® LP IDE Cohort and ACDF control treatment groups were performed (if zero is excluded from the 95% BCI of the difference of the event rates, the event rates are considered to be statistically different between the two groups). The only statistical difference between the control and PRESTIGE® LP Safety Cohort occurred in the Supplemental Fixation category, with the investigational cohort requiring fewer supplemental fixation procedures than the control. However, this category also included use of external

bone stimulators as “supplemental fixation,” which may inflate the numbers in the ACDF control group, as all “supplemental fixation” subjects were considered failures due to secondary surgery. Among the eight ACDF control subjects who had supplemental fixation, two had supplemental fixation without using any external bone stimulators, one had “supplemental fixation” with and without using an external bone stimulator and five subjects had “supplemental fixation” with external bone stimulators only. Excluding the five subjects only using external bone stimulators, the supplemental fixation rates are comparable between the two treatment groups.

Details for secondary surgical procedures involving explantation of the PRESTIGE® LP device and additional surgical interventions in the control group are summarized in **Table 19**.

Table 18: Secondary Interventions and Surgical Procedures Up to the 24-Month Visit

	Surgery			Postoperative (1 day - <4 Weeks)			6 Weeks (≥4 Wks - <9 Weeks)			3 Months (≥9 Wks - <5 Months)			6 Months (≥5 Mos- <9 Months)			12 Months (≥9 Mos- <19 Months)			24 Months ((≥19 Mos- <30 Months))			Total 24 Month # of Subjects Reporting & Total adverse events						Posterior Mean and 95% HPD of Secondary Surgery Rate		Posterior Mean and 95% BCI[17] of Difference of Secondary Surgery Rate between LP IDE Cohort and ACDF Control
Complication	IDE	Control	Safety Cohort	IDE	Control	Safety Cohort	IDE	Control	Safety Cohort	IDE	Control	Safety Cohort	IDE	Control	Safety Cohort	IDE	Control	Safety Cohort	IDE	Control	Safety Cohort	**IDE # Subjects (% of 280)**	**IDE Total # Events**	**Control # Subjects (% of 265)**	**Control Total # Events**	**Safety Cohort # Subjects (% of 333)**	**Safety Cohort Total # Event**	**PRESTIGE® LP IDE Cohort**	**ACDF Control**	**PRESTIGE(R) LP IDE – ACDF Control**
Revisions[18]	0	0	0	0	1	0	1	0	1	0	3	0	0	0	0	0	1	0	0	0	0	1 (0.4)	1	5 (1.9)	5	1 (0.3)	1	0.4% (0.0%, 1.1%)	1.6% (0.3%, 3.3%)	-1.3% (-3.2%, 0.4%)
Removals[19]	0	0	0	1	0	1	1	0	1	1	1	1	3	2	3	3	6	4	1	2	1	10 (3.6)	10	11 (4.2)	11	11 (3.3)	11	3.7% (1.6%, 6.0%)	3.8% (1.6%, 6.2%)	-0.1% (-3.7%, 3.2%)
Supplemental Fixations[20]	0	0	0	0	0	0	0	0	0	0	0	0	1	3	1	1	5	1	0	1	0	2 (0.7)	2	8 (3.0)	9	2 (0.6)	2	0.5% (0.0%, 1.3%)	3.2% (1.3%, 5.5%)	-2.7% (-5.0%, -0.5%)
Reoperations[21]	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	1	1	2	0	2	3 (1.1)	3	2 (0.8)	2	3 (0.9)	3	1.1% (0.1%, 2.3%)	0.6% (0.0%, 1.6%)	0.4% (-1.2%, 2.1%)
Total	0	0	0	1	1	1	2	1	2	1	4	1	4	5	4	5	13	6	3	3	3	14 (5.0)	16	21 (7.9)	27	15 (4.5)	17	5.3% (2.8%, 8.2%)	7.1% (4.1%, 10.4%)	-1.9% (-6.4%, 2.3%)

[17] BCI = Bayesian HPD Credible Interval

[18] A procedure that adjusts or in any way modifies the original implant configuration (e.g., adjusting position of the original configuration, removal with replacement with the same type of study implant).

[19] A procedure that removes one or more components of the original implant configuration without replacement with the same type of trial implant . Removals include elective removals.

[20] A procedure at the involved level in which additional spinal devices not approved as part of the protocol are placed. This categorization of Supplemental Fixations includes supplemental therapies (i.e. external bone growth stimulators). There were a total of six (6) external bone growth stimulators used in the ACDF Control group. Three (3) occurred at six (6) months, and three (3) occurred at 12 months. No external bone growth stimulators were used in the IDE or Safety Cohorts. Please note that since this additional device was used, and included as a supplemental fixation, these patients were considered failures in the Primary Endpoint.

[21] A procedure that involves any surgical procedure at the involved level that does not remove, modify, or add any components and that is not considered a Removal. Revision, or Supplemental Fixation.

Table 19: Secondary Surgical Interventions at the Index Level– Procedure Details

Group	Cause/Adverse Event	Action	Secondary Surgical Intervention Category	Time to Index Level Surgery
Safety Cohort IDE	C4-C5 displaced device with fractured vertebrae; subject's bone scan was positive for osteopenia	C4-C5 explant of PRESTIGE® LP artificial disc followed by anterior cervical fusion	Removal	01 Day- <4 Weeks (01 day)
Safety Cohort IDE	C4-C5 PRESTIGE® LP artificial disc compressed into the vertebral body and rotated within the disc space secondary to a fall	C4-C5 explant of PRESTIGE® LP artificial disc followed by anterior cervical fusion	Removal	06 Weeks (49 days)
Safety Cohort IDE	C5-C6 device extrusion	C5-C6 explant of PRESTIGE LP® artificial disc and replacement with new PRESTIGE LP® artificial disc; different size	Revision	06 Weeks (56 days)
Safety Cohort IDE	C6-C7 large recurrent disc herniation with cord compression and severe stenosis	C6-C7 explant of PRESTIGE® LP artificial disc with anterior cervical discectomy and fusion	Removal	03 Months (150 days)
Safety Cohort IDE	Severe neck pain	C5-C6 explant of PRESTIGE® LP artificial disc followed by anterior cervical fusion	Removal	06 Months (159 days)
Safety Cohort IDE	C6-C7 cervical radiculopathy with cervical stenosis	C6-C7 explant PRESTIGE® LP artificial disc,C5-C7 anterior cervical discectomy and fusion	Removal	06 Months (215 days)
Safety Cohort IDE	C5-C6 artificial disc dislodging posteriorly	C5-C6 explant of PRESTIGE® LP artificial disc followed by anterior cervical fusion	Removal	06 Months (259 days)
Safety Cohort IDE	C3-C4 foraminal stenosis; possible C4 impingement; C4-C5 foraminal disc protrusion	C3-C4 posterior cervical fusion	Supplemental Fixation	06 Months (262 days)
Safety Cohort IDE	C5-C6 herniated disc with right upper extremity radiculopathy	C6-C7 explant PRESTIGE® LP artificial disc, C5-C7 anterior cervical discectomy and fusion	Removal	12 Months (423 days)
Safety Cohort IDE	Radiating paracervical pain and right shoulder pain	C4-C5 explant of PRESTIGE® LP artificial disc, followed by anterior cervical fusion	Removal	12 Months (469 days)
Safety Cohort IDE	Neck pain radiating to shoulders	C6-C7 explant of PRESTIGE® LP artificial disc; anterior cervical fusion	Removal	12 Months (518 days)
Safety Cohort IDE	C3-C4, C5-C6 foraminal stenosis	C3-C4, C5-C6 left posterior laminectomy	Reoperation	12 Months (528 days)
Safety Cohort Continued Access	C7 subsidence into the vertebral body and lucency as a result of traumatic event	C6-C7 explant of PRESTIGE® LP artificial disc, anterior microdiscectomy and fusion	Removal	12 Months (546 days)
Safety Cohort IDE	C6-C7 cervical radiculopathy with cervical stenosis. Additionally, the subject had removal due to the same diagnosis at 215 days as referenced above.	C5-C7 posterior cervical fusion; C6-C7 posterior cervical foraminotomy	Supplemental Fixation	12 Months (568 days)

Group	Cause/Adverse Event	Action	Secondary Surgical Intervention Category	Time to Index Level Surgery
Safety Cohort IDE	C4-C5, C5-C6 left-sided neural foraminal narrowing as a result of a fall	C4-C5, C5-C6 left posterior foraminotomy	Reoperation	24 Months (708 days)
Safety Cohort IDE	C6-C7 disc herniation; C5-C6 osteophyte	C5-C6 explant of PRESTIGE® LP artificial disc; C5-C7 partial vertebrectomy and anterior cervical discectomy and fusion	Removal	24 Months (732 days)
Safety Cohort IDE	C5-C6 radiculopathy	C5-C6 left foraminotomy	Reoperation	24 Months (743 days)
Safety Cohort IDE	Lifting injury; C5-C6 changes (not specified, pre-existing) bilateral upper extremity radiculopathy; axial neck pain	C5-C6 explant of PRESTIGE® LP artificial disc with fusion, C6-C7 artificial disc replacement	Removal	36 Months (1161 days)
Safety Cohort IDE	Subsidence into C6, C4-C5 facet arthropathy, C4-C6 osteophytic spurring and stenosis, C6-C7 herniated nucleus pulposus	C5-C6 explant of PRESTIGE® LP artificial disc; C4-C7 anterior cervical discectomy and fusion	Removal	48 Months (1394 days)
Safety Cohort IDE	C4-C6 foraminal stenosis	C6-C7 explant PRESTIGE® LP artificial disc, C4-C6 anterior cervical discectomy and fusion	Removal	60 Months (1646 days)
Safety Cohort IDE	Shortened muscle syndrome resulting in shoulder and arm pain aggravated by altercation at work	C6-C7 explant of PRESTIGE® LP artificial disc, C5-C6 anterior decompression; C5-C7 anterior cervical fusion	Removal	84 Months (2431 days)
Control	C5-C6 residual foraminal stenosis; hematoma	C5-C6 left forminatomy and hematoma removal	Revision	01 Day- <4 Weeks (02 days)
Control	C5 small piece of disc material or hematoma per MRI, deltoid weakness	C5-C6 posterior microforaminotomy (C5)	Reoperation	06 Weeks (43 days)
Control	Esophageal perforation/fistula, abscess	C5-C6 removal of the cervical plate and allograft; exploration and debridement of an esophageal abscess, repair of an esophageal fistula	Removal	03 Months (63 days)
Control	C5-C6 herniated nucleus pulposus	C5-C7 anterior cervical discectomy and fusion	Revision	03 Months (88 days)
Control	C7 distribution pain and numbness	C5-C7 fusion	Revision	03 Months (98 days)
Control	C6-C7 disc herniation	C5-C6 Removal of cervical plate, exploration of fusion at C5-C6; C6-C7 anterior cervical discectomy and fusion	Revision	03 Months (140 days)

Group	Cause/Adverse Event	Action	Secondary Surgical Intervention Category	Time to Index Level Surgery
Control	C5-C6 Delayed nonunion	C5-C6 bone growth stimulator	Supplemental Fixation-External Bone Growth Stimulator	06 Months (183 days)
Control	C5-C6 nonunion	C5-C6 bone growth stimulator	Supplemental Fixation-External Bone Growth Stimulator	06 Months (185 days)
Control	C6-C7 pseudoarthrosis	C6-C7 bone growth stimulator	Supplemental Fixation-External Bone Growth Stimulator	06 Months (207 days)
Control	C5-C6 nonunion, failed fusion with motion present	C5-C6 removal of the cervical plate and allograft; partial corpectomy C5 with anterior cervical fusion	Removal	06 Months (241 days)
Control	Posterior cervical region and trapezius pain, spasms, and bilateral arm pain	C5-C6 removal of the cervical plate and allograft; anterior cervical fusion; bilateral foraminotomies	Removal	06 Months (272 days)
Control	C5-C6, C6-C7 nonunion	C5-C7 bone growth stimulator	Supplemental Fixation-External Bone Growth Stimulator	12 Months (278 days)
Control	C5-C6 nonunion	C5-C6 removal of the cervical plate and allograft; partial corpectomy at C6, microdissection, and fusion	Removal	12 Months (284 days)
Control	C5-C6 pseudoarthrosis	C5-C6 removal of the cervical plate and allograft; allograft and plate replaced	Removal	12 Months (293 days)
Control	C5-C6, C6-C7 nonunion; wound infection	C5-C7 removal of the cervical plate and allograft; revision anterior arthrodesis	Removal	12 Months (326 days)
Control	C5-C6 pseudoarthrosis	C5-C6 external bone growth stimulator	Supplemental Fixation-External Bone Growth Stimulator	12 Months (352 days)
Control	C6-C7 nonunion	C6-C7 bone growth stimulator	Supplemental Fixation-External Bone Growth Stimulator	12 Months (372 days)

Group	Cause/Adverse Event	Action	Secondary Surgical Intervention Category	Time to Index Level Surgery
Control	C5-C6 possible facet disease; neck pain with right posterior scapular pain	C6-C7 removal of the cervical plate to facilitate C5-C6 anterior cervical discectomy and fusion	Elective Removal	12 Months (385 days)
Control	C6-C7 non-union with motion present, neck and shoulder pain	C6-C7 removal of the cervical plate and allograft; C4-C7 anterior cervical fusion	Removal	12 Months (399 days)
Control	Shoulder pain and numbness in fingers	C5-C6 removal of the cervical plate to facilitate C6-C7 cervical discectomy and fusion	Elective Removal	12 Months (407 days)
Control	Neck and arm pain; possible recurrent nerve compression	C5-C6 posterior cervical fusion	Supplemental Fixation	12 Months (474 days)
Control	Involuntary movements thumb; gait abnormalities; upper and lower extremity deficits and findings suggestive of upper motor neuron lesion; body "jumps" when lays down; urinary incontinence	C4, C5, C6, C7, T1 laminectomies	Reoperation	12 Months (506 days)
Control	Cervical spondylosis, neck pain, glenohumeral joint	C5-C6 removal of the cervical plate to facilitate C6-C7 anterior cervical discectomy and fusion	Elective Removal	12 Months (513 days)
Control	C5-C6, C6-C7 nonunion	C5-C7 posterior fusion	Supplemental Fixation	12 Months (535 days)
Control	C5-C6 pseudoarthrosis	C5-C6 posterolateral cervical fusion	Supplemental Fixation	24 Months (613 days)
Control	C5-C6 discogenic pain confirmed via discogram	C6-C7 removal of the cervical plate to facilitate C5-C6 anterior cervical discectomy and fusion	Elective Removal	24 Months (756 days)
Control	C5-C6 lucency	C5-C6 removal of the cervical plate and allograft; anterior cervical fusion with autologous stem cells, and bone marrow aspiration (left anterior ilium)	Removal	24 Months (840 days)
Control	C5-C6, C6-C7 lateral stenosis	C5-C6, C6-C7 right foraminotomies with C6-C7 nerve root decompression	Revision	36 Months (1050 days)
Control	C6-C7 delayed fusion; possibly work related	C6-C7 posterior fusion	Supplemental Fixation	36 Months (1094 days)
Control	C6-C7 osteophytes, cord edema, herniated nucleus pulposus, spinal stenosis, radiating neck pain, motor vehicle accident	C5-C6 removal of the cervical plate to facilitate C6-C7 anterior cervical discectomy and fusion	Elective Removal	36 Months (1211 days)
Control	C6-C7 pseudoarthrosis; resorption of graft	C6-C7 posterior fusion	Supplemental Fixation	36 Months (1259 days)
Control	C6-C7 pseudoarthrosis; resorption of graft	Supplemental Fixation-C6-C7 bone growth stimulator	Supplemental Fixation-External Bone Grown Stimulator	48 Months (1391 days)

Group	Cause/Adverse Event	Action	Secondary Surgical Intervention Category	Time to Index Level Surgery
Control	C6-C7 herniation, foramen impingement, osteophyte compression	C5-C6 removal of the cervical plate to facilitate C6-C7 anterior discectomy and osteophytectomy with anterior interbody fusion	Elective Removal	48 Months (1512 days)
Control	Neck and left arm pain	C5-C6 removal of the cervical plate to facilitate C6-C7 foraminotomy with arthrodesis	Elective Removal	48 Months (1560 days)
Control	C3-C4 severe spondylitic changes with bilateral spurring, left paracentral disc osteophyte complex, bilateral foraminal encroachment, and C4-C5 severe spondylitic changes	C5-C6 removal of the cervical plate to facilitate C3-C5 anterior cervical discectomy and fusion	Elective Removal	60 Months (1665 days)
Control	C5-C6 herniation, C4-C6 foraminal stenosis	C6-C7 removal of the cervical plate to facilitate C5-C6 discectomy with anterior plate	Elective Removal	60 Months (1679 days)
Control	C5-C6 degenerative changes possible small disc protrusion, osteophytes	C6-C7 removal of the cervical plate to facilitate C5-C6 anterior cervical discectomy and fusion	Elective Removal	60 Months (1729 days)
Control	C3-C4 protrusion, hypertrophy; C5-C6 mild stenosis, protrusion, segment degeneration	C4-C5 removal of the cervical plate to facilitate C3-C4, C5-C6 anterior cervical discectomy and fusion	Elective Removal	60 Months (1806 days)
Control	C6-C7 spondylosis, disc bulge	C5-C6 removal of the cervical plate to facilitate C6-C7 artificial disc replacement	Elective Removal	72 Months (2242 days)
Control	C5-C6 osteophytosis and arthropathy	C6-C7 removal of the cervical plate to facilitate C5-C6 anterior cervical discectomy and fusion	Elective Removal	84 Months (2425 days)
Control	C6 right radiculopathy, C6-C7 foraminal narrowing	C5-C6 right anterolateral foraminotomy	Reoperation	84 Months (2486 days)
Control	C5-C6 epidural abscess	C5-C6 laminectomy with evacuation of epidural abscess	Reoperation	84 Months (2514 days)

Device-Related and Procedure-Related Adverse Events

The relationship between adverse events and the implant and/or surgical procedure was assessed separately by the Investigators and an independent Clinical Adjudication Committee (CAC) according to the following classifications: implant associated, surgical procedure associated, implant and surgical procedure associated, and undetermined, and not related. These adverse events are detailed in **Table 20**.

Based on the CAC's classification, there is no clinically meaningful difference in the device-related adverse event profiles (defined as either "implant associated" or "implant and surgical procedure associated") between the PRESTIGE® LP IDE Cohort, PRESTIGE® LP Safety Cohort and historical ACDF control groups, at 12.1%, 13.2%, and 15.5%, respectively.

Table 20: Adverse Events Classified as Device-Related or Device/Surgical Procedure-Related According to the Clinical Adjudication Committee through Month 24 – Safety Population

	PRESTIGE® LP IDE Cohort (N=280)		ACDF Control (N=265)		PRESTIGE® LP Safety Cohort (N=333)	
Device Relationship of Adverse Event Determined by CAC	**Events N**	**Subjects N (%)**	**Events N**	**Subjects N (%)**	**Events N**	**Subjects N (%)**
Dysphagia / Dysphonia	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)
Heterotopic Ossification	4	4 (1.4)	3	2 (0.8)	6	6 (1.8)
Implant Events	16	15 (5.4)	5	5 (1.9)	20	19 (5.7)
Neck and / or Arm Pain	9	7 (2.5)	6	4 (1.5)	13	11 (3.3)
Neurological	11	9 (3.2)	7	7 (2.6)	14	11 (3.3)
Non-Union	0	0 (0.0)	27	27 (10.2)	0	0 (0.0)
Other	2	2 (0.7)	2	2 (0.8)	3	3 (0.9)
Other Pain	5	5 (1.8)	4	3 (1.1)	5	5 (1.5%)
Spinal Event	13	8 (2.9)	4	2 (0.8)	13	8 (2.4%)
Trauma	1	1 (0.4)	0	0 (0.0)	2	2 (0.6)
Wound (Non-Infectious)	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)
Any Adverse Event	61	34 (12.1)	60	41 (15.5)	76	44 (13.2)

Adverse Event Severity

Severity of adverse events was assessed according to the 4-tier World Health Organization (WHO) Recommendations for Grading of Acute and Subacute Toxic Effects. Grade 3 and Grade 4 adverse events were summarized for the PRESTIGE® LP IDE Cohort, PRESTIGE® LP Safety Cohort and the ACDF control group (**Table 21**). The percentage of grade 3 and grade 4 adverse events in the IDE and Safety cohorts was greater than that found in the control group (47.5% and 48.9% vs. 37.0%; the 95% BCI for the difference of Grade 3/4 adverse events rates between the PRESTIGE® LP IDE Cohort and ACDF Control Cohort is (3.5%, 21.8%) excluding 0, indicating statistical difference).

The treatment group rates for the various categories were fairly similar. The largest differences were noted for other pain related events, which favored the control group over the IDE and Safety groups (10.2% vs. 15.4% and 16.5%, respectively). Although the rate of IDE subjects having at least one grade 3 or 4 adverse event was statistically higher than the control group rate, this finding may be attributable to the higher follow-up rates (and potentially, higher reporting of events) for investigational subjects as compared to the ACDF control subjects. Furthermore, a category-by category examination of areas demonstrating a statistical difference did not raise concerns about the nature of events seen with the investigational device.

Table 21: Summary of Severe (Grade 3/4) Adverse Events through Month 24[22]

	PRESTIGE® LP IDE Cohort (N=280)		ACDF Control (N=265)		PRESTIGE® LP Safety Cohort (N=333)	
Category	**Events N**	**Subjects N (%)**	**Events N**	**Subjects N (%)**	**Events N**	**Subjects N (%)**
Cancer	4	2 (0.7)	2	2 (0.8)	6	4 (1.2)
Cardiac Disorders	10	9 (3.2)	8	7 (2.6)	10	9 (2.7)
Dysphagia / Dysphonia	4	3 (1.1)	1	1 (0.4)	4	3 (0.9)
Gastrointestinal	22	13 (4.6)	20	12 (4.5)	31	19 (5.7)
Heterotopic Ossification	13	11 (3.9)	12	8 (3.0)	13	11 (3.3)
Implant Events	4	4 (1.4)	0	0 (0.0)	5	5 (1.5)
Infection	17	11 (3.9)	8	8 (3.0)	18	12 (3.6)
Neck and / or Arm Pain	52	37 (13.2)	36	24 (9.1)	66	49 (14.7)
Neurological	52	35 (12.5)	32	27 (10.2)	64	42 (12.6)
Non-Union	0	0 (0.0)	6	6 (2.3)	0	0 (0.0)
Other	45	28 (10.0)	30	22 (8.3)	52	34 (10.2)
Other Pain	67	43 (15.4)	34	27 (10.2)	85	55 (16.5)
Respiratory	9	7 (2.5)	1	1 (0.4)	9	7 (2.1)
Spinal Event	80	41 (14.6)	59	31 (11.7)	96	51(15.3)
Trauma	22	20 (7.1)	10	10 (3.8)	25	23 (6.9)
Urogenital	20	15 (5.4)	4	4 (1.5)	22	17 (5.1)
Vascular	7	6 (2.1)	0	0 (0.0)	7	6 (1.8)
Wound (Non-Infectious)	5	5 (1.8)	4	4 (1.5)	5	5 (1.5)
Any Adverse Event	433	133 (47.5)	267	98 (37.0)	518	163 (48.9)

Neurological Status

Neurological status was evaluated by assessment of motor function, sensory function, and reflexes. Overall neurological status at 6 weeks, 3 months, 6 months, 12 months and 24 months is provided for the PRESTIGE® LP and Control subjects in **Table 22** below. Neurologic success was defined as maintenance or improvement in neurologic status at 24 months compated to baseline. The success rates at 24 months postoperative were 93.3%, 94.0% and 83.6% for the PRESTIGE® LP IDE Cohort, PRESTIGE® LP Safety Cohort and Control group, respectively, indicating a numerically comparable number of stable or improved neurologic status. There were fewer subjects that exhibited neurologic deterioration in the Prestige® LP Safety Cohort (5.9%) as compared to the ACDF Control Cohort (16.4%).

[22] Denotes WHO Grade 3 or 4 Severe Adverse Events

Table 22: Neurological Status

Time Point	Variable	PRESTIGE® LP IDE Cohort (N=280) Subjects (%)	ACDF Control (N=265) Subjects (%)	PRESTIGE® LP Safety Cohort (N=333) Subjects (%)
6 Weeks	Overall			
	Improved	187 (67.3%)	144 (56.7%)	228 (69.1%)
	Stable	65 (23.4%)	78 (30.7%)	74 (22.4%)
	Deteriorated	26 (9.4%)	32 (12.6%)	28 (8.5%)
3 Months	Overall			
	Improved	194 (70.3%)	136 (56.4%)	237 (72.3%)
	Stable	63 (22.8%)	74 (30.7%)	72 (22.0%)
	Deteriorated	19 (6.9%)	31 (12.9%)	19 (5.8%)
6 Months	Overall			
	Improved	195 (72.2%)	141 (61.8%)	238 (73.9%)
	Stable	59 (21.9%)	64 (28.1%)	68 (21.1%)
	Deteriorated	1 (5.9%)	23 (10.1%)	16 (5.0%)
12 Months	Overall			
	Improved	198 (72.8%)	133 (58.8%)	241 (74.4%)
	Stable	59 (21.7%)	61 (27.0%)	68 (21.0%)
	Deteriorated	15 (5.5%)	32 (14.2%)	15 (4.6%)
24 Months	Overall			
	Improved	196 (72.6%)	123 (55.9%)	238 (74.1%)
	Stable	56 (20.7%)	61 (27.7%)	64 (19.9%)
	Deteriorated	18 (6.7%)	36 (16.4%)	19 (5.9%)

Continued Access and Metal Ion Cohorts

As described, 30 subjects were treated with the PRESTIGE® LP in a Metal Ion (MI) Cohort, and 24 subjects were treated with the PRESTIGE® LP in a Continued Access (CA) Cohort. An independent laboratory conducted metal ion serum level draws from subjects in the MI Cohort, and looked for complications related to metal ion sensitivity in these subjects. The analysis concluded that none of the subjects in the MI Cohort had symptoms consistent with metal ion sensitivity. The adverse events of the CA and MI Cohorts were also analyzed separately, and there was not a clinically meaningful difference as compared to the IDE Cohort. In addition, there were no explants in the MI Cohort, and only one explant in the CA Cohort.

Adjacent Level Symptoms and Treatments

The incidence and progression of adjacent level disease was not collected prospectively, but was assessed in terms of symptoms, treatment, and surgery performed at the adjacent level by a thorough review of adverse event source documentation for adverse events coded as pain (neck and/or upper extremity), dysesthesia (neck and/or upper extremity), neurological, weakness, muscle spasms, surgery, pseudoarthrosis, or headache to isolate possible adjacent level symptoms, diagnoses, treatments, and surgeries. Based on this review, the percentage of subjects undergoing surgery at the adjacent levels (including those having combined surgery of the index and adjacent levels) was 2.5% (7 subjects, 9 events) for the

PRESTIGE® LP IDE Cohort, 2.4% (8 subjects, 10 events) for the PRESTIGE® LP Safety Cohort and 4.2% (11 subjects, 14 events) for the ACDF control group as shown in **Table 23**. Additionally, the percentage of subjects undergoing surgery at any level other than the index procedure (adjacent cervical level surgeries, other cervical level surgeries, non-cervical spinal surgeries, and non-spinal surgeries) was similar for the PRESTIGE® LP IDE Cohort (22.1%), PRESTIGE® LP Safety Cohort (24.6%) and the ACDF control group (18.9%). All secondary surgical interventions at adjacent level discs are documented and listed below in **Table 24**.

Table 23: Subjects with Adjacent Level Surgical Treatment by Time Period

Time Point	PRESTIGE® LP IDE Cohort (N =280)		ACDF Control (N = 265)		PRESTIGE® LP Safety Cohort (N=333)	
	Subjects N (%)	Events N	Subjects N (%)	Events N	Subjects N (%)	Events N
Operative	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0
1 Day - < 4 Weeks	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0
6 Weeks	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0
3 Months	0 (0.0%)	0	3 (1.1%)	3	0 (0.0%)	0
6 Months	1 (0.4%)	1	0 (0.0%)	0	1 (0.3%)	1
12 Months	5 (1.8%)	5	8 (3.0%)	9	5 (1.5%)	5
24 Months	3 (1.1%)	3	2 (0.8%)	2	4 (1.2%)	4
Total (Up to 24 Months)	**7 (2.5%)**	**9**	**11 (4.2%)**	**14**	**8 (2.4%)**	**10**

Table 24. Secondary Surgical Interventions Including Levels Adjacent to Index Level

Group	Index Level	Study Surgery Date	Event Term(s)	Time to Adjacent Level Surgery	Description of Subsequent Adjacent Level Surgery
Safety Cohort IDE	C6-C7	22 SEP 2005	C6-C7 cervical radiculopathy with cervical stenosis	06 Months (215 days)	C6-C7 explant of PRESTIGE® LP artificial disc,C5-C7 anterior cervical discectomy and fusion
Safety Cohort IDE	C4-C5	05 AUG 2005	C5-C6, C6-C7 spinal stenosis; C5-C6 disc osteophyte; ossification at the posterior longitudinal ligament	12 Months (321 days)	C5-C7 anterior cervical discectomy and fusion with autograft; C6 corpectomy
Safety Cohort IDE	C5-C6	08 JUL 2005	C6-C7 right disc herniation; C7 radiculopathy secondary to diving into ocean	12 Months (377 days)	C6-C7 right anterior cervical microdiscectomy, decompression, and fusion
Safety Cohort IDE	C6-C7	05 AUG 2005	C5-C6 herniated disc with right upper extremity radiculopathy	12 Months (423 days)	C6-C7 explant of PRESTIGE® LP artificial disc, C5-C7 anterior cervical discectomy and fusion
Safety Cohort IDE	C5-C6	10 OCT 2005	C3-C4, C5-C6 foraminal stenosis	12 Months (528 days)	C3-C4, C5-C6 left posterior laminectomy
Safety Cohort IDE	C6-C7	22 SEP 2005	C6-C7 cervical radiculopathy with cervical stenosis (post-explant)	12 Months (568 days)	C5-C7 posterior cervical fusion; C6-C7 posterior cervical foraminotomy
Safety Cohort IDE	C4-C5	05 APR 2005	C4-C5, C5-C6 neural foraminal narrowing as a result of fall	24 Months (708 days)	C5-C6, C6-C7 left posterior foraminotomy
Safety Cohort IDE	C5-C6	25 JUL 2005	C6-C7 disc herniation; C5-C6 osteophyte	24 Months (732 days)	C5-C6 explant of PRESTIGE® LP artificial disc; C5-C7 partial vertebrectomy and anterior cervical discectomy and fusion
Safety Cohort IDE	C6-C7	22 SEP 2005	C6-C7 cervical radiculopathy with cervical stenosis (post explant)	24 Months (896 days)	C2-C5, C7-T1 bilateral medial branch neurotomy
Safety Cohort IDE	C6-C7	12 JUL 2005	C4-C5 central disc herniation, C5-C6 disc protrusion, annular tears at C4-C5, C5-C6; overall disc height narrowing at C4-C5 and C5-C6	36 Months (918 days)	C4-C5, C5-C6 discectomy; C4-C5 disc replacement; C5-C6 anterior cervical fusion

Group	Index Level	Study Surgery Date	Event Term(s)	Time to Adjacent Level Surgery	Description of Subsequent Adjacent Level Surgery
Safety Cohort IDE	C5-C6	12 AUG 2005	C6-C7 disc herniation; C7 radiculopathy with neurological defects related to left sided C7 foraminal stenosis	36 Months (973 days)	C6-C7 microdiscectomy and fusion
Safety Cohort IDE	C5-C6	10 OCT 2005	C6-C7 disc herniation/ protrusion	36 Months (997 days)	C6-C7 discectomy with artificial disc replacement
Safety Cohort IDE	C6-C7	24 AUG 2005	Neck pain and upper extremity radicular pain	36 Months (1003 days)	C5-C6 anterior cervical discectomy and fusion
Safety Cohort IDE	C5-C6	30 JUN 2005	C4 spur, C6-C7 segment degeneration, large central and right paracentral disc extrusion causing severe central canal stenosis and cord compression and right shoulder pain secondary to lifting boxes	36 Months (1043 days)	C6-C7 anterior cervical discectomy, spinal canal decompression, and fusion
Safety Cohort Metal Ion	C5-C6	20 MAR 2006	C6-C7 herniated disc, C6-C7 degenerative disc disease, C5-C7, C7-T1 nerve root sleeve cysts, and spasmodic torticollis	36 Months (1106 days)	C7 posterior hemilaminectomy, partial facetectomy, foraminotomy, and discectomy
Safety Cohort IDE	C5-C6	29 JUL 2005	C7 distribution multilevel degenerative disc disease; numbness; C7 tingling distribution	36 Months (1144 days)	C6-C7 anterior cervical microdiscectomy, canal decompression, and fusion
Safety Cohort IDE	C5-C6	20 SEP 2005	Lifting injury; C5-C6 changes (not specified, pre-existing) bilateral upper extremity radiculopathy; axial neck pain	36 Months (1161 days)	C5-C6 explant of PRESTIGE® LP artificial disc with fusion, C6-C7 artificial disc replacement
Safety Cohort IDE	C6-C7	10 MAY 2005	C5-C6 left disc extrusion, cervical neuroforaminal stenosis	36 Months (1171 days)	C5-C6 left partial hemi-laminectomy discectomy, osteophytectomy, foraminotomy decompression
Safety Cohort IDE	C5-C6	06 OCT 2005	C6-C7 disc herniation and radiculopathy	36 Months (1197 days)	C6-C7 anterior cervical microdiscectomy and fusion
Safety Cohort IDE	C5-C6	13 APR 2005	C4-C5 central disc protrusion and herniation with cord compression; osteophyte with compression of exiting nerve root; transverse myelitis; bilateral neural foraminal	36 Months (1252 days)	C4-C5 artificial disc replacement

Group	Index Level	Study Surgery Date	Event Term(s)	Time to Adjacent Level Surgery	Description of Subsequent Adjacent Level Surgery
			stenosis		
Safety Cohort IDE	C5-C6	27 MAY 2005	C3-C5 cervical stenosis	36 Months (1273 days)	C3-C5 posterior facetectomy
Safety Cohort IDE	C5-C6	07 JUN 2005	Subsidence into C6, C4-C5 facet arthropathy, C4-C6 osteophytic spurring and stenosis, C6-C7 herniated nucleus pulposus	48 Months (1394 days)	C5-C6 explant of PRESTIGE® LP artificial disc; C4-C7 anterior cervical discectomy and fusion
Safety Cohort IDE	C5-C6	17 OCT 2005	Neck pain radiating down to shoulders	48 Months (1409 days)	C6-C7 anterior cervical discectomy and fusion
Safety Cohort IDE	C5-C6	22 JUN 2005	C6-C7 degenerative disc disease, central stenosis, and left neuroforaminal stenosis	48 Months (1512 days)	C6-C7 anterior cervical discectomy and fusion
Safety Cohort IDE	C6-C7	15 MAR 2005	C4-C6 foraminal stenosis	60 Months (1646 days)	C6-C7 explant of PRESTIGE® LP artificial disc, C4-C6 anterior cervical discectomy and fusion
Safety Cohort IDE	C5-C6	31 MAY 2005	C4-C5, C5-C6 cord deformity, C4-C5 foraminal narrowing, C4-C5 right herniation, C6-C7 foraminal stenosis, C4-C5, C6-C7 spurring with possible nerve impingement at both levels, C5 right mononeuropathy consistent with carpal tunnel syndrome	60 Months (1672 days)	C4-C5 anterior cervical discectomy and fusion; decompression of spinal canal, removal of large extruded disc fragment, and fusion
Safety Cohort IDE	C5-C6	7 JUN 2005	C6-C7 pseudoarthrosis; C7 broken screws; occipital neuralgia	60 Months (1687 days)	C6-C7 anterior cervical discectomy and fusion
Safety Cohort IDE	C6-C7	29 JUL 2005	C5-C6 bilateral foraminal stenosis, progressive disc degeneration, possible cervical radiculopathy	60 Months (1785 days)	C5-C6 anterior cervical discectomy and fusion
Safety Cohort IDE	C6-C7	09 MAR 2005	C5-C6 disc protrusion and degenerative disc disease secondary to fall	72 Months (2203 days)	C5-C6 discectomy, osteophytectomy, and fusion
Safety Cohort IDE	C5-C6	16 MAY 2005	C4-C5 large disc herniation with compression of the lateral aspect of cord and foramen on right	72 Months (2174 days)	C4-C5 anterior cervical discectomy and fusion

Group	Index Level	Study Surgery Date	Event Term(s)	Time to Adjacent Level Surgery	Description of Subsequent Adjacent Level Surgery
Safety Cohort IDE	C5-C6	30 JUN 2005	C3-C4, C4-C5 herniated disc, C2-C3, C3-C4 foraminal stenosis	72 Months (2356 days)	C2-C5 anterior cervical discectomy and fusion
Safety Cohort IDE	C6-C7	04 OCT 2005	Shortened muscle syndrome resulting in shoulder and arm pain aggravated by altercation at work	84 Months (2431 days)	C6-C7 explant of PRESTIGE® LP artificial disc, C5-C6 anterior decompression and fusion; C6-C7 fusion
Control	C6-C7	09 JAN 2004	C5-C6 herniated nucleus pulposus	03 Months (88 days)	C5-C7 reanterior cervical discectomy and fusion
Control	C5-C6	25 FEB 2004	C7 distribution pain and numbness	03 Months (98 days)	C5-C7 fusion
Control	C5-C6	17 NOV 2003	C6-C7 disc herniation	03 Months (140 days)	C5-C6 Removal of cervical plate, exploration of fusion at C5-C6; C6-C7 anterior cervical discectomy and fusion
Control	C5-C6	25 FEB 2004	C5-C6, C6-C7 non-union; wound infection	12 Months (326 days)	C5-C6 removal of the cervical plate and allograft; C5-C7 revision anterior arthrodesis
Control	C6-C7	21 APR 2003	C5-C6 possible facet disease; neck pain with right posterior scapular pain	12 Months (385 days)	C6-C7 removal of the cervical plate to facilitate C5-C6 anterior cervical discectomy and fusion
Control	C6-C7	07 APR 2004	C6-C7 non-union with motion present, neck and shoulder pain	12 Months (399 days)	C6-C7 removal of the cervical plate and allograft; C4-C7 anterior fusion
Control	C5-C6	13 APR 2004	Shoulder pain and numbness in fingers	12 Months (407 days)	C5-C6 removal of the cervical plate to facilitate C6-C7 cervical discectomy and fusion
Control	C6-C7	14 JAN 2004	C3-C4 foraminal stenosis, C5-6 herniated disc	12 Months (482 days)	C3-C4, C5-C6 posterior cervical foraminotomy
Control	C6-C7	10 FEB 2003	Involuntary movements thumb; gait abnormalities; upper and lower extremity deficits and findings suggestive of upper motor	12 Months (506 days)	C4, C5, C6, C7, T1 cervical laminectomies

Group	Index Level	Study Surgery Date	Event Term(s)	Time to Adjacent Level Surgery	Description of Subsequent Adjacent Level Surgery
			neuron lesion; body "jumps" when lays down; urinary incontinence		
Control	C5-C6	25 NOV 2003	Cervical spondylosis, neck pain, glenohumeral joint	12 Months (513 days)	C5-C6 removal of the cervical plate to facilitate C6-C7 anterior cervical discectomy and fusion
Control	C5-C6	25 FEB 2004	C5-C6, C6-C7 non-union	12 Months (525 days)	C5-C7 posterior fusion
Control	C5-C6	13 NOV 2003	C6-C7 segment disease	12 Months (550 days)	C6-C7 anterior cervical discectomy and fusion
Control	C6-C7	08 APR 2004	C5-C6 discogenic pain confirmed via discogram	24 Months (756 days)	C6-C7 removal of the cervical plate to facilitate C5-C6 anterior cervical discectomy and fusion
Control	C5-C6	25 FEB 2004	C3-C4 disc degeneration, bulging, pseudoarthrosis; instability above C4-C5 fusion but C4-C5 level noted to be fused	24 Months (846 days)	C4-C5 anterior cervical discectomy and fusion; removal of plating C5-C7
Control	C5-C6	28 AUG 2003	C6-C7 herniated nucleus pulposus	36 Months (959 days)	C6-C7 anterior cervical discectomy and fusion
Control	C6-C7	08 APR 2004	C5-C6, C6-C7 lateral stenosis	36 Months (1050 days)	C5-C6, C6-C7 right foraminotomies with C6-C7 nerve root decompression
Control	C6-C7	01 DEC 2003	Headaches	36 Months (1183 days)	C3-C4 anterior cervical discectomy and fusion
Control	C5-C6	19 JUN 2003	C6-C7 osteophytes, cord edema, herniated nucleus pulposus, spinal stenosis, radiating neck pain, motor vehicle accident	36 Months (1211 days)	C5-C6 removal of the cervical plate to facilitate C6-C7 anterior cervical discectomy and fusion
Control	C5-C6	11 DEC 2003	C6-C7 herniation, foramen impingement, osteophyte compression	48 Months (1512 days)	C5-C6 removal of the cervical plate to facilitate C6-C7 anterior discectomy and osteophytectomy with anterior interbody fusion
Control	C5-C6	02 OCT 2003	Neck and left arm pain	48 Months (1560 days)	C5-C6 removal of the cervical plate to facilitate C6-C7

Group	Index Level	Study Surgery Date	Event Term(s)	Time to Adjacent Level Surgery	Description of Subsequent Adjacent Level Surgery
					foraminotomy with arthrodesis
Control	C5-C6	07 JAN 2004	C3-C4 severe spondylitic changes with bilateral spurring, left paracentral disc osteophyte complex, bilateral foraminal encroachment, and C4-C5 severe spondylitic changes	60 Months (1665 days)	C5-C6 removal of the cervical plate to facilitate C3-C5 anterior cervical discectomy and fusion
Control	C6-C7	22 JAN 2004	C5-C6 herniation, foraminal stenosis	60 Months (1679 days)	C6-C7 removal of the cervical plate to facilitate C5-C6 discectomy with anterior plating
Control	C6-C7	26 AUG 2003	C5-C6 degenerative changes possible small disc protrusion, osteophytes	60 Months (1729 days)	C6-C7 removal of the cervical plate to facilitate C5-C6 anterior cervical discectomy and fusion
Control	C5-C6	16 JUN 2003	C4-C5 disc herniation	60 Months (1768 days)	C3-C5 radiofrequency ablation of medial branch nerves
Control	C4-C5	30 MAR 2004	C3-C4 protrusion, hypertrophy; C5-C6 mild stenosis, protrusion, segment degeneration	60 Months (1806 days)	C4-C5 removal of the cervical plate to facilitate C3-C4, C5-C6 anterior cervical discectomy and fusion
Control	C5-C6	16 JUN 2003	C4-C5 disc herniation	60 Months (1901 days)	C3-C5 radiofrequency ablation of medial branch nerves
Control	C5-C6	25 FEB 2004	C3-C4 disc degeneration, bulging, pseudoarthrosis	60 Months (1959 days)	C4-C6 removal of anterior cervical plate; C3-C4 anterior cervical discectomy and fusion
Control	C5-C6	11 MAR 2004	C6-C7 chronic radiculopathy, C4-C5 mild spondylosis and foraminal narrowing	60 Months (1988 days)	C5-C6 anterior hardware removal with C6-C7 anterior cervical discectomy and fusion
Control	C5-C6	16 JUN 2003	Right-sided neck pain and shoulder pain	72 Months (2062 days)	C3-C5 right medial branch radiofrequency ablations

Group	Index Level	Study Surgery Date	Event Term(s)	Time to Adjacent Level Surgery	Description of Subsequent Adjacent Level Surgery
Control	C5-C6	25 FEB 2004	C3-C4 disc degeneration, bulging, pseudoarthrosis	72 Months (2183 days)	C3-C4 anterior cervical discectomy and fusion
Control	C5-C6	20 JAN 2004	C6-C7 spondylosis, disc bulge	72 Months (2242 days)	C5-C6 removal of the cervical plate to facilitate C6-C7 artificial disc replacement
Control	C5-C6	16 JUN 2003	Right-sided neck pain and shoulder pain	72 Months (2293 days)	C3-C5 right medial branch radiofrequency ablations
Control	C6-C7	21 APR 2003	C3-C4 foraminal narrowing and C4-C5 canal narrowing	84 Months (2401 days)	C4 right hemilaminectomy; C4-C5 medial facetectomy, foraminotomy
Control	C6-C7	22 JAN 2004	C4-C5 foraminal stenosis	84 Months (2423 days)	C4-C5 anterior cervical discectomy fusion
Control	C6-C7	20 FEB 2004	C5-C6 osteophytosis and arthropathy	84 Months (2425 days)	C6-C7 removal of the cervical plate to facilitate C5-C6 anterior cervical discectomy and fusion
Control	C6-C7	22 JAN 2004	C4-C5 pre-vertebral abscess	84 Months (2436 days)	C4-C5 drainage of possible abscess and removal of plating

Surgery and Hospitalization Data

Table 25 summarizes the information related to the surgical procedures and postoperative hospitalizations of subjects. The most common treated surgical levels were C5-C6 and C6-C7. The mean operative times for the IDE and control treatment groups were 1.5 hours and 1.4 hours, respectively, which is a mean difference of 0.1 hours, or 6 minutes and is unlikely to represent any significant clinical difference. Additionally, investigational subjects were found to have similar estimated blood loss to the control group subjects (50.5 ml for IDE cohort and 49.4 ml for Safety cohort versus 57.5 ml for control group). The median blood loss was 35 ml for the IDE cohort versus 50 ml for both the Safety and control groups. The mean hospital stays of subjects in all treatment groups were similar (1.0 days for all groups).

Table 25: Surgical Data

	PRESTIGE® LP IDE Cohort (N=280)	ACDF Control (N=265)	PRESTIGE® LP Safety Cohort (N=333)	Posterior Mean and 95% BCI[23] of the Difference of Mean between IDE Cohort and Control Group (lower, upper)
Spinal Level Treated				
C_{34} (%)	4 (1.4%)	10 (3.8%)	4 (1.2%)	N/A
C_{45} (%)	21 (7.5%)	15 (5.7%)	28 (8.4%)	N/A
C_{56} (%)	147 (52.5%)	149 (56.2%)	178 (53.5%)	N/A
C_{67} (%)	108 (38.6%)	91 (34.3%)	123 (36.9%)	N/A
Operative time (hrs)	1.5 ± 0.6 Range: 0.7 – 3.4 (n=280)	1.4 ± 0.5 Range: 0.6 – 3.4 (n=265)	1.4 ± 0.5 Range: 0.7 – 3.4 (n=333)	0.11 (0.02, 0.22)
Blood Loss (ml)	50.5 ± 73.5 Range: 3.0 – 700.0 Median: 35.0 (n=278)	57.5 ± 68.1 Range: 0.0 – 700.0 Median: 50.0 (n=263)	49.4 ± 67.9 Range: 3.0 – 700.0 Median 50.0 (n=333)	-4.7 (-16.8, 7.9)
Hospitalization (days)	1.0 ± 0.5 Range: 0.0 – 3.0 (n=280)	1.0 ± 0.5 Range: 0.0 – 4.0 (n=265)	1.0 ± 0.4 Range: 0.0 – 3.0 (n=333)	0.03 (-0.05, 0.11)
Median Return to Work Time (days)	40	60	42	N/A

Table 26 summarizes the PRESTIGE® LP Device implanted by size and level.

Table 26: All PRESTIGE® LP Devices Implanted by Size and Level

	PRESTIGE® LP IDE Cohort					PRESTIGE® LP Safety Cohort				
	C3-C4	C4-C5	C5-C6	C6-C7	Total	C3-C4	C4-C5	C5-C6	C6-C7	Total
6mm x 12mm Disc (%)	1	4	15	11	**31 (11.1%)**	1	8	28	12	**49(14.7%)**
6mm x 14mm Disc (%)	1	10	65	37	**113 (40.4%)**	1	13	76	42	**132 (39.6%)**
6mm x 16mm Disc (%)	2	1	35	23	**61 (21.8%)**	2	1	37	23	**63 (18.9%)**
6mm x 18mm Disc (%)	0	0	0	0	**0 (0.0%)**	0	0	0	0	**0 (0.0%)**
7mm x 12mm Disc (%)[24]	0	0	1	1	**2 (0.7%)**	0	0	1	2	**3 (0.9%)**
7mm x 14mm Disc (%)	0	2	5	8	**15 (5.4%)**	0	2	9	11	**22 (6.6%)**
7mm x 16mm Disc (%)	0	4	16	9	**29 (10.4%)**	0	4	17	12	**33 (9.9%)**
7mm x 18mm Disc (%)	0	0	9	11	**20 (7.1%)**	0	0	9	11	**20 (6.0%)**
8mm x 12mm Disc (%)	0	0	0	0	**0 (0.0%)**	0	0	0	0	**0 (0.0%)**
8mm x 14mm Disc (%)	0	0	0	3	**3 (1.1%)**	0	0	0	4	**4 (1.2%)**
8mm x 16mm Disc (%)	0	0	1	4	**5 (1.8%)**	0	0	1	5	**6 (1.8%)**
8mm x 18mm Disc (%)	0	0	0	1	**1 (0.4%)**	0	0	0	1	**1 (0.3%)**
Total (%)	**4 (1.4%)**	**21 (7.5%)**	**147 (52.5%**	**108 (38.6%)**	**280 (100.0%)**	**4 (1.2)**	**28 (8.4%)**	**178 (53.5%)**	**123 (36.9%)**	**333 (100.0%)**

[23] BCI = Bayesian HPD Credible Interval

[24] The 7mm x 12mm PRESTIGE® LP Cervical Disc was a part of the size offerings in the IDE study, but is not a part of the size offerings available for market.

2. Effectiveness Results

Primary Effectiveness Analysis

The effectiveness variables represent those measurements that describe the clinical outcomes of the study subjects. Again, the primary endpoint is a composite endpoint that takes into account the success of NDI, Neurological Status, FSU height and the absence of serious implant related adverse events or secondary surgeries. Additional secondary endpoints include radiographic success, indicators of pain relief, general health status, and doctor and subject perceptions of outcomes. Further details are discussed in the Study Design section. **Please note that this was a non-randomized study with a historical control.**

Study success was expressed as the number of individual subjects categorized as a success divided by the total number of subjects evaluated. **Table 27** below describes the observed success rates and Bayesian analyses for individual outcome parameters and overall success. Observed success rates are the 24-month outcomes of the clinical trial. Posterior means for each group can be interpreted as the average chance of success at 24 months, and the posterior mean of the difference can be interpreted as the average difference in the chance of success at 24 months. When a subject receives the PRESTIGE® LP device, the average chance of overall success (without FSU) as defined in the clinical study at 24 months is 78.9%. Given the results of the trial, there is a 95% probability that the chance of success ranges from 74.1% to 84.0%. When a subject receives the control treatment, the average chance of overall success (without FSU) at 24 months is 67.8%. Given the results of the trial, there is a 95% probability that the chance of success ranges from 61.2% to 74.0%. The average difference in the change of success (without FSU) between the IDE cohort and the ACDF control is 11.1% with 95% probability that this difference will fall in range of 2.7% to 19.6%. For overall success (without FSU) the posterior probability of non-inferiority of the IDE cohort to the ACDF control group is essentially 100%, reaching the primary objective.

All success probabilities were for the 24-month outcomes, and posterior probabilities of success were calculated using Bayesian statistical methods and are presented in **Table 27**.

Table 27: Observed Success Rates and Posterior Probabilities of Success at 24 Months

Primary Outcome Variable	24-Month Observed Success Rate		24-Month Posterior Mean (95% HPD Credible Interval)			24-Month Posterior Probabilities (IDE vs Control)	
	IDE Cohort	ACDF Control	IDE Cohort	ACDF Control	IDE Cohort – ACDF Control	Non-Inferiority	Superiority
NDI	237/270 (87.8%)	177/219 (80.8%)	87.2% (83.1%, 91.2%)	82.4% (77.0%, 87.5%)	4.8% (-2.0%, 11.8%)	~100.0%	91.2%
Neurological Status	252/270 (93.3%)	184/220 (83.6%)	93.4% (90.3%, 96.2%)	83.6% (78.2%, 88.5%)	9.9% (3.8%, 16.1%)	~100.0%	99.9%
FSU	205/224 (91.5%)	156/164 (95.1%)	91.7% (87.8%, 95.2%)	95.1% (91.6%, 98.3%)	-3.4% (-8.5%, 2.1%)	99.2%	9.7%
Overall Success (without FSU)[25]	215/271 (79.3%)	147/220 (66.8%)	78.9% (74.1%, 84.0%)	67.8% (61.2%, 74.0%)	11.1% (2.7%, 19.6%)	~100.0%	99.5%
Overall Success (with FSU)[26]	159/226 (70.4%)	108/171 (63.2%)	68.9% (62.7, 75.1%)	65.7% (58.3%, 73.4%)	3.2% (-7.0%, 13.4%)	99.5%	73.6%

Statistical superiority of the PRESTIGE® LP Cervical Disc group was demonstrated for overall success (when not including FSU data) and the neurological component for the population studied in the clinical trial at 24 months postoperatively since the posterior probability of superiority for both endpoints are over 99.0%, exceeding the threshold of 95.0%. With FSU data included, the average chance of overall success, as defined in the clinical study at 24 months, is 68.9%. These results are lower than the 78.9% success rate recorded for the investigational device after expluding FSU data. Given the results of the trial, there is a 95% probability that the chance of success ranges from 62.7% to 75.1%. However, the average chance of success for the control group (with FSU) is also lower, at 65.7%, with a 95% probability that the chance of success ranges from 58.3% to 73.4%. The average difference in the chance of success between the IDE cohort and the ACDF control group is 3.2% with 95% probability that this difference will fall in range of -7.0% to 13.4%. Thus, while the rates of success were lower for the investigational device when including FSU data, the success rates were also lower for the control group, and the probability of non-inferiority for the investigational device was statistically achieved. Therefore, it can be stated that the investigational device is statistically non-inferior to the control procedure as the posterior probability of non-inferiority is 99.5% regardless of the inclusion or exclusion of the FSU criteria in the composite success endpoint.

The NDI, FSU, and overall success (with FSU) variables were found to be statistically non-inferior at 24 months postoperatively. **Table 28** provides data on the time course of success rates for both treatment groups.

[25] A success is a patient who had successes in NDI and neurological status and had no additional surgery classified as 'failure' and no severe device or device/surgery associated adverse event.

[26] A success is a patient who had successes in NDI, neurological status, and FSU and had no additional surgery classified as 'failure' and no severe device or device/surgery associated adverse event.

Table 28: Time Course of Observed Success Rates

Primary Outcome Variable	3-Month Observed Success Rate		6-Month Observed Success Rate		12-Month Observed Success Rate		24-Month Observed Success Rate	
	IDE Cohort	ACDF Control	IDE Cohort	ACDF Control	IDE Cohort	ACDF Control	IDE Cohort	ACDF Control
NDI	241/276 (87.3%)	174/235 (74.0%)	241/271 (88.9%)	173/224 (77.2%)	241/272 (88.6%)	176/222 (79.3%)	237/270 (87.8%)	177/219 (80.8%)
Neurological Status	257/276 (93.1%)	210/241 (87.1%)	254/270 (94.1%)	205/228 (89.9%)	257/272 (94.5%)	194/226 (85.8%)	252/270 (93.3%)	184/220 (83.6%)
FSU	229/235 (97.4%)	182/182 (100%)	227/230 (98.7%)	174/175 (99.4%)	225/233 (96.6%)	164/172 (95.3%)	205/224 (91.5%)	156/164 (95.1%)
Overall Success (without FSU) [27]	223/277 (80.5%)	154/239 (64.4%)	224/271 (82.7%)	158/224 (70.5%)	227/274 (82.8%)	150/223 (67.3%)	215/271 (79.3 %)	147/220 (66.8%)
Overall Success (with FSU) [28]	187/238 (78.6%)	113/181 (62.4%)	189/233 (81.1%)	119/174 (68.4%)	187/234 (79.9%)	110/173 (63.6%)	159/226 (70.4 %)	108/171 (63.2 %)

Table 29 provides overall success data for each treatment group stratified by the treated level including post-hoc statistical analysis and comparisons between the PRESTIGE® LP IDE Cohort and the ACDF Control group through the 24-month time point using Frequentist methods. Overall success rates (without FSU) were not significantly different between the PRESTIGE® LP IDE Cohort and ACDF Control group at any treatment level except for at the C6-C7 level, in which the IDE cohort had a significantly higher success rate compared to the control group. Overall success rates (with FSU) at 24 months were not significantly different between the IDE cohort and control group at any treatment level.

[27] A success is a patient who had successes in NDI and neurological status and had no additional surgery classified as 'failure' and no severe device or device/surgery associated adverse event.

[28] A success is a patient who had successes in NDI, neurological status, and FSU and had no additional surgery classified as 'failure' and no severe device or device/surgery associated adverse event.

Table 29: Overall Success by Level Treated at 24 Months

	PRESTIGE® LP IDE Cohort (N = 280)	**ACDF Control (N = 265)**	**Point Estimate and 95% Confidence Interval[29] of Difference of Success Rate between IDE Cohort and ACDF Control Cohort**
Overall Success (without FSU) [30]			
• C3-C4	• 3/4 (75.0%)	• 4/8 (50.0%)	• 25.0% (-34.2%, 84.2%)
• C4-C5	• 16/20 (80.0%)	• 6/11 (54.5%)	• 25.5% (-7.9%, 58.9%)
• C5-C6	• 106/140 (75.7%)	• 84/125 (67.2%)	• 8.5% (-2.4%, 19.4%)
• C6-C7	• 90/107 (84.1%)	• 53/76 (69.7%)	• 14.4% (2.2%, 26.5%)
Overall Success (with FSU) [31]			
• C3-C4	• 2/3 (66.7%)	• 4/5 (80.0%)	• -13.3% (-75.3%, 48.6%)
• C4-C5	• 12/19 (63.2%)	• 5/10 (50.0%)	• 13.2% (-24.6%, 50.9%)
• C5-C6	• 93/133 (69.9%)	• 72/115 (62.6%)	• 7.3% (-4.5%, 19.1%)
• C6-C7	• 52/71 (73.2%)	• 27/41 (65.9%)	• 7.3% (-10.1%, 24.9%)

Sensitivity Analyses

A number of sensitivity analyses were conducted for the endpoints listed in **Table 27**, including

- A per-protocol analysis
- Using propensity score classification instead of propsensity score as the covariate in the logistic regression model, and
- A "missing equal to failure" analysis

Additional sensitivity analyses were conducted with each of the following conditions:

- All Missing Data = Success
- Last Observation Carried Forward (Assumes no change from the last outcome measurement)
- Worst Case (All missing investigational data = failure and all missing control data = success)
- Multiple Imputation

All sensitivity analyses demonstrate high probability that the investigational device was non-inferior to the control group.

[29] The 95% CI was provided using Frequentist Farrington and Manning methods

[30] A success is a patient who had successes in NDI and neurological status and had no additional surgery classified as 'failure' and no severe device or device/surgery associated adverse event.

[31] A success is a patient who had successes in NDI, neurological status, and FSU and had no additional surgery classified as 'failure' and no severe device or device/surgery associated adverse event.

A per-protocol analysis and missing equals failure analysis were also performed. The "per protocol" dataset was a subset of subjects who were included in the primary analysis dataset. Subjects who were excluded from the "per protocol" analysis had major protocol deviations, i.e., did not meet the inclusion/exclusion criteria or received the wrong study treatment, or other major protocol deviations that could potentially affect clinical outcomes.

The statistical comparison for the "per protocol" dataset yielded a posterior probability of non-inferiority of ≥ 95% for each of the individual components as well as the overall success calculations. The comparison also yielded a posterior probability of superiority of ≥ 95% for the neurological component and the overall success without FSU. The posterior probability of superiority of overall success with FSU was 76.7%.

For the "missing-equals-failure" data, secondary surgery failures, deaths, subjects lost-to-follow-up, and missing observations due to other causes resulted in missing observations for the outcome variables and, therefore, were included in the denominators of the calculated rates, i.e., considered as "failures." By including these subjects in the treatment failures group, the primary endpoint success rates in the "missing-equals-failure" analyses were lower than those observed in the primary analysis. The overall failure rates for the Investigational group including FSU data were very high, at 43.6%. However, the overall success rates of this group were still notably higher than those of the Control group, being 56.4% as compared to 40.8%. Therefore, results of this sensitivity analysis continue to support the effectiveness of the PRESTIGE® LP treatment.

For the sensitivity analysis using propensity score classification in the logistic regression model, similar results were achieved. The Bayesian analysis yielded a posterior probability of non-inferiority of essentially 100% for all the endpoints listed in **Table 26**. The comparison also yielded a posterior probability of superiority of ≥ 95% for the neurological success (essentially 100%) and overall success without FSU (99.5%).

Poolability Analysis

Analyses were also conducted to assess the poolability of data across sites, though there were limitations due to the nature of the study. Because the study conducted was a single arm study with historical control, treatment differences by site could in general not be assessed. However, the Breslow-Day test was conducted for the sites that were involved with both the PRESTIGE® LP and the historical control study. No correlation was found between the treatment outcome and sites.

Subgroup Analysis by Race

Overall success data stratified by subject race at the 24-month time point are also provided in **Table 30**. Due to the relatively small numbers of non-Caucasians treated in the IDE, statistical conclusion for outcomes based on race cannot be reliably made and will be evaluated further as part of an Enhanced Surveillance Study the applicant will conduct for 10 years postmarket.

Table 30: Overall Success by Subject Race at 24 months

Overall Success	PRESTIGE® LP IDE Cohort		ACDF Control		PRESTIGE® LP Safety Cohort	
	Caucasian (N = 271)	Non-Caucasian (N = 9)	Caucasian (N = 243)	Non-Caucasian (N = 22)	Caucasian (N = 320)	Non-Caucasian (N = 13)
Overall Success (without FSU) [32]	209/263 (79.5%)	6/8 (75.0%)	140/205 (68.3%)	7/15 (46.7%)	248/311 (79.7%)	10/12 (83.3%)
Overall Success (with FSU) [33]	155/219 (70.8%)	4/7 (57.1%)	103/159 (64.8%)	5/12 (41.7%)	190/262 (72.5%)	8/11 (72.7%)

Secondary Effectiveness Analysis

Results of Secondary Effectiveness Variables

Table 31 describes the results of the secondary effectiveness endpoints at 24 months.

Table 31: Secondary Endpoints and Other Measurements[34]

	24-Month Observed Success Rate		24-Month Posterior Mean (95% HPD Credible Interval)		
Variable	PRESTIGE ® LP IDE Cohort	ACDF Control	IDE Cohort	ACDF Control	IDE Cohort – ACDF Control
Neck pain					
Success	260 (96.3%)	213 (97.3%)	96.4%	97.3%	-1.0%
Failure	10 (3.7%)	6 (2.7%)	(94.0%, 98.4%)	(95.1%, 99.2%)	(-4.3%, 2.3%)
Arm pain					
Success	258 (96.3%)	208 (95.0%)	96.7%	94.7%	1.9%
Failure	10 (3.7%)	11 (5.0%)	(94.4%, 98.6%)	(91.6%, 97.5%)	(-1.8%, 5.8%)
SF-36 PCS					
Success	221 (83.7%)	186 (86.1%)	82.8%	87.6%	-4.7%
Failure	43 (16.3%)	30 (13.9%)	(78.0%, 87.4%)	(82.7%, 91.8%)	(-11.3%, 2.1%)
SF-36 MCS					
Success	205 (77.7%)	150 (69.4%)	78.7%	68.2%	10.5%
Failure	59 (22.3%)	66 (30.6%)	(73.5%, 83.6%)	(61.7%, 74.7%)	(2.0%, 19.0%)
Patient Perceived Effect					
Complete recovery	127 (47.0%)	88 (40.2%)			
Much improved	107 (39.6%)	89 (40.6%)	Not Available[38]	Not Available[38]	Not Available[38]
Doctor Perception					
Excellent	194 (71.6%)	125 (56.8%)			
Good	62 (22.9%)	69 (31.4%)	Not Available[38]	Not Available[38]	Not Available[38]
Gait					
Success	268 (99.3%)	219 (99.5%)			
Failure	2 (0.7%)	1 (0.5%)	Not Available[38]	Not Available[38]	Not Available[38]
Work Status					
Median days until return to work	40	60	Not Available[38]	Not Available[38]	Not Available[38]

[32] A success is a subject who had successes in NDI and neurological status and had no additional surgery classified as 'failure' and no severe device or device/surgery associated adverse event.

[33] A success is a subject who had successes in NDI, neurological status, and FSU and had no additional surgery classified as 'failure' and no severe device or device/surgery associated adverse event.

[34] Patient accounting in this table is affected by subjects lost of follow up and/or missing data.

Neck Disability Index

The time course of NDI improvement is presented in **Table 32**. The table indicates that the investigational group improvement rates at all postoperative periods were greater than the corresponding control group rates.

Table 32: Time Course of Neck Disability Index Improvement

Time Point	NDI Improvement[35]	PRESTIGE® LP IDE Cohort (N = 280)	ACDF Control (N = 265)
6 Weeks	Improved (≥ 15 pts)	215 (77.6%)	168 (68.6%)
	Maintained (-15, 15)	59 (21.3%)	72 (29.4%)
	Deteriorated (≤ -15 pts)	3 (1.1%)	5 (2.0%)
3 Months	Improved (≥ 15 pts)	241 (87.3%)	174 (74.0%)
	Maintained (-15, 15)	33 (12.0%)	59 (25.1%)
	Deteriorated (≤ -15 pts)	2 (0.7%)	2 (0.9%)
6 Months	Improved (≥ 15 pts)	241 (88.9%)	173 (77.2%)
	Maintained (-15, 15)	27 (10.0%)	50 (22.3%)
	Deteriorated (≤ -15 pts)	3 (1.1%)	1 (0.4%)
12 Months	Improved (≥ 15 pts)	241 (88.6%)	176 (79.3%)
	Maintained (-15, 15)	29 (10.7%)	44 (19.8%)
	Deteriorated (≤ -15 pts)	2 (0.7%)	2 (0.9%)
24 Months	Improved (≥ 15 pts)	237 (87.8%)	177 (80.8%)
	Maintained (-15, 15)	31 (11.5%)	40 (18.3%)
	Deteriorated (≤ -15 pts)	2 (0.7%)	2 (0.9%)

[35] If pre-op NDI minus post-op NDI ≥ 15 points then it is considered "Improved"; if -15 points < pre-op NDI minus post-op NDI < 15 points, then it is considered as "Maintained"; if pre-op NDI minus post-op NDI ≤ -15 points then it is considered as "Deteriorated".

VAS Neck and Arm Pain

The time course of neck and arm pain improvement is presented in **Table 33**. The improvement rates for the PRESTIGE® LP IDE Cohort and ACDF control group were similar at all postoperative time periods. At the 24-month primary endpoint, the investigational group had greater neck and arm pain improvement rates than the corresponding control rates.

Table 33: Time Course of Neck and Arm Pain Improvement

Time Point	Variable	PRESTIGE® LP IDE Cohort (N =280)	ACDF Control (N = 265)
6 Weeks	Neck Pain		
	Improved (≥ 20%)	259 (93.5%)	230 (93.9%)
	Maintained (-20%, 20%)	11 (4.0%)	8 (3.3%)
	Deteriorated (≤ -20%)	7 (2.5%)	7 (2.9%)
	Arm Pain		
	Improved (≥ 20%)	250 (90.3%)	218 (89.0%)
	Maintained (-20%, 20%)	19 (6.9%)	18 (7.3%)
	Deteriorated (≤ -20%)	8 (2.9%)	9 (3.7%)
3 Months	Neck Pain		
	Improved (≥ 20%)	266 (96.4%)	220 (93.2%)
	Maintained (-20%, 20%)	6 (2.2%)	11 (4.7%)
	Deteriorated (≤ -20%)	4 (1.4%)	5 (2.1%)
	Arm Pain		
	Improved (≥ 20%)	250 (90.6%)	209 (88.6%)
	Maintained (-20%, 20%)	17 (6.2%)	18 (7.6%)
	Deteriorated (≤ -20%)	9 (3.3%)	9 (3.8%)
6 Months	Neck Pain		
	Improved (≥ 20%)	256 (94.8%)	203 (91.4%)
	Maintained (-20%, 20%)	8 (3.0%)	16 (7.2%)
	Deteriorated (≤ -20%)	6 (2.2%)	3 (1.4%)
	Arm Pain		
	Improved (≥ 20%)	244 (90.0%)	195 (87.8%)
	Maintained (-20%, 20%)	14 (5.2%)	13 (5.9%)
	Deteriorated (≤ -20%)	13 (4.8%)	14 (6.3%)
12 Months	Neck Pain		
	Improved (≥ 20%)	252 (92.0%)	196 (88.7%)
	Maintained (-20%, 20%)	17 (6.2%)	17 (7.7%)
	Deteriorated (≤ -20%)	5 (1.8%)	8 (3.6%)
	Arm Pain		
	Improved (≥ 20%)	251 (91.6%)	188 (85.5%)
	Maintained (-20%, 20%)	11 (4.0%)	18 (8.2%)
	Deteriorated (≤ -20%)	12 (4.4%)	14 (6.4%)
24 Months	Neck Pain		
	Improved (≥ 20%)	251 (93.0%)	201 (91.8%)
	Maintained (-20%, 20%)	13 (4.8%)	14 (6.4%)
	Deteriorated (≤ -20%)	6 (2.2%)	4 (1.8%)
	Arm Pain		
	Improved (≥ 20%)	244 (91.0%)	193 (88.1%)
	Maintained (-20%, 20%)	16 (6.0%)	17 (7.8%)
	Deteriorated (≤ -20%)	8 (3.0%)	9 (4.1%)

SF-36

The Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) was used to assess general health status of all study subjects. **Table 34** presents the improvement rates of the Physical Component Score (PCS) and Mental Component Score (MCS) for the different study periods. As shown in the table, the improvement rates in PCS and MCS compared favorably to those values of the control group at each time period except for MCS at 6 months. Additionally, all mean postoperative scores were higher than the preoperative scores for both treatment groups.

Table 34: Time Course of SF-36 Health Survey Improvement

Time Point	Variable	PRESTIGE® LP IDE Cohort (N = 280)	ACDF Control (N = 265)
6 Months	PCS		
	Improved (≥ 15%)	213 (80.1%)	143 (65.0%)
	Maintained (-15%, 15%)	42 (15.8%)	62 (28.2%)
	Deteriorated (≤ -15%)	11 (4.1%)	15 (6.8%)
	MCS		
	Improved (≥ 15%)	117 (44.0%)	104 (47.3%)
	Maintained (-15%, 15%)	124 (46.6%)	93 (42.3%)
	Deteriorated (≤ -15%)	25 (9.4%)	23 (10.5%)
12 Months	PCS		
	Improved (≥ 15%)	221 (82.2%)	150 (68.2%)
	Maintained (-15%, 15%)	38 (14.1%)	56 (25.5%)
	Deteriorated (≤ -15%)	10 (3.7%)	14 (6.4%)
	MCS		
	Improved (≥ 15%)	127 (47.2%)	100 (45.5%)
	Maintained (-15%, 15%)	118 (43.9%)	93 (42.3%)
	Deteriorated (≤ -15%)	24 (8.9%)	27 (12.3%)
24 Months	PCS		
	Improved (≥ 15%)	198 (75.0%)	154 (71.3%)
	Maintained (-15%, 15%)	52 (19.7%)	49 (22.7%)
	Deteriorated (≤ -15%)	14 (5.3%)	13 (6.0%)
	MCS		
	Improved (≥ 15%)	131 (49.6%)	103 (47.7%)
	Maintained (-15%, 15%)	109 (41.3%)	83 (38.4%)
	Deteriorated (≤ -15%)	24 (9.1%)	30 (13.9%)

Patient Satisfaction

At each postoperative time period, subjects were asked to evaluate their overall impression of their study treatment effectiveness as a function of pain. The seven possible answers ranged from "completely recovered" to "vastly worsened". The results to this question are provided in **Table 35**. At 12 and 24 months following surgery, 86.1% and 86.6%, respectively, of the PRESTIGE® LP IDE subjects indicated that they had either "completely recovered" or were "much improved". These rates were higher than the 74.9% and 80.8% rates, respectively, for the ACDF control group.

Table 35: Time Course of Patient Perceived Effect

	Variable	PRESTIGE® LP IDE Cohort (N=280)	ACDF Control (N=265)
6 Weeks	Complete Recovery	54/277 (19.5%)	33/244 (13.5%)
	Much Improved	173/277 (62.5%)	151/244 (61.9%)
3 Months	Complete Recovery	76/275 (27.6%)	47/236 (19.9%)
	Much Improved	162/275 (58.9%)	129/236 (54.7%)
6 Months	Complete Recovery	101/271 (37.3%)	57/225 (25.3%)
	Much Improved	131/271 (48.3%)	122/225 (54.2%)
12 Months	Complete Recovery	123/274 (44.9%)	75/223 (33.6%)
	Much Improved	113/274 (41.2%)	92/223 (41.3%)
24 Months	Complete Recovery	127/270 (47.0%)	88/219 (40.2%)
	Much Improved	107/270 (39.6%)	89/219 (40.6%)

Physician Perception of Results

At each postoperative visit, the doctors were asked to provide their perceptions of the subjects' conditions. The responses could be "excellent", "good", "fair", or "poor". The results to this question are provided in **Table 36**. At 12 months following surgery, 93.8% of the doctors responded that the PRESTIGE® LP IDE Cohort subjects were in "excellent" or "good" condition. This rate is higher than the 87.5% value for the ACDF control group. Similarly, at 24 months postoperative, 94.5% of the physicans' perception responses to the IDE cohort results and 88.2% of their responses to the control results were either "excellent" or "good".

Table 36: Time Course of Doctor's Perception of Results

	Variable	PRESTIGE® LP IDE Cohort (N=280)	ACDF Control (N=265)
6 Weeks	Excellent	173/278 (62.2%)	108/254 (42.5%)
	Good	87/278 (31.3%)	130/254 (51.2%)
3 Months	Excellent	182/276 (65.9%)	106/237 (44.7%)
	Good	80/276 (29.0%)	116/237 (48.9%)
6 Months	Excellent	192/271 (70.8%)	98/229 (42.8%)
	Good	61/271 (22.5%)	110/229 (48.0%)
12 Months	Excellent	202/273 (74.0%)	109/224 (48.7%)
	Good	54/273 (19.8%)	87/224 (38.8%)
24 Months	Excellent	194/271 (71.6%)	125/220 (56.8%)
	Good	62/271 (22.9%)	69/220 (31.4%)

Gait

Assessments of subjects' gaits were made preoperatively and postoperatively using Nurick's classification[3]. Preoperatively 93.6% of the investigational subjects and 76.9% of the control subjects had "normal" gait scores. These values climbed postoperatively, with 99.3% of the investigational subjects and 96.4% of the control subjects having "normal" values at 24 months following surgery. The gait assessment outcomes for each postoperative study period are given in **Table 37**.

Table 37: Time Course of Gait Assessment Results

	Variable	PRESTIGE® LP IDE Cohort (N=280)	ACDF Control (N=265)
Preoperative	Normal	262 (93.6%) (N=280)	203 (76.9%) (N=264)
6 Weeks	Normal	276 (99.3%) (N=278)	242 (95.7%) (N=253)
3 Months	Normal	275 (99.6%) (N=276)	231 (95.9%) (N=241)
6 Months	Normal	268 (98.9%) (N=271)	220 (96.5%) (N=228)
12 Months	Normal	271 (99.3%) (N=273)	216 (96.0%) (N=225)
24 Months	Normal	268 (99.3%) (N=270)	212 (96.4%) (N=220)

Radiographic Assessments

The safety of the PRESTIGE® LP Disc was assessed by monitoring intraoperative and postoperative complications. Radiographs were examined for device subsidence, functional spinal unit (FSU) height maintenance, device migration and breakage. All radiographic endpoints were evaluated independently by a core laboratory and reviewed by independent radiographic reviewers. In addition, some radiographic observations reported by investigators, such as implant malposition, were handled as adverse events.

Table 38 shows radiographic success rates for the PRESTIGE® LP subjects with evaluable radiographic data (n=264) at the 24 month follow up time point. Data on the control devices are not presented because of the differences in radiographic success criteria between the investigational and control groups.

Table 38: Radiographic Success

24 Months PRESTIGE® LP	Angular Motion >4° to ≤20°	No Bridging Bone	Overall Radiographic Success
IDE Subjects			
Success (%)	181 (68.6%)	253 (94.1%)	179 (67.8%)
Failure (%)	83 (31.4%)	16 (5.9%)	85 (32.2%)
	(n=264)	(n=269)	(n=264)_
CA + MI Subjects			
Success (%)	42 (79.2%)	51 (96.2%)	41 (77.4%)
Failure (%)	11 (20.8%)	2 (3.8%)	12 (22.6%)
	(n=53)	(n=53)	(n=53)
Safety Cohort			
Success (%)	222 (70.3%)	303 (94.4%)	219 (69.3%)
Failure (%)	94 (29.7%)	18 (5.6%)	97 (30.7%)
	(n=316)	(n=321)	(n=316)

The range of motion values measured from flexion/extension radiographs at 24 months for the PRESTIGE® LP Cervical Disc subjects are presented in the histogram below. This histogram uses values obtained by rounding the recorded range of motion for each subject to the nearest integer.

Figure 1: Histogram of PRESTIGE® LP Cervical Disc Angular Range of Motion at 24 months

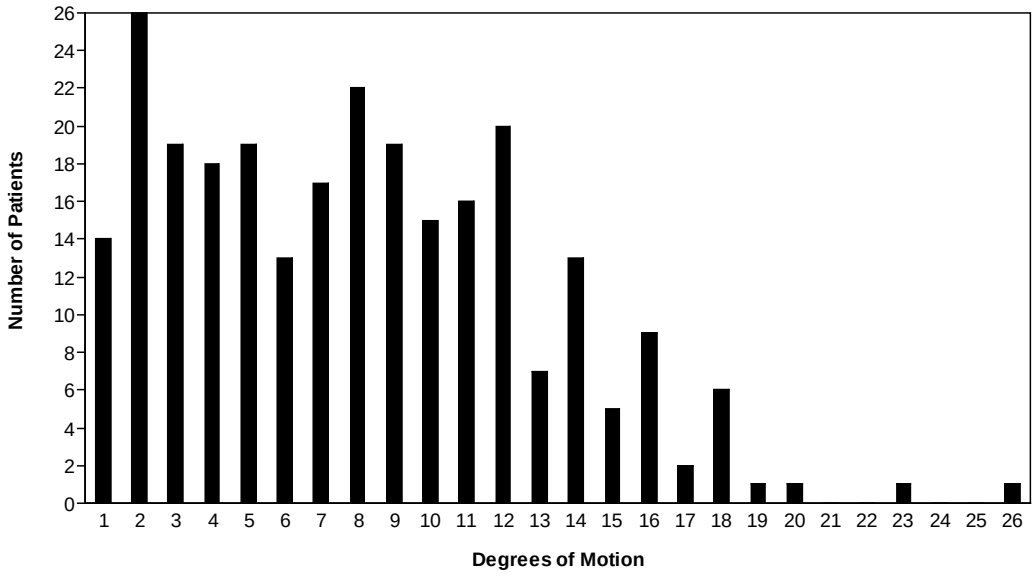

Table 39 describes the results of the angular motion, translational motion, and lateral bending.

Table 39: Time Course of Radiographic Range of Motion

Time Point	Variable	PRESTIGE® LP IDE Cohort (N =280)	ACDF Control (N=265)
Preoperative	ROM Angulation (º)	5.67° ± 3.69° Range: 0.27° - 18.10°	7.87° ± 4.32° Range: 0.74° - 21.34°
	ROM Translation (mm)	N/A	0.26mm ± 0.25mm Range: 0.00mm – 1.64mm
	Lateral Bending (º)	N/A	N/A
6 Weeks	ROM Angulation (º)	6.88° ± 3.79° Range: 0.45° - 21.27°	0.53°±1.94° Range: 0.04° - 23.10°
	ROM Translation (mm)	0.90mm ± 0.58mm Range: 0.00mm – 2.98mm	0.16mm ± 0.12mm Range: 0.00mm – 0.66mm
	Lateral Bending (º)	6.25 ° ± 3.06° Range: 0.35° - 16.55°	N/A
3 Months	ROM Angulation (º)	7.51° ± 4.05° Range: 0.10° - 19.45°	0.33° ± 0.34° Range: 0.01° - 2.71°
	ROM Translation (mm)	0.99mm ± 0.59mm Range: 0.00mm – 2.91mm	0.15mm ± 0.13mm Range: 0.00mm – 0.84mm
	Lateral Bending (º)	6.60° ± 3.34° Range: 0.27° - 15.83°	N/A
6 Months	ROM Angulation (º)	7.47° ± 4.46° Range: 0.23° - 21.03°	0.31°± 0.23° Range: 0.01° - 2.36°
	ROM Translation (mm)	0.96mm ± 0.59mm Range: 0.00mm – 3.15mm	0.20mm ± 0.62mm Range: 0.00 – 8.69mm
	Lateral Bending (º)	6.78° ± 3.58° Range: 0.33° - 16.60°	N/A
12 Months	ROM Angulation (º)	7.85° ± 4.32° Range: 0.34° - 19.75°	0.33° ± 0.30° Range: 0.02° - 3.09°
	ROM Translation (mm)	0.97mm ± 0.67mm Range: 0.00mm – 3.65mm	0.15mm ± 0.12mm Range: 0.00mm – 0.61mm
	Lateral Bending (º)	6.58° ± 3.75° Range: 0.36° - 17.52°	N/A
24 Months	ROM Angulation (º)	7.51° ± 4.87° Range: 0.19° - 26.43°	0.35° ± 0.33° Range: 0.02° - 3.42°
	ROM Translation (mm)	1.03mm ± 0.70mm Range: 0.00mm – 3.71mm	0.15mm ± 0.13mm Range: 0.00mm ± 0.60mm
	Lateral Bending (º)	6.15° ± 3.81° Range: 0.04° - 18.17°	N/A

Table 40 presents data on change in range of motion from the preoperative baseline for each time point by treatment group.

Table 40: Time Course of Radiographic Change in Range of Motion

Time Point	Change in Angular Range of Motion	PRESTIGE® LP IDE Cohort (N =280)	ACDF Control (N=265)
6 Weeks	Increased (≥2º)	120 (48.0%)	2 (1.4%)
	No Change(-2º to 2º)	70 (28.0%)	5 (3.4%)
	Decreased ≤-2º)	60 (24.0%)	138 (95.2%)
3 Months	Increased (≥2º)	128 (51.0%)	0 (0.0%)
	No Change(-2º to 2º)	71 (28.3%)	10 (6.4%)
	Decreased ≤-2º)	52 (20.7%)	146 (93.6%)
6 Months	Increased (≥2º)	119 (49.2%)	0 (0.0%)
	No Change(-2º to 2º)	72 (29.8%)	8 (5.3%)
	Decreased ≤-2º)	51 (21.1%)	144 (94.7%)
12 Months	Increased (≥2º)	131 (52.4%)	0 (0.0%)
	No Change(-2º to 2º)	71 (28.4%)	5 (3.5%)
	Decreased ≤-2º)	48 (19.2%)	138 (96.5%)
24 Months	Increased (≥2º)	118 (48.2%)	0 (0.0%)
	No Change(-2º to 2º)	68 (27.8%)	7 (5.0%)
	Decreased ≤-2º)	59 (24.1%)	134 (95.0%)

Available radiographs for the PRESTIGE® LP study subjects were assessed for bridging bone (Criteria was comparable to Class IV assessment on the McAfee[1] and Mehren[2] classification system for Heterotopic Ossification) between the vertebral bodies of the implanted motion segment. Bridging was defined as evidence of a continuous bony connection from the superior vertebral body to the inferior vertebral body laterally, anteriorly, and/or posteriorly. The radiographic results are shown in **Table 41**. More than 90% of the PRESTIGE® LP IDE subjects displayed no signs of bridging bone at each time point, with 94.1% of the subjects exhibiting no bridging bone at 24 months.

Table 41: Time Course of Bridging Bone

	Bridging Bone	PRESTIGE® LP IDE Cohort (N = 280)
6 Weeks	No	278 (100.0%)
	Yes	0 (0%)
3 Months	No	274 (99.6%)
	Yes	1 (0.4%)
6 Months	No	268 (99.3%)
	Yes	2 (0.7%)
12 Months	No	269 (98.2%)
	Yes	5 (1.8%)
24 Months	No	253 (94.1%)
	Yes	16 (5.9%)

The percentage of PRESTIGE® LP subjects with range of motion >4º and ≤ 20º for subjects with and without bridging bone at 24 months is described in **Table 42**.

Table 42: Range of Motion (ROM) at 24 Months by Subjects with Bridging Bone

	PRESTIGE® LP IDE Cohort			**PRESTIGE® LP Safety Cohort**		
	No Bridging Bone (N=253)	Bridging Bone (N=16)	Total (N=269)	No Bridging Bone (N=303)	Bridging Bone (N=18)	Total (N=321)
Subjects w/ 4º < ROM ≤ 20º	179/248 (72.2%)	2/16 (12.5%)	181/264 (68.6%)	219/298 (73.5%)	3/18 (16.7%)	222/316 (70.3%)
% Subjects ROM ≤ 4º	67/248 (27.0%)	14/16 (87.5%)	81/264 (30.7%)	77/298 (25.8%)	15/18 (83.3%)	92/316 (29.1%)
% Subjects ROM > 20º	2/248 (0.8%)	0/16 (0.0%)	2/264 (0.8%)	2/298 (0.7%)	0/18 (0.0%)	2/316 (0.6%)

An analysis of the correlation between the degree of segmental motion, NDI, neck, and arm pain scores was also performed, and statistically significant correlations were noted, but the magnitudes of the correlations were small.

Table 43 summarizes the effect of the PRESTIGE® LP device on adjacent levels.

Table 43: Adjacent Level Measurements Angular Motion

Time Point	Variable	PRESTIGE® LP IDE Cohort (N =280)	ACDF Control (N=265)
Pre-operative	Level Above Treated Segment (Mean)	8.51° ± 4.13° Range: 1.12° - 22.44°	10.77° ± 4.71° Range: 0.84° - 24.54°
	Level Below Treated Segment (Mean)	6.09° ± 4.02° Range: 0.32° - 18.47°	7.77° ± 4.17° Range: 0.58° - 19.05°
6 Weeks	Level Above Treated Segment (Mean)	7.83° ± 3.82° Range: 0.89° - 23.05°	9.66° ± 3.75° Range: 1.20° - 23.63°
	Level Below Treated Segment (Mean)	5.68° ± 3.76° Range: 0.09° - 17.55°	8.22° ± 4.51° Range: 0.57° - 19.11°
3 Months	Level Above Treated Segment (Mean)	8.82° ± 3.95° Range: 0.41° - 20.93°	11.03° ± 4.11° Range: 1.86° - 24.99°
	Level Below Treated Segment (Mean)	6.25° ± 3.99° Range: 0.39° - 18.28°	9.24° ± 4.64° Range: 0.86° - 20.04°
6 Months	Level Above Treated Segment (Mean)	9.35° ± 4.31° Range: 0.93° - 24.45°	11.33° ± 4.49° Range: 1.56° - 22.95°
	Level Below Treated Segment (Mean)	6.63° ± 4.31° Range: 0.18° - 21.75°	8.71° ± 4.73° Range: 0.72° - 22.45°
12 Months	Level Above Treated Segment (Mean)	9.79° ± 4.43° Range: 1.14° - 22.40°	12.05° ± 4.78° Range: 0.79° - 23.44
	Level Below Treated Segment (Mean)	6.95° ± 4.33° Range: 0.33° - 23.59°	9.53° ± 4.79° Range: 1.01° - 21.97°
24 Months	Level Above Treated Segment (Mean)	10.40° ± 4.26° Range: 1.08° - 23.90	11.88° ± 4.56° Range: 2.71° - 25.27°
	Level Below Treated Segment (Mean)	6.77° ± 4.38° Range: 0.44° - 20.83°	9.10° ± 4.82° Range: 1.05° - 24.21°

Radiographic evaluation of the mean disc height for the treated level at each time point is shown in **Table 44** for all subjects.

Table 44: Time Course of Radiographic Disc Height[36]

Time Point	PRESTIGE® LP IDE Cohort (N = 280)	ACDF Control (N = 265)
Pre-op	33.7mm ± 5.0mm Range: 18.0mm – 51.7mm	35.1mm ± 5.7mm Range: 24.7mm – 59.2mm
6 Weeks	34.8mm ± 5.4mm Range: 18.5mm – 54.4mm	36.3mm ± 5.6mm Range: 24.8mm – 59.8mm
3 Months	34.7mm ± 5.4mm Range: 18.4mm – 53.0mm	36.4mm ± 5.8mm Range: 24.7mm – 60.2mm
6 Months	34.6mm ± 5.4mm Range: 18.6mm – 53.4mm	36.3mm ± 5.9mm Range: 23.7mm – 59.8mm
12 Months	34.6mm ± 5.3mm Range: 18.2mm – 54.1mm	35.7mm ± 5.6mm Range: 25.2mm – 59.1mm
24 Months	34.3mm ± 5.4mm Range: 18.2mm – 58.7mm	36.1mm ± 5.8mm Range: 25.2mm – 58.3mm

Table 45 presents radiographic disc height success at each time point for each treatment group. Disc height success is achieved when the change of post-operative height from baseline (determined from the six-week post-operative height) is less than or equal to 2mm in either the anterior or posterior measurements. Disc height success was similar between the two treatment groups with greater than 90% of the subjects in both groups achieving success at each time point.

Table 45: Time Course of Radiographic Disc Height Success[37]

Time Point	PRESTIGE® LP IDE Cohort(N = 280)	ACDF Control (N = 265)
3 Months	229/235 (97.4%)	182/182 (100.0%)
6 Months	227/230 (98.7%)	174/175 (99.4%)
12 Months	225/233 (96.6%)	164/172 (95.3%)
24 Months	205/224 (91.5%)	156/164 (95.1%)

Medication Use and Postoperative Procedures for Pain Management

Summaries of the medications taken by investigational and control subjects at preoperative and 24-month time points are summarized in **Table 46** below. For subjects on medication, the frequency of medication use ranged anywhere from once a week to three or more times a day.

Table 46: Summary of Pain and Muscle Relaxant Medication Usage

[36] Disc Height is defined as the average of the anterior and posterior measurement of functional spine unit height (FSU).
[37] Disc height success is defined as Postoperative Height minus Six-Week Postoperative Height ≥ -2mm either at the anterior or posterior measurements

Variable	PRESTIGE® LP IDE Cohort (N=280)	ACDF Control (N=265)
Preoperative		
Non-Narcotic Medications	208 (74.3%)	187 (71.1%)
Weak Narcotic Medications	133 (47.7%)	127 (48.3%)
Strong Narcotic Medications	62 (22.2%)	58 (22.0%)
Muscle Relaxant Medications	100 (35.8%)	114 (43.2%)
24 Months		
Non-Narcotic Medications	105 (38.9%)	109 (50.0%)
Weak Narcotic Medications	34 (12.6%)	44 (20.3%)
Strong Narcotic Medications	14 (5.2%)	18 (8.3%)
Muscle Relaxant Medications	53 (19.6%)	50 (22.9%)

Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with overall success outcomes using a covariate analysis: external orthotic usage, gender, height, implant depth/height/level, age, alcohol consumption, compensation level, education level, presence of litigation, marital status, NSAID usage, arm pain, foraminal compression test (FCT), gait, herniated disc, SF36 MCS/PCS scores, muscle relaxant usage, NDI, neck pain, neurologic status (motor/reflex/sensory), non-narcotic usage, osteophytes, strong/weak narcotic usage, symptom length, work status, prior surgery, race, tobacco usage, weight and IDE subjects versus subjects in the Continued Access Cohort. Post-hoc subgroup analysis of the investigational group identified differences in outcomes based on race and gender that were statistically significant. Distinctions based on race were not meaningful due to a low number of subjects in the non-Caucasian subgroup. Differences were also noted based on gender, with an apparent increase in the rate of heterotopic ossification/bridging bone and loss of segmental motion in male subjects. Female subjects had a numerically (but not statistically) higher rate of post-surgical neck and arm pain. However, no conclusions can be drawn from these post-hoc analyses based upon this small sample within this investigational study, and further post-market evaluation will quantify any clinical significance of these findings.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 102 investigators of which none were full-time or part-time employees of the sponsor and 25 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 3 investigators
- Significant payment of other sorts: 25 investigators
- Proprietary interest in the product tested held by the investigator: 3 investigators

- Significant equity interest held by investigator in sponsor of covered study: 4 investigators

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. Analyses using Fisher exact testing found a statistically significant relationship between overall success rates (with and without FSU) and investigators' financial interest for the PRESTIGE® LP implant procedure. Success rates at 24 months were higher (with and without FSU) for investigators with a reported financial interest (79.5% and 86.0%, respectively) when compared to investigators without financial interest (65.5%, p=0.032; and 75.4%, p=0.044 with and without FSU data, respectively). Because the study conducted was a single arm study with historical control, treatment differences by site could not be assessed in general. However, the Breslow-Day test was conducted for the sites that were involved with both the PRESTIGE® LP and the historical control study to assess whether treatment effects in overall success at 24 months depended on the investigator's financial interests. The p-values from the test were 0.687 and 0.309 for overall success with and without FSU data, respectively, suggesting that treatment efforts in overall success (differences between investigational group and control group) were not significantly influenced by financial interest. The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Orthopaedic and Rehabilitation Devices Panel, an FDA advisory committee, for review and recommendations because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

In terms of effectiveness measures, a comparison of the NDI success rates (based on a 15-point improvement from baseline) showed that the investigational group had higher rates than the control treatment at all postoperative time periods. Statistical non-inferiority to the control group was demonstrated at 24 months.

Overall success was the primary endpoint for the clinical study, and it is the parameter on which the success of the clinical study is determined. Overall success (without FSU) is based on a subject having a successful NDI outcome and neurological status maintenance or improvement. Also, to be considered an overall success, a subject could not have undergone a second surgery classified as a "failure" or have had a severe adverse event that was judged as implant- or implant/surgical procedure-associated. Therefore, this parameter encompasses

important safety and effectiveness aspects of the treatment. At 24 months following surgery, the posterior probability for overall success (without FSU) for the investigational group was 78.9% and greater than 11 percentage points higher than the value of 67.8% for the control group. A difference of almost 16 points was seen at 12 months. Overall success rates were also calculated with FSU (disc height) success to the formula. Again at 12 and 24 months following surgery, the investigational group overall success rate was numerically higher than the control group rate, with the 24-month rate being more than 3 percentage points higher. Regardless of the definition used, the overall success rates for the investigational group were found to be statistically non-inferior to the control group rates, and the investigational group was also found to be statistically superior when FSU success was not included in the overall success definition.

Post-hoc subgroup analysis of the investigational group examined race and gender as covariates and identified differences in outcomes that were statistically significant. Distinctions based on race were not meaningful due to a low number of subjects in the non-Caucasian subgroup. Differences were also noted based on gender, with an apparent increase in the rate of heterotopic ossification/bridging bone and loss of segmental motion in male subjects. Female subjects had a numerically higher rate of post-surgical neck and arm pain. However, it must be stated that these observations should be considered exploratory, and further post-market evaluation is recommended to quantify the clinical significance, if any, of these findings.

a. Safety Conclusions

The investigational device was found to be as safe as the control treatment based on the assessment of adverse events, second surgeries, and neurological status. Although the rate of investigational device subjects having at least one adverse event was statistically higher than the control group rate, this corresponded to a higher rate of postoperative follow-up in investigational subjects. Furthermore, the rate of device or surgical procedure-related, and severe device or surgical procedure related adverse events were comparable between the investigational and control groups. Subjects undergoing secondary surgical procedures, which were automatically classified as study failures, totaled 12 for both treatment groups.

Maintenance or improvement in neurological status was found in greater than 90% of subjects in the investigational group. Furthermore, the 24-month overall neurological success rate of 93.3% for the investigational treatment group was found to be statistically superior to the rate of 83.6% seen in the control group. Based on the favorable neurological status outcome, as well as the adverse event and second surgery rates, the results of this study support the conclusion that the safety profile of the PRESTIGE® LP Cervical Disc is non-inferior to controls.

b. Benefit-Risk Conclusions

Over the 24 month period studied, the following benefits occurred:

- Radiographic success at 24 months, defined as angular motion >4° and ≤20° with no bridging bone was found in 67.8% of PRESTIGE® LP subjects. No comparison was

made to control group since fusion is not intended to allow for motion. While this was not a primary endpoint, this is one of the main benefits afforded by this device as compared to the control.

- Improvement in function (as measured by a 15-point improvement in NDI) achieved a higher rate of success compared to the ACDF control (PRESTIGE® LP: 87.8%; ACDF Control: 80.8%).
- Maintenance or improvement in neurological status for the investigational device achieved a higher rate of success compared to the ACDF control (PRESTIGE® LP: 93.3%; ACDF Control: 83.6%).
- Improvement in neck and arm pain (as measured by the VAS scale) was comparable to the control (PRESTIGE® LP: Neck 96.3%, Arm 96.3%; ACDF Control: Neck 97.3%, Arm 95.0%).
- Improvement of Quality of Life (as measured by the SF-36 scale) was comparable to the control (PRESTIGE® LP: PCS 83.7%, MCS 77.7%; ACDF Control: PCS 86.1%, MCS 69.4%).
- Patient satisfaction (as measured by Patient Perceived Effect) was comparable or better than the control. In the PRESTIGE® LP group, 47.0% stated they were "completely recovered" and 39.6% stated they were "much improved," while in the ACDF Control, 40.2% said they were "completely recovered" and 40.6% stated they were "much improved.".
- Physician satisfaction with subject outcomes (as measured by Physician Perceived Effect) was favorable compared to control with 71.6% in the PRESTIGE® LP group categorized as "Excellent" while only 56.8% were "Excellent" in the control group.
- The rate of device failures (revision, removal, or supplemental fixation classified as failure) is comparable to the control. (PRESTIGE® LP: 4.3%; ACDF Control: 4.9%).

Over the 24 month time period studied:

- The overall adverse event rate is higher than the control ACDF (PRESTIGE® LP: 91.8%; ACDF Control: 82.6%).
- The rate of severe adverse events is higher than the control ACDF, although it is high in general for both groups (PRESTIGE® LP: 47.5%; ACDF Control: 37.0%).
- The rate of device- or device/surgical procedure-related adverse events is lower than the control group (PRESTIGE® LP: 12.1%; ACDF Control: 15.5%).
- The rate of severe (grade III or IV) device- and device/procedure-related adverse events was comparable to controls (PRESTIGE® LP: 5.0%; ACDF Control: 4.9%).
- The rate of procedure-related adverse events is comparable to control ACDF (PRESTIGE® LP: 25.7%; ACDF Control: 26.8%).
- The rate of secondary surgical interventions is comparable to control (PRESTIGE® LP: 5.0%; ACDF Control: 7.9%).

Other factors considered during benefit/risk assessment include:

- This was a prospective, multi-center, historically controlled trial that was conducted and analyzed as intended.
- Subjectivity of some study endpoints (e.g., patient/physician perceived effect).

- Adverse event classification can be subjective, but independent CAC adjudication is beneficial.
- Study was not designed or powered to study effects of treatment in subgroups.
- No data were available on patient perceptions of risks and benefits.
- Risk mitigation will be provided in the product labeling and surgeon training.
- Post-market studies will be conducted to evaluate long term performance.

The primary endpoints and secondary endpoint measurements all were evaluated and showed comparable or better performance of the PRESTIGE® LP as compared to the ACDF control group. While the overall adverse events and severe adverse event rate appears to be higher for the PRESTIGE® LP IDE group at 24 months as compared to the control, which may be due to the higher follow-up rate in the investigational group as compared to the control group, it is important to note that when taking into account only device or procedure related adverse events, the rates are comparable. It is also important to note that while adverse event rates appear to be higher for this device when compared to similar devices that are currently commercially available, the adverse event rates are higher for both investigational and control groups in this study, which may be a result of training or different reporting metrics.

Additional theoretical benefits of cervical arthroplasty performed using the PRESTIGE® LP include maintenance of intersegmental spinal motion at the indicated cervical level, while the standard of care and control comparison is fusion. In this study, the effects of the PRESTIGE® LP, particularly in regards to motion, are captured in the radiographic outcome. These effects are not compared to the control, however, due to the expectation of no motion in the ACDF group. Additional benefits suggested in literature include the prevention of adjacent disc disease following the use of cervical arthroplasty as compared to fusion; however, this was not analyzed in this study.

In conclusion, given the available information, the data support that for reconstruction of the disc at one level from C3-7 following single level discectomy for intractable radiculopathy (arm pain and/or a neurological deficit) with or without neck pain, or myelopathy due to a single-level abnormality localized to the disc space and specific radiographic findings as outlined in the Indications for Use, the probable benefits of the PRESTIGE® LP cervical disc arthroplasty outweigh the probable risks through 2 years of follow-up.

c. Overall Conclusions

The goal of the PRESTIGE® LP Cervical Disc IDE clinical study (G040086) was to evaluate the reasonable assurance of safety and effectiveness of the use of the device in the treatment of subjects with symptomatic cervical disc disease when compared to the control treatment, a standard of care fusion procedure using structural allograft bone with an anterior cervical plate. As shown in this Summary of Safety and Effectiveness Data document, the clinical results from the use of the investigational device, the PRESTIGE® LP Cervical Disc, were shown to be statistically non-inferior to the control group results.

The scientific evidence that has been presented here supports the reasonable assurance of safety and effectiveness of the PRESTIGE® LP Cervical Disc in the treatment of intractable

radiculopathy and/or myelopathy at a single-level from C3 to C7. The study demonstrated that the treatment of intractable radiculopathy and/or myelopathy with the PRESTIGE® LP Cervical Disc was as effective as the control treatment (fusion with bone graft and plate stabilization). The results for the primary effectiveness outcome parameters for the investigational group were non-inferior to the control group. The investigational group demonstrated superiority to the control group for the neurological component and overall success (without FSU). The PRESTIGE® LP Cervical Disc was able to achieve comparable or better clinical performance while maintaining motion at the involved cervical level.

XIII. CDRH DECISION

CDRH issued an approval order on July 24, 2014. The final conditions of approval cited in the approval order are described below.

1. *Prestige LP Cervical Disc –Extended Follow-up:* This study will be conducted as per protocol dated April 14, 2014, Version P03-03-PAS (email). This study will consist of the extended prospective follow-up of the premarket cohort for 10-years post-implant to evaluate the longer term safety and effectiveness of the Prestige® LP Cervical Disc, by following all available Prestige® LP subjects (original n=280 pivotal investigation subjects and approximately n=50 continued access subjects) from the pivotal investigational device exemption (IDE) study. At the 120-month (±4 month) visit, the applicant will collect the following data: Neck Disability Index; The Short Form (36) Health Survey; adverse events and outstanding adverse events forms; radiographic images (AP-lateral, lateral, right/left AP lateral bend, lateral flexion/extension) with independent review of medical images; neurological data; postoperative subject survey; postoperative Gait Assessment and Foraminal Compression test; postoperative Neck and Arm Pain Questionnaire; patient satisfaction, medication usage and postoperative treatment for pain management, patient disposition; and work status. Specimens for metal ions will be collected for all the metal ion cohort subjects and any subject with an explant or revision. Radiographic information collected will include: range of motion on flexion/extension films (angulation and translation as well as the correlation of range of motion with outcomes), disc height (functional spinal unit), device conditions (bending, breakage, migration, and fracture); and bridging bone (stability over time and correlation with subject characteristics and postoperative outcomes). You will also collect radiographic and clinical data on adjacent level surgeries and adjacent level range of motion on flexion/extension films (angulation and translation)..

   The primary objective of the study is to evaluate the overall success at 10 years. A subject will be considered an overall success if all of the following conditions are met:
   Postoperative Neck Disability Index score improvement of at least 15-points from preoperative; maintenance or improvement in neurological status; Disc height success; no serious adverse event classified as implant associated or implant/surgical procedure associated; and no secondary surgical procedure classified as a "failure."
   An alternate overall success determination will also be made without the inclusion of disc height into the aforementioned criteria.

   The applicant will also summarize and analyze the data as follows:
   - Non-inferiority analysis comparing success rates between the PRESTIGE® LP Cervical Disc device group and the control group at 10 years— a Bayesian logistic regression model adjusting for the propensity score as the covariate will be carried out.

- All additional statistical comparisons between groups, at 10 year only, outlined in the original IDE study will utilize Bayesian statistical methods for the post- approval study.
- Time-to-event analyses and comparisons using the Cox regression model adjusting for the propensity score as the covariate for serious, possibly device-related adverse events; device failures, if any; second surgeries that are classified as failures at the target level; and additional surgical interventions at adjacent levels.
- Sensitivity analyses to assess the effect of missing data. These analyses will assume various proportions of successes and failures for overall success in the two groups for lost-to-follow-up, additional analyses will be carried out using Frequentist methods to assess the demographics characteristics, baseline information and the last observed overall success status of subjects who become lost-to-follow-up compared to those who remain in the study.

FDA will expect 80% follow-up at 10-years to provide sufficient data to evaluate safety and effectiveness.

2. *Prestige LP Cervical Disc –ESS:* This is a 10 year Enhanced Surveillance Study (ESS) of PRESTIGE® LP Cervical Disc to fully characterize adverse events and complaints when the device is used in the intended use population in the United States and in the rest of the world.

   The applicantwill collect, analyze, and submit all adverse event data including subsequent surgeries, heterotopic ossification, device malfunction, and other serious device-related complications. Information will be actively collected from annual surgeon surveys and on the company website. Information will also be collected passively through complaints, MDRs, and literature reviews.

   All of the surgeons who have been trained on the use of PRESTIGE® LP Cervical Disc Prosthesis in the U.S. will be surveyed annually and the number of surveys issued and received will be reported. If a survey response includes any information related to an adverse event, the applicant will collect additional data as specifically outlined in the ESS protocol and report that data to FDA.

3. *Prestige LP Cervical Disc –Device Failure:* This study will characterize the long-term modes and causes of failure. It will be conducted for a 10 year duration with a detailed analysis of all PRESTIGE® LP Cervical Disc explanted and retrieved components which were returned to the company. The analysis will include the following details:
   a. Explant and histologic analyses conducted by third-party vendor, metal ion analysis for explants obtained during extended follow-up investigation
   b. Internal device analysis, without histologic and metal ion analysis for all other post-market explants

The applicant's manufacturing facilitieshave been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for Use: See device labeling

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

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[3] Nurick, S. The pathogenesis of the spinal cord disorder associated with cervical spondylosis. *Brain* 1972; 95: 87-100.