SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Artificial Cervical Disc
Device Trade Name:	SECURE®-C Cervical Artificial Disc
Device Procode:	MJO
Applicant's Name and Address:	Globus Medical, Inc. Valley Forge Business Center 2560 General Armistead Ave. Audubon, PA 19403
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P100003
Date of FDA Notice of Approval:	September 28, 2012
Expedited:	Not Applicable

II. INDICATIONS FOR USE

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

III. CONTRAINDICATIONS

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

- Active systemic infection or localized infection at the surgical site
- Osteoporosis or osteopenia defined as a DEXA bone mineral density T-score ≤ -1
- Allergy or sensitivity to cobalt, chromium, molybdenum, titanium or polyethylene
- Marked cervical instability on neutral resting lateral or flexion/extension radiographs; translation >3mm and/or >11° rotational difference from that of either adjacent level

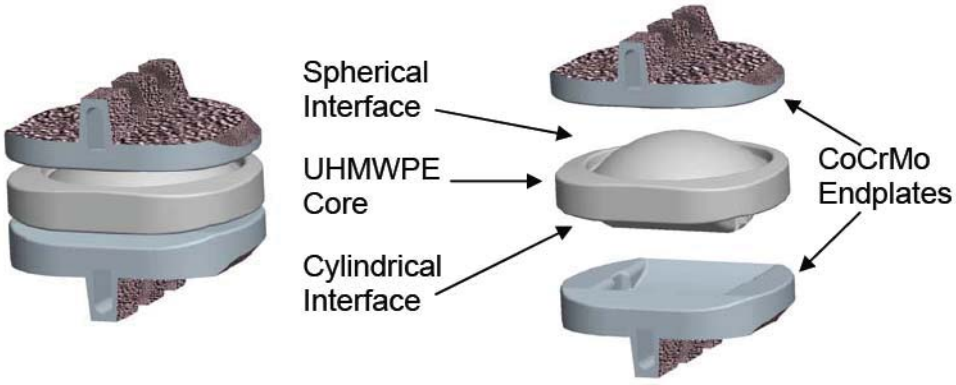
- Severe spondylosis at the level to be treated, characterized by bridging osteophytes, loss of disc height >50%, an absence of motion (<2°) as this may lead to a limited range of motion and may encourage bone formation (e.g. heterotopic ossification, fusion)
- Severe facet joint arthropathy
- Significant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

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the SECURE®-C Cervical Artificial Disc labeling.

V. DEVICE DESCRIPTION

The SECURE®-C Cervical Artificial Disc (SECURE®-C) is an articulating intervertebral device comprised of two endplates and a central core, and is inserted using an anterior cervical approach. The superior and inferior cobalt-chrome alloy (CoCrMo per ISO 5832-12, ASTM F1537) endplates feature multiple serrated keels and a commercially pure titanium plasma spray coating (per ISO 5832-2, ASTM F1580, F1978, F1147, and C-633) on the bone contacting surfaces. The sliding core is composed of ultra-high molecular weight polyethylene (UHMWPE per ISO 5834-2, ASTM F648), with a spherical superior interface and a cylindrical inferior interface articulating with the endplates.



SECURE®-C implants are offered in a variety of configurations to accommodate varied patient anatomy. Implant footprints are as follows (AP depth x ML width): 11x12mm, 13x14mm, and 14x16mm. SECURE®-C provides 0° or 6° lordosis options in its neutral position. Implant heights range from 7mm to 12mm, in 1mm increments. A list of SECURE®-C implants is provided in Table 1.

The SECURE®-C Cervical Artificial Disc is designed to allow motion in flexion and extension up to 30° (±15°), and in lateral bending to 20° (±10°). The design is intended to allow unlimited axial rotation, and is constrained by ligaments and posterior elements. The device is also designed to permit translation of ±1.25mm in the sagittal plane.

Table 1. SECURE®-C Cervical Artificial Disc Implants

Part Number	Description
414.107S	SECURE®-C Core, 11x12, 7mm
414.108S	SECURE®-C Core, 11x12, 8mm
414.109S	SECURE®-C Core, 11x12, 9mm
414.110S	SECURE®-C Core, 11x12, 10mm
414.111S	SECURE®-C Core, 11x12, 11mm
414.112S	SECURE®-C Core, 11x12, 12mm
414.207S	SECURE®-C Core, 13x14, 7mm
414.208S	SECURE®-C Core, 13x14, 8mm
414.209S	SECURE®-C Core, 13x14, 9mm
414.210S	SECURE®-C Core, 13x14, 10mm
414.211S	SECURE®-C Core, 13x14, 11mm
414.212S	SECURE®-C Core, 13x14, 12mm
414.307S	SECURE®-C Core, 14x16, 7mm
414.308S	SECURE®-C Core, 14x16, 8mm
414.309S	SECURE®-C Core, 14x16, 9mm
414.310S	SECURE®-C Core, 14x16, 10mm
414.311S	SECURE®-C Core, 14x16, 11mm
414.312S	SECURE®-C Core, 14x16, 12mm
714.100S	SECURE®-C Endplate Assembly, 11x12, 0°
714.106S	SECURE®-C Endplate Assembly, 11x12, 6°
714.200S	SECURE®-C Endplate Assembly, 13x14, 0°
714.206S	SECURE®-C Endplate Assembly, 13x14, 6°
714.300S	SECURE®-C Endplate Assembly, 14x16, 0°
714.306S	SECURE®-C Endplate Assembly, 14x16, 6°

SECURE®-C devices are implanted using instruments specific to the device, as well as manual surgical instruments. Instruments specifically designed for implanting SECURE®-C consist of trials, milling guides, broaching chisels, keel chisels, a chisel endcap, an implant holding block, implant holders, and endplate positioners. Manual surgical instruments include instruments for cervical distraction, discectomy preparation, and milling.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

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

- Nonoperative alternative treatments include, but are not limited to, physical therapy, medications, braces, chiropractic care, bed rest, spinal injections, or exercise programs.
- Surgical alternatives include, but are not limited to, surgical decompression and/or fusion using various bone grafting techniques or interbody fusion devices, which may be used in conjunction with anterior cervical plating (e.g., plate and screws), or posterior spinal systems (e.g., rods, hooks, wires). Anterior cervical discectomy and fusion (ACDF) with an

interbody graft or spacer is the most commonly used method for decompression and fusion. Intractable radiculopathy or myelopathy due to a single-level abnormality localized to the disc space may also be treated surgically using another FDA approved artificial cervical disc.

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

VII. MARKETING HISTORY

The SECURE®-C Cervical Artificial Disc has been commercially available outside of the United States since 2006. The device is available in the United Kingdom, Belgium, Germany, and India, and has not been withdrawn from the market for any reason.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the SECURE®-C Cervical Artificial Disc identified from the SECURE®-C Cervical Artificial Disc clinical study results, approved device labeling for other cervical total disc replacement devices, and published scientific literature including: (1) those associated with any surgical procedure; (2) those associated with anterior cervical spine surgery; and (3) those associated with a cervical artificial disc device, including the SECURE®-C Cervical Artificial 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.

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

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

3. Risks associated with a cervical artificial disc device, including the SECURE®-C Cervical Artificial Disc, include: early or late loosening of the components; disassembly; bending or breakage of any or all of the components; implant migration; implant malpositioning; implant

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

For the specific adverse events that occurred in the clinical study of the SECURE®-C Cervical Artificial Disc, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

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

Laboratory Studies
- Static Axial Compression
- Dynamic Axial Compression
- Static Compression-Shear
- Dynamic Compression-Shear
- Creep and Stress Relaxation
- Device Pushout
- Core Expulsion
- Subsidence
- Durability/Wear Testing

Animal Studies
- Particulate Animal Study

Additional Studies
- Sterilization Validation
- Shelf Life and Packaging Validation
- Biocompatibility

A. Laboratory Studies

Table 2. Summary of Laboratory Studies

Test Name	Purpose	Method	Acceptance Criteria	Results
Static Axial Compression	To evaluate the performance of the SECURE®-C device under static axial compressive loading, under worst case conditions.	Five (5) SECURE®-C specimens were tested under static compression in ambient air at a rate of 10mm/min until failure.	Yield load must be greater than the maximum compressive load that a cervical intervertebral disc can withstand (75N[1]).	The average 2% offset yield load was 1,677N ±129N, with an average displacement of 0.35mm ±0.1mm. SECURE®-C can withstand compressive loading that exceeds the anticipated physiologic loads on the cervical spine.
Dynamic Axial Compression	To evaluate the performance of the SECURE®-C device under dynamic axial compressive loading, under worst case conditions.	Two (2) SECURE®-C specimens were tested under dynamic compression in ambient air to 10 million cycles, using a sinusoidal wave form with R=10 at 10Hz.	Fatigue load must be greater than the maximum compressive load that a cervical intervertebral disc can withstand (75N[1]).	Both specimens ran out to 10 million cycles under a 150N load. These results suggest that the SECURE®-C device can withstand dynamic compressive loading that exceeds the anticipated physiologic loads on the cervical spine.
Static Compression-Shear	To evaluate the performance of the SECURE®-C device under static compression-shear, under worst case conditions.	Five (5) SECURE®-C specimens were tested under static compression-shear (45° angle) in ambient air at a rate of 10mm/min until failure.	Given that the shear failure load of the cervical intervertebral disc is 20N[1], the yield load must be greater than the vertical component of shear loading, 28N (20N/cos45).	The average 2% offset yield load was 494N ±73N, with an average displacement of 0.93mm ±0.22mm. These results suggest that the SECURE®-C can withstand compressive-shear loading that exceeds the anticipated physiologic loads on the cervical spine.
Dynamic Compression-Shear	To evaluate the performance of the SECURE®-C device under dynamic compressive-shear loading, under worst case	Two (2) SECURE®-C specimens were tested under dynamic compression shear in ambient air to 10 million cycles, using a sinusoidal wave form with R=10 at	Given that the shear failure load of the cervical intervertebral disc is 20N[1], the yield load must be greater than the vertical	Both specimens ran out to 10 million cycles under a 106N load. These results suggest that the SECURE®-C device can withstand dynamic compressive-shear loading that

Test Name	Purpose	Method	Acceptance Criteria	Results
	conditions.	10Hz.	component of shear loading, 28N (20N/cos45).	exceeds the anticipated physiologic loads on the cervical spine.
Creep and Stress Relaxation	To evaluate the creep and stress relaxation characteristics of the SECURE®-C device, under worst case conditions.	Five (5) SECURE®-C specimens were tested under static compression in physiologic saline solution. Alternating static and dynamic axial loading was applied, with three progressive dynamic loads applied at 1 Hz over a 36 hour period.	The average residual deformation must be less than the 1.5mm normal diurnal disc height change[2].	The average residual deformation following creep and stress relaxation was 0.195mm. These results suggest that the SECURE®-C device exhibits creep behavior that is less than normal anticipated physiologic conditions in the cervical spine.
Device Pushout	To evaluate the loads required to expulse the SECURE®-C device from the intervertebral disc space, under worst case conditions.	Five (5) SECURE®-C specimens were inserted into rigid polyurethane foam blocks, simulating bone, under a 50N pre-load, and tested to determine the amount of force required to displace the device by 3mm. Pushout load was applied at a rate of 10mm/min in ambient air.	Pushout load is greater than the shear failure load of the cervical intervertebral disc (20N[1]).	The average pushout load was 289N ±101N. These results suggest that the SECURE®-C device can resist pushout forces that exceed the anticipated physiologic loads on the cervical spine.
Core Expulsion	To evaluate the loads required to expulse the SECURE®-C core from the endplates, under worst case conditions.	Five (5) SECURE®-C specimens were pre-loaded with 50N and tested to determine the amount of force required to displace the core from the endplates by at least 3mm. Pushout load was applied at a rate of 10mm/min in ambient air.	Pushout load must be greater than the shear failure load of the cervical intervertebral disc (20N[1]).	The average pushout load was 488N ±27N. These results suggest that the SECURE®-C core can resist pushout forces that exceed the anticipated physiologic loads on the cervical spine.

Test Name	Purpose	Method	Acceptance Criteria	Results
Subsidence	To evaluate the SECURE®-C implant's resistance to subsidence into the vertebral endplate, under worst case conditions.	Five (5) SECURE®-C specimens were inserted into rigid polyurethane blocks simulating vertebral bone and loaded in compression to determine the amount of displacement resulting from a clinically relevant 150N load (2 x 75N). Compressive load was applied at a rate of 10mm/min in ambient air.	Subsidence at twice the maximum compressive load that a cervical intervertebral disc can withstand (2x75N[1]) should be less than the thickness of the endplate (minimum 0.65mm[3])	The average subsidence at 150N was 0.242mm ±0.156mm. These results suggest that the SECURE®-C device resists subsidence into the vertebral endplates.
Durability/ Wear Testing	To determine the wear and durability characteristics of the SECURE®-C device under complex physiologic loading and worst case conditions.	Six (6) SECURE®-C specimens were tested under physiologic conditions for 10 million cycles of complex loading at a frequency of 2Hz using combined flexion/extension (±7°), lateral bending (±7°), and axial rotation (±1.5°). An additional six specimens were tested with increased axial rotation (±6°). All specimens were subjected to a 150N constant compressive load for 10 million cycles. Specimens were placed in a calf serum and deionized water solution with EDTA, maintained at 37°C. Specimens were weighed and the solution was collected at each 1 million cycles.	The amount of wear debris should be similar to that reported for other cervical devices (2.59 ±0.36 mg per million cycles).	The average weight loss over the 10 million cycles was 2.57 mg ±1.21 mg per million cycles for the original testing. For the second round of testing, the average weight loss was 0.89 mg ±0.3 mg per million cycles. These results suggest that the SECURE®-C device demonstrates wear rates similar to that of other cervical devices.

[1, 2, 3] See Section XV References

Note that during the course of the clinical trial, the endplate keels were modified slightly for ease of manufacture and for clearer demarcation of the keel boundaries for radiographic imaging. The outer dimensions and profile of the keels were not changed. There were no observed migrations of the original design or other difficulties encountered during the IDE study. Specifically, the modification was not the result of any clinical problems, safety issues or adverse events, product complaints, or surgeon requests from within or outside the United States. As this modification was minor, it did not affect the mechanical behavior of the device or the anticipated clinical outcome.

Original Design

New Design

B. Animal Studies

Table 3. Summary of Animal Studies

Test Name	Purpose	Method	Acceptance Criteria	Results
Particulate Debris Animal Study	To evaluate the local and systemic effect of UHMWPE particles implanted into the epidural space of New Zealand white rabbits.	The animals were injected with either 1 million particles, 10 million particles, or control saline, mixed with contrast media, into the epidural space. Animals were sacrificed at 3 months and 6 months. There were six animals per group, for a total of 36 animals. Gross anatomic, histopathologic and systemic analyses were used to assess neurotoxicity, systemic toxicity, and local effects of the debris. Tissues were evaluated using irritant ranking scores.	There should be no evidence of neurotoxicity, systemic toxicity, or local effects associated with the UHMWPE particulate debris, based on histopathologic assessment. Irritant ranking scores < 2.9 indicate that the test material is a non-irritant.	There was no evidence of neurotoxicity, systemic toxicity, or local effects associated with the UHMWPE particulate debris for either the 3 month or 6 month animals. Microscopic evaluation of tissues surrounding the particles (muscle, vertebral segments, lymph nodes) and organs did not reveal any remaining wear debris or local or system lesions that could be attributed to wear debris. Both the low and high dose particulate spinal injections were determined to be non-irritants (Irritant ranking scores <2.9).

C. Additional Studies

Sterilization Validation
Sterilization validation according to ANSI/AAMI/ISO 11137-2:2006 was conducted to confirm that the sterility of the device is maintained through a sterile barrier.

Shelf Life and Packaging Validation
Shelf life and packaging validation studies, including packaging seal and integrity, accelerated aging, and real-time aging testing, were conducted to demonstrate that the device packaging can maintain a sterile barrier, with a shelf life of 5 years.

Biocompatibility
The materials used in the SECURE®-C Cervical Artificial Disc are standard materials used in permanently implanted orthopaedic implants, including cobalt-chrome alloy (CoCrMo per ISO 5832-12, ASTM F1537), commercially pure titanium plasma spray coating (per ISO 5832-2, ASTM F1580, F1978, F1147, and C-633), and ultra-high molecular weight polyethylene (UHMWPE per ISO 5834-2, ASTM F648).

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of reconstruction of the disc at one level from C3-C7 following single-level discectomy with the SECURE®-C Cervical Artificial Disc for intractable radiculopathy or myelopathy due to a single-level abnormality localized to the disc space in the United States under IDE #G050075. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between July 7, 2005 and April 25, 2008. The database for this PMA reflected data collected through January 31, 2011 and included 380 patients. There were 18 investigational sites.

The study was a prospective, multi-center, two-arm, randomized (1:1), unmasked, concurrently controlled, non-inferiority clinical study to compare the safety and effectiveness of the SECURE®-C Cervical Artificial Disc to the standard of care (a legally marketed alternative with similar indications for use), anterior cervical discectomy and fusion (ACDF) using a plate (ASSURE® Anterior Cervical Plate System) and structural allograft in treating patients with intractable symptomatic cervical disc disease (SCDD) at one level between C3 and C7. The first five subjects enrolled at each center were non-randomized subjects receiving the SECURE®-C Cervical Artificial Disc in order for the staff to become familiar with the implantation procedure for the device.

Both the investigator and the patient were to be blinded to the randomization until immediately prior to surgery. Immediately before surgery, preferably while the patient was under anesthesia, the investigator or designee opened the treatment assignment envelope corresponding to the patient's clinical trial number. After assigning treatment, the

investigator was not blinded to the treatment. Data on whether a randomized patient was blinded was not captured on any case report form. Surgeons were instructed as to blinding the patient to their treatment prior to surgery. The applicant is not aware of any randomized patient who was unblinded to their treatment.

Patients were evaluated preoperatively, intraoperatively, immediately postoperatively and then at 6 weeks, 3 months, 6 months, 12 months and 24 months and annually thereafter. The recommended postoperative care included use of an external orthosis for 3 weeks postoperatively, followed by a physical therapy program for active range of motion exercises. Patients were instructed to avoid lifting above their shoulders for 3 months, and to avoid athletic activities and repetitive bending or lifting for 6 months. Smokers were encouraged not to smoke. Patients were not treated with NSAIDs postoperatively in either treatment group.

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

The study was designed as a non-inferiority trial with a margin (delta) of 15%. Bayesian statistical methods were used to obtain the posterior probabilities of non-inferiority and superiority, using a delta of 15%. Additional analyses using a delta of 10% as requested by FDA were also incorporated. The Bayesian model incorporated postoperative data from the 24 month time point and also the 6 month and 12 month time points for purposes of imputing incomplete or missing data. The protocol specified a sample size of 140 randomized patients per group based on an assumed 70% success rate in both treatment groups, a 20% drop out rate, and 80% power for a one-sided 0.05 significance level. With the addition of up to 5 non-randomized patients per site, the total planned sample size was 380 (100 non-randomized SECURE®-C, 140 randomized SECURE®-C, 140 ACDF).

1. Clinical Inclusion and Exclusion Criteria
   Enrollment in the SECURE®-C study was limited to patients who met the following inclusion criteria.
   - Symptomatic cervical disc disease (SCDD) in one vertebral level between C3-C7, defined as neck or arm (radicular) pain, or functional or neurological deficit and radiographic confirmation (by CT, MRI, X-ray, etc.) of any of the following:
     - Herniated nucleus pulposus;
     - Radiculopathy or myelopathy;
     - Spondylosis (defined by the presence of osteophytes); or
     - Loss of disc height.
   - Age between 18 and 60 years
   - Failed at least 6 weeks of conservative treatment
   - Neck Disability Index (NDI) Questionnaire score of at least 30 (as percentage of 50 point total)

- Able to understand and sign informed consent form
- Psychosocially, mentally and physically able to fully comply with this protocol including adhering to follow-up schedule and filling out forms
- Able to meet the proposed follow-up schedule at 6 weeks, 3 months, 6 months, 12 months and 24 months
- Able to follow postoperative management program

Patients were not permitted to enroll in the SECURE®-C study if they met any of the following exclusion criteria.

- More than one vertebral level requiring treatment
- Prior fusion surgery adjacent to the vertebral level being treated
- Prior surgery at the level to be treated
- Clinically compromised vertebral bodies at the affected level(s) due to current or past trauma
- Radiographic confirmation of facet joint disease or degeneration, defined as apparent sclerosis and/or hypertrophy of the facets demonstrated on AP radiographs as a disruption of the normally smooth facet curve
- Marked cervical instability on resting lateral or flexion/extension radiographs:
  - Translation greater than 3mm, and/or
  - More than 11° of rotational difference from that of either adjacent level.
- Severe spondylosis at the level to be treated as characterized by any of the following:
  - Bridging osteophytes;
  - A loss of disc height greater than 50%; or
  - Absence of motion (<2°)
- Neck or arm pain of unknown etiology
- Osteoporosis, osteopenia, Paget's disease, osteomalacia or any other metabolic bone disease
- Pregnant or interested in becoming pregnant in the next 2 years
- Active systemic or local infection
- Known allergy to titanium, polyethylene, cobalt, chromium or molybdenum
- Taking medications or any drug known to potentially interfere with bone/soft tissue healing (e.g., steroids)
- Rheumatoid arthritis or other autoimmune disease
- Systemic disease including AIDS, HIV, Hepatitis
- Active malignancy: A patient with a history of any invasive malignancy (except non-melanoma skin cancer), unless he/she has been treated with curative intent and there has been no clinical signs or symptoms of the malignancy for at least 5 years
- Neuromuscular disorders such as muscular dystrophy, spinal muscular atrophy, amyotrophic lateral sclerosis, etc.
- Acute mental illness or substance abuse
- Use of bone growth stimulator within past 30 days
- Participation in other investigational device or drug clinical trials within 30 days of surgery
- Prisoners

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 6 weeks (±2 weeks), 3 months (±2 weeks), 6 months (±1 month), 12 months (±2 months), 24 months (±2 months), and annually thereafter (±2 months). The following parameters were measured:

Table 4. Clinical Evaluation Schedule

Evaluation	Pre-op	Surgery/ Hospital Discharge	6 wks	3 mo	6 mo	12 mo	24 mo & annually
Neck Disability Index	X		X	X	X	X	X
Neck and Arm Pain (VAS)	X		X	X	X	X	X
Health Status (SF-36)	X		X	X	X	X	X
Neurological Status	X				X	X	X
Adverse Events*	X	X	X	X	X	X	X
Demographic/Baseline Data	X						
Operative Data		X					
Medication Use	X				X	X	X
Imaging Studies:							
AP & lateral	X	X	X	X	X	X	X
Lateral flex/extension	X				X	X	X
CT and/or MRI	X						
Radiographic Outcomes:							
Range of motion	X				X	X	X
Disc height	X				X	X	X
Device migration			X	X	X	X	X
Fusion status					X	X	X
Radiolucency					X	X	X
Patient Satisfaction						X	X

*Adverse events and complications were recorded at all visits (both scheduled and unscheduled).

3. Clinical Endpoints

The safety of the SECURE®-C was assessed by comparing the nature and frequency of adverse events (overall and in terms of severity and relationship to the device and/or procedure) and secondary surgical procedures as well as maintenance or improvement in neurological status to the ACDF control group.

The effectiveness of the SECURE®-C was assessed by evaluating 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 36 questionnaire (SF-36) as well as patient satisfaction compared to the ACDF control group.

In addition, several radiographic endpoints were considered in evaluating both safety and effectiveness, including range of motion, disc height, device displacement or migration, radiolucency, spinal fusion status, and heterotopic ossification.

Per the protocol, an individual patient was considered a success if the following criteria were met at 24 months:

- Pain/disability improvement of at least 25% in NDI compared to baseline;
- No device failures requiring revision, removal, reoperation, or supplemental fixation;
- Absence of major complications defined as major vessel injury, neurological damage, or nerve injury; and
- For control fusion patients only, radiographic fusion, as defined by the presence of bridging trabecular bone, without evidence of pseudarthrosis (defined radiographically as no apparent bridging trabecular bone and range of motion >3mm in translation and >2° in rotation).

In addition, FDA requested an additional analysis in which an individual patient was considered a success if the following criteria were met at 24 months:

- Pain/disability improvement of at least 15 points in NDI compared to baseline;
- No secondary surgery at the index level including revision, removal, reoperation or supplemental fixation;
- No potentially device-related adverse events;
- Maintenance or improvement in all components of neurologic status; and
- No SECURE®-C intraoperative changes in treatment.

Overall study success criteria were based on a comparison of individual patient success rates, such that the patient success rate for the SECURE®-C investigational group must be non-inferior to that of the ACDF fusion control group. Bayesian statistical methods were used to obtain the posterior probabilities of non-inferiority and superiority. The IDE study was approved using a non-inferiority margin (delta) of 15% with an advisory that a non-inferiority margin of 10% would be required to demonstrate a reasonable assurance of the device's effectiveness. According to the statistical analysis plan, if non-inferiority was demonstrated, then superiority would be evaluated as defined more specifically in the analysis plan. Of note, the statistical analysis plan pre-specified that the analysis technique would involve predicting 24 month outcomes for those without them, based on interim 6 month and 12 month observed outcomes, and integrating over the predictions to obtain posterior probabilities of non-inferiority and superiority.

Secondary effectiveness evaluations specified in the protocol included comparisons of:

- Components of the primary
    - Pain/Disability Improvement (NDI)
    - No device failures requiring revision, re-operation or removal
    - Absence of major complications
- Neck Disability Index: 25% improvement from baseline
- VAS pain scales (neck, right, and left arm): 20mm improvement from baseline
- Health Status Survey SF-36 (mental and physical composite scores): 15% improvement from baseline
- Neurological status (maintenance, worsening, or improvement): proportion of patients maintained or improved
- Mean range of motion (angulation and translation)
- Disc height on standard lateral radiograph: 2mm changes compared to baseline
- No significant radiolucency for the SECURE®-C device: proportion of patients

- Spinal fusion in the control arm
- Patient satisfaction (definitely/mostly): proportion of patients
- Device displacement or migration (>3mm)
- Operative time
- Operative blood loss
- Return to work

B. Accountability of PMA Cohort

At the time of database lock, of the 380 patients enrolled in the PMA study, all had reached the 24 month post-operative visit and 331 (87.1%) had data available for analysis at the completion of the study. Complete primary endpoint data (including fusion status for control group patients) was available for 215 investigational (77 non-randomized, 138 randomized) and 98 control patients at 24 months. A total of 5 investigational (2 non-randomized and 3 randomized) and 10 control patients had failures at or prior to the 24 month visit. 36 month follow-up data was also provided in the PMA for some of the study patients. A summary of patient accountability data for the 12 month, 24 month, and 36 month follow-up visits is provided in Table 5, and a summary of data available at 24 months for each specific evaluation is provided in Table 6.

Table 5. Patient Accountability (based on treatment assignment*)

Number of Patients	12 Months (±2 Months)			24 Months (±2 Months)			36 Months (±2 Months)		
	NR SEC	R SEC	R ACDF	NR SEC	R SEC	R ACDF	NR SEC	R SEC	R ACDF
Enrolled	89	151	140	89	151	140	89	151	140
Theoretical	89	151	140	89	151	140	89	151	140
Deaths[1]	1	0	0	1	0	0	1	0	0
Failures[1]	1	1	6	2	3	10	2	4	11
Not yet overdue	0	0	0	0	0	0	1	15	8
Expected[2]	87	150	134	86	148	130	85	132	121
Actual, efficacy[3] (% Follow-up)	82 (94.3%)	140 (93.3%)	114 (85.1%)	77 (89.5%)	138 (93.2%)	98 (75.4%)	60 (70.6%)	60 (45.5%)	38 (31.4%)
Actual, efficacy in window[4] (% Follow-up)	81 (93.1%)	127 (84.7%)	99 (73.9%)	70 (81.4%)	110 (74.3%)	83 (63.8%)	38 (44.7%)	43 (32.6%)	26 (21.5%)
Actual, any data[5] (% Follow-up)	82 (94.3%)	140 (93.3%)	121 (90.3%)	78 (90.7%)	138 (93.2%)	115 (88.5%)	60 (70.6%)	60 (45.5%)	47 (38.8%)

NR SEC=Non-randomized SECURE®-C; R SEC=Randomized SECURE®-C; R ACDF=Control

*A total of 380 patients at 18 sites were enrolled and treated in the IDE clinical trial; 236 received SECURE®-C (88 non-randomized, 148 randomized) and 144 received control treatment. Four patients intended to be treated with SECURE®-C (1 non-randomized and 3 randomized) were intraoperatively treated with ACDF; 1 was due to a randomization error by the site, 1 was due to inability to visualize the disc space due to the patient's large shoulders, and 2 were due to small patient anatomy.

1 Deaths and failures are cumulative

2 Theoretical patients minus the number of deaths, failures, and not yet overdue

3 Patients with complete efficacy data

4 Patients with complete efficacy data within the specified visit window

5 Patients with any information recorded at the visit

Table 6. 24 Month Data Accounting

Parameter	NR SEC	R SEC	R ACDF
Intended to be implanted	89	151	140
Expected* (As-randomized)	86	148	131
Implanted	88	148	144
Expected† (As-treated)	85	145	133
NDI	78 (90.7%)	139 (93.9%)	116 (88.5%)
VAS Neck and Arm Pain‡	75 (87.2%)	133 (89.9%)	108 (82.4%)
SF-36	78 (90.7%)	138 (93.2%)	115 (87.8%)
Patient Survey	78 (90.7%)	139 (93.9%)	116 (88.5%)
Neurological Exam†	75 (88.2%)	123 (84.8%)	101 (75.9%)
Radiologic Assessments†			
• Disc height	• 74 (87.1%)	• 119 (82.1%)	• 99 (74.4%)
• Change in disc height	• 71 (83.5%)	• 118 (81.4%)	• 95 (71.4%)
• Radiolucency	• 75 (88.2%)	• 122 (84.1%)	• 104 (78.2%)
• Migration	• 75 (88.2%)	• 122 (84.1%)	• N/A
• ROM	• 75 (88.2%)	• 120 (82.8%)	• 101 (75.9%)
• Change in ROM from baseline	• 67 (78.8%)	• 113 (77.9%)	• 91 (68.4%)
• Translation	• 74 (87.1%)	• 120 (82.8%)	• 99 (74.4%)
• Change in translation from baseline	• 67 (78.8%)	• 113 (77.9%)	• 90 (67.7%)

NR SEC=Non-randomized SECURE®-C; R SEC=Randomized SECURE®-C; R ACDF=Control
*3 randomized SECURE®-C subjects and 1 non-randomized SECURE®-C subject are included in their respective SECURE®-C group, but actually received ACDF. Expected is intended minus failures and deaths.
† Neurologic and radiographic data are reported for subjects as-treated . Expected is treated minus failures/deaths.
‡Per FDA, VAS data excludes one site in which some scores were reported verbally.

In the tables that follow throughout this summary, the as-treated population is used for safety analyses (88 non-randomized SECURE®-C, 148 randomized SECURE®-C, 144 ACDF) and the as-randomized population is used for efficacy analyses (89 non-randomized SECURE®-C, 151 randomized SECURE®-C, 140 ACDF). Statistical comparisons for efficacy are made between randomized groups, for patients as they were intended to be treated, referred to as the "As-Randomized" population. Safety comparisons such as adverse events and radiographic measurements are made between randomized groups, for patients as they were actually treated, referred to as the "As-Treated" population.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a cervical artificial disc study conducted in the US. Demographic data and preoperative evaluations for all patients enrolled and treated in the study are included in Table 7 and Table 8. Bayesian Credible Intervals (BCIs) for the difference (SECURE®-C – ACDF) between the randomized groups are presented.

Table 7. Patient Demographics and Baseline Characteristics

Demographic Measure	Non-Randomized SECURE-C (N=89)	Randomized SECURE-C (N=151)	Randomized ACDF (N=140)	95% BCI (Randomized Groups)
Gender Male Female	 47 (52.8%) 42 (47.2%)	 81 (53.6%) 70 (46.4%)	 68 (48.6%) 72 (51.4%)	(-6.4%, 16.3%)
Age (years)	41.6 ±8.13 Range: 20 - 60	43.4 ±7.50 Range: 24 - 60	44.4 ±7.86 Range: 25 - 59	(-2.7, 0.8)
Race Caucasian Black Asian Hispanic Other	 79 (88.8%) 6 (6.7%) 0 2 (2.2%) 2 (2.2%)	 136 (90.1%) 10 (6.6%) 0 2 (1.3%) 3 (2.0%)	 126 (90.0%) 10 (7.1%) 0 3 (2.1%) 1 (0.7%)	(-6.8%, 7.2%)*
Height (in)	67.3 ±4.03 Range: 59 - 76	68.1 ±3.68 Range: 60 - 76	67.3 ±4.07 Range: 60 - 77	(-0.1, 1.7)
Weight (lbs)	181.6 ±46.05 Range: 110 - 330	191.6 ±45.87 Range: 104 - 365	187.1 ±40.32 Range: 107 - 320	(-5.5, 14.4)
BMI (kg/m^2)	27.9 ±5.36 Range: 19 - 43	28.9 ±5.53 Range: 18 - 48	29.0 ±5.47 Range: 20 - 45	(-1.4, 1.2)
Current tobacco use (yes)**	21 (23.6%)	51 (33.8%)	53 (37.9%)	(-14.9%, 6.9%)
Symptom duration (mo)	25.4 ±44 Range: 1 – 304	16.6 ±27 Range: 0 – 189	19.8 ±40 Range: 0 – 272	(-11.2, 4.7)
History non-op care (yes) • Narcotics use • Injections • Physical therapy • Brace • Chiropractic • Other	85 (95.5%) • 63 (70.8%) • 47 (52.8%) • 53 (59.6%) • 13 (14.6%) • 20 (22.5%) • 13 (14.6%)	147 (97.4%) • 108 (71.5%) • 57 (37.7%) • 85 (56.3%) • 12 (7.9%) • 35 (23.2%) • 44 (29.1%)	138 (98.6%) • 104 (74.3%) • 62 (44.3%) • 77 (55.0%) • 14 (10.0%) • 44 (31.4%) • 37 (26.4%)	(-5.0%, 2.5%)
History prior surgery (yes) • Discectomy • Other	4 (4.5%) • 0 • 4 (4.5%)	2 (1.3%) • 0 • 2 (1.3%)	4 (2.9%) • 2 (1.4%) • 3 (2.1%)	(-5.6%, 2.1%)
Medication use in prior week for neck/arm pain (yes) • Non-narcotics • Weak narcotics • Strong narcotics • Muscle relaxants	 • 63 (70.8%) • 41 (46.1%) • 25 (28.1%) • 33 (37.1%)	 • 109 (72.2%) • 71 (47.0%) • 50 (33.1%) • 51 (33.8%)	 • 96 (68.6%) • 62 (44.3%) • 44 (31.4%) • 57 (40.7%)	 (-6.8%, 14.0%) (-8.7%, 14.0%) (-9.0%, 12.3%) (-17.9%, 4.2%)
Preoperative pain status: • Arm and neck pain • Arm pain only • Neck pain only	 • 82 (92.1%) • 2 (2.2%) • 4 (4.5%)	 • 144 (95.4%) • 4 (2.6%) • 2 (1.3%)	 • 134 (95.7%) • 5 (3.6%) • 1 (0.7%)	 (-5.3%, 4.8%) (-5.5%, 3.3%) (-2.4%, 3.6%)
Preoperative radiographic findings: • Herniated nucleus	 • 62 (69.7%)	 • 127 (84.1%)	 • 123 (87.9%)	 (-11.6%, 4.3%)

Demographic Measure	Non-Randomized SECURE-C (N=89)	Randomized SECURE-C (N=151)	Randomized ACDF (N=140)	95% BCI (Randomized Groups)
pulposus • Spondylosis • Loss of disc height	 • 55 (61.8%) • 14 (15.7%)	 • 83 (55.0%) • 16 (10.6%)	 • 79 (56.4%) • 19 (13.6%)	 (-12.7%, 9.9%) (-10.6%, 4.5%)

*Caucasian vs. other; **Data on amount and length of tobacco use was not captured.

Table 8. Preoperative Evaluation of Endpoints

Variable	Non-Randomized SECURE-C (N=89)	Randomized SECURE-C (N=151)	Randomized ACDF (N=140)	95% BCI (Randomized Groups)
NDI	50.1 ±15.03	51.8 ±13.84	51.5 ±14.86	(-3.0, 3.7)
VAS Neck Pain*	64.1 ±26.18	65.2 ±26.84	63.4 ±27.34	(-4.8, 8.2)
VAS Left Arm Pain*	38.8 ±35.48	45.1 ±37.35	39.8 ±36.28	(-3.5, 14.1)
VAS Right Arm Pain*	34.9 ±36.71	33.8 ±37.03	37.9 ±37.09	(-12.9, 4.8)
SF-36 PCS	33.8 ±7.71	33.9 ±7.41	32.0 ±6.48	(0.2, 3.4)
SF-36 MCS	42.9 ±11.01	44.0 ±13.16	44.4 ±11.97	(-3.3, 2.5)
Neurological Status (normal) • Motor • Sensory • Reflexes • Other assessments	 22 (24.7%) • 50 (56.2%) • 59 (66.3%) • 60 (67.4%) • 58 (65.2%)	 31 (20.5%) • 68 (45.0%) • 69 (45.7%) • 92 (60.9%) • 97 (64.2%)	 28 (20.0%) • 68 (48.6%) • 66 (47.1%) • 95 (67.9%) • 86 (61.4%)	(-8.8%, 9.7%)
Baseline ROM angulation (°)	9.5 ±5.2 Range: 0.3 – 23.4	8.5 ±4.8 Range: 0.1 – 23.3	7.2 ±4.3 Range: 0.1 – 19.3	(0.2, 2.4)
Baseline ROM translation (mm)	1.0 ±0.75 Range: 0 – 3.4	0.9 ±0.62 Range: 0 – 3.4	0.8 ±0.59 Range: 0 – 2.7	(0.0, 0.3)

* Per FDA, VAS data excludes one site in which some scores were reported verbally

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the as-treated cohort of 380 total patients (88 non-randomized SECURE®-C patients, 148 randomized SECURE®-C patients, and 144 ACDF patients).

Adverse events that occurred in the PMA clinical study:

A summary of the total number of adverse events, events classified by the Clinical Events Committee (CEC) as device-related, events classified by the CEC as surgery-related, events classified by the CEC as severe or life-threatening, events within 48 hours of the original procedure, and device failures (defined as a revision, removal, reoperation or supplemental fixation) are shown in Table 9.

Table 9. Adverse Event Summary

Adverse Event Type	Measure	NR SEC (N=88)	R SEC (N=148)	R ACDF (N=144)	Statistics*
All Adverse Events (AEs)	Patients (%)	60 (68.2%)	107 (72.3%)	114 (79.2%)	(-17.0%, 2.4%)
	Events (E/pt)	130 (1.48)	247 (1.67)	294 (2.04)	0.9978
Device-Related AEs	Patients (%)	2 (2.3%)	4 (2.7%)	14 (9.7%)	(-13.0%, -1.5%)
	Events (E/pt)	2 (0.02)	4 (0.03)	17 (0.12)	0.9990
Surgery-Related AEs	Patients (%)	4 (4.5%)	9 (6.1%)	18 (12.5%)	(-13.3%, 0.2%)
	Events (E/pt)	4 (0.05)	10 (0.07)	20 (0.14)	0.9789
Severe or Life-Threatening AEs	Patients (%)	17 (19.3%)	29 (19.6%)	34 (23.6%)	(-13.6%, 5.3%)
	Events (E/pt)	23 (0.26)	38 (0.26)	44 (0.31)	0.8378
AEs within 48 hrs of surgery	Patients (%)	1 (1.1%)	3 (2.0%)	7 (4.9%)	Not provided
	Events	1 (0.01)	4 (0.03)	8 (0.06)	Not provided
Device Failures (revision, reoperation, removal, or supplemental fixation)		2	4	17	0.9990

NR SEC=Non-randomized SECURE®-C; R SEC=Randomized SECURE®-C; R ACDF=Control
*For patient comparison: 95% BCI (lower, upper) for comparison of the difference (SECURE®-C - control) between randomized groups
*For event comparison: Posterior probability that the event rate (E/pt) is lower in the SECURE®-C group than the ACDF group
Note: For statistical comparisons of only randomized patients, ACDF group excludes 1 non-randomized patient, therefore N=143.
This table includes data collected beyond 24 months.

Table 10 provides data on the total number of adverse events in each treatment group stratified by level treated. The percentage of subjects with adverse events was similar for the SECURE®-C and ACDF groups, for all treated levels.

Table 10. Total Adverse Events by Level Treated

Level Treated	NR SEC	R SEC	R ACDF	95% BCI (lower, upper)
C3-4	1/3 (33.3%)	5/5 (100%)	4/4 (100%)	(-35.3%, 42.4%)
C4-5	5/7 (71.4%)	5/8 (62.5%)	11/11 (100%)	(-64.6%, -1.2%)
C5-6	30/47 (63.8%)	56/74 (75.7%)	56/72 (77.8%)	(-16.5%, 10.5%)
C6-7	24/31 (77.4%)	41/61 (67.2%)	43/57 (75.4%)	(-23.8%, 8.2%)

NR SEC=Non-randomized SECURE®-C; R SEC=Randomized SECURE®-C; R ACDF=Control
Note: This table includes data collected beyond 24 months.

The adverse events reported in the PMA clinical study from all 236 SECURE®-C patients and 144 ACDF patients are shown in Table 11. This table includes adverse events from all patients, randomized and non-randomized, to establish the safety profile of the device. Adverse events are listed in alphabetical order. Definitions of the adverse event categories are provided in Table 12. Adverse event rates are based on the number of patients having at least one occurrence of an adverse event, divided by the number of patients in that treatment group. Events per patient are based on the number of adverse events, divided by the number of patients. Note that patients with the same event reported within a window are counted once but may appear in multiple time points for the same event. The overall adverse event profile (percentage of patients experiencing at least one adverse event) is qualitatively lower

for the randomized SECURE®-C group (70.8%) than the control ACDF group (79.2%), but is not statistically different. In addition, the overall number of adverse events per patient is lower for the SECURE®-C group(s) than the ACDF group (posterior probability 0.9978). In the SECURE®-C group, the most common adverse events were neck pain, upper extremity pain, back and/or lower extremity pain, and trauma.

One non-randomized SECURE®-C patient died of cardiopulmonary arrest 210 days after surgery. The patient had poor cardiovascular fitness and the event was not considered to be associated with the device by the investigator or the Clinical Events Committee (CEC). One randomized ACDF patient died of unknown causes 1111 days after surgery. No other patients died during the study.

Table 11. All Adverse Events (All Patients As Treated)

Adverse Event	Intra-Op (0-2 days)		Peri-Op (>2days-6wks)		Short Term (>6wks-12mo)		Long Term (>12mo -24mo)		Longer Term (>24mo)		ALL SECURE-C (N=236)		ACDF (N=144)	
	SEC	ACF	SEC	ACF	SEC	ACF	SEC	ACF	SEC	ACF	Patients (%)	Events (E/Pt)	Patients (%)	Events (E/Pt)
All Adverse Events											**167 (70.8%)**	**377 (1.60)**	**114 (79.2%)**	**294 (2.04)**
Cancer[1]	0	0	0	0	1	0	1	0	2	0	4 (1.7%)	4 (0.02)	0 (0.0%)	0 (0.00)
Cardiovascular	0	0	1	0	4	0	4	0	0	1	8 (3.4%)	10 (0.04)	1 (0.7%)	1 (0.01)
Carpal Tunnel Syndrome (CTS)	0	0	1	0	8	5	2	3	1	0	12 (5.1%)	12 (0.05)	8 (5.6%)	8 (0.06)
Cerebrovascular	0	0	1	0	1	0	1	1	0	1	3 (1.3%)	3 (0.01)	2 (1.4%)	3 (0.02)
Compressive Peripheral Neuropathy (Non-CTS)	0	0	2	0	2	0	2	0	1	0	7 (3.0%)	7 (0.03)	0 (0.0%)	0 (0.00)
Death	0	0	0	0	1	0	0	0	0	1	1 (0.4%)	1 (0.01)	1 (0.7%)	1 (0.01)
Dysesthesia - Lower Extremities	0	0	0	0	2	1	0	0	0	0	2 (0.8%)	2 (0.01)	1 (0.7%)	1 (0.01)
Dysesthesia – Other	0	0	2	1	0	2	0	0	0	0	2 (0.8%)	2 (0.01)	3 (2.1%)	3 (0.02)
Dysesthesia - Upper Extremities	1	0	3	5	10	9	3	2	5	1	20 (8.5%)	25 (0.11)	15 (10.4%)	18 (0.13)
Dysphagia	0	4	4	3	1	1	1	0	0	0	6 (2.5%)	6 (0.02)	8 (5.6%)	8 (0.06)
Dysphonia	0	1	0	1	1	0	0	0	0	0	1 (0.4%)	1 (0.01)	2 (1.4%)	2 (0.01)
Gastrointestinal	0	0	0	1	4	0	2	0	0	0	6 (2.5%)	6 (0.02)	1 (0.7%)	1 (0.01)
Headache	0	0	1	2	4	5	1	3	2	1	8 (3.4%)	8 (0.03)	11 (7.6%)	11 (0.08)
Infection – Other	0	0	0	1	2	2	1	0	0	0	3 (1.3%)	3 (0.01)	3 (2.1%)	3 (0.02)
Infection - Superficial Wound	0	0	0	2	0	0	0	0	0	0	0 (0.0%)	0 (0.00)	2 (1.4%)	2 (0.01)
Muscle Spasms	0	0	0	0	0	0	0	1	0	0	0 (0.0%)	0 (0.00)	1 (0.7%)	1 (0.01)
Musculoskeletal	0	0	4	1	16	5	8	2	3	2	30 (12.7%)	36 (0.15)	9 (6.3%)	10 (0.07)
Neurological	0	0	1	1	1	2	0	1	1	0	3 (1.3%)	3 (0.01)	4 (2.8%)	7 (0.05)
Other*	1	1	1	2	5	1	2	1	2	1	11 (4.7%)	11 (0.05)	4 (2.8%)	6 (0.04)
Pain - Back and/or Lower Extremities	0	0	2	3	16	11	8	4	10	7	36 (15.3%)	37 (0.16)	23 (16.0%)	28 (0.20)
Pain - Neck	1	0	13	17	21	21	6	5	12	4	50 (21.2%)	53 (0.22)	41 (28.5%)	51 (0.35)
Pain - Neck and Upper Extremities	0	0	8	7	13	13	4	5	3	3	26 (11.0%)	29 (0.12)	28 (19.4%)	28 (0.19)
Pain - Neck and Upper Extremities with Dysesthesia	0	0	1	0	0	3	0	0	0	0	1 (0.4%)	1 (0.01)	3 (2.1%)	3 (0.02)
Pain - Neck with Dysesthesia	0	0	0	1	2	3	0	0	0	0	2 (0.8%)	2 (0.01)	4 (2.8%)	4 (0.03)
Pain – Other	1	0	0	0	1	0	0	0	0	1	2 (0.8%)	2 (0.01)	1 (0.7%)	1 (0.01)
Pain - Upper Extremities	1	2	10	9	12	8	9	3	6	5	32 (13.6%)	43 (0.18)	24 (16.7%)	28 (0.20)
Pain - Upper Extremities with Dysesthesia	0	0	1	0	3	1	0	1	1	0	5 (2.1%)	5 (0.02)	2 (1.4%)	3 (0.02)
Psychological	0	0	1	0	0	0	0	0	0	1	1 (0.4%)	1 (0.01)	1 (0.7%)	1 (0.01)

Adverse Event	Intra-Op (0-2 days)		Peri-Op (>2days-6wks)		Short Term (>6wks-12mo)		Long Term (>12mo -24mo)		Longer Term (>24mo)		ALL SECURE-C (N=236)		ACDF (N=144)	
	SEC	ACF	SEC	ACF	SEC	ACF	SEC	ACF	SEC	ACF	Patients (%)	Events (E/Pt)	Patients (%)	Events (E/Pt)
Surgery - Adjacent Level	0	0	0	0	2	0	0	0	2	2	4 (1.7%)	4 (0.02)	2 (1.4%)	3 (0.02)
Surgery - Index Level	0	0	1	4	2	4	2	2	2	4	6 (2.5%)	7 (0.03)	14 (9.7%)	17 (0.00)
Surgery - Lumbar Level	0	0	0	2	4	2	1	0	1	1	6 (2.5%)	6 (0.03)	5 (3.5%)	7 (0.05)
Surgery - Other Cervical	0	0	0	0	0	0	0	0	0	1	0 (0.0%)	0 (0.00)	1 (0.7%)	1 (0.00)
Surgery - Thoracic Level	0	0	0	0	1	0	0	0	0	0	1 (0.4%)	1 (0.01)	0 (0.0%)	0 (0.00)
Trauma	0	0	7	3	13	8	6	7	6	2	30 (12.7%)	42 (0.18)	17 (11.8%)	28 (0.20)
Urogenital	0	0	0	0	0	0	0	0	1	0	1 (0.4%)	1 (0.01)	0 (0.0%)	0 (0.00)
Weakness	0	0	0	0	2	1	1	0	0	0	3 (1.3%)	3 (0.01)	1 (0.7%)	1 (0.01)
Wound Issue	0	0	0	4	0	0	0	0	0	0	0 (0.0%)	0 (0.00)	4 (2.8%)	4 (0.03)

SEC = all SECURE®-C Cervical Artificial Disc; ACDF = Anterior Cervical Discectomy and Fusion (Control)

[1] 3 non-randomized SEC: prostate cancer at 692 days, metastatic colon cancer at 959 days, metastatic esophageal cancer at 979 days; 1 randomized SEC: lymphoma at 358 days

*Other: diabetes (SEC, ACDF), thyroid disease (2 SEC, ACDF), hemolytic syndrome (SEC), Wegener's granulomatosis (SEC), CSF leak after lumbar ESI (SEC), corneal abrasion (SEC), allergic reaction to medication (SEC) or to cervical collar material (2 ACDF), lightheadedness (SEC), flu symptoms (ACDF), occasional clicking (ACDF), mild lump in throat without dysphagia (SEC), and snoring (SEC).

Note: This table includes data collected beyond 24 months.

Table 12. Adverse Event Categories

Category	Definition
Cancer	A malignancy or malignant tumor/neoplasm
Cardiovascular	Any condition of the heart and/or blood vessels (excluding the blood vessels that supply the brain)
Carpal Tunnel Syndrome (CTS)	Condition with entrapment of the median nerve in the carpal tunnel
Cerebrovascular	Any condition relating to the brain and the blood vessels that supply it
Compressive Peripheral Neuropathy (Non-CTS)	Dysfunction of one or more nerves excluding Carpal Tunnel Syndome
Death	The termination of life
Dysesthesia - Lower Extremities	Dysesthesia in the lower extremities including hips, buttocks, legs, knees, feet, toes
Dysesthesia - Other	Dysesthesia in areas excluding the upper and lower extremities
Dysesthesia - Upper Extremities	Dysesthesia in the upper extremities including include neck, shoulders, arms, elbows, hands, fingers
Dysphagia	Difficulty in swallowing
Dysphonia	Difficulty in speaking
Gastrointestinal	Any condition pertaining to the stomach and intestines
Headache	Pain in various parts of the head, but not confined to the area of distribution of any nerve
Infection - Superficial Wound	An infection near the surface of the surgical incision
Infection - Other	An infection in an area other than the surgical incision
Muscle Spasms	A sudden contraction of muscle(s), excluding neck or upper extremity spasms which are considered to be pain
Musculoskeletal	Any condition pertaining to the muscles and skeleton, such as fracture, ligament tear, arthritis of any kind, and degenerative conditions, excluding muscle spasms and events related to spinal degenerative conditions
Neurological	Any condition pertaining to a disorder of the nervous system, e.g. Multiple Sclerosis, Parkinson's Disease, Alzheimer's
Other	An adverse event not associated with any other term
Pain - Back and/or Lower Extremities	Pain (including stiffness, strain, tightness) in back, and/or hip, leg, ankle, feet, or buttock; includes pain with or without dysesthesia

Category	Definition
Pain - Neck	Pain (including stiffness, strain, tightness) in the neck
Pain - Neck and Upper Extremities	Pain (including stiffness, strain, tightness) in the neck *and* shoulder, arm, wrist, or hand
Pain - Neck and Upper Extremities with Dysesthesia	Pain (including stiffness, strain, tightness) in the neck *and* shoulder, arm, wrist, or hand w/ dysesthesia
Pain - Neck with Dysesthesia	Pain (including stiffness, strain, tightness) in the neck with dysesthesia
Pain - Other	Pain (including stiffness, strain, tightness) in an area that is not the back or lower extremities, or the neck or upper extremities
Pain - Upper Extremities	Pain (including stiffness, strain, tightness) in the shoulder, arm, wrist or hand
Pain - Upper Extremities with Dysesthesia	Pain (including stiffness, strain, tightness) in the shoulder, arm, wrist or hand with dysesthesia
Psychological	Any psychological condition
Surgery - Index Level	A secondary surgical procedure performed at the index level (originally treated) of the cervical spine, which may include an adjacent level if the index level is operated at same time
Surgery - Adjacent Level	A surgical procedure performed at an adjacent level or level(s) to the index surgery only
Surgery - Other Cervical	A surgical procedure performed at a cervical level that is not the index level or adjacent level(s)
Surgery - Thoracic Level	A surgical procedure performed at a thoracic level or levels, that is an adjacent level(s) to the index surgery
Surgery - Lumbar Level	A surgical procedure performed at a lumbar level.
Trauma	Physical injury caused by a physical force or traumatic event (e.g. motor vehicle accident, fall, etc.)
Urogenital	Any condition of, relating to, affecting, treating, or being the organs or functions of excretion and reproduction
Weakness	Any symptom of weakness or fatigue of the neck and/or upper extremities, not associated with pain or dysesthesia
Wound Issue	Any issue of surgical incision, such as hematoma, excluding infection

Bayesian methods were used to analyze the primary endpoint, and were also used to compare adverse events in the randomized groups. The analysis results are provided in Table 13, with 95% Bayesian Credible Intervals (BCI) for the difference in adverse event rates (SECURE-C – ACDF). BCIs that include zero indicate no statistical difference in proportions between randomized groups. Based on the BCIs, there were no differences between groups for all adverse events, except neck and upper extremity pain and surgery-index level, which is statistically lower for SECURE®-C, and musculoskeletal (which excludes spinal events), which is statistically higher for SECURE®-C.

Table 13. Statistical Comparison of Adverse Events (Randomized Patients As Treated)

Adverse Event	Patients Experiencing Adverse Events (%)		95% BCI (lower, upper)
	SEC (N=148)	ACDF (N=144)	
Any Adverse Event	**107 (72.3%)**	**114 (79.7%)**	**(-17.0%, 2.4%)**
Cancer	1 (0.7%)	0 (0.0%)	(-1.6%, 3.2%)
Cardiovascular	2 (1.4%)	1 (0.7%)	(-2.3%, 3.7%)
Carpal Tunnel Syndrome (CTS)	10 (6.8%)	8 (5.6%)	(-4.6%, 6.9%)
Cerebrovascular	1 (0.7%)	2 (1.4%)	(-3.9%, 2.2%)
Compressive Peripheral Neuropathy	4 (2.7%)	0 (0.0%)	(-0.2%, 6.2%)
Death	0 (0.0%)	1 (0.7%)	(-3.3%, 1.5%)
Dysesthesia - Lower Extremities	2 (1.4%)	1 (0.7%)	(-2.3%, 3.7%)

Adverse Event	Patients Experiencing Adverse Events (%)		95% BCI (lower, upper)
	SEC (N=148)	ACDF (N=144)	
Dysesthesia – Other	2 (1.4%)	3 (2.1%)	(-4.4%, 2.7%)
Dysesthesia - Upper Extremities	13 (8.8%)	15 (10.5%)	(-8.7%, 5.2%)
Dysphagia	4 (2.7%)	8 (5.6%)	(-7.9%, 1.9%)
Dysphonia	1 (0.7%)	2 (1.4%)	(-3.9%, 2.2%)
Gastrointestinal	3 (2.0%)	1 (0.7%)	(-1.8%, 4.7%)
Headache	7 (4.7%)	11 (7.7%)	(-8.8%, 2.7%)
Infection – Other	3 (2.0%)	3 (2.1%)	(-3.9%, 3.7%)
Infection - Superficial Wound	0 (0.0%)	2 (1.4%)	(-4.4%, 1.0%)
Muscle Spasms	0 (0.0%)	1 (0.7%)	(-3.3%, 1.5%)
Musculoskeletal	20 (13.5%)	9 (6.3%)	(0.3%, 14.1%)
Neurological	1 (0.7%)	4 (2.8%)	(-5.9%, 1.2%)
Other*	7 (4.7%)	4 (2.8%)	(-2.7%, 6.7%)
Pain - Back and/or Lower Extremities	20 (13.5%)	23 (16.1%)	(-10.8%, 5.6%)
Pain - Neck	35 (23.6%)	41 (28.7%)	(-15.0%, 5.1%)
Pain - Neck and Upper Extremities	16 (10.8%)	28 (19.6%)	(-17.0%, -0.5%)
Pain - Neck and Upper Extremities with Dysesthesia	1 (0.7%)	3 (2.1%)	(-4.9%, 1.7%)
Pain - Neck with Dysesthesia	0 (0.0%)	4 (2.8%)	(-6.4%, 0.1%)
Pain - Other	2 (1.4%)	1 (0.7%)	(-2.3%, 3.7%)
Pain - Upper Extremities	25 (16.9%)	24 (16.8%)	(-8.5%, 8.7%)
Pain - Upper Extremities with Dysesthesia	4 (2.7%)	2 (1.4%)	(-2.4%, 5.1%)
Psychological	1 (0.7%)	1 (0.7%)	(-2.8%, 2.7%)
Surgery - Adjacent Level	2 (1.4%)	2 (1.4%)	(-3.4%, 3.2%)
Surgery - Index Level	4 (2.7%)	14 (9.8%)	(-13.0%, -1.5%)
Surgery - Lumbar Level	4 (2.7%)	5 (3.5%)	(-5.3%, 3.5%)
Surgery - Other Cervical	0 (0.0%)	1 (0.7%)	(-3.3%, 1.5%)
Trauma	18 (12.2%)	17 (11.9%)	(-7.3%, 7.8%)
Weakness	3 (2.0%)	1 (0.7%)	(-1.8%, 4.7%)
Wound Issue	0 (0.0%)	4 (2.8%)	(-6.4%, 0.1%)

SEC = all SECURE®-C Cervical Artificial Disc; ACDF = Anterior Cervical Discectomy and Fusion (Control)
*Other previously defined in Table 11
Note: This table includes data collected beyond 24 months.

Table 14 provides a higher level comparison of all pain adverse events that occurred in the study. There were no statistical differences between randomized groups for all pain categories listed. Rates were higher for ACDF than for SECURE®-C in all categories, but the differences were not statistically significant.

Table 14. Pain Adverse Events (All Treated Subjects)

Category	NR SEC (N=88)	R SEC (N=148)	R ACDF (N=144)	95% BCI (lower, upper)*
Subjects with ≥1 pain AE	39 (44.3%)	78 (52.7%)	88 (61.1%)	(-19.9%, 2.5)
Total pain AEs	58	122	157	--

Category	NR SEC (N=88)	R SEC (N=148)	R ACDF (N=144)	95% BCI (lower, upper)*
Subjects with ≥1 cervical spine related pain AE	30 (34.1%)	68 (45.9%)	81 (56.3%)	(-21.8%, 0.8%)
Total cervical spine related pain AEs	41	100	128	--
Pain AEs by location:				
• Neck	• 26 (29.5%)	• 51 (34.5%)	• 63 (43.8%)	• (-20.5%, 1.6%)
• Arm	• 17 (19.3%)	• 44 (29.7%)	• 50 (34.7%)	• (-15.8%, 5.5%)
• Neck and arm	• 30 (34.1%)	• 67 (45.3%)	• 76 (52.8%)	• (-19.1%, 3.6%)
• Headache	• 1 (1.1%)	• 7 (4.7%)	• 11 (7.6%)	• (-8.8%, 2.7%)
• Back and/or LE	• 16 (18.2%)	• 20 (13.5%)	• 23 (16.0%)	• (-10.8%, 5.6%)
• Other	• 0	• 2 (1.4%)	• 1 (0.7%)	• (-2.3%, 3.7%)

NR SEC=Non-randomized SECURE®-C; R SEC=Randomized SECURE®-C; R ACDF=Control
*For statistical comparisons of only randomized patients, ACDF group excludes 1 non-randomized patient, therefore N=143.
Note: This table includes data collected beyond 24 months.

Some adverse events resulted in surgical intervention at the index level, subsequent to the initial surgery. Secondary surgical interventions, classified as revisions, removals, reoperations or supplemental fixations at the index level, are study failures and are reported in Table 15, with details provided in Table 16. The percentage of patients experiencing secondary surgery at the index level was lower for the SECURE®-C group (2.5%) than the ACDF group (9.7%), and was statistically superior between randomized groups at 24 months (95% BCI: 0.3%, 10.8%).

Table 15. Secondary Surgical Interventions at the Index Level (All Patients As Treated)

Adverse Event	Intra-Op (0-2 days)		Peri-Op (>2days-6wks)		Short Term (>6wks-12mo)		Long Term (>12mo -24mo)		Longer Term (>24mo)		TOTAL Patients (%)	
	SEC	ACDF	SEC	ACDF	SEC	ACDF	SEC	ACDF	SEC	ACDF	SEC (N=236)	ACDF (N=144)
Revision	0	0	0	1	0	2	0	2	0	1	0 (0.0%)	6 (4.2%)
Removal	0	0	0	0	2	2	1	2	1	3	4 (1.7%)	7 (4.9%)
Reoperation	0	0	0	0	0	1	1	0	1	0	2 (0.8%)	1 (0.7%)
Suppl Fixation	0	0	0	0	0	0	0	0	0	0	0 (0.0%)	0 (0.0%)
Total	0	0	0	1	2	5	2	4	2	4	6 (2.5%)	14 (9.7%)

SEC = all SECURE®-C Cervical Artificial Disc; ACDF = Anterior Cervical Discectomy and Fusion (Control)
Note: 1 SECURE®-C and 4 ACDF secondary surgeries occurred beyond the 24 month visit window (24 + 6 months) and therefore do not count as 24 month failures.
This table includes data collected beyond 24 months.

Table 16. Secondary Surgical Procedure Details

Group	Cause/Adverse Event	Action	Postop Days
NR SEC	Arm and parascapular pain	Removal C5-6, fusion same level	880
NR SEC	Neck and shoulder pain; device not properly placed in disc space	Removal C5-6, fusion same level	183

Group	Cause/Adverse Event	Action	Postop Days
R SEC	Neck pain	Removal C5-6, fusion C5-7	507
R SEC	C5-6 foraminal stenosis	Posterior decompression C5-6; SECURE-C device remains implanted	942
R SEC	C5-7 bilateral radiculopathy & foraminal stenosis	Posterior decompression C5-7; SECURE-C device remains implanted	575
R SEC	Neck pain	Removal C6-7, fusion same level	310
ACDF	C5-6 degenerated disc (adjacent level)	Removal C4-5, cervical arthroplasty inserted at C5-6	1576
ACDF	Continued neck pain, numbness, failure to fuse on CT and MRI	Removal C5-6, plate and spacer inserted same level	441
ACDF	Neck pain and right arm pain	Removal C5-6 (fusion solid), plate and cage inserted C6-7	266
ACDF	Right shoulder pain, inadequate fusion	Removal C6-7, plate and autograft inserted same level	400
ACDF	Neck pain, pseudoarthrosis on x-ray and CT	Removal C5-6 (no replacement; fusion intact on exploration, neck pain felt due to hardware)	776
ACDF	Left C5 radiculopathy	Removal C5-6, 2-level plate/1 spacer inserted C4-6	54
ACDF	C4-5, C6-7 disc herniation	Removal C5-6, 3-level plate/spacers inserted C4-7	623
ACDF	C4-5 degenerated disc	Removal C5-6 (no evidence pseudoarthrosis on exploration), plate and spacer inserted C4-5	1216
ACDF	Neck pain, C5-6 disc herniation	Removal C4-5 (solid fusion on radiographs), plate and allograft inserted C5-6	1058
ACDF	Neck pain and thumb paresthesia	Posterior decompression and PLF C6-7; original plate remains implanted *(non-study surgeon)*	418
ACDF	Myelopathy (not improved from baseline)	Removal C4-5, plate same level *(non-study surgeon)*	263
ACDF	Left arm pain, numbness	Removal C6-7 (solid fusion on radiographs and exploration), plate and allograft at C5-6	1162
ACDF	*Unknown (non-study surgeon)*	Removal C4-5, 2-level plate inserted	215
ACDF	Neck and left arm pain	Removal C6-7 (solid fusion on radiographs), plate and cage inserted C5-6	735

NR SEC=Non-randomized SECURE®-C; R SEC=Randomized SECURE®-C; ACDF=Control

The number and percentage of patients who experienced a device-related adverse event as determined by the Clinical Events Committee (CEC) is provided in Table 17. Note that the CEC used a relatively narrow definition in that device-related events were identified as having etiology, temporal association, or cause, that is related to the device, such as: revision, removal, reoperation, or supplemental fixation at the index level, surgery at the index level to remove or alter the device, fracture or mechanical failure of device(s), pseudarthrosis, radiolucency around device(s), migration, subsidence, loosening, etc. The CEC felt that it was not appropriate to broadly classify events such as neck or arm pain as potentially device related, as these are commonly reported symptoms for patients entering a study with preoperative neck and/or arm pain.

Based on the CEC's classification, the device-related adverse event profile is lower for the SECURE®-C (2.5%) group than the ACDF (9.7%) group because there were less secondary surgeries at the index level in the SECURE®-C group. The number of device-related adverse events per patient is also lower for SECURE®-C than ACDF, as previously described in Table 9.

Table 17. Device-Related Adverse Events

Adverse Event	Intra-Op (0-2 days)		Peri-Op (>2days-6wks)		Short Term (>6wks-12mo)		Long Term (>12mo -24mo)		Longer Term (>24mo)		Patients (%)	
	SEC	ACDF	SEC	ACDF	SEC	ACDF	SEC	ACDF	SEC	ACDF	SEC (N=236)	ACDF (N=144)
Surgery - Index Level	0	0	1	4	2	4	2	2	1	4	6 (2.5%)	14 (9.7%)

SEC = all SECURE®-C Cervical Artificial Disc; ACDF = Anterior Cervical Discectomy and Fusion (Control)
Note: This table includes data collected beyond 24 months.

The total number and percentage of patients who experienced a surgery-related adverse event as determined by the Clinical Events Committee (CEC) is provided in Table 18. Surgery-related adverse events were defined as those identified as having etiology, temporal association, or cause that is related to the surgical procedure, such as: dysphagia, dysphonia, or postoperative infection. Based on the CEC's classification, the surgery-related adverse event profile is lower for the SECURE®-C (5.5%) group compared to the ACDF (12.5%) group, but is not statistically different.

Table 18. Total Surgery-Related Adverse Events

Adverse Event	SEC (N=236)		ACDF (N=144)	
	Patients (%)	Events (E/Pt)	Patients (%)	Events (E/Pt)
Surgery-Related Adverse Event	13 (5.5%)	14 (0.06)	18 (12.5%)	20 (0.14)
Cardiovascular	1 (0.4%)	1 (0.01)	0 (0.0%)	0 (0.00)
Cerebrovascular	1 (0.4%)	1 (0.01)	0 (0.0%)	0 (0.00)
Dysesthesia – Other	0 (0.0%)	0 (0.00)	1 (0.7%)	1 (0.01)
Dysesthesia – Upper Extremities	1 (0.4%)	1 (0.01)	0 (0.0%)	0 (0.00)
Dysphagia	5 (2.1%)	5 (0.02)	7 (4.9%)	7 (0.05)
Dysphonia	0 (0.0%)	0 (0.00)	2 (1.4%)	2 (0.01)
Infection – Superficial Wound	0 (0.0%)	0 (0.00)	2 (1.4%)	2 (0.01)
Musculoskeletal	1 (0.4%)	1 (0.01)	0 (0.0%)	0 (0.00)
Other	1 (0.4%)	1 (0.01)	0 (0.0%)	0 (0.00)
Pain – Other	1 (0.4%)	1 (0.01)	0 (0.0%)	0 (0.00)
Pain – Upper Extremities	3 (1.3%)	3 (0.01)	4 (2.8%)	4 (0.03)
Wound Issue	0 (0.0%)	0 (0.00)	4 (2.8%)	4 (0.03)

SEC = all SECURE®-C Cervical Artificial Disc; ACDF = Anterior Cervical Discectomy and Fusion (Control)
Note: This table includes data collected beyond 24 months.

The total number and percentage of patients who experienced a severe or life-threatening adverse event as determined by the CEC is provided in Table 19. A severe event was defined as an AE that significantly limits the patient's ability to perform routine activities despite

symptomatic therapy, and a life-threatening event was defined as an AE that required removal of the implant or put the patient at immediate risk of death (including death). Based on the CEC's classification, the severe or life-threatening adverse event profile is similar for the SECURE®-C (19.5%) group and the ACDF (23.6%) group.

Table 19. Total Severe or Life-Threatening Adverse Events

Adverse Event	SEC (N=236)		ACDF (N=144)	
	Patients (%)	Events (E/Pt)	Patients (%)	Events (E/Pt)
Severe or Life-Threatening Event	46 (19.5%)	61 (0.26)	34 (23.6%)	44 (0.31)
Cancer	2 (0.8%)	2 (0.01)	0 (0.0%)	0 (0.00)
Cardiovascular	5 (2.1%)	6 (0.03)	0 (0.0%)	0 (0.00)
Carpal Tunnel Syndrome (CTS)	6 (2.5%)	6 (0.03)	3 (2.1%)	3 (0.02)
Cerebrovascular	2 (0.8%)	2 (0.01)	0 (0.0%)	0 (0.00)
Compressive Periph Neuro (Non-CTS)	3 (1.3%)	3 (0.01)	0 (0.0%)	0 (0.00)
Death	1 (0.4%)	1 (0.01)	1 (0.7%)	1 (0.01)
Dysphagia	0 (0.0%)	0 (0.00)	1 (0.7%)	1 (0.01)
Gastrointestinal	4 (1.7%)	4 (0.02)	0 (0.0%)	0 (0.00)
Infection - Other	0 (0.0%)	0 (0.00)	1 (0.7%)	1 (0.01)
Musculoskeletal	13 (5.5%)	14 (0.06)	5 (3.5%)	5 (0.03)
Neurological	0 (0.0%)	0 (0.00)	2 (1.4%)	2 (0.01)
Other	1 (0.4%)	1 (0.01)	1 (0.7%)	1 (0.01)
Pain – Back and/or Lower Extremities	2 (0.8%)	2 (0.01)	0 (0.0%)	0 (0.00)
Pain - Upper Extremities	0 (0.0%)	0 (0.00)	1 (0.7%)	1 (0.01)
Psychological	1 (0.4%)	1 (0.01)	0 (0.0%)	0 (0.00)
Surgery – Adjacent Level	4 (1.7%)	4 (0.02)	2 (1.4%)	3 (0.02)
Surgery – Index Level	6 (2.5%)	7 (0.03)	14 (9.7%)	17 (0.12)
Surgery – Lumbar Level	6 (2.5%)	6 (0.03)	5 (3.5%)	7 (0.05)
Surgery – Other Cervical	0 (0.0%)	0 (0.00)	1 (0.7%)	1 (0.01)
Surgery – Thoracic Level	1 (0.4%)	1 (0.01)	0 (0.0%)	0 (0.00)
Trauma	0 (0.0%)	0 (0.00)	1 (0.7%)	1 (0.01)
Urogenital	1 (0.4%)	1 (0.01)	0 (0.0%)	0 (0.00)

SEC = all SECURE®-C Cervical Artificial Disc; ACDF = Anterior Cervical Discectomy and Fusion (Control)
Note: This table includes data collected beyond 24 months.

Neurological Status:

The change in neurologic status at each study timepoint is provided in Table 20 for all patient groups. If any one of the four neurologic assessments deteriorated, then the overall neurologic status is considered deteriorated. For overall neurologic status and for each of the four individual assessments, the percentage of patients with stable or improved status was similar for both groups. The randomized SECURE®-C group demonstrated numerically greater percentages of patients with stable/improved neurologic status than the control ACDF group at each time point, with statistical significance at 6 and 36 months; statistical comparisons of 24 month neurologic status success demonstrate non-inferiority with a posterior probability of 100%.

Table 20. Neurological Status

Timepoint	Status	Non-Randomized SECURE-C (N=88)	Randomized SECURE-C (N=148)	Randomized ACDF (N=144)	95% BCI[#] (lower, upper)
6 months	Improved	49/83 (59.0%)	81/139 (58.3%)	71/130 (54.6%)	(0.7%, 12.6%)
	Stable	29/83 (34.9%)	54/139 (38.8%)	47/130 (36.2%)	
	Deteriorated	5/83 (6.0%)	4/139 (2.9%)	12/130 (9.2%)	
12 months	Improved	47/81 (58.0%)	78/136 (57.4%)	67/124 (54.0%)	(-1.6%, 11.1%)
	Stable	28/81 (34.6%)	52/136 (38.2%)	46/124 (37.1%)	
	Deteriorated	6/81 (7.4%)	6/136 (4.4%)	11/124 (8.9%)	
24 months	Improved	45/75 (60.0%)	73/123 (59.3%)	57/101 (56.4%)	(-2.9%, 9.2%)
	Stable	26/75 (34.7%)	46/123 (37.4%)	38/101 (37.6%)	
	Deteriorated	4/75 (5.3%)	4/123 (3.3%)	6/101 (5.9%)	
36 months	Improved	34/52 (65.4%)	35/53 (66.0%)	23/43 (53.5%)	(0.9%, 20.6%)
	Stable	14/52 (26.9%)	18/53 (34.0%)	16/43 (37.2%)	
	Deteriorated	4/52 (7.7%)	0/53 (0%)	4/43 (9.3%)	

#95% Credible Interval on difference (SECURE-C randomized – ACDF) between proportions of improved/stable vs. deteriorated

Adjacent Level Symptoms and Treatments:

The incidence and progression of adjacent level disease was not collected prospectively, but was assessed in terms of symptoms, treatment, and surgery performed at the adjacent level by a thorough review of adverse event source documentation for adverse events coded as pain (neck and/or upper extremity), dysesthesia (neck and/or upper extremity), neurological, weakness, muscle spasms, surgery, pseudoarthrosis, or headache to isolate possible adjacent level symptoms, diagnoses, treatments, and surgeries. Based on this review, the percentage of patients with adjacent level symptoms was numerically higher for the control ACDF group (18.8%) than for the SECURE®-C group (11.5% randomized, 8% non-randomized). Some patients with adjacent level symptoms went on to receive postoperative treatment at the adjacent level; however, the percentage of patients with adjacent level treatment was low for all groups at all time points, with few patients receiving treatment. Some patients with adjacent level symptoms (with or without adjacent level treatment) went on to receive postoperative surgical treatment at the adjacent level. The percentage of patients having adjacent level surgery by 24 months was low for both groups (0% SECURE®-C non-randomized, 2.7% SECURE®-C randomized, 4.2% ACDF).

Surgery and Hospitalization Data:

Surgical data is provided in Table 21. The posterior probability that the mean or proportion is lower in the randomized SECURE®-C group than the ACDF group is included in the table. The most common treated surgical levels were C5-C6 and C6-C7. Mean surgery time was 15.6 min longer for the randomized investigational SECURE®-C group than for the control ACDF group, and was statistically different. Mean blood loss was also 9.6 ml more for the randomized SECURE®-C group, and this was borderline statistically significant although likely not clinically significant. Mean return to work time was 6 days shorter for the SECURE®-C group than the ACDF group, however this was not statistically different. Note that data on the amount/type of decompression and handling of the posterior longitudinal ligament for each procedure is not available.

Table 21. Surgical Data

Measure	Non-Randomized SECURE-C (N=89)	Randomized SECURE-C (N=151)	Randomized ACDF (N=140)	Posterior Probability *	Posterior Probability **
Treated Level					
C3-C4 (%)	3 (3.4%)	5 (3.3%)	4 (2.9%)	0.4230	0.5529
C4-C5 (%)	7 (7.9%)	8 (5.3%)	11 (7.9%)	0.8075	0.7977
C5-C6 (%)	48 (53.9%)	75 (49.7%)	70 (50.0%)	0.5226	0.7366
C6-C7 (%)	31 (34.8%)	63 (41.7%)	55 (39.3%)	0.3372	0.1482
Surgery Time (min)	98.4 ±34.80	87.7 ±33.02	72.1 ±25.41	<0.0001	0.9878
Blood Loss (mls)	55.6 ±43.93	55.2 ±44.22	45.6 ±33.21	0.0254	0.4540
Classification					
Inpatient (<23 hrs)	62 (69.7%)	92 (60.9%)	87 (62.1%)	0.5830	0.9112
Outpatient (>23 hrs)	27 (30.3%)	59 (39.1%)	52 (37.9%)		
Hospitalization (days)	1.2 ±0.56	1.0 ±0.46	0.9 ±0.46	0.4058	0.9878
Return to Work Time (days)	46.4 ±32.40	44.0 ±74.47	50.0 ±72.21	0.5545	0.9934

Mean ± standard deviation

*Posterior probability that mean or proportion is lower in the randomized SECURE-C group compared to ACDF

**Posterior probability that mean or proportion is lower in the randomized SECURE-C group compared to the non-randomized SECURE-C group

A total of 236 SECURE®-C devices were implanted during the study. The design, footprint and height of the SECURE®-C devices used are presented in Table 22.

Table 22. SECURE®-C Implants Used

Size/Option	Devices (%)	Size/Option	Devices (%)
Design		*Height*	
0° (Parallel)	54 (22.9%)	7mm	210 (89.0%)
6° (Lordotic)	182 (77.1%)	8mm	25 (10.6%)
Footprint		9mm	1 (0.4%)
11mm x 12mm	69 (29.2%)	10mm	0 (0.0%)
13mm x 14mm	159 (67.4%)	11mm	0 (0.0%)
14mm x 16mm	8 (3.4%)	12mm	0 (0.0%)
Device Combination			
11mm x 12mm footprint and 7mm height			69 (29.2%)
13mm x 14mm footprint and 7mm height			136 (57.6%)
13mm x 14mm footprint and 8mm height			22 (9.3%)
13mm x 14mm footprint and 9mm height			1 (0.4%)
14mm x 16mm footprint and 7mm height			5 (2.1%)
14mm x 16mm footprint and 8mm height			3 (1.3%)

2. Effectiveness Results

Primary Effectiveness Analysis:

The analysis of effectiveness was based on the as-randomized cohort of 380 total patients (89 non-randomized SECURE®-C patients, 151 randomized SECURE®-C patients, and 144 ACDF patients). The individual patient success rate was defined in the original IDE protocol

as the number of patients classified as success divided by the number of patients evaluated at 24 months. The success rates at 24 months postoperative for each of the individual success components and the overall success is provided in Table 23. Posterior probabilities of non-inferiority and superiority were calculated using Bayesian statistical methods. The statistical analysis plan pre-specified that the analysis technique would involve predicting 24 month outcomes for those without them, based on interim 6 month and 12 month observed outcomes, and integrating over the predictions to obtain posterior probabilities of non-inferiority and superiority. The study was approved using a non-inferiority margin (delta) of 15%; FDA advised that additional analysis be performed with a margin of 10% at the time of PMA. Only the 10% delta analysis is presented; 15% non-inferiority is always met for all variables demonstrating non-inferiority at 10%. According to the statistical analysis plan, if non-inferiority is determined, then superiority is evaluated; these results are also presented.

In addition to the protocol-defined overall success criteria, FDA requested an additional alternative definition of overall success as described above to include improvement in NDI of 15 points, maintenance or improvement in neurologic status, absence of device-related adverse events, exclusion of the fusion criterion in the control group, and no intraoperative changes in SECURE®-C treatment (i.e., intraoperative conversion to fusion). Analysis using the alternative FDA-defined endpoint is provided in Table 24.

Table 23. Overall Success (Protocol-Specified) at 24 Months

Component	Non-Randomized SECURE-C (N=89)	Randomized SECURE-C (N=151)	ACDF (N=140)	Posterior Probability		95% BCI[#] (lower, upper)
				Non-Inferiority	Superiority	
NDI (≥25% impr)	67/78 (85.9%)	127/139 (91.4%)	101/116 (87.1%)	100.0%	87.8%	(-3.2%, 12.6%)
No removals etc.	84/86 (97.7%)	142/145 (97.9%)	123/133 (92.5%)	100.0%	98.2%	(0.3%, 10.8%)
No Complications	85/85 (100%)	143/143 (100.0%)	127/127 (100.0%)	100.0%	52.9%	(-2.0%, 2.3%)
Fusion (control)	N/A	N/A	90/101 (89.1%)	N/A	N/A	N/A
Overall Success	**67/79 (84.8%)**	**127/141 (90.1%)**	**81/114 (71.1%)**	**100.0%**	**100.0%**	**(8.2%, 27.0%)**

[#]BCI for difference in proportions (SECURE-C randomized – ACDF), using Bayesian methods with predictions

Table 24. Overall Success (FDA-Defined) at 24 Months

Component	Non-Randomized SECURE-C (N=89)	Randomized SECURE-C (N=151)	ACDF (N=140)	Posterior Probability		95% BCI[#] (lower, upper)
				Non-Inferiority	Superiority	
NDI (≥15pt impr)	64/78 (82.1%)	124/139 (89.2%)	98/116 (84.5%)	100.0%	88.6%	(-3.3%, 13.8%)
Neuro success	72/76 (94.7%)	120/125 (96.0%)	93/98 (94.9%)	100.0%	69.0%	(-4.1%, 7.3%)
No removals etc.	84/86 (97.7%)	142/145 (97.9%)	123/133 (92.5%)	100.0%	98.2%	(0.3%, 10.8%)
No device AEs	84/86 (97.7%)	141/145 (97.2%)	120/131 (91.6%)	100.0%	96.0%	(-0.6%, 10.2%)
No change in tx	88/89 (98.9%)	148/151 (98.0%)	N/A	N/A	N/A	N/A
Overall Success	**60/78 (76.9%)**	**109/130 (83.8%)**	**82/112 (73.2%)**	**100.0%**	**98.1%**	**(0.6%, 20.2%)**

[#]BCI for difference in proportions (SECURE-C randomized – ACDF), using Bayesian methods with predictions

As specified in the analysis plan, the threshold for establishing success for non-inferiority or superiority is a posterior probability of 95.4%. Therefore, overall success results demonstrate non-inferiority of the SECURE®-C group to the control group for both the protocol-specified and FDA alternative definition of overall success. In addition, all components of overall success of the SECURE®-C group were non-inferior to the control group for both definitions. Superiority of the SECURE®-C investigational group to the control was also established for overall success, with a posterior probability of 100% for the protocol-specified definition of overall success and 98.1% for the FDA alternative definition of overall success. Table 25 provides data on the timecourse of overall success for each treatment group.

Table 25. Timecourse of Overall Success

Definition	Group	6 mo	12 mo	24 mo	36 mo	48 mo
Protocol – Specified	**NR SEC (N=89)**	76/84 (90.5%)	75/83 (90.4%)	67/79 (84.8%)	54/62 (87.1%)	21/26 (80.8%)
	R SEC (N=151)	133/142 (93.7%)	126/140 (90.0%)	127/141 (90.1%)	54/63 (85.7%)	8/14 (57.1%)
	R ACDF (N=140)	20/129 (15.5%)	76/123 (61.8%)	81/114 (71.1%)	33/49 (67.3%)	1/16 (6.3%)
FDA Defined Alternative	**NR SEC (N=89)**	67/84 (79.8%)	68/83 (81.9%)	60/78 (76.9%)	42/55 (76.4%)	19/25 (76.0%)
	R SEC (N=151)	122/142 (85.9%)	122/140 (87.1%)	109/130 (83.8%)	49/61 (80.3%)	7/13 (53.8%)
	R ACDF (N=140)	104/128 (81.3%)	98/123 (79.7%)	82/112 (73.2%)	34/50 (68.0%)	1/16 (6.3%)

NR SEC=Non-randomized SECURE®-C; R SEC=Randomized SECURE®-C; R ACDF=Control

Table 26 provides data on overall success in each treatment group stratified by level treated. There were no statistical differences in overall success between the randomized groups at C3-4 and C4-5 for either definition of success, and at C5-6 and C6-7 for the FDA definition, as evidenced by BCIs including zero. However, at C5-6 and C6-7, the proportion of SECURE®-C patients achieving overall success was statistically higher than ACDF patients, using the protocol-specified definition.

Table 26. Overall Success by Level Treated at 24 Months

Overall Success	Non-Randomized SECURE-C (N=89)	Randomized SECURE-C (N=151)	ACDF (N=140)	95% BCI[#] (lower, upper)
Protocol-specified:				
• C3-4	• 2/2 (100%)	• 5/5 (100%)	• 4/4 (100%)	• (-35.3%, 42.5%)
• C4-5	• 5/6 (83.3%)	• 8/8 (100%)	• 7/10 (70.0%)	• (-8.4%, 54.4%)
• C5-6	• 35/42 (83.3%)	• 60/69 (87.0%)	• 38/55 (69.1%)	• (3.2%, 32.1%)
• C6-7	• 25/29 (86.2%)	• 54/59 (91.5%)	• 32/45 (71.1%)	• (5.4%, 35.2%)
FDA defined:				
• C3-C4	• 2/2 (100%)	• 5/5 (100%)	• 4/4 (100%)	• (-35.4%, 42.4%)
• C4-C5	• 3/6 (50.0%)	• 7/8 (87.5%)	• 7/10 (70.0%)	• (-22.7%, 47.4%)
• C5-C6	• 29/41 (70.7%)	• 51/62 (82.3%)	• 40/55 (72.7%)	• (-5.5%, 24.4%)

Overall Success	Non-Randomized SECURE-C (N=89)	Randomized SECURE-C (N=151)	ACDF (N=140)	95% BCI[#] (lower, upper)
• C6-C7	• 26/29 (89.7%)	• 46/55 (83.6%)	• 31/43 (72.1%)	• (-4.8%, 27.9%)

[#]BCI for difference in proportions (SECURE-C randomized – ACDF), using Bayesian methods with predictions

Sensitivity Analyses:

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

- Overall success stratified by radiographic findings at enrollment (herniated nucleus pulposus, spondylosis, loss of disc height), pain status at enrollment (arm pain only, neck pain only, arm/neck pain, neither), neurologic status at enrollment (normal, abnormal), preoperative instability, preoperative motion, duration of neck symptoms, and history of conservative care.

- Overall success without any Bayesian predictions (i.e., completers only), without incorporation of 6 month data in the predictions, and with missing interim outcomes set to worst case values.

- Overall success with ACDF patients who underwent subsequent surgery in which the device was removed but not replaced at the time of an adjacent level procedure considered successes rather than failures.

- Overall success using only in-window data.

- Overall success with various imputations for missing 24 month values (10 randomized SECURE®-C and 26 ACDF patients for the protocol-specified endpoint and 21 randomized SECURE®-C and 28 ACDF patients for the FDA-defined alternative endpoint) including a last observation carried forward analysis, a worst case analysis, and a tipping point analysis.

- Overall success excluding subjects with major protocol violations.

Non-inferiority was established for nearly all of these scenarios for both the protocol-specified and FDA-defined alternate endpoints except the most extreme case in which all missing investigational outcomes are considered failures and all missing control outcomes are considered successes where non-inferiority was only established for the protocol-specified endpoint. For the FDA-defined analysis, the tipping point was when 8 subjects were adjusted in each treatment group (8 SECURE®-C subjects flipped to failures and 8 ACDF subjects flipped to successes from the beginning position where the success proportion in the missing values followed the same pattern as the observed data).

Additional data was provided which stratified outcomes by patient race as shown in Tables 27 and 28.

Table 27. Overall Success by Patient Race at 24 Months

Overall Success	Randomized SECURE-C		ACDF		95% BCI[#] (lower, upper)	
	Caucasian (N=136)	Non-Caucasian (N=15)	Caucasian (N=126	Non-Caucasian (N=14)	Randomized SECURE-C	ACDF
Protocol-specified	118/127 (92.9%)	9/14 (64.3%)	75/105 (71.4%)	6/9 (66.7%)	(8.1%, 54.3%)	(-18.5%, 37.5%)
FDA defined	100/116 (86.2%)	9/14 (64.3%)	77/103 (74.8%)	5/9 (55.6%)	(0.9%, 47.9%)	(-8.4%, 49.2%)

[#]BCI for difference in proportions (Caucasian – Non-Caucasian), without predictions

Table 28. Overall Success by Patient Race with Treatment Comparison at 24 Months

Overall Success	Caucasian		Non-Caucasian		95% BCI[#] (lower, upper)	
	Randomized SECURE-C (N=136)	ACDF (N=126)	Randomized SECURE-C (N=15)	ACDF (N=14)	Caucasian	Non-Caucasian
Protocol-specified	118/127 (92.9%)	75/105 (71.4%)	9/14 (64.3%)	6/9 (66.7%)	(11.7%, 31.1%)	(-35.9%, 35.0%)
FDA defined	100/116 (86.2%)	77/103 (74.8%)	9/14 (64.3%)	5/9 (55.6%)	(0.9%, 21.8%)	(-28.3%, 44.0%)

[#]BCI for difference in proportions (SECURE-C randomized – ACDF), without predictions

For patients randomized to SECURE®-C, the Caucasian group had higher success rates than the non-Caucasian group for both overall success definitions whereas for patients randomized to ACDF, there was no difference between the Caucasian and non-Caucasian groups particularly for the protocol-specified definition of overall success. Within the Caucasian group, those treated with the SECURE®-C have higher success rates than those treated with ACDF whereas within the non-Caucasian group, the outcomes are more similar. It is notable that the non-Caucasian subjects appear to have somewhat worse overall outcomes in both treatment groups and in the SECURE®-C group in particular; however, it is important to note that the non-Caucasian sample size was relatively small (10 non-randomized SECURE®-C patients, 15 randomized SECURE®-C patients, and 14 ACDF patients). Upon more detailed investigation, the primary drivers for lower overall success were NDI improvement, neurologic success, and removals. In addition, the non-Caucasian patients who were overall failures had, on average, higher preoperative NDI and VAS pain scores than the non-Caucasians who were successes (perhaps indicative of more severe preoperative symptoms and pathology than the average study patient). Due to the relatively small numbers of non-Caucasians treated in the IDE, this potential variability in outcomes based on race will be evaluated further as part of an Enhanced Surveillance Study the applicant will conduct for 10 years postmarket.

Financial Disclosure Analysis:

Analyses using logistic regression models did not find a statistically significant relationship between success rates and surgeon or site financial interest. No evidence of bias was found towards SECURE®-C resulting from financial interest of the site or surgeon.

Poolability Analysis:

Analyses were also conducted to assess poolability of data across sites using the Woolf test of homogeneity of odds ratio and poolability of data across surgeons using Zelen's exact test for homogeneity of odds ratio. Overall success data according to the protocol-specified definition and the FDA-defined alternative criteria at 24 months were evaluated. All tests were non-significant, indicating that there is no particular evidence of a differential treatment effect among sites. These outcomes provide confidence in pooling the data across investigational sites.

Comparison of Randomized and Non-Randomized SECURE®-C Outcomes:

A statistical comparison of the primary endpoint and components, secondary endpoints, and adverse events for the randomized and non-randomized SECURE®-C groups is provided in Table 29. For both the protocol-specified and FDA-defined primary endpoints, there were no statistical differences between the two groups, with all BCIs including zero. Likewise for the NDI, VAS, and adverse event rates, there were no statistical differences between the two groups, for means or proportions, as shown by all BCIs including zero. As shown above in Table 21, surgery time, hospitalization and length of stay was statistically longer for the non-randomized group compared to the randomized group.

Table 29. Comparison of Randomized and Non-Randomized Patient Outcomes at 24 Months

Outcome Measure	Randomized SECURE-C (N=151)	Non-Randomized SECURE-C (N=89)	95% BCI[#] (lower, upper)
Protocol-Specified Primary Endpoint: • NDI ≥25% improvement • No removals, etc. • No complications	127/141 (90.1%) • 127/139 (91.4%) • 142/145 (97.9%) • 143/143 (100%)	67/79 (84.8%) • 67/78 (85.9%) • 84/86 (97.7%) • 85/85 (100%)	(-3.4%, 15.4%) • (-2.9%, 15.4%) • (-3.6%, 5.8%) • (-1.8%, 3.7%)
FDA-Defined Primary Endpoint: • NDI ≥15pt improvement • Neuro success • No removals, etc. • No device AEs • No change in treatment	109/130 (83.8%) • 124/139 (89.2%) • 120/125 (96.0%) • 142/145 (97.9%) • 141/145 (97.2%) • 148/151 (98.0%)	60/78 (76.9%) • 64/78 (82.1%) • 72/76 (94.7%) • 84/86 (97.7%) • 84/86 (97.7%) • 88/89 (98.9%)	(-3.9%, 18.6%) • (-2.2%, 17.8%) • (-4.5%, 8.8%) • (-3.6%, 5.8%) • (-4.5%, 5.2%) • (-4.2%, 3.9%)
Secondary Endpoints: • NDI (Mean ± SD) • Neck Pain VAS (Mean ± SD) • Left Arm Pain VAS (Mean ± SD) • Right Arm Pain VAS (Mean ± SD)	 • 13.2 ± 17.8 • 14.3 ± 22.5 • 9.0 ± 20.7 • 6.6 ± 17.5	 • 14.1 ± 18.0 • 17.1 ± 25.9 • 8.9 ± 20.3 • 4.6 ± 12.7	 • (-6.0, 4.1) • (-9.7, 4.2) • (-5.6, 5.9) • (-2.1, 6.1)
Patients with any AE	109/151 (72.2%)	60/89 (67.4%)	(-6.9%, 16.9%)
Patients with any Device Related AE	4/151 (2.6%)	2/89 (2.2%)	(-5.1%, 4.3%)

[#]BCI for difference (Randomized – Non-Randomized) between means or proportions, without predictions

Secondary Effectiveness Analysis:

In addition to the components of the primary endpoint presented above, secondary effectiveness variables were also assessed and the results are provided below. As discussed for primary objectives, only the 10% delta analysis is presented; 15% non-inferiority is always met for all variables demonstrating non-inferiority at 10%. If non-inferiority was achieved, then superiority was also evaluated; these results are also presented. As specified in the analysis plan, the threshold for establishing non-inferiority or superiority for secondary objectives was 95%.

The following secondary endpoint success definitions were specified:

- NDI success: improvement of both ≥25% and ≥15 points from baseline
- VAS pain success: improvement of ≥20mm
- SF-36 success: improvement of ≥15%
- Satisfaction: response of definitely or mostly satisfied

Success rates at 24 months based on these definitions are presented in Table 30. SECURE®-C was non-inferior to ACDF for all measures, except right arm pain, as discussed below.

Table 30. Secondary Effectiveness Endpoints – Function, Health, and Satisfaction (24 Months)

Component	Randomized SECURE-C (N=151)	ACDF (N=140)	Posterior Probability		95% BCI[#] (lower, upper)
			Non-Inferiority	Superiority	
Neck Disability Index (≥25% improvement)	127/139 (91.4%)	101/116 (87.1%)	100.0%	87.8%	(-3.2%, 12.6%)
Neck Disability Index (≥15pt improvement)	124/139 (89.2%)	98/116 (84.5%)	100.0%	88.6%	(-3.3%, 13.8%)
VAS Neck Pain	104/133 (78.2%)	76/108 (70.4%)	100.0%	95.1%	(-1.7%, 19.9%)
VAS Left Arm Pain	74/133 (55.6%)	55/108 (50.9%)	99.7%	85.6%	(-5.5%, 18.4%)
VAS Right Arm Pain	57/133 (42.9%)	49/108 (45.4%)	83.8%	25.5%	(-15.9%, 7.9%)
VAS Neck Pain*	108/133 (81.2%)	78/108 (72.2%)	100.0%	98.4%	(0.9%, 21.0%)
VAS Left Arm Pain*	101/133 (75.9%)	73/108 (67.6%)	99.9%	88.6%	(-3.7%, 15.6%)
VAS Right Arm Pain*	98/133 (73.7%)	76/108 (70.4%)	99.9%	82.7%	(-4.6%, 13.4%)
SF-36 PCS	109/138 (79.0%)	89/114 (78.1%)	98.8%	62.6%	(-8.5%, 12.0%)
SF-36 MCS	70/138 (50.7%)	48/114 (42.1%)	99.9%	94.0%	(-2.5%, 21.2%)
Satisfaction	133/139 (95.7%)	98/115 (85.2%)	100.0%	99.7%	(2.9%, 17.8%)

[#]BCI for difference in proportions (Randomized SECURE-C – ACDF)
*Alternate definition of VAS success defined post hoc as either 20mm pain improvement or 0mm pain at the postoperative visit.

Neck Disability Index

The time course of success for NDI improvement is presented below in Table 31. Both randomized groups demonstrated similar postoperative improvement in NDI.

Table 31. Timecourse of Neck Disability Index Improvement

	6 wks			3 mo			6 mo			12 mo			24 mo		
	NR	**SEC**	**ACDF**	**NR**	**SEC**	**ACDF**	**NR**	**SEC**	**ACDF**	**NR**	**SEC**	**ACDF**	**NR**	**SEC**	**ACDF**
N	**88**	**151**	**139**	**86**	**147**	**131**	**84**	**142**	**128**	**82**	**140**	**124**	**78**	**139**	**116**
Improved (≥15 pts)	74%	79%	71%	83%	89%	85%	86%	90%	89%	87%	91%	89%	82%	89%	85%
Improved (≥25%)	*75%*	*85%*	*73%*	*88%*	*92%*	*89%*	*91%*	*94%*	*91%*	*92%*	*91%*	*91%*	*86%*	*91%*	*87%*
Maintained	17%	15%	24%	14%	8%	12%	12%	8%	8%	9%	6%	9%	15%	8%	11%
Deteriorated	9%	6%	6%	4%	3%	4%	2%	2%	3%	5%	3%	2%	3%	3%	4%

NR=Non-randomized SECURE®-C; SEC=Randomized SECURE®-C; ACDF=Control

VAS Neck and Arm Pain

The time course of VAS neck and arm pain improvement is presented in Table 32. Both randomized groups demonstrated similar postoperative improvement in VAS neck and left arm pain. For VAS right arm pain, fewer SECURE®-C patients had improvement than ACDF patients, except at 3 and 24 months.

An additional post-hoc analysis for neck, right arm and left arm pain was performed in which success was defined as *either* 20mm improvement *or* zero (0mm) pain at the postoperative visit. With this analysis, SECURE®-C is non-inferior to ACDF at 24 months for VAS neck, left arm and right arm pain improvement.

Note that during clinical inspections of two IDE sites, FDA noted possible errors in the VAS results due to incorrect measurement/scaling, and completion of the forms by study personnel rather than the patient at one of the sites. Therefore, the applicant remeasured all completed VAS forms at all sites; however, the difference between the original VAS data and the re-measured data was generally small and therefore did not alter the conclusions. Because the VAS data at one site was completed by some of the patients verbally rather than in writing, Table 32 and all VAS data in the SSED excludes the data from that one site, per FDA.

Table 32. Timecourse of VAS Neck and Arm Pain Improvement

Component	6 wks			3 mo			6 mo			12 mo			24 mo		
	NR	**SEC**	**ACDF**	**NR**	**SEC**	**ACDF**	**NR**	**SEC**	**ACDF**	**NR**	**SEC**	**ACDF**	**NR**	**SEC**	**ACDF**
Neck Pain, N	83	143	130	81	140	122	79	135	120	77	133	116	75	133	108
Improved (≥20mm)	74%	76%	75%	75%	84%	72%	77%	79%	76%	75%	81%	78%	72%	78%	70%
Maintained	21%	19%	12%	17%	12%	16%	14%	17%	17%	17%	12%	14%	25%	17%	22%
Deteriorated	6%	5%	13%	7%	4%	12%	9%	4%	8%	8%	7%	8%	3%	5%	7%
Improved (≥20mm)*	*77%*	*79%*	*76%*	*79%*	*86%*	*74%*	*81%*	*82%*	*78%*	*79%*	*84%*	*81%*	*75%*	*81%*	*72%*
L Arm Pain, N	83	143	130	81	140	122	79	135	120	77	133	116	75	133	108
Improved (≥20mm)	47%	57%	52%	51%	60%	49%	51%	59%	51%	48%	55%	53%	49%	56%	51%
Maintained	46%	36%	33%	40%	33%	39%	39%	36%	37%	42%	40%	35%	43%	37%	37%
Deteriorated	7%	7%	15%	10%	7%	12%	10%	5%	13%	10%	5%	12%	8%	8%	12%
Improved (≥20mm)*	*70%*	*79%*	*69%*	*74%*	*80%*	*69%*	*68%*	*82%*	*69%*	*70%*	*77%*	*71%*	*73%*	*76%*	*68%*
R Arm Pain, N	83	143	130	81	140	122	79	135	120	77	133	116	75	133	108
Improved (≥20mm)	45%	40%	46%	40%	42%	43%	44%	42%	43%	43%	42%	45%	48%	43%	45%

Component	6 wks			3 mo			6 mo			12 mo			24 mo		
	NR	SEC	ACDF	NR	SEC	ACDF	NR	SEC	ACDF	NR	SEC	ACDF	NR	SEC	ACDF
Maintained	46%	52%	43%	42%	54%	44%	46%	53%	49%	46%	50%	48%	47%	51%	43%
Deteriorated	10%	8%	11%	19%	4%	13%	10%	5%	8%	12%	8%	7%	5%	6%	12%
Improved (≥20mm)*	*68%*	*71%*	*68%*	*63%*	*76%*	*65%*	*70%*	*75%*	*68%*	*66%*	*74%*	*69%*	*73%*	*74%*	*70%*

NR=Non-randomized SECURE®-C; SEC=Randomized SECURE®-C; ACDF=Control
*Alternative success defined as either 20mm pain improvement or 0mm pain at the postoperative visit.

SF-36

The time course of success for SF-36 improvement is presented below in Table 33. Both randomized groups demonstrated similar postoperative improvement in SF-36.

Table 33. Timecourse of SF-36 Improvement

Component	6 wks			3 mo			6 mo			12 mo			24 mo		
	NR	SEC	ACDF	NR	SEC	ACDF	NR	SEC	ACDF	NR	SEC	ACDF	NR	SEC	ACDF
N	**88**	**151**	**138**	**86**	**147**	**130**	**84**	**141**	**126**	**82**	**140**	**123**	**78**	**138**	**114**
PCS															
Impr ≥15%	58%	60%	61%	72%	82%	77%	71%	82%	78%	74%	79%	78%	68%	79%	78%
Maintained	13%	25%	16%	7%	11%	11%	16%	14%	17%	12%	12%	14%	13%	10%	11%
Deteriorated	30%	15%	23%	21%	8%	12%	13%	5%	6%	13%	9%	8%	19%	11%	11%
MCS															
Impr ≥15%	44%	44%	40%	57%	47%	40%	52%	45%	43%	52%	49%	44%	58%	51%	42%
Maintained	27%	32%	25%	21%	27%	24%	26%	28%	30%	21%	29%	28%	19%	20%	23%
Deteriorated	28%	24%	35%	22%	26%	36%	21%	27%	27%	27%	23%	29%	23%	30%	35%

NR=Non-randomized SECURE®-C; SEC=Randomized SECURE®-C; ACDF=Control

Patient Satisfaction

The percentage of patients satisfied ("definitely" or "mostly") with surgery results at 12 months and 24 months, presented in Table 34 for the as-randomized population, was greater for the SECURE®-C group than the ACDF group.

Table 34. Patient Satisfaction (Definitely or Mostly Satisfied)

Visit	Non-randomized SECURE-C (N=89)	Randomized SECURE-C (N=151)	ACDF (N=140)	95% BCI[#] (lower, upper)
12 months	73/82 (89.0%)	135/140 (96.4%)	109/124 (87.9%)	(2.1%, 15.4%)
24 months	72/78 (92.3%)	133/139 (95.7%)	98/115 (85.2%)	(2.9%, 17.8%)

[#]BCI for difference in proportions (Randomized SECURE-C – ACDF), without predictions for 12 months, and with predictions for 24 months

Radiographic Assessments

Radiographic evaluations of mean range of motion, angulation and translation (during flexion and extension) for the treated level at the preoperative, 12 month and 24 month time points are shown in Table 35 for all subjects.

Table 35. Timecourse of Radiographic Range of Motion

Component	Preoperative			12 months			24 months		
	NR SEC	R SEC	ACDF	NR SEC	R SEC	ACDF	NR SEC	R SEC	ACDF
Range of Motion – Angulation (°)	9.5 ±5.2	8.5 ±4.82	7.2 ±4.32	11.0 ±5.3	9.5 ±5.58	1.1 ±1.22	10.2 ±6.1	9.3 ±5.91	0.7 ±0.72
Range of Motion – Translation (mm)	1.0 ±0.75	0.9 ±0.62	0.8 ±0.59	1.4 ±0.81	1.3 ±0.85	0.1 ±0.15	1.3 ±0.92	1.2 ±0.82	0.1 ±0.10

NR SEC=Non-randomized SECURE®-C; R SEC=Randomized SECURE®-C; ACDF=Control

The average angulation range of motion (flexion-extension) and range of results for all SECURE®-C patients at the preoperative, 6 month, 12 month and 24 month visit are shown in Figure 1.

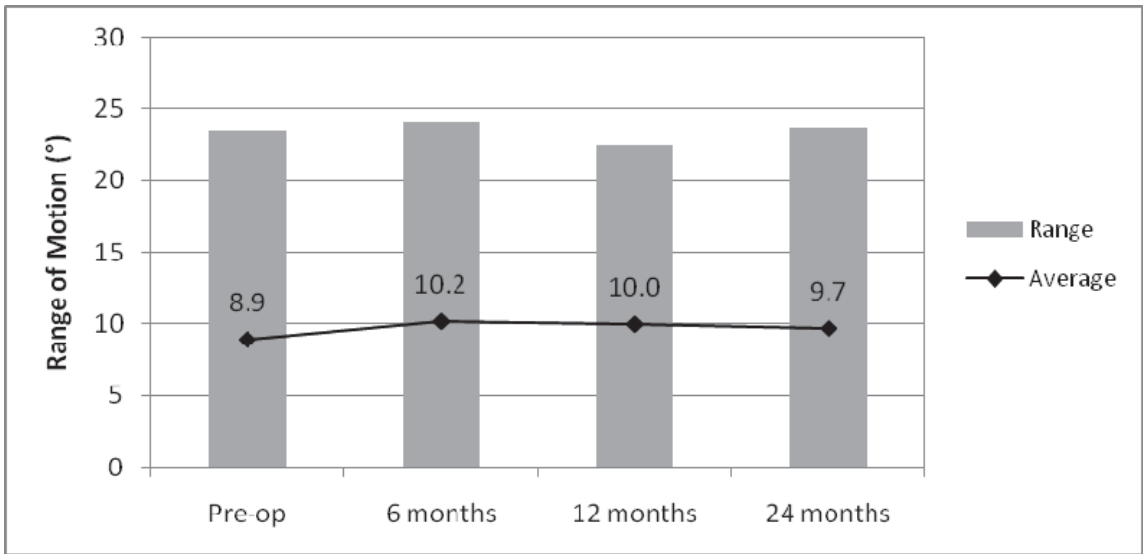


Figure 1. Average flexion/extension range of motion at each protocol visit for all patients receiving SECURE®-C.

Range of motion success for the SECURE®-C group was defined as ≥4° of motion in flexion-extension or maintenance of motion relative to preoperative baseline. Of the 165/195 (84.6%) SECURE®-C patients who were considered range of motion successes at 24 months (including both non-randomized and randomized patients), 160/165 (97.0%) achieved ≥4° of motion in flexion-extension, 101/165 (61.2%) maintained motion from preoperative baseline, and 96/165 (58.1%) were successes under both criteria. Only 5/165 (3.0%) maintained motion from preoperative baseline but had <4° of motion.

Table 36 presents data on change in range of motion from preoperative baseline for each timepoint by treatment group.

Table 36. Timecourse of Radiographic Change in Range of Motion for SECURE®-C

Group	Change	6 mo	12 mo	24 mo
NR SEC	Increased (>2°)	36/74 (48.6%)	35/73 (47.9%)	34/68 (50.0%)
	No change (-2 to 2)	17/74 (23.0%)	20/73 (27.4%)	12/68 (17.6%)
	Decreased (<-2)	21/74 (28.4%)	18/73 (24.7%)	22/68 (32.4%)

Group	Change	6 mo	12 mo	24 mo
R SEC	Increased (>2°)	55/130 (42.3%)	53/128 (41.4%)	48/112 (42.9%)
	No change (-2 to 2)	52/130 (40.0%)	36/128 (28.1%)	27/112 (24.1%)
	Decreased (<-2)	23/130 (17.7%)	39/128 (30.5%)	37/112 (33.0%)
All SEC	Increased (>2°)	91/204 (44.6%)	88/201 (43.8%)	82/180 (45.6%)
	No change (-2 to 2)	69/204 (33.8%)	56/201 (27.9%)	39/180 (21.7%)
	Decreased (<-2)	44/204 (21.6%)	57/201 (28.4%)	59/180 (32.8%)

NR SEC=Non-randomized SECURE®-C; R SEC=Randomized SECURE®-C; All SEC=Both Non-randomized and Randomized SECURE®-C

A histogram of angular range of motion on flexion/extension radiographs at 24 months for all patients treated with SECURE®-C is provided in Figure 2 below. This histogram uses values obtained by rounding recorded range of motion for each subject to the nearest integer.

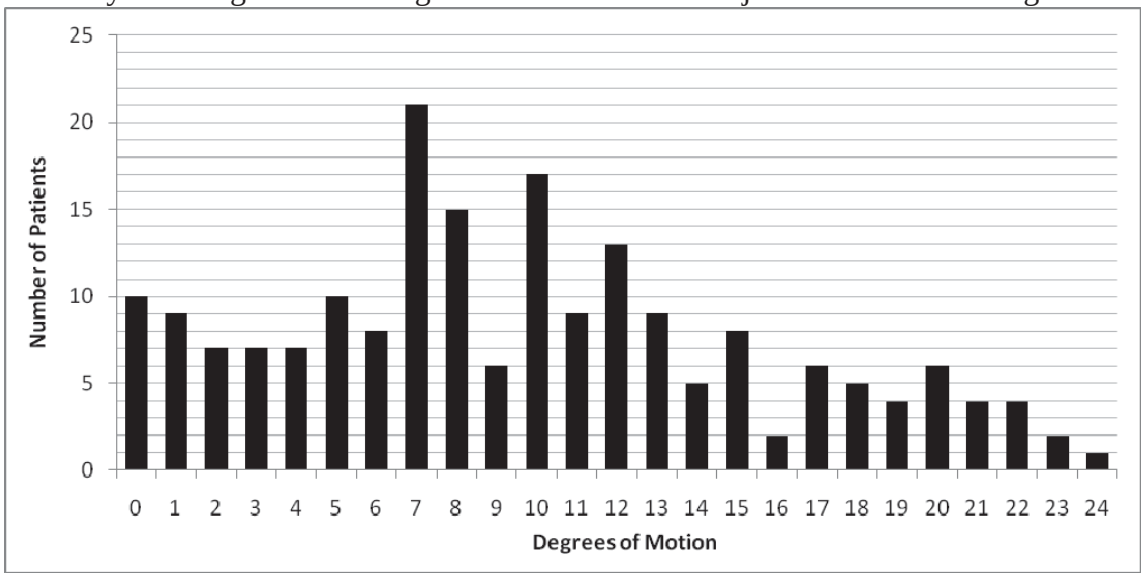


Figure 2. Histogram of flexion/extension range of motion at 24 months for all patients receiving SECURE®-C.

The applicant evaluated the correlation between range of motion and overall success (both definitions), NDI and VAS pain scores by evaluating the percentage of patients successful on each outcome stratified by range of motion status (≥4° or <4° on flexion/extension) as well as evaluating correlation plots. They found no meaningful correlations between range of motion and overall success or NDI or VAS pain outcomes for absolute values or changes from baseline.

Radiographic evaluation of mean disc height for the treated level at the preoperative, 12 month and 24 month time points are shown in Table 37 for all subjects.

Table 37. Timecourse of Radiographic Disc Height

Component	Preoperative			12 months			24 months		
	NR SEC	R SEC	ACDF	NR SEC	R SEC	ACDF	NR SEC	R SEC	ACDF
Disc Height	3.7 ±0.77	3.8 ±0.75	3.7 ±0.72	5.9 ±0.84	5.7 ±0.95	4.2 ±1.33	5.8 ±0.81	5.7 ±0.99	4.3 ±1.32

NR SEC=Non-randomized SECURE®-C; R SEC=Randomized SECURE®-C; ACDF=Control

Table 38 presents data on change in disc height from preoperative baseline at the 6 month, 12 month and 24 month time points by treatment group. Table 39 compares the change in disc height success (>2mm) for both treatment groups.

Table 38. Timecourse of Radiographic Change in Disc Height (>2mm)

Group	6 mo	12 mo	24 mo
NR SEC	51/78 (65.4%)	47/77 (61.0%)	42/71 (59.2%)
R SEC	67/136 (49.3%)	60/135 (44.4%)	47/118 (39.8%)
All SEC	118/214 (55.1%)	107/212 (50.5%)	89/189 (47.1%)
ACDF	15/121 (12.4%)	15/112 (13.4%)	15/95 (15.8%)

NR SEC=Non-randomized SECURE®-C; R SEC=Randomized SECURE®-C; All SEC=Both Non-randomized and Randomized SECURE®-C; ACDF=Control

Table 39. Secondary Effectiveness Endpoints – Radiographic Measurements (24 Months)

Component	Randomized SECURE-C	ACDF	Posterior Probability#	95% BCI# (lower, upper)
			Superiority	
Disc Height Change (>2mm)	47/118 (39.8%)	14/94 (14.9%)	100.0%	(12.9%, 35.5%)

#Comparison on the difference (SECURE-C - control) between proportions in randomized groups

Radiolucencies around the implant of more than 25% were evaluated; none (0%) of the SECURE®-C patients and 4/104 (3.8%) ACDF patients demonstrated radiolucencies around the implant at 24 months. There were no device migrations or displacements, including superior or inferior subsidence observed in any SECURE®-C patients.

Radiographic fusion for control patients was defined by the presence of bridging trabecular bone, without evidence of pseudarthrosis, and flexion-extension range of motion ≤2° in rotation and ≤3mm in translation. Fusion status of the control ACDF group at the 6 month, 12 month and 24 month time points is provided in Table 40.

Table 40. Timecourse of Radiographic Fusion Status for Control ACDF

Component	6 mo	12 mo	24 mo
Fusion status	24/128 (18.8%)	84/119 (70.6%)	90/101 (89.1%)

Global range of motion (C2-C7) and overall lordosis (C2-C7) were also measured at the 24 month visit. The means and standard deviations are presented in Table 41 for all groups.

Table 41. Global Range of Motion and Overall Lordosis at 24 Months for All Subjects

Component	Non-Randomized SECURE-C (N=88)	Randomized SECURE-C (N=148)	Randomized ACDF (N=144)
Global ROM (°)	51.1 ±15.00	48.8 ±16.33	40.0 ±12.14
Overall Lordosis (°)	9.7 ±12.25	10.0 ±12.23	8.4 ±10.55

Available radiographs for all treated SECURE®-C patients at the 6, 12, 24 month and later time points were assessed by an independent radiographic evaluator for heterotopic ossification (HO) grade, based on the Mehren[4] classification system (shown below), as well as to determine the number of patients with stable or "worsening" (progressing by at least one grade) HO from visit to visit.

Characterization of the Different Grades of Heterotopic Ossification (HO) in Total Cervical Disc Replacement (from Mehren et al.[4])

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

Results are shown in Table 42. Patients with HO findings (Grade II-Grade IV) at the 24 month timepoint began showing earlier grades of HO at the 6 and 12 month visits. HO will be studied further as part of both a seven year Postapproval Study and a ten year Enhanced Surveillance Postmarket Study that will be conducted by the applicant.

Table 42. Timecourse of Heterotopic Ossification for All SECURE®-C Subjects

Time Period/ Grade	Non-Randomized SECURE-C	Randomized SECURE-C	ALL SECURE-C
6 months			
Grade 0	57/82 (69.5%)	75/138 (54.3%)	132/220 (60.0%)
Grade I	16/82 (19.5%)	39/138 (28.3%)	55/220 (25.0%)
Grade II	7/82 (8.5%)	20/138 (14.5%)	27/220 (12.3%)
Grade III	2/82 (2.4%)	4/138 (2.9%)	6/220 (2.7%)
Grade IV	0/82 (0.0%)	0/138 (0.0%)	0/220 (0.0%)
12 months			
Grade 0	34/81 (42.0%)	50/136 (36.8%)	84/217 (38.7%)
Grade I	24/81 (29.6%)	32/136 (23.5%)	56/217 (25.8%)
Grade II	20/81 (24.7%)	42/136 (30.9%)	62/217 (28.6%)
Grade III	1/81 (1.2%)	8/136 (5.9%)	9/217 (4.1%)
Grade IV	2/81 (2.5%)	4/136 (2.9%)	6/217 (2.8%)
Stable	49/79 (62.0%)	73/131 (55.7%)	122/210 (58.1%)
Worsening	30/79 (38.0%)	58/131 (44.3%)	88/210 (41.9%)
24 months			
Grade 0	21/76 (27.6%)	30/122 (24.6%)	51/198 (25.8%)
Grade I	18/76 (23.7%)	22/122 (18.0%)	40/198 (20.2%)
Grade II	26/76 (34.2%)	43/122 (35.2%)	69/198 (34.8%)
Grade III	9/76 (11.8%)	16/122 (13.1%)	25/198 (12.6%)
Grade IV	2/76 (2.6%)	11/122 (9.0%)	13/198 (6.6%)
Stable	44/75 (58.7%)	69/116 (59.5%)	113/191 (59.2%)
Worsening	31/75 (41.3%)	47/116 (40.5%)	78/191 (40.8%)

The percentage of patients with range of motion ≥4° at 24 months for each HO grade is shown in Table 43. Overall, 82.1% of SECURE®-C patients have ≥4° motion at 24 months.

Table 43. Range of Motion (ROM) ≥4° at 24 months by HO Grade for All SECURE®-C Subjects

Variable	Grade 0 (N=51)	Grade I (N=40)	Grade II (N=69)	Grade III (N=25)	Grade IV (N=13)	Total
Patients w/ ROM ≥4°	50/51	37/40	59/67	14/24	0/13	160/195
% Patients ROM ≥4°	98.0%	92.5%	88.1%	58.3%	0.0%	82.1%

Demographic and baseline characteristics and clinical outcomes were evaluated for potential correlation with HO status (Grade 0/I and Grade II/II/IV). Patient height and weight were greater for the Grade II/III/IV group, while preoperative baseline NDI and VAS neck pain were higher for the Grade 0/I group. Based on the available data, no other demographic or baseline characteristics were found to correlate with HO. There was no correlation found between HO status and clinical outcomes, including NDI, VAS neck and arm pain, NDI 15 point improvement, and overall success (protocol-specified and FDA defined) after taking into account the baseline values of NDI and VAS neck and arm pain in the respective analyses.

Medication Use and Postoperative Procedures for Pain Management
Medication use at baseline preoperative and 24 months postoperative is reported for each group in Table 44. The rate of medication use was similar for all groups at both time points.

Table 44. Medication Use at Baseline Preoperative and 24 months Postoperative

Procedure	Non-Randomized SECURE-C (N=89)	Randomized SECURE-C (N=151)	Randomized ACDF (N=140)
Baseline Preoperative			
No Pain Medication	5 (5.6%)	11 (7.3%)	6 (4.3%)
Any Pain Medication	84 (94.4%)	140 (92.7%)	134 (95.7)
Non-Narcotics	*63 (70.8%)*	*109 (72.2%)*	*96 (68.6%)*
Weak Narcotics	*41 (46.1%)*	*71 (47.0%)*	*62 (44.3%)*
Strong Narcotics	*25 (28.1%)*	*50 (33.1%)*	*44 (31.4%)*
Muscle Relaxants	*33 (37.1%)*	*51 (33.8%)*	*57 (40.7%)*
24 months Postoperative			
No Pain Medication	36 (46.8%)	69 (50.4%)	55 (46.6%)
Any Pain Medication	41 (53.2%)	68 (49.6%)	63 (53.4%)
Non-Narcotics	*31 (40.3%)*	*58 (42.3%)*	*52 (44.1%)*
Weak Narcotics	*14 (18.2%)*	*27 (19.7%)*	*15 (12.7%)*
Strong Narcotics	*7 (9.1%)*	*12 (8.8%)*	*17 (14.4%)*
Muscle Relaxants	*13 (16.9%)*	*31 (22.6%)*	*24 (20.3%)*

Patients who underwent postoperative procedures for pain management, such as epidural injections, nerve blocks, etc., are reported for each group in Table 45. The rates of postoperative procedures are similar for all groups, with few patients receiving any particular treatment. Postoperative procedures may be performed for either diagnostic or therapeutic

purposes or both, therefore these data may overstate the number of patients with procedures truly performed for management of postoperative conditions.

Table 45. Patients Receiving Any Postoperative Procedure by Procedure Type

Procedure	Non-Randomized SECURE-C (N=88)	Randomized SECURE-C (N=148)	Randomized ACDF (N=144)
Nerve/Facet Treatment	**5 (5.7%)**	**8 (5.4%)**	**6 (4.2%)**
Epidural Steroid Injection	4 (4.5%)	4 (2.7%)	5 (3.5%)
Facet Injection	1 (1.1%)	4 (2.7%)	1 (0.7%)
Occipital Nerve Injection	0 (0.0%)	2 (1.4%)	1 (0.7%)
Foraminal Nerve Block	1 (1.1%)	0 (0.0%)	0 (0.0%)
Radiofrequency Lesioning	1 (1.1%)	0 (0.0%)	0 (0.0%)
Muscular Injections	**3 (3.4%)**	**4 (2.7%)**	**5 (3.5%)**
Trigger Point Injections	3 (3.4%)	2 (1.4%)	4 (2.8%)
Intramuscular Injection	0 (0.0%)	2 (1.4%)	1 (0.7%)
Botox Injection	0 (0.0%)	1 (0.7%)	0 (0.0%)
Other Procedures	**0 (0.0%)**	**0 (0.0%)**	**1 (0.7%)**
Acupuncture	0 (0.0%)	0 (0.0%)	1 (0.7%)

Note: This table includes data collected beyond 24 months.

Some patients went on to receive postoperative surgical treatment at the adjacent level, as shown in Table 46, with specific procedures reported in Table 47. ACDF patients had adjacent level surgery more often than SECURE®-C patients.

Table 46. Patients with Adjacent Level Surgical Treatment by Time Period

Period	Non-Randomized SECURE-C (N=88)	Randomized SECURE-C (N=148)	Randomized ACDF (N=144)
6 weeks	0/88 (0.0%)	0/148 (0.0%)	1/144 (0.7%)
3 months	0/88 (0.0%)	0/148 (0.0%)	0/144 (0.0%)
6 months	0/88 (0.0%)	0/148 (0.0%)	0/144 (0.0%)
12 months	0/88 (0.0%)	1/148 (0.7%)	3/144 (2.1%)
24 months	0/88 (0.0%)	3/148 (2.0%)	2/144 (1.4%)
36 months	1/88 (1.1%)	1/148 (0.7%)	2/144 (1.4%)
48 months	1/82 (1.2%)	0/86 (0.0%)	3/98 (3.1%)
60 months	0/49 (0.0%)	0/23 (0.0%)	1/31 (3.2%)

Table 47. Patients with Adjacent Level Surgical Treatment - Details

Procedure	Non-Randomized SECURE-C (N=88)	Randomized SECURE-C (N=148)	Randomized ACDF (N=144)
ACDF at adjacent level (1-level)	2 (2.3%)	0 (0.0%)	4 (2.8%)
ACDF at adjacent level (2-level)	0 (0.0%)	1 (0.7%)	6 (4.2%)
ACDF at adjacent level (3-level)	0 (0.0%)	0 (0.0%)	1 (0.7%)
CTDR at adjacent level	0 (0.0%)	1 (0.7%)	1 (0.7%)
Posterior Foraminotomy (2-level)	0 (0.0%)	2 (1.4%)	0 (0.0%)
Posterolateral Fusion (2-level)	0 (0.0%)	1 (0.7%)	0 (0.0%)

CTDR: Cervical Total Disc Replacement

3. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with overall success outcomes using a covariate analysis: gender, age, race, height, weight, BMI, current tobacco use, duration of neck symptoms, baseline NDI, baseline VAS neck and arm pain, and baseline SF-36 PCS and MCS. Only one baseline variable, height, was identified as having a statistically significant covariate and treatment interaction for the FDA-defined primary endpoint, consistent with a decreasing response for taller subjects for SECURE®-C compared to ACDF. Additional ad hoc analysis showed greater success for SECURE®-C subjects at all height quartiles, indicating that the finding is not indicative of a trend or concern for SECURE®-C.

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

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

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

In the clinical study of the SECURE®-C, 380 patients were enrolled and treated, all had reached the 24 month post-operative visit, and 331 (87.1%) had 24-month data available for analysis. Statistical analysis demonstrated that the results from all sites were poolable to determine safety and effectiveness. Analysis of patient demographic and baseline data showed no statistically significant differences between the treatment groups. Mean surgery time was 15.6 min longer for the randomized SECURE®-C group than for the control ACDF group, and was statistically different, though the magnitude of the difference is likely not clinically significant.

Overall success was defined in the study protocol as improvement in pain and disability using the Neck Disability Index, no complications or subsequent surgery at the index level, and fusion for the control treatment at 24 months. Additional analysis requested by FDA was defined as improvement in pain and disability using the Neck Disability Index, no potentially device-related adverse events, no subsequent surgery at the index level, maintenance or improvement in neurologic success, and no intraoperative change in treatment. The results of overall success, using both sets of success criteria, indicate that the SECURE®-C device is statistically superior to the ACDF control group at 24 months with a 24 month overall success rate of 90.1% in the randomized SECURE®-C group as compared to 71.1% in the ACDF control group for the Protocol-Specified Overall Success endpoint and a 24 month overall success rate of 83.8% in the randomized SECURE®-C group as compared to 73.2% in the ACDF control group for the FDA-Defined Overall Success endpoint.

To assess the impact of patients with unknown outcomes at 24 months or other potential biases, various sensitivity analyses were also conducted to confirm the robustness of the study conclusions. The results of nearly all sensitivity analyses indicate that the SECURE®-C is non-inferior to ACDF at 24 months.

In addition, the SECURE®-C group is at least non-inferior to the ACDF control group at 24 months for all components of both definitions of overall success, while for the subsequent surgery and device-related adverse event components, the SECURE®-C group achieves statistical superiority at 24 months as compared to the ACDF control group.

Range of motion success for the SECURE®-C group was defined as ≥4° of motion in flexion-extension at 24 months or maintenance of motion at 24 months relative to preoperative baseline, and 165/195 (84.6%) SECURE®-C patients were considered range of motion successes at 24 months according to this definition (including both non-randomized and randomized patients). Range of motion at 24 months was not found to correlate with overall success (either definition), or NDI or VAS pain scores by comparative statistical analyses.

In conclusion, the study data indicate that, at 24 months postoperatively, the SECURE®-C device is at least as effective as the ACDF control group in terms of clinically significant improvement on the Neck Disability Index and maintenance or improvement in neurological status and is statistically superior to the ACDF control group in terms of subsequent surgeries at the index level, device-related adverse event rates, and overall success according to both composite definitions analyzed.

B. Safety Conclusions

The risks of the SECURE®-C device are based on nonclinical laboratory and animal studies as well as data collected in the clinical study conducted to support PMA approval as described above.

Preclinical testing performed on the device demonstrated that the SECURE®-C should withstand the expected physiologic loads in the cervical spine.

In the clinical study, the investigational SECURE®-C device was found to have a reasonable assurance of safety and to be at least as safe as the ACDF control treatment. Specifically, the rate of SECURE®-C patients having at least one adverse event, an event classified by the Clinical Events Committee (CEC) as a surgery-related adverse event, or an event classified by the CEC as a severe or life threatening adverse event was not statistically different from the control group rate. The rate of SECURE®-C patients classified as having a device-related adverse event by the CEC (2.7% for randomized SECURE®-C patients) was statistically lower than the ACDF control group rate (9.7%); however, it is important to consider that the CEC used a relatively narrow definition as described above. The percentage of patients experiencing secondary surgeries at the index level was also lower for the SECURE®-C group (2.5%) as compared to the ACDF control group (9.7%), and was statistically superior at 24 months when randomized groups were compared. The randomized SECURE®-C and

ACDF control groups demonstrated similar percentages of patients with stable or improved neurologic status at each time point including 24 months (96.7% stable or improved in the SECURE®-C group at 24 months as compared to 94.1% stable or improved in the ACDF control group at 24 months), and statistical comparisons of 24 month neurologic status demonstrate non-inferiority of the SECURE®-C as compared to the ACDF control group.

In conclusion, the clinical study data indicate that, at 24 months postoperatively, the SECURE®-C device has a reasonable assurance of safety and is at least as safe as the ACDF control group in regards to adverse event rates and neurologic status, and statistically superior to the ACDF control group in terms of the need for secondary surgery at the index level.

C. Benefit-Risk Conclusions

The probable benefits of the SECURE®-C device are also based on data collected in the clinical study conducted to support PMA approval as described above.

The clinical study demonstrated several benefits of the SECURE®-C device over the 24 month time period studied.

- The benefit of the SECURE®-C in terms of clinically meaningful improvement in function (as measured by a 15 point improvement on the Neck Disability Index) at 24 months postoperatively was comparable to the standard of care, ACDF, in that the majority of patients in both treatment groups in the clinical study experienced this benefit (89.2% of randomized SECURE®-C patients and 84.5% of ACDF patients).

- The benefit of the SECURE®-C in terms of maintenance or improvement in neurologic status (as measured during the neurological examination done by the investigator) at 24 months postoperatively was also comparable to the standard of care, ACDF, in that the majority of patients in both treatment groups in the clinical study experienced this benefit (96.0% of randomized SECURE®-C patients and 94.9% of ACDF patients).

- In terms of improvement in neck and arm pain (as measured by either a 20mm improvement in pain on a Visual Analog Scale as compared to baseline or 0mm of pain at the visit), at 24 months postoperatively, the benefit of the SECURE®-C was at least comparable to the standard of care, ACDF, and possibly superior for neck pain improvement. Again, the majority of patients in both treatment groups in the clinical study experienced the benefit of improvement in neck and/or arm pain (81.2% of randomized SECURE®-C patients and 72.2% of ACDF patients with clinically meaningful neck pain improvement at 24 months; 73.7% of randomized SECURE®-C patients and 70.4% of ACDF patients with clinically meaningful right arm pain improvement at 24 months; and 75.9% of randomized SECURE®-C patients and 67.6% of ACDF patients with clinically meaningful left arm pain improvement at 24 months).

In addition, although the sponsor did not formally collect data on patient tolerance for risk and patient perception on benefit, the patients' perception of their benefit and risk was

indirectly measured through a patient satisfaction survey. At 24 months, the majority of SECURE®-C patients responded that they were definitely or mostly satisfied with their treatment (95.7% of randomized SECURE®-C patients) as compared to a numerically lower satisfaction rate in the ACDF control group (85.2% of ACDF patients who responded that they were definitely or mostly satisfied with their treatment at 24 months).

In addition, there was a relatively low rate of secondary surgical interventions at the index level in the SECURE®-C patients over the clinical study period (2.5% of all SECURE®-C patients including both randomized and non-randomized patients), and the index level secondary surgery rate in the SECURE®-C group was statistically lower than the standard of care, ACDF (9.7% of ACDF patients with an index level secondary surgery) at 24 months.

Several additional factors were considered in determining the probable benefits and risks for the SECURE®-C device. Limitations of the clinical study design, including the inability to mask patients to their treatment assignment, reliance on subjective endpoints, concerns about potential placebo effect, and subjectivity in adverse event classification, were considered. In addition, the impact of missing data and the robustness of the sensitivity analyses provided to address the missing data as well as the generalizability of the study results were also considered. Finally, alternative available treatments and risk mitigation strategies were considered as was the fact that the only available indicator of patient tolerance for risk and perspective on benefit was patient satisfaction data.

Note that other theoretical benefits of total disc replacement devices, such as the SECURE®-C, include preservation of range of motion and decreased risk of adjacent segment degeneration; however, the clinical study conducted to support PMA approval of the SECURE®-C was not specifically designed or powered to study these potential benefits as primary endpoints, and any potential benefit in terms of clinically significant reduction in adjacent level degeneration would not necessarily be expected in the two year time period of the clinical study.

In conclusion, given the available information above, the data support that for reconstruction of the disc at one level from C3-C7 following single-level discectomy for intractable radiculopathy (arm pain and/or a neurological deficit) with or without neck pain, or myelopathy due to a single-level abnormality localized to the disc space and specific radiographic findings as outlined above in the Indications for Use, the probable benefits of the SECURE®-C 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 SECURE®-C device when used in accordance with the indications for use. Based on the clinical study results, it is reasonable to conclude that a significant portion of the indicated patient population will achieve clinically significant results and that the clinical benefits of the use of the SECURE®-C device in terms of improvement in pain and disability, and the potential for motion preservation, outweigh the risks associated with the device and surgical procedure through two years follow-up when used in the indicated population in accordance with the directions for use.

XIII. CDRH DECISION

CDRH issued an approval order on September 28, 2012. The final conditions of approval cited in the approval order are described below.

The sponsor has agreed to provide the following data as part of the annual report:

The sponsor must attempt to retrieve all explanted SECURE-C devices (including but not limited to those retrieved from patients in the PAS and ESS) for analysis. All retrievals will be analyzed and reported per the agreed Explant Analysis protocol.

In addition to the Annual Report requirements, the sponsor must provide the following data in post-approval study reports (PAS).

1. *Extended Follow-up of Premarket Cohort:* The sponsor must perform a 7-year post-approval study (PAS) to evaluate the longer term safety and effectiveness of the SECURE-C Cervical Artificial Disc as compared to ACDF by following the 334 subjects from the pivotal investigational device exemption (IDE) study (220 SECURE-C subjects, and 114 ACDF subjects) annually through 7 years. At each annual (±4 month) visit, the sponsor will collect the following data: Neck Disability Index, neck and right/left arm pain Visual Analog Scale (VAS), health status survey (SF-36), patient satisfaction, neurological status, radiographic information, medication usage and postoperative treatment for pain management, work status, and all adverse events regardless of cause. Radiographic information collected will include: range of motion on flexion/extension films (angulation and translation as well as the correlation of range of motion with outcomes), disc height, radiolucency, device displacement or migration, spinal fusion (control arm only), and heterotopic ossification (including grade, stability over time, and correlation with patient characteristics and postoperative outcomes). The sponsor will also collect data on adjacent level degeneration/disease including both surgical and non-surgical adjacent level treatments as well as adjacent level diagnoses and adjacent level range of motion.

   The primary objective of the study is to evaluate the overall success rate, using Overall Success Definition 1, defined as:
   - Pain/Disability Improvement of at least 25% in the Neck Disability Index (NDI) at 5 years and 7 years compared with the score at baseline;
   - No device failures (at the index level) requiring revision, re-operation, removal or supplemental fixation;
   - Absence of major complications defined as major vessel injury, neurological damage, or nerve injury; and
   - For control fusion patients only, radiographic fusion, as defined by the presence of bridging trabecular bone, without evidence of pseudarthrosis.

   The sponsor also has agreed to conduct an additional analysis evaluating Overall Success Definition 2, defined as follows:
   - Pain/Disability Improvement of at least 15 points in the Neck Disability Index (NDI) at 5 years and 7 years compared with the score at baseline;

- No secondary surgery at the index level, including revision, removal, reoperation and supplemental fixation
- No potentially device-related adverse events
- Maintenance or improvement in all components of neurologic status
- No SECURE-C intraoperative changes in treatment

Success rates between the randomized investigational and control groups will be compared and assessed for non-inferiority based on a ten percent non-inferiority margin for both overall success analyses. Patients who were non-recoverable non-responders prior to 24 months will carry forward as failures for each subsequent annual visit. Several sensitivity analyses will also be done.

FDA will expect at least 85% follow-up at the 7-year time point to provide sufficient data to evaluate safety and effectiveness.

2. *Enhanced Surveillance System:* The sponsor must perform a 10-year Enhanced Surveillance Study (ESS) of the SECURE®-C Cervical Artificial Disc to fully characterize adverse events when the device is used in the intended patient population under general conditions of use in the United States and in the rest of the world. The sponsor will collect, analyze, and submit all adverse event data including subsequent surgeries, heterotopic ossification, and other device issues. Information will be actively collected from annual surgeon surveys and on the company website. Information will also be collected passively through complaints and MDRs, explant analysis, and literature review.

   In addition, the sponsor will actively collect surgeon feedback annually to elicit information related to heterotopic ossification, device malfunction, device removal, or other serious device-related complications. This information will be collected using surgeon surveys. All of the surgeons who have been trained on the use of SECURE®-C in the U.S. will be surveyed annually and the number of surveys issued and received will be reported. If a survey response includes any information related to an adverse event, the sponsor will collect additional data as specifically outlined in the ESS protocol and report that data to FDA.

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

XIV. APPROVAL SPECIFICATIONS

Directions for Use: See device labeling

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

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

[1]White AA and Panjabi MM. Clinical Biomechanics of the Spine. 2nd Edition, Lippincott Williams and Wilkins, Philadelphia, Chapters 1 and 2, 1990.

[2]Adams MA, Dolan P, Hutton WC and Porter RW. Diurnal changes in spinal mechanics and their clinical significance. JBJS Br 72(2):266-70, 1990.

[3]Pitzen T, Schmitz B, Georg T, Barbier D, Beuter T, Steudel WI, and Reith A. Variation in endplate thickness in the cervical spine. Eur Spine J 13:235-240, 2004.
[4]Mehren C, Suchomel P, Grochulla F, Barsa P, Sourkova P, Hradil J, Korge A, Mayer H. Heterotopic Ossification in Total Cervical Artificial Disc Replacement. Spine 31(24):2802-2806, 2006.