SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Artificial Cervical Disc
Device Trade Name:	M6-C™ Artificial Cervical Disc
Device Product Code	MJO
Applicant's Name/Address:	Spinal Kinetics LLC 501 Mercury Drive Sunnyvale, CA 94085
Date of Panel Recommendation:	None
Premarket Approval Application: (PMA Number)	P170036
Date of FDA Notice of Approval:	February 6, 2019

II. INDICATIONS FOR USE

The M6-C™ Artificial Cervical Disc is indicated for reconstruction of the disc following single level discectomy in skeletally mature patients with intractable degenerative cervical radiculopathy with or without spinal cord compression at one level from C3 – C7. Degenerative cervical radiculopathy is defined as arm pain and/or a neurological deficit (numbness, weakness, deep tendon reflexes changes) with or without neck pain due to disc herniation and/or osteophyte formation and confirmed by radiographic imaging (CT, MRI, x-rays). The M6-C™ Artificial Cervical Disc is implanted via an anterior approach. Patients should have failed at least 6 weeks of conservative treatment or exhibit progressive neurological symptoms which could lead to permanent impairment prior to implantation of the M6-C™ Artificial Cervical Disc.

III. CONTRAINDICATIONS

The M6-C™ Artificial Cervical Disc should not be implanted in patients with the following conditions:

- Advanced cervical anatomical deformity (e.g., ankylosing spondylitis, scoliosis) at the operative or adjacent levels
- Symptomatic facet arthrosis defined as pain in the neck that is worse when in extension and/or rotation and/or stiffness or the inability to move part of the neck attributable to the facets as confirmed by imaging (x-ray, CT, MRI, bone scan)
- Advanced degenerative changes (e.g., spondylosis) at the index vertebral level as evidenced by bridging osteophytes, excessive translation or kyphotic deformity > 11º on neutral x-rays
- Active systemic infection or infection at the operative site

- Osteoporosis defined as DEXA bone mineral density T-score ≤ -2.5
- Known allergy to titanium, stainless steel, polyurethane, polyethylene, or ethylene oxide residuals

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the M6-C™ Artificial Cervical Disc Instructions for Use.

V. DEVICE DESCRIPTION

The M6-C™ Artificial Cervical Disc is an intervertebral disc prosthesis designed to permit motion of a functional spinal unit in the cervical spine when replacing a degenerated native disc. The device is comprised of ultra-high molecular weight polyethylene (UHMWPE) fiber wound in a specific pattern, with multiple redundant layers, creating a fiber matrix (artificial annulus). The fiber is wound around a polycarbonate urethane polymer (PCU) core (artificial nucleus) and through the slots in two Ti6Al4V titanium alloy inner endplates (see **Figure 1**). The core is situated between and in contact with the two inner endplates, but not affixed to them. A PCU sheath surrounds the fiber matrix and is retained by two Ti6Al4V weld bands that are welded to the inner endplates. Two Ti6Al4V outer endplates are also welded to the inner endplates. The exterior surfaces of the outer endplates include low profile fins and are coated with titanium plasma spray (TPS).

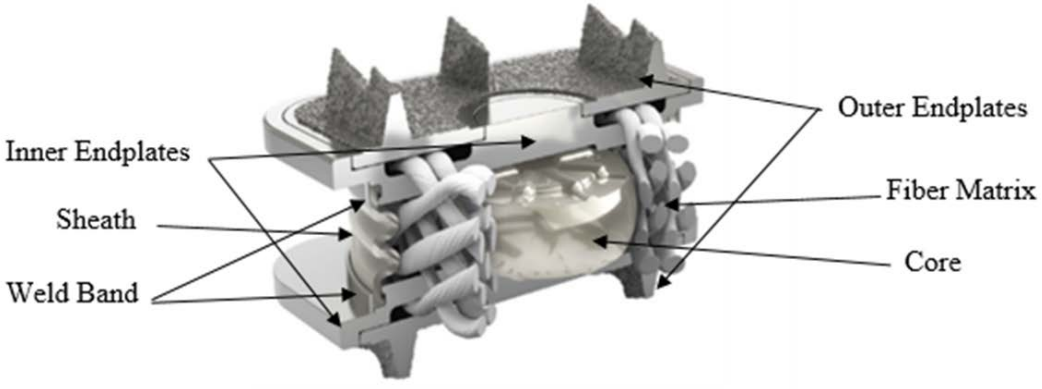

Figure 1: Cross-Section View of the M6-C™ Artificial Cervical Disc

The M6-C™ Artificial Cervical Disc is designed to maintain the natural behavior of a functional spinal unit by replicating the biomechanical characteristics of the native disc. This design enables the M6-C™ Artificial Cervical Disc to move in all six degrees of freedom, with independent angular rotations (flexion-extension, lateral bending and axial rotation) along with independent translational motions (anterior-posterior and lateral translations as well as axial compression). The device is intended to replicate the physiological phenomenon of progressive resistance to motion in all six degrees of freedom. The sheath is designed to minimize any tissue ingrowth as well as the migration of wear debris. The serrated fins provide acute fixation to the superior and inferior vertebral bodies. The TPS coating increases the bone contact surface area.

The M6-C™ Artificial Cervical Disc is currently offered in four different footprint sizes and two heights, as shown below in **Figure 2** and **Table 1**.

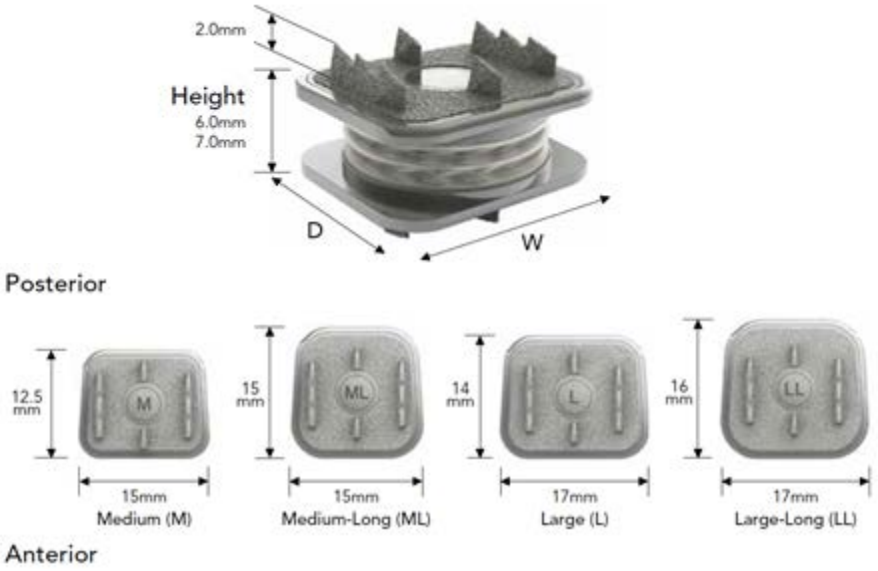

Figure 2: M6-C™ Artificial Cervical Disc Heights and Footprint Sizes

Table 1: M6-C™ Part Listing and Size Overview

Catalog Number	Description	Provided Sterile
CDM-625	Cervical Disc – 6 Medium (15mm W x 12.5mm D x 6mm H)	Yes
CDM-725	Cervical Disc – 7 Medium (15mm W x 12.5mm D x 7mm H)	Yes
CDL-627	Cervical Disc – 6 Large (17mm W x 14mm D x 6mm H)	Yes
CDL-727	Cervical Disc – 7 Large (17mm W x 14mm D x 7mm H)	Yes
CDM-635L	Cervical Disc – 6 Medium-Long (15mm W x 15mm D x 6mm H)	Yes
CDM-735L	Cervical Disc – 7 Medium-Long (15mm W x 15mm D x 7mm H)	Yes
CDL-637L	Cervical Disc – 6 Large-Long (17mm W x 16mm D x 6mm H)	Yes
CDL-737L	Cervical Disc – 7 Large-Long (17mm W x 16mm D x 7mm H)	Yes

VI. ALTERNATIVE PRACTICES AND PROCEDURES

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

- Nonoperative alternative treatments, which include, but are not limited to, physical therapy, medications, braces, chiropractic care, bed rest, spinal injections, or exercise programs.
- Surgical alternatives, which include, but are not limited to:
    - Surgical decompression alone

- Surgical decompression via an anterior approach with fusion using various bone grafting and anterior plating techniques
- Surgical decompression using intervertebral cages, with various bone grafting techniques, with or without supplemental anterior plating
- Decompression with posterior spinal systems (e.g., rods, hooks, wires)
- Another FDA-approved artificial cervical disc

Each alternative has advantages and disadvantages. Patients should fully discuss the available alternatives with his or her physician to select the option that best meets their clinical condition, lifestyle and expectations.

VII. MARKETING HISTORY

The M6-C™ Artificial Cervical Disc has been marketed outside of the United States since 2006. The M6-C™ Artificial Cervical Disc has not been withdrawn from distribution/ marketing in any country for any safety or effectiveness reasons. The M6-C™ Artificial Cervical Disc has been, and/or currently is, distributed in the following countries: Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Czech Republic, France, Germany, Greece, Italy, Mexico, Netherlands, Poland, Portugal, Russia, South Africa, Spain, Sweden, Switzerland, Turkey, United Arab Emirates, 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) identified from the M6-C™ Artificial Cervical Disc clinical study results, approved device labeling for other cervical total disc replacement devices, and published scientific literature including: (1) those associated with any general surgical procedure; (2) those associated with anterior cervical spine surgery; and (3) those associated with a cervical artificial disc device, including the M6-C™ Artificial Cervical Disc. In addition to the risks listed below, there is also the risk that surgery may not be effective in relieving symptoms, or may cause worsening of symptoms. Additional surgery may be required to correct some of the adverse effects.

General Surgery Risks

General surgical risks are, but may not be limited to:

- Infection/abscess/cyst, localized or systemic
- Blood clots, including pulmonary emboli
- Medication and anesthesia reactions
- Phlebitis
- Pneumonia
- Atelectasis
- Soft tissue damage
- Septicemia
- Hemorrhage possibly requiring a blood transfusion, with possible transfusion reaction
- Myocardial infarction
- Paralysis
- Poor tissue healing
- Cerebrovascular accident (CVA)
- Death

Anterior Cervical Surgery Risks

Anterior cervical surgical risks are, but may not be limited to:

- Infection/abscess/cyst, localized or systemic
- Injury or damage to the trachea, esophagus, nerves or blood vessels
- Dysphagia
- Hoarseness
- Vocal cord paralysis
- Paresis
- Recurrent laryngeal nerve palsy
- Soft tissue damage
- Spinal cord damage
- Dural tear with cerebrospinal fluid leakage
- Arm weakness or numbness
- Bowel, bladder or sexual dysfunction
- Nerve root injury
- Airway obstruction
- Epidural hematoma or bleeding
- Epidural fibrosis
- Vertebral body fracture
- Dysesthesia or numbness
- Paresthesia
- Unresolved pain
- Surgical intervention at incorrect level
- Need for supplemental fixation
- Spinal instability
- Death

Cervical Artificial Disc Risks

Risks specific to cervical artificial discs, including the M6-C™ Artificial Cervical Disc, are but may not be limited to:

- Infection/abscess/cyst, localized or systemic
- Allergic reaction to the implant materials
- Implant failure
- Device migration
- Device subsidence
- Device fatigue or fracture or breakage
- Device instability
- Separation of device components
- Placement difficulties, device malposition
- Improper device sizing
- Excessive device height loss
- Wear debris
- Disc space collapse
- Material degradation
- Excessive facet loading
- Kyphosis or hyper-extension
- Loss of flexibility
- Asymmetric range of motion
- Vertebral body fracture
- Spinal cord damage,
- Dural tear with cerebrospinal fluid leakage
- Soft tissue damage
- Epidural fibrosis
- Nerve injury, paralysis or weakness that is temporary or permanent
- Injury or damage to the trachea, esophagus, or blood vessels
- Epidural hematoma or bleeding
- Dysesthesia or numbness
- Paresthesia
- Failure to relieve symptoms including unresolved pain
- Additional surgery due to loss of fixation, infection or injury
- Spontaneous fusion due to heterotopic ossification, development of bridging bone or osteophytes
- Periarticular calcification and fusion
- Development of spinal conditions, including but not limited to spinal stenosis, spondylolisthesis, or retrolisthesis
- Removal, revision, reoperation or supplemental fixation of the disc
- Osteolysis, bone loss, or bone resorption
- Death

These conditions do not include all potential adverse events that may occur, but are important considerations in relation to the use of the M6-C™ Artificial Cervical Disc. For the specific adverse events that occurred in the M6-C™ clinical study, please see Section X.

IX. SUMMARY OF NON-CLINICAL STUDIES

A variety of testing was conducted to characterize the performance of the M6-C™ Artificial Cervical Disc, as follows:

Laboratory Studies

- Static Axial Compression
- Dynamic Axial Compression
- Static Compression-Shear
- Dynamic Compression-Shear
- Static Torsion
- Dynamic Torsion
- Functional and Kinematic Wear Assessment
- Clinical Experience Testing
- Migration/Expulsion
- Compressive Creep
- Subsidence
- Cadaveric Biomechanics Assessment
- Sheath Retention
- Translation
- Finite Element Modeling
- Instrument Testing

Animal Studies

- Caprine Studies
- Rabbit Particulate Studies

Additional Studies

- Magnetic Resonance (MR) Imaging
- TPS Coating Assessment
- Biocompatibility
- Sterilization Validation
- Shelf Life and Packaging Validation

A. Laboratory Studies

Table 2: Overview of Laboratory Studies

Test Name	Purpose	Method	Acceptance Criteria	Results

Test Name	Purpose	Method	Acceptance Criteria	Results
Static Axial Compression	To evaluate the performance of the M6-C™ Artificial Cervical Disc under static axial compressive loading	Five (5) M6-C™ specimens were tested under static compression in 37°C phosphate buffered saline at a rate of 0.2mm/sec until failure or approximately 25,000N (capacity of largest available load cell) was reached. Testing per ASTM F2346.	Ultimate load must be ≥ 3200N	No mechanical failure could be achieved under axial compressive loading to approximately 25,000N. The acceptance criteria were met.
Dynamic Axial Compression	To evaluate the performance of the M6-C™ Artificial Cervical Disc under dynamic axial compressive loading	Two (2) M6-C™ specimens were tested under dynamic compression in 37°C phosphate buffered saline to 10 million cycles, using a sinusoidal wave form with R=10 at 2 Hz. Testing per ASTM F2346.	The minimum total runout load for compression was 150N.	Two samples were tested to 10 million cycles from 15 to 150 N of axial compression. No mechanical or functional failures were observed; the acceptance criteria were met.
Static Compression-Shear	To evaluate the performance of the M6-C™ Artificial Cervical Disc under static compression-shear loading	Five (5) M6-C™ specimens were tested under static compression-shear (45°), with the devices in 7.5° of extension, in 37°C phosphate buffered saline at a rate of 0.01mm/sec until failure. Testing per ASTM F2346.	The ultimate compression shear load must be ≥ 845N.	The average load at failure for the 5 samples tested in compression shear (including a full extension angle of 7.5°) to failure was 6714 ± 113N. The acceptance criteria were met.
Dynamic Compression-Shear	To evaluate the performance of the M6-C™ Artificial Cervical Disc under dynamic compression-shear loading	Two (2) M6-C™ specimens were tested under dynamic compression-shear in 37°C phosphate buffered saline to 10 million cycles, using a sinusoidal wave form with R=10 at 2 Hz. Testing per ASTM F2346.	The minimum total runout load for compression-shear was 150 N.	Two samples were tested to 10 million cycles from 15 to 150N of compression shear with full extension. No mechanical or functional failures were observed; the acceptance criteria were met.

Test Name	Purpose	Method	Acceptance Criteria	Results
Static Torsion	To evaluate the performance of the M6-C™ Artificial Cervical Disc under static torsional loading	Five (5) M6-C™ specimens were tested under static torsion in 37°C phosphate buffered saline at a rate of 0.5°/sec until failure. Testing per ASTM F2346.	Ultimate load must be ≥ 4 Nm.	The maximum torque was 10.26 ± 1.23 Nm. The acceptance criteria were met.
Dynamic Torsion	To evaluate the performance of the M6-C™ Artificial Cervical Disc under dynamic torsion loading	Two (2) M6-C™ specimens were tested under dynamic torsion in 37°C phosphate buffered saline to 10 million cycles, using a sinusoidal wave form with R=-1 at 2 Hz. Testing per ASTM F2346.	The minimum total runout moment for torsion was ±0.35 Nm.	Two devices were tested to 10 million cycles at ±0.35 Nm. No mechanical or functional failures were observed; the acceptance criteria were met.
Functional & Kinematic Wear Assessment	To evaluate the functional and kinematic wear properties of the M6-C™ Artificial Cervical Disc to ensure that the structural integrity of the device is sufficient for the projected life of the implant and that the device does not generate excessive wear debris	Testing per ASTM F2423 for 10 million cycles of flexion/extension and 10 million cycles of coupled lateral bending and axial rotation at 2 Hz. Six (6) samples were tested in Bovine Calf Serum (BCS) and six (6) were tested in DI water.	The total wear debris mass must be less than 40 mg.	The M6-C™ Artificial Cervical Disc met the acceptance criterion as defined in the test protocol. In BCS, the debris mass at 20 million cycles was 0.54 ± 0.08 mg, or 0.03 mg/MC. In DI water, the debris mass at 20 million cycles was 12.27 ± 4.41 mg, or 0.61 mg/MC. These results suggest that the M6-C™ Artificial Cervical Disc generates an acceptable level of wear debris for clinical use.

Test Name	Purpose	Method	Acceptance Criteria	Results
Functional & Kinematic Wear Assessment	To evaluate the functional and kinematic wear properties of the M6-C™ Artificial Cervical Disc to ensure that the structural integrity of the device is sufficient for the projected life of the implant and that the device does not generate excessive wear debris	Testing per ISO 18192-1 for 10 million cycles of clinically derived coupled flexion/extension, lateral bending, and torsion at 1 Hz. Six (6) samples were tested in Bovine Calf Serum and six (6) were tested in DI water.	The total wear debris mass must be less than 40 mg.	The M6-C™ Artificial Cervical Disc met the acceptance criterion as defined in the test protocol. In BCS, the debris mass at 10 million cycles was 3.36 ± 0.54 mg, or 0.34 mg/MC. In DI water, the debris mass at 10 million cycles was 9.38 ± 3.30 mg, or 0.94 mg/MC. These results suggest that the M6-C™ Artificial Cervical Disc generates an acceptable level of wear debris for clinical use.
Clinical Experience Testing	To assess the functional and kinematic wear properties of the M6-C™ Artificial Cervical Disc under clinically derived atypical conditions	Twelve (12) samples were tested in total under 3 different sets of conditions. Six (6) samples (primary test) were tested under three clinically derived atypical conditions. Three (3) samples were tested under two clinically derived typical conditions. Three (3) samples were tested under one clinically derived atypical condition. All samples were tested in Bovine Calf Serum (BCS) for 2 million cycles at 1 Hz.	This test was performed for characterization only.	Testing under more clinically derived atypical conditions resulted in varying degrees of device wear. The M6-C™ Artificial Cervical Disc is robust when subjected to clinically derived atypical conditions.

Test Name	Purpose	Method	Acceptance Criteria	Results
Migration and Expulsion	To evaluate the acute migration potential of the M6-C™ Artificial Cervical Disc	Nine (9) M6-C™ specimens were implanted into a cadaveric model and tested in monotonic axial compression (4) to a load of 3000N with the spinal segment at 7.5° of extension, and in cyclic fatigue (5) at ±7.5° of flexion/extension to 20,000 cycles.	The device must not migrate or subluxate over the course of the test (defined as superior or inferior endplate moving ≥3.5mm or 20% from its initial position.	Monotonic compression: The average migration was 0.4 ± 0.5mm. The normalized subluxation was 5.5 ± 3.5%. Cyclic fatigue: The average migration was 0.3 ± 0.5mm. The normalized subluxation was 1.3 ± 2.5%. All acceptance criteria were met.
Compressive Creep	To evaluate the compressive creep characteristics of the M6-C™ Artificial Cervical Disc	Six (6) M6-C™ specimens were tested per ASTM D2990-01 and loaded at an axial compressive load of 100N for 42 days followed by a simulated sleep/wake cycle (100N for 16hr and 53N for 8hr) for an additional 10 days.	Maintenance of inter-endplate distance of 1.0mm at 100 N extrapolated to 100 years, and maintain appropriate stiffness.	All samples were met the acceptance criteria for height loss and resulting inter-endplate distance when evaluated at 1000 hours, a calculated 100 years, and after 10 days of sleep/wake cycling. All samples exhibited acceptable axial compressive stiffness.
Subsidence	To characterize the M6-C™ implant's resistance to subsidence into the vertebral endplate, under worst case conditions	Six (6) M6-C™ specimens were tested per ASTM F2267.	N/A: for characterization purposes.	The M6-C™ Artificial Cervical Disc had a mean yield load of 1147 ± 9.7N. These results of the subsidence testing can be correlated with the available clinical data and will constitute a baseline that can be used to assess the possible impact on subsidence potential of any future design iteration.
Cadaveric Biomechanics Assessment	To characterize the biomechanical behavior of the M6-C™ Artificial Cervical Disc and to compare to native disc biomechanics	Six (6) M6-C™ specimens were tested in three scenarios: a follower load model with 150N preload and a 1.5 Nm F/E bending moment; a ±1.5 Nm axial rotation moment; and a 1.5 Nm lateral bending moment	N/A: for characterization purposes.	The results of the testing indicate that the M6-C™ Artificial Cervical Disc has similar biomechanical performance to that of a native human disc.

Test Name	Purpose	Method	Acceptance Criteria	Results
Sheath Retention	To evaluate the sheath retention mechanism in a worst-case scenario	Six (6) M6-C™ specimens were tested from neutral to 18° of extension for 30,000 cycles at 2 Hz.	The sheath must be retained.	The results of the testing indicated that all sheaths were retained. The acceptance criteria were met.
Translation	To characterize the static translation behavior of the M6-C™ Artificial Cervical Disc	M6-C™ Artificial Cervical Disc was tested in static lateral translation to 2000 N, the limit of the test machine, while under a physiologic axial load (100N). Because the device is symmetric, this assessment is also applicable to AP translation.	N/A: for characterization purposes.	At the highly non-physiologic (>10x) shear load of 2000N, the device translated while remaining intact with no fiber breakage. Non-physiologic shear loads were required to achieve 3.5 mm of translation, the level at which a natural disc is considered unstable. Therefore, the M6-C™ design provides for significant patient safety with regard to device translation.
Finite Element Modeling	To characterize the biomechanical response of total disc arthroplasty with the M6-C™ Artificial Cervical Disc	Both an intact C5-C6 model and a model with a 6 mm Medium M6-C™ replacement were assessed under a compressive load of 150N alone as well as under a compressive load of 150N in combination with 1.5 Nm of each of the following: flexion, extension, torsion, and lateral bending.	N/A: for characterization purposes.	The results indicated a close correlation between the intact model and the M6-C™ replacement was obtained for all loading conditions; the M6-C™ Artificial Cervical Disc had performance commensurate with an intact disc, and no excessive loads beyond material strengths.
Instrument Testing	To verify and validate the functionality of the M6-C™ Surgical Instruments	Various verification and validation activities.	Various	The instruments met all acceptance criteria.

Two minor design changes have been made to the M6-C™ Artificial Cervical Disc and have been evaluated via the appropriate verification and validation activities to supplement the original testing.

B. Animal Studies

Table 3: Overview of Animal Studies

Test Name	Purpose	Method	Acceptance Criteria	Results
Caprine Studies	To evaluate the biological response of the implant	The M6-C™ Artificial Cervical Disc was implanted in a goat cervical spine and evaluated histologically for the biological response at 0, 3, 6, and 12 months.	N/A: for characterization purposes	The following concerns were observed. However, these results were attributed to inadequate implantation technique and the use of skeletally immature goats. a. Relatively thick periprosthetic fibrous membrane indicative of a host inflammatory response/immune response that prevented adequate device fixation. b. Osteoclastic activity that shows bone remodeling and bone resorption (osteolysis). c. At 12 months, macrophages with hemosiderin were still evident which is indicative of hemorrhage. d. Macrophages associated with hemosiderin, bone wax, and occasional polyethylene fibers or metallic particles were observed suggesting a local inflammatory response; however, there was no evidence of adaptive immune response or unexpected inflammatory reaction to the particles. There was wear particulate at the final time point (12 months) in this study; however, it is not clear how this observation can be extrapolated to humans given the limitations of this study. e. Fixation and stability were not completely achieved. Despite the sources of uncertainty discussed above, there was no histologic evidence of systemic

Test Name	Purpose	Method	Acceptance Criteria	Results
				toxicity at one year. There was no evidence of an adaptive immune reaction to the implants or debris.
Rabbit Particulate Study	To evaluate the local and systemic responses to the potential wear debris in an animal model	Potential wear debris particles with material proportions representative of the device were implanted into rabbits. The amount and number of particles were chosen based on the worst case kinematic wear assessment debris profile with added margin of safety. Two different doses (low and high) along with sham control were injected into the epidural space of the lumbar region (L4-L6) of each rabbit (n=54). The animals were evaluated for clinical and neurological observations as well as hematological, histological, and gross pathologic methods. These evaluations occurred at 2, 3, and 6 months.	N/A: for characterization purposes	The following issues added uncertainty to the study results: a. The presence of certain liver and brain related pathology in the treated 3-month rabbit group (4 out of 12 animals), that were attributed to a parasitic infection confounded the test data interpretation. b. In the 6-month group, the particles injected into the animals were contaminated with other inorganic matter. With these sources of uncertainty in mind, the measured systemic toxicity and inflammatory responses did not identify significant biocompatibility concerns with the device.

C. Additional Studies

Magnetic Resonance (MR) Imaging

The safety and compatibility of the M6-C™ Artificial Cervical Disc in the Magnetic Resonance (MR) environment was evaluated. Specifically, it was tested for magnetic field interactions, heating, and artifacts associated with clinically relevant magnetic resonance imaging.

The magnetic field interaction evaluations consisted of translational attraction and torque assessments. For the assessment of translational attraction, an angular deflection test was performed in accordance with ASTM F2052-15, *Standard Test Method for Measurement of Magnetically Induced Displacement Force on Medical Devices in the Magnetic Resonance Environment*. The evaluation of magnetic torque was performed in accordance with ASTM F2213-06 (2011), *Standard Test Method for Measurement of Magnetically Induced Torque on Medical Devices in the Magnetic Resonance Environment*. The M6-C™ Artificial Cervical Disc was tested for MRI-related heating in accordance with ASTM F2182–11a, *Standard Test Method for Measurement of Radio Frequency Induced Heating On or Near Passive Implants During Magnetic Resonance Imaging*. MR imaging artifacts were assessed in accordance with ASTM F2119-07 (Reapproved 2013), *Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants*.

The results of the assessments demonstrated that the M6-C™ Artificial Cervical Disc is MR Conditional. A patient with the M6-C™ Artificial Cervical Disc can be scanned safely in an MR system under the following conditions:

- Static magnetic field of 1.5-Tesla or 3-Tesla, only
- Maximum spatial gradient magnetic field of 4,000-Gauss/cm (40-T/m)
- Maximum MR system reported whole body averaged specific absorption rate (SAR) of 2-W/kg for 15 minutes of scanning (i.e., per pulse sequence) in the Normal Operating Mode.

Under the scan conditions defined, the M6-C™ Artificial Cervical Disc is expected to produce a maximum temperature rise of 2.2°C after 15-minutes of continuous scanning (i.e., per pulse sequence).

In non-clinical testing, the image artifact caused by the M6-C™ Artificial Cervical Disc extends approximately 10-mm from this device when imaged using a gradient echo pulse sequence and a 3-Tesla MR system.

Biocompatibility

The M6-C™ Artificial Cervical Disc is manufactured from titanium alloy, polycarbonate urethane (PCU), UHMWPE and commercially pure titanium plasma spray (TPS). All implant materials have a long history of successful orthopedic clinical use and well-established biocompatibility. There are no color additives in the M6-C™ Artificial Cervical Disc.

Biocompatibility testing was performed on the M6-C™ Artificial Cervical Disc in its final sterilized state in accordance with ISO 10993-1, for the level of contact duration of a permanent implant contacting tissue and bone. The battery of biocompatibility tests conducted included: Cytotoxicity (ISO 10993-5), Sensitization (ISO 10993-10), Irritation/Intracutaneous Reactivity (ISO 10993-10), Systemic Toxicity (10993-11), Genotoxicity (10993-3), Implantation (ISO 10993-6), Subchronic Toxicity (10993-11), and Pyrogen Testing (ISO 10993-11). All test results met the acceptance criteria demonstrating biocompatibility in line with the requirements of ISO 10993-1.

Sterilization Validation
Full sterilization validation has been conducted for the M6-C™ implants per BS-EN-ISO 11135 - *Sterilization of health-care products- Ethylene oxide -Requirements for the development, validation and routine control of a sterilization process for medical devices.*

Full sterilization validation has been conducted for the M6-C™ instruments per BS-EN-ISO 17665 - *Sterilization of health care products – Moist heat, Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices.*

Shelf Life and Transit Validation
Shelf life and transit validation studies, including assessments of packaging seal integrity and real-time aging testing, were conducted to demonstrate that the device packaging can maintain a sterile barrier over a 5-year shelf life.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of replacement of the diseased native disc with the M6-C™ Artificial Cervical Disc following single level discectomy in skeletally mature subjects with intractable degenerative cervical radiculopathy (arm pain and/or a neurological deficit) with or without spinal cord compression at one level from C3 – C7. Degenerative cervical radiculopathy is defined as discogenic neck and/or arm pain and is demonstrated by signs and/or symptoms (e.g., numbness, weakness, pathologic reflexes, etc.) of disc herniation and/or osteophyte formation and is confirmed by subject history and radiographic imaging (CT, MRI, x-rays). The study was performed in the United States under IDE #G050254 with additional control ACDF data from a separate IDE study performed in the United States. A summary of the clinical study is presented below.

A. Study Design

Subjects in the M6-C™ pivotal study ("M6-C™ IDE study") were treated between May 2014 and June 2016. The database for this PMA reflects data collected through May 2018 and included 160 M6-C™ subjects at 12 sites and 72 ACDF subjects treated at 11 sites. An additional 192 ACDF treated subjects were available from a previously conducted cervical disc IDE study, with subjects treated between November 2005 and October 2007.

The prospective, non-randomized, concurrently controlled study was performed in the United States under IDE #G050254 combined with additional control ACDF data from a previous multi-center, prospective, randomized concurrently-controlled cervical disc IDE study performed in the United States. This previous study incorporated a similar study design, indications for use, study entry criteria, study endpoints, and data collected. The two studies were not identical, and differences were identified in some categories and are discussed below.

A statistical plan utilizing propensity score (PS) modeling was developed to incorporate both the concurrent control and historical control and to match the baseline covariates to the M6-C™ group. The resultant PS Selected study cohort used for the primary analysis population thus included all investigational M6-C™ subjects and the pooled concurrent and historical control subjects and is termed the "**ITT (PS Selected) Cohort**."

1. Clinical Inclusion and Exclusion Criteria

To be eligible for the M6-C™ IDE study, subjects had to be eligible for a fusion procedure and meet all of the inclusion criteria and none of the exclusion criteria:

Table 4: Study Inclusion/Exclusion Criteria

Study Inclusion Criteria	Study Exclusion Criteria
1. Diagnosis of degenerative cervical radiculopathy with or without spinal cord compression requiring surgical treatment at one level from C3 to C7 demonstrated by signs and/or symptoms of disc herniation and/or osteophyte formation (e.g. neck and/or arm pain, radiculopathy, etc.) and is confirmed by patient history and radiographic studies (e.g. MRI, CT, x-rays, etc.) 2. Inadequate response to conservative medical care over a period of at least 6 weeks 3. Neck Disability Index score of ≥ 30% (raw score of ≥ 15/50) 4. Neck or arm pain VAS ≥ 4 on a scale of 0 to 10 5. Willing and able to comply with the requirements of the protocol including follow-up requirements 6. Willing and able to sign a study specific informed consent 7. Skeletally mature and ≥ 18 years old and ≤ 75 years old	1. More than one cervical level requiring surgery 2. Previous anterior cervical spine surgery 3. Axial neck pain as the solitary symptom 4. Previous posterior cervical spine surgery (e.g., posterior element decompression) that destabilizes the cervical spine 5. Advanced cervical anatomical deformity (e.g., ankylosing spondylitis, scoliosis) at the operative or adjacent levels 6. Symptomatic facet arthrosis 7. Less than 4º of motion in flexion/extension at the index level 8. Instability as evidenced by subluxation > 3 mm at the index or adjacent levels as indicated on flexion/extension x-rays 9. Advanced degenerative changes (e.g., spondylosis) at the index vertebral level as evidenced by bridging osteophytes, central disc height < 4mm and/or < 50% of the adjacent normal intervertebral disc, or kyphotic deformity > 11º on neutral x-rays 10. Severe cervical myelopathy (i.e., Nurick's Classification > 2) 11. Active systemic infection or infection at the operative site 12. Co-morbid medical conditions of the spine or upper extremities that may affect the cervical spine neurological and/or pain assessment 13. Metabolic bone disease such as osteoporosis that contradicts spinal surgery (for females over 50 and males over 55 years old, or if the score on the Osteoporosis Self-Assessment Test is < 2, a dual energy x-ray absorptiometry [DEXA scan] of the spine is required; if the bone mineral density T-score in the spine is = -2.5 the patient must be excluded) 14. History of an osteoporotic fracture of the spine, hip or wrist 15. History of an endocrine or metabolic disorder (e.g., Paget's disease) known to affect bone and mineral metabolism 16. Taking medications that may interfere with bony/soft tissue healing including chronic steroid use 17. Known allergy to titanium, stainless steels, polyurethane, polyethylene, or ethylene oxide residuals

Study Inclusion Criteria	Study Exclusion Criteria
	18. Rheumatoid arthritis or other autoimmune disease or a systemic disorder such as HIV, active hepatitis B or C or fibromyalgia 19. Insulin-dependent type 1 or type 2 diabetes 20. Medical condition (e.g., unstable cardiac disease, cancer) that may result in patient death or have an effect on outcomes prior to study completion 21. Pregnant, or intend to become pregnant, during the course of the study 22. Severe obesity (Body Mass Index > 40) 23. Physical or mental condition (e.g., psychiatric disorder, senile dementia, Alzheimer's disease, alcohol or drug addiction) that would interfere with patient self-assessment of function, pain or quality of life. 24. Involved in current or pending spinal litigation where permanent disability benefits are being sought 25. Incarcerated at the time of study enrollment 26. Current participation in other investigational study that may impact study outcomes

2. Control

Control subjects received Anterior Cervical Discectomy and Fusion (ACDF). The M6-C™ IDE study was not randomized and the study sites were device-specific (i.e. performed either ACDF or implantation with the M6-C™ Artificial Cervical Disc). This concurrent control was supplemented with subjects from the control arm (ACDF) of a historical IDE study in the cervical spine.

Comparison of the data from the two control sources demonstrated that the cohorts were comparable, though not identical. There were some differences in the study protocols, the patient population, and the resulting data. Specifically:

- A detailed comparison of the inclusion/exclusion criteria of the two cohorts was conducted to determine if the historical data were adequate to serve as comparator and support a PMA application. The sponsor reviewed the protocol and case report forms as submitted to the FDA and remained blinded to the aggregate study results. Based on this review, the sponsor determined that the historical study was similar to the IDE study in its Indications for Use and Inclusion/Exclusion criteria. As clinical confirmation of the comparability of the study populations, 3 independent surgeons who also serve on the Clinical Events Committee (CEC) for the M6-C™ IDE study reviewed the inclusion and exclusion criteria for both the M6-C™ IDE study and the historical control study. The independent surgeons concluded that although some of the criteria are worded differently, and some are written in more detail than their comparable criteria, the result of both sets of inclusion/exclusion criteria describe a similar population: patients presenting with single level symptomatic degenerative cervical radiculopathy qualifying for single level surgery from C3-C7.

- The historical study collected the parameters used to calculate overall success, success of the individual components of the composite primary endpoint, secondary endpoints, and safety assessments per the defined assessments in the M6-C™ IDE study protocol.
- In some cases, the data was inadequate for analysis explicitly per the M6-C™ IDE study protocol. In these instances, the results were harmonized.

A PS method was used to address selection bias in the observational study design when pooling data from the concurrent and historical controls. The objective of the observational design was to select from the candidate pool of concurrent and historical controls those subjects whose baseline covariate distribution was approximately the same as M6-C™ subjects within five PS subclasses. The final ITT (PS Selected) analysis set included all 160 M6-C™ subjects, 46 of 72 available concurrent control subjects and 143 of 192 historical control subjects for a total control sample size of 189 subjects. Rigorous statistical criteria and graphical analyses demonstrated that within PS subclasses, M6-C™ subjects and selected controls had approximately the same multivariate baseline covariate distribution. Consequently, controlling for PS subclass, selection bias was eliminated for a rich set of observed demographic and baseline covariates.

3. Follow-up Schedule

All subjects were evaluated preoperatively (within 30 days prior to surgery), postoperatively (prior to discharge) and postoperatively at 6 weeks (±2 weeks), 3 months (±2 weeks), 6 months (±1 month), 1 year (±2 months), 2 years (±2 months), and annually thereafter (±2 months). The following parameters were measured throughout the study:

Table 5: M6-C™ IDE Study Assessment Schedule

Evaluation	Pre-op	Operative/ Discharge	6 Weeks	3 Months	6 Months	1 Year	2+ Years
Demographics	X						
Work Status	X		X	X	X	X	X
Medications	X		X	X	X	X	X
Neurological Examination	X	X	X	X	X	X	X
Neck Disability Index (NDI)	X		X	X	X	X	X
Neck and Arm Pain (VAS)	X		X	X	X	X	X
SF-36	X				X	X	X
Patient Satisfaction							X
Odom's Criteria							X
Surgery Data		X					
Adverse Event Assessment		X	X	X	X	X	X
AP & Lateral X-rays	X	X	X	X	X	X	X
Flexion/Extension X-rays	X			X	X	X	X
L & R Lateral Bending X-rays	M6-C™			M6-C™	M6-C™	M6-C™	M6-C™
MRI within 3 Months	X						

4. Clinical Endpoints

The effectiveness of the M6-C™ Artificial Cervical Disc was assessed using a composite endpoint. Effectiveness was further evaluated by assessing improvement in the Neck Disability Index (NDI), neck and arm pain based on a Visual Analog Scale (VAS), and quality of life using the short-form questionnaire as well as patient satisfaction of the investigational group compared to the ACDF control group. Similar criteria were used to measure success in both groups.

The safety of the M6-C™ Artificial Cervical Disc was assessed by comparison to the ACDF control group with respect to the nature and frequency of adverse events (overall and in terms of seriousness and relationship to the implant), additional index level surgical procedures and maintenance or improvement in neurological status.

Primary Endpoint (Overall Subject Success)

All subjects were assessed for overall success using the parameters defined in the M6-C™ IDE study protocol including the safety components. A subject was considered a study success at two years follow-up if he/she met all of the following criteria:

- No serious adverse event(s) classified as device or device procedure related (as determined by the Clinical Events Committee),
- No supplemental surgical procedure at the index level (including revision, removal, reoperation, or supplemental fixation),
- Maintenance or improvement in neurological function compared to baseline, and
- Improvement of the NDI of at least 15 points (on a 100-point scale).

The parameters needed to assess subjects for overall success as defined in the M6-C™ IDE study were collected on a patient level basis in the historical control study. As such, pooling of the control data from the two studies did not interfere with the ability to assess the M6-C™ primary endpoint and provide an assessment of the safety and effectiveness of the M6-C™ Artificial Cervical Disc compared to the control subjects selected via the propensity score method. The statistical team utilized the patient level adverse event, surgical intervention, and neurological data from both study datasets for each of the above criteria to determine a subject's success or failure.

Secondary Endpoints and Assessments

Secondary objectives, measured in both groups, included:

- Neck Pain and Arm Pain as assessed using a 10-cm Visual Analog Scale (VAS)
- Health-Related Quality of Life (SF-12 or SF-36v2)
- Radiographic assessment including assessment of fusion status
- Pain Medication Use
- Surgery Time
- Length of Hospital Stay
- Return to Work
- Patient Satisfaction
- Odom's Criteria
- Adverse Events

In addition, quantitative and qualitative radiographic measurements were performed in the M6-C™ IDE study by an independent core laboratory and included range of motion, center of rotation, disc angle, disc height, device condition, device subsidence, device migration, radiolucency, spinal fusion status, heterotopic ossification, neural impingement, and soft tissue impingement. Independent radiographic assessments were performed in the historical controls at a temporal distance, and included angular and translational motion (range of motion), center of rotation, disc angle, disc height, device condition, device subsidence, device migration, radiolucency, and spinal fusion status.

5. Clinical Events Committees (CEC)

A CEC was utilized for the M6-C™ IDE study to mitigate reporting bias of safety-related events. The CEC was comprised of three (3) independent spine surgeons, and a CEC charter was used to define the role of the CEC. The committee was responsible for adjudication of adverse events (i.e., relationship to device/procedure, seriousness, and unanticipated adverse device effects), protocol deviations (i.e., classification as Major or Minor), and neurological success criterion (assessment if any neurological deficits reported from baseline vs. two years were clinically relevant).

An independent CEC was also used in the historical control study at the time of that study and reviewed all cervical spine post-operative surgical interventions and made the final determination of whether the intervention was considered device-related or serious. All reports of serious adverse events (whether or not device related), serious adverse device effects (SADEs), and unanticipated adverse device effects (UADEs) were reviewed by the CEC. Additionally, the CEC assessed changes in individual neurological parameters to determine whether the change in the individual neurological parameter is a sustained neurological deficit.

B. Accountability of PMA Cohort

Two hundred fifty-eight (258) subjects were consented under the M6-C™ IDE study. Twenty-six (26) subjects were withdrawn prior to surgery resulting in 232 subjects treated, comprising 160 M6-C™ and 72 ACDF subjects. The historical control population resulted in an additional 192 available control subjects.

The 424 available subjects (160 M6-C™, 72 concurrent ACDF, and 192 historical ACDF) were assessed via the Propensity Score (PS) sub-classification process. After applying an established heuristic for 9 iterations (18 models), a total of 160 M6-C™ investigational subjects and 189 pooled control subjects (46 concurrent ACDF and 143 historical ACDF) were retained in the final PS designed sample. Inclusion into a PS subclass is the observational study analogue to randomized treatment allocation. For subjects at 24 months, the follow-up rates are 95.0% for the M6-C™ subjects and 87.7% for the PS Selected ACDF subjects.

Table 6: Subject Accounting and Follow-up Compliance of the M6-C™ and PS Selected Pooled Controls Subjects (ACDF) – ITT (PS Selected) Cohort

	Pre-Op		Month 12		Month 24	
	M6-C™	**ACDF**	**M6-C™**	**ACDF**	**M6-C™**	**ACDF**
[1] Theoretical Due	160	189	160	189	160	189
[2] Cumulative Deaths	0	0	1	0	1	0
[3] Cumulative Terminal Failures[1]	0	0	4	6	5	10
[4] Not Yet Overdue	0	0	0	0	0	2
[5] Expected[2]	160	189	156	183	155	177
[6] Expected + Terminal Failures among Theoretical Due	160	189	160	189	160	187
[7] Actual % Follow-Up for Overall Success[3]	160 (100%)	189 (100%)	153 (95.6%)	175 (92.6%)	152 (95.0%)	164 (87.7%)
[8] Actual % Within Window[4]	160 (100%)	189 (100%)	140 (87.5%)	167 (88.4%)	136 (85.0%)	151 (80.7%)

[1]Subsequent surgical intervention and definitely device- or procedure- related SAEs
[2]Expected = [1] – [4] – ([2] + [3])
[3]The number of subjects with overall success (denominator = [6])
[4]The number of subjects with overall success within window (denominator = [6])

The subject accountability for Month 12 and Month 24 clinical evaluations is presented in **Table 7**.

Table 7: Data Accounting and Follow-up Compliance for Month 12 and Month 24 Outcomes - ITT (PS Selected) Cohort

	Month 12				Month 24			
	M6-C™		**ACDF**		**M6-C™**		**ACDF**	
	n	**%**	**n**	**%**	**n**	**%**	n	**%**
ITT (PS Selected Cohort)	**160**	**--**	**189**	**--**	**160**	**--**	**189**	**--**
Deaths (not surgery-related)	*0*	--	*0*	--	*0*	--	*0*	--
Not Yet Overdue/Not Yet Due	*0*	--	*0*	--	*0*	--	*2*	--
Expected Due	**160**	**--**	**189**	**--**	**160**	**--**	**187**	**--**
• Overall Success Evaluation	153	95.6	175	92.6	152	95.0	164	87.7
• Neurological Evaluation	152	95.0	175	92.6	150	93.8	164	87.7
Terminal Failures[1]	*4*	--	*6*	--	*5*	--	*10*	--
Expected for Clinical Evaluation	**156**	**--**	**183**	**--**	**155**	**--**	**177**	**--**
• NDI Evaluation	149	95.5	168	92.8	147	94.8	154	87.0
• VAS Neck Pain Evaluation	148	94.9	168	92.8	147	94.8	154	87.0
• VAS Arm Pain Evaluation	148	94.9	168	92.8	147	94.8	154	87.0
• SF-12/36 Evaluation	148	94.9	164	89.6	147	94.8	150[2]	84.7
• Radiographic Evaluation	143	91.7	162	88.5	141	91.0	140	79.1
• Odom's Criteria	-	-	-	-	150	93.8	164	86.8
• Patient Satisfaction	-	-	-	-	150	93.8	162	85.7

[1]Subsequent surgical intervention and definitely device- or procedure- related SAEs
[2]Two subjects did not have baseline SF-12/36 measurement. Change from baseline scores in PMA Results section use 148 subjects.

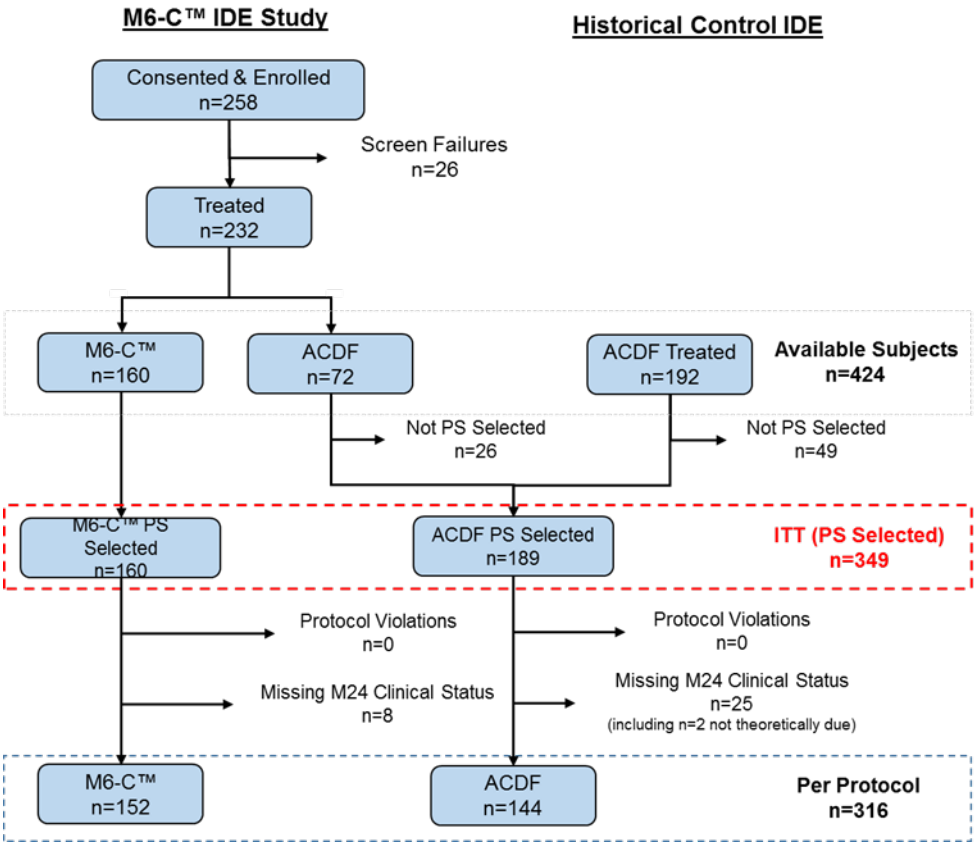

Figure 3: Subject Accountability Tree

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are consistent with demographics reported for prior cervical artificial disc studies conducted in the US. Demographic data showed that the treatment groups were well-balanced and no statistically significant differences were noted in the demographic characteristics and categorical values (**Table 8** and **Table 9**). The mean baseline pre-operative assessments for NDI, VAS neck pain, VAS arm pain, the MCS component of SF-12/SF-36, and baseline radiographic parameters were also similar between treatment groups. The Short Form Physical Function scores were slightly higher in the M6-C™ group; however, when adjusting for PS subclass, there was no significant difference between groups in baseline NDI, indicating similar neck pain and function.

Table 8: Summary of Demographic and Baseline Continuous Variables (Clinical) with Two-Sided 95% CI's – ITT (PS Selected) Cohort

	M6-C™						ACDF						M6-C™ - ACDF[1]			Unadj[2]
Demographics - All	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**	**Diff**
Age at surgery (yrs)	160	43.64	9.10	42.35	21.8	68.4	189	44.74	7.87	44.60	24.0	65.4	-0.22	-2.18	1.74	-1.10
Height (inches)	160	67.86	3.98	68.00	58.0	83.0	189	67.93	3.85	68.00	59.0	77.0	-0.04	-0.95	0.86	-0.07
Weight (lbs)	160	178.93	38.03	183.00	85.0	283.0	189	183.67	39.33	183.00	104.0	315.0	-0.94	-9.91	8.03	-4.75
BMI (k/m^2)	160	27.18	4.77	26.85	17.8	39.6	189	27.84	4.86	27.30	19.1	47.8	-0.05	-1.16	1.07	-0.66
Osteo Self Assessment Test	160	80.73	18.84	81.46	34.4	132.1	189	82.89	19.42	82.00	43.4	146.3	-0.43	-4.86	4.01	-2.15
Duration of Symptoms	153	18.21	36.77	8.00	0.5	360.0	178	21.32	32.17	9.00	0.9	253.0	0.02	-8.21	8.25	-3.11
Demographics - Male	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**	**Diff**
Age at surgery (yrs)	82	45.47	8.89	43.75	28.2	68.4	93	45.07	7.51	45.00	26.0	65.4	0.12	-2.47	2.72	0.41
Height (inches)	82	70.43	3.06	70.00	61.0	83.0	93	70.80	2.63	71.00	63.0	77.0	-0.12	-1.02	0.78	-0.37
Weight (lbs)	82	199.68	28.95	195.00	140.0	283.0	93	202.82	33.31	200.00	130.0	315.0	-1.68	-11.63	8.26	-3.14
BMI (k/m^2)	82	28.35	4.08	28.00	20.9	38.4	93	28.38	3.97	28.10	20.4	42.3	-0.04	-1.32	1.25	-0.03
Osteo Self Assessment Test	82	90.75	14.57	89.26	62.9	132.1	93	92.40	16.31	91.60	57.2	146.3	-0.87	-5.78	4.04	-1.65
Duration of Symptoms	78	13.05	16.55	7.00	1.0	107.0	85	18.31	23.75	9.00	1.0	119.0	-1.89	-8.48	4.71	-5.26
Demographic - Female	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**	**Diff**
Age at surgery (yrs)	78	41.71	8.96	41.00	21.8	60.5	96	44.42	8.23	44.25	24.0	63.0	-0.02	-2.85	2.81	-2.71
Height (inches)	78	65.17	2.92	66.00	58.0	71.0	96	65.15	2.59	66.00	59.0	71.0	0.00	-0.95	0.96	0.02
Weight (lbs)	78	157.10	34.12	152.50	85.0	246.0	96	165.13	35.78	155.00	104.0	270.0	0.02	-11.92	11.97	-8.02
BMI (k/m^2)	78	25.96	5.14	24.70	17.8	39.6	96	27.32	5.56	26.40	19.1	47.8	0.02	-1.80	1.84	-1.36
Osteo Self Assessment Test	78	70.21	17.04	67.84	34.4	112.2	96	73.68	17.73	69.37	43.4	128.2	0.02	-5.96	5.99	-3.47
Duration of Symptoms	75	23.58	49.34	8.00	0.5	360.0	93	24.08	38.20	9.00	0.9	253.0	2.30	-13.15	17.76	-0.50
Baseline Functional Status[3]	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**	**Diff**
Neck Disability Index (NDI)	160	54.83	14.08	54.00	26.0	96.0	189	51.86	14.47	50.00	30.0	90.0	-0.09	-3.31	3.13	2.96
VAS Neck Pain	160	7.25	1.86	7.60	0.00	10.0	189	7.05	1.95	7.40	0.40	10.0	-0.01	-0.46	0.43	0.20
VAS Left Arm/Shoulder Pain	160	4.63	3.74	5.57	0.00	10.0	189	4.48	3.56	5.10	0.00	10.0	0.46	-0.38	1.31	0.16
VAS Right Arm/Shoulder Pain	160	4.19	3.61	4.51	0.00	10.0	189	4.63	3.65	5.00	0.00	10.0	-0.55	-1.39	0.29	-0.44
VAS Worst Arm Pain	160	7.26	2.19	7.60	0.15	10.0	189	7.46	1.91	7.70	0.10	10.0	-0.07	-0.54	0.40	-0.21
PCS (SK SF-36v2 / CC SF-12v2)[4]	160	34.88	7.71	34.56	16.1	55.0	187	32.66	8.04	32.37	10.8	56.9	2.84	1.01	4.67	2.22
MCS (SK SF-36v2 / CC SF-12v2)[4]	160	41.38	13.88	42.08	7.7	66.6	187	42.47	12.77	42.04	16.0	73.6	0.47	-2.58	3.53	-1.09

Notes:

[1] Device group differences and 95% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using two-way analysis of variance. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worst arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and symptom duration (<9 mo. vs. ≥9 mo.).

[2] Comparison of the PS adjusted group differences to the unadjusted group differences in this column demonstrate the covariate balance obtained using the PS model. The adjusted mean differences are always smaller than unadjusted values for variables in the PS model, and for some variables, the difference is very large.

[3] VAS Worst Arm/Shoulder Pain was included in PS modeling but not individual Left and Right VAS scores.

[4] PCS and MCS were not included in PS model due to uncertainty concerning comparability between SF-36 and SF-12 versions.

Table 9: Summary of Demographic and Baseline Categorical Variables – ITT (PS Selected) Cohort

	M6-C™		ACDF		M6-C™ - ACDF[1]		
	n	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Number of subjects	160		189				
Males	82	51.3	93	49.2	-0.2	-11.6	11.1
Females	78	48.8	96	50.8			
Use of Nicotine Products	**n**	**%**	**n**	**%**	**p[2]**		
No, never smoked	103	64.4	107	56.6			
No, but prior history	40	25.0	56	29.6	0.789		
Current smoker	17	10.6	26	13.8			
Narcotics Use[3,4]	**n**	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Yes	88	55.0	117	62.2	-2.3	-13.7	9.2
No	72	45.0	71	37.8			
Prior Cervical Surgery[5]	**n**	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Yes	3	1.9	1	0.5	1.4	-10.6	13.4
No	157	98.1	188	99.5			

Notes:

[1] Device group differences and 95% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using two-way generalized linear model for dichotomous variables. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and symptom duration (<9 mo. vs. ≥9 mo.).

[2] P-values are from Mantel-Haenszel PS subclass stratified comparisons between device groups.

[3] For M6-C™ and concurrent controls based on yes/no narcotics use variables. For supplemental controls based on collapsing "INTERMITTENT SHORT-ACTING NARCOTICS", "CHRONIC DAILY SHORT-ACTING NARCOTICS", "CHRONIC DAILY LONG-ACTING NARCOTICS", and "IV OR INJECTED NARCOTICS".

[4] One supplemental control value missing was set to "Yes" in in PS modeling.

[5] Variable not included as covariate in PS modeling due to insufficient sample size.

Table 10: Summary of Operative Continuous Variables with Two-Sided 95% CI's – ITT (PS Selected) Cohort

	M6-C™						ACDF						M6-C™ - ACDF[1]		
Demographics - All	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
Time in Surgery in mins	160	74.5	23.2	75.0	28.0	146.0	188	120.2	39.4	116.5	27.0	275.0	-45.7	-53.3	-38.1
Length of Hospital Stay in days	160	0.61	0.62	1.00	0.00	5.00	189	1.10	0.58	1.00	0.00	4.00	-0.53	-0.66	-0.39
Demographics - Male	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**			
Time in Surgery in mins	82	77.2	24.7	77.5	28.0	146.0	93	125.0	41.2	119.0	39.0	275.0	-46.7	-57.6	-35.7
Length of Hospital Stay in days	82	0.67	0.72	1.00	0.00	5.00	93	1.11	0.50	1.00	0.00	3.00	-0.47	-0.66	-0.27
Demographic - Female	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**			
Time in Surgery in mins	78	71.7	21.4	72.5	28.0	127.0	95	115.5	37.1	113.0	27.0	216.0	-44.7	-55.4	-34.1
Length of Hospital Stay in days	78	0.55	0.50	1.00	0.00	1.00	96	1.08	0.64	1.00	0.00	4.00	-0.58	-0.78	-0.38

Notes:

[1] Device group differences and 95% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using two-way generalized linear model for dichotomous variables.. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and symptom duration (<9 mo. vs. ≥9 mo.).

Table 11: Summary of Operative Categorical Variables – ITT (PS Selected) Cohort

	M6-C™		ACDF		
	n	**%**	**n**	**%**	
Number of Subjects	160		187		
Operative Blood Loss	**n**	**%**	**n**	**%**	**p[1]**
<25 cc	72	45.0	85	45.5	0.490
25-<50 cc	46	28.8	61	32.6	
50-<100 cc	40	25.0	38	20.3	
>=100 cc	2	1.3	3	1.6	
Treated Levels	**n**	**%**	**n**	**%**	**p[1]**
C3-C4	4	2.5	4	2.1	0.887
C4-C5	10	6.3	10	5.3	
C5-C6	82	51.3	102	54.0	
C6-C7	64	40.0	73	38.6	

Note:

[1] P-value is from Mantel-Haenszel PS subclass stratified comparisons between device groups. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and symptom duration (<9 mo. vs. ≥9 mo.).

D. Safety and Effectiveness Results

Statistically significant differences were observed in both surgery time and length of hospital stay. The mean surgery time for the M6-C™ subjects was 74.5 minutes compared to 120.2 minutes for the ACDF group. Length of stay was significantly shorter in the M6-C™ group (0.61 days) compared to the ACDF group (1.10 days). Similar trends were observed when these operative details were evaluated by gender. There was no statistically significant difference between the two groups in operative blood loss or level treated.

1. Safety Results

At the 24-month time-point, higher rates of any adverse event, any serious adverse event, and device related adverse events occurred in the ACDF group. At the same time-point, a higher rate of procedure-related adverse events occurred in the M6-C™ group. The combined device and procedure-related adverse event rate for each study arm is also higher in the control arm, although this difference is small. Adverse events rates were comparable in the two study arms. These data should be viewed in the context of the different classification categories and definitions used in the two studies. Specifically, adverse events were not classified as procedure related in the historical study. To harmonize the data, patient level adverse event data were reviewed by the sponsor, at which time 49 adverse events in 32 subjects were identified as procedure related. These events were adjudicated by the CEC and subsequently classified for procedure-relatedness.

In summary, there were 358 adverse events in 108 M6-C™ subjects and 594 adverse events in 157 control subjects (**Table 12**).

Table 12: Comparisons of Summary Adverse Event Rates between M6-C™ and ACDF Groups with Two-Sided 95% CI's – ITT (PS Selected) Cohort through 24 Months

	M6-C™ (I) (N=160)		ACDF (C) (N=189)		I vs. C[1]		
	n	%	n	%	Diff (%)	LB	UB
Any adverse event (per patient)[4]	108	67.5	157	83.1	-13.7	-23.3	-4.2
Any device related AE[2]	4	2.5	26	13.8	-11.9	-17.6	-6.1
Any procedure related AE[2]	59	36.9	51	27.0	11.6	1.2	21.9
Any AE related to device or procedure[2]	60	37.5	69	36.5	1.9	-8.8	12.6
Any serious AE	15	9.4	28	14.8	-6.3	-13.3	0.8
Serious AE that is either device or procedure related[2]	6	3.8	12	6.3	-2.7	-7.3	1.9
Deaths[3]	1	0.6	0	0.0	0.7	-0.7	2.1

Notes:

1 Device group differences and 95% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using two-way generalized linear model for dichotomous variables. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and radicular symptom duration (<9 mo. vs. ≥9 mo.).

2 Includes possible, probable, or definite.

3 The very low event rates for these variables required that PS subclass be included in the generalized linear model as a continuous variable (df=1) rather than as a stratification variables (df=4).

4 Historical control follow-up exceed two-years in many cases. Therefore, in order to provide meaningful comparisons between groups, AEs with onset dates more than 790 days (24 months + 60 days) post index surgery were excluded from primary safety tables for all subjects.

Table 13: Counts of Specific Adverse Events by Time of Occurrence – ITT (PS Selected) Cohort through 24 Months (I = M6-C™, C = ACDF)

	Day of Surgery		Immed. Post-Op to Month 3 (Day 1-90)		>Mo. 3 to Mo 6 (Day 91-180)		>Mo. 6 to Mo. 12 (Day 181-365)		>Mo. 12 to Mo. 24 (Day 365-730)		Post Month 24 (Day>730)		Totals	
	I	C	I	C	I	C	I	C	I	C	I	C	I	C
ANATOMY\TECHNICAL DIFFICULTY	0	0	0	1	0	0	0	1	0	0	0	0	0	2
Cervical - Non-StudySurgery	0	0	0	0	0	0	0	1	0	0	0	0	0	1
Cervical - StudySurgery	0	0	0	1	0	0	0	0	0	0	0	0	0	1
CANCER	0	0	0	0	1	0	2	1	4	0	1	2	8	3
CARDIOVASCULAR	0	0	1	3	0	1	0	1	2	2	0	2	3	9
DEATH	0	0	1	0	0	0	0	0	0	0	0	0	1	0
DYSPHAGIA \DYSPHONIA	0	0	14	9	1	0	2	2	0	1	0	0	17	12
Dysphagia	0	0	13	8	1	0	2	2	0	0	0	0	16	10
Dysphonia	0	0	1	1	0	0	0	0	0	1	0	0	1	2
GASTROINTESTINAL	0	0	6	12	2	1	0	3	2	8	0	2	10	26
INFECTION	0	0	4	9	1	1	1	5	2	11	0	0	8	26
Local	0	0	1	2	1	1	1	4	1	8	0	0	4	15
Superficial Wound - Cervical	0	0	3	5	0	0	0	0	0	0	0	0	3	5
Deep Wound - Cervical	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Systemic	0	0	0	2	0	0	0	1	0	2	0	0	0	5
Other Wound - Non StudySurgery	0	0	0	0	0	0	0	0	0	1	0	0	0	1
NECK AND/OR ARM PAIN	0	0	17	22	14	11	12	15	16	27	3	5	62	80
Arm Pain	0	0	6	7	3	3	4	6	4	7	1	3	18	26
Neck Pain	0	0	9	14	10	8	5	8	10	19	1	2	35	51
Neck and Arm Pain	0	0	2	1	1	0	3	1	2	1	1	0	9	3
NEUROLOGICAL	0	0	17	35	10	16	16	26	21	34	4	4	68	115
Neck	0	0	4	11	3	2	5	1	3	2	0	0	15	16
Back	0	0	0	3	1	0	0	3	3	0	0	1	4	7
Gait Disturbance	0	0	0	1	0	0	1	0	0	0	0	0	1	1
Spinal Cord Disturbance	0	0	2	0	0	0	0	0	0	0	0	0	2	0
Upper Extremity	0	0	9	19	4	9	8	15	10	21	3	3	34	67
Lower Extremity	0	0	1	1	2	5	1	6	3	7	1	0	8	19
Non-Specific	0	0	1	0	0	0	1	0	2	0	0	0	4	0
Other	0	0	0	0	0	0	0	1	0	4	0	0	0	5
NON-UNION	0	0	0	0	0	1	0	5	0	5	0	0	0	11
OTHER PAIN	0	0	27	42	20	20	20	28	19	33	5	4	91	127
Back	0	0	2	14	7	5	4	10	9	8	1	3	23	40
Headache	0	0	5	7	5	3	7	4	3	3	3	1	23	18
Lower Extremity	0	0	2	5	3	3	3	4	4	10	1	0	13	22
Shoulder	0	0	11	12	5	7	5	9	2	10	0	0	23	38
Torso	0	0	1	1	0	0	0	1	0	0	0	0	1	2
Other	0	0	6	3	0	2	1	0	1	1	0	0	8	6
RESPIRATORY	0	0	2	1	0	1	1	3	1	3	0	0	4	8
SPINAL DISORDER	0	0	1	2	0	3	1	5	5	16	0	2	7	28
"No subcategory for CerviCore"	0	0	0	1	0	1	0	0	0	3	0	2	0	7
Cervical - Non-StudySurgery	0	0	0	1	0	1	0	1	3	5	0	0	3	8
Cervical - StudySurgery	0	0	0	0	0	1	0	0	1	0	0	0	1	1
Non Cervical	0	0	1	0	0	0	1	4	1	8	0	0	3	12
TRAUMA	0	0	3	7	2	7	4	13	7	16	0	2	16	45
UPPER EXTREMITY NERVE ENTRAPMENT	0	0	5	4	1	0	0	5	1	6	0	0	7	15
UROGENITAL	0	0	1	3	0	2	0	2	2	2	1	0	4	9
WOUND ISSUE NON-INFECTION	0	0	21	6	0	0	0	3	0	1	0	0	21	10
OTHER	0	0	10	23	9	6	8	10	4	19	0	10	31	68
Total AE Categories	0	0	130	179	61	70	67	128	86	184	14	33	358	594

At 24 months, the nature and incidence of specific adverse events were comparable in the two study arms. In both study arms, the highest counts of adverse events were dysphagia/dysphonia, neck and arm pain, neurological events and wound complications. In each of these categories, the counts were numerically higher for the control group, with the exception of dysphagia and dysphonia and wound complications, which were higher for the M6-C™ group.

Definitely Device Related Adverse Events

There was 1 event in the M6-C™ group (in 1 subject, 0.6% rate) and 13 events in the ACDF group (in 7 subjects, 3.7% rate) that were determined to be definitely related to the device (**Table 14**). The event categories where the ACDF rate is higher than the M6-C™ rate included neurological (upper extremity). The non-union adverse event rate for the ACDF group was 2.6%. Adverse events related to non-union were not expected in the M6-C™ group since it is a motion-sparing technology. There were no categories where the M6-C™ rate was higher than the ACDF rate. These data should be interpreted in the context of different adverse event categorizations and definitions for device-related adverse events between the two studies.

Table 14: Counts and Percentages of Subjects with Specific Definitely Device Related Adverse Event Sub-Categories with Two-Sided 95% CI's – ITT (PS Selected) Cohort through 24 Months

	M6-C™ (I) (N=160)			ACDF (C) (N=189)			I vs C[1]		
Adverse Event Category/Sub Category	**No. of Events**	**No. of Pts.**	**% of Pts.**	**No. of Events**	**No. of Pts.**	**% of Pts.**	**Diff**	**LB**	**UB**
ANATOMY\TECHNICAL DIFFICULTY	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
Cervical - Study Surgery	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
DYSPHAGIA\DYSPHONIA	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
Dysphagia	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
INFECTION	1	1	0.6	0	0	0.0	0.6	-9.9	11.1
Deep Wound - Cervical	1	1	0.6	0	0	0.0	0.6	-9.9	11.1
NECK AND\OR ARM PAIN	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
Arm Pain	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
NEUROLOGICAL	0	0	0.0	4	4	2.1	-2.1	-12.6	8.4
Upper Extremity	0	0	0.0	4	4	2.1	-2.1	-12.6	8.4
NON-UNION	0	0	0.0	5	5	2.6	-2.6	-13.1	7.9
RESPIRATORY	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
Subjects with at least 1 adverse event		1			7				

Notes:

[1] Exact 95% binomial confidence interval without PS adjustment.

Serious Adverse Events (SAEs)

There were a total of 25 SAEs in the M6-C™ group in 15 subjects and 62 SAEs in 28 subjects in the control group (**Table 15**). Categories where the rates were higher in the ACDF control included gastrointestinal (2.6%) and other pain (4.2%). The non-union adverse event rate for the ACDF control was 3.2%. Adverse events related to non-union were not expected in the M6-C™ group since it is a motion-sparing technology. There was one category where the M6-C™ group had a higher rate than the ACDF group (Infection, deep wound – cervical; 0.6%).

Table 15: Counts and Percentages of Subjects with Specific Serious Adverse Event Sub-Categories with Two-Sided 95% CI's – ITT (PS Selected) Cohort through 24 Months

	M6-C™ (I) (N=160)			ACDF (C) (N=189)			I vs C[1]		
Adverse Event Category/Sub Category	No. of Events	No. of Pts.	% of Pts.	No. of Events	No. of Pts.	% of Pts.	Diff	LB	UB
ANATOMY\TECHNICAL DIFFICULTY	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
Cervical - Study Surgery	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
CANCER	7	3	1.9	1	1	0.5	1.3	-9.2	11.8
CARDIOVASCULAR	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
DEATH	1	1	0.6	0	0	0.0	0.6	-9.9	11.1
DYSPHAGIA\DYSPHONIA	0	0	0.0	2	2	1.1	-1.1	-11.5	9.4
Dysphagia	0	0	0.0	2	2	1.1	-1.1	-11.5	9.4
GASTROINTESTINAL	1	1	0.6	6	5	2.6	-2.0	-12.5	8.5
INFECTION	1	1	0.6	3	3	1.6	-1.0	-11.5	9.5
Local	1	1	0.6	3	3	1.6	-1.0	-11.5	9.5
NECK AND\OR ARM PAIN	1	1	0.6	3	3	1.6	-1.0	-11.5	9.5
Arm Pain	1	1	0.6	0	0	0.0	0.6	-9.9	11.1
Neck Pain	0	0	0.0	3	3	1.6	-1.6	-12.1	8.9
NEUROLOGICAL	5	4	2.5	8	8	4.2	-1.7	-12.2	8.8
Neck	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
Back	1	1	0.6	0	0	0.0	0.6	-9.9	11.1
Spinal Cord Disturbance	1	1	0.6	0	0	0.0	0.6	-9.9	11.1
Upper Extremity	3	2	1.3	3	3	1.6	-0.3	-10.8	10.2
Lower Extremity	0	0	0.0	2	2	1.1	-1.1	-11.5	9.4
Other	0	0	0.0	2	2	1.1	-1.1	-11.5	9.4
NON-UNION	0	0	0.0	7	6	3.2	-3.2	-13.6	7.3
OTHER PAIN	1	1	0.6	9	8	4.2	-3.6	-14.1	6.9
Back	1	1	0.6	3	3	1.6	-1.0	-11.5	9.5
Headache	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
Lower Extremity	0	0	0.0	2	2	1.1	-1.1	-11.5	9.4
Shoulder	0	0	0.0	2	2	1.1	-1.1	-11.5	9.4
RESPIRATORY	2	2	1.3	1	1	0.5	0.7	-9.8	11.2
SPINAL DISORDER	4	4	2.5	9	5	2.6	-0.1	-10.6	10.4
"No subcategory for CerviCore"	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
Cervical - Non-Study Surgery	2	2	1.3	2	2	1.1	0.2	-10.3	10.7
Cervical - Study Surgery	1	1	0.6	0	0	0.0	0.6	-9.9	11.1
Non Cervical	1	1	0.6	6	3	1.6	-1.0	-11.5	9.5
TRAUMA	0	0	0.0	4	4	2.1	-2.1	-12.6	8.4
UPPER EXTREMITY NERVE ENTRAPMENT	1	1	0.6	1	1	0.5	0.1	-10.4	10.6
UROGENITAL	1	1	0.6	1	1	0.5	0.1	-10.4	10.6
WOUND ISSUE NON-INFECTION	0	0	0.0	2	2	1.1	-1.1	-11.5	9.4
OTHER	0	0	0.0	3	2	1.1	-1.1	-11.5	9.4
Subjects with at least 1 adverse event		15			28				

Notes:
[1] Exact 95% binomial confidence interval without PS adjustment.

Definitely Device- or Procedure- Related Serious Adverse Events

There were 3 M6-C™ subjects (1.88%) and 8 control subjects (4.23%) with at least one SAE definitely related to the device or procedure. Based on the lower and upper bounds, there were no notable observed differences in the reported device- and procedure- related SAEs between the two study groups.

Table 16: Counts and Percentages of Subjects with Specific Serious, Definitely Device/Procedure Related Adverse Event Sub-Categories with Two-Sided 95% CI's – ITT (PS Selected) Cohort through 24 Months

	M6-C™ (I) (N=160)			ACDF (C) (N=189)			I vs C[1]		
Adverse Event Category/Sub Category	**No. of Events**	**No. of Pts.**	**% of Pts.**	**No. of Events**	**No. of Pts.**	**% of Pts.**	**Diff**	**LB**	**UB**
ANATOMY\TECHNICAL DIFFICULTY	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
Cervical - Study Surgery	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
DEATH	1	1	0.6	0	0	0.0	0.6	-9.9	11.1
DYSPHAGIA\DYSPHONIA	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
Dysphagia	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
NEUROLOGICAL	3	2	1.3	3	3	1.6	-0.3	-10.8	10.2
Spinal Cord Disturbance	1	1	0.6	0	0	0.0	0.6	-9.9	11.1
Upper Extremity	2	1	0.6	3	3	1.6	-1.0	-11.5	9.5
NON-UNION	0	0	0.0	5	5	2.6	-2.6	-13.1	7.9
RESPIRATORY	1	1	0.6	1	1	0.5	0.1	-10.4	10.6
SPINAL DISORDER	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
Cervical - Non-Study Surgery	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
WOUND ISSUE NON-INFECTION	0	0	0.0	1	1	0.5	-0.5	-11.0	10.0
Subjects with at least 1 adverse event		3			8				

Notes:
[1] Exact 95% binomial confidence interval without PS adjustment.

Adverse Events Requiring Subsequent Surgical Intervention

Some adverse events resulted in subsequent surgical interventions at the index level. Subsequent surgical interventions (SSIs), prospectively classified as revisions, removals, reoperations or supplemental fixations, qualified as study failures in concert with FDA's Guidance Document, Clinical Data Presentations for Orthopedic Device Applications (2004). There were 3 SSIs in the M6-C™ group and 9 SSIs in the ACDF group.

Table 17: SSI Summary Table – ITT (PS Selected) Cohort through 24 Months

SSI	**M6-C™ (n=160)**	**ACDF (n=189)**
Revision	0 (0.0%)	2 (1.1%)
Removal	1 (0.6%)	3 (1.6%)
Reoperation	1 (0.6%)	1 (0.5%)
Supplemental Fixation	1 (0.6%)	3 (1.6%)
Total	**3 (1.9%)**	**9 (4.8%)**

Table 18: SSI by Time of Occurrence

SSI	**Event Time Course (months)**						**Total (events)**
	<1.5	**1.5-3**	**3-6**	**6-12**	**12-18**	**18-24**	
M6-C™							
Revision	-	-	-	-	-	-	0
Removal	-	-	-	-	1	-	1
Reoperation	1	-	-	-	-	-	1
Supplemental Fixation	-	-	-	1	-	-	1
Total	**1**	**-**	**-**	**1**	**1**	**-**	**3**

SSI	Event Time Course (months)						Total (events)
	<1.5	1.5-3	3-6	6-12	12-18	18-24	
ACDF							
Revision	-	-	-	-	-	2	2
Removal	-	-	-	1	2	-	3
Reoperation	1	-	-	-	-	-	1
Supplemental Fixation	-	-	-	2	-	1	3
Total	**1**	**-**	**-**	**3**	**2**	**2**	**9**

Based on the results presented in **Table 17**, the SSI incidence rate is 1.9% for the M6-C™ subjects and 4.8% for the control subjects. In the M6-C™ group, one subject required posterior decompression (reoperation) at the index level (C5-C6) 1 month postoperatively, one subject required posterior fusion (supplemental fixation) at C4-C6 at 12 months postoperatively, leaving the M6-C™ Artificial Cervical Disc in place and intact, and one subject had their M6-C™ Artificial Cervical Disc removed with additional treatment at C3-C7 at 17 months.

Adjacent Level Disease and Symptoms

Adjacent level disease or symptoms which required subsequent surgical intervention up to 24 months were documented and are reported in **Table 19**. This table reports all known adjacent level surgeries and not the total number subjects with adjacent level disease/symptoms. The rates were comparable: 3.1% (5/160) for the M6-C™ group compared to 2.1% (4/189) for the ACDF group.

These data should be interpreted in the context that adjacent level data were not collected in the historical control subjects.

Table 19: Subsequent Surgical Interventions (SSI) including Level(s) Adjacent to Index Level through 24 Months

Group	Index Level	Event	Time to SSI	Description of SSI
M6-C™	C5-C6	Neck and right shoulder and arm pain along with numbness in right arm/hand.	12 Months	Posterior fusion from C4-C6
M6-C™	C5-C6	Neck pain and bilateral arm pain/radiculopathy	12 Months	Microdiscectomy C3-C7 and 3-level M6-C™
M6-C™	C4-C5	Continued neck pain with right arm pain/radiculopathy	24 Months	ACDF C6-C7 and TDR C5-C6
M6-C™	C5-C6	Continued neck pain with right arm pain/ radiculopathy	24 Months	TDR C6-C7
M6-C™	C5-C6	New onset bilateral arm radiculopathy	24 Months	ACDF at C6-C7; M6-C™ at C5-C6 left in place
ACDF	C5-C6	Right arm pain and radiculopathy	3 Months	ACDF C6-C7
ACDF	C5-C6	Progressive severe left upper extremity pain and weakness	14 Months	ACDF C5-C7
ACDF	C5-C6	Increasing pain in the shoulder blade	17 Months	Posterior fusion C5-C7
ACDF	C4-C5	Increased neck and right arm pain/radiculopathy	20 Months	ACDF C3-C4, C5-C6; removal of hardware at C4-C5

Neurological Status

Neurological success was defined as maintenance or improvement in neurologic status at 24 months. As such, neurologic failure at 24 months was any decrease in neurologic function compared to baseline. At 24 months, 150 (93%) M6-C™ subjects and 144 (76.1%) control subjects were evaluated for this endpoint.

Table 20: Neurological Decrease from Baseline at 24 Months - ITT (PS Selected) Cohort

Neurological Component	M6-C™			ACDF		
	N	n	%	N	n	%
Sensory	150	6	4.0%	164	5	3.0%
Reflexes	150	3	2.0%	164	16	9.8%
Motor Function	150	3	2.0%	164	1	0.6%
Total*	**150**	**10**	**6.7%**	**164**	**21**	**12.8%**

*Total number of subjects; subjects may have one or more components with decrease from baseline.

At Month 24, ten (10) M6-C™ subjects were considered neurological failures (6.7%) and twenty-one (21) ACDF subjects were considered neurological failures (12.8%).

Adverse events categorized as neurological were as follows:

Table 21: Summary of Neurological Adverse Events

	M6-C™		ACDF	
	Events	Subjects	Events	Subjects
Total	68	46	115	73
Device-related	0	0	14	12
Serious	5	4	8	8
Serious, Definitely device- or procedure -related	3	2	3	3

2. Effectiveness Results

Primary Overall Success Analysis

The primary study endpoint is success rate assessed at 24-months after treatment. The success rate is a composite endpoint including both safety and effectiveness measures:

1) No supplemental surgical procedure at the index level
2) NDI improvement of 15 points
3) No device /procedure definitely related SAE
4) Neurological success (maintained or improved from baseline)

The data presented in **Table 22** demonstrate the non-inferiority of the M6-C™ Artificial Cervical Disc to ACDF controls on the overall primary endpoint. The counts and percentages provided for the M6-C™ and ACDF groups are not adjusted for PS subclass. The device group difference and 90% confidence interval lower bound (LB) and upper bound (UB) are calculated after controlling for PS subclass. Therefore, the reported difference does not match the difference between the presented unadjusted percentages. Subjects who are missing outcome data at the Month 24 time point who were not a prior terminal failure are excluded from the overall composite success assessment and addressed in missing data analyses in **Table 23**. This includes 26 ACDF subjects from the M6-C™ IDE study in the PS cohort who had not yet reached the month 24 time point following surgery.

For the composite success using subjects with complete data at month 24, the unadjusted success rate was 86.8% for the M6-C™ group compared with 79.3% for the ACDF group. Adjusted for

PS subclass, the difference between the M6-C™ and ACDF groups was 5.2%. The lower-bound of the 1-sided 95% confidence interval (identical to the lower-bound of the two-sided 90% confidence interval) for the group difference controlling for PS subclass was -2.1%. Since -2.1% is greater than -10%, the results from this comparison demonstrate that the study success criterion for non-inferiority has been achieved.

Using multiple imputation to account for missing data, the adjusted success rate was 85.7% for the M6-C™ group compared with 78.9% for the ACDF group, with the difference between the M6-C™ and ACDF groups being 6.9%. The lower-bound of the 1-sided 95% confidence interval for the group difference controlling for PS subclass was -0.9%. Since -0.9% is greater than -10%, the results from this comparison demonstrate that the study success criterion for non-inferiority has been achieved.

In all components of the composite endpoint, the M6-C™ population performed numerically better than the ACDF controls. The largest numerical difference was present in the NDI component of the primary endpoint with a group difference of 3.7% adjusted for PS subclass.

Table 22: ITT (PS Selected) Cohort [1] Descriptive Comparisons of the Percentages of Subjects Achieving Month 24 Overall Success with PS Adjusted Group Differences and Two-Sided 90% CI's for the Overall Success Endpoint and its Components

	M6-C™[5]			ACDF[5]			M6-C™ - ACDF[6]		
	N	n	%	N	n	%	Diff (%)	LB	UB
Overall Success (Completed Cases)	152	132	86.8	164	130	79.3	5.2	-2.1	12.5
ITT (PS Selected) using Multiple Imputation (MI)[2,3]	160	---	85.7	189	---	78.9	6.9	-0.9	14.7
Per Protocol (Completed Cases)[4]	152	---	86.0	164	---	80.8	5.2	-2.1	12.5
(1) No supplemental surgical procedure at the index level (including revision, removal, reoperation, or supplemental fixation)[7]	160	157	98.1	189	180	95.2	3.0	-0.2	6.3
(2) NDI Responder (improvement of at least 15 points)[8]	147	133	90.5	154	131	85.1	3.7	-2.8	10.2
(3) No Device/Procedure Definitely Related SAE	160	157	98.1	189	181	95.8	1.8	-1.3	5.0
(4) Neurological Success (maintenance or improvement compared to baseline)[8,9]	150	149	99.3	164	162	98.8	0.7	-1.2	2.5

Notes:

1. Includes all M6-C™ subjects (N=160) and control subjects selected into a propensity score subclass (N=189).
2. The primary ITT analysis set includes all M6-C™ subjects (N=160) and controls selected into a propensity score subclass (N=189). Among 72 prospective controls, 46 were selected into a PS subclass. 39 (86.7%) were evaluable for overall success. Overall, among all 189 PS selected controls, 164 (86.8%) were evaluable for primary overall success endpoint. 152 of 160 (95%) M6-C™ subjects were evaluable for Month 24 overall success.
3. A fully conditional specification (FCS) approach was used to produce 20 multiply imputed completed data sets. To implement the MI, the overall success endpoints were determined at intermediate time points. The FCS approach was used to accommodate non-monotonicity in the pattern of missing overall success over time and requires models to be specified for each variable with missing values. All models included PS subclass and treatment group. Overall success variables were sequentially added to account for longitudinal temporality. The model for Month 24 included PS subclass, treatment groups, and all intermediate overall success values.
4. Since there were no exclusions from the ITT analysis set due to protocol violations the Per Protocol analysis set is a completers analysis set. The Per Protocol (PP) analysis set includes N=152 M6-C™ subjects and N=164 ACDF controls that were evaluable for Month 24 Overall Success.

5. All counts and percentages presented for subjects meeting the overall success endpoint (completed cases) and components of overall success are not adjusted for PS subclass, with the exception of the overall success endpoint in the ITT (PS Selected) using Multiple Imputation cohort and the per protocol assessment that are adjusted for PS subclass.
6. Device group differences and two-sided 90% confidence intervals (CI) for group differences were calculated controlling for propensity score (PS) subclass using Proc GENMOD with dist=binomial, link=logit, and ilink option in LSMEANS statements. The LB of the two-sided 90% CI is identical to the LB of the one-sided 95% CI. For overall success and NDI, PS subclass was included in the model as a stratification variable (df=4). The very high success rates for the other variables required that the ordinal PS subclass be included in the model as a continuous variable (df=1).
   Note that in this table, the PS-adjusted group difference in success rates does not equal the difference in the unadjusted percentages since these do not control for PS subclass. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and radicular symptom duration (<9 mo. vs. ≥9 mo.).
7. Subject 007-017 (M6-C™) died on relative day 18. This subject is included in this row as not experiencing an SSI. This subject experienced an SAE on day 8 that was classified as definitely related to the device or procedure and is included in row (3) as an SAE failure.
8. NDI Responder is censored for terminal failure (SSI and device / procedure related SAE). Neurologic success is not censored for terminal failure.
9. Neurological success for the primary endpoint was adjudicated for clinical relevance to the subject's index level by the CEC for the subjects who exhibited a numerical decline in neurological status.

When imputing all missing data as either successes or failures, the non-inferiority assessment is maintained, with the lower bound of the confidence interval being greater than -10% for both measurements.

The "best case" and "worst case" assessments for the M6-C™ group were developed via modeling, as the inclusion of the PS sub-classification into the model creates another dimension to the missing data analysis, with the "worst case" combination not necessarily being the case where all missing M6-C™ subjects are considered failures and all missing ACDF subjects are considered as successes. In the "worst case" assessment for the M6-C™ group, the lower bound of the confidence interval is -8.4% indicating that even in the "worst case" assessment the lower bound of the confidence is greater than -10% and, thus, non-inferiority is met.

Table 23: ITT (PS Selected) Cohort Month 24 Overall Success Comparison and Missing Value Sensitivity Analyses for PS Adjusted Month 24 Overall Success and Device Group Differences with Two-Sided 90% CI's

	M6-C™[4]			ACDF[4]			M6-C™ - ACDF[4]		
	N	n	%	N	n	%	Diff (%)	LB[5]	UB
ITT (PS Selected) using Multiple Imputation (MI)[1,2]	160	---	85.7	189	---	78.9	6.9	-0.9	14.7
Per Protocol (Completed Cases)[3]	152	---	86.0	164	---	80.8	5.2	-2.1	12.5
All Missing as Success	160	---	86.6	189	---	83.6	3.0	3.0	9.6
All Missing as Failure	160	---	82.6	189	---	68.9	13.8	6.0	21.6
Best Case (M6-C missing as success, ACDF as failures)	160	---	87.4	189	---	69.5	17.9	10.5	25.3
Worst Case (M6-C missing as failures, ACDF as success)	160	---	81.8	189	---	83.0	-1.2	-8.4	5.9

Notes:

1 The primary ITT analysis set includes all M6-C™ subjects (N=160) and controls selected into a propensity score subclass (N=189). Among 72 prospective controls, 46 were selected into a PS subclass. 39 (86.7%) were evaluable for overall success. Overall, among all 189 PS selected controls 164 (86.8%) were evaluable for primary overall success endpoint. 152 of 160 (95%) of M6-C™ subjects were evaluable for Month 24 overall success.

2 A fully conditional specification (FCS) approach was used to produce 20 multiply imputed completed data sets. To implement the MI, the overall success endpoints were determined at intermediate timepoints. The FCS approach was used to accommodate non-monotonicity in the pattern of missing overall success over time and requires models to be specified for each variable with missing values. All models included PS subclass and treatment group. Overall success variables were sequentially added to account for longitudinal temporality. The model for Month 24 included PS subclass, treatment groups, and all intermediate overall success values.

3 Since there were no exclusions from the ITT analysis set due to protocol violations the Per Protocol analysis set is a completers analysis set. The Per Protocol (PP) analysis set includes N=152 M6-C™ subjects and N=164 ACDF controls that were evaluable for Month 24 overall success. Percentages in this row adjust for PS subclass and and not determined as n/N. This is why the n column is suppressed.

4 Estimated overall success rates for each device group as well as the device group differences and 90% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using Proc GENMOD with dist=binomial and link=logit. The ilink option in the lsmeans statement was used to obtain estimated success rates and standard errors on the probability scale. The lower bound (LB) of the 90% CI is equivalent to the LB of the 1-sided 95% non-inferiority CI. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and radicular symptom duration (<9 mo. vs. ≥9 mo.).

5 The Study Success criterion is a 1-sided 95% CI LB for the overall success that is greater than or equal to -10% in both the ITT and PP analysis sets. Since LB = -0.9% > -10% and -2.1% > -10%, the Study Success criterion is achieved.

Secondary Effectiveness Analyses

This section focuses on secondary clinical endpoints from a number of relevant domains (i.e., Neck Disability Index (NDI), Visual Analog Scale (VAS), Short-Form Questionnaire (SF-36/SF-12), and Radiographic Measurements, which were assessed at preoperative (baseline) and at prescribed clinical intervals throughout the follow-up period. In addition, Odom's criteria and patient satisfaction were assessed post-operatively at 24 months. Overall, subjects treated with the M6-C™ Artificial Cervical Disc exhibited significant improvement across the broad spectrum of secondary analyses.

Table 24: Secondary Effectiveness Subject Outcomes at 24 Months Compared to Baseline – ITT (PS Selected) Cohort

Component	M6-C™ (N=160)	ACDF (N=189)
NDI Improvement ≥ 15 points	133/147 (90.5%)	131/154 (85.1%)
VAS Neck Pain Improvement ≥ 2.0cm	134/147 (91.2%)	120/154 (77.9%)
VAS Worse Side Shoulder/Arm Pain Improvement ≥ 2.0cm	133/147 (90.5%)	123/154 (79.9%)
SF-12/SF-36 PCS Maintenance or Improvement	143/147 (97.3%)	132/148 (89.2%)
SF-12/SF-36 MCS Maintenance or Improvement	114/147 (77.6%)	114/148 (77.0%)
Patient Satisfaction*	138/150 (92.0%)	156/160 (95.1%)
Odom's Criteria (Excellent or Good)	142/150 (94.6%)	146/164 (89.0%)
Work Status (Working Full/Part Time w/ or w/out Restrictions)	127/152 (83.6%)	130/171 (76.0%)
Overall Pain Medication Usage (# of Subjects Using)	21/150 (14.0%)	68/178 (38.2%)
NSAID Usage (# of Subjects Using)	15/150 (10.0%)	36/178 (20.2%)
Opioid Usage (# of Subjects Using)	3/150 (2.0%)	27/178 (15.2%)

*Historical control satisfaction categories were dichotomized into "yes" or "no"

Neck Disability Index (NDI)

Table 25: Descriptive Statistics including Two-Sided 95% CI's for the Neck Disability Index (NDI) – ITT (PS Selected) Cohort

	M6-C™						ACDF						M6-C™ - ACDF[1]		
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	Diff	LB	UB
Pre-Op	160	54.8	14.1	54.0	26.0	96.0	189	51.9	14.5	50.0	30.0	90.0	-0.1	-3.3	3.1
Week 6	156	22.4	15.2	21.0	0.0	64.0	186	29.0	18.8	27.0	0.0	86.0	-5.3	-9.3	-1.2
Month 3	153	15.4	14.7	12.0	0.0	64.0	179	22.2	18.4	18.0	0.0	82.0	-5.9	-9.9	-1.8
Month 6	152	13.1	13.8	9.0	0.0	70.0	176	19.8	18.8	14.0	0.0	72.0	-5.8	-9.8	-1.7
Month 12	149	12.1	13.6	8.0	0.0	62.0	168	18.1	18.9	10.0	0.0	78.0	-5.9	-10.0	-1.8
Month 24	147	12.1	14.4	6.0	0.0	64.0	154	17.9	19.3	12.0	0.0	80.0	-5.4	-9.7	-1.1

Notes:

1 Device group differences and 95% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using two-way analysis of variance. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and radicular symptom duration (<9 mo. vs. ≥9 mo.).

Table 26: Descriptive Comparisons of the Percentages of Subjects Achieving a Decrease in NDI Score of at Least 15 Points with Two-Sided 95% CI's – ITT (PS Selected) Cohort

	Number and Percentage Meeting Criteria								
	M6-C™			ACDF			M6-C™ - ACDF[1]		
	N	n	%	N	n	%	Diff (%)	LB	UB
Week 6	156	125	80.1%	186	128	68.8%	4.8	-5.1	14.7
Month 3	153	138	90.2%	179	143	79.9%	7.2	-0.6	15.0
Month 6	152	141	92.8%	176	142	80.7%	8.5	0.9	16.0
Month 12	149	139	93.3%	168	145	86.3%	3.4	-3.5	10.2
Month 24	147	133	90.5%	154	131	85.1%	3.7	-4.1	11.5

Notes:
1 Device group differences and 95% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using two-way generalized linear model for dichotomous variables. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and radicular symptom duration (<9 mo. vs. ≥9 mo.).

Success for the Neck Disability Index (NDI) was defined as an improvement of at least 15 points on a 100-point scale at 24 months. At 24 months, 147 M6-C™ subjects and 154 control subjects were assessed for this parameter. Mean scores at 24 months were 12.1 and 17.9 for the M6-C™ and control subjects, respectively. These scores represent a success rate of 90.5% and 85.1% respectively.

It should be noted that while the NDI questionnaires used in the historical control and in the M6-C study were identical, with the same relative weight assigned to each answer, the raw scores were converted to a 100 point scale in the M6-C study to facilitate comparison with the historical control, which reported NDI on a 100 point scale. This conversion is commonly performed and does not affect the comparability of the results.

Functional improvement assessed using NDI appears comparable in the study arms.

Visual Analog Scale (VAS) – Neck Pain

Table 27: Descriptive Statistics including Two-Sided 95% CI's for VAS Neck Pain – ITT (PS Selected) Cohort

	M6-C™ Neck Pain VAS						ACDF Neck Pain VAS						M6-C™ - ACDF[1]		
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	Diff	LB	UB
Pre-Op	160	7.3	1.9	7.6	0	10	189	7.1	2.0	7.4	0	10	0.0	-0.5	0.4
Week 6	156	2.0	1.9	1.5	0	9	186	2.6	2.4	1.6	0	10	-0.5	-1.0	0.0
Month 3	152	1.4	1.9	0.4	0	8	179	2.2	2.5	1.3	0	10	-0.7	-1.3	-0.2
Month 6	151	1.2	1.7	0.4	0	9	176	2.2	2.5	1.2	0	9	-1.0	-1.5	-0.5
Month 12	148	1.2	1.7	0.2	0	8	168	2.0	2.7	0.5	0	10	-1.0	-1.5	-0.4
Month 24	147	1.1	2.0	0.1	0	10	154	2.2	2.7	0.8	0	10	-1.0	-1.6	-0.4

Notes:
1 Device group differences and 95% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using two-way analysis of variance. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and radicular symptom duration (<9 mo. vs. ≥9 mo.).

Table 28: Improvement in VAS Neck Pain Scores of at Least 2.0 cm with Two-Sided 95% CI's – ITT (PS Selected) Cohort

	Number and Percentage Meeting Criteria								
	M6-C™			ACDF			M6-C™ - ACDF[1]		
	N	n	%	N	n	%	Diff (%)	LB	UB
Week 6	156	138	88.5%	186	144	77.4%	9.7	1.4	17.9
Month 3	152	137	90.1%	179	146	81.6%	5.1	-2.7	12.9
Month 6	151	139	92.1%	176	136	77.3%	14.1	6.1	22.1
Month 12	148	136	91.9%	168	135	80.4%	12.3	4.4	20.1
Month 24	147	134	91.2%	154	120	77.9%	11.6	3.1	20.1

Notes:
1 Device group differences and 95% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using two-way generalized linear model for dichotomous variables. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and radicular symptom duration (<9 mo. vs. ≥9 mo.).

Success for the Visual Analog Score (VAS) was defined as an improvement of at least 2cm on a 10cm scale compared to baseline at 24 months. The M6-C™ IDE study specified a baseline threshold score of 4cm, and the propensity method was used to match control subjects to this baseline value.

At 24 months, 147 M6-C™ subjects and 154 control subjects were evaluated for this parameter. The mean VAS scores at 24 months were 1.1 and 2.2, respectively. Success for this parameter was 91.2% and 77.9%, respectively. The M6-C™ Artificial Cervical Disc appears to be more effective in relieving neck pain than ACDF.

Visual Analog Scale (VAS) – Shoulder/Arm Pain (Worse Side)

Table 29: Descriptive Statistics including Two-Sided 95% CI's for VAS Shoulder/Arm Pain (Worse Side) – ITT (PS Selected) Cohort

	M6-C™ Shoulder/Arm Pain (worse side)						ACDF Shoulder/Arm Pain (worse side)						M6-C™ - ACDF[1]		
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	Diff	LB	UB
Pre-Op	160	7.3	2.2	7.6	0	10	189	7.5	1.9	7.7	0	10	-0.1	-0.5	0.4
Week 6	155	1.2	2.0	0.2	0	9	186	2.5	2.7	1.1	0	10	-1.1	-1.7	-0.5
Month 3	152	0.9	1.8	0.1	0	8	179	2.3	2.6	1.3	0	9	-1.0	-1.6	-0.5
Month 6	151	0.7	1.6	0.1	0	9	176	2.2	2.6	0.9	0	9	-1.2	-1.7	-0.7
Month 12	148	0.9	1.9	0.0	0	10	168	2.1	2.8	0.5	0	10	-1.2	-1.8	-0.7
Month 24	147	0.8	1.8	0.0	0	9	154	2.4	2.9	1.0	0	10	-1.5	-2.1	-0.9

Notes:
1 Device group differences and 95% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using two-way analysis of variance. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and radicular symptom duration (<9 mo. vs. ≥9 mo.).

Table 30: Improvement in VAS Shoulder/Arm Pain (Worse Side) Scores of at Least 2.0 cm with Two-Sided 95% CI's – ITT (PS Selected) Cohort

	Number and Percentage Meeting Criteria								
	M6-C™			ACDF			M6-C™ - ACDF[1]		
	N	n	%	N	n	%	Diff (%)	LB	UB
Week 6	155	135	87.1%	186	150	80.6%	5.8	-2.3	13.9
Month 3	152	137	90.1%	179	144	80.4%	10.0	2.1	17.8
Month 6	151	139	92.1%	176	142	80.7%	13.7	6.1	21.3
Month 12	148	131	88.5%	168	138	82.1%	11.5	3.6	19.4
Month 24	147	133	90.5%	154	123	79.9%	14.5	6.3	22.7

Notes:
1 Device group differences and 95% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using two-way generalized linear model for dichotomous variables. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and radicular symptom duration (<9 mo. vs. ≥9 mo.).

Pain in the shoulder/arm was also assessed at 24-months using the VAS with the same success criteria. At 24 months, 147 M6-C™ subjects and 154 control subjects were evaluated for this parameter. No threshold baseline score was required; however, the baseline scores were similar. At 24 months, mean VAS worse side shoulder and arm pain scores were 0.8 and 2.4 for the M6-C™ and control subjects, respectively. Success for this parameter was 90.5% and 79.9%, respectively. The M6-C™ Artificial Cervical Disc appears to be more effective in relieving shoulder and arm pain than ACDF.

SF-12/SF-36

Health-related quality of life was assessed using the SF-36 tool in the M6-C™ IDE study and the SF-12 tool in the historical control, which precluded pooling of the concurrent and historical control groups. The sponsor addressed this by calculating the subscores of PCS and MCS and pooling them. This is not a validated method and the outcomes should be viewed in this context.

Physical Component Summary (PCS)

Table 31: Descriptive Statistics including Two-Sided 95% CI's for SF-12/SF-36 Physical Component Summary Scores – ITT (PS Selected) Cohort

	M6-C™ Physical Component Summary						ACDF Physical Component Summary						M6-C™ - ACDF[1]		
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	Diff	LB	UB
Pre-Op	160	34.9	7.7	34.6	16.1	55.0	187	32.7	8.0	32.4	10.8	56.9	2.8	1.0	4.7
Month 6	151	50.7	8.9	53.2	14.5	63.4	170	47.2	10.6	50.0	19.4	68.9	2.3	-0.1	4.7
Month 12	148	51.3	8.6	54.0	23.5	65.2	164	48.8	10.4	51.7	15.9	70.0	2.4	0.1	4.8
Month 24	147	51.3	8.4	53.4	22.5	63.2	150	48.2	10.8	52.4	17.5	64.3	2.5	0.1	5.0

Notes:
1 Device group differences and 95% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using two-way analysis of variance. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/ disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and radicular symptom duration (<9 mo. vs. ≥9 mo.).

Table 32: Descriptive Comparisons of the Percentages of Subjects Maintaining or Improving SF-12/SF-36 Physical Function Component Summary Score with Two-Sided 95% CI's – ITT (PS Selected) Cohort

	Number and Percentage Meeting Criteria								
	M6-C™			ACDF			M6-C™ - ACDF[1]		
	N	n	%	N	n	%	Diff (%)	LB	UB
Month 6	151	143	94.7%	168	153	91.1%	2.6	-3.2	8.3
Month 12	148	141	95.3%	162	150	92.6%	2.0	-3.5	7.5
Month 24	147	143	97.3%	148	132	89.2%	7.6	1.6	13.6

Notes:
1 Device group differences and 95% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using two-way generalized linear model for dichotomous variables. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and radicular symptom duration (<9 mo. vs. ≥9 mo.).

At 24 months, 147 M6-C™ subjects and 148 control subjects were assessed. Both groups reported improvement of this score compared to baseline (measurement at pre-operative timepoint). The scores for the M6-C™C subjects were numerically higher.

Mental Health Component Summary (MCS)

Table 33: Descriptive Statistics including Two-Sided 95% CI's for SF-12/SF-36 Mental Health Component Summary Scores – ITT (PS Selected) Cohort

	M6-C™ Mental Health Summary						ACDF Mental Health Summary						M6-C™ - ACDF[1]		
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	Diff	LB	UB
Pre-Op	160	41.4	13.9	42.1	7.7	66.6	187	42.5	12.8	42.0	16.0	73.6	0.5	-2.6	3.5
Month 6	151	53.6	9.3	56.3	15.0	69.4	170	50.5	10.7	53.6	17.3	66.7	3.0	0.5	5.4
Month 12	148	53.0	8.9	55.9	15.8	64.6	164	49.7	11.3	52.9	9.6	66.3	3.3	0.7	5.8
Month 24	147	52.9	9.7	56.0	20.1	65.0	150	51.7	10.4	56.2	21.1	72.5	1.9	-0.7	4.4

Notes:
1 Device group differences and 95% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using two-way analysis of variance. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/ disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and radicular symptom duration (<9 mo. vs. ≥9 mo.).

Table 34: Descriptive Comparisons of the Percentages of Subjects Maintaining or Improving SF-12/SF-36 Mental Health Component Summary Score with Two-Sided 95% CI's – ITT (PS Selected) Cohort

	Number and Percentage Meeting Criteria								
	M6-C™			ACDF			M6-C™ - ACDF[1]		
	N	n	%	N	n	%	Diff (%)	LB	UB
Month 6	151	123	81.5%	168	132	78.6%	0.3	-9.0	9.5
Month 12	148	114	77.0%	162	115	71.0%	5.1	-5.2	15.5
Month 24	147	114	77.6%	148	114	77.0%	0.5	-9.5	10.6

Notes:
1 Device group differences and 95% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using two-way generalized linear model for dichotomous variables. P-values are from Mantel-Haenszel PS subclass stratified comparisons between device groups. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and radicular symptom duration (<9 mo. vs. ≥9 mo.).

At 24 months, 147 M6-C™ subjects and 131 control subjects were assessed for the MCS. When compared to baseline, both arms showed improvement and the rates were similar.

Odom's Criteria

The surgeon's rating of subject outcomes was assessed using Odom's criteria. Different definitions of the categories were used in the two studies, which precluded pooling of the concurrent and historical control groups. No method was available to address this issue and therefore no comparison could be made between the two study arms.

Table 35: Odom's Criteria – Month 24 – M6-C™ and ACDF Pooled Controls – ITT (PS Selected) Cohort

	M6-C™		ACDF	
Odom's Criteria	**n**	**%**	**n**	**%**
Excellent	113	75.3	106	64.6
Good	29	19.3	40	24.4
Fair	7	4.7	13	7.9
Poor	1	0.7	5	3.0

At 24 months, 150 M6-C™ subjects and 164 control subjects were assessed for this parameter. The majority of subjects in both arms were rated by the surgeon as "Excellent".

Patient Satisfaction

Different questions were used in assessing patient satisfaction and preclude direct comparison. The 5-point responses of the historical control were converted into a binary response and then pooled with the concurrent control for comparison to the Investigational group. As this not a validated method, no comparison can be made between the study arms.

Table 36: Patient Satisfaction with Surgery – Month 24 – M6-C™ and ACDF Control – ITT (PS Selected) Cohort

	M6-C™		ACDF	
Satisfaction	**n**	**%**	**n**	**%**
Yes	138	92.0	156	95.1
No	12	8.0	8	4.9
Would you have Surgery Again	**n**	**%**	**n**	**%**
Yes	140	93.3	154	95.1
No	10	6.7	8	4.9

At 24 months, 150 M6-C™ subjects and 162 control subjects were asked if they would have surgery again. The majority of subjects in both arms responded "Yes".

Radiographic Assessments

Radiographic data were collected from both study arms. There were differences in some radiographic assessments and definitions. Assessments were performed by the same independent core laboratory, but there was a temporal difference in these assessments. In instances where there were differences in definitions or assessments, the results were harmonized.

Quantitative Radiographic Assessments

Rotation (Flexion to Extension)

Table 37: Flexion Extension Rotation (F to E) (deg) – ITT (PS Selected) Cohort

	M6-C™			ACDF		
	At Level of Implant					
	N	Mean	SD	N	Mean	SD
Pre-Op	153	8.33	4.95	180	8.02	4.93
Month 24	144	8.78	4.55	152	1.16	1.34

The flexion to extension measurement reflects the range of motion at the index level. At 24 months, 144 M6-C™ subjects and 152 control subjects were evaluated for this endpoint. The mean ROM at baseline was slightly higher for the M6-C™ subjects than the controls. At 24 months, motion was maintained for the M6-C™ subjects. Motion was reduced in the fusion controls.

Translation (Flexion to Extension)

Table 38: Translation (F to E) (mm) – ITT (PS Selected) Cohort

	M6-C™			ACDF		
	At Level of Implant					
	N	Mean	SD	N	Mean	SD
Pre-Op	153	0.83	0.62	179	0.87	0.65
Month 24	144	0.82	0.55	152	0.13	0.16

Translational motion is a measure of stability. No difference was observed in the M6-C™ subjects. Translational motion was reduced in the fusion control subjects at 24 months.

Disc Angle

Table 39: Disc Angle (deg) – ITT (PS Selected) Cohort

	M6-C™			ACDF		
	At Level of Implant					
	N	Mean	SD	N	Mean	SD
Pre-Op	158	2.21	4.59	184	1.96	4.50
Month 24	149	7.21	4.98	152	5.87	4.57

At 24 months disc angle was increased in both cohorts, and the measurements were comparable.

Disc Height (Average)

Table 40: Average Disc Height (mm) – ITT (PS Selected) Cohort

	M6-C™			ACDF		
	At Level of Implant					
	N	Mean	SD	N	Mean	SD
Pre-Op	158	3.22	0.73	183	3.32	0.81
Month 24	149	5.31	1.02	152	4.27	1.28

Disc height increased in both study arms at 24 months compared to baseline. The increase was numerically greater in the M6-C™ group.

AP Rotation (Left to Right)

Table 41: AP Rotation (L to R) (deg) – ITT (PS Selected) Cohort

	M6-C™			ACDF		
	At Level of Implant					
	N	Mean	SD	N	Mean	SD
Pre-Op	142	5.78	2.75	135	5.77	3.33
Month 24	149	6.88	3.25	124	1.34	1.22

Rotational motion was comparable at baseline for both arms of the study. At 24 months, motion was maintained in the M6-C™ group. Motion was reduced in the ACDF group.

Qualitative Radiographic Assessments

Radiolucency was assessed in both the M6-C™ and ACDF groups according to the following definitions:

1) None: No radiolucent lines along the device/endplate interface
2) Mild: < 25% radiolucency
3) Moderate: 25 - 50% radiolucency
4) Severe: > 50% radiolucency

Table 42: Qualitative Assessment of Radiolucency – ITT (PS Selected) Cohort

	M6-C™		ACDF	
	n	%	n	%
1-None	144	96.0	156	98.7
2-Mild	6	4.0	0	0
3-Moderate	0	0	2	1.3
4-Severe	0	0	0	0

At 24 months, 150 M6-C™ subjects and 158 control subjects were evaluated for radiolucency. At Month 24, there was a 4% (6/150) rate of mild radiolucency in the M6-C™ group and a 1.3% (2/158) rate of moderate radiolucency in the ACDF group.

Device condition was only assessed in the M6-C™ group. At 24 months, 150 subjects were assessed for device condition. There were 4 radiographic observations of device loosening (2.6%) and no incidences of disassembly or device fracture.

At Month 24, 150 M6-C™ subjects and 159 control subjects were evaluated for subsidence. In M6-C™ group, subsidence of the device was measured; in the control group, subsidence of the graft was measured. One (1) M6-C™ subject and 2 control subjects showed subsidence.

There were no radiographic observations of migration in either the control or the M6-C™ group at any timepoint.

Fusion was assessed in the control subjects. The definition of fusion differed in the two studies. In order to pool fusion outcomes, the definition used in the M6-C™ IDE study was applied to the historical control. Fusion was defined as:

- Evidence of continuous bridging bone across treated disc space; where bridging is defined as plain radiographic evidence of a continuous connection of bone from the superior vertebral body to the inferior vertebral body, AND
- $\leq 2^{o}$ total angular motion (from flexion to extension), AND
- ≤ 1.25 mm translational motion (from flexion to extension).

Fusion was observed in 78.6% (125/159) of the control subjects at 24 months.

Heterotopic ossification (HO) was assessed only in subjects that received the M6-C™ Artificial Cervical Disc. 81 subjects were prescribed NSAIDs prophylactically for 6 weeks post-operatively for HO. At 24 months, 150 subjects were assessed for heterotopic ossification.

Heterotopic ossification was graded as follows:

> Class 0: No evidence of osteophyte formation or heterotopic ossification.
> Class I: HO is detectable in the front or sides of the vertebral body, or as islands of bone in the adjacent soft tissue, but is not in the disc space. Bone is not present between the planes formed by the two vertebral endplates.
> Class II: HO is growing into the disc space. Bone is present between the planes formed by the two adjacent endplates but is not significantly blocking or articulating between adjacent vertebral endplates or osteophytes.
> Class III: The range of motion of the vertebral endplates is blocked by the formation of HO and/or postoperative osteophytes on flexion-extension or lateral bending radiographs. However, the ossifications still allow some movement of the prosthesis.
> Class IV: HO is causing bony ankylosis. An apparent continuous connection of bridging bone exists between the adjacent vertebral endplates with little or no motion occurring across the treated segment.

Table 43: Qualitative Assessment of HO at 24 Months – ITT (PS Selected) Cohort (M6-C™ Only)

Class	n	%
0	61	40.7
I	22	14.7
II	50	33.3
III	16	10.7
IV	1	0.7

At 24 months, 59.3% (89/150) of subjects had HO. One subject had Class IV heterotopic ossification at Month 24 (0.7%).

Pain Medication Use

Table 44: Overall Pain Medication Use (Any) – ITT (PS Selected) Cohort

	M6-C™			ACDF		
	N	n	%	N	n	%
Preoperative	160	129	80.6%	189	162	85.7%
Week 6	158	46	29.1%	189	91	48.1%
Month 3	156	30	19.2%	189	78	41.3%
Month 6	154	32	20.8%	186	76	40.9%
Month 12	152	27	17.8%	185	69	37.3%
Month 24	150	21	14.0%	178	68	38.2%

Table 45: Pain Medication Use (Anti-Inflammatory and Antirheumatic Products, Non-Steroids) – ITT (PS Selected) Cohort

	M6-C™			ACDF		
	N	n	%	N	n	%
Preoperative	160	81	50.6%	189	71	37.6%
Week 6	158	29	18.4%	189	13	6.9%
Month 3	155	14	9.0%	189	29	15.3%
Month 6	154	18	11.7%	186	38	20.4%
Month 12	152	18	11.8%	184	35	19.0%
Month 24	150	15	10.0%	178	36	20.2%

Table 46: Pain Medication Use (Opioid) – ITT (PS Selected) Cohort

	M6-C™			ACDF		
	N	n	%	N	n	%
Preoperative	160	71	44.4%	189	115	60.8%
Week 6	158	11	7.0%	189	62	32.8%
Month 3	155	9	5.8%	189	38	20.1%
Month 6	154	7	4.5%	186	32	17.2%
Month 12	152	8	5.3%	184	31	16.8%
Month 24	150	3	2.0%	178	27	15.2%

As shown in **Table 44**, **Table 45**, and **Table 46**, overall pain medication, anti-inflammatory and antirheumatic products, non-steroids (NSAIDs), and opioid use was markedly higher in the ACDF group compared to the M6-C™ group at Month 24. In the ITT (PS Selected) cohort at Month 24, 38.2% (68/178) of ACDF subjects reported overall pain medication usage compared to 14.0% (21/150) of M6-C™ subjects, 20.2% (36/178) of ACDF subjects reported NSAID usage compared to 10.0% (15/150) of M6-C™ subjects, and 15.2% (27/178) of ACDF subjects reported opioid usage compared to 2.0% (3/150) of M6-C™ subjects. This observed reduction in pain medication usage at later time points demonstrates an additional benefit of the M6-C™ Artificial Cervical Disc compared to ACDF.

3. Long Term Clinical Results (36 Months)

An analysis of the 36-month data using the same safety and effectiveness endpoints was conducted. For subjects theoretically due for 36-month follow-up, the M6-C™ cohort had a follow-up rate of 82.3% (93/113) and the ACDF control cohort had a follow-up rate of 88.2% (134/152). **Table 47** shows the secondary effectiveness results at 36 months. While these analyses were not pre-specified, the results suggest that the M6-C™ Artificial Cervical Disc remains comparable to the ACDF control for clinical outcomes at 36 months.

Table 47: Secondary Effectiveness Subject Outcomes at 36 Months Compared to Baseline

Component	M6-C™ (N=139)	ACDF (N=158)
NDI Improvement ≥ 15 points	82/88 (93.2%)	109/126 (86.5%)
VAS Neck Pain Improvement ≥ 2.0cm	80/87 (92.0%)	103/126 (81.7%)
VAS Worse Side Shoulder/Arm Pain Improvement ≥ 2.0cm	75/87 (86.2%)	105/126 (83.3%)
SF-12/SF-36 PCS Maintenance or Improvement	83/88 (94.3%)	107/122 (87.7%)
SF-12/SF-36 MCS Maintenance or Improvement	72/88 (81.8%)	99/122 (81.1%)
Overall Pain Medication Usage (# of Subjects Using)	7/89 (7.9%)	57/147 (38.8%)
NSAID Usage (# of Subjects Using)	6/89 (6.7%)	30/146 (20.5%)
Opioid Usage (# of Subjects Using)	3/89 (3.4%)	25/147 (17.0%)

At 36 months, differences in adverse event rates are noted between the M6-C™ and control groups, with higher percentages of any adverse event, any serious adverse event, and device related adverse events in the ACDF group, while there is a higher rate of procedure-related adverse events in the M6-C™ group (**Table 48**). This difference in procedure-related adverse events may be due to differences in the classification of procedure-related adverse events in the M6-C™ and historical control IDE studies.

Table 48: Comparisons of Summary Adverse Event Rates between M6-C™ and ACDF Groups with Two-Sided 95% CI's – ITT (PS Selected) Cohort through 36 Months

	M6-C™ (I) (N=160)		ACDF (C) (N=189)		I vs. C[1]		
	n	%	n	%	Diff (%)	LB	UB
Any adverse event (per patient)[4]	111	69.4	160	84.7	-13.7	-23.0	-4.4
Any device related AE[2]	5	3.1	26	13.8	-11.3	-17.2	-5.4
Any procedure related AE[2,3]	60	37.5	51	27.0	12.1	1.8	22.5
Any AE related to device or procedure[2]	61	38.1	69	36.5	2.5	-8.3	13.2
Any serious AE	22	13.8	35	18.5	-5.6	-13.6	2.5
Serious AE that is either device or procedure related[2]	6	3.8	12	6.3	-2.7	-7.3	1.9
Deaths[3]	3	1.9	1	0.5	0.9	-1.4	3.3

Notes:

1 Device group differences and 95% confidence intervals (CI) for group differences controlling for propensity score (PS) subclass using two-way generalized linear model for dichotomous variables. The PS model included main effects and important interactions and squared terms for the following baseline variables: age; BMI; height; gender; NDI; VAS neck pain; VAS worse arm pain; narcotics use (Y vs N); workers compensation/disability (Y vs N); work status (not working due to neck problems); smoking status (never, past, current); treated level (C3-C4, C4-C5, C5-C6 or C6-C7); and radicular symptom duration (<9 mo. vs. ≥9 mo.).

2 Includes possible, probable, or definite.

3 The very low event rates for these variables required that PS subclass be included in the generalized linear model as a continuous variable (df=1) rather than as a stratification variables (df=4).

4 Historical control follow-up exceed two-years in many cases. Therefore, in order to provide meaningful comparisons between groups, AEs with onset dates more than 1155 days (36 months + 60 days) post index surgery were excluded from primary safety tables for all subjects.

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 27 principal investigators of which none were full-time or part-time employees of the sponsor and 9 principal investigators 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: 0 investigators
- Significant payment of other sorts: 0 investigators
- Proprietary interest in the product tested held by the investigator: 0 investigators
- Significant equity interest held by investigator in sponsor of covered study: 9 investigators

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were requested by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. FDA determined the information provided did not raise questions about the reliability of the data due to any association between financial interest and the treatment effect in favor of the M6-C™ in the primary endpoints. No additional actions were taken or deemed necessary to ensure the reliability of the data (21 CFR 54.5(c)).

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The Sponsor initiated a feasibility study in December 2007 at three (3) sites in the United States under IDE #G050254. A total of 30 subjects were enrolled and implanted in the Non-Randomized, Single Arm M6-C™ Artificial Cervical Disc Feasibility Study. The subjects were followed for 6 months with additional follow up periods as required. Planned follow up visits were concluded at 24 months, the database was locked, and a final progress report submitted. Subsequent to the 24-month visit, an additional follow up was scheduled at the 42-month anniversary. Twenty-seven (27) subjects returned for the planned 42-month visit with one additional subject returning after database lock.

A subject was considered a success if there were:

- No serious adverse event(s) classified as device or device procedure related, and
- No removals, revisions, or supplemental fixations required to modify the device, and
- Maintenance or improvement in neurological function, and
- Improvement on the Neck Disability Index of at least 15 points

There were twelve (12) subjects who received the M6-C™ Artificial Cervical Disc at a single level and eighteen (18) subjects who received the device at two levels, adjacent to each other. There were no device removals, revisions, or supplemental fixations at the treated level through 42 months follow-up. 94.4% (28/30) of subjects were considered an individual subject success.

XII. PANEL RECOMMENDATIONS

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.

XIII. CONCLUSIONS DRAWN FROM THE PRECLINICAL AND CLINICAL STUDIES

The valid scientific evidence presented in the preceding sections provides reasonable assurance that the M6-C™ Artificial Cervical Disc is a safe and effective disc replacement in skeletally mature patients for reconstruction of the disc from C3-C7 following discectomy at one level for treatment of intractable radiculopathy defined as discogenic neck and/or arm pain and demonstrated by signs and/or symptoms (numbness, weakness, changes in deep tendon reflexes) due to disc herniation and/or osteophyte formation and is confirmed by patient history and radiographic imaging (CT, MRI, x-rays).

A. Effectiveness Conclusions

Two hundred fifty-eight (258) subjects were consented under the M6-C™ Artificial Cervical Disc IDE study. Twenty-six (26) subjects were withdrawn prior to surgery resulting in 232 subjects treated, comprising 160 M6-C™ and 72 ACDF subjects. The historical control population resulted in an additional 192 available control subjects. The 424 available subjects (160 M6-C™, 72 concurrent ACDF, and 192 historical control ACDF subjects) were assessed via the PS subclassification process. Of these subjects, 160 M6-C™ and 189 ACDF controls were PS selected. Analysis of subject demographic and baseline data showed no meaningful differences between the treatment groups. Mean surgery time was on average 45.7 minutes longer for the control ACDF group than for the M6-C™ group.

Overall success was defined in the study protocol as:

- No serious adverse event(s) classified as device or device procedure related (as determined by the Clinical Events Committee), and
- No supplemental surgical procedure at the index level (including revision, removal, reoperation, or supplemental fixation), and
- Maintenance or improvement in neurological function compared to baseline, and
- Improvement of the NDI of at least 15 points (on a 100-point scale).

The overall success rate for the protocol specified primary endpoint for the M6-C™ subjects was 86.8% (132/152) at the Month 24 visit and 79.3% (130/164) in the ACDF subjects. Non-inferiority was statistically demonstrated from these data.

To assess the impact of subjects with unknown outcomes at 24 months or other potential biases, various sensitivity analyses were conducted. All components of overall success of the M6-C™ group are non-inferior to the control group. Additionally, subsequent surgical intervention and device/procedure-related adverse events rates are lower for the M6-C™ group compared to the control group rates.

Range of motion for the M6-C™ group was maintained through 24 months. Comparatively, the range of motion in the ACDF group decreased. This is expected when comparing a motion-preserving device (artificial cervical disc) versus a motion-eliminating device (fusion).

In conclusion, the study data indicate that, at 24 months postoperatively, the M6-C™ Artificial Cervical Disc is at least as effective as the control treatment (ACDF), for the patient population and indications studied in this investigation, in terms of overall success according to the protocol-specified primary endpoint.

B. Safety Conclusions

The risks of the M6-C™ Artificial Cervical Disc are based on non-clinical laboratory studies as well as data collected in the clinical study conducted to support PMA approval as described above.

Preclinical testing performed on the device demonstrated that the M6-C™ Artificial Cervical Disc is designed to withstand the expected physiologic loads in the cervical spine.

In the clinical study conducted to support PMA approval, the investigational M6-C™ Artificial Cervical Disc was found to have a reasonable assurance of safety and to be at least as safe as the control treatment. The safety assessment considers Adverse Event rates (AEs), Subsequent Surgical Interventions, and Neurological Success. Specifically, the observed adverse event rate for the M6-C™ group was 67.5% (108/160) compared with 83.1% (157/189) in the ACDF group, with a serious adverse event rate of 9.4% (15/160) in the M6-C™ group and 14.8% (28/198) in the ACDF group. The rate of subsequent surgical intervention for the M6-C™ group through the most current data lock was lower than the control group with 3/160 (1.9%) M6-C™ subjects requiring subsequent surgical interventions at the treated level compared to 9/189 (4.8%) control subjects. The neurological success rate for the M6-C™ group was 93.3% (140/150) and 87.2% (143/164) for the control group. There were no M6-C™ device failures (e.g., disassembly, breakage).

In conclusion, the safety profile of the M6-C™ Artificial Cervical Disc demonstrates that the device has a reasonable assurance of safety. The study results indicate that the M6-C™ Artificial Cervical Disc is at least as safe as the ACDF control in regards to adverse event rates, neurologic status, and need for subsequent surgical intervention.

C. Benefit-Risk Determination

The probable benefits of the M6-C™ Artificial Cervical Disc 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 M6-C™ Artificial Cervical Disc at a single cervical level over the 24-month time period studied.

- The benefit of the M6-C™ Artificial Cervical Disc in terms of clinically meaningful improvement in function (as measured by an improvement in NDI of at least 15 points) at 24 months postoperatively was comparable to the standard of care, ACDF. The majority of subjects in both treatment groups in the clinical study experienced this benefit: 90.5% (133/147) of M6-C™ subjects and 85.1% (131/154) of ACDF subjects.

- The benefit of the M6-C™ Artificial Cervical Disc in terms of maintenance or improvement in neurologic status (as measured during the neurological examination done by the investigator) at 24 months postoperatively was similar for the M6-C™ subjects compared to the standard of care, ACDF. The majority of subjects in both treatment groups in the clinical study experienced this benefit: 99.3% (140/150) of M6-C™ subjects and 87.5% (126/144) of ACDF subjects.

- In terms of improvement in neck pain (as measured by a 2.0 cm improvement in pain on a Visual Analog Scale as compared to baseline), at 24 months postoperatively, M6-C™ subjects demonstrated a statistically significant difference relative to the standard of care, ACDF: (91.2% (133/147) of M6-C™ subjects and 77.9% (131/154) of ACDF subjects with neck pain improvement at 24 months). Similar percentages of subjects in both treatment groups in the clinical study experienced the benefit of improvement in shoulder/arm pain (90.5% (133/147) of M6-C™ subjects and 79.9% (123/154) of ACDF subjects with shoulder/arm pain (worse side) improvement at 24 months).

- In terms of pain medication usage at 24 months postoperatively, M6-C™ subjects demonstrated a lower rate of pain medication use compared to the standard of care, ACDF subjects (14.0% (21/150) of M6-C™ subjects and 38.2% (68/178) of ACDF subjects with any pain medication use at 24 months). Also, at 24 months, M6-C™ subjects demonstrated a lower rate of opioid pain medication use compared to ACDF subjects (2.0% (3/150) of M6-C™ subjects and 15.2% (27/178) of ACDF subjects with any opioid pain medication use at 24 months).

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. At the 24-month time-point, higher rates of any adverse event, any serious adverse event, and device related adverse events occurred in the ACDF group. At the same time-point, a higher rate of procedure-related adverse events occurred in the M6-C™ group. In addition, there were fewer subsequent surgeries at the index level in the M6-C™ group compared to the ACDF control group. With respect to subsequent surgical interventions, 3/160 (1.9%) M6-C™ subjects and 9/189 (4.8%) control subjects reported subsequent surgical interventions qualifying as study failures (i.e., at the index level) through 24 months.

Additional factors that were considered in determining the probable benefits and risks for the M6-C™ Artificial Cervical Disc included limitations of the clinical study design, including the inability to mask subjects to their treatment assignment, reliance on subjective endpoints, and subjectivity in adverse event classification. The use of a control that combined concurrent

subjects with historical control subjects introduced some uncertainty, as some differences existed in endpoint definitions. This uncertainty was reduced by the availability of patient level data for the historical control.

Sensitivity analyses were performed to address the missing data and to demonstrate the generalizability of the study results. These sensitivity analyses support the robustness of the non-inferiority result with respect to missing data and demonstrate that the results are generalizable to the overall population studied.

There are additional theoretical benefits of cervical total disc replacement devices, such as the M6-C™ Artificial Cervical Disc, which include preservation of range of motion and decreased risk of adjacent segment degeneration. However, the clinical study conducted to support PMA approval of M6-C™ Artificial Cervical Disc did not study these potential benefits. Study of these benefits will be the subject of Post Approval Study.

Specific information on patient perspectives for this device was not directly measured. However, the subjects' perception of their benefit and risk was indirectly measured through a questionnaire. At 24 months following the index procedure, 93.3% (140/150) of M6-C™ and 95.1% (154/162) of control subjects reported that they would have the surgery again.

In conclusion, given the available information above, the data support that, for reconstruction of the disc at a single level from C3-C7 following discectomy for intractable radiculopathy defined as discogenic neck and/or arm pain demonstrated by signs and/or symptoms (numbness, weakness, changes in deep tendon reflexes) due to disc herniation and/or osteophyte formation and confirmed by subject history and specific radiographic findings as outlined above in the Indications for Use, the probable benefits of the M6-C™ Artificial Cervical Disc outweigh the probable risks through two years follow-up.

D. Overall Conclusions

The preclinical and clinical data in this application support the reasonable assurance of safety and effectiveness of the M6-C™ Artificial Cervical Disc when used in accordance with the indications for use. Based on the clinical study results, it is reasonable to conclude that the clinical benefits of the use of the M6-C™ Artificial Cervical Disc in terms of improvement in pain and disability, and the potential for motion preservation, outweigh the risks, both in terms of the risks associated with the M6-C™ Artificial Cervical Disc and surgical procedure when used in the indicated population in accordance with the directions for use, and as compared to the ACDF control treatment in the same indicated population.

XIV. CDRH DECISION

CDRH issued an approval order on February 6, 2019. The final conditions of the approval cited in the approval order are described below.

1. *M6-C™ Artificial Cervical Disc – Extended Follow-up:* The primary study objective is to evaluate the overall success at 10-years. This study will consist of extended prospective follow-up of the premarket cohort for 10-years post-implantation to evaluate the long-term safety and effectiveness of the M6-C™ Artificial Cervical Disc. The study will follow all

available M6-C™ and ACDF patients from the pivotal investigational device study. The annual visits will include the collection of the following data: work status, medication usage, neurological assessment, Neck Disability Index (NDI), neck and arm pain Visual Analog Scale (VAS), SF-36 questionnaires, patient satisfaction surveys, Odom's Criteria, and radiographic assessments (AP & Lateral, Flexion/Extension, and Lateral Bending). In addition, adverse event data, subsequent surgical intervention data, radiographic and clinical data on adjacent level surgeries, and adjacent level range of motion on flexion/extension films will be collected.

FDA will expect 85% follow-up at 10-years to provide sufficient data to evaluate safety and effectiveness.

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

XV. 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 Labeling.

Post Approval Requirements and Restrictions: See approval order.