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 / S003

Date of FDA Notice of Approval: July 7, 2016

The original PMA (P090029) was approved on July 24, 2014 and is indicated for use 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. The SSED to support the previously approved one level indication is available on the CDRH website (http://www.accessdata.fda.gov/cdrh_docs/pdf9/P090029B.pdf) and is incorporated by reference here. The current supplement was submitted to expand the indication for the PRESTIGE LP™ Cervical Disc to include use of the device at two (2) contiguous levels and to add a 5 mm device height option.

II. INDICATIONS FOR USE

The PRESTIGE LP™ Cervical Disc is indicated in skeletally mature patients for reconstruction of the disc from C3-C7 following discectomy at one level or two contiguous levels for intractable radiculopathy (arm pain and/or a neurological deficit) with or without neck pain, or myelopathy due to 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 or osteopenia defined as a DEXA bone mineral density T-score ≤ -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 level adjacent to the treated levels;
- Severe spondylosis at the level to be treated, characterized by bridging osteophytes, loss of disc height >50%, or 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(s) 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), or
- Significant kyphotic deformity or significant reversal of lordosis.

IV. WARNINGS AND PRECAUTIONS

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

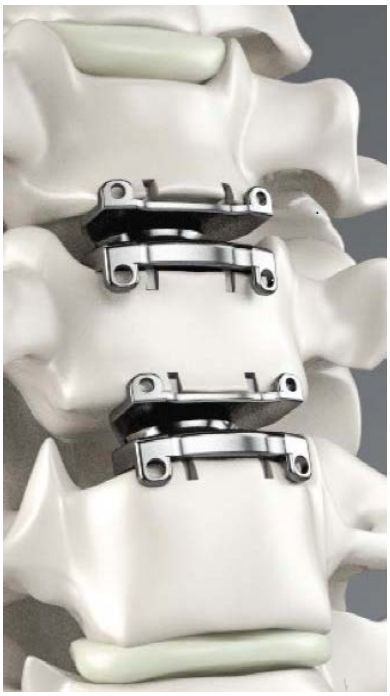
V. DEVICE DESCRIPTION

The PRESTIGE LP™ Cervical Disc is a two-piece articulating device that is inserted into the intervertebral disc space as a pre-assembled unit at one or two contiguous cervical levels 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 that contacts the vertebral endplate has a commercially pure titanium (CP Ti) plasma thermal sprayed coating per ASTM F1580, designed to permit bony on-growth for additional device incorporation. The remaining portion of the flat surface is titanium ceramic roughened to enhance fixation. Each component also contains two anterior tab features

designed to aid in device insertion and to minimize the risk of implanting the device too far into the intervertebral space.

Figure 1: PRESTIGE LP™ Cervical Disc

Figure 2: PRESTIGE LP™ Cervical Disc at two contiguous levels



The PRESTIGE LP™ Cervical Disc is 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 (Height x AP Dimension x ML Dimension)
6972250	5mm x 12mm x 15mm
6972450	5mm x 14mm x 15mm
6972650	5mm x 16mm x 15mm
6972260	6mm x 12mm x 17.8mm
6972460	6mm x 14mm x 17.8mm

6972660	6mm x 16mm x 17.8mm
6972860	6mm x 18mm x 17.8mm
6972470	7mm x 14mm x 17.8mm
6972670	7mm x 16mm x 17.8mm
6972870	7mm x 18mm x 17.8mm
6972480	8mm x 14mm x 17.8mm
6972680	8mm x 16mm x 17.8mm
6972880	8mm x 18mm x 17.8mm

The PRESTIGE LP™ Cervical Disc is designed to allow a minimum of 10 degrees lateral bending (from neutral) and a minimum of 10 degrees flexion/extension (from neutral). The design is also intended to allow unlimited axial rotation (constrained by ligaments and posterior elements) and translation of ±2 mm in the sagittal plane.

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

The PRESTIGE LP™ Cervical Disc approved in this supplement is identical to the PRESTIGE LP™ Cervical Disc approved in P090029 with the exception of the addition of 5mm device height options (5mm x 12mm, 5mm x 14mm, 5mm x 16mm) and their corresponding instruments (which were included in the 2-level IDE study, G050202) to the system.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

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

- 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 or multi-level abnormality localized to the level of the disc space at one or two contiguous levels may also be treated surgically using another FDA approved artificial cervical disc.

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The device has been marketed outside of the United States since 2004, and has not been withdrawn from the market in any country, for any reason. The PRESTIGE LP™ Cervical Disc 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 identified from the PRESTIGE LP™ Cervical Disc clinical study results, use of the PRESTIGE LP™ Cervical Disc outside of the United States, approved device labeling for other cervical total disc replacement devices, and published scientific literature including: (1) those associated with any surgical procedure; (2) those associated with anterior cervical spine surgery; and (3) those associated with a cervical artificial disc device, including the PRESTIGE LP™ Cervical Disc. These risks may occur singly or in combination. In addition to the risks listed below, there is also the risk that the procedure may not be effective and may not relieve symptoms or may cause worsening of symptoms. Additional surgery may be required to correct some of the adverse effects.

1. Risks associated with any surgical procedure:
   - Anesthesia complications including an allergic reaction or anaphylaxis;
   - Infection (wound, local, and/or systemic) or abscess;
   - Wound dehiscence or necrosis;
   - Edema;
   - Soft tissue damage or fluid collections, including hematoma or seroma;
   - Pain/discomfort at the surgical incision and/or skin or muscle sensitivity over the incision which may result in skin breakdown, pain, and/or irritation;
   - Heart or vascular complications including bleeding, hemorrhage or vascular damage resulting in catastrophic or potentially fatal bleeding, ischemia, myocardial infarction, abnormal blood pressure, venous thromboembolism including deep vein thrombosis and pulmonary embolism, thrombophlebitis, or stroke;
   - Pulmonary complications including atelectasis or pneumonia;
   - Impairment of the gastrointestinal system including ileus or bowel obstruction;
   - Impairment of the genitourinary system including incontinence, bladder dysfunction, or reproductive system complications;
   - Neurological complications including nerve damage, paralysis, seizures, changes to mental status, or reflex sympathetic dystrophy;
   - Complications of pregnancy including miscarriage or congenital defects;
   - Inability to resume activities of daily living; and
   - Death.

2. Risks associated with anterior cervical spine surgery:

- Injury to surrounding organs and structures including the spinal cord, nerve roots, other neurologic structures adjacent to the spinal column, vocal cords, adjacent vertebrae, lymphatic vessels, blood vessels, soft tissue, dura, the trachea, the esophagus, the larynx, or the pharynx;
- Dysphagia, dysphonia, hoarseness, vocal cord paralysis, laryngeal palsy; or sore throat;
- Tracheal, esophageal, or pharyngeal perforation, fistula, recurrent aspiration, or airway obstruction;
- Neurological complications, including damage to nerve roots, the spinal cord, or other nerves possibly resulting in muscle weakness or paralysis, changes in sensation (including numbness, dysesthesias, or paresthesias), bowel/bladder dysfunction, or pain;
- Neck pain, arm pain, or headache;
- Dural tear or leak or cerebrospinal fistula;
- Discitis, arachnoiditis, or other type of inflammation;
- Loss of disc height; loss of anatomic sagittal plane curvature or vertebral listhesis, spinal stenosis, or spondylolysis; and
- Scarring, herniation or degeneration of adjacent discs.

3. Risks associated with a cervical artificial disc device, including the PRESTIGE LP™ Cervical Disc:
   - Risks directly related to the device including malposition, migration/displacement, subsidence/loss of disc height, device breakage, device disassembly, or early or late loosening of the device. Any of these issues may cause pain or injury to surrounding organs and structures including the spinal cord, nerve roots, or other neurologic structures adjacent to the spinal column (which could cause pain, paralysis, or numbness) or blood vessel damage or erosion (which could cause catastrophic or fatal bleeding);
   - Deterioration in neurologic status including muscle weakness or paralysis, changes in sensation (including numbness, dysesthesias, or paresthesias), decreased reflexes, or loss of bowel and/or bladder control;
   - Development of new radiculopathy, myelopathy, or pain;
   - Failure of the device to improve symptoms or function;
   - Problems during placement of the device including trouble sizing the device, anatomical or technical difficulties implanting the device, or issues with the device instruments (e.g., bending or breakage) including the possibility that a fragment of a broken instrument may remain in the patient after implantation;
   - Adverse reaction or allergy to the device materials (titanium, aluminum or vanadium), device wear debris or metal ions which may lead to a systemic reaction or a local adverse tissue reaction or chronic inflammation which may lead to implant loosening or failure of the device, osteolysis, bone resorption, tumor formation, autoimmune disease, metallosis, scarring, or other symptoms;
   - Change in the alignment of the spine or loss of proper anatomic curvature, correction, height or reduction of the spine including spondylolisthesis, change in lordosis, or instability of the spine;
   - Degeneration of other parts of the spine including the facet joints or adjacent discs;
   - Fracture of the surrounding vertebrae;

- Unintended bone formation (i.e., heterotopic ossification) that may result in bridging trabecular bone and may reduce spinal motion or result in unintended fusion at either the treated level or adjacent levels;
- Device failure which may require a subsequent surgical intervention (including removal of the PRESTIGE LP™ Cervical Disc, revision, re-operation, or supplemental fixation); and
- Interference with radiographic imaging because of the presence of the implant.

Some of the adverse effects listed above were observed in the 2-level PRESTIGE LP™ Cervical Disc clinical study. For more detailed information on the specific adverse events that occurred during the clinical study, please refer to Section X (Summary of Primary Clinical Study). Some of the most common adverse effects experienced by study subjects were cervical arm pain, cervical neck pain, and cervical neurological events.

IX. SUMMARY OF NONCLINICAL STUDIES

A variety of preclinical 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
- Impingement 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 1	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 (5mm x 12mm) device assembly was assembled to mating foam blocks and axial load was 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 793±28.3N. 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.
Subsidence 2	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 12mm) device assembly was assembled to mating foam blocks and axial load was 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 1	To determine overall resistance to push-out for the PRESTIGE LP™ device	A 100 N preload was applied to n=1 (5mm x 12mm) device assembly while an axial force was applied in the anterior/posterior and medial lateral directions at 6 mm/min until failure was 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 156±4N. 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.

Test Description	Purpose	Methods	Medtronic's Acceptance Criteria	Results
Push-Out 2	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 was applied in the anterior/posterior and medial lateral directions at 6mm/min until failure was 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 5mm x 12mm PRESTIGE LP™ device's ability to withstand axial compressive loads by determining the ultimate failure load of the construct over multiple specimens	n=1 (5mm x 12mm) device assemblies were tested in accordance with ASTM Standard F2346 "Standard Test Method for Static and Dynamic Characterization of Spinal Artificial Discs"	The axial compressive failure load must exceed the clinically acceptable value of 74N.[1]	The mean failure load was 8070N. The result of the static compression test far exceeded the clinically acceptable load of 74N. This result suggests that the device can resist compressive loading that exceeds anticipated physiologic loads on the cervical spine.
Static Compression 2	To characterize the 5mm x 16mm PRESTIGE LP™ device's ability to withstand axial compressive loads by determining the ultimate failure load of the construct over multiple specimens	n=1 (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 axial compressive failure load must exceed the clinically acceptable value of 74N.[1]	The mean failure load was 6494N. The result of the static compression test far exceeded the clinically acceptable load of 74N. This result suggests 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 3	To characterize the 6mm x18mm 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 21,096N/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.
Static Compression 4	To characterize the 7mm x 18mm PRESTIGE LP™ device's ability to provide resistance to axial compressive loading	n=5 (7mm x 18mm) 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.
Compression Fatigue 1	To characterize the 7mm x 18mm 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 12mm) 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, 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 at 2 Hz 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 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 at 1 Hz 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 $0.25\pm0.03mm^3$/MC The total accumulated wear was $2.81\pm0.14mm^3$ Characterization only.

Test Description	Purpose	Methods	Medtronic's Acceptance Criteria	Results
Wear Test 4 (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 5 (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.

Test Description	Purpose	Methods	Medtronic's Acceptance Criteria	Results
Impingement Testing	To determine the wear and durability characteristics of the PRESTIGE LP™ Device under conditions simulating device impingement.	n=6 (6mm x 16mm) device assemblies using a set of custom test fixtures. Each device assembly underwent combined flexion-extension (FE) and axial rotation (AR) motions for 1 million cycles (MC) under static load of 150N.	This test was used to generate benchmark impingement data, and there was no acceptance criteria quantified.	The total volumetric wear after 1 MC was $0.17\pm0.04mm^3$ ($0.83\pm0.18mg$). All endplate impingement patterns observed were aligned with the median plane at the anterior endplate edge of the male components and at the anterior edge of the trough for female components. There was no evidence of structural damage due to endplate impingement. The average surface roughness of the female specimens.

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 1.5 Tesla and 3.0 Tesla MRI environment	n=4 (5mm x 12mm, 6mm x 12mm, 6mm x 16mm, and 8mm x 18mm) devices 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 1.5 Tesla or 3.0-Tesla MRI environment with regard to translational attraction, migration, or torque. 2.) MRI-related heating: Highest temperature change recorded was not considered 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. Animal Testing

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 with 10% Ti-6Al-4V/TiC 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 with 10% Ti-6Al-4V/TiC 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 within the United States under IDE #G050202 to establish a reasonable assurance of safety and effectiveness of the PRESTIGE LP™ Cervical Disc for reconstruction of the disc from C3-C7 following discectomy at two contiguous levels in skeletally mature subjects with intractable radiculopathy (arm pain and/or a neurological deficit) with or without neck pain or myelopathy localized to the two disc space levels. The subjects had been unresponsive to at least 6 weeks of non-operative treatment or had the presence of progressive symptoms or signs of nerve root/spinal cord compression in the face of continued non-operative management. 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 June 20, 2006 and November 29, 2007. The database for this PMA reflected data collected through September 29, 2014 and included a total of 397 subjects treated (209 investigational subjects and 188 control subjects) at 30 investigational sites in the United States.

The study was a prospective, multi-center, randomized (1:1), unmasked, concurrently controlled, non-inferiority study. The study was designed to compare the safety and effectiveness of the 2-level PRESTIGE LP™ Cervical Disc to the standard of care, 2-level anterior cervical discectomy and fusion (ACDF) using cortical ring allograft and stabilization with an ATLANTIS® Anterior Cervical Plate, in reconstruction of the disc from C3-C7 following discectomy at two contiguous levels in skeletally mature subjects with intractable radiculopathy or myelopathy localized to the two disc space levels who had been unresponsive to at least 6 weeks of non-operative treatment or had the presence of progressive symptoms or signs of nerve root/spinal cord compression in the face of continued non-operative management.

Subjects were evaluated pre-operatively, intra-operatively, immediately post-operatively and at 6 weeks, 3 months, 6 months, 12 months, 24 months and annually thereafter until the last subject in the study had completed his/her 24-month follow-up evaluation. The recommended post-operative care in both treatment groups included avoidance of overhead lifting, heavy lifting, repetitive neck bending, high-impact exercise and athletic activity for 60 days post-operatively. Avoidance of prolonged (beyond 2 weeks post-op) non-steroidal anti-inflammatory drug (NSAID) use was specified in the post-operative regimen, although the use of NSAIDs was recommended for the first two weeks post-operatively in the 2-level PRESTIGE LP™ group. 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. 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. All adverse events were independently adjudicated (for severity and relationship to the device and/or procedure) by a Clinical Adjudication Committee (CAC) composed of three independent, practicing spine surgeons.

Overall success was a composite endpoint which required the following for success:

- Neck Disability Index (NDI) score improvement of at least 15 points from pre-operative;
- Maintenance or improvement in neurological status;
- No serious adverse event classified as implant associated or implant/surgical procedure associated; and
- No additional surgical procedure classified as a "failure."

Overall success was determined based on data collected during the initial 24 months of follow-up.

The study was designed as a non-inferiority study with a margin (delta) of 10%. The protocol specified a sample size of 209 2-level PRESTIGE LP™ IDE subjects and 188 2-level ACDF control subjects, based on assumed success rates of 75% in the investigational group and 70% in the control group, a 15% lost-to-follow-up rate, and 80% power for a one-sided 0.05 significance level. The protocol also specified secondary superiority evaluations of the primary endpoint if non-inferiority was demonstrated. For the secondary endpoints and other measurements, multiple comparisons were carried out without adjusting for multiplicity.

The statistical plan pre-defined that the data would initially be analyzed after approximately 250 subjects (investigational and control subjects combined) had reached the 24-month evaluation timepoint at which time all subjects would have reached the 12-month timepoint. The applicant then also planned to analyze the data when the entire cohort had reached the 24-month timepoint. Due to rapid study enrollment and timing considerations, the pre-defined interim analysis was not performed.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the 2-level PRESTIGE LP™ Cervical Disc study was limited to subjects who met the following inclusion criteria:

- Cervical degenerative disc disease at two (2) adjacent cervical levels (from C3-C7) requiring surgical treatment and involving intractable radiculopathy, myelopathy, or both;
- Herniated disc and/or osteophyte formation at each level to be treated that is producing symptomatic nerve root and/or spinal cord compression. The condition is documented by patient history (e.g., neck and/or arm pain, functional deficit and/or neurological deficit), and the requirement for surgical treatment is evidenced by radiographic studies (e.g., CT, MRI, x-rays, etc.);
- 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 the involved levels or any subsequent, planned/staged surgical procedure at the involved or adjacent levels;
- At least 18 years of age and skeletally mature at the time of the surgery;

- Pre-operative Neck Disability Index (NDI) score ≥ 30;
- Pre-operative neck pain score ≥ 8 on Pre-operative Neck and Arm Pain Questionnaire;
- If a female of child-bearing potential, subject is non-pregnant, non-nursing, and agrees not to become pregnant during the study period;
- Willing to comply with the study plan and sign the Patient Informed Consent Form.

Subjects were <u>not</u> permitted to enroll in the 2-level PRESTIGE LP™ Cervical Disc study if they met any of the following exclusion criteria:

- A cervical spinal condition other than symptomatic cervical degenerative disc disease requiring surgical treatment at the involved levels;
- Documented or diagnosed cervical instability relative to adjacent segments at either level, defined by dynamic (flexion/extension) radiographs showing sagittal plane translation > 3.5 mm or sagittal plane angulation > 20°;
- More than two cervical levels requiring surgical treatment;
- A fused level adjacent to the levels to be treated;
- Severe pathology of the facet joints of the involved vertebral bodies;
- Previous surgical intervention at either one or both of the involved levels or at adjacent levels;
- Previously diagnosed with osteopenia or osteomalacia;
- 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 was required to determine eligibility):
  - Postmenopausal non-Black female over 60 years of age who weighs less than 140 pounds.
  - Postmenopausal female who has sustained a non-traumatic hip, spine, or wrist fracture.
  - Male over the age of 70;
  - Male over the age of 60 who has sustained a non-traumatic hip or spine fracture;

  If the level of bone mineral density (BMD) was a T score of -3.5 or lower (i.e., -3.6, -3.7, etc.) or a T score of -2.5 or lower (i.e., -2.6, -2.7, etc.) with vertebral crush fracture, then the subject was excluded from the study;
- Presence of spinal metastases;
- Overt or active bacterial infection, either local or systemic;
- Insulin dependent diabetes;
- A tobacco user who does not agree to suspend smoking prior to surgery;
- Chronic or acute renal failure or prior history of renal disease;
- A documented allergy or intolerance to stainless steel, titanium, or a titanium alloy;
- Mentally incompetent (If questionable, obtain psychiatric consult);
- A prisoner;
- Pregnant;
- An alcohol and/or drug abuser currently undergoing treatment for alcohol and/or drug abuse;
- Involved with current or pending litigation regarding a spinal condition;
- Received drugs that 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;

- 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);
- A condition that requires post-operative medications that interfere with the stability of the implant, such as steroids. (This does not include low dose aspirin for prophylactic anticoagulation and routine perioperative anti-inflammatory drugs);
- 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. All subjects were scheduled to return for post-operative follow-up examinations at 6 weeks (±2 weeks), 3 months (±2 weeks), 6 months (±1 month), 12 months (±2 months), 24 months (±2 months), and annually thereafter until the last subject enrolled in the study had been seen for his/her 24-month evaluation. Additional evaluations were approved by FDA for 36 months (±2 months), 60 months (±3 months), 84 months (±3 months), and 120 months (±3 months).

Evaluations were done according to the visit schedule below. Adverse events and complications were recorded at all visits.

Table 6: Schedule of Study Assessments

Procedure	**Pre-/Peri-operative**		**Post-operative**				
	Pre-op	**Surgery/ Hospital Discharge**	**6 wks (±2 wks)**	**3 mos (±2 wks)**	**6 mos (±1 mo)**	**12 mos, 24 mos 36 mos, (±2 mos)**	**60 mos, 84 mos, 120 mos (±3 mos)**
Clinical Evaluations:							
Inclusion/Exclusion Determination	X						
Osteoporosis/Osteopenia Screen	X						
Informed Consent and HIPAA Authorization	X						
Baseline Medical History/Physical Exam	X						
Surgery and Hospital Discharge Data		X					
Neck Disability Index (NDI)	X		X	X	X	X	X
Neck and Arm Pain Questionnaire	X		X	X	X	X	X
Health Status Questionnaire (SF-36)	X				X	X	X
Neurological Status	X		X	X	X	X	X
Preoperative Gait Assessment and Foraminal Compression Test	X		X	X	X	X	X
Medication Use	X		X	X	X	X	X
Work Status	X		X	X	X	X	X
Satisfaction and Perceived Effect (subject & physician)	X		X	X	X	X	X

Procedure	Pre-/Peri-operative		Post-operative				
	Pre-op	Surgery/ Hospital Discharge	6 wks (±2 wks)	3 mos (±2 wks)	6 mos (±1 mo)	12 mos, 24 mos 36 mos, (±2 mos)	60 mos, 84 mos, 120 mos (±3 mos)
Radiologic Review	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X
Subject Disposition*	X	X	X	X	X	X	X
Radiographic Procedures:							
Anterior/Posterior and Lateral Neutral X-rays	X	X	X	X	X	X	X
Lateral Flexion/Extension X-rays	X		X	X	X	X	X
CT and/or MRI	X						
DEXA Scan **	X						

* While the Subject Disposition CRF could be filled out at any time, it was only filled out once for each subject.
** A DEXA Scan was only required if the subject had a risk factor that may be associated with a diagnosis of osteoporosis as outlined in the clinical protocol.

3. Clinical Endpoints

The safety of the 2-level PRESTIGE LP™ Cervical Disc was assessed by comparing the nature and frequency of adverse events (overall and in terms of seriousness and relationship to the device and/or procedure) and subsequent surgical procedures as well as maintenance or improvement in neurological status to the 2-level ACDF control group.

The effectiveness of the 2-level PRESTIGE LP™ Cervical Disc was assessed by evaluating improvement in NDI score, improvement in neck and arm pain measured at rest using a neck and arm pain questionnaire, improvement in quality of life measured using the Short-Form 36 (SF-36) questionnaire, subject satisfaction, medication usage, and work status compared to the 2-level ACDF control group.

In addition, several radiograph endpoints were considered in evaluating both safety and effectiveness including range of motion, functional spinal unit (FSU) height maintenance, implant condition, and heterotopic ossification.

Per the protocol, an individual subject in either treatment group was considered a success if the following criteria were met at 24 months post-operative:

1. Improvement (reduction) of at least 15 points in NDI score at 24 months compared to pre-operative baseline;
2. Maintenance or improvement in neurological status at 24 months compared to pre-operative baseline as measured based on motor function, sensory function, and reflexes;
3. No serious adverse event classified as implant associated, or implant/surgical procedure associated; and
4. No additional surgical procedure classified as a “failure.”

Note that because the additional surgical procedure component of the primary endpoint did not consider all subsequent surgeries at the index level as failures, FDA requested an additional analysis of overall success in which all subsequent surgeries at the index level and all intra-operative treatment conversions were considered failures.

Overall study success criteria were based on a comparison of individual subject success rates, such that the subject success rate for the 2-level PRESTIGE LP™ group was required to be non-inferior to that of the 2-level ACDF control group. The study was designed as a non-inferiority study with a margin (delta) of 10%. For the analysis of overall success, individual effectiveness variables and neurological status, the Bayesian model incorporated data from both the 12-month and 24-month follow-up visits, including data from the 12-month only or 24-month only visits, to statistically compare the outcomes at the 24-month visit between the two treatment groups. The study hypothesis was that the success rate of the 2-level PRESTIGE LP™ group was statistically non-inferior to the success rate in the 2-level ACDF control group by a margin of 10%. Non-inferiority was to be claimed if the posterior probability that the success rate in the 2-level PRESTIGE LP™ group was not lower than the success rate in the 2-level ACDF control group by more than 10% was greater than 95%. The protocol also specified secondary superiority evaluations if non-inferiority was demonstrated. For comparison of adverse events and subsequent surgical procedures, a beta-binomial model was used.

Secondary endpoints, measured in both treatment groups, included neck pain, arm pain, quality of life (SF-36 Physical Component Score [PCS] and Mental Component Score [MCS]), gait assessment (Nurick's classification), subject satisfaction, subject perceived effect, physician perception of results, radiographic success (defined differently in the two treatment groups), range of motion, Functional Spinal Unit (FSU) height, implant condition, heterotopic ossification, and return to work. For the secondary endpoints and other measurements, multiple comparisons were carried out without adjusting for multiplicity.

B. Accountability of PMA Cohort

A total of 397 subjects (209 2-level PRESTIGE LP™, 188 2-level ACDF control) were treated in the 2-level PRESTIGE LP™ Cervical Disc study at 30 sites. At the time of database lock (September 29, 2014), of the 397 subjects enrolled in the PMA study, all had reached the 24 month post-operative visit and 363 of the 396 expected subjects (92%) had any 24-month data available for analysis. Complete 24-month overall success (primary endpoint) data was available for 199 2-level PRESTIGE LP™ subjects (95.2%) and 160 2-level ACDF control subjects (88.9%).

A summary of subject accountability data for the 12-month, 24-month, 36-month, 60-month, and 84-month follow-up visits is provided in **Table 7**.

Table 7: Subject Accountability

	12 Months		24 Months		36 Months		60 Months		84 Months	
	INV	**CTR**	**INV**	**CTR**	**INV**	**CTR**	**INV**	**CTR**	**INV**	**CTR**
Enrolled and treated	209	188	209	188	209	188	209	188	209	188
Deaths (cumulative)	0	0	0	1	0	1	1	1	1	2
Not Yet Overdue	0	0	0	0	0	0	0	0	21	15
Expected[1]	209	188	209	187	209	187	208	187	187	171
Withdrawn (cumulative)	*0*	*4*	*0*	*7*	*1*	*10*	*5*	*12*	*5*	*16*
Actual, primary endpoint data (% follow-up)[2]	202 (97%)	166 (88%)	199 (95%)	160 (86%)	185 (89%)	149 (80%)	166 (80%)	138 (74%)	126 (67%)	99 (58%)
Actual, primary endpoint data in window (% follow-up)[3]	191 (91%)	162 (86%)	181 (87%)	140 (75%)	Not Available					
Actual, any data (% follow-up)[4]	203 (97%)	168 (89%)	199 (95%)	164 (88%)	187 (89%)	152 (81%)	167 (80%)	139 (74%)	126 (67%)	101 (59%)

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)

[1] Treated subjects – (Deaths + Not yet overdue).

[2] Subjects with complete data for the primary endpoint (overall success), regardless of in-window status.

[3] Subjects with complete data for the primary endpoint (overall success), evaluated in-window.

[4] Subjects with any follow-up data reviewed or evaluated.

In addition to the study subjects described above, 17 investigational subjects and 42 control subjects were consented but declined participation in the study prior to receiving the assigned treatment. The demographic and pre-operative characteristics of the subjects who declined to participate in the study were comparable to the characteristics of the subjects who participated in the study.

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

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

Parameter	INV	CTR
Treated	209	188
Expected	209	187
Primary Endpoint:		
NDI (% of Expected)	199 (95%)	159 (85%)
Neurological assessment (% of Expected)	199 (95%)	159 (85%)
Device failure (% of Expected)	209 (100%)	187 (100%)
SD AE (% of Expected)	209 (100%)	187 (100%)
All primary endpoint components (% of Expected)	199 (95%)	160 (89%)
Secondary Clinical Endpoints:		
SF-36 Physical Component Summary (% of Expected)	197 (94%)	156 (83%)
SF-36 Mental Component Summary (% of Expected)	197 (94%)	156 (83%)
Neck Pain (% of Expected)	199 (95%)	159 (85%)
Arm Pain (% of Expected)	199 (95%)	159 (85%)
Subject Perceived Effect (% of Expected)	199 (95%)	159 (85%)
Doctor's Perception (% of Expected)	199 (95%)	159 (85%)
Subject Satisfaction (% of Expected)	199 (95%)	159 (85%)
Gait (% of Expected)	199 (95%)	159 (85%)
Foraminal Compression Test (% of Expected)	199 (95%)	157 (84%)
Adverse events (% of Expected)	209 (100%)	187 (100%)

Parameter	INV	CTR
Secondary Radiographic Endpoints:		
Disc height superior level (% of Expected)	199 (95%)	155 (83%)
Disc height inferior level (% of Expected)	190 (91%)	151 (81%)
Angulation superior level (% of Expected)	198 (95%)	154 (82%)
Angulation inferior level (% of Expected)	196 (94%)	151 (81%)
Translation superior level (% of Expected)	198 (95%)	154 (82%)
Translation inferior level (% of Expected)	196 (94%)	151 (81%)
Device subsidence (FSU Height) (% of Expected)	170 (11%)	132 (70%)
Device migration (% of Expected)	195 (93%)	159 (85%)
Heterotopic Ossification Evaluation (% of Expected)	198 (95%)	N/A

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)

The primary analysis dataset (209 2-level PRESTIGE LP™, 188 2-level ACDF control) included all subjects who completed the surgical procedure and received a study device in either treatment group according to the treatment received (as-treated). Subjects who had subsequent surgical procedures classified as "failure", were deemed "failures" for overall success, and since these subsequent surgical procedures had potential to alter the original study treatment's outcomes, for all neurological status and all individual effectiveness variables, the last observation obtained before the subsequent surgery occurred was carried forward.

Primary statistical comparisons were based on the observed data, and missing data due to lost-to-follow-ups were not imputed. Therefore, the denominators varied for the primary study endpoint (overall success) and individual effectiveness variables such as NDI and neurological status.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a cervical artificial disc device study performed in the United States. **Table 9** presents the summary statistics for demographic and baseline characteristics for the 2-level PRESTIGE LP™ group and the 2-level ACDF control group.

The investigational and control treatment groups were similar demographically, and there were no statistically significant differences ($p<0.05$) for any of the variables except for pre-operative work status (70% working pre-operatively in the 2-level PRESTIGE LP™ group as compared to 60% in the 2-level ACDF control group).

Table 9: Study Population Demographics and Baseline Characteristics

Demographic Measure/ Baseline Characteristic	INV (N=209)	CTR (N=188)	p-value (INV - CTR)
Age (years; mean ± standard deviation)	47.1 ± 8.3 Range: 22 – 75	47.**3** ± 7.7 Range: 25 – 69	0.844
Gender (n(%))			0.480
Male	92 (44.0%)	90 (47.9%)	
Female	117 (56.0%)	98 (52.1%)	
Race (n(%))			0.879
Caucasian	195 (93.3%)	172 (91.5%)	
Black	8 (3.8%)	8 (4.3%)	
Asian	1 (0.5%)	3 (1.6%)	
Hispanic	4 (1.9%)	4 (2.1%)	
Other	1 (0.5%)	1 (0.5%)	
BMI (kg/m^2; mean ± standard deviation)	28.2 ± 5.6 Range: 16 – 46	28.6 ± 4.9 Range: 18 – 43	0.481
Marital Status (n(%))			0.698
Single	25 (12.0%)	29 (15.4%)	
Married	146 (69.9%)	133 (70.7%)	
Divorced	32 (15.3%)	23 (12.2%)	
Separated	4 (1.9%)	2 (1.1%)	
Widowed	2 (1.0%)	1 (0.5%)	
Education Level (n(%))			0.652
< High School	21 (10.0%)	20 (10.6%)	
High School	63 (30.1%)	64 (34.0%)	
> High School	125 (59.8%)	104 (55.3%)	
Previous Neck Surgery (n(%))			0.224
Yes	0 (0.0%)	2 (1.1%)	
No	209 (100.0%)	186 (98.9%)	
Pre-operative Medication Use			
Non-Narcotics	138/208 (66.3%)	133/185 (71.9%)	0.275
Weak Narcotics	83/208 (39.9%)	78/186 (41.9%)	0.758
Strong Narcotics	52/207 (25.1%)	44/188 (23.4%)	0.725
Muscle Relaxants	75/208 (36.1%)	73/188 (38.8%)	0.604
Pre-operative Pain Status[1]			0.078
Arm and Neck Pain	180 (86.1%)	173 (92.0%)	
Arm Pain Only	0 (0.0%)	0 (0.0%)	
Neck Pain Only	29 (13.9%)	15 (8.0%)	
Pre-operative Diagnosis (n(%))			0.837
Radiculopathy and myelopathy	54 (25.8%)	45 (23.9%)	
Radiculopathy only	150 (71.8%)	137 (72.9%)	
Myelopathy only	5 (2.4%)	6 (3.2%)	
Duration of Symptoms			0.340
< 6 wks.	5 (2.4%)	8 (4.3%)	
6 wks. – 6 mos.	56 (26.8%)	58 (30.9%)	
> 6 mos.	148 (70.8%)	122 (64.9%)	
Working pre-operatively	146 (69.9%)	113 (60.1%)	0.045
Worker's Compensation	26 (12.4%)	19 (10.1%)	0.527
Unresolved Spinal Litigation	0 (0.0%)	1 (0.5%)	0.474
Smoking Status	Not provided. Protocol excluded tobacco users who did not agree to stop smoking prior to surgery.		
Current Alcohol Use	116 (55.5%)	88 (46.8%)	0.088

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)

[1] Pre-operative arm and neck pain defined as both arm and neck pain scores ≥ 8/10; pre-operative neck pain only defined as neck pain score ≥ 8/10 and arm pain score < 8/10. There were no subjects with only arm pain because neck pain score ≥ 8/10 was a study inclusion criterion.

The mean baseline pre-operative assessments for the 2-level PRESTIGE LP™ group and the 2-level ACDF control group are presented in **Table 10**. There were no statistical differences between the 2-level PRESTIGE LP™ group and the 2-level ACDF control group for any of the variables identified in the table.

Table 10: Pre-operative Evaluation of Endpoints

Variable	INV (N=209)	CTR (N=188)	p-value (INV - CTR)
NDI; mean ± standard deviation	52.1 ± 13.4 Range: 30 – 84	53.2 ± 14.8 Range: 30 – 94	0.441
SF-36 PCS; mean ± standard deviation	31.8 ± 7.8 Range: 11.7 – 55.5	30.8 ± 7.4 Range: 11.1 – 51.1	0.189
SF-36 MCS; mean ± standard deviation	43.9 ± 11.8 Range: 16.7 – 70.6	43.8 ± 12.2 Range: 15.9 – 67.1	0.930
Neck Pain Score; mean ± standard deviation	16.2 ± 2.9 Range: 8 – 20	16.3 ± 2.6 Range: 8 – 20	0.720
Arm Pain Score; mean ± standard deviation	13.8 ± 5.6 Range: 0 – 20	14.4 ± 4.3 Range: 0 – 20	0.208
Neurological Status Normal (n(%))			
Motor	97 (46.4%)	88 (46.8%)	1.000
Sensory	85 (40.7%)	66 (35.1%)	0.257
Reflexes	90 (43.1%)	75 (39.9%)	0.542
Overall[1]	42 (20.1%)	31 (16.5%)	0.367
ROM flexion/extension angulation (º) Superior Target Level; mean ± standard deviation	6.75 ± 4.16 Range: 0.08 – 18.15	7.12 ± 4.14 Range: 0.45 – 19.72	0.387
ROM flexion/extension angulation (º) Inferior Target Level; mean ± standard deviation	5.56 ± 3.89 Range: 0.37 – 18.20	5.37 ± 3.26 Range: 0.37 – 18.51	0.637
ROM flexion/extension translation (mm) Superior Target Level; mean ± standard deviation	1.48 ± 1.08 Range: 0.13 – 9.17	1.57 ± 1.14 Range: 0.03 – 8.96	0.446
ROM flexion/extension translation (mm) Inferior Target Level; mean ± standard deviation	1.04 ± 0.74 Range: 0.06 – 3.42	1.14 ± 0.93 Range: 0.00 – 6.60	0.267
Baseline radiographic findings – superior target level (n(%))			0.240
Herniated disc	63 (30.1%)	54 (28.7%)	
Osteophyte formation	48 (23.0%)	32 (17.0%)	
Both	98 (46.9%)	102 (54.3%)	
Baseline radiographic findings – inferior target level (n(%))			0.480
Herniated disc	67 (32.1%)	62 (33.0%)	
Osteophyte formation	42 (20.1%)	29 (15.4%)	
Both	100 (47.8%)	97 (51.6%)	

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)

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

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the as-treated cohort of 397 total subjects which included all subjects who completed the surgical procedure and received a study device in either treatment group according to the treatment received (209 2-level PRESTIGE LP™ subjects

and 188 2-level ACDF control subjects). The key safety outcomes for this study are presented below in **Tables 11** to **27**.

Summary of adverse events that occurred in the PMA clinical study
A summary of the adverse event (AE) data is presented in **Table 11**. Adverse events were classified by an independent Clinical Adjudication Committee (CAC) for severity and relationship to the device and/or surgical procedure.

The severity of an AE was assessed as mild (grade 1), moderate (grade 2), severe (grade 3), or life-threatening (grade 4) according to the World Health Organization (WHO) Recommendations for Grading of Acute and Subacute Toxic Effects.

The relationship between an AE and the device/surgical procedure was assessed based on the following definitions:

- Implant Associated: AE for which there is a reasonable possibility that the AE may have been caused primarily by the device;
- Implant/Surgical Procedure Associated AE: AE for which there is a reasonable possibility that the AE may have been caused both by the device and the surgical procedure;
- Surgical Procedure Associated AE: AE for which there is a reasonable possibility that the AE may have been caused primarily by the surgical procedure;
- Undetermined: AE for which sufficient information is not available at the time of the AE to determine its causality;
- Not Related: AE for which sufficient information exists to indicate that the etiology is unrelated to the device or surgical procedure.

The overall AE rates were similar in the 2-level PRESTIGE LP™ group (93.3%) and in the 2-level ACDF control group (92.0%) through 24 months.

Table 11: Summary of Adverse Events (AEs) Through 24-Month Interval (≤30 Months)

	INV (N=209)		CTR (N=188)		Posterior Mean and 95% BCI* of the Difference of Event Rate between INV and CTR**
	Events	Subjects (n (%))	Events	Subjects (n (%))	
All Adverse Events	1477	195 (93.3%)	1593	173 (92.0%)	1.3% (-3.9%, 6.6%)
Subsequent Surgeries at Index Level	6	5 (2.4%)	17	15 (8.0%)	-5.6% (-10.2%, -1.1%)
Device Related AEs	38	16 (7.7%)	35	16 (8.5%)	-0.9% (-6.4%, 4.6%)
Device/Surgical Procedure Related AEs	57	19 (9.1%)	80	26 (13.8%)	-4.7% (-11.1%, 1.6%)
Device or Device/Surgical Procedure Related AEs	95	33 (15.8%)	115	39 (20.7%)	-4.9% (-12.6%, 2.6%)
Surgical Procedure Related AEs	127	60 (28.7%)	106	45 (23.9%)	4.7% (-3.9%, 13.3%)
Severe AEs (Grade 3 or 4)	293	72 (34.4%)	430	90 (47.9%)	-13.3% (-22.8%, -3.7%)
Severe Device or Device/Surgical Procedure Related AEs (Grade 3 or 4)	8	4 (1.9%)	28	11 (5.9%)	-3.9% (-8.1%, 0.0%)

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)
* BCI = Bayesian HPD Credible Interval
**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.

Timecourse of all Adverse Events

The timecourse of adverse events reported in the PMA clinical study from all 397 total subjects (209 2-level PRESTIGE LP™ subjects and 188 2-level ACDF control subjects) through all available follow-up are shown in **Table 12**. This table includes adverse events from all subjects to establish the safety profile of the device. Adverse events are listed in alphabetical order by main category with clinically relevant subcategories also detailed. Definitions of the adverse event categories and subcategories are provided in **Table 13**. Subject 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. Subjects experiencing adverse events in more than one category are represented in each category in which they experienced an adverse event. The percentage of subjects experiencing at least one adverse event is comparable in the 2-level PRESTIGE LP™ group and the 2-level ACDF control group.

Some of the more commonly reported clinically relevant adverse events through all available follow-up were cervical neck and/or arm pain (in 62.7% of 2-level PRESTIGE LP™ subjects and 63.3% of 2-level ACDF control subjects), cervical neurological adverse events (in 39.7% of 2-level PRESTIGE LP™ subjects and 38.8% of 2-level ACDF control subjects), cervical study surgery spinal events (in 19.1% of 2-level PRESTIGE LP™ subjects and 10.6% of 2-level ACDF control subjects), cervical Heterotopic Ossification (in 15.8% of 2-level PRESTIGE LP™ subjects and 13.3% of 2-level ACDF control subjects), dysphagia/dysphonia (in 8.6% of 2-level PRESTIGE LP™ subjects and 12.2% of 2-level ACDF control subjects), non-infectious wound adverse events (in 8.6% of 2-level PRESTIGE LP™ subjects and 7.4% of 2-level ACDF control subjects), and implant adverse events (in 7.2% of 2-level PRESTIGE LP™ subjects and 8.5% of 2-level ACDF control subjects).

Table 12: Adverse Events Through All Available Follow-up

	Surgery		Peri-Op (1 day - <4 Weeks)		Short Term								Long Term						Longer Term			
					6 Weeks (≥4 Wks - < 9 Weeks)		3 Months (≥9 Wks – <5 Mo)		6 Months (≥5 Mo- <9 Mo)		12 Months (≥9 Mo- <19 Mo)		24 Months (≥19 Mo- <30 Mo)		# of Patients Reporting & Total adverse events (≤ 24 Months)				# of Patients Reporting & Total adverse events (≤ 84 Months)			
Adverse Event	Invest	Control	Invest	Control	Invest	Control	Invest	Control	Invest	Control	Invest	Control	Invest	Control	INV Subj. (% of 209)	INV Events (N)	CTR Subj. (% of 188)	CTR Events (N)	INV Subj. (% of 209)	INV Events (N)	CTR Subj. (% of 188)	CTR Events (N)
Total Adverse Events	54	38	166	221	116	119	228	266	245	240	372	390	296	319	195 (93.3%)	1477	173 (92.0%)	1593	204 (97.6%)	2146	179 (95.2%)	2147
Cancer	0	0	0	0	0	1	0	0	0	0	0	1	0	1	0 (0.0%)	0	3 (1.6%)	3	3 (1.4%)	3	8 (4.3%)	10
Cardiac Disorders	2	3	2	0	3	0	1	1	8	3	8	8	4	3	18 (8.6%)	28	16 (8.5%)	18	27 (12.9%)	40	27 (14.4%)	43
Death	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0 (0.0%)	0	1 (0.5%)	1	1 (0.5%)	1	2 (1.1)%	2
Dysphagia / Dysphonia	1	2	5	11	2	4	1	5	0	0	4	3	1	2	14 (6.7%)	14	21 (11.2%)	27	18 (8.6%)	18	23 (12.2%)	29
• Dysphagia	1	1	4	9	1	3	0	4	0	0	3	3	1	2	10 (4.8%)	10	20 (10.6%)	22	14 (6.7%)	14	22 (11.7%)	24
• Dysphonia	0	1	1	2	1	1	1	1	0	0	1	0	0	0	4 (1.9%)	4	5 (2.7%)	5	4 (1.9%)	4	5 (2.7%)	5
Gastrointestinal	5	2	13	16	0	3	12	7	16	6	38	28	17	17	43 (20.6)	101	38 (20.2%)	79	58 (27.8%)	142	45 (23.9%)	97
Heterotopic Ossification	0	0	1	2	0	2	3	5	3	5	9	3	11	7	22 (10.5%)	27	21 (11.2%)	24	33 (15.8%)	40	32 (17.0%)	37
• Cervical	0	0	1	2	0	2	3	4	3	3	8	2	11	2	21 (10.0%)`	26	14 (7.4%)	15	32 (15.3%)	38	25 (13.3%)	26
• Non-Cervical	0	0	0	0	0	0	0	1	0	2	1	1	0	5	1 (0.5%)	1	8 (4.3%)	9	2 (1.0%)	2	10 (5.3%)	11
Implant Events	4	0	2	2	1	2	0	2	3	2	0	4	5	0	13 (6.2%)	15	10 (5.3%)	12	15 (7.2)	18	16 (8.5%)	18
• Breakage	1	0	0	1	0	0	0	1	0	0	0	0	0	0	1 (0.5%)	1	2 (1.1%)	2	2 (1.0%)	2	4 (2.1%)	4
• Displacement	1	0	0	0	1	0	0	0	1	0	0	1	3	0	6 (2.9%)	6	1 (0.5%)	1	7 (3.3%)	7	2 (1.1%)	2
• Displacement - Subsidence	0	0	0	0	0	2	0	0	2	2	0	2	1	0	2 (1.0%)	3	6 (3.2%)	6	3 (1.4%)	4	6 (3.2%)	6
• Loosening	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0 (0.0%)	0	3 (1.6%)	3	0 (0.0%)	0	6 (3.2%)	6
• Malpositioning	2	0	1	0	0	0	0	0	0	0	0	0	0	0	3 (1.4%)	3	0 (0.0%)	0	3 (1.4%)	3	0 (0.0%)	0
• Other	0	0	1	0	0	0	0	0	0	0	0	0	1	0	2 (1.0%)	2	0 (0.0%)	0	2 (1.0%)	2	0 (0.0%)	0
Infection*	0	1	5	6	3	3	3	7	8	3	20	11	9	9	35 (16.9%)	47	31 (16.5%)	40	39 (18.7)	60	37 (19.7%)	54
Cervical Neck and / or Arm Pain	13	2	37	49	28	24	49	41	33	41	44	47	43	40	112 (53.6%)	247	104 (55.3%)	244	131 (62.7)	325	119 (63.3%)	314
•Cervical Neck Pain	6	1	16	23	13	14	25	19	17	22	25	20	21	24	83 (39.7%)	123	80 (42.6%)	23	105(50.2)	167	97 (51.6%)	165
• Cervical Arm Pain	7	1	21	26	15	10	24	22	16	19	19	27	22	16	76 (36.4%)	124	76 (40.4%)	121	89(42.6)	158	88 (46.8%)	149
Non-Cervical Arm and/or Neck Pain	0	0	1	3	8	4	10	15	11	9	8	11	9	7	36 (17.2%)	47	36 (19.1%)	49	55 (26.3)	73	49 (26.1)	74
Cervical Neurological	5	4	16	16	13	16	26	20	23	10	21	21	23	14	66 (31.6%)	127	59 (31.4%)	101	83 (39.7%)	1167	73 (38.8%)	2133
• Spinal Cord Disturbance	0	0	0	0	0	1	1	0	0	0	0	1	0	0	1 (0.5%)	1	2 (1.1%)	2	1(0.5%)	1	3 (1.6%)	3
• Upper Extremity-Motor	0	1	2	0	3	4	2	7	3	4	4	1	4	1	15 (7.2%)	18	13 (6.9%)	18	21 (10.0%)	25	19 (10.1%)	27
• Upper Extremity-																						

	Surgery		Peri-Op (1 day - <4 Weeks)		Short Term								Long Term						Longer Term			
					6 Weeks (≥4 Wks - < 9 Weeks)		3 Months (≥9 Wks – <5 Mo)		6 Months (≥5 Mo- <9 Mo)		12 Months (≥9 Mo- <19 Mo)		24 Months (≥19 Mo- <30 Mo)		# of Patients Reporting & Total adverse events (≤ 24 Months)				# of Patients Reporting & Total adverse events (≤ 84 Months)			
Adverse Event	Invest	Control	Invest	Control	Invest	Control	Invest	Control	Invest	Control	Invest	Control	Invest	Control	INV Subj. (% of 209)	INV Events (N)	CTR Subj. (% of 188)	CTR Events (N)	INV Subj. (% of 209)	INV Events (N)	CTR Subj. (% of 188)	CTR Events (N)
Sensory	5	3	14	16	10	11	23	13	20	6	17	19	19	13	60(28.7%)	108	52(27.7%)	81	75 (35.9%)	141	65 (34.6%)	103
Non-Cervical Neurological	2	4	7	9	8	7	19	21	14	12	12	23	10	15	54 (25.8%)	72	50 (26.6%)	91	62 (29.7%)	100	60 (31.9%)	115
Non-Union	0	0	0	1	0	1	0	7	0	6	0	2	0	1	0 (0.0%)	0	18 (9.6%)	18	1 (0.5%)	1	21 (11.2%)	22
Other	8	6	27	24	13	9	20	27	34	22	52	71	41	57	97 (46.4%)	195	87 (46.3%)	216	114 (54.5%)	281	103 (54.8%)	299
Other Pain**	4	6	26	36	23	21	45	40	44	57	68	74	49	61	125 (59.8%)	259	113 (60.1%)	295	147 (70.3%)	401	127 (67.6%)	392
Respiratory	4	5	8	6	1	2	3	8	3	10	14	13	14	8	29 (13.9%)	47	34 (18.1%)	52	38 (18.2%)	68	43(22.9%)	66
Spinal Event	2	0	3	26	7	12	20	45	32	38	45	47	40	29	74 (35.4%)	149	80 (42.6%)	197	97 (46.4%)	2231	96 (51.1%)	2267
• Cervical (Study Surgery)	2	0	0	12	0	1	2	7	9	4	9	4	13	2	29 (13.9%)	35	17 (9.0%)	30	40 (19.1%)	52	20 (10.6%)	33
•Cervical (Non-Study Surgery)	0	0	1	9	0	3	3	8	4	12	17	15	13	7	26 (12.4%)	38	34(18.1%)	54	38 (18.2%)	56	59 (31.4%)	109
•Non-Cervical	0	0	2	5	7	8	15	30	19	22	19	28	14	20	38 (18.2%)	76	52 (27.7%)	113	58 (27.8%)	123	56 (29.8%)	125
Trauma	0	0	0	6	5	2	8	6	8	8	15	14	9	24	37 (17.7%)	45	39 (20.7%)	60	57 (27.3%)	83	55 (29.3%)	88
Urogenital	1	1	5	4	0	5	6	3	2	4	9	5	8	14	25 (12.0%)	31	19 (10.1%)	36	42 (20.1%)	60	28 (14.9%)	53
Vascular	1	0	0	1	0	1	1	2	0	0	3	1	1	9	5 (2.4%)	6	8 (4.3%)	14	10 (4.8%)	12	10 (5.3%)	16
• Injury Intra-op	1	0	0	1	0	0	0	0	0	0	1	0	0	0	2 (1.0%)	2	1 (0.5%)	1	2 (1.0%)	2	1 (0.5%)	1
• Other	0	0	0	0	0	1	1	2	0	0	2	1	1	9	3(1.4%)	4	7 (3.7%)	13	8 (3.8%)	10	9 (4.8%)	15
Wound (Non-Infectious)	2	2	8	3	2	0	1	4	3	4	2	2	2	1	16 (7.7%)	20	12 (6.4%)	16	18 (8.6%)	22	14 (7.4%)	18
• CSF Leak	0	1	0	0	0	0	0	2	0	0	0	0	0	0	0 (0.0%)	0	2 (1.1%)	3	0 (0.0%)	0	2 (1.1%)	3
• Dehiscence	0	0	1	0	0	0	0	0	2	1	0	0	2	0	4 (1.9%)	5	1 (0.5%)	1	4 (1.9%)	5	1 (0.5%)	1
• Hematoma	0	0	2	0	0	0	1	0	1	0	1	0	0	0	5 (2.4%)	5	0 (0.0%)	0	6 (2.9%)	6	1 (0.5%)	1
•Cervical superficial surgical site	0	0	0	1	1	0	0	0	0	0	0	0	0	0	1 (0.5%)	1	1 (0.5%)	1	1 (0.5%)	1	1 (0.5%)	1
• Other	2	1	5	2	1	0	0	2	0	3	1	2	0	1	8 (3.8%)	9	8 (4.3%)	11	9 (4.3%)	10	9 (4.8%)	12

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)

* All other wound infections (non-surgical/non-study site), urinary tract infections, or other infection.

** 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 13: Adverse Event Categories and Subcategories

Adverse Event	Definition
Cancer	A malignancy or malignant tumor/neoplasm
Cardiac Disorders	Any condition of the heart
Death	Termination of life due to any cause
Dysphagia/Dysphonia • Dysphagia • Dysphonia	 • Difficulty in swallowing • Difficulty in speaking
Gastrointestinal	Any condition pertaining to the stomach and intestines
Heterotopic Ossification • Heterotopic Ossification – Cervical • Heterotopic Ossification - Non-Cervical	 • Event involving heterotopic ossification at any region of the cervical spine • Event involving heterotopic ossification at any region of the spine that is not cervical or any other region of the body
Implant Events • Implant Events – Breakage • Implant Events - Displacement • Implant Events – Displacement – Subsidence • Implant Events - Loosening • Implant Events - Malpositioning • Implant Events - Other	 • Breakage of any implant or implant component • Incomplete or partial dislocation of the implant • Event associated with implant subsidence into the vertebral body when the reported term includes "subsidence" • Wear around the implant and/or loosening of the implant surface • Poor or inappropriate placement of the implant • Event that is implant-related, but does not meet the definition of malpositioned implant, implant displacement, implant loosening, or implant breaking
Infection	Any wound infection that is non-surgical or is not of the surgical site, an infection of any part of the urinary system, or any infection occurring in other surgical would not involving the study
Cervical Arm and/or Neck Pain • Cervical Neck Pain • Cervical Arm Pain	 • Pain involving the neck region, which does not include neurological systems. These symptoms are such that cervical spine etiology cannot be ruled out. • Pain involving the arm, which does not include neurological symptoms. These symptoms are such that a cervical spine etiology cannot be ruled out.
Non-Cervical Arm and/or Neck Pain	Pain involving the arm and/or neck which does not include neck neurological symptoms. Information is available at the reported event time to reasonably rule out a cervical spine etiology.
Cervical Neurological • Spinal Cord Disturbance • Upper Extremity – Motor • Upper Extremity - Sensory	 • Condition in which there is a disruption or disturbance to the spinal cord • Event that involves stimulation of the motor neurons that induce movements, as nerves or muscles. Such events would affect any part of the upper extremity including the shoulder, brachium, elbow, forearm, hand, and fingers and may be muscular in nature. • Event that involves a feeling or awareness of condition within the body resulting from stimulation of sensory receptors. Such sensation would affect any part of the upper extremity including the shoulder, brachium, elbow, forearm, hand and fingers and may be radiating, continuing, extending, or spreading to an adjacent anatomy.
Non-Cervical Neurological	Neurological event not associated with the cervical spine
Non-Union	Failure of the vertebral bodies to fuse at the treated level
Other	Event not associated with any other categories (e.g., weight loss, tinnitus, substance abuse, insomnia)
Other Pain	Pain (including stiffness, strain, tightness) in an area that is not of the cervical spine region, occurring in the back (e.g., low back pain, thoracic back pain, back pain), occurring in the head (e.g. headache, migraine headache, head pain), occurring in the lower extremity and using the term "pain" (e.g., leg pain, knee pain, calf pain, foot pain), and/or occurring in parts of the body that are not classified as a headache, back pain, or lower extremity pain (e.g. earache, fibromyalgia, non-cardiac chest pain, sore throat, arthritis)
Respiratory	Ailments or symptoms associated with respiration or the respiratory system

Adverse Event	Definition
Spinal Event	
• Spinal Event – Cervical Study Surgery	• Event involving cervical spine diagnoses at the study treatment level; usually confirmed via radiologic findings
• Spinal Event – Cervical Non-Study Surgery	• Event involving cervical spine diagnoses at one or more cervical spine level(s), with the exception of the treated level; usually confirmed via radiologic findings
• Spinal Event - Non-Cervical	• Event involving diagnoses at one or more spine levels other than cervical spine; usually confirmed via radiologic findings
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	
• Vascular – injury (intra-operative)	• Injury to a vascular structure that is sustained during the course of the operative procedure; initial study surgery only
• Vascular – Other	• Disorder or condition in which the vascular system is affected
Wound (Non-Infectious)	
• Wound (Non-Infectious) - CSF Leak	• Compromise or tear of the dura mater resulting in leakage of cerebral spinal fluid, excluding infection. Fluid is clear and free of microorganisms
• Wound (Non-Infectious) –Dehiscence	• A bursting open or separation of a wound without the presence of microorganisms
• Wound (Non-Infectious) – Hematoma	• Swelling or mass of blood (usually clotted) confined to an organ, tissue, or space and caused by a break in a blood vessel. Wound is not limited to a specific anatomic region and there is an absence of microorganisms
• Wound (Non-Infectious) - Cervical superficial surgical site	• An infection near the surface of the surgical incision
• Wound (Non-Infectious) -Other	• Wound condition in which there is an absence of infection or other feature (e.g., wound oozing, scar tissue, incisional edemas, scratches to skin surface)

Bayesian analyses were conducted to compare adverse events in main categories and subcategories using non-informative priors. The results are presented in **Table 14** with 95% Bayesian Credible Intervals (BCI) for the difference in adverse event rates (2-level PRESTIGE LP™ – 2-level ACDF). BCIs that exclude zero indicate statistical differences in the adverse event rates between the 2-level PRESTIGE LP™ group and the 2-level ACDF control group without adjusting for multiplicity. Based on the BCIs, there were no statistical differences between the two treatment groups in the total number of adverse events or the number of adverse events in any category except for non-union, in which the difference favored the 2-level PRESTIGE LP™ group.

Table 14: Bayesian Comparison of Posterior Probabilities of Adverse Events in Main Categories Through 24-Month Interval (≤30 Months)

Adverse Event	Subjects Experiencing Adverse Events (%)		Posterior Mean and 95% HPD of Adverse Event Rate		Posterior Mean and 95% BCI* of the Difference of Adverse Event Rate between INV and CTR
	INV (N=209)	CTR (N=188)	INV	CTR	INV - CTR
Total Subjects Experiencing Adverse Events	195 (93.3%)	173 (92.0%)	92.9 (89.4%, 96.2%)	91.6% (87.5%, 95.3%)	1.3% (-3.9%, 6.6%)
Cancer	0 (0.0%)	3 (1.6%)	0.5% (0.0%, 1.4%)	2.1% (0.4%, 4.2%)	-1.6% (-4.0%, 0.4%)
Cardiac Disorders	18 (8.6%)	16 (8.5%)	9.0% (5.3%, 12.9%)	8.9% (5.1%, 13.1%)	0.1% (-5.5%, 5.7%)
Death	0 (0.0%)	1 (0.5%)	0.5% (0.0%, 1.4%)	1.1% (0.0%, 2.5%)	-0.6% (-2.5%, 1.1%)
Dysphagia / Dysphonia	14 (6.7%)	21 (11.2%)	7.1% (3.8%, 10.6%)	11.6% (7.2%, 16.2%)	-4.5% (-10.2%, 1.2%)
Gastrointestinal	43 (20.6%)	38 (20.2%)	20.9% (15.5%, 26.4%)	20.5% (14.9%, 26.3%)	0.3 % (-7.6%, 8.2%)
Heterotopic Ossification	22 (10.5%)	21 (11.2%)	10.9% (6.8%, 15.1%)	11.6% (7.2%, 16.2%)	-0.7% (-6.9%, 5.5%)
Implant Events	13 (6.2%)	10 (5.3%)	6.6% (3.5%, 10.1%)	5.8% (2.7%, 9.2%)	0.8% (-3.9%, 5.6%)
Infection	36 (17.2%)	32 (17.0%)	17.5% (12.6%, 22.8%)	17.4% (12.1%, 22.8%)	0.2% (-7.3%, 7.6%)
Neck and / or Arm Pain	127 (60.8%)	114 (60.6%)	60.7% (54.0%, 67.2%)	60.5% (53.6%, 67.5%)	0.1% (-9.3%, 9.8%)
Neurological	89 (42.6%)	85 (45.2%)	42.7% (36.0%, 49.3%)	45.3% (38.3%, 52.4%)	-2.6% (-12.3%, 7.1%)
Non-Union	0 (0.0%)	18 (9.6%)	0.5% (0.0%, 1.4%)	10.0% (5.9%, 14.3%)	-9.5% (-14.0%, -5.4%)**
Other	97 (46.4%)	87 (46.3%)	46.4% (39.8%, 53.2%)	46.3% (39.2%, 53.4%)	0.1% (-9.6%, 9.9%)
Other Pain	125 (59.8%)	113 (60.1%)	59.7% (53.1%, 66.2%)	60.0% (53.1%, 67.0%)	-0.3% (-9.9%, 9.3%)
Respiratory	29 (13.9%)	34 (18.1%)	14.2% (9.7%, 19.0%)	18.4% (13.0%, 24.0%)	-4.2% (-11.5%, 3.0%)
Spinal Event	74 (35.4%)	80 (42.6%)	35.5% (29.2%, 42.0%)	42.6% (35.7%, 49.7%)	-7.1% (-16.5%, 2.5%)
Trauma	37 (17.7%)	39 (20.7%)	18.0% (13.0%, 23.3%)	21.1% (15.4%, 26.9%)	-3.0% (-10.8%, 4.7%)
Urogenital	25 (12.0%)	19 (10.1%)	12.3% (8.1%, 16.8%)	10.5% (6.4%, 15.0%)	1.8% (-4.4%, 8.0%)
Vascular	5 (2.4%)	8 (4.3%)	2.8% (0.9%, 5.1%)	4.7% (2.0%, 7.8%)	-1.9% (-5.7%, 1.9%)
Wound (Non-Infectious)	15 (7.2%)	11 (5.9%)	7.6% (4.2%, 11.2%)	6.3% (3.1%, 9.8%)	1.3% (-3.8%, 6.2%)

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)
* BCI = Bayesian HPD Credible Interval
**BCI excluding 0

Table 15 provides a comparison of the pain adverse events that occurred in the study up to the 24-month visit. As shown in **Table 15**, the number of subjects experiencing pain and the incidence of all pain adverse events in the in the 2-level PRESTIGE LP™ group was comparable to the 2-level ACDF control group except for arm pain and lower extremity pain which were both nominally higher in the ACDF control group.

Table 15: Pain Adverse Events through 24-Month Interval (≤30 Months)

Pain Adverse Event Category	INV (N = 209)		CTR (N=188)	
	Subjects n (%)	Events N	Subjects n (%)	Events N
≥ 1 Pain AE	163 (78.0%)	553	150 (79.8%)	588
Pain Adverse Events by Location:				
• Neck	60 (28.7%)	84	55 (29.3%)	79
• Arm	72 (34.4%)	114	68 (36.2%)	113
• Neck and Arm	34 (16.3%)	96	40 (21.3%)	101
• Back Pain	36 (17.2%)	43	40 (21.3%)	48
• LE Pain	10 (4.8%)	10	20 (10.6%)	21
• Headache	42 (20.1%)	46	43 (22.9%)	56
• Other Pain*	98 (46.9%)	160	87 (46.3%)	170

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)
*Other pain in Table 17 consists of all adverse events classified as "Other Pain" for the study except for the back and/or LE pain and headache adverse events.

Deaths

Through all available follow-up, there was one reported death in the 2-level PRESTIGE LP™ group (due to a motor vehicle accident in the 48 month window), and there were two reported deaths in the ACDF control group (one due to cardiac arrest possibly due to overdose in the 12 month and the other due to a motor vehicle accident in the 72 month windows). The deaths were evaluated by the CAC, and based upon available information were determined to be unrelated to the study treatments.

Subsequent Surgical Interventions at the Index Level

Some adverse events resulted in surgical intervention at one or both of the index levels, subsequent to the initial surgery. Subsequent surgical interventions at the index level(s) were classified as revisions, supplemental fixations, non-elective removals, elective removals, reoperations or other surgical procedures. Per the study protocol, revisions, supplemental fixations, and non-elective removals were considered subsequent surgery failures, whereas reoperations, elective removals, and other surgical procedures were not considered subsequent surgery failures. Overall, there were 10 subsequent surgical interventions at the index level(s) in 8 (3.8%) 2-level PRESTIGE LP™ subjects and 26 subsequent surgical interventions at the index level(s) in 22 (11.7%) 2-level ACDF control subjects. The timecourse of the subsequent surgical interventions through all available follow-up is summarized in **Table 16**.

Table 16 also presents the Bayesian statistical comparison of subsequent surgeries at the index level(s) through 24 months between the 2-level PRESTIGE LP™ and 2-level ACDF control treatment groups. Through 24 months, there were a greater number of subjects who underwent subsequent surgical procedures at the index level(s) in the 2-level ACDF control group [15 (8.0%)] compared to the 2-level PRESTIGE LP™ group [5 (2.4%)], and the rates were nominally statistically different without adjusting for multiplicity.

Table 16: Subsequent Surgical Interventions at the Index Level(s) Through All Available Follow-up

	Surgery		Peri-Op (1 day - <4 Weeks)		Short Term								Long Term								Longer Term			
					6 Weeks (≥4 Wks - < 9 Weeks)		3 Months (≥9 Wks – <5 Mo)		6 Months (≥5 Mo- <9 Mo)		12 Months (≥9 Mo- <19 Mo)		24 Months (≥19 Mo- <30 Mo)		Posterior Mean and 95% HPD of Subsequent Surgery Rate		Posterior Mean and 95% BCI* of Difference of Subsequent Surgery Rate between INV and CTR	# of Patients Reporting & Total Events (≤ 24 Months)				# of Patients Reporting & Total Events (≤ 84 Months)			
Type	INV	CTR	INV	CTR	INV	CTR	INV	CTR	INV	CTR	INV	CTR	INV	CTR	INV	CTR		INV Subj. (% of 209)	INV Events (N)	CTR Subj. (% of 188)	CTR Events (N)	INV Subj. (% of 209)	INV Events (N)	CTR Subj. (% of 188)	CTR Events (N)
Revision[1]	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0.5% (0.0%, 1.4%)	1.1% (0.0%, 2.5%)	-0.6% (-2.5%, 1.1%)	0 (0.0%)	0	1 (0.5%)	1	0 (0.0%)	0	1 (0.5%)	1
Supplemental fixation[2]	0	0	0	0	0	0	0	0	0	1	1	2	0	0	0.9% (0.0%, 2.3%)	2.1% (0.4%, 4.2%)	-1.2% (-3.7%, 1.2%)	1 (0.5%)	1	3 (1.6%)	3	1 (0.5%)	1	7 (3.7%)	7
Non-elective removal[3]	0	0	0	0	1	0	0	1	0	2	1	2	1	1	1.9% (0.3%, 3.7%)	3.7% (1.3%, 6.4%)	-1.8% (-5.1%, 1.4%)	3 (1.4%)	3	6 (3.2%)	6	6 (2.9%)	6	6 (3.2%)	6
Elective removal[4]	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0.5% (0.0%, 1.4%)	1.6% (0.2%, 3.3%)	-1.1% (-3.3%, 0.8%)	0 (0.0%)	0	2 (1.1%)	2	0 (0.0%)	0	6 (3.2%)	6
Reoperation	0	0	0	0	0	0	0	2	1	0	1	2	0	1	1.4% (0.1%, 3.0%)	2.6% (0.7%, 4.9%)	-1.2% (-4.1%, 1.5%)	2 (1.0%)	2	4 (2.1%)	5	3 (1.4%)	3	5 (2.7%)	6
TOTAL	0	0	0	0	1	1	0	4	1	3	3	6	1	3	2.8% (0.8%, 5.1%)	8.4% (4.7%, 12.5%)	-5.6% (-10.2%, -1.1%)	5 (2.4%)	6	15 (8.0%)	17	8 (3.8%)	10	22 (11.7%)	26
External bone growth stimulator[6]	0	0	0	0	0	0	0	0	0	4	0	1	0	0	0.5% (0.0%, 1.4%)	3.2% (1.0%, 5.7%)	-2.7% (-5.5%, -0.2%)	0 (0.0%)	0	5 (2.7%)	5	0 (0.0%)	0	5 (2.7%)	5

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)

* BCI = Bayesian HPD Credible Interval

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

[2] A procedure at the involved level(s) in which additional spinal devices not approved as part of the protocol are placed. This categorization of Supplemental Fixations does not include supplemental therapies (i.e. external bone growth stimulators).

[3] Any procedure that removes the device as the result of an adverse event..

[4] A procedure that removes the device at the discretion of the investigator and/or the patient and is not the result of an adverse event..

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

[6] There were a total of 6 external bone growth stimulators used in the 2-level ACDF control group. While the use of external bone growth stimulators were not considered a secondary surgery, these subjects were considered failures in the original primary endpoint analysis. However, a sensitivity analysis was provided to FDA in which they were not considered failures.

Table 17 provides detailed information on each 2-level PRESTIGE LP™ subsequent surgical intervention at the index level(s). Similarly, **Table 18** provides detailed information on each 2-level ACDF control group subsequent surgical intervention at the index level(s).

Table 17: Detailed Information on 2-level PRESTIGE LP™ Subsequent Surgical Interventions at the Index Level(s)*

Surgical Intervention Type	Procedure Type	Procedure Level(s)	Adverse Event Type	Days From Index Procedure	Device(s) Removed?
Supplemental Fixation	C4, C5, C6 laminectomy and C7 partial laminectomy; C3-C4, C4-C5, C5-C6, and C6-C7 arthrodesis; posterior cervical spinal instrumentation	C4-C5 & C5-C6	Cervical spondylotic myelopathy; cervical radiculopathy	553	No
Non-Elective Removal	Explant both PRESTIGE LP™ (C5-C6 & C6-C7); C5-C6 and C6-C7 partial corpectomy and fusion with allograft bone; C5-C6 and C6-C7 revision of foraminotomy and scar tissue debridement	C5-C6 & C6-C7	Right arm radicular pain; positive foraminal compression test	40	Yes, both levels
Non-Elective Removal	Explant both PRESTIGE LP™ (C5-C6 & C6-C7); C4-C5, C5-C6, and C6-C7 anterior decompression and discectomy; C4-C7 anterior cervical fusion	C5-C6 & C6-C7	Post-surgical cervical kyphosis; sagittal imbalance	486	Yes, both levels
Non-Elective Removal	Explant both PRESTIGE LP™ (C5-C6 and C6-C7); C5-C6 and C6-C7 anterior cervical discectomy and fusion; C4-C5 artificial disc (PRESTIGE ST)	C5-C6 & C6-C7	C4-C5 disc bulge/protrusion; C4-C5 left paracentral foraminal narrowing; C5-C6 and C6-C7 mid-foraminal encroachment; C6-C7 right foraminal narrowing; C5-C6 and C6-C7 posterior osteophytes	624	Yes, both levels
Non-Elective Removal	Explant one level PRESTIGE LP™ (C6-C7); iliac crest allograft arthrodesis and stabilization by plate	C5-C6 & C6-C7	Failed cervical disc arthroplasty with cervical stenosis and C6-C7 cord compression	929	Yes, one level
Non-Elective Removal	Explant both PRESTIGE LP™ (C5-C6 and C6-C7); redo anterior cervical microdiscectomy, bilateral anterior foraminotomies and central canal decompression at C5-C6 and C6-C7; anterior fusion using PEEK spacer and demineralized bone matrix plus anterior cervical titanium plate	C5-C6 & C6-C7	Foraminal stenosis secondary to loosening of hardware; Exacerbation of residual symptoms secondary to motor vehicle accident	994	Yes, both levels

Non-Elective Removal	Explant both PRESTIGE LP™(C4-C5 and C5-C6); C5 corpectomy; C4 to C6 anterior fusion; revision bilateral C4-C5 and C5-C6 decompressive foraminotomy; C6-C7 anterior cervical discectomy and fusion using PEEK interbody cage and local autograft bone; combined C4 to C7 instrumented posterolateral fusion	C4-C5 & C5-C6	Progressive subsidence of C4-C5 and C5-C6 artificial discs, recurrent C4-C5 and C5-C6 bilateral foraminal stenosis, advanced C6-C7 cervical spondylitic degenerative change with bilateral C6-C7 foraminal stenosis, intractable neck pain and bilateral upper extremity radiculopathy, intractable cervicogenic headache	1641	Yes, both levels
Reoperation	C5-C6 and C6-C7 Microforaminotomy and C5, C6, and C7 partial right hemilaminectomy	C5-C6 & C6-C7	C5-C6 and C6-C7 foraminal stenosis on the right	222	No
Reoperation	Rhizotomy C2-C3, C6-C7, and C7-T1 left/right	C5-C6 & C6-C7	Increased neck pain	529	No
Reoperation	C4-C5 explant of PRESTIGE® ST artificial disc followed by removal of anterior cervical plate from C5 through C7, exploration of cervical spinal fusion mass C5 through C7 (solid), anterior partial vertebral corpectomy inferior C5 and superior C4, decompression of nerve roots and resection of spurs posteriorly with resection of scar tissue at C4-C5, anterior fusion, bone morphogenetic protein at C4-C5, anterior instrumentation with cervical plate at C4-5-6-7 with rescue screws and conventional screws	C5-C6 & C6-C7	C4-C5 central canal narrowing due to spurring behind the artificial disc replacement; cord compression	2061	No

* As of September 29, 2014.

Table 18: Detailed Information on 2-Level ACDF Control Group Subsequent Surgical Interventions at the Index Level(s)*

Surgical Intervention Type	Procedure Type	Procedure Level(s)	Adverse Event Type	Days From Index Procedure	Device(s) Removed?
Revision	C5-C6 and C6-C7 removal of plate and screws; C6-C7 allograft removal; C6-C7 replacement of C6-C7 allograft; new plate and screws	C5-C6 & C6-C7	C6-C7 recurrent disc herniation after traumatic injury	37	Yes, both levels
Supplemental Fixation	C5 to C7 posterior fusion and posterior lateral mass instrumentation; left iliac crest bone graft	C5-C6 & C6-C7	C5-C6 and C6-C7 pseudarthrosis; intractable neck pain	257	No

Supplemental Fixation	C5-C6 and C6-C7 left laminotomy and foraminotomy; C5 to C7 posterior fusion; BMP and local graft	C5-C6 & C6-C7	C5-C6 and C6-C7 failed fusion; left cervical radiculopathy	319	No
Supplemental Fixation	C5-C6 bilateral foraminotomies and C5-C7 posterior fusion with autograft and instrumentation	C5-C6 & C6-C7	C5-C6 nonunion; cervical spondylosis	429	No
Supplemental Fixation	C6-C7 and C7-T1 posterior cervical laminotomy and foraminotomy; C6-C7 cervical wiring; posterior fusion using collagen sponge and iliac crest graft aspirate	C5-C6 & C6-C7	C6-C7 nonunion with cervical radiculopathy	1176	No
Supplemental Fixation	C5-C6 posterior fusion and posterior lateral mass screws and rods; BMP	C5-C6 & C6-C7	C5-C6 pseudarthrosis; neck pain	1351	No
Supplemental Fixation	C3, C4, C5, C6, and C7 laminoplasty and C3, C4, C5, C6, and C7 posterior fusion with allograft bone	C5-C6 & C6-C7	Cervical spinal cord compression	1861	No
Supplemental Fixation	C3 to C7 decompression and posterior spinal fusion	C5-C6 & C6-C7	C3-C4 osteophyte with central disc protrusion; cervical pain	2497	No
Non-Elective Removal	C5-C6 and C6-C7 anterior cervical removal of interbody grafts; C5, C6, and C7 partial vertebral corpectomies; anterior interbody arthrodesis with PEEK graft with Hydrosorb and BMP, anterior instrumentation	C5-C6 & C6-C7	C5-C6 and C6-C7 nonunion; biomechanical cervical pain; upper extremity radiculopathy	122	Yes, both levels
Non-Elective Removal	C5-C6 and C6-C7 removal of anterior instrumentation and interbody grafts; C5-C6 and C6-C7 decompression of spinal cord nerve root bilaterally; C5-C6 and C6-C7 anterior interbody arthrodesis with PEEK and BMP	C5-C6 & C6-C7	C6-C7 nonunion	162	Yes, both levels
Non-Elective Removal	C5-C6 and C6-C7 removal anterior cervical instrumentation and removal of interbody grafts; C5, C6, and C7 partial vertebral corpectomies; C5-C6 and C6-C7 anterior interbody fusion with PEEK and BMP; anterior instrumentation	C5-C6 & C6-C7	C5-C6 and C6-C7 nonunion with loosened hardware	223	Yes, both levels
Non-Elective Removal	C5-C6 hardware removal; C5-C6 corpectomy; C5-C6 fusion with PEEK cage and autograft; C5-C7 instrumentation	C4-C5 & C5-C6	Cervical spondylosis; C5-C6 cord compression; C6-C7 neural foraminal stenosis from osteophyte	550	Yes, one level

Non-Elective Removal	C5-C6 and C6-C7 removal of anterior instrumentation; C5-C6 removal of interbody graft; C4-C5 anterior discectomy; C5-C6 arthrodesis with Hydrosorb and BMP; C5, C6 and C7 anterior cervical plate; C4-C5 PRESTIGE ST disc	C5-C6 & C6-C7	C5-C6 nonunion; fall; C4-C5 degenerative herniated disc	553	Yes, both levels
Non-Elective Removal	C4-C5 and C5-C6 anterior hardware removal; C4-C5 and C5-C6 exploration of fusion (C4-C5 with solid fusion); C5-C6 partial corpectomy; C5-C6 fusion; BMP; C5-C6 plate	C4-C5 & C5-C6	C5-C6 nonunion; headaches	624	Yes, both levels
Elective Removal	C5, C6, and C7 removal of anterior plate; C4-C5 discectomy; C4-C5 anterior decompression foraminotomy; C4-C5 interbody arthrodesis with structural allograft; C4, C5, C6, and C7 anterior plating	C5-C6 & C6-C7	Cervical spondylosis status post C5-C6 and C6-C7 anterior cervical discectomy and interbody arthrodesis; cervical radiculopathy	84	Yes, both levels
Elective Removal	C4-C5 and C5-C6 removal of anterior cervical plate; C4-C5 and C5-C6 exploration (solid bony union at these levels); C6 and C7 partial corpectomy; C6-C7 anterior cervical disc arthroplasty	C4-C5 & C5-C6	Cervical spondylosis; C6-C7 foraminal stenosis; intractable neck, shoulder, and arm pain	755	Yes, both levels
Elective Removal	C5-C6 and C6-C7 hardware removed; C4-C5 anterior cervical discectomy and fusion	C5-C6 & C6-C7	C4-C5 disc protrusion and spinal cord compression	1285	Yes, both levels
Elective Removal	C5, C6, and C7 removal of anterior cervical instrumentation; C4-C5 microdiscectomy	C5-C6 & C6-C7	C4-C5 extruded herniated disc fragment with myelopathy and radiculopathy; head struck dashboard during a motor vehicle accident	1739	Yes, both levels
Elective Removal	C4 to C6 removal of anterior cervical hardware; C3-C4 anterior cervical discectomy and disc arthroplasty; C3 and C4 partial corpectomy; PRESTIGE ST disc	C4-C5 & C5-C6	C3-C4 broad protrusion indenting the cervical cord	2044	Yes, both levels
Elective Removal	C4 to C6 removal of plate and screws (fusion noted); C6-C7 anterior cervical discectomy and fusion with bone graft; osteophytectomy; microforaminotomy	C4-C5 & C5-C6	C6-C7 herniated nucleus pulposus; C6-C7 osteophyte	2145	Yes, both levels
Reoperation	C5-C6 posterior laminoforaminotomy with nerve root decompression and C7-T1 laminoforaminotomy with nerve root decompression	C5-C6 & C6-C7	C5-C6 foraminal narrowing; C5-C6 interbody graft subsidence; C7-T1 foraminal narrowing and bone spur extending into the foramen on the left side; cervical radiculopathy	82	No

Reoperation	C5-C6 and C7-T1 posterior cervical wound exploration; repair of dural tear and cerebrospinal fluid leak	C5-C6 & C6-C7	Postoperative cerebrospinal fluid leak	108	No
Reoperation	C5, C6, C7 right median branch nerve therapeutic blocks with subsequent radiofrequency ablation	C5-C6 & C6-C7	C5-C6 graft subsidence; neck pain; C5-C6 and C6-C7 possible pseudarthrosis; C2-C3 and C3-C4 facet joints with severe degenerative arthropathy	419	No
Reoperation	C5-C7 exploration of fusion mass posteriorly	C5-C6 & C6-C7	C5-C6 halo around the screw; neck pain/burning (rule out C5-C6 pseudarthrosis)	453	No
Reoperation	C4-C5, C6-C7, and C7-T1 left posterior decompression	C4-C5 & C5-C6	Left upper extremity radiculopathy and arm weakness; motor vehicle accident	641	No
Reoperation	C5-C7 removal of anterior cervical hardware; C4-C5 anterior cervical discectomy and bilateral foraminotomies; C4-C5 anterior interbody arthrodesis with allograft and PEEK intervertebral body device; C4, C5, C6, and C7 anterior cervical instrumentation	C5-C6 & C6-C7	C4-C5 spondylosis	1494	Yes, both levels
Bone Growth Stimulator	C5-C6 bone growth stimulator	C4-C5 & C5-C6	C5-C6 nonunion; headaches	187	No
Bone Growth Stimulator	C5-C6 bone growth stimulator	C4-C5 & C5-C6	C5-C6 pseudarthrosis	188	No
Bone Growth Stimulator	Bone growth stimulator	C5-C6 & C6-C7	Fell postoperative day 9; headaches; difficulty lifting right arm over head	188	No
Bone Growth Stimulator	C6-C7 bone growth stimulator	C5-C6 & C6-C7	C6-C7 nonunion	206	No
Bone Growth Stimulator	C5-C6 bone growth stimulator	C5-C6 & C6-C7	C5-C6 nonunion; fall; C4-C5 degenerative herniated disc	507	No

* As of September 29, 2014.

Device-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, undetermined, and not related as outlined above. The timecourse and total number and percentage of subjects who experienced an adverse event classified by the CAC as either implant associated or implant and surgical procedure associated by adverse event category are provided in **Table 19**.

Considering events classified by the CAC as either implant associated or implant and surgical procedure associated as device-related, through all available follow-up, 125 device-related events occurred in 48 (23.0%) 2-level PRESTIGE LP™ subjects and 126 device-related events occurred in 45 (23.9%) 2-level ACDF control subjects. Some of the more commonly reported device-related adverse events through all available follow-up were cervical neck and/or arm pain (in 7.2% of 2-level PRESTIGE LP™ subjects and

10.6% of 2-level ACDF control subjects), cervical neurological adverse events (in 6.7% of 2-level PRESTIGE LP™ subjects and 6.4% of 2-level ACDF control subjects), cervical study surgery spinal events (in 9.1% of 2-level PRESTIGE LP™ subjects and 3.7% of 2-level ACDF control subjects), cervical Heterotopic Ossification (in 7.7% of 2-level PRESTIGE LP™ subjects and 2.1% of 2-level ACDF control subjects), implant adverse events (in 6.2% of 2-level PRESTIGE LP™ subjects and 5.3% of 2-level ACDF control subjects), and non-union in the 2-level ACDF control group (9.0%). Any numerical differences were most likely due to chance based on examining a great number of categories of adverse events.

Table 19: Adverse Events Classified as Device-Related (Implant Associated or Implant and Surgical Procedure Associated) by the Clinical Adjudication Committee through All Available Follow-up

	Surgery		Peri-Op (1 day - < 4 Weeks)		Short Term								Long Term		# of Patients Reporting & Total adverse events (≤ 24 Months)				Longer Term										# of Patients Reporting & Total adverse events (≤ 84 Months)			
					6 Weeks (≥4 Wks - < 9 Weeks)		3 Months (≥9 Wks – <5 Mo)		6 Months (≥5 Mo- <9 Mo)		12 Months (≥9 Mo- <19 Mo)		24 Months (≥19 Mo- <30 Mo)						36 Months (≥30 Mo- <42 Mo)		48 Months (≥42 Mo- <54 Mo)		60 Months (≥54 Mo- <66 Mo)		72 Months (≥66 Mo- <78 Mo)		84 Months (≥78 Mo- <90 Mo)					
Adverse Event	Invest	Control	Invest	Control	Invest	Control	Invest	Control	Invest	Control	Invest	Control	Invest	Control	INV Subj. (% of 209)	INV Events (N)	CTR Subj. (% of 188)	CTR Events (N)	Invest	Control	Invest	Control	Invest	Control	Invest	Control	Invest	Control	INV Subj. (% of 209)	INV Events (N)	CTR Subj. (% of 188)	CTR Events (N)
Total Adverse Events	18	5	26	40	8	24	1	28	3	12	19	6	20	0	33 (15.8%)	95	39 (20.7%)	115	9	4	6	0	9	4	0	0	6	3	48 (23.0%)	125	45 (23.9%)	126
Dysphagia / Dysphonia	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	1	1	1 (0.5%)	1	1 (0.5%)	1
• Dysphagia	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	1	1	1 (0.5%)	1	1 (0.5%)	1
Heterotopic Ossification	0	0	0	1	0	1	0	2	0	1	3	0	7	0	9 (4.3%)	10	4 (2.1%)	5	1	0	1	0	3	0	0	0	3	0	16 (7.7%)	18	4 (2.1%)	5
• Cervical	0	0	0	1	0	1	0	2	0	1	3	0	7	0	9 (4.3%)	10	4 (2.1%)	5	1	0	1	0	3	0	0	0	3	0	16 (7.7%)	18	4 (2.1%)	5
Implant Events	4	0	2	2	1	1	0	2	1	0	0	3	4	0	11 (5.3%)	12	6 (3.2%)	8	2	0	0	0	1	3	0	0	0	1	13 (6.2%)	15	10 (5.3%)	12
• Breakage	1	0	0	1	0	0	0	1	0	0	0	0	0	0	1 (0.5%)	1	2 (1.1%)	2	1	0	0	0	0	0	0	0	0	0	2 (1.0%)	2	2 (1.1%)	2
• Displacement	1	0	0	0	1	0	0	0	0	0	0	1	2	0	4 (1.9%)	4	1 (0.5%)	1	1	0	0	0	0	0	0	0	0	1	5 (2.4%)	5	2 (1.1%)	2
• Displacement - Subsidence	0	0	0	0	0	1	0	0	1	0	0	1	1	0	2 (1.0%)	2	2 (1.1%)	2	0	0	0	0	1	0	0	0	0	0	3 (1.4%)	3	2 (1.1%)	2
• Loosening	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0 (0.0%)	0	3 (1.6%)	3	0	0	0	0	0	3	0	0	0	0	0 (0.0%)	0	6 (3.2%)	6
• Malpositioning	2	0	1	0	0	0	0	0	0	0	0	0	0	0	3 (1.4%)	3	0(0.0%)	0	0	0	0	0	0	0	0	0	0	0	3 (1.4%)	3	0 (0.0%)	0
• Other	0	0	1	0	0	0	0	0	0	0	0	0	1	0	2 (1.0%)	2	0(0.0%)	0	0	0	0	0	0	0	0	0	0	0	2 (1.0%)	2	0 (0.0%)	0
Cervical Neck and / or Arm Pain	7	2	12	16	2	9	0	1	0	1	7	0	2	0	12 (5.7)	30	18 (9.6)	29	3	1	1	0	1	1	0	0	0	0	15 (7.2%)	35	20 (10.6%)	31
•Cervical Neck Pain	4	1	7	6	0	4	0	1	0	1	4	0	1	0	11 (5.3)	16	11 (5.9)	13	2	1	1	0	1	1	0	0	0	0	14 (6.7%)	20	13 (6.9%)	15
• Cervical Arm Pain	3	1	5	10	2	5	0	0	0	0	3	0	1	0	10 (4.8)	14	13 (6.9)	16	1	0	0	0	0	0	0	0	0	0	11 (5.3%)	15	13 (6.9%)	16
Non-Cervical Arm and/or Neck Pain	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0 (0.0)	0	1 (0.5)	2	0	0	0	0	0	0	0	0	0	0	0 (0.0%)	0	1 (0.5%)	2
Cervical Neurological	4	1	8	6	4	7	1	5	1	0	1	0	0	0	13 (6.2%)	19	12 (6.4%)	19	0	0	3	0	0	0	0	0	0	0	14 (6.7%)	22	12 (6.4%)	19
• Spinal Cord Disturbance	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0 (0.0%)	0	1 (0.5%)	1	0	0	0	0	0	0	0	0	0	0	0 (0.0%)	0	1 (0.5%)	1
• Upper Extremity-Motor	0	1	1	0	2	0	0	2	0	0	1	0	0	0	4 (1.9%)	4	3 (1.6%)	3	0	0	1	0	0	0	0	0	0	0	5 (2.4%)	5	3 (1.6%)	3
• Upper Extremity-Sensory	4	0	7	6	2	6	1	3	1	0	0	0	0	0	10 (4.8%)	15	10 (5.3%)	15	0	0	2	0	0	0	0	0	0	0	11 (5.3%)	17	10 (5.3%)	15
Non-Cervical Neurological	0	0	1	0	0	2	0	0	0	0	0	0	0	0	1(0.5%)	1	1 (0.5%)	2	0	0	0	0	0	0	0	0	0	0	1 (0.5%)	1	1 (0.5%)	2
Non-Union	0	0	0	1	0	1	0	6	0	4	0	2	0	0	0 (0.0%)	0	14 (7.4%)	14	0	3	0	0	0	0	0	0	0	0	0 (0.0%)	0	17 (9.0%)	17
Other	1	0	0	0	0	0	0	1	0	0	1	0	0	0	2 (1.0%)	2	1 (0.5%)	1	0	0	0	0	0	0	0	0	0	0	2 (1.0%)	2	1 (0.5%)	1
Other Pain	1	1	3	2	1	2	0	0	0	0	2	0	0	0	5 (2.4%)	7	5 (2.7%)	5	0	0	0	0	0	0	0	0	0	1	5 (2.4%)	7	6 (3.2%)	6

	Surgery		Peri-Op (1 day - < 4 Weeks)		Short Term								Long Term		# of Patients Reporting & Total adverse events (≤ 24 Months)				Longer Term										# of Patients Reporting & Total adverse events (≤ 84 Months)			
					6 Weeks (≥4 Wks - < 9 Weeks)		3 Months (≥9 Wks – <5 Mo)		6 Months (≥5 Mo- <9 Mo)		12 Months (≥9 Mo- <19 Mo)		24 Months (≥19 Mo- <30 Mo)						36 Months (≥30 Mo- <42 Mo)		48 Months (≥42 Mo- <54 Mo)		60 Months (≥54 Mo- <66 Mo)		72 Months (≥66 Mo- <78 Mo)		84 Months (≥78 Mo- <90 Mo)					
Adverse Event	Invest	Control	Invest	Control	Invest	Control	Invest	Control	Invest	Control	Invest	Control	Invest	Control	INV Subj. (% of 209)	INV Events (N)	CTR Subj. (% of 188)	CTR Events (N)	Invest	Control	Invest	Control	Invest	Control	Invest	Control	Invest	Control	INV Subj. (% of 209)	INV Events (N)	CTR Subj. (% of 188)	CTR Events (N)
Spinal Event	1	0	0	12	0	1	0	9	1	5	4	1	7	0	12 (5.7%)	13	13 (6.9%)	28	3	0	1	0	4	0	0	0	2	0	21 (10.0%)	23	13 (6.9%)	28
• Cervical (Study Surgery)	1	0	0	9	0	0	0	4	1	2	4	1	5	0	10 (4.8%)	11	7 (3.7%)	16	3	0	1	0	4	0	0	0	1	0	19 (9.1%)	20	7 (3.7%)	16
•Cervical (Non-Study Surgery)	0	0	0	3	0	1	0	5	0	3	0	0	2	0	2 (1.0%)	2	8 (4.3%)	12	0	0	0	0	0	0	0	0	1	0	3 (1.4%)	3	8 (4.3%)	12
Trauma	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0 (0.0%)	0	1 (0.5%)	1	0	0	0	0	0	0	0	0	0	0	0 (0.0%)	0	1 (0.5%)	1
Vascular	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1 (0.5%)	1	0 (0.0%)	0	0	0	0	0	0	0	0	0	0	0	1 (0.5%)	1	0 (0.0%)	0
• Injury Intra-op	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1 (0.5%)	1	0 (0.0%)	0	0	0	0	0	0	0	0	0	0	0	1 (0.5%)	1	0 (0.0%)	0
Wound (Non-Infectious)	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0 (0.0%)	0	1 (0.5%)	1	0	0	0	0	0	0	0	0	0	0	0 (0.0%)	0	1 (0.5%)	1
• CSF Leak	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0 (0.0%)	0	1 (0.5%)	1	0	0	0	0	0	0	0	0	0	0	0 (0.0%)	0	1 (0.5%)	1

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)

* 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.

Procedure-Related Adverse Events

The total number and percentage of subjects who experienced an adverse event classified by the CAC as surgical procedure associated by adverse event category are provided in **Table 20**.

Through all available follow-up, 127 procedure-related events occurred in 60 (28.7%) 2-level PRESTIGE LP™ subjects and 106 procedure-related events occurred in 45 (23.9%) 2-level ACDF control subjects. Some of the more commonly reported procedure-related adverse events through all available follow-up were dysphagia/dysphonia (in 4.3% of 2-level PRESTIGE LP™ subjects and 6.9% of 2-level ACDF control subjects), cervical neck and/or arm pain (in 8.1% of 2-level PRESTIGE LP™ subjects and 4.3% of 2-level ACDF control subjects), cervical neurological adverse events (in 3.3% of 2-level PRESTIGE LP™ subjects and 2.1% of 2-level ACDF control subjects), other pain adverse events (in 6.7% of 2-level PRESTIGE LP™ subjects and 6.9% of 2-level ACDF control subjects), and other adverse events (in 6.7% of 2-level PRESTIGE LP™ subjects and 5.3% of 2-level ACDF control subjects).

Table 20: Adverse Events Classified as Procedure-Related by the Clinical Adjudication Committee through All Available Follow-up

Adverse Event	INV (N=209)		CTR (N=188)	
	Subjects n (%)	Events N	Subjects n (%)	Events N
Total Procedure-Related Adverse Events	60 (28.7%)	127	45 (23.9%)	106
Cardiac Disorders	1 (0.5%)	2	2 (1.1%)	3
Dysphagia/Dysphonia	9 (4.3%)	9	13 (6.9%)	18
• Dysphagia	6 (2.9%)	6	12 (6.4%)	14
• Dysphonia	3 (1.4%)	3	4 (2.1%)	4
Gastrointestinal	6 (2.9%)	9	5 (2.7%)	12
Infection (other)	1 (0.5%)	1	2 (1.1%)	2
Cervical Arm and/or Neck Pain	17 (8.1%)	37	8 (4.3%)	12
• Cervical Neck Pain	10 (4.8%)	15	6 (3.2%)	6
• Cervical Arm Pain	13 (6.2%)	22	5 (2.7%)	6
Non-Cervical Arm and/or Neck Pain	1 (0.5%)	1	0 (0.0%)	0
Cervical Neurological	7 (3.3%)	9	4 (2.1%)	5
• Upper Extremity – Motor	1 (0.5%)	1	0 (0.0%)	0
• Upper Extremity - Sensory	6 (2.9%)	8	4 (2.1%)	5
Non-Cervical Neurological	2 (1.0%)	2	4 (2.1%)	4
Other	14 (6.7%)	18	10 (5.3%)	15
Other Pain	14 (6.7%)	14	13 (6.9%)	18
Respiratory	5 (2.4%)	7	5 (2.7%)	6
Spinal Event	2 (1.0%)	2	1 (0.5%)	1
• Cervical (Study Surgery)	1 (0.5%)	1	0 (0.0%)	0
• Cervical (Non-Study Surgery)	0 (0.0%)	0	1 (0.5%)	1
• Non-Cervical	1 (0.5%)	1	0 (0.0%)	0
Urogenital	2 (1.0%)	2	3 (1.6%)	3
Vascular	1 (0.5%)	1	2 (1.1%)	2
• Injury Intra-op	1 (0.5%)	1	1 (0.5%)	1
• Other	0 (0.0%)	0	1 (0.5%)	1

Adverse Event	INV (N=209)		CTR (N=188)	
	Subjects n (%)	Events N	Subjects n (%)	Events N
Wound (Non-Infectious)	12 (5.7%)	13	5 (2.7%)	5
• Dehiscence	2 (1.0%)	2	0 (0.0%)	0
• Hematoma	2 (1.0%)	2	0 (0.0%)	0
• Cervical superficial surgical site	1 (0.5%)	1	1 (0.5%)	1
• Other	7 (3.3%)	8	4 (2.1%)	4

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)

Severe Adverse Events

Severity of adverse events was assessed according to the 4-tier World Health Organization (WHO) Recommendations for Grading of Acute and Subacute Toxic Effects. The total number and percentage of subjects who experienced an adverse event classified by the CAC as severe (grade 3 or 4) by adverse event category through all available follow-up is provided in **Table 21**.

Through 24 months follow-up, the percentage of subjects who experienced a grade 3 or grade 4 adverse event was higher in the 2-level ACDF control group as compared to the 2-level PRESTIGE LP™ group (47.9% vs. 34.4%). The 95% BCI for the difference of grade 3/4 adverse event rates (2-level PRESTIGE LP™ - 2-level ACDF) was (-22.8%, -3.7%) which excludes 0, indicating a nominal statistical difference when not adjusted for multiplicity.

Some of the clinically relevant grade 3 or 4 adverse events through all available follow-up were cervical neck and/or arm pain (in 5.3% of 2-level PRESTIGE LP™ subjects and 13.8% of 2-level ACDF control subjects), cervical neurological adverse events (in 4.3% of 2-level PRESTIGE LP™ subjects and 4.8% of 2-level ACDF control subjects), cervical study surgery spinal events (in 3.3% of 2-level PRESTIGE LP™ subjects and 3.7% of 2-level ACDF control subjects), cervical Heterotopic Ossification (in 2.9% of 2-level PRESTIGE LP™ subjects and 5.9% of 2-level ACDF control subjects), implant adverse events (in 1.4% of 2-level PRESTIGE LP™ subjects and 4.3% of 2-level ACDF control subjects), and non-union in the 2-level ACDF control group only (6.4%).

Table 21: Adverse Events Classified as Severe (Grade 3 or 4) by the Clinical Adjudication Committee through All Available Follow-up

Adverse Event	INV (N=209)		CTR (N=188)	
	Subjects n (%)	Events N	Subjects n (%)	Events N
Total Severe (Grade 3/4) Adverse Events	103 (49.3%)	449	110 (58.5%)	602
Cancer	3 (1.4%)	3	7 (3.7%)	9
Cardiac Disorders	8 (3.8%)	12	13 (6.9%)	21
Death	1 (0.5%)	1	2 (1.1%)	2
Dysphagia/Dysphonia	4 (1.9%)	4	1 (0.5%)	1
• Dysphagia	4 (1.9%)	4	1 (0.5%)	1
Gastrointestinal	27 (12.9%)	53	17 (9.0%)	29

Adverse Event	INV (N=209)		CTR (N=188)	
	Subjects n (%)	Events N	Subjects n (%)	Events N
Heterotopic Ossification	8 (3.8%)	9	15 (8.0%)	16
• Cervical	6 (2.9%)	7	11 (5.9%)	11
• Non-Cervical	2 (1.0%)	2	5 (2.7%)	5
Implant Events	3 (1.4%)	3	8 (4.3%)	9
• Breakage	0 (0.0%)	0	3 (1.6%)	3
• Displacement	2 (1.0%)	2	0 (0.0%)	0
• Displacement - Subsidence	1 (0.5%)	1	4 (2.1%)	4
• Loosening	0 (0.0%)	0	2 (1.1%)	2
Infection*	13 (6.2%)	19	15 (8.0%)	18
Cervical Arm and/or Neck Pain	11 (5.3%)	14	26 (13.8%)	47
• Cervical Neck Pain	4 (1.9%)	5	17 (9.0%)	20
• Cervical Arm Pain	9 (4.3%)	9	19 (10.1%)	27
Non-Cervical Arm and/or Neck Pain	13 (6.2%)	15	13 (6.9%)	20
Cervical Neurological	9 (4.3%)	10	9 (4.8%)	11
• Spinal Cord Disturbance	1 (0.5%)	1	0 (0.0%)	0
• Upper Extremity - Sensory	9 (4.3%)	9	9 (4.8%)	11
Non-Cervical Neurological	15 (7.2%)	18	17 (9.0%)	25
Non-Union	0 (0.0%)	0	12 (6.4%)	12
Other	30 (14.4%)	71	45 (23.9%)	89
Other Pain	48 (23.0%)	75	45 (23.9%)	92
Respiratory	10 (4.8%)	12	16 (8.5%)	21
Spinal Event	30 (14.4%)	74	48 (25.5%)	116
• Cervical (Study Surgery)	7 (3.3%)	12	7 (3.7%)	12
• Cervical (Non-Study Surgery)	9 (4.3%)	15	26 (13.8%)	42
• Non-Cervical	18 (8.6%)	47	25 (13.3%)	62
Trauma	21 (10.0%)	25	27 (14.4%)	34
Urogenital	12 (5.7%)	21	10 (5.3%)	17
Vascular	3 (1.4%)	4	4 (2.1%)	10
• Injury Intra-op	1 (0.5%)	1	0 (0.0%)	0
• Other	2 (1.0%)	3	4 (2.1%)	10
Wound (Non-Infectious)	5 (2.4%)	6	2 (1.1%)	3
• CSF Leak	0 (0.0%)	0	2 (1.1%)	3
• Dehiscence	2 (1.0%)	3	0 (0.0%)	0
• Hematoma	1 (0.5%)	1	0 (0.0%)	0
• Other	2 (1.0%)	2	0 (0.0%)	0

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)
* All either other wound infection (non-surgical/non-study site) or other infection.

Severe Device-Related Adverse Events

Of the events classified by the CAC as device-related, those classified as grade 3 or 4 according to the World Health Organization Recommendations for Grading of Acute and Subacute Toxic Effects were considered severe device-related adverse events. Through all available follow-up, 9 severe device-related events occurred in 5 (2.4%) 2-level PRESTIGE LP™ subjects and 30 severe device-related events occurred in 12 (6.4%) 2-level ACDF control subjects.

Some of the more commonly reported severe device-related adverse events through all available follow-up were cervical neck and/or arm pain in zero 2-level PRESTIGE LP™ subjects and 3 (1.6%) 2-level ACDF control subjects, cervical study surgery spinal events

in 3 (1.4%) 2-level PRESTIGE LP™ subjects and 2 (1.1%) 2-level ACDF control subjects, cervical non-study surgery spinal events in zero 2-level PRESTIGE LP™ subjects and 4 (2.1%) 2-level ACDF control subjects, cervical Heterotopic Ossification in zero 2-level PRESTIGE LP™ subjects and 3 (1.6%) 2-level ACDF control subjects, implant adverse events in 2 (1.0%) 2-level PRESTIGE LP™ subjects and 3 (1.6%) 2-level ACDF control subjects, and non-union in zero 2-level PRESTIGE LP™ subjects and 9 (4.8%) 2-level ACDF control group subjects.

The total number and percentage of subjects who experienced an adverse event classified by the CAC as severe (grade 3 or 4) and either implant associated or implant and surgical procedure associated by adverse event category are provided in **Table 22**.

Table 22: Adverse Events Classified as Severe (Grade 3 or 4) and Device-Related (Implant Associated or Implant and Surgical Procedure Associated) by the Clinical Adjudication Committee through All Available Follow-up

Adverse Event	INV (N=209)		CTR (N=188)	
	Subjects n (%)	Events N	Subjects n (%)	Events N
Total Severe Device-Related Adverse Events	5 (2.4%)	9	12 (6.4%)	30
Dysphagia/Dysphonia	1 (0.5%)	1	0 (0.0%)	0
• Dysphagia	1 (0.5%)	1	0 (0.0%)	0
Heterotopic Ossification	0 (0.0%)	0	3 (1.6%)	3
• Cervical	0 (0.0%)	0	3 (1.6%)	3
Implant Events	2 (1.0%)	2	3 (1.6%)	4
• Breakage	0 (0.0%)	0	1 (0.5%)	1
• Displacement	1 (0.5%)	1	0 (0.0%)	0
• Displacement - Subsidence	1 (0.5%)	1	1 (0.5%)	1
• Loosening	0 (0.0%)	0	2 (1.1%)	2
Neck and/or Arm Pain	0 (0.0%)	0	3 (1.6%)	3
• Cervical Neck Pain	0 (0.0%)	0	3 (1.6%)	3
Cervical Neurological	0 (0.0%)	0	1 (0.5%)	1
• Upper Extremity – Sensory	0 (0.0%)	0	1 (0.5%)	1
Non-Union	0 (0.0%)	0	9 (4.8%)	9
Other	1 (0.5%)	1	0 (0.0%)	0
Spinal Event	3 (1.4%)	4	5 (2.7%)	8
• Cervical (Study Surgery)	3 (1.4%)	4	2 (1.1%)	4
• Cervical (Non-Study Surgery)	0 (0.0%)	0	4 (2.1%)	4
Trauma	0 (0.0%)	0	1 (0.5%)	1
Vascular	1 (0.5%)	1	0 (0.0%)	0
• Injury Intra-op	1 (0.5%)	1	0 (0.0%)	0
Wound (Non-Infectious)	0 (0.0%)	0	1 (0.5%)	1
• CSF Leak	0 (0.0%)	0	1 (0.5%)	1

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)

By Treatment Levels

Table 23 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 2-level PRESTIGE LP™ group and the 2-level ACDF control group through the 24-

month timepoint using Frequentist methods. The percentage of subjects with any adverse events was not statistically different between the two groups for all levels

Table 23: Summary of Adverse Events (AEs) by Level Treated through 24-Month Interval (≤30 Months)

	Superior C3-C4 Inferior C4-C5		Superior C4-C5 Inferior C5-C6		Superior C5-C6 Inferior C6-C7	
	INV	CTR	INV	CTR	INV	CTR
All Adverse Events	3/3 (100%)	2/3 (66.7%)	41/43 (95.3%)	40/44 (90.9%)	151/163 (92.6%)	131/141 (92.9%)
Statistics*	33.3% (-26.3%, 93.0%)		4.4% (-6.2%, 15.1%)		-0.3% (-6.1%, 5.6%)	
Device or Device/Surgical Procedure Related AEs	0/3 (0.0%)	0/3 (0.0%)	9/43 (20.9%)	9/44 (20.5%)	24/163 (14.7%)	30/141 (21.3%)
Surgical Procedure Related AEs	0/3 (0.0%)	1/3 (33.3%)	13/43 (30.2%)	10/44 (22.7%)	47/163 (28.8%)	34/141 (24.1%)
Severe AEs (Grade 3 or 4)	2/3 (66.7%)	0/3 (0.0%)	16/43 (37.2%)	20/44 (45.5%)	54/163 (33.1%)	70/141 (49.6%)
Severe Device or Device/Surgical Procedure Related AEs (Grade 3 or 4)	0/3 (0.0%)	0/3 (0.0%)	1/43 (2.3%)	3/44 (6.8%)	3/163 (1.8%)	8/141 (5.7%)

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)

* Point Estimate and 95% Confidence Interval of Difference of Adverse Rate between INV and CTR. The 95% CI was provided using Frequentist Farrington and Manning methods.

By Gender

Adverse events were also analyzed by subject gender (**Table 24**). Adverse event rates were generally comparable when comparing the male and female cohorts .

Table 24: Summary of All Adverse Events by Subject Gender through 24-Month Interval (≤30 Months)

Adverse Event	2-level PRESTIGE LP™			
	Subjects		Events	
	Male (N=92)	Female (N=117)	Male (N=92)	Female (N=117)
Cardiac Disorders	4 (4.3%)	14 (12.0%)	5	23
Dysphagia / Dysphonia	4 (4.3%)	10 (8.5%)	4	10
• Dysphagia	3 (3.3%)	7 (6.0%)	3	7
• Dysphonia	1 (1.1%)	3 (2.6%)	1	3
Gastrointestinal	17 (18.5%)	26 (22.2%)	33	68
Heterotopic Ossification	13 (14.1%)	9 (7.7%)	15	12
• Cervical	13(14.1%)	8 (6.8%)	15	11
• Non-Cervical	0 (0.0%)	1 (0.9%)	0	1
Implant Events	8 (8.7%)	5 (4.3%)	10	5
• Breakage	1 (1.1%)	0 (0.0%)	1	0
• Displacement	4 (4.3%)	2 (1.7%)	4	2
• Displacement – Subsidence	1 (1.1%)	1 (0.9%)	2	1
• Malpositioning	2 (2.2%)	1 (0.9%)	2	1
• Other	1 (1.1%)	1 (0.9%)	1	1
Infection	13 (14.1%)	22 (18.8%)	17	31
Cervical Neck and/or Arm Pain	42 (45.7%)	70 (59.8%)	83	164
• Cervical Neck Pain	27 (29.3%)	56 (47.9%)	42	81
• Cervical Arm Pain	28 (30.4%)	48 (41.0%)	41	83
Non-Cervical Neck and/or Arm Pain	17 (18.5%)	19 (16.2%)	24	23

Adverse Event	2-level PRESTIGE LP™			
	Subjects		Events	
	Male (N=92)	Female (N=117)	Male (N=92)	Female (N=117)
Cervical Neurological	26 (28.3%)	40 (34.2%)	49	78
• Spinal Cord Disturbance	0 (0.0%)	1 (0.9%)	0	1
• Upper Extremity-Motor	8 (8.7%)	7 (6.0%)	11	7
• Upper Extremity-Sensory	23 (25.0%)	37 (31.6%)	38	70
Non-Cervical Neurological	25 (27.2%)	29 (24.8%)	33	39
Other	40 (43.5%)	57 (48.7%)	79	116
Other Pain	53 (57.6%)	72 (61.5%)	108	151
Respiratory	12 (13.0%)	17 (14.5%)	20	27
Spinal Event	34 (37.0%)	40 (34.2%)	72	77
• Cervical (Study Surgery)	17 (18.5%)	12 (10.3%)	22	13
• Cervical (Non-Study Surgery)	13 (14.1%)	13 (11.1%)	19	19
• Non-Cervical	15 (16.3%)	23 (19.7%)	31	45
Trauma	17 (18.5%)	20 (17.1%)	19	26
Urogenital	11 (12.0%)	14 (12.0%)	12	19
Vascular	1 (1.1%)	4 (3.4%)	1	5
• Injury Intra-op	0 (0.0%)	2 (1.7%)	0	2
• Other	1 (1.1%)	2 (1.7%)	1	3
Wound (Non-Infectious)	8 (8.7%)	8 (6.8%)	11	9
• Dehiscence	2 (2.2%)	2 (1.7%)	3	2
• Hematoma	3 (3.3%)	2 (1.7%)	3	2
• Cervical superficial surgical site	0 (0.0%)	1 (0.9%)	0	1
• Other	4 (4.4%)	4 (3.4%)	5	4
Any adverse Event	82 (89.1%)	113 (96.6%)	595	882

Neurological Status

Neurological status was evaluated by assessment of motor function, sensory function, and reflexes. Available neurological status data at 6 weeks, 3 months, 6 months, 12 months, 24 months, 36 months, 60 months and 84 months is provided for the 2-level PRESTIGE LP™ and 2-level Control subjects in **Table 25** below. Neurologic success was defined as maintenance or improvement in all elements of neurologic status compared to baseline. The success rates at 24 months post-operative were 91.5% for the 2-level PRESTIGE LP™ group and 86.2% for the 2-level ACDF control group. At 24 months post-operative, there were numerically fewer subjects who exhibited neurologic deterioration in the 2-level PRESTIGE LP™ group (8.5%) as compared to the 2-level ACDF control group (13.8%).

Table 25: Timecourse of Overall Neurological Status

Timepoint	Neurological Status	INV (N=209)	CTR (N=188)
6 weeks	Improved	141/206 (68.4%)	126/182 (69.2%)
	Stable	36/206 (17.5%)	25/182 (13.7%)
	Deteriorated	29/206 (14.1%)	31/182 (17.0%)
3 months	Improved	147/205 (71.7%)	119/178 (66.9%)
	Stable	37/205 (18.0%)	30/178 (16.9%)
	Deteriorated	21/205 (10.2%)	29/178 (16.3%)
6 months	Improved	143/204 (70.1%)	121/174 (69.5%)
	Stable	42/204 (20.6%)	29/174 (16.7%)

Timepoint	Neurological Status	INV (N=209)	CTR (N=188)
	Deteriorated	19/204 (9.3%)	24/174 (13.8%)
12 months	Improved	142/203 (70.0%)	109/165 (66.1%)
	Stable	40/203 (19.7%)	27/165 (16.4%)
	Deteriorated	21/203 (10.3%)	29/165 (17.6%)
24 months	Improved	146/199 (73.4%)	108/159 (67.9%)
	Stable	36/199 (18.1%)	29/159 (18.2%)
	Deteriorated	17/199 (8.5%)	22/159 (13.8%)
36 months	Improved	134/185 (72.4%)	97/148 (65.5%)
	Stable	33/185 (17.8%)	27/148 (18.2%)
	Deteriorated	18/185 (9.7%)	24/148 (16.2%)
60 months	Improved	116/166 (69.9%)	95/136 (69.9%)
	Stable	34/166 (20.5%)	24/136 (17.6%)
	Deteriorated	16/166 (9.6%)	17/136 (12.5%)
84 months	Improved	92/126 (73.0%)	63/96 (65.6%)
	Stable	24/126 (19.0%)	17/96 (17.7%)
	Deteriorated	10/126 (7.9%)	16/96 (16.7%)

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)

Surgery and Hospitalization Data

Table 26 summarizes the information related to the surgical procedures and post-operative hospitalizations of subjects. The most common treated surgical levels were the C5-C6 and C6-C7 levels. The mean operative times for the 2-level PRESTIGE LP™ and 2-level ACDF control groups were 2.1 hours and 1.7 hours, respectively, which is a mean difference of 0.4 hours (24 minutes), and is statistically longer for the 2-level PRESTIGE LP™ group compared to the 2-level ACDF control group when not adjusting for multiplicity. Additionally, 2-level PRESTIGE LP™ subjects were found to have statistically more estimated blood loss compared to 2-level ACDF control group subjects (67.2 ml for 2-level PRESTIGE LP™ group versus 55.7 ml for 2-level ACDF control group) when not adjusting for multiplicity. The mean hospital stays for subjects in both treatment groups were similar (1.2 days versus 1.3 days for the 2-level PRESTIGE LP™ and 2-level ACDF control groups, respectively).

Table 26: Surgical Data

Procedural Characteristic	INV	CTR	Posterior Mean and 95% BCI of the Difference of Mean between INV and CTR (lower, upper)
Treated Level (n(%) C3-C4 and C4-C5 C4-C5 and C5-C6 C5-C6 and C6-C7	 3 (1.4%) 43 (20.6%) 163 (78.0%)	 3 (1.6%) 44 (23.4%) 141 (75.0%)	N/A
Operative time (hrs); mean ± standard deviation	2.1 ± 0.8 Range: 0.8 – 5.0	1.7 ± 0.7 Range: 0.7 – 4.9	0.4 (0.25, 0.55)
Blood Loss (ml); mean ± standard deviation	67.2 ± 64.1 Range: 0.0 – 600 (n=208)	55.7 ± 46.3 Range: 0.0 – 250.0	11.5 (0.56, 22.44)
Hospitalization (days); mean ± standard deviation	1.2 ± 0.5 Range: 0.0 – 4.0	1.3 ± 1.0 Range: 0.0 – 8.0	-0.1 (-0.26, 0.06)
Median Return to Work Time (days)	49	55	N/A

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)
BCI = Bayesian HPD Credible Interval

Table 27 summarizes the PRESTIGE LP™ Devices implanted during the clinical study by size and level.

Table 27: PRESTIGE LP™ Devices Implanted by Size and Treatment Level

Superior Level PRESTIGE LP™ Size	Inferior Level PRESTIGE LP™ Size	C3-C4, C4-C5	C4-C5, C5-C6	C5-C6, C6-C7	Total (N=209)
5mm x 12mm	5mm x 12mm	0	1	0	**1 (0.5%)**
5mm x 12mm	5mm x 14mm	0	0	1	**1 (0.5%)**
5mm x 12mm	6mm x 14mm	0	1	0	**1 (0.5%)**
5mm x 14mm	5mm x 14mm	1	5	13	**19 (9.1%)**
5mm x 14mm	5mm x 16mm	0	0	3	**3 (1.4%)**
5mm x 14mm	6mm x 12mm	0	1	0	**1 (0.5%)**
5mm x 14mm	6mm x 14mm	0	1	9	**10 (4.8%)**
5mm x 14mm	6mm x 16mm	0	0	2	**2 (1.0%)**
5mm x 14mm	8mm x 14mm	0	0	1	**1 (0.5%)**
5mm x 16mm	5mm x 14mm	0	2	0	**2 (1.0%)**
5mm x 16mm	5mm x 16mm	2	6	15	**23 (11.0%)**
5mm x 16mm	6mm x 16mm	0	2	10	**12 (5.7%)**
6mm x 12mm	5mm x 14mm	0	1	0	**1 (0.5%)**
6mm x 12mm	6mm x 12mm	0	0	3	**3 (1.4%)**
6mm x 12mm	6mm x 14mm	0	1	0	**1 (0.5%)**
6mm x 12mm	7mm x 12mm	0	0	3	**3 (1.4%)**
6mm x 14mm	5mm x 14mm	0	0	2	**2 (1.0%)**
6mm x 14mm	5mm x 16mm	0	1	0	**1 (0.5%)**
6mm x 14mm	6mm x 12mm	0	0	1	**1 (0.5%)**
6mm x 14mm	6mm x 14mm	0	6	23	**29 (13.9%)**
6mm x 14mm	6mm x 16mm	0	1	8	**9 (4.3%)**
6mm x 14mm	7mm x 16mm	0	0	2	**2 (1.0%)**
6mm x 14mm	8mm x 14mm	0	0	1	**1 (0.5%)**
6mm x 14mm	8mm x 16mm	0	0	1	**1 (0.5%)**
6mm x 16mm	5mm x 16mm	0	1	1	**2 (1.0%)**
6mm x 16mm	6mm x 14mm	0	0	1	**1 (0.5%)**
6mm x 16mm	6mm x 16mm	0	6	25	**31 (14.8%)**
6mm x 16mm	7mm x 16mm	0	0	4	**4 (1.9%)**
6mm x 16mm	7mm x 18mm	0	0	2	**2 (1.0%)**
7mm x 12mm	6mm x 12mm	0	0	2	**2 (1.0%)**
7mm x 14mm	5mm x 14mm	0	0	1	**1 (0.5%)**
7mm x 14mm	6mm x 14mm	0	2	0	**2 (1.0%)**
7mm x 14mm	6mm x 16mm	0	0	1	**1 (0.5%)**
7mm x 14mm	7mm x 14mm	0	1	0	**1 (0.5%)**
7mm x 14mm	7mm x 16mm	0	0	1	**1 (0.5%)**
7mm x 16mm	5mm x 16mm	0	1	0	**1 (0.5%)**

7mm x 16mm	6mm x 16mm	0	0	7	**7 (3.3%)**
7mm x 16mm	7mm x 16mm	0	2	5	**7 (3.3%)**
7mm x 16mm	7mm x 18mm	0	0	1	**1 (0.5%)**
7mm x 18mm	7mm x 16mm	0	0	1	**1 (0.5%)**
7mm x 18mm	7mm x 18mm	0	1	12	**13 (6.2%)**
7mm x 18mm	8mm x 18mm	0	0	1	**1 (0.5%)**
Total (%)		**3 (1.4%)**	**43 (20.6%)**	**163 (78.0%)**	**209 (100%)**

Metal Ion Status

Metal ion data was not collected as part of the PRESTIGE LP™ two-level IDE study. However, Medtronic will conduct a single arm, non-randomized metal ion post-approval study on thirty subjects (n=30) at up to five (5) clinical sites in the U.S. to assess the concentrations of metal ions (specifically titanium, vanadium, and aluminum) through 24 months post-operatively in blood serum of subjects implanted with the PRESTIGE LP™ Cervical Disc at two contiguous levels from C3-C7. Additional data will also be collected on NDI, neck and arm pain, adverse events, subsequent surgeries, and neurologic status to evaluate the correlation (if any) between metal ion levels and clinical outcomes.

2. Effectiveness Results

The analysis of effectiveness was based on the as-treated cohort of 397 total subjects which included all subjects who completed the surgical procedure and received a study device in either treatment group according to the treatment received (209 2-level PRESTIGE LP™ subjects and 188 2-level ACDF control subjects). The key effectiveness outcomes for this study are presented below in **Tables 28** to **51**.

Primary Effectiveness Analysis

Overall Success at 24 Months

As outlined above, the primary endpoint was a composite endpoint (referred to as "Overall Success (Protocol Definition)" in the overall success tables below) that defined a subject as a success if the following criteria were met at 24 months post-operative:

- Improvement (reduction) of at least 15 points in NDI score at 24 months compared to pre-operative baseline;
- Maintenance or improvement in neurological status at 24 months compared to pre-operative baseline as measured based on motor function, sensory function, and reflexes;
- No serious adverse event classified as implant associated, or implant/surgical procedure associated; and
- No additional surgical procedure classified as a "failure."

As described above, because the additional surgical procedure component of the primary endpoint did not consider all subsequent surgeries at the index level as failures, FDA requested an additional analysis of overall success in which all subsequent surgeries at the index level and all intra-operative treatment conversions were considered failures (referred to as Overall Success Alternate Analysis in **Table 28** and **Table 29** below).

Overall study success criteria were based on a comparison of individual subject success rates, such that the subject success rate for the 2-level PRESTIGE LP™ group was required to be non-inferior to that of the 2-level ACDF control group. The study was designed as a non-inferiority study with a margin (delta) of 10%. Non-inferiority was to be claimed if the posterior probability that the success rate in the 2-level PRESTIGE LP™ group was not lower than the success rate in the 2-level ACDF control group by more than 10% was greater than 95%. The protocol also specified secondary superiority evaluations of the primary endpoint if non-inferiority was demonstrated.

The observed success rates at 24 months post-operative for each of the overall success components and composite overall success (both Overall Success Protocol Definition and Overall Success Alternate Analysis) as well as the Bayesian analyses are provided in **Table 28**. The posterior means for each treatment group can be interpreted as the average chance of component or overall success at 24 months, and the posterior mean of the difference between the two treatment groups can be interpreted as the average difference in the chance of component or overall success at 24 months. For example, given the results of the study, when a subject receives the 2-level PRESTIGE LP™ device, the average chance of success (Overall Success Protocol Definition) at 24 months is 80.3%, and there is a 95% probability that the chance of success ranges from 75.0% to 85.8%. Similarly, given the results of the study, when a subject receives the 2-level ACDF control treatment, the average chance of success (Overall Success Protocol Definition) at 24 months is 69.0%, and there is a 95% probability that the chance of success ranges from 61.8% to 75.7%. Then the average difference in the chance of success (Overall Success Protocol Definition) between the 2-level PRESTIGE LP™ group and the 2-level ACDF control group at 24 months is 11.3% with 95% probability that this difference falls in the range of 2.2% to 20.1%. Similarly, based on the Alternate Analysis of Overall Success, at 24 months post-operative, the posterior probability of success (Overall Success Alternate Analysis) in the 2-level PRESTIGE LP™ group is 79.5% as compared to 68.5% in the 2-level ACDF control group. Considering both definitions of overall success, the posterior probability of non-inferiority of the 2-level PRESTIGE LP™ group to the 2-level ACDF control group at 24 months post-operative is essentially 100%, demonstrating non-inferiority. In addition, the posterior probability of superiority of the 2-level PRESTIGE LP™ group to the 2-level ACDF control group at 24 months post-operative is above the 95% threshold for both analyses of overall success, demonstrating statistical superiority. For the component endpoints of NDI and neurological success, multiple comparisons were carried out without adjustment for multiplicity.

Table 28: Observed Component and Overall Success Rates and Posterior Probabilities of Success at 24 Months

Primary Outcome Component	24 Month Observed Success Rate		24 Month Posterior Mean (95% HPD Credible Interval)			24-Month Posterior Probabilities (INV vs CTR)	
	INV	CTR	INV	CTR	INV - CTR	Non-Inferiority	Superiority
NDI Success (≥15 point improvement)*	175/199 (87.9%)	126/159 (79.2%)	87.1% (82.6%, 91.7%)	78.3% (71.9%, 84.1%)	8.8% (1.2%, 16.7%)	~100.0%	99.0%
Neurological Success (maintenance/ improvement)*	182/199 (91.5%)	137/159 (86.2%)	90.2% (86.2%, 94.2%)	85.2% (80.0%, 90.6%)	5.0% (-1.4%, 11.9%)	~100.0%	93.1%
Serious implant or implant/surgical procedure associated AE**	2	11	Not Available				
Additional surgical procedure classified as "failure"*	4	12	Not Available				
Overall success (Protocol Definition)	162/199 (81.4%)	111/160 (69.4%)	80.3% (75.0%, 85.8%)	69.0% (61.8%, 75.7%)	11.3% (2.2%, 20.1%)	~100.0%	99.3%
Overall Success (Alternate Analysis***)	162/201 (80.6%)	110/160 (68.8%)	79.5% (73.7%, 84.8%)	68,5% (61.5%, 75.3%)	11.0% (2.0%, 19.8%)	~100.0%	99.3%

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)

* Analyses were conducted without adjustment for multiplicity.

** For the "Serious implant or implant/surgical procedure associated AE" and "Additional surgical procedure classified as failure" rows, only the number of subjects experiencing these events were presented.

***All subsequent surgeries at index level and all intra-operative anatomical/technical difficulties considered failures.

Timecourse of Overall Success

Table 29 provides data on the timecourse of overall success rates for both treatment groups for Overall Success (Protocol) and Overall Success (Alternate Analysis).

Table 29: Timecourse of Observed Overall Success Rates

Primary Outcome Component	6 Months		12 Months		24 Months	
	INV	CTR	INV	CTR	INV	CTR
NDI Success (≥15 point improvement)	185/203 (91.1%)	141/172 (82.0%)	183/202 (90.6%)	136/165 (82.4%)	175/199 (87.9%)	126/159 (79.2%)
Neurological Success (maintenance/ improvement)	185/204 (90.7%)	150/174 (86.2%)	182/203 (89.7%)	136/165 (82.4%)	182/199 (91.5%)	137/159 (86.2%)
Serious implant or implant/surgical procedure associated AE*	0	6	1	8	2	11
Additional surgical procedure classified as "failure"*	1	4	2	9	4	12
Overall success (Protocol Definition)	169/203 (83.3%)	126/174 (72.4%)	167/202 (82.7%)	117/166 (70.5%)	162/199 (81.4%)	111/160 (69.4%)
Overall Success (Alternate Analysis**)	Not Available		167/204 (81.9%)	117/166 (70.5%)	162/201 (80.6%)	110/160 (68.8%)

Primary Outcome Component	36 Months		60 Months		84 Months	
	INV	CTR	INV	CTR	INV	CTR
NDI Success (≥15 point improvement)	166/185 (89.7%)	121/147 (82.3%)	148/166 (89.2%)	105/135 (77.8%)	110/126 (87.3%)	72/96 (75.0%)
Neurological Success (maintenance/ improvement)	167/185 (90.3%)	124/148 (83.8%)	150/166 (90.4%)	119/136 (87.5%)	116/126 (92.1%)	80/96 (83.3%)
Serious implant or implant/surgical procedure associated AE*	3	11	4	12	5	11
Additional surgical procedure classified as "failure"*	6	12	7	15	7	15
Overall success (Protocol Definition)	151/185 (81.6%)	105/149 (70.5%)	132/166 (79.5%)	91/138 (65.9%)	99/126 (78.6%)	62/99 (62.6%)
Overall Success (Alternate Analysis**)	Not Available					

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)

* For the "Serious implant or implant/surgical procedure associated AE" and "Additional surgical procedure classified as failure" rows, only the number of subjects experiencing these events were presented.

** All subsequent surgeries at index level and all intra-operative anatomical/technical difficulties considered failures.

Note: To be consistent with how NDI and neurological status success are determined, the subsequent surgery determination for the overall success timecourse table is based on the subject follow-up visit. For example, if a subsequent surgery occurred before the 6 month-visit, then it was counted as a failure at 6 months. If the subsequent surgery occurred after the 6-month visit, even if it was still within the 6-month visit window, it was counted as a failure at 12 months.

Sensitivity Analyses

Various post-hoc sensitivity analyses were conducted to assess the robustness of the study conclusions. Specifically, the following analyses were provided:

- Overall success considering all subjects who experienced a subsequent surgery at the index levels or who experienced intra-operative technical or anatomical difficulty and did not receive the treatment intended as failures. For this analysis, a formal Bayesian analysis was carried out by using the same model as the one for the primary dataset (refer to Alternate Analysis of Overall Success data in **Tables 28-29** above).
- Overall success analysis in which ACDF control group subjects requiring use of a bone growth stimulator were not considered failures.
- Per-protocol dataset (excluding subjects with major protocol deviations that could potentially affect clinical outcomes) for which formal Bayesian analysis was carried out using the same model as the one for the primary dataset.
- "Missing-equals-failure" analysis without formal statistical comparisons.
- Overall success stratified by treatment levels without formal statistical comparisons.
- Tipping point analysis using Frequentist methods.

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

By Treatment Levels

Table 30 provides overall success data for each treatment group stratified by the treated levels including post-hoc statistical analysis and comparisons between the 2-level PRESTIGE LP™ group and the 2-level ACDF control group through the 24 month timepoint using Frequentist methods. Overall success rates were not significantly different between the 2-level PRESTIGE LP™ group and the 2-level ACDF control group at any treatment levels except for at the C5-C6 (superior) and C6-C7 (inferior) levels in which the 2-level PRESTIGE LP™ group had a higher success rate compared to the 2-level ACDF control group at 24 months without adjustment for multiplicity.

Table 30: Timecourse of Observed Overall Success Rates by Levels Treated

Timepoint	Superior C3-C4 Inferior C4-C5		Superior C4-C5 Inferior C5-C6		Superior C5-C6 Inferior C6-C7	
	INV	CTR	INV	CTR	INV	CTR
6 Months	3/3 (100%)	2/3 (66.7%)	33/42 (78.6%)	29/41 (70.7%)	133/158 (84.2%)	95/130 (73.1%)
Statistics*	33.3% (-26.3%, 93.0%)		7.8% (-10.9%, 26.5%)		11.1% (1.7%, 20.5%)	
12 Months	2/2 (100%)	1/2 (50%)	32/41 (78.0%)	28/40 (70%)	133/159 (83.6%)	88/124 (71.0%)
Statistics*	50.0% (-34.9%, 100%)		8.0% (-11.0%, 27.1%)		12.7% (3.0%, 22.4%)	
24 Months	1/2 (50.0%)	1/2 (50.0%)	31/39 (79.5%)	28/39 (71.8%)	130/158 (82.3%)	82/119 (68.9%)
Statistics*	0.0% (-98.0%, 98.0%)		7.7% (-11.4%, 26.7%)		13.4% (3.3%, 23.5%)	
36 Months	3/3 (100%)	1/2 (50.0%)	33/40 (82.5%)	24/37 (64.9%)	115/142 (81.0%)	80/110 (72.7%)
Statistics*	50.0% (-21.6%, 100%)		17.6% (-2.0%, 37.2%)		8.3% (-2.2%, 18.7%)	
60 Months	0/1 (0%)	0/1 (0%)	26/35 (74.3%)	23/31 (74.2%)	106/130 (81.5%)	68/106 (64.2%)
Statistics*	Not Available		0.1% (-21.0%, 21.2%)		17.4% (6.1%, 28.7%)	

Timepoint	Superior C3-C4 Inferior C4-C5		Superior C4-C5 Inferior C5-C6		Superior C5-C6 Inferior C6-C7	
	INV	CTR	INV	CTR	INV	CTR
84 Months	0/1 (0%)	0/0	22/27 (81.5%)	18/24 (75.0%)	77/98 (78.6%)	44/75 (58.7%)
Statistics*	Not Available		6.5% (-16.1%, 29.1%)		19.9% (6.1%, 33.7%)	

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)

* Point Estimate and 95% Confidence Interval of Difference of Success Rate between 2-level PRESTIGE LP™ and 2-level ACDF control. The 95% CI was provided using Frequentist Farrington and Manning methods.

By Gender

Overall success data stratified by subject gender at the 24-month timepoint are provided in Table 31 below. The rates for the primary outcome components were similar between males and females within each study group. Additionally, the success rates for both males and females were nominally higher in the 2-level PRESTIGE LP™ group than in the 2-level ACDF control group.

Table 31: Overall Success (Protocol Definition) Stratified by Gender at 24 months

Primary Outcome Component	INV		CTR	
	Male (N = 92)	Female (N = 117)	Male (N = 90)	Female (N = 98)
NDI Success (≥15 point improvement)	77/87 (88.5%)	98/112 (87.5%)	58/76 (76.3%)	68/83 (81.9%)
Neurological Success (maintenance/ improvement)	80/87 (92.0%)	102/112 (91.1%)	66/76 (86.8%)	71/83 (85.5%)
Serious implant- or implant/surgical procedure-associated AE	1	1	7	4
Additional surgical procedure classified as "failure"	1	3	7	5
Overall Success (Protocol Definition)	72/87 (82.8%)	90/112 (80.4%)	52/77 (67.5%)	59/83 (71.1%)

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)

By Race

Overall success data stratified by subject race at the 24 month timepoint are provided in **Table 32**. Due to the relatively small numbers of non-Caucasians treated in the IDE study, statistical conclusion regarding overall success outcomes based on race cannot be reliably made; however, qualitative differences were not observed.

Table 32: Overall Success (Protocol Definition) Stratified by Subject Race at 24 months

Primary Outcome Component	INV		CTR	
	Caucasian (N = 195)	Non-Caucasian (N = 14)	Caucasian (N = 172)	Non-Caucasian (N = 16)
NDI Success (≥15 point improvement)	162/185 (87.6%)	13/14 (92.9%)	115/146 (78.8%)	11/13 (84.6%)
Neurological Success (maintenance/ improvement)	169/185 (91.4%)	13/14 (92.9%)	126/146 (86.3%)	11/13 (84.6%)
No serious implant- or implant/surgical procedure-associated AE	2	0	9	2

Primary Outcome Component	INV		CTR	
	Caucasian (N = 195)	Non-Caucasian (N = 14)	Caucasian (N = 172)	Non-Caucasian (N = 16)
No additional surgical procedure classified as "failure"	4	0	10	2
Overall Success (Protocol Definition)	150/185 (81.1%)	12/14 (85.7%)	102/147 (69.4%)	9/13 (69.2%)

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)

Site Poolability Analysis

Statistical analyses were conducted to assess the poolability of data across study sites using the Breslow-Day test for overall success, NDI success, and neurological success at 24 months. The results of all tests were non-significant, indicating that there is no particular evidence of differential treatment effects among sites. These outcomes provide confidence in pooling the data across investigational sites. At FDA's request, the applicant also conducted a Bayesian hierarchical model to assess the homogeneity of the primary endpoint across sites at 24 months. Results show the non-inferiority of 2-level PRESTIGE LP™ as compared to 2-level ACDF control.

At FDA's request, the applicant also provided several sensitivity analyses where specific sites were excluded for various reasons (e.g., disclosed financial relationships between investigators and the applicant as outlined in Section E). The sensitivity analysis results demonstrated that the study conclusion of non-inferiority of 2-level PRESTIGE LP™ as compared to 2-level ACDF control was robust.

Secondary Effectiveness Analysis

Overview

In addition to the components of the primary endpoint presented above, secondary effectiveness variables were also assessed.

The following secondary endpoint success definitions were specified in the clinical protocol:

- Neck pain: any improvement in post-operative neck pain score as compared to pre-operative score. Note that the applicant also provided a responder analysis where a responder was defined as ≥2/10 point decrease in neck pain intensity from baseline.
- Arm pain: any improvement in post-operative arm pain score as compared to pre-operative score. Note that the applicant also provided a responder analysis where a responder was defined as ≥2/10 point decrease in arm pain intensity from baseline.
- SF-36 Physical Component Score (PCS) and Mental Component Score (MCS) success: maintenance or improvement in post-operative scores as compared to pre-operative values. Note that the applicant also provided data on improvement ≥15%.
- Disc Height (Functional Spinal Unit Height): Anterior or posterior measurement must be no more than 2mm less than 6 week post-operative measurement.
- Gait assessment (Nurick's classification): maintenance or improvement of pre-operative status.

Additional secondary endpoints evaluated include radiographic assessments of motion at index and adjacent levels as well as fusion assessment for control subjects, medication use, subject satisfaction, work status, and doctor and subject perception of outcomes.

Table 33 provides a summary of the key secondary effectiveness outcomes at 24 months post-operatively. The results were comparable between the two treatment groups.

Table 33: Summary of Secondary Effectiveness Endpoints at 24 Months

Outcome Measure	24-Month Observed Success Rate		24-Month Posterior Mean (95% HPD Credible Interval)		
	INV	CTR	INV	CTR	INV - CTR
Neck pain (any improvement)	195/199 (98.0%)	152/159 (95.6%)	96.9% (94.4%, 99.0%)	94.8% (91.4%, 97.7%)	2.1% (-1.9%, 6.2%)
Neck pain (≥2/10 point decrease in neck pain intensity from baseline)	185/199 (93.0%)	136/159 (85.5%)	91.7% (87.9%, 95.4%)	84.9% (79.3%, 90.0%)	6.9% (0.2%, 13.4%)
Arm pain (any improvement)	177/199 (88.9%)	143/159 (89.9%)	88.0% (83.6%, 92.4%)	88.9% (84.0%, 93.3%)	-0.8% (-7.3%, 5.6%)
Arm pain (≥2/10 point decrease in arm pain intensity from baseline)	169/199 (84.9%)	130/159 (81.8%)	83.8% (78.7%, 88.7%)	81.2%, (75.1%, 86.9%)	2.6% (-5.1%, 10.5%)
SF-36 PCS (any improvement)	178/197 (90.4%)	137/156 (87.8%)	89.6% (85.5%, 93.6%)	87.2% (82.1%, 92.1%)	2.4% (-4.2%, 8.8%)
SF-36 PCS (≥15% improvement)	158/197 (80.2%)	118/156 (75.6%)	79.6% (74.1%, 84.9%)	74.9% (68.2%, 81.3%)	4.7% (-4.2%, 12.8%)
SF-36 MCS (any improvement)	136/197 (69.0%)	113/156 (72.4%)	68.8% (62.5%, 75.3%)	71.2% (64.0%, 77.8%)	-2.4% (-12.0%, 6.7%)
SF-36 MCS (≥15% improvement)	100/197 (50.8%)	69/156 (44.2%)	50.9% (43.8%, 57.5%)	43.9% (36.5%, 51.4%)	7.0% (-3.6%, 17.0%)
Gait assessment (maintenance or improvement of pre-operative status)	199/199 (100%)	157/159 (98.7%)	99.0% (97.7%, 100%)	97.7% (95.5%, 99.5%)	1.3% (-1.3%, 4.0%)

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)

Neck Disability Index

The timecourse of NDI improvement is presented in **Table 34**. The 2-level PRESTIGE LP™ group demonstrated numerically greater improvement rates than the 2-level ACDF control group at all post-operative timepoints.

Table 34: Timecourse of Neck Disability Index Improvement

	6 Weeks		3 Months		6 Months		12 Months		24 Months	
	INV	**CTR**	**INV**	**CTR**	**INV**	**CTR**	**INV**	**CTR**	**INV**	**CTR**
NDI (points), N	204	181	203	178	203	172	202	165	199	159
Improvement (≥ 15 points)	148 (72.5%)	109 (60.2%)	172 (84.7%)	141 (79.2%)	185 (91.1%)	141 (82.0%)	183 (90.6%)	136 (82.4%)	175 (87.9%)	126 (79.2%)
Maintained (-15, 15 points)	56 (27.5%)	71 (39.2%)	31 (15.3%)	37 (20.8%)	18 (8.9%)	30 (17.4%)	18 (8.9%)	29 (17.6%)	24 (12.1%)	33 (20.8%)
Deteriorated (≤ -15 points)	0 (0%)	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)

	36 Months		60 Months		84 Months	
	INV	**CTR**	**INV**	**CTR**	**INV**	**CTR**
NDI (points), N	185	147	166	135	126	96
Improvement (≥ 15 points)	166 (89.7%)	121 (82.3%)	148 (89.2%)	105 (77.8%)	110 (87.3%)	72 (75.0%)
Maintained (-15, 15 points)	19 (10.3%)	25 (17.0%)	18 (10.8%)	29 (21.5%)	14 (11.1%)	23 (24.0%)
Deteriorated (≤ -15 points)	0 (0%)	1 (0.7%)	0 (0%)	1 (0.7%)	2 (1.6%)	1 (1.0%)

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)

Note: If pre-operative NDI minus post-operative NDI ≥ 15 points then the subject is considered "Improved"; if -15 points < pre-operative NDI minus post-operative NDI < 15 points, then the subject is considered "Maintained"; if pre-operative NDI minus post-operative NDI ≤ -15 points then the subject is considered "Deteriorated".

Neck and Arm Pain

The timecourse of neck and arm pain improvement is presented in **Table 35**. The improvement rates for the 2-level PRESTIGE LP™ group and the 2-level ACDF control group were similar at all post-operative time periods.

Table 35: Timecourse of Neck and Arm Pain Improvement

Evaluation	6 Weeks		3 Months		6 Months		12 Months		24 Months	
	INV	**CTR**	**INV**	**CTR**	**INV**	**CTR**	**INV**	**CTR**	**INV**	**CTR**
Neck Pain, N	204	181	203	178	203	172	203	165	199	159
Improvement (≥ 20%)	180 (88.2%)	157 (86.7%)	181 (89.2%)	151 (84.8%)	187 (92.1%)	147 (85.5%)	192 (94.6%)	146 (88.5%)	186 (93.5%)	142 (89.3%)
Maintained (-20%, 20%)	24 (11.8%)	24 (13.3%)	20 (9.9%)	26 (14.6%)	15 (7.4%)	25 (14.5%)	10 (4.9%)	19 (11.5%)	11 (5.5%)	16 (10.1%)
Deteriorated (≤ -20%)	0 (0%)	0 (0%)	2 (1.0%)	1 (0.6%)	1 (0.5%)	0 (0%)	1 (0.5%)	0 (0%)	2 (1.0%)	1 (0.6%)
Arm Pain, N	204	181	203	178	203	172	203	165	199	159
Improvement (≥ 20%)	174 (85.3%)	157 (86.7%)	169 (83.3%)	151 (84.8%)	171 (84.2%)	147 (85.5%)	178 (87.7%)	136 (82.4%)	172 (86.4%)	136 (85.5%)
Maintained (-20%, 20%)	25 (12.3%)	16 (8.8%)	27 (13.3%)	20 (11.2%)	29 (14.3%)	19 (11.0%)	17 (8.4%)	21 (12.7%)	18 (9.0%)	14 (8.8%)
Deteriorated (≤ -20%)	5 (2.5%)	8 (4.4%)	7 (3.4%)	7 (3.9%)	3 (1.5%)	6 (3.5%)	8 (3.9%)	8 (4.8%)	9 (4.5%)	9 (5.7%)

	36 Months		60 Months		84 Months	
	INV	**CTR**	**INV**	**CTR**	**INV**	**CTR**
Neck Pain, N	184	147	166	135	125	96
Improvement (≥ 20%)	173 (94.0%)	129 (87.8%)	151 (91.0%)	112 (83.0%)	114 (91.2%)	78 (81.3%)
Maintained (-20%, 20%)	10 (5.4%)	18 (12.2%)	11 (6.6%)	23 (17.0%)	9 (7.2%)	18 (18.8%)
Deteriorated (≤ -20%)	1 (0.5%)	0 (0.0%)	4 (2.4%)	0 (0.0%)	2 (1.6%)	0 (0.0%)
Arm Pain, N	184	147	166	135	124	96
Improvement (≥ 20%)	161 (87.5%)	128 (87.1%)	145 (87.3%)	110 (81.5%)	102 (82.3%)	84 (87.5%)
Maintained (-20%, 20%)	18 (9.8%)	14 (9.5%)	13 (7.8%)	20 (14.8%)	15 (12.1%)	7 (7.3%)
Deteriorated (≤ -20%)	5 (2.7%)	5 (3.4%)	8 (4.8%)	5 (3.7%)	7 (5.6%)	5 (5.2%)

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)

Short Form-36 (SF-36)

The Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) was used to assess the general health status of all study subjects. **Table 36** presents the timecourse of improvement rates of the Physical Component Score (PCS) and Mental Component Score (MCS). The improvement rates for the 2-level PRESTIGE LP™ group and the 2-level ACDF control group were similar at all post-operative time periods.

Table 36: Timecourse of SF-36 Health Survey Improvement

Evaluation	6 Months		12 Months		24 Months	
	INV	CTR	INV	CTR	INV	CTR
SF-36 PCS, N	201	168	200	161	197	156
Improvement (≥ 15%)	152 (75.6%)	124 (73.8%)	164 (82.0%)	123 (76.4%)	158 (80.2%)	118 (75.6%)
Maintained (-15%, 15%)	45 (22.4%)	27 (22.0%)	32 (16.0%)	34 (21.1%)	34 (17.3%)	29 (18.6%)
Deteriorated (≤ -15%)	4 (2.0%)	7 (4.2%)	4 (2.0%)	4 (2.5%)	5 (2.5%)	9 (5.8%)
SF-36 MCS, N	201	168	200	161	197	156
Improvement (≥ 15%)	98 (48.8%)	68 (40.5%)	99 (49.5%)	64 (39.8%)	100 (50.8%)	69 (44.2%)
Maintained (-15%, 15%)	83 (41.3%)	85 (50.6%)	80 (40.0%)	78 (48.4%)	80 (40.6%)	72 (46.2%)
Deteriorated (≤ -15%)	20 (10.0%)	15 (8.9%)	21 (10.5%)	19 (11.8%)	17 (8.6%)	15 (9.6%)

	36 Months		60 Months		84 Months	
	INV	CTR	INV	CTR	INV	CTR
SF-36 PCS, N	182	144	161	131	123	93
Improvement (≥ 15%)	144 (79.1%)	111 (77.1%)	128 (79.5%)	93 (71.0%)	94 (76.4%)	66 (71.0%)
Maintained (-15%, 15%)	27 (14.8%)	28 (19.4%)	25 (15.5%)	28 (21.4%)	21 (17.1%)	16 (17.2%)
Deteriorated (≤ -15%)	11 (6.0%)	5 (3.5%)	8 (5.0%)	10 (7.6%)	8 (6.5%)	11 (11.8%)
SF-36 MCS, N	182	144	161	131	123	93
Improvement (≥ 15%)	96 (52.7%)	69 (47.9%)	88 (54.7%)	66 (50.4%)	66 (53.7%)	49 (52.7%)
Maintained (-15%, 15%)	74 (40.7%)	63 (43.8%)	63 (39.1%)	50 (38.2%)	51 (41.5%)	34 (36.6%)
Deteriorated (≤ -15%)	12 (6.6%)	12 (8.3%)	10 (6.2%)	15 (11.5%)	6 (4.9%)	10 (10.8%)

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)

Gait Assessment

Assessment of subjects' gaits were made pre-operatively and post-operatively using Nurick's classification [3]. Pre-operatively, 77.0% of the 2-level PRESTIGE LP™ subjects and 70.2% of the 2-level ACDF control subjects had "normal" gait scores. At 24 months post-operative, 99.5% of the 2-level PRESTIGE LP™ subjects and 98.1% of the 2-level ACDF control subjects had "normal" gait scores. The gait assessment outcomes for each post-operative study period are provided in **Table 37**.

Table 37: Timecourse of Gait Assessment Results (Normal Nurick Score)

	INV	CTR
Pre-operative	161/209 (77.0%)	132/188 (70.2%)
6 Weeks	197/206 (95.6%)	169/182 (92.9%)
3 Months	197/205 (96.1%)	168/178 (94.4%)
6 Months	199/204 (97.5%)	163/174 (93.7%)
12 Months	198/203 (97.5%)	161/165 (97.6%)
24 Months	198/199 (99.5%)	156/159 (98.1%)
30 Months	183/185 (98.9%)	141/148 (95.3%)
60 Months	164/166 (98.8%)	129/136 (94.9%)
84 Months	125/126 (99.2%)	92/96 (95.8%)

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)

Subject Satisfaction

At each post-operative time period, subjects were asked to respond to three statements regarding their satisfaction with the study treatment:
1) I am satisfied with the results of my surgery.
2) I was helped as much as I thought I would be with my surgery.
3) All things considered I would have the surgery again for the same condition.
Each question had a series of possible responses ranging from "Definitely True" to "Definitely False." Success for each statement was defined as either a "Definitely True" or "Mostly True" response.

Subject satisfaction data are shown in **Table 38**. Both treatment groups demonstrated similar subject satisfaction rates.

Table 38: Timecourse of Subject Satisfaction Success*

Statement	12 mo		24 mo		36 mo		60 mo	
	INV	CTR	INV	CTR	INV	CTR	INV	CTR
I am satisfied with the results of my surgery	191/203 (94.1%)	149/164 (90.9%)	188/199 (94.5%)	142/159 (89.3%)	176/185 (95.1%)	135/146 (92.5%)	157/166 (94.6%)	126/135 (93.3%)
I was helped as much as I thought I would be by my surgery	187/203 (92.1%)	140/164 (85.4%)	186/198 (93.9%)	136/159 (85.5%)	171/184 (92.9%)	129/146 (88.4%)	152/164 (92.7%)	119/135 (88.1%)
All things considered I would have the surgery again for the same condition	189/203 (93.1%)	145/165 (87.9%)	185/198 (93.4%)	141/159 (88.7%)	172/184 (93.5%)	130/145 (89.7%)	153/165 (92.7%)	119/135 (88.1%)

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)
* Success = 'Definitely true' or 'Mostly true' response to statement.

Subject Perceived Effect

At each post-operative time period, subjects were asked a question regarding the perceived effect of the surgical treatment. The seven possible answers ranged from "completely recovered" to "vastly worsened." Success was defined as a “Completely Recovered,” “Much Improved,” or “Slightly Improved” response.

The results of this evaluation are provided in **Table 39**. At 24 months following surgery, 91.4% of the 2-level PRESTIGE LP™ subjects and 82.4% of the 2-level ACDF control subjects indicated that they had either “completely recovered” or were “much improved”.

Table 39: Timecourse of Subject Perceived Effect

Timepoint	Subject Response	INV	CTR
12 Months	Complete Recovery	90/203 (44.3%)	56/165 (33.9%)
	Much Improved	95/203 (46.8%)	80/165 (48.5%)
24 Months	Complete Recovery	91/199 (45.7%)	61/159 (38.4%)
	Much Improved	91/199 (45.7%)	70/159 (44.0%)
36 Months	Complete Recovery	93/185 (50.3%)	56/146 (38.4%)
	Much Improved	78/185 (42.2%)	67/146 (45.9%)
60 Months	Complete Recovery	89/166 (53.6%)	50/135 (37.0%)
	Much Improved	61/166 (36.7%)	62/135 (45.9%)

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)

Physician Perception of Results

At each post-operative visit, the physician investigators were asked to provide their perception of the subjects’ condition (“excellent”, “good”, “fair”, or “poor”).

The results of this evaluation are provided in **Table 40**. At 24 months post-operative, 96.9% of physicians responded either “excellent” or “good” for the 2-level PRESTIGE LP™ group as compared to 84.3% for the 2-level ACDF control group.

Table 40: Timecourse of Physician Perception of Results

Timepoint	Physician Response	INV	CTR
12 Months	Excellent	148/203 (72.9%)	93/165 (56.4%)
	Good	49/203 (24.1%)	48/165 (29.1%)
	Fair	5/203 (2.5%)	21/165 (12.7%)
	Poor	1/203 (0.5%)	3/165 (1.8%)
24 Months	Excellent	139/199 (69.8%)	89/159 (56.0%)
	Good	54/199 (27.1%)	45/159 (28.3%)
	Fair	4/199 (2.0%)	21/159 (13.2%)
	Poor	2/199 (1.0%)	4/159 (2.5%)
36 Months	Excellent	139/185 (75.1%)	75/148 (50.7%)
	Good	39/185 (21.1%)	51/148 (34.5%)
	Fair	6/185 (3.2%)	16/148 (10.8%)
	Poor	1/185 (0.5%)	6/148 (4.1%)
60 Months	Excellent	119/166 (71.7%)	66/136 (48.5%)
	Good	40/166 (24.1%)	52/136 (38.2%)
	Fair	5/166 (3.0%)	15/136 (11.0%)
	Poor	2/166 (1.2%)	3/136 (2.2%)

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)

Work Status
Pre-operatively, 69.9% (146/209) of 2-level PRESTIGE LP™ subjects and 60.1% (113/188) of 2-level ACDF control subjects reported working. At 24 months following surgery, 72.9% (145/199) of 2-level PRESTIGE LP™ subjects and 71.1% (113/159) of 2-level ACDF control subjects reported working. The median return-to-work time following surgery was 49 days for 2-level PRESTIGE LP™ subjects and 55 days for 2-level ACDF control subjects, respectively.

Radiographic Assessments
Radiographs were examined to evaluate bridging bone, implant condition, functional spinal unit (FSU) height maintenance, angular motion, translation, and heterotopic ossification. The applicant utilized an independent imaging core laboratory. The imaging core laboratory employed independent, board-certified, fellowship-trained, practicing radiologists to conduct the radiographic assessments. In addition, some radiographic observations reported by investigators, such as implant malposition, were considered adverse events (see Safety Results section above).

Radiographic Success
In the 2-level PRESTIGE LP™ group, radiographic success was defined as angular motion on lateral flexion/extension radiographs >4° but ≤20° and no radiographic evidence of bridging trabecular bone that forms a continuous bony connection with the vertebral bodies (i.e., no bridging bone) at both treated levels.

In the 2-level ACDF control group, radiographic success was defined as radiographic evidence of bone spanning the two vertebral bodies (i.e., bridging bone), angular motion on lateral flexion/extension radiographs ≤4°, and evidence of radiolucency covering more than 50% of either the superior or inferior surface of either graft. For this study, both treated levels were required to have evidence of fusion in order to claim overall radiographic fusion success.

Table 41 shows the radiographic success rates for the 2-level PRESTIGE LP™ subjects (n=196) and the 2-level ACDF control subjects (n=145) who had evaluable radiographic data at 24 months.

Table 41: Radiographic Success at 24 Months

	Treatment Level	Angular Motion >4° and ≤20°	No Bridging Bone	Radiolucency	Overall Radiographic Success
INV	Superior Level Only	141/198 (71.2%)	184/198 (92.9%)	Not Applicable	137/197 (69.5%)
	Inferior Level Only	136/196 (69.4%)	177/198 (89.4%)	Not Applicable	126/195 (64.6%)
	Both Treated Levels	106/197 (53.8%)	176/198 (88.9%)	Not Applicable	100/196 (51.0%)
	Treatment Level	**Angular Motion ≤4°**	**Bridging Bone**	**No Radiolucency**	**Overall Radiographic Success**
CTR	Superior Level Only	146/153 (95.4%)	154/154 (100%)	158/158 (100%)	144/151 (95.4%)
	Inferior Level Only	127/148 (85.8%)	149/151 (98.7%)	158/158 (100.0%)	125/146 (85.6%)
	Both Treated Levels	121/147 (82.3%)	149/151 (98.7%)	158/158 (100.0%)	119/145 (82.1%)

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)

Range of Motion

Radiographic evaluations of mean range of motion, including angulation and translation (during flexion and extension), for the treated levels at the pre-operative, 12 month, 24 month, 36 month, 60 month, and 84 month timepoints are provided in **Table 42**.

Table 42: Timecourse of Radiographic Mean Range of Motion

Timepoint	Treatment Level	Evaluation	INV	CTR
Pre-operative	Superior	Flexion/extension angulation (º)	6.75° ± 4.16° Range: 0.08° - 18.15°	7.12° ± 4.14° Range: 0.45° - 19.72°
		Flexion/extension translation (mm)	1.48mm ± 1.08mm Range: 0.13mm – 9.17mm	1.57mm ± 1.14mm Range: 0.03mm – 8.96mm
	Inferior	Flexion/extension angulation (º)	5.56° ± 3.89° Range: 0.37° - 18.20°	5.37° ± 3.26° Range: 0.37° - 18.51°
		Flexion/extension translation (mm)	1.04mm ± 0.74mm Range: 0.06mm – 3.42mm	1.14mm ± 0.93mm Range: 0.00mm – 6.60mm
12 Months	Superior	Flexion/extension angulation (º)	6.89° ± 4.04° Range: 0.11° - 20.56°	1.51° ± 1.21° Range: 0.07° - 8.53°
		Flexion/extension translation (mm)	1.06mm ± 0.67mm Range: 0.00mm – 3.22mm	0.65mm ± 0.42mm Range: 0.01mm – 1.85mm
	Inferior	Flexion/extension angulation (º)	6.70° ± 4.49° Range: 0.20° - 19.39°	1.70° ± 1.67° Range: 0.06° - 10.90°
		Flexion/extension translation (mm)	1.02mm ± 0.63mm Range: 0.00mm – 3.31mm	0.72mm ± 0.53mm Range: 0.05mm – 3.78mm
24 Months	Superior	Flexion/extension angulation (º)	6.92° ± 3.96° Range: 0.21° - 18.89°	1.79° ± 1.33° Range: 0.09° - 7.51°
		Flexion/extension translation (mm)	1.33mm ± 0.78mm Range: 0.00mm – 4.05mm	0.81mm ± 0.54mm Range: 0.03mm – 2.91mm
	Inferior	Flexion/extension angulation (º)	6.85° ± 4.25° Range: 0.23° - 21.88°	2.31° ± 2.36° Range: 0.08° - 18.35°
		Flexion/extension translation (mm)	1.16mm ± 0.71mm Range: 0.05mm – 4.04mm	0.98mm ± 0.67mm Range: 0.00mm – 3.49mm
36 Months	Superior	Flexion/extension angulation (º)	6.64° ± 4.37° Range: 0.22° - 19.83°	2.35° ± 1.78° Range: 0.05° - 10.56°
		Flexion/extension translation (mm)	1.42mm ± 0.76mm Range: 0.00mm – 3.71mm	0.84mm ± 0.56mm Range: 0.12mm – 3.26mm
	Inferior	Flexion/extension angulation (º)	7.08° ± 4.76° Range: 0.35° - 24.98°	2.04° ± 1.71° Range: 0.10° - 8.47°
		Flexion/extension translation (mm)	1.27mm ± 0.79mm Range: 0.11mm – 4.34mm	1.01mm ± 0.72mm Range: 0.07mm – 3.46mm
60 Months	Superior	Flexion/extension angulation (º)	6.32° ± 4.12° Range: 0.13° - 18.97°	0.77° ± 1.37° Range: 0.06° - 7.22°
		Flexion/extension translation (mm)	1.09mm ± 0.74mm Range: 0.00mm – 3.85mm	0.40mm ± 0.36mm Range: 0.03mm – 1.89mm
	Inferior	Flexion/extension angulation (º)	6.47° ± 4.66° Range: 0.10° - 22.37°	0.56° ± 1.15° Range: 0.02° - 8.47°
		Flexion/extension translation (mm)	0.92mm ± 0.58mm Range: 0.09mm – 3.19mm	0.47mm ± 0.46mm Range: 0.00mm – 2.48mm
84 Months	Superior	Flexion/extension angulation (º)	6.81° ± 4.07° Range: 0.08° - 17.26°	0.82° ± 1.18° Range: 0.04° - 4.74°
		Flexion/extension translation (mm)	1.20mm ± 0.83mm Range: 0.00mm – 3.57mm	0.43mm ± 0.54mm Range: 0.01mm – 3.00mm
	Inferior	Flexion/extension angulation (º)	6.75° ± 4.80° Range: 0.11° - 18.70°	0.73° ± 1.64° Range: 0.06° - 8.47°
		Flexion/extension translation (mm)	0.89mm ± 0.58mm Range: 0.10mm – 2.34mm	0.38mm ± 0.35mm Range: 0.03mm – 1.75mm

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)

The average angular range of motion (flexion/extension) and range of results for all 2-level PRESTIGE LP™ subjects at the pre-operative, 6 month, 12 month, 24 month, 36 month, 60 month, and 84 month timepoints are shown in **Figures 3 and 4**. The points represent the means, while the bars represent the range between the maximum and minimum at each timepoint.

Figure 3: Time Course of PRESTIGE LP™ Cervical Disc Mean Flexion/Extension Range of Motion at Superior Index Level

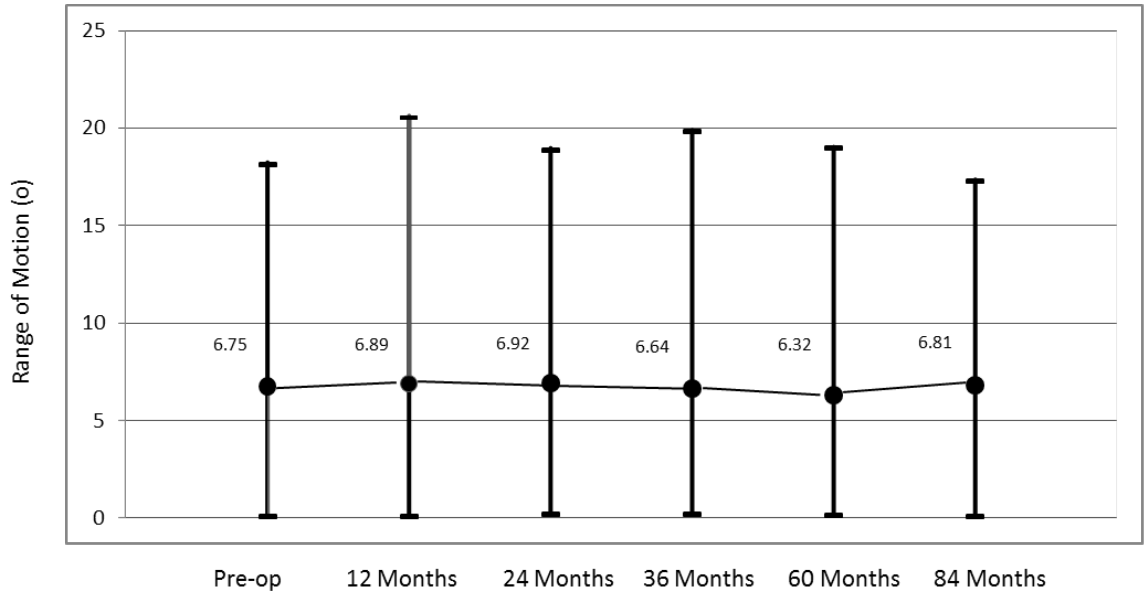


Figure 4: Time Course of PRESTIGE LP™ Cervical Disc Mean Flexion/Extension Range of Motion at Inferior Index Level

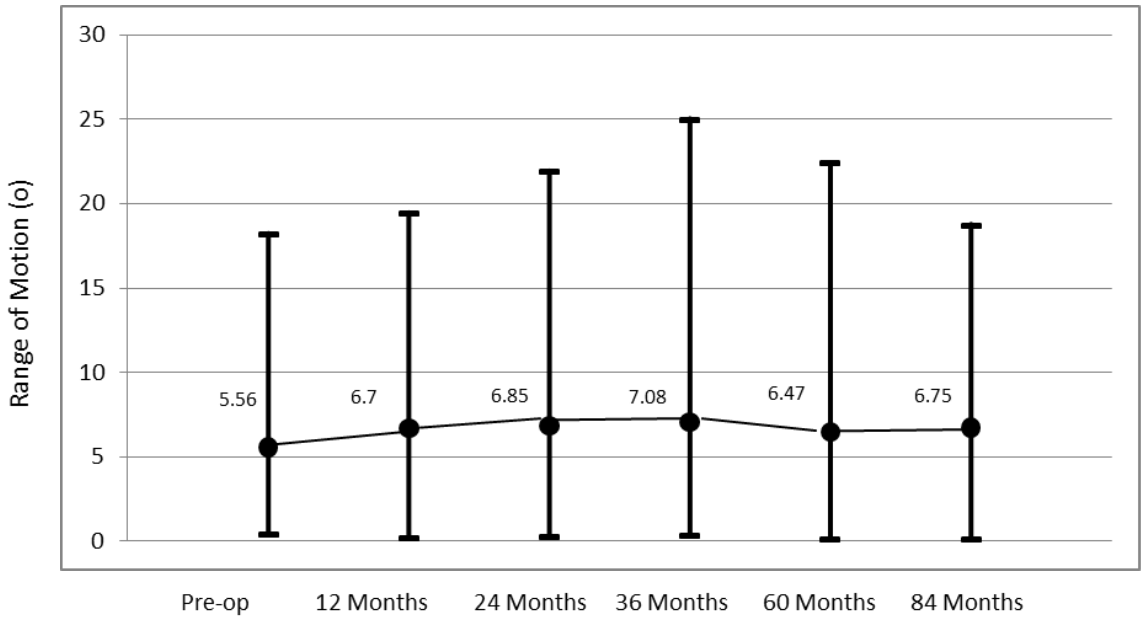


Table 43 presents data on change in range of motion from the pre-operative baseline for each timepoint by treatment group.

Table 43: Timecourse of Radiographic Change in Range of Motion

Timepoint	Treatment Level	Change in Angular Range of Motion	INV	CTR
12 Months	Superior Level Only	Increased (≥ 2º)	71/193 (36.8%)	2/155 (1.3%)
		No Change (-2º to 2º)	58/193 (30.1%)	34/155 (21.9%)
		Decreased ≤ -2º)	64/193 (33.2%)	119/155 (76.8%)
	Inferior Level Only	Increased (≥ 2º)	77/181 (42.5%)	4/140 (2.9%)
		No Change (-2º to 2º)	58/181 (32.0%)	37/140 (26.4%)
		Decreased ≤ -2º)	46/181 (25.4%)	99/140 (70.7%)
	Both Treated Levels	Increased (≥ 2º)	87/181 (48.1%)	4/140 (2.9%)
		No Change (-2º to 2º)	34/181 (18.8%)	13/140 (9.3%)
		Decreased ≤ -2º)	60/181 (33.1%)	123/140 (87.9%)
24 Months	Superior	Increased (≥ 2º)	72/190 (37.9%)	1/148 (0.7%)
		No Change (-2º to 2º)	56/190 (29.5%)	40/148 (27.0%)
		Decreased ≤ -2º)	62/190 (32.6%)	107/148 (72.3%)
	Inferior	Increased (≥ 2º)	77/180 (42.8%)	9/137 (6.6%)
		No Change (-2º to 2º)	52/180 (28.9%)	38/137 (27.7%)
		Decreased ≤ -2º)	51/180 (28.3%)	90/137 (65.7%)
	Both Treated Levels	Increased (≥ 2º)	85/180 (47.2%)	5/137 (3.6%)
		No Change (-2º to 2º)	38/180 (21.1%)	17/137 (12.4%)
		Decreased ≤ -2º)	57/180 (31.7%)	115/137 (83.9%)
36 Months	Superior	Increased (≥ 2º)	61/175 (34.9%)	4/135 (3.0%)
		No Change (-2º to 2º)	44/175 (25.1%)	38/135 (28.1%)
		Decreased ≤ -2º)	70/175 (40.0%)	93/135 (68.9%)
	Inferior	Increased (≥ 2º)	76/164 (46.3%)	5/121 (4.1%)
		No Change (-2º to 2º)	41/164 (25.0%)	38/121 (31.4%)
		Decreased ≤ -2º)	47/164 (28.7%)	78/121 (64.5%)

	Both Treated Levels	Increased (≥ 2º)	73/164 (44.5%)	4/121 (3.3%)
		No Change (-2º to 2º)	28/164 (17.1%)	12/121 (9.9%)
		Decreased ≤ -2º)	63/164 (38.4%)	105/121 (86.8%)
60 Months	Superior	Increased (≥ 2º)	56/158 (35.4%)	0/119 (0.0%)
		No Change (-2º to 2º)	45/158 (28.5%)	16/119 (13.4%)
		Decreased ≤ -2º)	57/158 (36.1%)	103/119 (86.6%)
	Inferior	Increased (≥ 2º)	60/147 (40.8%)	1/104 (1.0%)
		No Change (-2º to 2º)	41/147 (27.9%)	21/104 (20.2%)
		Decreased ≤ -2º)	46/147 (31.3%)	82/104 (78.8%)
	Both Treated Levels	Increased (≥ 2º)	70/147 (47.6%)	1/104 (1.0%)
		No Change (-2º to 2º)	26/147 (17.7%)	1/104 (1.0%)
		Decreased ≤ -2º)	51/147 (34.7%)	102/104 (98.1%)
84 Months	Superior	Increased (≥ 2º)	24/69 (34.8%)	0/59 (0.0%)
		No Change (-2º to 2º)	19/69 (27.5%)	12/59 (20.3%)
		Decreased ≤ -2º)	26/69 (37.7%)	47/59 (79.7%)
	Inferior	Increased (≥ 2º)	30/67 (44.8%)	1/54 (1.9%)
		No Change (-2º to 2º)	14/67 (20.9%)	5/54 (9.3%)
		Decreased ≤ -2º)	23/67 (34.3%)	48/54 (88.9%)
	Both Treated Levels	Increased (≥ 2º)	29/67 (43.3%)	1/54 (1.9%)
		No Change (-2º to 2º)	12/67 (17.9%)	1/54 (1.9%)
		Decreased ≤ -2º)	26/67 (38.8%)	52/54 (96.3%)

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)

Figures 5, 6, and 7 present histograms of angular range of motion on lateral flexion/extension radiographs at 24 months for all subjects treated with the 2-level PRESTIGE LP™ (superior treated level only, inferior treated level only, and combined superior and inferior treated levels). These histograms use values obtained by rounding the recorded angular range of motion for each subject to the nearest integer.

Figure 5: Histogram of PRESTIGE LP™ Cervical Disc Flexion/Extension Angular Range of Motion at 24 months (Superior Treated Level Only)

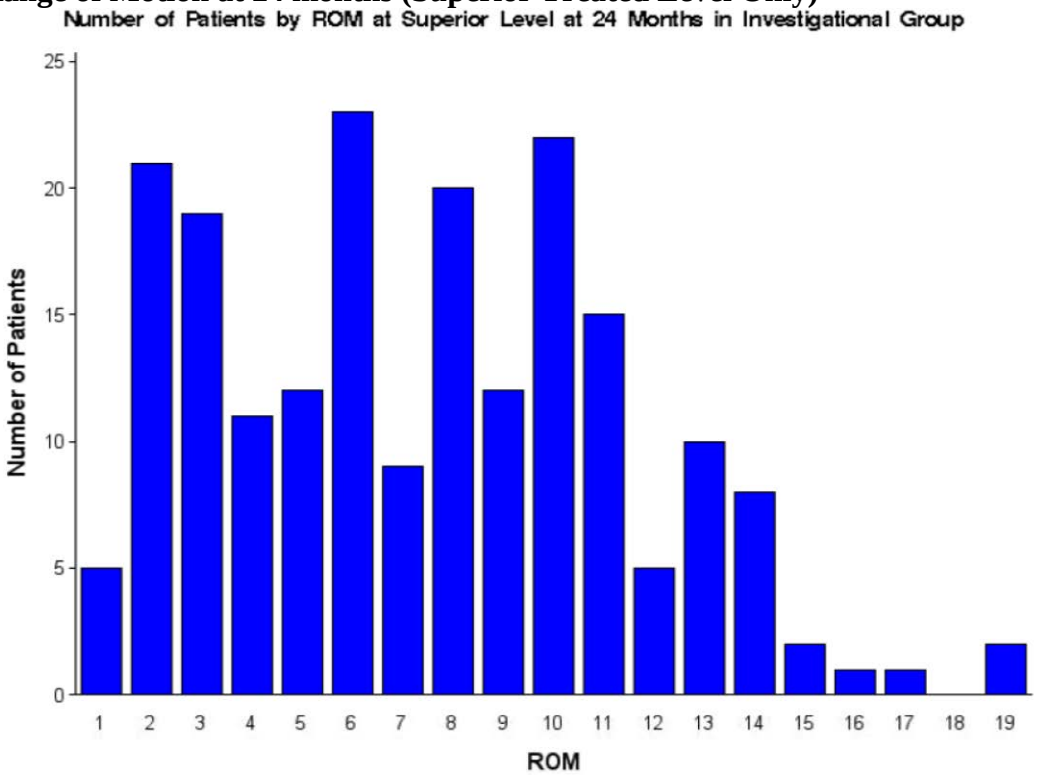


Figure 6: Histogram of PRESTIGE LP™ Cervical Disc Flexion/Extension Angular Range of Motion at 24 months (Inferior Treated Level Only)

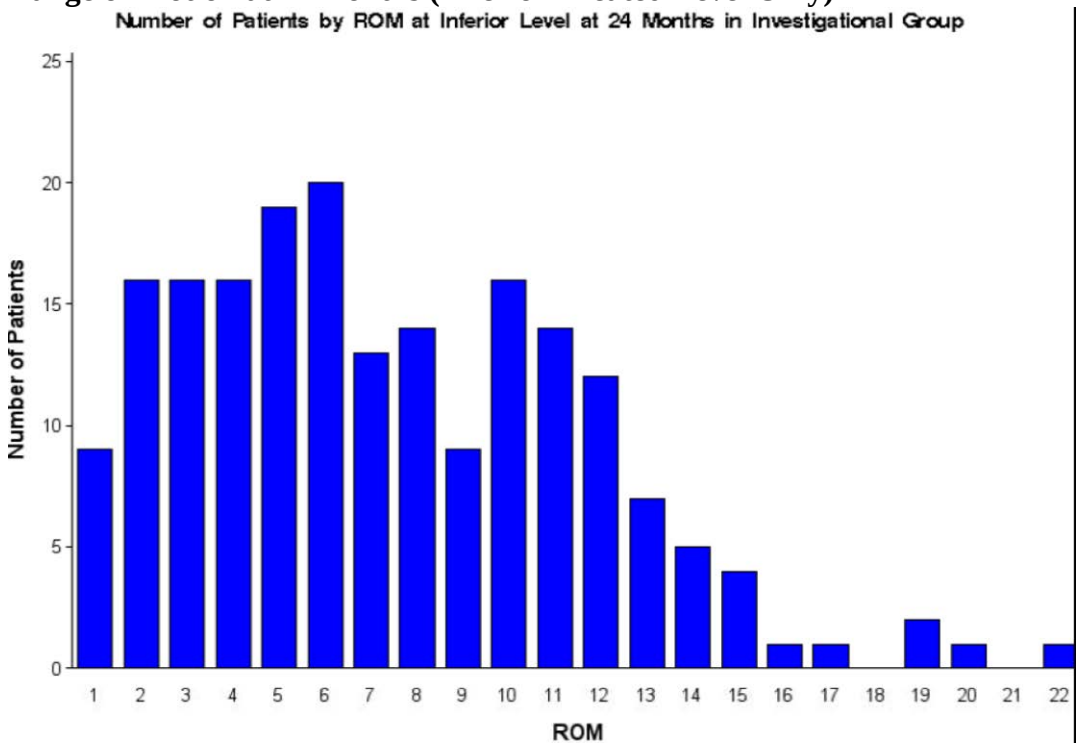
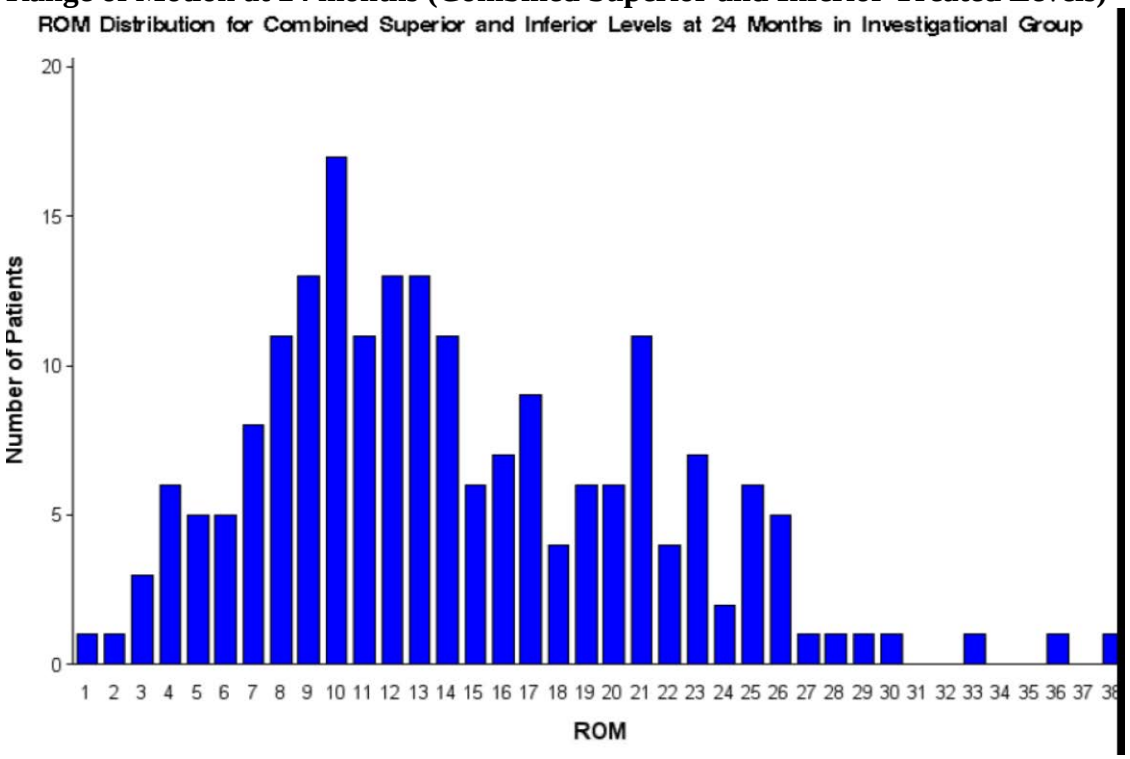


Figure 7: Histogram of PRESTIGE LP™ Cervical Disc Flexion/Extension Angular Range of Motion at 24 months (Combined Superior and Inferior Treated Levels)



The applicant also evaluated the correlation between 24 month angular range of motion and 24 month NDI and neck and arm pain scores as shown in **Table 44**. The results show that there is little correlation between the range of motion and NDI score, neck pain score, and back pain score at 24 months.

Table 44: Correlation Between 24 Month Angular Motion and Pain/Function Outcomes

Treatment Level	ROM vs. NDI Score	ROM vs. Neck Pain Score	ROM vs. Arm Pain Score
Superior Level (N=198)	0.143 (0.003, 0.277)	0.167 (0.029, 0.300)	0.082 (-0.058, 0.219)
Inferior Level (N=196)	0.009 (-0.132, 0.149)	-0.026 (-0.166, 0.114)	-0.039 (-0.178, 0.102)
Combined Superior and Inferior Levels	0.087 (-0.054, 0.225)	0.080 (-0.060, 0.218)	0.022 (-0.118, 0.162)

Note: Numbers reported in cells are Pearson Correlation Coefficients (95% Confidence Intervals).

Functional Spinal Unit (FSU) Height

Post-operative measurement of FSU height was considered a surrogate measure of subsidence due to loss of disc space height. A subject was considered a FSU height success if either the anterior or posterior post-operative FSU height was no more than 2 mm less than the 6 week post-operative FSU height at both treated levels.

Table 45 presents timecourse data on observed FSU height success rates. FSU height success was similar between the two treatment groups at all timepoints, and FSU height

success rates at 24 months following surgery were 93.5% in the 2-level PRESTIGE LP™ group and 95.7% in the 2-level ACDF control group.

Table 45: Timecourse of Radiographic FSU Height Success

Timepoint	INV	CTR
3 Months	155/173 (89.6%)	141/149 (94.6%)
6 Months	158/167 (94.6%)	143/149 (96.0%)
12 Months	163/171 (95.3%)	129/137 (94.2%)
24 Months	159/170 (93.5%)	132/138 (95.7%)
36 Months	146/159 (91.8%)	121/127 (95.3%)
60 Months	130/140 (92.9%)	109/117 (93.2%)
84 Months	53/58 (91.4%)	50/55 (90.9%)

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)

Radiographic evaluation of the mean FSU height (average of the anterior and posterior FSU height measurements) for each treated level separately and for the average of the two treated levels at each timepoint is shown in **Table 46**.

Table 46: Timecourse of Mean Radiographic FSU Height

	INV			CTR		
	Superior Level	Inferior Level	Average	Superior Level	Inferior Level	Average
Pre-operative	33.93 ± 3.69 (26.49 – 47.78) N=203	34.72 ± 3.36 (27.49 – 50.56) N=191	34.20 ± 3.36 (27.90 – 49.17) N=191	34.31 ± 3.72 (26.07 – 48.48) N=178	35.30 ± 3.97 (26.51 – 48.40) N=160	34.76 ± 3.81 (26.29 – 48.44) N=160
6 Week	33.94 ± 3.86 (25.06 – 45.20) N=206	35.40 ± 3.68 (27.81 – 46.96) N=181	34.51 ± 3.58 (26.56 – 46.08) N=181	34.46 ± 3.91 (24.77 – 48.26) N=180	35.58 ± 3.63 (27.25 – 46.91) N=166	34.93 ± 3.63 (26.69 – 47.59) N=166
3 Months	33.70 ± 4.05 (24.44 – 45.85) N=203	35.24 ± 3.90 (26.46 – 46.35) N=181	34.33 ± 3.80 (25.89 – 44.90) N=181	34.39 ± 3.91 (25.54 – 48.57) N=170	35.38 ± 3.75 (27.63 – 46.60) N=159	34.80 ± 3.72 (26.63 – 47.08) N=159
6 Months	33.68 ± 4.00 (24.49 – 44.70) N=202	35.16 ± 3.60 (27.63 – 44.73) N=180	34.21 ± 3.59 (26.06 – 42.79) N=180	34.68 ± 3.97 (25.05 – 50.02) N=170	35.62 ± 3.70 (27.42 – 47.88) N=154	35.01 ± 3.63 (26.70 – 46.82) N=154
12 Months	33.86 ± 4.00 (25.48 – 46.33) N=202	35.61 ± 4.14 (27.66 – 55.36) N=189	34.62 ± 3.92 (26.90 – 50.84) N=189	34.84 ± 3.96 (26.24 – 47.92) N=164	35.57 ± 3.63 (27.67 – 47.53) N=148	35.05 ± 3.60 (26.96 – 47.72) N=148
24 Months	33.81 ± 4.05 (24.09 – 45.18) N=199	35.51 ± 3.95 (25.57 – 45.61) N=190	34.59 ± 3.90 (24.83 – 45.07) N=190	34.87 ± 3.77 (26.10 – 47.85) N=155	35.71 ± 3.83 (27.11 – 49.02) N=151	35.25 ± 3.66 (27.32 – 47.75) N=151
36 Months	33.52 ± 4.33 (24.86 – 46.85) N=185	35.30 ± 4.36 (26.24 – 53.88) N=180	34.37 ± 4.25 (25.99 – 48.75) N=180	34.70 ± 3.90 (25.10 – 47.36) N=145	35.70 ± 3.97 (27.05 – 47.71) N=138	35.14 ± 3.86 (26.07 – 47.14) N=138
60 Months	33.50 ± 4.45 (24.96 – 49.26) N=166	35.24 ± 4.31 (26.34 – 48.91) N=162	34.36 ± 4.31 (25.65 – 48.57) N=162	34.46 ± 3.63 (26.33 – 45.27) N=132	35.71 ± 3.83 (26.91- 46.97) N=128	35.05 ± 3.59 (27.51 – 44.88) N=128
84 Months	33.43 ± 3.93 (24.20 – 42.32) N=72	35.45 ± 4.28 (25.22 – 46.26) N=68	34.41 ± 4.04 (24.97 – 44.29) N=68	34.56 ± 3.55 (28.07 – 49.16) N=61	35.93 ± 3.85 (27.90 – 48.74) N=60	35.23 ± 3.55 (27.98 – 48.95) N=60

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)

Implant Condition

In all of the post-operative radiographic reviews, implant condition was assessed for both treatment groups by independent radiologists. If a plate/screw/graft (control group) or PRESTIGE LP™ (investigational group) was found to be fractured, bent, broken or had migrated, the findings were recorded on the study Case Report Forms.

Through 84 months following surgery, one implant in the 2-level ACDF control group was found to have migrated (at the 12 month visit) and another was found to have broken (at the 60 month visit). In addition, there were 3 instances where at least one of the independent radiologists commented on radiolucency near a PRESTIGE LP™ device (all at the 24 month visit). Note that these assessments were not pre-specified and therefore only limited data are available.

Heterotopic Ossification (HO)

Available radiographs for the 2-level PRESTIGE LP™ study subjects were assessed by an independent radiographic evaluator to determine Heterotopic Ossification (HO) grade (grade 0 to grade IV) at both the superior and inferior treated levels according to the following grade definitions established by Mehren[2]:

- Grade 0: No HO present.
- Grade I: HO detectable in front of the vertebral body but not in the anatomic interdiscal space.
- Grade II: HO growing into the disc space. Possible affection of the function of the prosthesis.
- Grade III: Bridging ossifications which still allow movement of the prosthesis.
- Grade IV: Complete fusion of the treated segment without movement in flexion/extension.

In addition, the independent radiographic evaluator determined the number of subjects with stable or "worsening" (progressing by at least one grade) HO from visit to visit.

The results are shown in **Table 47**. The majority of 2-level PRESTIGE LP™ subjects were assessed as having non-severe HO (grades 0, I, or II). At 24 months post-operative, 14.1% and 16.7% of 2-level PRESTIGE LP™ subjects were assessed as having grade III HO at the superior and inferior treated levels, respectively. Grade IV HO was present in 2.0% of 2-level PRESTIGE LP™ subjects at the superior treated level and 3.0% of 2-level PRESTIGE LP™ subjects at the inferior treated level at 24 months post-operative. HO will be studied further as part of the applicant's planned post-approval studies.

Table 47: Timecourse of Heterotopic Ossification (HO)

	Grade	Superior Level	Inferior Level
6 Months	Grade 0	185/202 (91.6%)	173/202 (85.6%)
	Grade I	5/202 (2.5%)	14/202 (6.9%)
	Grade II	10/202 (5.0%)	9/202 (4.5%)
	Grade III	2/202 (1.0%)	6/202 (3.0%)
	Grade IV	0/202 (0.0%)	0/202 (0.0%)
	Stable vs. Previous visit	188/201 (93.5%)	176/201 (87.6%)
	Worsening vs. Previous visit	13/201 (6.5%)	25/201 (12.4%)

	Grade	Superior Level	Inferior Level
12 Months	Grade 0	164/202 (81.2%)	151/202 (74.8%)
	Grade I	9/202 (4.5%)	11/202 (5.4%)
	Grade II	15/202 (7.4%)	18/202 (8.9%)
	Grade III	14/202 (6.9%)	21/202 (10.4%)
	Grade IV	0/202 (0.0%)	1/202 (0.5%)
	Stable vs. Previous visit	174/200 (87.0%)	162/199 (81.4%)
	Worsening vs. Previous visit	26/200 (13.0%)	37/199 (18.6%)
24 Months	Grade 0	143/198 (72.2%)	126/198 (63.6%)
	Grade I	10/198 (5.1%)	11/198 (5.6%)
	Grade II	13/198 (6.6%)	22/198 (11.1%)
	Grade III	28/198 (14.1%)	33/198 (16.7%)
	Grade IV	4/198 (2.0%)	6/198 (3.0%)
	Stable vs. Previous visit	162/198 (81.8%)	153/197 (77.7%)
	Worsening vs. Previous visit	36/198 (18.2%)	44/197 (22.3%)
36 Months	Grade 0	119/184 (64.7%)	111/184 (60.3%)
	Grade I	11/184 (6.0%)	7/184 (3.8%)
	Grade II	19/184 (10.3%)	18/184 (9.8%)
	Grade III	26/184 (14.1%)	39/184 (21.2%)
	Grade IV	9/184 (4.9%)	9/184 (4.9%)
	Stable vs. Previous visit	150/182 (82.4%)	158/182 (86.8%)
	Worsening vs. Previous visit	32/182 (17.6%)	24/182 (13.2%)
60 Months	Grade 0	83/165 (50.3%)	75/165 (45.5%)
	Grade I	10/165 (6.1%)	15/165 (9.1%)
	Grade II	26/165 (15.8%)	28/165 (17.0%)
	Grade III	32/165 (19.4%)	33/165 (20.0%)
	Grade IV	14/165 (8.5%)	14/165 (8.5%)
	Stable vs. Previous visit	121/161 (75.2%)	123/161 (76.4%)
	Worsening vs. Previous visit	40/161 (24.8%)	38/161 (23.6%)
84 Months	Grade 0	36/71 (50.7%)	34/71 (47.9%)
	Grade I	5/71 (7.0%)	4/71 (5.6%)
	Grade II	6/71 (8.5%)	13/71 (18.3%)
	Grade III	17/71 (23.9%)	14/71 (19.7%)
	Grade IV	7/71 (9.9%)	6/71 (8.5%)
	Stable vs. Previous visit	61/71 (85.9%)	60/71 (84.5%)
	Worsening vs. Previous visit	10/71 (14.1%)	11/71 (15.5%)

Available radiographs for the 2-level PRESTIGE LP™ study subjects were also assessed for bridging bone (criteria were comparable to grade 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. At 24 months post-operatively, 88.9% (176/198) of the subjects treated with the 2-level PRESTIGE LP™ exhibited no bridging bone at either treatment level whereas 11.1% (22/198) exhibited bridging bone at one or both treatment levels [7.1% (14/198) at the superior treated level and 10.6% (21/198) at the inferior treated level]. Although grade IV HO and bridging bone assessments are interrelated, the results are similar but not identical because the assessment methods were different and independent.

Demographic and baseline characteristics were evaluated for potential correlation with HO grade, and no correlation was found. In addition, to assess the effect of HO on clinical outcomes, the applicant evaluated overall success (and component) outcomes as well as NDI outcomes and arm and neck pain outcomes in subjects with non-severe HO (defined as grades 0, I, and II) and in subjects with severe HO (defined as grades III and IV). No clinically meaningful correlation was found.

Pain Management

Table 48 presents data on pain and muscle relaxant medication use at baseline pre-operative and at 24 months post-operative by treatment group. Use of pain medication was similar in both treatment groups. For subjects on medication, the frequency of medication use ranged from once a week to three or more times a day.

Table 48: Pain and Muscle Relaxant Medication Usage Pre-operative and at 24 Months Post-operative

	INV	CTR
Pre-operative		
Non-Narcotic Medications	138/208 (66.3%)	133/185 (71.9%)
Weak Narcotic Medications*	83/208 (39.9%)	78/186 (41.9%)
Strong Narcotic Medications**	52/207 (25.1%)	44/188 (23.4%)
Muscle Relaxant Medications	75/208 (36.1%)	73/188 (38.8%)
24 Months		
Non-Narcotic Medications	85/199 (42.7%)	63/157 (40.1%)
Weak Narcotic Medications*	25/197 (12.7%)	30/157 (19.1%)
Strong Narcotic Medications**	15/196 (7.7%)	16/158 (10.1%)
Muscle Relaxant Medications	35/197 (17.8%)	36/157 (22.9%)

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)
*Weak narcotic medications include such examples as Tylenol #3, Darvocet N-100, Darvon, and Vicodin.
** Strong narcotic medications include such examples as Percodan, Percocet, Morphine, and Demerol.

Some subjects required additional non-surgical procedures at one or both of the index levels, subsequent to the initial surgery. Through all available follow-up, there were 101 additional procedures at the index level(s) in 52 (24.9%) 2-level PRESTIGE LP™ subjects and 116 additional procedures at the index level(s) in 42 (22.3%) 2-level ACDF

control subjects. The timecourse of the additional procedures through all available follow-up is summarized in **Table 49**.

Table 49: Additional Procedures at the Index Level(s) Through All Available Follow-up Classified by Procedure Type

Procedure	INV	CTR
Facet Injection	4/209 (1.9%)	7/188 (3.7%)
Medial Branch Block	0/209 (0.0%)	3/188 (1.6%)
Selective Nerve Root Block	3/209 (1.4%)	3/188 (1.6%)
Series of Epidural Steroid Injections	8/209 (3.8%)	7/188 (3.7%)
Single Epidural Steroid Injection	18/209 (8.6%)	14/188 (7.4%)
Steroid Injection	16/209 (7.7%)	20/188 (10.6%)
Sympathetic Block (Including Ganglion)	0/209 (0.0%)	1/188 (0.5%)
Trial Spinal Cord Stimulator	1/209 (0.5%)	2/188 (1.1%)
Trigger Point Injection	3/209 (1.4%)	8/188 (4.3%)
Other	21/209 (10.0%)	16/188 (8.5%)
Total	52/209 (24.9%)	42/188 (22.3%)

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)

Adjacent Level Treatments

Some subjects went on to receive post-operative treatment at adjacent level(s). The incidence and progression of adjacent level disease was not collected prospectively, but was assessed in terms of symptoms, treatment, and surgery performed at adjacent level(s) 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 who underwent surgery at adjacent level(s) (including those who had combined subsequent surgery at the index and adjacent level(s)) was 2.4% (5 subjects, 5 events) for the 2-level PRESTIGE LP™ group and 3.2% (6 subjects, 8 events) for the 2-level ACDF control group as shown in **Table 50**.

Table 50: Timecourse of Subjects with Adjacent Level Surgical Treatment

Timepoint	INV	CTR

Timepoint	INV		CTR	
	Subjects N (%)	Events N	Subjects N (%)	Events N
Operative	0 (0.0%)	0	0 (0.0%)	0
1 Day - < 4 Weeks	0 (0.0%)	0	0 (0.0%)	0
6 Weeks	0 (0.0%)	0	0 (0.0%)	0
3 Months	0 (0.0%)	0	2 (1.1%)	3
6 Months	1 (0.5%)	1	0 (0.0%)	0
12 Months	3 (1.4%)	3	3 (1.6%)	3
24 Months	1 (0.5%)	1	2 (1.1%)	2
Total (≤ 24 Months)	**5 (2.4%)**	**5**	**6 (3.2%)**	**8**
36 Months	4 (1.9%)	4	3 (1.6%)	3
48 Months	0 (0.0%)	0	3 (1.6%)	4
60 Months	2 (1.0%)	2	1(0.5%)	2
72 Months	1 (0.5%)	1	3 (1.6%)	3
84 Months	0 (0.0%)	0	1 (0.5%)	1
Total (All Follow-up)	**12 (5.7%)**	**12**	**17 (9.0%)**	**21**

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)

The types of adjacent level procedures that were performed are summarized in **Table 51**.

Table 51: Types of Adjacent Level Treatments

Adjacent Level Treatment	INV	CTR
Adjacent level fusion-1 level	7 (3%)	7 (4%)
Adjacent level fusion- 2 level	1 (0.5%)	2 (1%)
Adjacent level decompression-1 Level	6 (3%)	10 (5%)
Adjacent level decompression-2 Level	0 (0%)	4 (2%)
Bone Growth Stimulator	0 (0%)	1 (0.5%)
Cervical Total Disc Replacement- 1 Level	1 (0.5%)	4 (2%)
Cervical Total Disc Replacement- 2 Level	1 (0.5%)	0 (0%)
Cervical wound exploration and repair of dural tear and CSF leak	0 (0%)	1 (0.5%)
Rhizotomy	1 (0.5%)	0 (0%)
Total	17 (8%)	29 (15%)

INV=2-level PRESTIGE LP™ (N=209); CTR = 2-level ACDF control (N=188)
Decompression includes foraminotomy, laminotomy, laminoplasty, corpectomy, osteophytectomy, micorforaminotomy, laminoforaminotomy, hemilaminectomy, and laminectomy
Most surgical interventions required more than one treatment type.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit marketing applications 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 of the 2-level PRESTIGE LP™ included 105 investigators of which none were full-time or part-time employees of the applicant and 9 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: 4 investigators
- Significant payment of other sorts: 9 investigators
- Proprietary interest in the PRESTIGE LP™ held by the investigator: 1 investigator
- Significant equity interest held by investigator in applicant of covered study: 3 investigators

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by the Applicant, and confirmed by FDA, to determine whether the financial interests/arrangements had any impact on the clinical study outcome at 12- and 24- months. The difference of overall success at 24 months between the two treatment groups is 14.4% for the sites with financial interest while this difference is 10.01% for the sites without financial interest. The interactions between the financial interest and treatment effects were not significant. The Cochran-Mantel-Haenszel (CMH) test with p-value 0.626 further supports that the treatment effects were not statistically influenced by the financial interests. The applicant also analyzed the overall success rates at 12- and 24- months by financial interest of surgeons. The analyses show similar results for comparing the sites with and without financial interests. There is no significant interaction between the treatment effects and financial interests, and the treatment effects were not statistically influenced by the financial interests.

The applicant listed the following steps taken to minimize the potential bias of the clinical study results by the disclosed arrangements or interests:

- Centrally produced randomization schedule generated using the Plan Procedure in Statistical Analysis System (SAS) Version 6.12 or higher
- 1:1 Investigational: Control treatment randomization and stratified on a site basis
- Blocked randomization with varying block sizes
- Investigators were blinded to the randomization code during the Informed Consent process
- Patient were blinded to the randomization code during the Informed Consent process
- Randomization schedule could only be accessed by limited sponsor study personnel
- Opaque envelopes were used to conceal the treatment code for each patient
- Sealed envelopes with treatment code for each patient was distributed to the clinical investigational sites as ordered by the patient number
- Patients were assigned a sequential clinical trial number from the investigational site's list of clinical trial numbers
- After all inclusion/exclusion criteria were met and the Informed Consent process was properly completed, the investigator or designee opened the envelope that corresponds to the patient's assigned clinical trial number to determine if the patient will be randomized into the investigational or control group

The study employed the same protocol and surgical technique across the sites. Any single site was not permitted to enroll more than 20% subjects of the total study sample size.

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 recommendation 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 the clinical study to support PMA approval of the PRESTIGE LP™ Cervical Disc for use at two contiguous levels, 397 subjects were treated (209 2-level PRESTIGE LP™ subjects and 188 2-level ACDF control subjects) at 30 U.S. sites, all had reached the 24 month post-operative visit and 363 of the 396 expected subjects (92%) had any 24-month data available for analysis. Complete 24-month overall success (primary endpoint) data was available for 199 2-level PRESTIGE LP™ subjects and 160 2-level ACDF control subjects. Statistical analysis demonstrated that the results from all sites were poolable to determine safety and effectiveness. Analysis of subject demographic and baseline covariates showed that the two randomized treatment groups were comparable at baseline.

Overall success at 24 months post-operative was the primary endpoint for the clinical study, and was defined in the protocol as improvement in pain and function based on the Neck Disability Index, maintenance or improvement in neurological status, no subsequent surgery at the index level classified as a "failure," and no severe adverse event that was judged as implant associated or implant/surgical procedure associated (referred to as Overall Success (Protocol Definition) above). In addition, because the additional surgical procedure component of the primary endpoint did not consider all subsequent surgeries at the index level as failures, FDA requested an additional analysis of overall success in which all subsequent surgeries at the index level and all intra-operative treatment conversions were considered failures (referred to as Overall Success (Alternate Analysis) above).

The randomized study results, based on both sets of overall success criteria, indicate that the 2-level PRESTIGE LP™ is non-inferior (10% delta) to the 2-level ACDF control group at 24 months post-operative. Based on the Protocol Definition of Overall Success, at 24 months following surgery, the posterior probability of overall success in the 2-level PRESTIGE LP™ group was 80.3% as compared to 69.0% in the 2-level ACDF control group. Similarly, based on the Alternate Analysis of Overall Success, at 24 months post-operative, the posterior probability of overall success in the 2-level PRESTIGE LP™ group was 79.5% as compared to 68.5% in the 2-level ACDF control group. Considering both definitions of overall success, the posterior probability of non-inferiority of the 2-

level PRESTIGE LP™ group to the 2-level ACDF control group at 24 months post-operative is essentially 100%, demonstrating non-inferiority. In addition, the posterior probability of superiority of the 2-level PRESTIGE LP™ group to the 2-level ACDF control group at 24 months post-operative is above the 95% threshold for both analyses of overall success, demonstrating statistical superiority.

To assess the impact of subjects with unknown outcomes at 24 months post-operative or other potential biases, various sensitivity analyses were conducted to confirm the robustness of the study conclusions. The results of nearly all sensitivity analyses indicate that the 2-level PRESTIGE LP™ Cervical Disc is non-inferior to the 2-level ACDF control group in terms of overall success.

In addition, the results of numerous secondary effectiveness analyses further demonstrate similar outcomes when comparing the 2-level PRESTIGE LP™ Cervical Disc and the 2-level ACDF control group.

In the 2-level PRESTIGE LP™ group, radiographic success was defined as angular motion on lateral flexion/extension radiographs >4° but ≤20° and no radiographic evidence of bridging trabecular bone that forms a continuous bony connection with the vertebral bodies (i.e., no bridging bone) at both treated levels. Based on this definition, 100/196 (51.0%) 2-level PRESTIGE LP™ subjects evaluated at 24 months post-operative were considered a radiographic success at both treated levels.

In conclusion, the study data indicate that, at 24 months post-operative, the PRESTIGE LP™ Cervical Disc used for reconstruction of the disc following discectomy at two contiguous levels from C3-C7 is at least as effective as 2-level ACDF in subjects with intractable radiculopathy (arm pain and/or a neurological deficit) with or without neck pain, or myelopathy due to 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 who 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.

B. Safety Conclusions

The risks of the PRESTIGE LP™ Cervical Disc used at two contiguous levels are based on nonclinical laboratory and animal studies as well as data collected in the clinical study conducted to support PMA approval as described above.

Nonclinical testing performed on the device demonstrated that the PRESTIGE LP™ Cervical Disc used at two contiguous levels should withstand the expected physiologic loads in the cervical spine.

In the clinical study to support PMA approval of the PRESTIGE LP™ Cervical Disc for use at two contiguous levels, the investigational 2-level PRESTIGE LP™ was found to

have a reasonable assurance of safety and to be at least as safe as 2-level ACDF. Specifically, the rates of 2-level PRESTIGE LP™ subjects who experienced at least one adverse event, an event classified by the CAC as device or device/surgical procedure related (including those also classified as severe), or an event classified by the CAC as severe were generally comparable to the corresponding rates in the 2-level ACDF control group. In addition, the rates of subsequent surgeries at the index level were lower in the 2-level PRESTIGE LP™ group (2.4% of subjects) as compared to the 2-level ACDF control group (8.0% of subjects).

In addition, at 24 months post-operative, the proportion of subjects with no decline in neurological status was comparable between the two treatment groups (91.5% of subjects in the 2-level PRESTIGE LP™ group; 86.2% of subjects in the 2-level ACDF control group).

In conclusion, the study data indicate that, at 24 months post-operative, the PRESTIGE LP™ Cervical Disc used for reconstruction of the disc following discectomy at two contiguous levels from C3-C7 has a reasonable assurance of safety and is at least as safe as 2-level ACDF with regards to adverse event rates, the need for subsequent surgery at the index level, and neurologic status in subjects with intractable radiculopathy (arm pain and/or a neurological deficit) with or without neck pain, or myelopathy due to 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 who have failed at least 6 weeks of non-operative treatment or have the presence of progressive symptoms or signs of nerve root/spinal cord compression in the face of continued non-operative management.

C. Benefit-Risk Determination

The probable benefits of the PRESTIGE LP™ Cervical Disc used at two contiguous levels are based on data collected in the clinical study conducted to support PMA approval as described above.

The clinical study demonstrated several benefits of the PRESTIGE LP™ Cervical Disc used at two contiguous levels over the 24-month time period studied:

- The benefit of the PRESTIGE LP™ Cervical Disc used at two contiguous levels in terms of clinically meaningful improvement in function (as measured by a 15 point improvement in the Neck Disability Index) at 24 months post-operative was comparable to the 2-level ACDF control group. The majority of subjects in both treatment groups experienced this benefit (87.9% of 2-level PRESTIGE LP™ subjects and 79.2% of 2-level ACDF control subjects).
- The benefit of the PRESTIGE LP™ Cervical Disc used at two contiguous levels in terms of neurologic success (maintenance or improvement in neurologic status as measured during the neurologic examination done by the investigator) at 24 months post-operative was comparable to the 2-level ACDF control group. The majority of

subjects in both treatment groups in the clinical study experienced this benefit (91.5% of 2-level PRESTIGE LP™ subjects and 86.2% of 2-level ACDF control subjects).

- In terms of improvement in neck and arm pain (as measured by ≥20% improvement at rest using a neck and arm pain questionnaire as compared to baseline), at 24 months post-operative, the benefit of the PRESTIGE LP™ Cervical Disc used at two contiguous levels was at least comparable to the 2-level ACDF control group. The majority of subjects in both treatment groups experienced clinically meaningful improvement in neck pain at 24 months (93.5% of 2-level PRESTIGE LP™ subjects and 89.3% of 2-level ACDF control subjects). Similarly, the majority of subjects in both treatment groups experienced clinically meaningful improvement in arm pain at 24 months(86.4% of 2-level PRESTIGE LP™ subjects and 85.5% of 2-level ACDF control subjects).
- In the 2-level PRESTIGE LP™ group, radiographic success was defined as angular motion on lateral flexion/extension radiographs >4° but ≤20° and no radiographic evidence of bridging trabecular bone that forms a continuous bony connection with the vertebral bodies (i.e., no bridging bone) at both treated levels. Based on this definition, 100/196 (51.0%) 2-level PRESTIGE LP™ subjects evaluated at the 24 month post-operative time point were considered a radiographic success at both treated levels. No comparison was made to the 2-level ACDF control group since fusion is not intended to allow for motion.
- The benefit of the PRESTIGE LP™ Cervical Disc used at two contiguous levels was also comparable to the 2-level ACDF control group in terms of improvement in quality of life (as measured by the SF-36), subject satisfaction (as measured by subject satisfaction questions as well as Subject Perceived Effect), and physician satisfaction with subject outcomes (as measured by Physician Perceived Effect).

The clinical trial demonstrated that the risks associated with use of the PRESTIGE LP™ Cervical Disc used at two contiguous levels were comparable to those associated with 2-level ACDF through follow-up beyond 24 months. In addition, there was a numerically lower rate of subsequent surgical intervention at the index level in the 2-level PRESTIGE LP™ group (2.4% of subjects) as compared to the 2-level ACDF control group (8.0% of subjects) through 24 months, as well as through all available follow-up (3.8% of subjects in the 2-level PRESTIGE LP™ group; 11.7% of subjects in the 2-level ACDF group). Also, the 2-level PRESTIGE LP™ group was comparable to the 2-level ACDF control group in terms of adverse event rates and maintenance or improvement in neurologic status through follow-up beyond 24 months.

Metal ion data was not collected as part of the PRESTIGE LP™ two-level IDE study. However, Medtronic will conduct a single arm, non-randomized metal ion post-approval study on thirty subjects (n=30) at up to five (5) clinical sites in the U.S. to assess the concentrations of metal ions (specifically titanium, vanadium, and aluminum) in blood serum of subjects implanted with the PRESTIGE LP™ Cervical Disc at two contiguous levels from C3-C7 through 24 months post-operatively. Additional data will also be collected on NDI, neck and arm pain, adverse events, subsequent surgeries, and neurologic status to evaluate the correlation (if any) between metal ion levels and clinical outcomes.

Several additional factors were considered in determination of the probable benefits and risks for the PRESTIGE LP™ Cervical Disc used at two contiguous levels. Limitations of the clinical study design included lack of subject masking with regard to treatment assignment, reliance on subjective endpoints, subjectivity regarding adverse event classification, and lack of power to study effects of treatment in subgroups. The impact of missing data and the robustness of the sensitivity analyses provided to address the missing data, as well as the generalizability of the study results were also considered. Alternative available treatments and risk mitigation strategies were considered, as was the fact that the only available indicator of subject tolerance for risk and perspective on benefit was subject satisfaction data.

1. Patient Perspectives

This submission did not include specific information on patient perspectives for this device. Theoretical benefits of cervical arthroplasty devices, such as the PRESTIGE LP™, include preservation of range of motion and potential for decreased risk of adjacent segment degeneration. However, the clinical study conducted to support PMA approval of the PRESTIGE LP™ Cervical Disc used at two contiguous levels was not specifically designed or powered to study these potential benefits as primary endpoints.

In conclusion, given the available information above, the data support that for reconstruction of the disc at two contiguous level from C3-7 following discectomy for intractable radiculopathy (arm pain and/or a neurological deficit) with or without neck pain, or myelopathy due to an abnormality localized to the level of the disc space and specific radiographic findings as outlined in the Indications for Use in subjects who have failed at least 6 weeks of non-operative treatment or have progressive symptoms or signs of nerve root/spinal cord compression in the face of continued non-operative management, the probable benefits of the 2-level PRESTIGE LP™ Cervical Disc outweigh the probable risks through 24 months of follow-up.

D. Overall Conclusions

The nonclinical and clinical data presented in this application support the reasonable assurance of safety and effectiveness of the PRESTIGE LP™ Cervical Disc used at two contiguous levels when used in accordance with the indications for use. Based on the clinical study results, it is reasonable to conclude that a significant portion of the indicated patient population will achieve clinically significant results. The clinical benefits of the use of the PRESTIGE LP™ Cervical Disc at two contiguous levels in terms of improvement in pain and function, and the potential for motion preservation, outweigh the risks associated with the device and surgical procedure through 24 months of follow-up when used in the indicated population in accordance with the directions for use.

XIII. CDRH DECISION

CDRH issued an approval order on July 7, 2016. The final conditions of approval cited in the approval order are described below.

1. The applicant has agreed to provide the following data as part of the Annual Report: Results from *The PRESTIGE LP™ Cervical Disc Post-Market Device Failure Study and Complaint Analysis* that will be conducted for the 10 years following approval of this PMA supplement. *The PRESTIGE LP™ Cervical Disc Post-Market Device Failure Study and Complaint Analysis* is a 10 year study designed to fully characterize adverse events, complaints, and the long-term modes and causes of failure when the PRESTIGE LP™ Cervical Disc is used in the intended patient population under general conditions of use in the United States and in the rest of the world, as well as to identify new safety concerns that were not observed in the clinical study. This study will include the following elements:

    a. Adverse event and complaint analysis for 10 years following approval of this PMA supplement through which the applicant will collect, analyze, and submit to FDA data regarding all adverse events including subsequent surgeries, heterotopic ossification, device malfunction, and other serious device-related complications. Information will be collected passively through complaints, MDRs, and literature reviews.

    b. An analysis of all available explanted PRESTIGE LP™ Cervical Discs for 10 years following approval of this PMA supplement (including, but not limited to, those retrieved from subjects in the Office of Device Evaluation (ODE)-Lead PMA Post-Approval Study (*10 Year Extended Follow-up of IDE Subjects Treated with the PRESTIGE LP™ Cervical Disc at Two Contiguous Levels*) as outlined below, those retrieved from subjects in the Office of Surveillance and Biometrics (OSB)-Lead PMA Post-Approval Study (*PRESTIGE LP™ 2-Level Metal Concentrations*) as outlined below, and those retrieved from commercial use of the PRESTIGE LP™ Cervical Disc (including in patients treated at one level, two contiguous levels, or off-label at more than two levels).

    Surgeon training on the use of the PRESTIGE LP™ Cervical Disc will include detailed training on the requirements of this *Post-Market Device Failure Study and Complaint Analysis*. Also, as part of the active collection of surgeon feedback, the applicant will regularly interact with the surgeon users of the device to gather data on the number of PRESTIGE LP™ Cervical Discs implanted as well as subsequently explanted and to encourage participation in this *Post-Market Device Failure Study and Complaint Analysis*. In cases where a PRESTIGE LP™ Cervical Disc is explanted but not submitted for analysis as part of the *Post-Market Device Failure Study and Complaint Analysis*, the applicant will be responsible for documenting the reason as part of the Annual Report.

    For each known device removal since the prior Annual Report, the applicant will report the following information or explain why certain information is not available: a detailed clinical narrative, a copy of the operative report from the original PRESTIGE LP™

Cervical Disc implantation surgery, copies of operative reports from all subsequent surgeries including the removal surgery, copies of any available histologic analyses of the host response to the device and any particulate debris conducted by an independent laboratory (or the hospital where the device was removed if the surgeon did not send the sample to the independent laboratory) for explants in the United States, copies of any available metal ion data analysis conducted by an independent laboratory for the ODE-Lead and OSB-Lead PMA Post-Approval Studies outlined below, and any available explant analysis including a detailed explant analysis conducted by an independent laboratory (for explants in the United States) per the *Plan For The Retrieval And Analysis Of Explanted PRESTIGE LP™ Artificial Cervical Disc Device Used In The PRESTIGE LP™ Cervical Disc (Two-Level) Post-Approval Study* (Version A, provided by email 06/16/2016) reviewed and approved by FDA.

2. ODE-Lead PMA Post-Approval Study – *10 Year Extended Follow-up of IDE Subjects Treated with the PRESTIGE LP™ Cervical Disc at Two Contiguous Levels*: The Office of Device Evaluation (ODE) will have the lead for this clinical study, which was initiated prior to device approval. This study will be conducted per the protocol dated January 2015 and approved by FDA on March 5, 2015 (Version G) and the Statistical Analysis Plan dated June 2016 (Version 2.0).

   The *10 Year Extended Follow-up of IDE Subjects Treated with the PRESTIGE LP™ Cervical Disc at Two Contiguous Levels* is a 10-year post-approval study (PAS) to evaluate the longer term safety and effectiveness of the PRESTIGE LP™ Cervical Disc used for reconstruction of the disc at two contiguous levels from C3-C7 in subjects with intractable radiculopathy (arm pain and/or a neurological deficit) with or without neck pain or myelopathy due to abnormality localized to the level of the disc space as compared to 2-level Anterior Cervical Discectomy and Fusion (ACDF). This PAS will follow the 397 subjects treated in the pivotal investigational device exemption (IDE) study (209 2-level PRESTIGE LP™ subjects and 188 2-level ACDF control subjects) annually through 10 years post-operative.

   At each periodic (±3 months) visit, the applicant will collect the following data: Neck Disability Index (NDI), Neck and Arm Pain Questionnaire, health status questionnaire (SF-36), neurological status, gait assessment and foraminal compression test, subject satisfaction, subject perceived effect, physician perception of results, medication use and postoperative treatment for pain management, work status, radiographic information, and all adverse events regardless of cause including all subsequent surgical interventions. Radiographic information collected will include: range of motion (ROM) on flexion/extension films (angulation and translation as well as the correlation of range of motion with clinical outcomes), functional spinal unit (FSU) height, implant condition (including evaluation of implant migration), radiolucency, heterotopic ossification (including grade, progression over time and correlation with subject characteristics and post-operative clinical outcomes). The applicant will also collect clinical and radiographic data on adjacent level degeneration including both surgical and non-surgical adjacent level treatment as well as adjacent level diagnoses and adjacent level range of motion.

The applicant will analyze all PRESTIGE LP™ Cervical Discs that are explanted as part of this Post-Approval Study per the Plan for the Retrieval and Analysis of Explanted PRESTIGE LP™ Artificial Cervical Disc Devices reviewed and approved by FDA and will present the results in the relevant section of each PMA Annual Report, as outlined above.

The primary objective of this PAS is to evaluate Overall Success (Protocol Definition) at 120 months, which is defined consistent with the IDE study as:

a. Improvement (reduction) of at least 15 points in the NDI score at 120 months compared to pre-operative baseline;

b. Maintenance or improvement in neurological status at 120 months compared to pre-operative baseline as measured based on motor function, sensory function, and reflexes;

c. No serious adverse event classified as implant associated, or implant/surgical procedure associated by the independent Clinical Adjudication Committee (CAC); and

d. No additional surgical procedure classified as a "failure."

In addition, consistent with the IDE study, because the additional surgical procedure component of Overall Success (Protocol Definition) did not consider all subsequent surgeries at the index level as failures, the applicant have also agreed to conduct the following additional analysis referred to as Overall Success (Alternate Analysis) in which all subsequent surgeries at the index level and all intra-operative treatment conversions were considered failures.

Overall Success (Protocol Definition) and Overall Success (Alternate Analysis) rates in the 2-level PRESTIGE LP™ Cervical Disc group and the 2-level ACDF control group will be compared and assessed for non-inferiority based on a ten percent non-inferiority margin. Subjects who were non-recoverable non-responders prior to 24 months will carry forward as failures for each subsequent annual visit. Numerous sensitivity analyses as specified in the protocol and statistical analysis plan will be done to assess the robustness of the study conclusions. As outlined in the study protocol, the applicant will conduct all of the same analyses as were included in the FDA Summary of Safety and Effectiveness Data.

FDA will expect at least 85% follow-up at the 10-year timepoint to provide sufficient data to evaluate longer-term safety and effectiveness. The applicant will submit progress reports to FDA for this study every six months during the first two years of the study and annually thereafter. The applicant will submit a final study report within 6 months of the last subject visit.

3. OSB-Lead PMA Post-Approval Study – *PRESTIGE LP 2-Level Metal Concentrations*: The Office of Surveillance and Biometrics (OSB) will have the lead for studies initiated after device approval. This study will be conducted per protocol dated June 22, 2016 (Version A, provided by email).

   The *PRESTIGE LP™ 2-Level Metal Concentrations* study is a prospective, one-arm cohort study of thirty (30) new subjects who will be enrolled and treated with the PRESTIGE LP™ Cervical Disc at 2 contiguous levels from C3–C7 in accordance with the approved indications for use. The 30 newly enrolled patients will be followed for 24 months post-operative to assess the metal concentrations (titanium, vanadium, and aluminum) present in blood serum after implantation with the PRESTIGE LP™ Cervical Disc at two contiguous levels.

   The applicant will collect the following data at baseline, 6 weeks, 3 months, 6 months, 12 months, and 24 months: blood samples for serum metal concentration testing (titanium, vanadium, aluminum), Neck Disability Index (NDI), Neck and Arm Pain Questionnaire, neurological status, medication use, work status, and all adverse events regardless of cause including all subsequent surgical interventions.

   Metal concentration data will be collected, stored, tested and analyzed in accordance with the methodology employed for the *1-Level PRESTIGE LP™ Metal Ion* study protocol (P090029/S002/A005). The applicant will evaluate the change in metal concentrations at each study time-point.

   The applicant will also analyze all PRESTIGE LP™ Cervical Discs that are explanted as part of this Post-Approval Study per the *Plan For The Retrieval And Analysis Of Explanted PRESTIGE LP™ Artificial Cervical Disc Device Used In The PRESTIGE LP™ Cervical Disc (Two-Level) Post-Approval Study* reviewed and approved by FDA and will present the results in the relevant section of each PMA Annual Report, as outlined above.

   The applicant will evaluate Overall Success at 24 months which is defined consistent with the IDE study as:

   a. NDI score improvement of at least 15 points from baseline;

   b. Maintenance or improvement in neurological status (as measured based on motor function, sensory function, and reflexes);

   c. No serious adverse event classified as implant associated or implant/surgical procedure associated by the independent Clinical Adjudication Committee (CAC);

   d. No additional surgical procedures classified as a “failure.”

   In addition, consistent with the IDE study, because the additional surgical procedure

component of Overall Success (Protocol Definition) did not consider all subsequent surgeries at the index level as failures, the applicant will also conduct an additional analysis referred to as Overall Success (Alternate Analysis) in which all subsequent surgeries at the index level and all intra-operative treatment conversions were considered failures.

As outlined in the study protocol, the applicant will summarize and analyze the data as follows:

a. The metal concentrations of titanium, aluminum, and vanadium in blood serum at all study time-points will be summarized descriptively using mean, standard deviation, median, minimum and maximum.

b. Changes in metal concentrations of titanium, aluminum, and vanadium at all study time-points as compared to pre-operative concentrations will be assessed using a paired t-test for normally distributed data or a Wilcoxon signed rank test for not normally distributed data.

c. Secondary measurements, including time-course data on the rate of overall success and the rates of NDI and neurological success (as defined in the study protocol) will be summarized in frequency tables.

d. Changes in NDI score, neck pain score and arm pain score at all study time-points as compared to pre-operative will be assessed using a paired t-test for normally distributed data or a Wilcoxon signed rank test for not normally distributed data.

e. Correlation analyses will be conducted as outlined in the study protocol to assess possible trends between metal concentrations and clinical variables (including overall success, neurological success, NDI outcomes, and neck and arm pain outcomes).

FDA will expect at least 90% (n=27) follow-up at the 2-year time-point to provide sufficient data to evaluate possible changes in the metal concentrations.

The applicant's manufacturing facilities have 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

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

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[3] McAfee PC, et al. Classification of heterotopic ossification (HO) in artificial disc replacement. *J Spinal Disorders & Techniques* 2003; 16(4):384-389.