SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Artificial Cervical Disc
Device Trade Name:	Simplify® Cervical Artificial Disc
Device Product Code	MJO
Applicant's Name/Address:	Simplify Medical, Inc. 685 North Pastoria Avenue Sunnyvale, CA 94085
Date of Panel Recommendation:	None
Premarket Approval Application: (PMA Number)	P200022
Date of FDA Notice of Approval:	September 18, 2020

II. INDICATIONS FOR USE

Simplify® Cervical Artificial Disc is indicated for use in skeletally mature patients for reconstruction of the disc at one level from C3-C7 following single-level discectomy for intractable radiculopathy (arm pain and/or a neurological deficit) with or without neck pain, or myelopathy due to a single-level abnormality localized to the level of the disc space and manifested by at least one of the following conditions confirmed by radiographic imaging (e.g., X-rays, computed tomography (CT), magnetic resonance imaging (MRI)): herniated nucleus pulposus, spondylosis (defined by the presence of osteophytes), and/or visible loss of disc height as compared to adjacent levels. Patients receiving Simplify® Cervical Artificial Disc should have failed at least six weeks of non-operative treatment or have the presence of progressive symptoms (e.g., numbness or tingling) prior to implantation. Simplify® Cervical Artificial Disc is implanted via an open anterior approach.

III. CONTRAINDICATIONS

Simplify® Cervical Artificial Disc should not be implanted in patients with the following conditions:

- An active systemic infection or an infection at the operative site.
- Intractable radiculopathy or myelopathy necessitating surgical treatment at more than one cervical level.
- Osteoporosis or osteopenia defined as DEXA bone mineral density T-score less than -1.5.
- Known allergy to the implant materials (PEEK, ceramic, titanium).
- Severe facet disease or facet degeneration.
- Bridging osteophytes.

- Marked cervical instability on neutral lateral or flexion/extension radiographs (e.g., radiographic signs of subluxation > 3.0mm or angulation of the disc space more than 11° greater than adjacent segments).
- Significant cervical anatomical deformity at the index level or clinically compromised cervical vertebral bodies at the index 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).

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Simplify® Cervical Artificial Disc Instructions for Use.

V. DEVICE DESCRIPTION

The Simplify® Cervical Artificial Disc is a cervical artificial intervertebral device manufactured from PEEK endplates and a mobile, zirconia-toughened alumina ceramic core. The PEEK endplates have a plasma-sprayed titanium coating per ISO 5832-2 and ASTM F1580. The articulating surfaces on the endplates have a concave surface and the core has two convex surfaces. The device is pictured in the figures below (**Figure 1** and **Figure 2**).

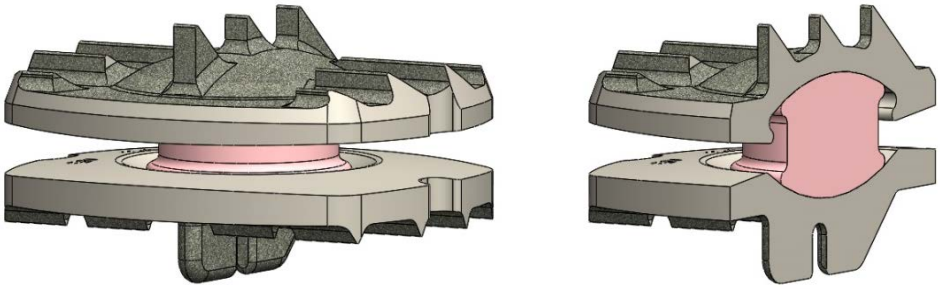


Figure 1: Schematic of Simplify® Cervical Artificial Disc: assembly (left) and mid-sagittal section (right).

For the Simplify® Cervical Artificial Disc family, two core options (i.e., either small or large) are used for all assemblies. The articulating features of superior and inferior endplates are identical and congruent with the appropriate core. Superior and inferior endplates are available in three footprints (Small, Medium, Large), three thicknesses resulting in three device heights (4 mm, 5 mm, 6 mm), and two lordosis angles (0° and 5°), as shown in **Figure 3** and **Table 1** below. The superior endplates have a retention ring feature. All endplates are titanium coated on the bone interfacing surfaces, with two options available for coating thickness (80 µm or 160µm). All endplate components, regardless of configuration, have identical manufacturing process flow, including packaging and sterilization.

The Simplify® Cervical Artificial Disc is designed to provide a theoretical maximum of ± 12° in any combination of flexion-extension and lateral bending, unlimited axial rotation, and 1-2 mm translation. These ranges of motion are intended to permit the patient's anatomy to determine actual range of motion without imposing an artificial limit that may be restrictive to the patient's

kinematic profile. The maximum range of motion *in vivo* will be dictated by the patient's anatomical boundaries or the device limits, whichever is smaller.

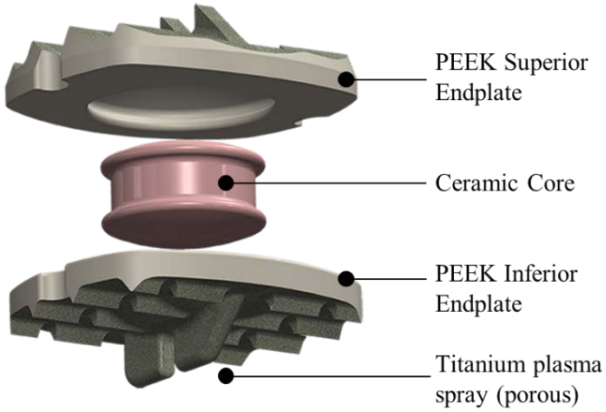


Figure 2: Exploded Schematic of the Simplify® Cervical Artificial Disc

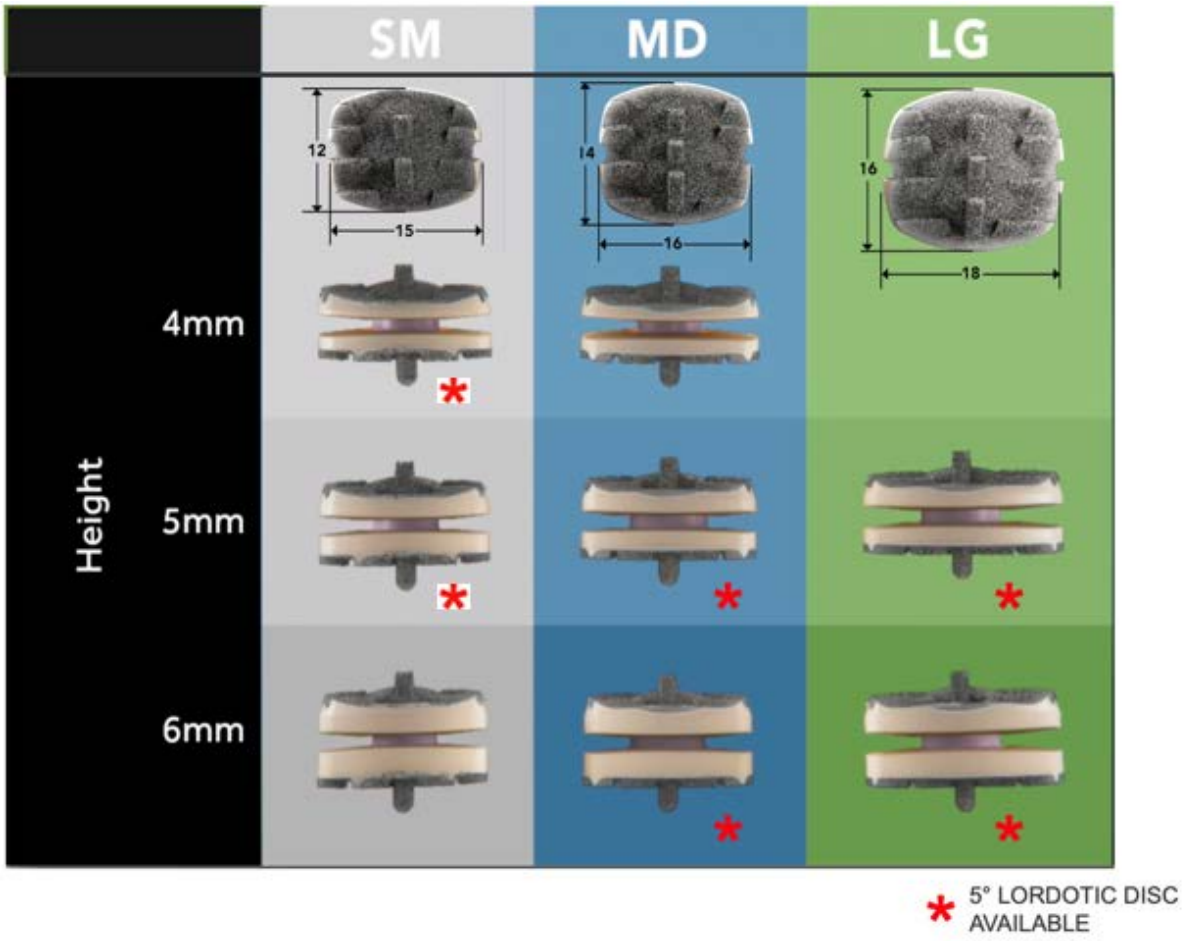


Figure 3: Simplify® Cervical Artificial Disc Heights and Sizes

Table 1: Simplify® Cervical Artificial Disc Part Listing and Size Overview

Disc Sizes	Catalog Number	A/P Width (mm)	Lateral Width (mm)	Height (mm)	Lordosis (°)
80 Micron Coating					
Simplify® Cervical Artificial Disc Size SM, Height 4	SM-4-T	12	15	4	0
Simplify® Cervical Artificial Disc Size SM, Height 4, 5° Lordosis	SM-4L-T	12	15	4	5
Simplify® Cervical Artificial Disc Size SM, Height 5	SM-5-T	12	15	5	0
Simplify® Cervical Artificial Disc Size SM, Height 5, 5° Lordosis	SM-5L-T	12	15	5	5
Simplify® Cervical Artificial Disc Size SM, Height 6	SM-6-T	12	15	6	0
Simplify® Cervical Artificial Disc Size MD, Height 4	MD-4-T	14	16	4	0
Simplify® Cervical Artificial Disc Size MD, Height 5	MD-5-T	14	16	5	0
Simplify® Cervical Artificial Disc Size MD, Height 5, 5° Lordosis	MD-5L-T	14	16	5	5
Simplify® Cervical Artificial Disc Size MD, Height 6	MD-6-T	14	16	6	0
Simplify® Cervical Artificial Disc Size MD, Height 6, 5° Lordosis	MD-6L-T	14	16	6	5
Simplify® Cervical Artificial Disc Size LG, Height 5	LG-5-T	16	18	5	0
Simplify® Cervical Artificial Disc Size LG, Height 5, 5° Lordosis	LG-5L-T	16	18	5	5
Simplify® Cervical Artificial Disc Size LG, Height 6	LG-6-T	16	18	6	0
Simplify® Cervical Artificial Disc Size LG, Height 6, 5° Lordosis	LG-6L-T	16	18	6	5
160 Micron Coating					
Simplify® Cervical Artificial Disc Size SM, Height 4	SM-4	12	15	4	0
Simplify® Cervical Artificial Disc Size SM, Height 4, 5° Lordosis	SM-4L	12	15	4	5
Simplify® Cervical Artificial Disc Size SM, Height 5	SM-5	12	15	5	0
Simplify® Cervical Artificial Disc Size SM, Height 5, 5° Lordosis	SM-5L	12	15	5	5
Simplify® Cervical Artificial Disc Size SM, Height 6	SM-6	12	15	6	0
Simplify® Cervical Artificial Disc Size MD, Height 4	MD-4	14	16	4	0
Simplify® Cervical Artificial Disc Size MD, Height 5	MD-5	14	16	5	0
Simplify® Cervical Artificial Disc Size MD, Height 5, 5° Lordosis	MD-5L	14	16	5	5
Simplify® Cervical Artificial Disc Size MD, Height 6	MD-6	14	16	6	0
Simplify® Cervical Artificial Disc Size MD, Height 6, 5° Lordosis	MD-6L	14	16	6	5
Simplify® Cervical Artificial Disc Size LG, Height 5	LG-5	16	18	5	0
Simplify® Cervical Artificial Disc Size LG, Height 5, 5° Lordosis	LG-5L	16	18	5	5
Simplify® Cervical Artificial Disc Size LG, Height 6	LG-6	16	18	6	0
Simplify® Cervical Artificial Disc Size LG, Height 6, 5° Lordosis	LG-6L	16	18	6	5

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives available for the treatment of symptomatic degeneration of the cervical spine at a single-level presenting with arm pain and/or neurological deficit (intractable radiculopathy), with or without neck pain or myelopathy and radiographic abnormality.

- Nonoperative alternative treatments, which include, but are not limited to, physical therapy, medications, braces, chiropractic care, bed rest, spinal injections, or exercise programs.
- Surgical alternatives, which include, but are not limited to:
    - Surgical decompression alone
    - Surgical decompression using intervertebral cages or bone grafting techniques, with or without supplemental anterior plating
    - Decompression with posterior spinal systems (e.g., rods, hooks, wires)
    - Another FDA-approved artificial cervical disc

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

VII. MARKETING HISTORY

The Simplify® Cervical Artificial Disc has been marketed outside of the United States since 2016. The Simplify® Cervical Artificial Disc is currently distributed in the United Kingdom and Germany. The Simplify® Cervical Artificial Disc has not been withdrawn from any distribution/marketing in any country for safety or effectiveness reasons.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) identified from the Simplify® 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 general surgical procedure; (2) those associated with anterior cervical spine surgery; and (3) those associated with a cervical artificial disc device, including the Simplify® 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.

General Surgery Risks

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

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

Anterior Cervical Surgery Risks

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

- Infection/abscess/cyst, localized or systemic
- Injury or damage to the trachea, esophagus, nerves or blood vessels
- Dysphagia
- Hoarseness
- Vocal cord paralysis
- Paresis
- Recurrent laryngeal nerve palsy

- Soft tissue damage
- Spinal cord damage
- Dural tear with cerebrospinal fluid leakage
- Arm weakness or numbness
- Bowel, bladder or sexual dysfunction
- Nerve root injury
- Airway obstruction
- Epidural hematoma or bleeding
- Epidural fibrosis
- Vertebral body fracture
- Dysesthesia or numbness
- Paresthesia
- Unresolved pain
- Surgical intervention at incorrect level
- Need for supplemental fixation
- Spinal instability
- Death

Cervical Artificial Disc Risks

Risks specific to cervical artificial discs, including the Simplify® Cervical Artificial Disc, are but may not be limited to:

- Infection/abscess/cyst, localized or systemic
- Allergic reaction to the implant materials
- Implant failure
- Device migration
- Device subsidence
- Device fatigue or fracture or breakage
- Device instability
- Separation of device components
- Placement difficulties, device malposition
- Improper device sizing
- Excessive device height loss
- Wear debris
- Disc space collapse
- Material degradation
- Excessive facet loading
- Kyphosis or hyper-extension
- Loss of flexibility
- Asymmetric range of motion
- Vertebral body fracture
- Spinal cord damage,
- Dural tear with cerebrospinal fluid leakage
- Soft tissue damage

- Epidural fibrosis
- Nerve injury, paralysis or weakness that is temporary or permanent
- Injury or damage to the trachea, esophagus, or blood vessels
- Epidural hematoma or bleeding
- Dysesthesia or numbness
- Paresthesia
- Failure to relieve symptoms including unresolved pain
- Additional surgery due to loss of fixation, infection or injury
- Spontaneous fusion due to heterotopic ossification, development of bridging bone or osteophytes
- Periarticular calcification and fusion
- Development of spinal conditions, including but not limited to spinal stenosis, spondylolisthesis, or retrolisthesis
- Removal, revision, reoperation or supplemental fixation of the disc
- Osteolysis, bone loss, or bone resorption
- Death

For the specific adverse events (AEs) that occurred in the Simplify® Cervical Artificial Disc 1-Level clinical study, please see Section X.

IX. SUMMARY OF NON-CLINICAL STUDIES

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

Laboratory Studies

- Static Axial Compression
- Dynamic Axial Compression
- Static Compression Shear
- Dynamic Compression Shear
- Static Peripheral Supported Compression
- Dynamic Peripheral Supported Compression
- Subluxation/ Expulsion
- Subsidence
- Wear (Mode I Wear)
- Third Body Wear (Mode 3 Wear)
- Impingement (Mode 4 Wear)
- Range of Motion
- Coating Testing

Additional Studies

- MR Compatibility
- Biocompatibility/ Pyrogenicity/ Neurotoxicity
- Device Sterilization
- Shelf Life and Transit Validation

A. Laboratory Studies

A summary of the conducted laboratory testing is presented in the following table, stratified by the above classifications (**Table 2**).

Table 2: Non-Clinical Study Summary

Test Name	Purpose	Test Method	Acceptance Criteria	Results
Static and Dynamic Strength				
Static and Fatigue under Axial Compression	Verify static and fatigue performance under simulated physiologic conditions are sufficient to withstand in vivo compressive loads	Six (6) Simplify® Cervical Artificial Disc specimens were tested under static compression in 37°C deionized water at a rate of 25mm/min until failure or ≈10 kN (capacity of load cell) was reached. Three (3) Simplify® Cervical Artificial Disc specimens were tested	Must withstand ≥ 300 N static load without functional failure Fatigue load (10×10^6 cycles runout) ≥ 150 N	Static strength: ≥10 kN Static stiffness: 2317 N/mm (for information only) Dynamic strength: 375 N Change in disc height: 0.24 mm All acceptance criteria were met.

Test Name	Purpose	Test Method	Acceptance Criteria	Results
		under dynamic compression in 37°C 0.9% saline to 10 x 10^6 cycles, using a sinusoidal wave form with R=10 at 2 Hz. Testing per ASTM F2346	Average residual height loss after runout ≤ 1.5mm	
Static and Fatigue Shear Strength	Verify that the static and fatigue performance are sufficient to withstand anticipated in vivo shear compressive loads	Six (6) Simplify® Cervical Artificial Disc specimens were tested under static compression-shear (27°) in 37°C deionized water at a rate of 25 mm/min until failure. Three (3) Simplify® Cervical Artificial Disc specimens were tested under dynamic compression-shear in 37°C 0.9% saline to 10 x 10^6 cycles, using a sinusoidal wave form with R=10 at 2 Hz. Testing per ASTM F2346	Must withstand ≥ 20 N static shear without functional failure Fatigue load (10 x10^6 cycles runout) ≥ 20 N	Static compressive shear strength: 284 N Dynamic compressive shear strength: ≥ 123 N All acceptance criteria were met.
Endplate Strength under Peripheral Support	Characterize the strength of the Simplify® Cervical Artificial Disc under the special case of a peripherally supported endplate	Five (5) Simplify® Cervical Artificial Disc specimens were tested under static compression in 37°C deionized water at a rate of 25mm/min until failure. Custom fixturing left the central 14 mm diameter region unsupported. Seven (7) Simplify® Cervical Artificial Disc specimens were tested under dynamic compression in 37°C 0.9% saline at various loads using a sinusoidal wave form with R=10 at 2 Hz. Runout was considered 2 x 10^6 cycles, Testing was based on ASTM F2346	N/A (for characterization purposes)	Ultimate static strength was 1253 N. Linear regression analysis of dynamic tests indicates fatigue strength ≈388 N. Results compare favorably to static strength requirements.
Subluxation/ Expulsion				
Subluxation/ Expulsion	Verify ability of Simplify® Cervical Artificial Disc to	Simplify® Cervical Artificial Discs implanted in Grade 15 polyurethane	Force ≥ 20 N required to cause subluxation or	Resistance to expulsion at 0°: 223 N; at 12 °: 193 N.

Test Name	Purpose	Test Method	Acceptance Criteria	Results
	resist expulsion and subluxation using simulated physiologic conditions	foam with 100N static axial preload were subjected to 6 mm/min anterior shear. Load was applied to both endplates (expulsion) or one endplate (subluxation) with endplate parallel or in 12° extension. Twenty test specimens, five (5) per test configuration, were tested.	expulsion (defined as movement ≥ 3 mm)	Resistance to subluxation at 0°: 117N; at 12°: 154 N All acceptance criteria were met.
Subsidence				
Subsidence	Verify the ability of the Simplify® Cervical Artificial Disc to resist subsidence using simulated physiologic conditions	Five (5) Simplify® Cervical Artificial Disc specimens were compressed between Grade 15 polyurethane foam blocks at a rate 0.1 mm/sec per ASTM F2267.	Subsidence force ≥ 300 N	Subsidence force: 768.0 N. Acceptance criterion was met.
Wear				
Device Wear, Mode I	Characterize *in vitro* wear properties	Six (6) Simplify® Cervical Artificial Disc test specimens were subjected to 10 x 10^6 cycles of combined 50-150 N axial load, ±7.5° flexion/extension, ±6°axial rotation, and ±6° lateral bending at 1 Hz per ISO 18192-1 and ASTM F2423 while submerged in bovine serum solution with a protein concentration of 5 g/L Two (2) test specimens served as load soak controls.	Wear rate ≤ 7 mg/MC (70 mg total) No fracture, functional failure or impingement	Cumulative mass loss: 9.0 mg Average gravimetric wear rate: 0.9 mg/MC (Average volumetric wear rate: 0.7 mm^3/MC)No devices demonstrated signs of fracture, functional failure, or impingement. All acceptance criteria were met.
Wear, Mode III (Third Body)	To characterize in vivo wear properties under third-body abrasive wear conditions (Mode III)	A titanium scar was created on both articulating surfaces of the core in Simplify® Cervical Artificial Disc test specimens. Six (6) specimens were then subjected to 5 x 10^6 cycles of combined 50-150 N axial load, ±7.5° flexion/extension, ±6° axial rotation, and ±6° lateral bending at 1 Hz per ISO 18192-1 and ASTM F2423 while submerged in bovine serum solution with a protein concentration of 5	N/A (for characterization purposes)	Average mass wear rate: 2.8 mg/MC No devices demonstrated signs of fracture or functional failure.

Test Name	Purpose	Test Method	Acceptance Criteria	Results
		g/L. Two (2) test specimens served as load soak controls.		
Wear, Mode IV (Impingement)	Characterize the impingement properties using simulated physiologic conditions (Mode IV wear)	Six (6) Simplify® Cervical Artificial Disc test specimens, three (3) SM and three (3) LG, were subjected to 1 x 10^6 cycles of combined 150 N axial load, 17-18° extension, and ±6° axial rotation at 1 Hz per ASTM F3295 while submerged in bovine serum solution with a protein concentration of 5 g/L. Two (2) test specimens, one per size, served as load soak controls.	N/A (for characterization purposes)	Gravimetric wear rates: Size SM: 1.0 mg/MC Size LG: 1.9 mg/MC No devices demonstrated signs of fracture or functional failure.
Range of Motion				
Range of Motion	Characterize range of motion of Simplify® Cervical Artificial Disc using finite element techniques.	Finite Element (FE) methods compared range of motion for an intact spine and the same spine with a Simplify® Cervical Artificial Disc implanted at C5/C6 subjected to 100 N axial load and various 1.5 Nm moments (flexion, extension, lateral bending, and axial rotation).	N/A (for characterization purposes)	The range of motion for the Simplify® Cervical Artificial Disc is similar to the intact spine model and generally falls within the range of previously published finite element models and cadaver tests.
Coating Testing				
Coating Shear Fatigue	Evaluate coating in shear fatigue testing	Six (6) test specimens were subjected to sinusoidal tensile stress of 10 MPa for 10 x 10^6 cycles per ASTM F1160	No failure of the coating	None of the test specimens showed any evidence of coating failure. The acceptance criterion was met.
Coating Static Shear Strength	Evaluate coating in static shear testing	Twenty (20) test specimens were tested per ASTM F1044	≥ 20 MPa	32.04 MPa. The acceptance criterion was met.
Coating Static Tensile Strength	Evaluate coating in tensile testing	Twenty (20) test specimens were tested per ASTM F1147	≥ 22 MPa	36.2 MPa. The acceptance criterion was met.
Coating Abrasion	Coating taper abrasion testing	Six (6) test specimens were tested per ASTM F1978	≤ 65 mg mass loss after 100 cycles	49 mg mass loss. The acceptance criterion was met.
Coating Characterization	Characterize coating morphology	Coating thickness per ASTM F1854, n=60	160 ± 20 µm	156.3 µm. Acceptance criterion was met.
		Roughness Ra per DIN EN ISO 4288 & DIN EN ISO 4287, n=20	20 ± 5 µm	19.4 µm. Acceptance criterion was met.
		Porosity per ASTM F1854, n=59	20-40%	36.54%. Acceptance criterion was met.

Test Name	Purpose	Test Method	Acceptance Criteria	Results
		Visual appearance, n=59	Uniform	Uniform. Acceptance criterion was met.
Coated Endplate Characterization	Demonstrate that titanium coating does not degrade or adversely affect the PEEK substrate	Three (3) coated PEEK endplates were characterized per ASTM F2026 using FTIR (chemical composition), DSC (thermal transitions and crystallinity), and GPC (molecular weight and polydispersity), with results compared to those from the original PEEK bar stock used to manufacture the endplates. The PEEK-coating interface was evaluated with optical microscopy for signs of polymer degradation.	N/A (for characterization purposes only)	Coated endplates showed no discernable physiochemical differences from original bar stock and no visual evidence of degradation.

B. Additional Studies

Magnetic Resonance (MR) Imaging

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

The magnetic field interaction evaluations consisted of displacement and torque assessments. For the assessment of displacement, an induced displacement force test was performed in accordance with ASTM F2052. The evaluation of magnetic torque was performed in accordance with ASTM F2052. The Simplify® Cervical Artificial Disc was tested for MRI-related heating in accordance with ASTM F2182. MR imaging artifacts were assessed in accordance with ASTM F2119.

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

- Static magnetic field of 1.5 Tesla (1.5T) or 3.0 Tesla (3.0T).
- Maximum spatial gradient field less than or equal to 5990 Gauss/cm (59.9 T/m).
- Maximum whole-body specific absorption rate (SAR) of 2.0 W/kg for 15 minutes of scanning in Normal Operating Mode.
- Transmit/receive body coil.

Under the scan conditions defined, the Simplify® Cervical Artificial Disc is expected to produce a maximum temperature rise of less than 3.0°C after 15 minutes of continuous scanning.

In non-clinical testing per ASTM F2119, the image artifact caused by the Simplify® Cervical Artificial Disc extends approximately 5-mm at 1.5T and 8 mm at 3.0T from Simplify® Cervical Artificial Disc when imaged using a gradient echo pulse sequence.

Biocompatibility
The Simplify® Cervical Artificial Disc is manufactured from PEEK, zirconia-toughened alumina (ZTA) ceramic, and commercially pure titanium plasma spray (TPS). All implant materials have a long history of successful orthopedic clinical use and well-established biocompatibility. There are no color additives in the Simplify® Cervical Artificial Disc.

Biocompatibility testing was performed on the Simplify® Cervical Artificial Disc in its final sterilized state in accordance with ISO 10993-1, ISO 10993-12, ISO 10993-17, and ISO 10993-18, for the level of contact duration of a permanent implant contacting tissue and bone. The battery of biocompatibility tests conducted included: Cytotoxicity (ISO 10993-5), Pyrogenicity (ISO 10993-11), Bacterial Endotoxin Evaluation (ANSI/AAMI ST72, USP<85>, USP<161>), Neurotoxicity Assessment (ASTM F2423, ISO 18192-1, ASTM WK33006), and Biological Risk Assessment (ISO 10993-1, -12, -17, -18). All test results met the acceptance criteria demonstrating biocompatibility in line with the requirements of ISO 10993-1.

Sterilization Validation
Full sterilization validation has been conducted for the Simplify® Cervical Artificial Disc implants per ISO 11137. Full sterilization validation has been conducted for the Simplify® Cervical Artificial Disc Instruments per ANSI/AAMI ST79, AAMI TIR12, and ISO 17665-1.

Shelf Life and Transit Validation
Shelf life and transit validation studies, including assessments of packaging seal integrity and real-time aging testing, were conducted to demonstrate that the device packaging can maintain a sterile barrier over a 4-year shelf life.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant conducted a clinical study to establish a reasonable assurance of safety and effectiveness of replacement of the degenerated native disc with the Simplify® Cervical Artificial Disc following single-level discectomy for intractable radiculopathy (arm pain and/or a neurological deficit) with or without neck pain, or myelopathy due to a single-level abnormality localized to the level of the disc space and manifested by at least one of the following conditions confirmed by radiographic imaging (e.g., X-rays, computed tomography (CT), magnetic resonance imaging (MRI)): herniated nucleus pulposus, spondylosis (defined by the presence of osteophytes), and/or visible loss of disc height as compared to adjacent levels. The study was performed in the United States under IDE #G140154 with additional control anterior cervical discectomy and fusion (ACDF) data from a separate IDE study performed in the United States. A summary of the clinical study is presented below.

A. Study Design

Subjects in the Simplify® Cervical Artificial Disc pivotal study ("Simplify® Cervical Artificial Disc IDE study") were treated between February 2016 and February 2018. The database for this

PMA reflects data collected through March 2020 and included 150 Simplify® Cervical Artificial Disc subjects (166 including training subjects) at 16 sites and 133 historical ACDF control subjects treated at 21 sites. Control subjects were treated between July 2005 and August 2007.

The prospective, non-randomized, historically controlled, multi-center study was performed in the United States under IDE #G140154 combined with additional control ACDF data from a previous multi-center, prospective, randomized concurrently-controlled cervical disc IDE study performed in the United States. This previous study incorporated a similar study design, indications for use, study entry criteria, study endpoints, and data collected. The two studies were not identical, and differences were identified in some categories and are discussed below.

A statistical plan utilizing propensity score (PS) modeling was developed to incorporate both the concurrent control and historical control and to match the baseline covariates to the Simplify® Cervical Artificial Disc group. The resultant PS Selected study cohort used for the primary analysis population thus included all investigational Simplify® Cervical Artificial Disc subjects (excluding training subjects) and historical control subjects (excluding trimmed subjects) and is termed the "Primary Analysis Set."

1. Clinical Inclusion and Exclusion Criteria

To be eligible for the Simplify® Cervical Artificial Disc IDE study, subjects had to be eligible for a fusion procedure and meet all of the inclusion criteria and none of the exclusion criteria (**Table 3**):

Table 3: Study Inclusion/Exclusion Criteria

Study Inclusion Criteria	Study Exclusion Criteria

• Be between 18 and 60 years of age;
• Have symptoms of cervical degenerative disc disease (DDD) at ***one cervical level*** from C3 to C7 defined as intractable radiculopathy (arm pain and /or a neurological deficit) with or without neck pain or myelopathy due to a single-level abnormality localized to the level of the disc space and radiographic evidence of at least one of the following;
  • Spondylosis (defined by the presence of osteophytes or dark disc) on CT or MRI or;
  • Disc height decreased by ≥ 1 mm when compared to adjacent levels on radiographic film, CT, or MRI or
  • Disc herniation on CT or MRI;
• Have at least one of the following radiculopathy or myelopathy symptoms in neck and/or arm;
  • Pain or paresthesias in a specific nerve root distribution from C3 to C7,
  • Decreased muscle strength of at least one level on the 0-5 scale, or
  • Abnormal sensation, including hyperesthesia or hypoesthesia.
• Have at least one of the following:
	• Marked cervical instability on resting lateral or flexion/ extension X-ray (translation > 3 mm or > 11 degrees rotation to that of either adjacent non-treatment level);
	• Non discogenic neck pain or non-discogenic source of symptoms (e.g., tumor, rotator cuff injury, etc.);
	• Radiographic confirmation of severe facet disease or facet degeneration;
	• Bridging osteophytes;
	• Less than 2 degrees of motion at index level;
	• Prior surgery at the level to be treated, except laminotomy without accompanying facetectomy;
	• Prior fusion or artificial disc replacement at any cervical level;
	• More than one neck surgery via anterior approach;
	• Previous trauma to the C3-C7 levels resulting in compression or bursting;
	• Documented presence of a free nuclear fragment at cervical levels other than the study level;
	• Axial neck pain only (no radicular or myelopathy symptoms);

Study Inclusion Criteria	Study Exclusion Criteria

• At least six weeks of prior conservative treatment (e.g., physical therapy and/or use of anti-inflammatory medications and muscle relaxants at the manufacturer's recommended therapeutic dose);
• The presence of progressive symptoms (e.g., increasing numbness or tingling) or
• Signs of nerve root compression.
• Have a Neck Disability Index (NDI) greater than or equal to 40 on a scale of 100 (moderate disability);
• Be appropriate for treatment using an anterior surgical approach;
• Be likely to return for all follow-up visits[1] and
• Be willing and able to provide Informed Consent for study participation.
 	
Muscle strength will be graded for the deltoid (C5), biceps (C6), and triceps (C7) according to a 6-point scale where 0 = no movement, 1 = trace of muscle contraction; 2 = active movement without gravity; 3 = active movement against gravity; 4 = active movement against gravity/resistance; and 5 = normal response. [2]
 	
For the purpose of this study, conservative therapy may include, but is not limited to, injections of steroids, physical therapy, bracing, traction, acupuncture, yoga, life style changes, neck support or massage chairs, exercise, ice, heat, massage, water therapy, chiropractic, and medications prescribed for pain, muscle tightness, muscle cramping or inflammation of muscles or nerves or other symptoms typically involved with chronic neck conditions such as DDD.
	• Symptomatic DDD at more than one cervical level;
	• Severe myelopathy (less than 3/5 muscle strength);
	• Any paralysis;
	• Recent history (within previous six months) of chemical or alcohol dependence;
	• Active systemic infection;
	• Infection at the site of surgery;
	• Prior disc space infection or osteomyelitis in the cervical spine;
	• Any terminal, systemic or autoimmune disease;
	• Metabolic bone disease (e.g., osteoporosis/osteopenia [3], gout, osteomalacia, Paget's disease);
	• Any disease, condition or surgery which might impair healing, such as;
	  • Diabetes mellitus requiring daily insulin management,
	  • Active malignancy,
	  • History of metastatic malignancy.
	• Current or extended use (> 6 months) of any drug known to interfere with bone or soft tissue healing;
	• Known PEEK, ceramic, titanium allergy;
	• Arachnoiditis;
	• Significant cervical anatomical deformity at the index level or clinically compromised cervical vertebral bodies at the index 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);
	• Currently experiencing an episode of major mental illness (psychosis, major affective disorder, or schizophrenia), or manifesting physical symptoms without a diagnosable medical condition to account for the symptoms, which may indicate symptoms of psychological rather than physical origin;

[1] Please note that patients who live significant distances away from a treatment center are statistically likely to be present for treatment, but are not likely to return for all follow-up visits. For this reason, patients who live over **150** miles from a treatment center are not eligible for treatment in this clinical study without **prior approval** from the study Sponsor.

[2] *See* Hacker *et al., supra* note 7, at 2648; Aids to the Investigation of Peripheral Nerve Injuries (UK Medical Research Council, War Memorandum No. 7 (2d ed. Rev. 1943).

[3] Patients at risk for osteoporosis/osteopenia must be screened using a dual X-ray absorptiometry scan (DXA). Patients meeting the WHO definition for osteoporosis/osteopenia for risk of fracture, i.e., have a bone mineral content greater than 1.5 standard deviations below the mean for young, healthy adults (DXA score), are ineligible for study participation.

Study Inclusion Criteria	Study Exclusion Criteria
	• Pregnancy at time of enrollment, or planning to become pregnant, since this would contraindicate surgery [4]; • Use of spinal stimulator at any cervical level prior to surgery; • Currently a prisoner; • Currently involved in spinal litigation which may influence the subjects reporting of symptoms **or** • Participation in any other investigational drug, biologic or medical device study within the last 30 days prior to study surgery.

2. Control

Control subjects received ACDF. The historical control was collected from the control arm of a previously completed multi-center, prospective, randomized non-inferiority clinical trial.

Comparison of the data collected from the Simplify® Cervical Artificial Disc Pivotal IDE study and historical ACDF control demonstrated that the cohorts were comparable, though not identical.

- A detailed comparison of the indications and inclusion/exclusion criteria of the historical ACDF cohort and the Simplify® Cervical Artificial Disc IDE study protocol was conducted to determine if the historical data were adequate to serve as comparator and support a PMA application. The sponsor reviewed the protocol and case report forms as submitted to the FDA. Based on this review and discussion with FDA, it was determined that the historical study was similar to the IDE study in its Indications for Use and Inclusion/Exclusion criteria.
- The historical study collected the parameters used to calculate overall success, success of the individual components of the composite primary endpoint, secondary endpoints, and safety assessments per the defined assessments in the Simplify® Cervical Artificial Disc IDE study protocol.

A PS method was used to address selection bias in the observational study design when pooling data from the historical control and actively enrolled Simplify® Cervical Artificial Disc group. The objective of the observational design was to select from the candidate pool of historical controls those subjects whose baseline covariate distribution was approximately the same as Simplify® Cervical Artificial Disc subjects within PS subclasses. The final Primary Analysis set included all 150 Simplify® Cervical Artificial Disc subjects (166 including training subjects) and 117 of 133 historical control subjects. Rigorous statistical criteria and graphical analyses demonstrated that within PS subclasses, Simplify® Cervical Artificial Disc subjects and PS-selected historical controls had approximately the same multivariate baseline covariate distribution.

[4] Pregnancy during participation in this study should also be discouraged, since pregnancy may prohibit exposure to X-rays during necessary follow-up timeframes.

3. Follow-up Schedule

All subjects were evaluated preoperatively, postoperatively (up to 2-weeks post-treatment) and postoperatively at 6 weeks (±2 weeks), 3 months (±2 weeks), 6 months (±1 month), 1 year (±2 months), 2 years (±2 months), and annually thereafter (±2 months). The following parameters (**Table 4**) were measured throughout the study:

Table 4: Simplify® Cervical Artificial Disc IDE Study Assessment Schedule

Evaluation	Pre-op	Treatment	Post-op	6 Weeks	3 Months	6 Months	12 Months	24 Months
Informed Consent	X							
Medical History & Physical Examination	X							
DXA (as described in protocol)	X							
AP & Lateral X-rays	X		X	X	X	X	X	X
Flexion & Extension X-rays	X				X	X	X	X
Lateral bending X-rays	X					X	X	X
MRI (Simplify® Cervical Artificial Disc Subjects only)	X							X
Radiographic Core Lab Assessments	X		X	X	X	X	X	X
Dysphagia Handicap Index (Simplify® Cervical Artificial Disc Subjects only)	X			X	X	X	X	X
Neck Disability Index (NDI)	X			X	X	X	X	X
SF-12v2 Health Survey (Simplify® Cervical Artificial Disc Subjects only)	X					X	X	X
Visual Analog Scale (VAS)	X		X	X	X	X	X	X
Odom's Criteria			X	X	X	X	X	X
Neurologic Exam	X		X	X	X	X	X	X
Medications Taken	X		X	X	X	X	X	X
Work Status	X				X	X	X	X
Treatment Assessments		X						
Treatment Satisfaction Assessment							X	X
Adverse Event Assessment	N/A	*As Needed*						

4. Clinical Endpoints

The effectiveness of the Simplify® Cervical Artificial Disc was assessed using a composite endpoint, as described below. Effectiveness was further evaluated by assessing improvement in the Neck Disability Index (NDI), neck and arm pain based on a Visual Analog Scale (VAS), and health-related quality of life using the short-form questionnaire (SF-12v2), work status, as well as patient satisfaction of the Simplify® Cervical Artificial Disc group compared to the historical ACDF control group. Similar criteria were used to measure success in both groups.

The safety of the Simplify® Cervical Artificial Disc was assessed by comparison to the historical ACDF control group with respect to the nature and frequency of AEs (overall and in terms of

seriousness and relationship to the implant), secondary index level surgical procedures and maintenance or improvement in neurological status.

Primary Endpoints

The study hypothesis for the Simplify® Cervical Artificial Disc IDE study was that the Month 24 (i.e., 24 months post-operatively) composite clinical success (CCS) rate of the Simplify® Cervical Artificial Disc would be no worse than conventional ACDF when success of ACDF is evaluated at Month 24 in patients with intractable radiculopathy (arm pain and/or a neurological deficit) with or without neck pain or myelopathy due to a single-level abnormality localized to the level of the disc space at one level from C3 to C7 that are unresponsive to conservative management or have presence of progressive symptoms.

- Individual success for the investigational Simplify® Cervical Artificial Disc is defined as at least a 15 point (out of 100) improvement in NDI percentage at Month 24 compared with baseline; maintenance or improvement in neurologic status at Month 24 compared with baseline; no device failures or revision, reoperation, removal and/or supplemental fixation within 24 months of index procedure; and, the absence of major AEs within 24 months as defined below.

- Individual success for the historical control ACDF device is defined as at least a 15 point (out of 100) improvement in NDI percentage at Month 24 compared with baseline; maintenance or improvement in neurologic status at Month 24 compared with baseline; no device failures or revision, reoperation, removal and/or supplemental fixation within 24 months; and the absence of major AEs within 24 months as defined below.

Device failure is defined as breakage, migration, or mechanical failure of the components. For purpose of determining individual patient success, a major AE is defined as any of the following which are definitely-related to the device system or to a device component as determined by the Clinical Events Committee (CEC):

- Permanent neurologic damage or permanent nerve root injury related to a level at or below the level treated;
- Implant or component breakage or migration that does not require revision, reoperation or removal, but causes persistent or moderate to severe dysphagia and/or
- Patient death.

Per the FDA Guidance for the Preparation of IDEs for Spinal Systems, the following definitions apply:

- Reoperation – Any surgical procedure at the index level that does not involve modification, addition or removal of any components of the device in the postoperative or follow-up period.
- Revision – Any procedure in the postoperative or follow-up period that adjusts, modifies, or removes part of the original implant configuration with or without replacement of a

component – may include adjusting the position of the original configuration in the postoperative or follow-up period.
- Removal – A procedure where the entire device is removed with or without replacement of the device in the postoperative or follow-up period.
- Supplemental fixation – A procedure in which additional instrumentation not under study is implanted (e.g., supplemental placement of a rod/ screw system).

Secondary Endpoints

Secondary objectives, measured in both groups (except as noted), included:

- Clinically significant improvement in one or more radicular symptoms or myelopathy at Month 24 compared to baseline for the investigational Simplify® Cervical Artificial Disc and the historical ACDF control subjects. The data collected reflect the number of subjects who improved (numbers are stratified to reflect clinical improvement), who remain unchanged, and who deteriorated at each study timepoint. These endpoints are graded and defined as follows:
    - VAS for the following pain locations:
        - Neck and arm pain (to allow comparison to historical ACDF control);
        - Neck, Arm (Right/Left) pain (Simplify® Cervical Artificial Disc group only);

      Changes of at least 20 mm on a 100 mm scale is regarded as clinically significant.
    - Motor status - A change of one or more grade levels in muscle strength is regarded as clinically significant.
    - Sensory status - Sensation is graded as normal or abnormal (diminished or absent). Any changes from abnormal to normal or absent to diminished is regarded as clinically significant improvement.
- Time to recovery (earliest time at which a minimum 15-point (out of 100) NDI improvement is reached).
- Disc height at Month 24 compared to baseline.
- Adjacent level deterioration at Month 24 compared to baseline.
- Displacement or migration of the device defined as a change of 3mm or greater compared to the position at implantation.
- Treatment satisfaction at Month 24.
- Health-related Quality of Life Survey (SF-12v2) at Month 24 compared to baseline (Simplify® Cervical Artificial Disc group only).
- Dysphagia Handicap Index (DHI scale) at Month 24 compared to baseline (Simplify® Cervical Artificial Disc group only).
- Facet deterioration at Month 24 compared to baseline (Simplify® Cervical Artificial Disc group only).
- Results at Month 24 as categorized by the physician according to Odom's Criteria.

5. Clinical Events Committees

A CEC was utilized for the Simplify® Cervical Artificial Disc IDE study, including the historical ACDF control population, to mitigate reporting bias of safety-related events. The CEC was comprised of three (3) independent spine surgeons, and a CEC charter was used to define the role of the CEC. The committee was responsible for adjudication of AE (i.e., AE code, relationship to device/procedure, seriousness, severity, determination of major AE and unanticipated adverse

device effects), secondary surgical intervention (SSI) (i.e., classification of revision, removal, reoperation or supplemental fixation), protocol deviations (i.e., classification as Major or Minor), and neurological success criterion (classification of neurologic status at Month 24 as compared to baseline).

B. Accountability of PMA Cohort

One-hundred sixty-six (166) subjects were enrolled in the Simplify® Cervical Artificial Disc population. Of these, 16 Simplify® Cervical Artificial Disc subjects were training subjects. The historical ACDF control population included 133 subjects.

The 283 available subjects (150 Simplify® Cervical Artificial Disc (excluding training subjects) and 133 historical ACDF control) were assessed via the PS subclassification sequential model-building process. After applying an established heuristic for 3 iterations, a total of 150 Simplify® Cervical Artificial Disc and 117 historical ACDF control subjects were retained in the final PS designed sample. Inclusion into a PS subclass is the observational study analogue to randomized treatment allocation. When accounting for the PS design, there was excellent balance across all considered baseline covariates. For subjects at Month 24, the visit compliance rates were 97% for Simplify® Cervical Artificial Disc subjects and 86% for the PS Selected ACDF subjects.

The subject accountability for Month 12 and Month 24 clinical evaluations is presented in **Table 5** and **Figure 4**.

Table 5: Subject Accounting Summary (Primary Analysis Population)

	Month 12		Month 24	
	I	C	I	C
Accounting				
(1) Theoretical follow-up	150	117	150	117
(2) Cumulative Death	0	0	0	0
(3a) Intra-Op Deviations	2	0	2	0
(3b) Cumulative SSI Failures	1	2	4	5
(4) Not Yet Overdue	0	0	0	0
(5) Deaths+SSI failures+Intra-Op Deviations among theoretically due	3	2	6	5
(6) Expected Due [(6)=(1)-(4)-(5)]	147	115	144	112
(7) SSI failures+Intra-Op Deviations among theoretically due	3	2	6	5
(8) Expected due+SSI failures+Intra-Op Deviations among theoretically Due [(8)=(6)+(7)]	150	117	150	117
All Evaluated Accounting (Actual ^{B}) Among Expected Due Procedures				
(9) Procedures with any clinical data in interval†	144	101	139	96
(10) Visit Compliance (%)	98%	88%	97%	86%
(11) Change in NDI	143	100	138	96
(12) Change in VAS	142	100	139	95
(13) Neuro evaluations	143	100	139	95
(14) Composite Clinical Success (CCS)			136	91
(15) Actual^{B} % Follow-up for CCS			94%	81%
Within Window Accounting (Actual ^{A}) Among Expected Due Procedures				
(16) Procedures with any clinical data in interval†	141	89	128	79
(17) Visit Compliance (%)	96%	77%	89%	71%
(18) Change in NDI	140	88	127	79
(19) Change in VAS	139	88	128	79
(20) Neuro evaluations	140	88	128	78
(21) Composite Clinical Success (CCS)			125	74
(22) Actual ^{A} % Follow-up for CCS			87%	66%

†Change in NDI, change in VAS, or Neuro overall status;
Source: Table Follow-up Compliance.sas; Analyzed: 27AUG2020

Actual^{A}: Patients with complete data for each endpoint, within window.
Actual^{B}: Patients with any follow-up data reviewed or evaluated by investigator ("all evaluated" accounting).

(1) Theoretical follow-up: The theoretical follow-up is the number of devices at one level that would have been examined if all subjects returned on the exact anniversary of their respective initial surgery dates. The date of database closure for these analyses was March 27th, 2020. All subjects were theoretically due for Month 12 and Month 24 follow-up at the date of database closure.

(2) Cumulative deaths: Cumulative deaths up to the date of the exact anniversary defining the current interval. Deaths occurring after the exact anniversary are recorded in the next interval.

(3a) Intra-Op Deviations: Subjects who were to be treated with Simplify® Cervical Artificial Disc but converted to alternate treatment intra-operatively. Intra-operative deviation subjects are considered a treatment failure in the CCS primary endpoint calculation and censored at day 0 for SSI and device survivorship. At the time of surgery, due to anatomical challenges, the surgeons could not implant the TDR for 2 subjects enrolled to be treated with Simplify® Cervical Artificial Disc and performed an ACDF surgery. Since these 2 subjects do not meet the definition of an SSI, they are accounted for separately. They will be considered a treatment failure in the CCS primary endpoint calculation and censored at day 0 for SSIs and device survivorship.

(3b) Cumulative SSI Failures: Failures are defined as any result that removes the subject from further evaluation of effectiveness, that is, these Failures are "***terminal failures***". As per FDA Guidance (2004), failure includes SSIs categorized as reoperations, revisions, removals, reoperations or supplemental fixation. It also includes other severe AEs or other parameters that would define the device as ineffective or unsafe from that point on. Failures are counted up to the date of the exact anniversary defining the current interval. Terminal failures occurring after the exact anniversary are recorded in the next interval. Terminal failures on this row do not include radiographic failure since radiographic failure does not remove a subject from the study. It also does not include clinical failures determined on the basis of clinical scores such NDI, VAS, or deteriorating neurological status because these types of failure do not remove the subject from further follow-up. Although the cumulative number of failures is recorded on this row, only failures among devices that are theoretically due for that interval are subtracted from theoretically due to determine the number expected due for clinical indices.

(4) Not Yet Overdue: Includes subjects whose surgical anniversary has occurred; however, clinical data has not yet been collected (i.e., NDI or VAS/NRS is currently unavailable) but the subject is still in the protocol specified follow-up window. Such subjects may yet be observed and so follow-up compliance estimates account for this by removing such subjects from the denominator as well as from the numerator when determining compliance ratios.

(5) Deaths+SSI Failures+Intra-Op Deviations among theoretically due: This row records the sum of deaths, SSI Failures, and Intra-Op Deviations among those theoretically due for follow-up according to the exact anniversary of the scheduled follow-up visit. Only deaths, SSI Failures, and Intra-Op Deviations among procedures that are theoretically due for that interval are subtracted from theoretically due to determine the number expected due for clinical index evaluation.

(6) Expected due for clinic visit: This row is the number of subjects expected for a given time interval. These include the theoretical number of subjects who were due to be evaluated, less the number of subjects who died or who were considered failures by that time interval and less the subjects in the "Not yet overdue" category. **Expected = Theoretical - [Deaths + Failures + Not yet overdue]** where the counts of the numbers of Deaths, Failures, and Not yet overdue are determined from among the theoretically due subjects. This row serves as denominator for evaluation % follow-up for clinical indices (e.g., NDI, VAS/NRS). The Expected row includes subjects lost to follow-up, and major protocol violations are included in the expected group for all time points.

(7) SSI Failures + Intra-Op Deviations among theoretical due: SSI failures and intra-op deviations among theoretically due is the count of theoretically due Failures that need to be "added back" to the number of expected due to serve as the correct denominator for CCS counts when determining CCS follow-up compliance.

(8) Expected due + SSI Failures + Intra-Op Deviations among theoretical due: Expected due plus theoretical due Failures is computed by adding expected due in row (6) to the number of cumulative Failures among theoretically due devices in row (7). This row serves as the denominator for composite clinical success (CCS) outcomes since CCS status is known for subjects with a Failure as defined in row (3).

(9) and (16) Procedures with any clinical data in interval: These rows indicate the number of subjects with any clinical data that report a change in NDI, VAS, or neurological status for all evaluated subjects among expected due subjects **(9)** and for all subjects that are within window among expected due subjects **(16)**.

(10) and (17) Visit Compliance (%): These rows indicate the percentage of subjects compliant with the specified visit scheduled for all evaluated subjects among expected due subjects **(10)** and for all subjects that are within window among expected due subjects **(17)**.

(11) and (18) Change in NDI: These rows indicate the number of subjects reporting a change in NDI for all evaluated subjects among expected due procedures **(11)** and for all subjects that are within window among expected due procedures **(18)**.

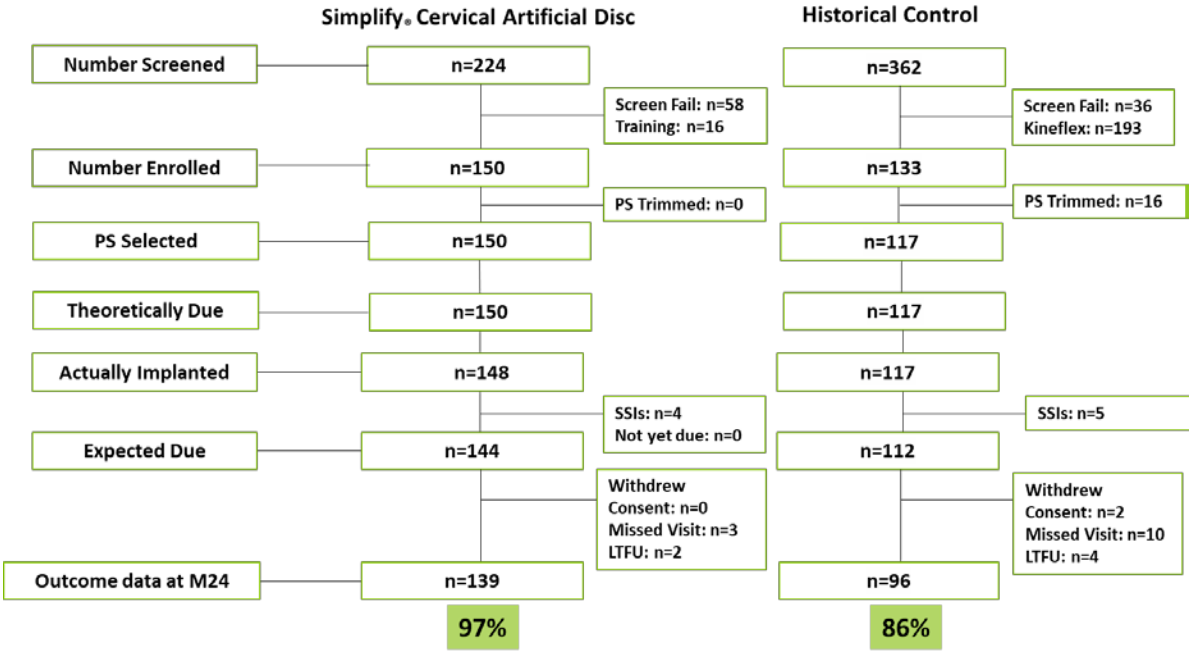
(12) and (19) Change in VAS: These rows indicate the number of subjects reporting a change in VAS for all evaluated subjects among expected due procedures **(12)** and for all subjects that are within window among expected due procedures **(19)**.

(13) and (20) Neuro evaluations: These rows indicate the number of subjects reporting a change in neurological status for all evaluated subjects among expected due procedures **(13)** and for all subjects that are within window among expected due procedures **(20)**.

(14) and (21) Composite Clinical Success: These rows indicate the number of subjects with enough data available for evaluation of clinical composite success for all evaluated subjects among expected due procedures **(14)** and for all subjects that are within window among expected due procedures **(21)**.

(15) and (22) Actual Follow-up for CCS: These rows indicate the percentage of subjects with follow-up data available used to evaluate CCS for all evaluated subjects among expected due procedures **(15)** and for all subjects that are within window among expected due procedures **(22)**.

Figure 4. Subject Accountability Tree



C. Study Population Demographics and Baseline Parameters

After adjusting for PS subclass, the demographic data appear to demonstrate that the treatment groups were well-balanced and no statistically significant differences were noted in the demographic characteristics and categorical values (**Table 6** and **Table 7**). The mean baseline pre-operative assessments for NDI, VAS Neck and Arm, and baseline radiographic parameters were also similar between treatment groups. Baseline VAS Neck and Arm were significantly higher in

the Simplify® Cervical Artificial Disc group; however, when adjusting for PS subclass, there was no significant difference between groups, indicating similar neck pain and function.

Table 6: Summary of Demographic and Baseline Continuous Variables (Clinical) (Primary Analysis Population)

	Simplify Disc						ACDF						Group Difference*			
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p	Δ	LB	UB
All																
Age (years)	150	43.0	8.9	43.2	18.1	60.9	117	44.1	7.0	43.9	23.6	59.3	0.765	-0.3	-2.5	1.8
BMI (kg/m^2)	150	27.5	5.2	26.6	18.2	40.3	117	28.7	5.6	27.3	19.5	48.4	0.914	0.1	-1.3	1.5
Height (inches)	150	67.7	4.0	67.0	59.0	76.0	117	67.3	4.1	67.0	57.0	79.0	0.927	-0.1	-1.1	1.0
Weight (pounds)	150	180.3	42.9	178.5	103.0	308.0	117	185.3	41.4	180.0	103.0	298.0	0.855	1.1	-10.4	12.5
Female																
Age (years)	91	43.0	8.7	43.1	18.1	60.4	68	44.7	6.8	45.6	30.5	58.8	0.678	-0.6	-3.3	2.1
BMI (kg/m^2)	91	26.7	5.5	25.5	18.2	40.3	68	28.9	6.5	27.1	19.5	48.4	0.404	-0.8	-2.8	1.1
Height (inches)	91	65.3	2.5	65.0	59.0	72.0	68	65.0	3.0	66.0	57.0	72.0	0.416	-0.4	-1.3	0.5
Weight (pounds)	91	162.2	36.2	160.0	103.0	265.0	68	173.7	40.9	167.0	103.0	292.0	0.343	-6.3	-19.4	6.8
Male																
Age (years)	59	42.8	9.2	43.9	22.1	60.9	49	43.2	7.2	43.7	23.6	59.3	0.797	-0.5	-4.1	3.2
BMI (kg/m^2)	59	28.7	4.5	27.4	21.5	39.5	49	28.4	4.0	27.5	20.5	38.3	0.177	1.3	-0.6	3.2
Height (inches)	59	71.4	2.9	72.0	64.0	76.0	49	70.4	3.1	70.0	66.0	79.0	0.440	0.5	-0.8	1.9
Weight (pounds)	59	208.2	37.4	195.0	150.0	308.0	49	201.4	36.7	200.0	127.0	298.0	0.171	11.7	-5.1	28.4
Clinical Scores																
Neck Disability Index	150	63.3	12.5	61.0	40.0	94.0	117	62.4	12.6	64.0	40.0	90.0	0.950	0.1	-3.3	3.5
VAS Neck and Arm	150	81.6	12.4	84.0	41.0	100.0	117	77.6	13.5	79.0	42.0	100.0	0.717	0.6	-2.7	4.0
VAS Neck	150	77.1	18.2	81.0	0.0	100.0										
VAS Left Arm	150	54.3	36.3	67.5	0.0	100.0										
VAS Right Arm	150	48.8	39.4	60.0	0.0	100.0										
DHI Score	150	6.2	8.8	3.0	0.0	50.0										
SF12 PCS	150	31.1	7.4	30.3	11.2	56.1										
SF12 MCS	150	42.4	12.2	42.3	15.6	67.5										
Radiography																
Disc Angle	148	2.1	4.5	2.4	-8.2	14.0	116	2.6	4.4	2.4	-8.4	14.0	0.249	-0.7	-1.9	0.5
Average Disc Height	148	3.3	0.7	3.3	1.1	5.7	115	3.3	0.8	3.2	1.4	5.2	0.813	0.0	-0.2	0.2
Anterior Disc Height	148	3.6	1.0	3.5	1.6	6.5	115	3.6	1.1	3.5	1.4	6.9	0.419	-0.1	-0.4	0.2
Posterior Disc Height	148	3.0	0.9	3.1	0.6	5.4	115	2.9	0.9	2.8	0.9	5.2	0.537	0.1	-0.2	0.3
Rotation	143	7.3	4.2	6.4	0.0	21.4	110	7.3	4.4	6.8	-0.8	19.0	0.588	-0.3	-1.5	0.9
Translation (mm)	143	0.7	0.5	0.6	0.0	2.4	109	0.8	0.6	0.7	-0.1	2.7	0.061	-0.1	-0.3	0.0
Translation (%)	143	4.6	3.1	3.9	0.0	13.9	110	5.2	3.9	4.6	-0.7	16.0	0.090	-0.8	-1.8	0.1
AP Rotation	144	6.1	2.8	5.6	0.3	15.4	106	5.2	3.1	4.7	0.0	12.9	0.211	0.5	-0.3	1.4
Spondylolisthesis (mm)	148	0.9	1.0	0.9	-1.8	3.9	115	1.2	0.9	1.0	-0.5	3.8	0.078	-0.2	-0.5	0.0
Spondylolisthesis (%)	148	6.0	6.1	5.7	-10.5	24.9	116	7.4	5.8	6.1	-4.1	25.7	0.091	-1.4	-3.1	0.2

*Device group mean differences and 95% CI adjusting for propensity score (PS) subclass using two-way analysis of variance.
Source: Tables Baseline Demo.sas; Analyzed: 14MAY2020

Table 7: Summary of Baseline Categorical Variables – (Primary Analysis Population)

	Simplify® Cervical Artificial Disc			ACDF			Group Difference*			
	N	n	%**	N	n	%**	p	Δ	LB	UB
Conservative Therapy with Injection	150	70	46.7%	117	52	44.4%	0.953	0.4%	-12.6%	13.4%
Conservative Therapy with Narcotics	150	66	44.0%	117	67	57.3%	0.994	0.1%	-13.5%	13.6%
Neurological Motor Deficit	150	53	35.3%	117	62	53.0%	0.772	0.2%	-15.7%	11.5%
Neurological Sensory Deficit	150	66	44.0%	117	66	49.6%	0.855	-0.1%	-14.2%	11.7%
Work Status = Employed	150	120	80.0%	117	82	70.1%	0.617	2.9%	-8.1%	13.9%

*Device group differences and 95% CI adjusting for propensity score (PS) subclass using two-way generalized linear model. **Unadjusted proportions calculated as x/n.
Source: Table Clinical Follow-up.sas; Analyzed: 19JUN2020

Table 8 summarizes the available race and ethnicity data. Please note, complete race and ethnicity data were not collected.

Table 8: Summary of Demographic and Baseline Variables – Race and Ethnicity (Primary Analysis Population)

	Simplify Disc			ACDF			
	N	n	%	N	n	%	p*
Race and Ethnicity							0.822
Caucasian	150	131	87.3%	117	103	88.0%	
Black		10	6.7%		7	6.0%	
Hispanic		4	2.7%		6	5.1%	
Other		5	3.3%		1	0.9%	

*p-value adjusted for PS subclass using two-way analysis of variance with race dichotomized as Caucasian vs. Non-Caucasian.
Source: Tables Baseline Demo.sas; Analyzed: 27FEB2020

The radiographic findings used to qualify a subject for enrollment are provided with post-hoc nominal measures of significance are presented in **Table 9**.

Table 9: Summary of Baseline Variables – Radiographic Data (Primary Analysis Population)

	Simplify Disc			ACDF			Group Difference*			
	N	n	%	N	n	%	p**	Δ	LB	UB
Spondylosis (defined by the presence of osteophytes or dark disc on CT/MRI†	150	72	48.0%	117	66	56.4%	0.490	-5.7%	-18.6%	7.2%
Decrease disc height ≥1mm compared to adjacent levels on x-rays, CT, or MRI	150	59	39.3%	117	53	45.3%	0.490	-4.7%	-17.4%	8.0%
Disc herniation on CT or MRI	150	139	92.7%	117	98	83.8%	0.117	8.0%	-0.6%	16.6%

*Post-hoc nominal Device group differences and 95% CI adjusting for propensity score (PS) subclass using two-way generalized linear model. **PS adjusted Hochberg p-values corrected for multiplicity (3 tests). †Historical control criterion wording reads 'degenerated / dark disc on MRI'.
Source: IR3 - Question 7c.sas; Analyzed: 10JUN2020

Table 10: Summary of Operative Continuous Variables (Primary Analysis Population)

	Simplify Disc						ACDF						Group Difference*			
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p	Δ	LB	UB
Operative Time (minutes)	150	73.6	21.8	70.0	32.0	170.0	117	74.0	27.1	69.0	29.0	157.0	0.987	-0.05	-6.66	6.55
Blood Loss (cc)	150	31.2	38.6	20.0	0.0	250.0	117	42.4	33.9	30.0	0.0	200.0	0.013	-12.62	-22.55	-2.69
Length of Stay (days)	150	0.6	1.9	0.0	0.0	23.0	117	1.1	0.5	1.0	0.0	3.0	0.134	-0.31	-0.71	0.09

*Device group mean differences and 95% CI adjusting for propensity score (PS) subclass using two-way analysis of variance.

Source: Tables Intra-op.sas; Analyzed: 09JAN2020

As evidenced by **Table 10**, a statistically significant difference was observed in blood loss, favoring the Simplify® Cervical Artificial Disc subjects. The mean blood loss for the Simplify® Cervical Artificial Disc subjects was 31.2cc while the mean blood loss for the historical ACDF control subjects was 42.4cc. The operative time and length of stay were not significantly different.

Table 11: Summary of Operative Categorical Variables (Primary Analysis Population)

	Simplify Disc (N= 150)		ACDF (N= 117)	
	n	%	n	%
C3/C4	3	2%	3	3%
C4/C5	7	5%	6	5%
C5/C6	80	53%	71	61%
C6/C7	60	40%	37	32%
Posterior Ligament Cut				
No	6	4%	17	15%
Yes	144	96%	91	78%
Not available	0	0%	9	8%
Device Size				
Height 4	**58**	**39%**		
SM-4	22	15%		
MD-4	36	24%		
Height 5	**78**	**53%**		
SM-5	9	6%		
SM-5S	18	12%		
MD-5	20	14%		
MD-5L	12	8%		
LG-5	10	7%		
LG-5L	9	6%		
Height 6	**12**	**8%**		
SM-6	1	1%		
MD-6	1	1%		
MD-6L	0	0%		
LG-6	8	5%		
LG-6L	2	1%		
Source: Tables Intra-op.sas; Analyzed: 09JAN2020				

As evidenced by **Table 11**, the majority of procedures occurred in C5/C6 and C6/C7 for both the Simplify® Cervical Artificial Disc subjects and historical ACDF control subjects.

D. Safety and Effectiveness Results

Please note: The counts and percentages provided for the Simplify® Cervical Artificial Disc and ACDF control groups correspond to the values unadjusted for PS subclass. The device group difference and 95% confidence interval lower bound (LB) and upper bound (UB) are calculated controlling for PS subclass, accounting for why the reported difference does not match the difference between the presented unadjusted percentages.

1. Safety Results

Similar rates of any AE and any SAE occurred in the Simplify® Cervical Artificial Disc cohort and the historical ACDF control cohort through Month 24 (safety results shown through post-operative day 790, the end of the Month 24 visit window). Over the same timecourse, a similar

rate of device- and procedure-related AEs occurred in both groups. While not significantly different, the Simplify® Cervical Artificial Disc subjects experienced a numerically greater number of AEs (245 events in 98 subjects) than the historical ACDF control subjects (192 events in 69 subjects) (**Table 12**).

Table 12: Comparisons of Summary AE Rates between Simplify® Cervical Artificial Disc and ACDF Groups (Primary Analysis Population through Day 790)

	Simplify Disc (N= 150)			ACDF (N= 117)			Group Difference*			
	Events	Subjs	%|	Events	Subjs	%|	p	Δ	LB	UB
Adverse Events										
All	245	98	65.3%	192	69	59.0%	0.234	8.0%	-4.5%	20.5%
Device Related†	77	54	36.0%	86	46	39.3%	0.364	-6.1%	-18.6%	6.4%
Device Related - Definitely	2	1	0.7%	1	1	0.9%	0.663	-0.5%	-2.7%	1.7%
Procedure Related†	108	64	42.7%	93	49	41.9%	0.823	-1.5%	-14.2%	11.2%
Procedure Related - Definitely	24	16	10.7%	7	6	5.1%	0.298	3.4%	-3.1%	9.9%
Serious Adverse Events										
All	26	16	10.7%	24	16	13.7%	0.686	1.5%	-6.5%	9.5%
Device Related†	5	5	3.3%	9	5	4.3%	0.825	0.5%	-4.0%	5.0%
Major	0	0	0.0%	0	0	0.0%				
Device Related - Definitely	1	1	0.7%	0	0	0.0%				
Procedure Related†	11	5	3.3%	9	5	4.3%	0.825	0.5%	-4.0%	5.0%
Procedure Related - Definitely	6	1	0.7%	0	0	0.0%				
AE by Severity										
Mild	112	58	38.7%	68	43	36.8%	0.912	0.7%	-11.7%	13.2%
Moderate	103	59	39.3%	99	40	34.2%	0.307	6.8%	-5.5%	19.1%
Severe	30	21	14.0%	22	15	12.8%	0.241	4.9%	-3.3%	13.2%
Life Threatening	0	0	0.0%	3	2	1.7%				
SAE by Severity										
Mild	1	1	0.7%	0	0	0.0%				
Moderate	2	2	1.3%	7	7	6.0%	0.155	-3.4%	-8.3%	1.5%
Severe	23	15	10.0%	14	10	8.5%	0.230	4.0%	-3.0%	10.9%
Life Threatening	0	0	0.0%	3	2	1.7%				
Death										
All	0	0	0.0%	0	0	0.0%				

*Device group differences and 95% CI adjusting for propensity score (PS) subclass using two-way generalized linear model;
Comparisons with less than 6 subjects in each group includes PS as a continuous variable (df=1) for model stability;
|Percentage of subjects experiencing specific event; †Definite, probable, possibly, and unknown;
‡Subjects censored at Index level secondary surgical interventions.
Source: Tables Safety - AE Summary - Primary.sas; Analyzed: 28APR2020

Counts and percentages of subjects with specific AEs are presented in **Table 13** and counts of AEs by timecourse are presented in **Table 14**. The most commonly occurring events reported to have occurred in the Simplify® Cervical Artificial Disc cohort include radiculopathy (n=35), spasm (n=24), and inflammation conditions, such as discitis, joint and other types of inflammation (n=17). In the historical ACDF control cohort, the most commonly reported AEs include radiculopathy (n=29), pain with narcotic given (n=29), and pain with no narcotic given (n=18). Through Month 24, the nature and incidence of specific AEs were comparable in the two study groups.

Table 13. Counts and Percentages of Subjects with Specific AEs – (Primary Analysis Population through Day 790)

	Simplify Disc (N= 150)			ACDF (N= 117)			Group Difference*			
	Events	Subjs	%‖	Events	Subjs	%‖	p	Δ	LB	UB
All Events	245	98	65.3%	192	69	59.0%	0.234	8.0%	-4.5%	20.5%
Spasm	24	23	15.3%	6	5	4.3%	0.012	10.8%	3.6%	18.1%
Trauma	11	11	7.3%	8	7	6.0%	0.271	3.2%	-2.6%	9.0%
Other	15	13	8.7%	8	6	5.1%	0.381	3.0%	-3.3%	9.2%
Infection (All Other Infections - NOT at cervical surgical site)	13	9	6.0%	7	5	4.3%	0.377	2.6%	-2.8%	8.0%
Dysphagia	9	8	5.3%	3	3	2.6%	0.342	2.6%	-2.3%	7.4%
Injury To Muscles Or Organs	4	4	2.7%	1	1	0.9%	0.164	2.3%	-0.7%	5.4%
Psychological Illness	5	5	3.3%	2	2	1.7%	0.432	1.7%	-2.2%	5.6%
Allergic Reaction	6	5	3.3%	1	1	0.9%	0.400	1.6%	-1.8%	5.0%
Soft Tissue Damage	3	3	2.0%	1	1	0.9%	0.161	1.4%	-1.1%	4.0%
Pneumonia	2	2	1.3%	1	1	0.9%	0.258	0.7%	-1.2%	2.6%
Surgical Wound Dehiscence	2	2	1.3%	1	1	0.9%	0.979	0.0%	-2.5%	2.6%
Tingling - increased from pre-op or prior visit	1	1	0.7%	2	2	1.7%	0.935	-0.1%	-2.0%	1.9%
Implant/Joint Noise	1	1	0.7%	1	1	0.9%	0.848	-0.2%	-2.5%	2.0%
Cardiac Event	1	1	0.7%	1	1	0.9%	0.848	-0.2%	-2.5%	2.0%
Spinal Stenosis	1	1	0.7%	1	1	0.9%	0.663	-0.5%	-2.7%	1.7%
Facet Joint Deterioration	1	1	0.7%	2	2	1.7%	0.635	-0.6%	-3.4%	2.1%
Inflammation Conditions, Such As Discitis, Joint And Other Types Of Inflammation	17	15	10.0%	14	12	10.3%	0.856	-0.7%	-8.4%	6.9%
Numbness - increased from pre-op or prior visit	8	7	4.7%	8	5	4.3%	0.748	-0.9%	-6.2%	4.4%
Adjacent Segment Degeneration	11	10	6.7%	8	8	6.8%	0.791	-0.9%	-7.4%	5.5%
Weakness - increased from pre-op or prior visit	2	2	1.3%	2	2	1.7%	0.429	-1.1%	-4.2%	1.9%
Radiculopathy	35	29	19.3%	29	21	17.9%	0.753	-1.7%	-11.8%	8.4%
Pseudoarthrosis	1	1	0.7%	4	4	3.4%	0.161	-2.8%	-6.7%	1.1%
Pain (No Narcotic Given)	15	14	9.3%	18	15	12.8%	0.305	-4.4%	-12.5%	3.8%
Compressive Neuropathy	4	4	2.7%	10	9	7.7%	0.035	-6.4%	-12.4%	-0.4%
Headache	8	6	4.0%	14	12	10.3%	0.008	-9.1%	-16.1%	-2.1%
Pain (Narcotic Given)	11	11	7.3%	29	21	17.9%	0.011	-11.6%	-20.4%	-2.8%
Gastrointestinal Complications Including Ileus, Nausea and Vomiting	8	7	4.7%	0	0	0.0%				
Infection Localized To Cervical Surgical Site	5	5	3.3%	0	0	0.0%				
Surgery At A Location Other than the Spine	8	4	2.7%	0	0	0.0%				
Hematoma or Seroma	2	2	1.3%	0	0	0.0%				
Tremors	2	2	1.3%	0	0	0.0%				
Difficulty With Urination	2	2	1.3%	0	0	0.0%				
Otitis Media	1	1	0.7%	0	0	0.0%				
Stroke	1	1	0.7%	0	0	0.0%				
Esophageal Perforation	1	1	0.7%	0	0	0.0%				
Hypertension	1	1	0.7%	0	0	0.0%				
Ischemia	1	1	0.7%	0	0	0.0%				
Deep wound infection localized to cervical surgical site	1	1	0.7%	0	0	0.0%				
Skin disorders	1	1	0.7%	0	0	0.0%				
Airway Obstruction	0	0	0.0%	1	1	0.9%				
Dural Injury	0	0	0.0%	1	1	0.9%				
Dysphonia	0	0	0.0%	1	1	0.9%				
Implant Collapse Or Subsidence	0	0	0.0%	1	1	0.9%				
Pulmonary Embolism	0	0	0.0%	1	1	0.9%				
Thrombosis	0	0	0.0%	1	1	0.9%				
Swelling (Edema)	0	0	0.0%	1	1	0.9%				
Hypotension	0	0	0.0%	1	1	0.9%				
Cancer	0	0	0.0%	2	2	1.7%				

*Device group differences and 95% CI adjusting for propensity score (PS) subclass using two-way generalized linear model;
Comparisons with less than 6 subjects in each group includes PS as a continuous variable (df=1) for model stability;
‖Percentage of subjects experiencing specific event; †Definite, probable, possibly, and unknown;
‡Subjects censored at Index level secondary surgical interventions.
Source: Tables Safety - All AEs - Primary.sas; Analyzed: 11JUN2020

Table 14: Counts of Specific AEs by Time of Occurrence – (Primary Analysis Population through Day 790) (I = Simplify® Cervical Artificial Disc, C = ACDF))

	Days Post-Op																	
	Missing		0-2		2-30		30-90		90-180		180-365		365-730		730-790		Total	
	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C
All Events	0	0	8	8	35	16	50	30	51	43	51	41	48	44	2	10	245	192
Radiculopathy	0	0	0	2	5	1	6	6	6	8	9	3	9	6	0	3	35	29
Spasm	0	0	0	0	2	0	3	2	9	3	6	1	4	0	0	0	24	6
Inflammation Conditions, Such As Discitis, Joint And Other Types Of Inflammation	0	0	0	0	2	0	4	1	3	1	1	5	7	7	0	0	17	14
Pain (No Narcotic Given)	0	0	0	0	2	3	3	2	7	5	1	3	2	5	0	0	15	18
Other	0	0	0	1	1	0	4	1	1	1	6	4	2	0	1	1	15	8
Infection (All Other Infections - NOT at cervical surgical site)	0	0	0	0	2	3	3	1	2	1	2	2	4	0	0	0	13	7
Pain (Narcotic Given)	0	0	0	0	1	1	3	4	3	9	1	7	3	5	0	3	11	29
Trauma	0	0	0	0	0	1	3	1	1	0	3	4	4	2	0	0	11	8
Adjacent Segment Degeneration	0	0	0	0	0	0	1	2	2	0	3	0	4	4	1	2	11	8
Dysphagia	0	0	0	0	3	0	3	1	2	2	1	0	0	0	0	0	9	3
Numbness - increased from pre-op or prior visit	0	0	1	0	2	0	3	3	1	2	1	2	0	1	0	0	8	8
Surgery At A Location Other than the Spine	0	0	1	0	1	0	3	0	0	0	2	0	1	0	0	0	8	0
Gastrointestinal Complications Including Ileus, Nausea and Vomiting	0	0	0	0	1	0	2	0	0	0	3	0	2	0	0	0	8	0
Headache	0	0	0	0	1	0	1	1	4	6	2	2	0	4	0	1	8	14
Allergic Reaction	0	0	4	1	1	0	0	0	0	0	1	0	0	0	0	0	6	1
Infection Localized To Cervical Surgical Site	0	0	0	0	4	0	1	0	0	0	0	0	0	0	0	0	5	0
Psychological Illness	0	0	0	0	1	1	0	0	2	0	1	1	1	0	0	0	5	2
Compressive Neuropathy	0	0	0	2	0	2	0	0	1	1	2	3	1	2	0	0	4	10
Injury To Muscles Or Organs	0	0	0	0	0	0	1	0	2	0	1	1	0	0	0	0	4	1
Soft Tissue Damage	0	0	0	1	0	0	1	0	0	0	1	0	1	0	0	0	3	1
Hematoma or Seroma	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2	0
Pneumonia	0	0	0	0	0	0	2	1	0	0	0	0	0	0	0	0	2	1
Tremors	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	2	0
Weakness - increased from pre-op or prior visit	0	0	0	0	0	0	1	1	1	0	0	0	0	1	0	0	2	2
Difficulty With Urination	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	2	0
Surgical Wound Dehiscence	0	0	0	0	2	1	0	0	0	0	0	0	0	0	0	0	2	1
Facet Joint Deterioration	0	0	0	0	0	1	0	0	1	1	0	0	0	0	0	0	1	2
Otitis Media	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0
Pseudoarthrosis	0	0	0	0	0	0	0	0	0	1	0	2	1	1	0	0	1	4
Spinal Stenosis	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	1	1
Tingling - increased from pre-op or prior visit	0	0	0	0	0	0	0	0	1	0	0	0	0	2	0	0	1	2
Cardiac Event	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Implant/Joint Noise	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	1	1
Stroke	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
Esophageal Perforation	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Hypertension	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
Ischemia	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Deep wound infection localized to cervical surgical site	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0
Skin disorders	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0
Airway Obstruction	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Dural Injury	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Dysphonia	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1
Implant Collapse Or Subsidence	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Pulmonary Embolism	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Thrombosis	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Swelling (Edema)	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1
Hypotension	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Cancer	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	2

‡Subjects censored at Index level secondary surgical interventions.
Source: Tables Safety - All AEs - Primary.sas; Analyzed: 11JUN2020

Definitely Device-Related Adverse Events

There were two events in one subject in the Simplify® Cervical Artificial Disc group and one event in the historical ACDF control group that were determined to be definitely device-related by the CEC. In the Simplify® Cervical Artificial Disc group, the definitely device-related AE rate was

0.7% (2/150), with the two events related to implant/joint noise and inflammation. In the historical ACDF control group, the definitely device-related AE rate was 0.9% (1/117), with the event being related to pseudarthrosis. Additional details regarding the device-related AEs are presented in **Table 15** below.

Table 15: Counts and Percentages of Subjects with Specific Definitely Device Related AE – (Primary Analysis Population through Day 790)

	Simplify Disc (N= 150)			ACDF (N= 117)			Group Difference*			
	Events	Subjs	%|	Events	Subjs	%|	p	Δ	LB	UB
All Events	2	1	0.7%	1	1	0.9%	0.663	-0.5%	-2.7%	1.7%
Implant/Joint Noise	1	1	0.7%	0	0	0.0%				
Inflammation Conditions, Such As Discitis, Joint And Other Types Of Inflammation	1	1	0.7%	0	0	0.0%				
Pseudoarthrosis	0	0	0.0%	1	1	0.9%				

*Device group differences and 95% CI adjusting for propensity score (PS) subclass using two-way generalized linear model;
Comparisons with less than 6 subjects in each group includes PS as a continuous variable (df=1) for model stability;
|Percentage of subjects experiencing specific event; †Definite, probable, possibly, and unknown;
‡Subjects censored at Index level secondary surgical interventions.
Source: Tables Safety - Definitely Device Related - Primary.sas; Analyzed: 11JUN2020

Table 16 includes a timecourse of definitely device-related AEs for all subjects in the study through post-operative day 790 by day of occurrence. As shown below, the definitely device-related events occurred 365-730 days post-operatively.

Table 16: Definitely Device-Related AEs (Timecourse) by Code (Primary Analysis Population through Day 790)

	Days Post-Op																	
	Missing		0-2		2-30		30-90		90-180		180-365		365-730		730-790		Total	
	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C
All Events	0	0	0	0	0	0	0	0	0	0	0	0	2	1	0	0	2	1
Implant/Joint Noise	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Inflammation Conditions, Such As Discitis, Joint And Other Types Of Inflammation	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Pseudoarthrosis	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1

‡Subjects censored at Index level secondary surgical interventions.
Source: Tables Safety - Definitely Device Related - Primary.sas; Analyzed: 11JUN2020

Table 17 includes definitely device-related AEs by severity for subjects in the Simplify® Cervical Artificial Disc group through post-operative day 790. As shown below, one event was categorized as mild in severity, and the other was categorized as severe.

Table 17: Definitely Device-Related AEs (Severity) by Code (Simplify® Cervical Artificial Disc Group, N=150)

	Mild		Moderate		Severe		Life Threatening		Total
	Events	%*	Events	%*	Events	%*	Events	%*	Events
All Events	1	50.0%	0	0.0%	1	50.0%	0	0.0%	2
Implant/Joint Noise	1	100.0%	0	0.0%	0	0.0%	0	0.0%	1
Inflammation Conditions, Such As Discitis, Joint And Other Types Of Inflammation	0	0.0%	0	0.0%	1	100.0%	0	0.0%	1

*Percentage of total events;
‡Subjects censored at Index level secondary surgical interventions.
Source: Tables Safety - Definitely Device Related - Primary.sas; Analyzed: 11JUN2020

Table 18 includes definitely device-related AEs by severity for subjects in the historical ACDF control group through post-operative day 790. As shown below, the one event designated as definitely device-related was categorized as moderate in severity.

Table 18: Definitely Device-Related AEs (Severity) by Code (Historical ACDF Control Group, N=117)

	Mild		Moderate		Severe		Life Threatening		Total
	Events	%*	Events	%*	Events	%*	Events	%*	Events
All Events	0	0.0%	1	100.0%	0	0.0%	0	0.0%	1
Pseudoarthrosis	0	0.0%	1	100.0%	0	0.0%	0	0.0%	1

*Percentage of total events;
‡Subjects censored at Index level secondary surgical interventions.
Source: Tables Safety - Definitely Device Related - Primary.sas; Analyzed: 11JUN2020

Definitely Device- or Procedure- Related Adverse Events

Table 19 through **Table 22** present AEs that were determined by the CEC to be 'definitely' related to the device or procedure.

Table 19 includes definitely device- or procedure-related AEs by code for all subjects in the study through post-operative day 790. As shown below, sixteen (16) subjects in the Simplify® Cervical Artificial Disc group and six (6) subjects in the historical ACDF control group had 'definitely' device- or procedure-related events. The most commonly occurring AEs categorized as definitely device- or procedure-related in the Simplify® Cervical Artificial Disc cohort were allergic reaction (2.7% - 4/150), infection localized to cervical surgical site (2.7% - 4/150), and dysphagia (2.0% - 3/150). In the historical ACDF control cohort, the most commonly occurring AEs categorized as definitely device- or procedure-related were dysphagia (0.9% - 1/117), cardiac event (0.9% - 1/117), and surgical wound dehiscence (0.9% - 1/117).

Table 19: Definitely Device- or Procedure-Related AEs by Code (Primary Analysis Population through Day 790)

	Simplify Disc (N= 150)			ACDF (N= 117)			Group Difference*			
	Events	Subjs	%|	Events	Subjs	%|	p	Δ	LB	UB
All Events	26	16	10.7%	7	6	5.1%	0.298	3.4%	-3.1%	9.9%
Dysphagia	3	3	2.0%	1	1	0.9%	0.261	1.6%	-1.1%	4.3%
Cardiac Event	1	1	0.7%	1	1	0.9%	0.848	-0.2%	-2.5%	2.0%
Surgical Wound Dehiscence	1	1	0.7%	1	1	0.9%	0.663	-0.5%	-2.7%	1.7%
Infection Localized To Cervical Surgical Site	4	4	2.7%	0	0	0.0%				
Allergic Reaction	5	4	2.7%	0	0	0.0%				
Hematoma or Seroma	2	2	1.3%	0	0	0.0%				
Surgery At A Location Other than the Spine	5	1	0.7%	0	0	0.0%				
Implant/Joint Noise	1	1	0.7%	0	0	0.0%				
Inflammation Conditions, Such As Discitis, Joint And Other Types Of Inflammation	1	1	0.7%	0	0	0.0%				
Spasm	1	1	0.7%	0	0	0.0%				
Esophageal Perforation	1	1	0.7%	0	0	0.0%				
Deep wound infection localized to cervical surgical site	1	1	0.7%	0	0	0.0%				
Pseudoarthrosis	0	0	0.0%	1	1	0.9%				
Infection (All Other Infections - NOT at cervical surgical site)	0	0	0.0%	1	1	0.9%				
Radiculopathy	0	0	0.0%	2	1	0.9%				

*Device group differences and 95% CI adjusting for propensity score (PS) subclass using two-way generalized linear model;
Comparisons with less than 6 subjects in each group includes PS as a continuous variable (df=1) for model stability;
|Percentage of subjects experiencing specific event; †Definite, probable, possibly, and unknown;
‡Subjects censored at Index level secondary surgical interventions.
Source: Tables Safety - Definitely Device or Procedure Related - Primary.sas; Analyzed: 11JUN2020

Table 20 includes a timecourse of definitely device- or procedure-related AEs for all subjects in the study through post-operative day 790 by day of occurrence. As shown below, majority of definitely device- or procedure-related events occurred within the first 3 months (0-90 days post-op) of treatment.

Table 20: Definitely Device- or Procedure-Related AEs (Timecourse) by Code (Primary Analysis Population through Day 790)

	Days Post-Op																	
	Missing		0-2		2-30		30-90		90-180		180-365		365-730		730-790		Total	
	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C
All Events	0	0	7	3	12	2	5	1	0	0	0	0	2	1	0	0	26	7
Surgery At A Location Other than the Spine	0	0	1	0	1	0	3	0	0	0	0	0	0	0	0	0	5	0
Allergic Reaction	0	0	4	0	1	0	0	0	0	0	0	0	0	0	0	0	5	0
Infection Localized To Cervical Surgical Site	0	0	0	0	4	0	0	0	0	0	0	0	0	0	0	0	4	0
Dysphagia	0	0	0	0	1	0	2	1	0	0	0	0	0	0	0	0	3	1
Hematoma or Seroma	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2	0
Cardiac Event	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Implant/Joint Noise	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Inflammation Conditions, Such As Discitis, Joint And Other Types Of Inflammation	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Spasm	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0
Esophageal Perforation	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Surgical Wound Dehiscence	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1
Deep w ound infection localized to cervical surgical site	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0
Pseudoarthrosis	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Infection (All Other Infections - NOT at cervical surgical site)	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Radiculopathy	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	2

‡Subjects censored at Index level secondary surgical interventions.
Source: Tables Safety - Definitely Device or Procedure Related - Primary.sas; Analyzed: 11JUN2020

Table 21 includes definitely device- or procedure-related AEs by severity for subjects in the Simplify® Cervical Artificial Disc group through post-operative day 790. As shown below, there were no life-threatening definitely device- or procedure-related events in the Simplify® Cervical Artificial Disc group. The most commonly occurring AEs categorized as definitely device- or procedure-related in the Simplify® Cervical Artificial Disc cohort include surgery at a location other than the spine (n=5 *(one subject experienced a complication during the TDR procedure (esophageal perforation) resulting in five (5) subsequent procedures to repair the perforation)*), allergic reaction (n=5), and infection localized to cervical surgical site (n=4).

Table 21: Definitely Device- or Procedure-Related AEs (Severity) by Code (Simplify® Cervical Artificial Disc Group, N=150)

	Mild		Moderate		Severe		Life Threatening		Total
	Events	%*	Events	%*	Events	%*	Events	%*	Events
All Events	9	34.6%	9	34.6%	8	30.8%	0	0.0%	26
Surgery At A Location Other than the Spine	0	0.0%	0	0.0%	5	100.0%	0	0.0%	5
Allergic Reaction	2	40.0%	3	60.0%	0	0.0%	0	0.0%	5
Infection Localized To Cervical Surgical Site	2	50.0%	2	50.0%	0	0.0%	0	0.0%	4
Dysphagia	2	66.7%	1	33.3%	0	0.0%	0	0.0%	3
Hematoma or Seroma	2	100.0%	0	0.0%	0	0.0%	0	0.0%	2
Cardiac Event	0	0.0%	1	100.0%	0	0.0%	0	0.0%	1
Implant/Joint Noise	1	100.0%	0	0.0%	0	0.0%	0	0.0%	1
Inflammation Conditions, Such As Discitis, Joint And Other Types Of Inflammation	0	0.0%	0	0.0%	1	100.0%	0	0.0%	1
Spasm	0	0.0%	1	100.0%	0	0.0%	0	0.0%	1
Esophageal Perforation	0	0.0%	0	0.0%	1	100.0%	0	0.0%	1
Surgical Wound Dehiscence	0	0.0%	1	100.0%	0	0.0%	0	0.0%	1
Deep w ound infection localized to cervical surgical site	0	0.0%	0	0.0%	1	100.0%	0	0.0%	1

*Percentage of total events;
‡Subjects censored at Index level secondary surgical interventions.
Source: Tables Safety - Definitely Device or Procedure Related - Primary.sas; Analyzed: 11JUN2020

Table 22 includes all definitely device- or procedure-related AEs by severity for subjects in the historical ACDF control group through post-operative day 790. As shown below, there were no severe or life-threatening definitely device- or procedure-related events in the historical ACDF

control group. The most commonly occurring AEs categorized as definitely device- or procedure-related in the historical ACDF control cohort include radiculopathy (n=2) and dysphagia (n=2).

Table 22: Definitely Device- or Procedure-Related AEs (Severity) by Code (Historical ACDF Control Group, N=117)

	Mild		Moderate		Severe		Life Threatening		Total
	Events	%*	Events	%*	Events	%*	Events	%*	Events
All Events	3	42.9%	4	57.1%	0	0.0%	0	0.0%	7
Radiculopathy	0	0.0%	2	100.0%	0	0.0%	0	0.0%	2
Dysphagia	1	100.0%	0	0.0%	0	0.0%	0	0.0%	1
Pseudoarthrosis	0	0.0%	1	100.0%	0	0.0%	0	0.0%	1
Cardiac Event	1	100.0%	0	0.0%	0	0.0%	0	0.0%	1
Infection (All Other Infections - NOT at cervical surgical site)	1	100.0%	0	0.0%	0	0.0%	0	0.0%	1
Surgical Wound Dehiscence	0	0.0%	1	100.0%	0	0.0%	0	0.0%	1

*Percentage of total events;
‡Subjects censored at Index level secondary surgical interventions.
Source: Tables Safety - Definitely Device or Procedure Related - Primary.sas; Analyzed: 11JUN2020

Serious Adverse Events (SAEs)

There were a total of 26 Serious AEs (SAEs) in the Simplify® Cervical Artificial Disc group in 16 subjects and 24 SAEs in 16 subjects in the historical ACDF control group (**Table 23**). There were no significant differences in SAE rates between groups. The most commonly occurring events categorized as SAEs in the Simplify® Cervical Artificial Disc cohort were infection at a location other than the cervical surgical site (1.3% - 2/150), pain with narcotic given (1.3% - 2/150), adjacent segment degeneration (1.3% - 2/150), and surgery at a location other than the spine (1.3% - 2/150). In the historical ACDF control cohort, the most commonly occurring events categorized as SAEs were pain with narcotic given (2.6% - 3/117) and adjacent segment degeneration (2.6% - 3/117).

Table 23: Counts and Percentages of Subjects with Specific SAEs– (Primary Analysis Population through Day 790)

	Simplify Disc (N= 150)			ACDF (N= 117)			Group Difference*			
	Events	Subjs	%|	Events	Subjs	%|	p	Δ	LB	UB
All Events	26	16	10.7%	24	16	13.7%	0.686	1.5%	-6.5%	9.5%
Infection (All Other Infections - NOT at cervical surgical site)	2	2	1.3%	2	1	0.9%	0.826	0.3%	-2.3%	2.9%
Pseudoarthrosis	1	1	0.7%	1	1	0.9%	0.772	0.2%	-1.5%	2.0%
Trauma	1	1	0.7%	1	1	0.9%	0.594	0.2%	-1.1%	1.5%
Headache	1	1	0.7%	1	1	0.9%	0.848	-0.2%	-2.5%	2.0%
Radiculopathy	1	1	0.7%	4	2	1.7%	0.779	-0.3%	-2.7%	2.1%
Psychological Illness	1	1	0.7%	1	1	0.9%	0.365	-0.4%	-2.1%	1.3%
Pain (Narcotic Given)	2	2	1.3%	3	3	2.6%	0.518	-1.2%	-4.9%	2.4%
Adjacent Segment Degeneration	3	2	1.3%	3	3	2.6%	0.341	-1.8%	-5.4%	1.9%
Surgery At A Location Other than the Spine	5	2	1.3%	0	0	0.0%				
Gastrointestinal Complications Including Ileus, Nausea and Vomiting	2	2	1.3%	0	0	0.0%				
Pneumonia	1	1	0.7%	0	0	0.0%				
Spinal Stenosis	1	1	0.7%	0	0	0.0%				
Inflammation Conditions, Such As Discitis, Joint And Other Types Of Inflammation	1	1	0.7%	0	0	0.0%				
Esophageal Perforation	1	1	0.7%	0	0	0.0%				
Infection Localized To Cervical Surgical Site	1	1	0.7%	0	0	0.0%				
Ischemia	1	1	0.7%	0	0	0.0%				
Deep w ound infection localized to cervical surgical site	1	1	0.7%	0	0	0.0%				
Implant Collapse Or Subsidence	0	0	0.0%	1	1	0.9%				
Pain (No Narcotic Given)	0	0	0.0%	2	2	1.7%				
Pulmonary Embolism	0	0	0.0%	1	1	0.9%				
Thrombosis	0	0	0.0%	1	1	0.9%				
Other	0	0	0.0%	1	1	0.9%				
Cancer	0	0	0.0%	2	2	1.7%				

*Device group differences and 95% CI adjusting for propensity score (PS) subclass using two-way generalized linear model;
Comparisons with less than 6 subjects in each group includes PS as a continuous variable (df=1) for model stability;
|Percentage of subjects experiencing specific event; †Definite, probable, possibly, and unknown;
‡Subjects censored at Index level secondary surgical interventions.
Source: Tables Safety - Serious AEs - Primary.sas; Analyzed: 11JUN2020

No subjects in the historical ACDF control group had definitely device-related SAEs. One (1) subject in the Simplify® Cervical Artificial Disc group had an SAE that was determined by the CEC to be 'definitely' device-related. The AE was categorized as 'inflammation conditions, such as discitis, joint and other types of inflammation' and occurred 365-730 days post-operatively. The event was categorized as severe.

Secondary Surgical Intervention

Some AEs resulted in SSIs that were prospectively classified as revisions, removals, reoperations or supplemental fixations, qualified as study failures in accordance with FDA's Guidance Document, Clinical Data Presentations for Orthopedic Device Applications (2004) and were reviewed and adjudicated by the CEC.

Based on the results presented in **Table 24**, a total of four (4) SSIs occurred in the Simplify® Cervical Artificial Disc group and six (6) SSIs occurred in the ACDF group. Of the ACDF SSIs, one (1) occurred on post-operative day 746 (post 2-year anniversary but prior to close of Month 24 window) and is therefore not included in the subject accounting table and overall success table. The timecourse of these events demonstrates that the majority of SSIs occurred between 12 and 24 months in both groups; however, meaningful conclusions cannot be made with respect to timing due to the low number of SSI events in both groups.

Table 24: Surgical Intervention Timecourse by Treatment Type – (Primary Analysis Population through Day 790)

Treatment Group	SSI Type	Event Timecourse (months)					Total (events)
		<1.5	1.5-3	3-6	6-12	12-24	
Simplify® Cervical Artificial Disc (N=150)	Removal	-	1	-	-	1	2
	Revision	-	-	-	-	-	0
	Reoperation	-	-	-	-	1	1
	Supplemental Fixation	-	-	-	-	1	1
ACDF (N=117)	Removal	-	-	2	-	3*	5
	Revision	-	-	-	-	1	1
	Reoperation	-	-	-	-	-	0
	Supplemental Fixation	-	-	-	-	-	0

**One SSI occurred on day 746 (post 2-year anniversary but prior to close of Month 24 window) and is therefore not included in the survival analysis, subject accounting table, and overall success table.*

The procedure and reason for SSI are detailed below in **Table 25**. Of the four (4) SSIs observed in the Simplify® Cervical Artificial Disc cohort, two (2) resulted in device removal. Of the six (6) SSIs reported in the historical ACDF control cohort, five (5) resulted in device removal.

Table 25: Surgical Intervention Procedure and Indication for Procedure

Group	Procedure	Index Level	Procedure	Indication for Procedure
Simplify®	Removal	C6/7	Staged procedure involving explant of the Simplify® Cervical Artificial Disc at C6/C7, C7 corpectomy, anterior spinal fusion of C6-T1, and posterior spinal fusion at C6-T2.	Esophageal perforation and deep wound infection localized to cervical surgical site.
Simplify®	Removal	C6/7	C6/C7 Simplify® Cervical Artificial Disc explanted, ACDF performed at C6/C7	Recurrent stenosis with worsening disc degeneration status
Simplify®	Supplemental Fixation	C6/7	Anterior cervical corpectomy at C6 with PEEK interbody spacer, anterior plating at C4-C7, and fusion exploration	Symptomatic pseudarthrosis at C5/C6 (adjacent level)
Simplify®	Reoperation	C6/7	C6/C7 foraminotomy for decompression	Radiculopathy at C7
ACDF	Removal	C5/6	Removal of implant at C5/C6 and placement of a Prestige implant at C6/C7	Radiculopathy
ACDF	Removal	C6/7	Removal of implant at C6/C7 and application of anterior cervical plate at C5-C7	Adjacent segment degeneration
ACDF	Removal	C5/6	Removal of the implant at C5/C6 and supplemental fixation of C5/C6 using an interbody bone graft and titanium anterior cervical plate and screws	Subsidence of graft

Group	Procedure	Index Level	Procedure	Indication for Procedure
ACDF	Removal	C5/6	Removal of implant at C5/C6 revised to total disc replacement at C5/C6	Symptomatic pseudarthrosis at C5/C6
ACDF	Revision	C5/6	Removal of anterior plate at C5/C6. Placement of a 9 x 7mm spacer with Slimlock plate to the ventral surface of the vertebral bodies at C6/C7	Adjacent segment degeneration at C6/C7
ACDF	Removal	C5/6	Removal of the fusion implant and re-do of cervical fusion at C5/C6	Symptomatic pseudarthrosis at C5/C6

Neurological Status

Neurological success was defined as maintenance or improvement in neurologic status at Month 24. The CEC reviewed investigator assigned neurologic status (stable/ improved/ deteriorated) at Month 24 as compared to baseline for all subjects to confirm or reclassify neurologic status. At Month 24, one (1) Simplify® Cervical Artificial Disc subject was considered a neurological failure (0.7% - 1/139) and five (5) historical ACDF control subjects were considered neurological failures (5.3% - 5/95) as shown in **Table 26**.

Table 26: Neurological Status at Month 24 - (Primary Analysis Population)

	Simplify® Cervical Artificial Disc			ACDF		
	N	N	%	N	n	%
Improved	139	111	79.9%	95	52	54.7%
Maintained		27	19.4%		38	40.0%
Deteriorated		1	0.7%		5	5.3%

The one (1) Simplify® Cervical Artificial Disc subject was classified as 'deteriorated' based on decline in sensory status at Month 24. Of the five (5) historical ACDF control subjects who were classified as 'deteriorated', two were based on decline in sensory status, two based on decline in motor function and one based on decline in sensory status and motor function at Month 24.

2. Effectiveness Results

Primary Overall Success Analysis

The success measurement was developed to measure safety and effectiveness of the Simplify® Cervical Artificial Disc when compared to ACDF. A subject was considered a study success at the Month 24 if he/she met all of the following criteria:

- Improvement in NDI of at least 15 percentage-points (out of 100) as compared to baseline at Month 24,
- Maintenance or improvement in neurologic status as compared to baseline at Month 24 (as determined by the CEC),
- No device failures within 24 months of index procedure,

- No SSI at the index level within 24 months of index procedure (as determined by the CEC), and
- No major AEs within 24 months of index procedure (as determined by the CEC).

For overall success, the proportion of subjects meeting the success criteria in each group was determined and the difference (Simplify® Cervical Artificial Disc minus ACDF) and the one-sided 90% confidence interval for the difference between treatment groups was calculated. The one-sided 90% lower confidence interval was greater than the non-inferiority margin (-10%); consequently, the primary endpoint was met. Additionally, the one-sided 95% confidence interval for the difference between treatment groups was calculated. The one-sided 95% lower confidence interval was greater than the superiority margin (0%), and as a result, the Simplify® Cervical Artificial Disc group is confirmed to be superior to the historical ACDF control group. The primary overall success outcomes are presented in **Table 27**.

Table 27: Overall Efficacy (Primary Analysis Population)

	Simplify Disc			ACDF			Group Difference*			
Outcome	**N**	**n**	**%|**	**N**	**n**	**%|**	**p**	**Δ**	**90% LB**	**95% LB**
Implanted	150	148	99.5%	117	117	100.0%				
No secondary surgical intervention‡	**148**	**144**	**97.1%**	**117**	**112**	**97.1%**	**0.979**	**-0.1%**	**-3.6%**	**-4.3%**
No removals‡	148	146	98.6%	117	113	98.0%				
No revisions§	148	148	100.0%	117	116	100.0%				
No reoperations‡	148	147	99.3%	117	117	100.0%				
No supplemental fixations‡	148	147	99.3%	117	117	100.0%				
No device failure†§	**137**	**137**	**100.0%**	**90**	**83**	**92.2%**				
No device condition failure†§	137	137	100.0%	92	85	92.4%				
No device migration failure†§	137	137	100.0%	90	90	100.0%				
NDI 15-point Responder†	**138**	**135**	**97.9%**	**96**	**83**	**88.0%**	**0.009**	**9.9%**	**3.2%**	**1.9%**
No Neurological Deterioration (CEC)†	**139**	**138**	**99.6%**	**95**	**90**	**94.1%**	**0.015**	**5.6%**	**1.0%**	**0.2%**
No Major Adverse Event (CEC)†§	**150**	**150**	**100.0%**	**117**	**117**	**100.0%**				
Composite Clinical Success (CCS)¶	**150**	**--**	**93.0%**	**117**	**--**	**73.6%**	**<.001**	**19.4%**	**10.9%**	**9.3%**
CCS: Observed data only	142	132	93.0%	96	68	71.3%	<.001	21.6%	12.4%	10.7%
CCS: Best-Case	150	140	93.3%	117	68	58.8%	<.001	34.5%	25.4%	23.6%
CCS: Worst-Case	150	132	88.1%	117	89	76.4%	0.025	11.7%	3.3%	1.8%

*Device group differences and 90% and 95% LB adjusting for propensity score (PS) subclass using two-way generalized linear model;□
|Equally weighted PS adjusted within group proportion. This will not equal n/N which is the observed data;□
†Subjects censored at Index level secondary surgical interventions;□
‡Propensity Score treated as continuous variable to promote convergence;□
§Not estimable due to zero cell. Unadjusted within group rate shown;□
¶A Fully Conditional Specification (FCS) approach was used to produce 20 multiply imputed completed data sets. The FCS approach accommodates non-monotonicity in the pattern of missing data and requires regression models to be specified for each variable with missing values needing imputation. All models included the PS subclass and treatment group. NDI responder status and secondary surgical interventions over time were sequentially added to account for longitudinal temporality. The resulting completed datasets were combined using Rubin's Rules.□
Source: Tables Overall Efficacy.sas; Analyzed: 27AUG2020

Using multiple imputation to account for missing data, the adjusted success rate was 93.0% for Simplify® Cervical Artificial Disc cohort and 73.6% for the historical ACDF control cohort. The adjusted difference between groups was 19.4%. The lower-bound of the 1-sided 90% confidence interval for the group difference controlling for PS subclass was 10.9%. Since 10.9% is greater than -10%, the results from this comparison demonstrate that the study success criterion for non-inferiority has been achieved. Further, the 1-sided 95% confidence interval for the group difference controlling for PS subclass was 9.3%. Since 9.3% is greater than 0%, the results from this comparison demonstrate that the study success criterion for superiority has been achieved.

Sensitivity analyses were performed to evaluate the composite success measurement using observed data only, best case evaluation and worst-case evaluation. All sensitivity analyses demonstrate that the study success criterion for non-inferiority has been achieved. Further, the sensitivity analyses confirm the superiority of the Simplify® Cervical Artificial Disc group as compared to the historical ACDF control group.

Secondary Effectiveness Analyses

This section focuses on secondary clinical endpoints from a number of relevant domains (i.e., NDI, VAS, SF-12v2, Dysphagia Handicap Index (DHI), medication usage, neurological assessments, work status, and Radiographic Measurements)), which were assessed at preoperative (baseline) and at prescribed clinical intervals throughout the follow-up period. In addition, Odom's criteria, treatment satisfaction, and time to recovery, were assessed post-operatively at Month 24. **Table 28** shows the secondary effectiveness subject outcomes at Month 24 compared to baseline. Overall, subjects treated with the Simplify® Cervical Artificial Disc exhibited improvement and numerically favorable rates of success as compared to the historical ACDF control cohort across the broad spectrum of secondary analyses.

Table 28: Secondary Effectiveness Subject Outcomes at Month 24 Compared to Baseline (Primary Analysis Population)

Secondary Effectiveness Endpoint	Simplify® Cervical Artificial Disc (N=150)	ACDF (N=117)
NDI Improvement ≥ 15 percentage-points (out of 100)	135/138 (97.8%)	83/96 (86.5%)
VAS Neck and Arm Pain Improvement ≥ 20mm	134/139 (96.4%)	83/95 (87.4%)
SF-12 PCS Maintenance or Improvement	129/138 (93.5%)	-
SF-12 MCS Maintenance or Improvement	105/138 (76.1%)	-
Treatment Satisfaction (Very Satisfied)	122/138 (88%)	67/96 (70%)
Odom's Criteria (Excellent or Good)	133/139 (95.8%)	82/95 (86.3%)
Narcotic Use (No. of Subjects Using)	15/139 (10.8%)	35/95 (36.8%)

Neck Disability Index

Table 29 and **Table 30** present the NDI percentage-points for all treated subjects. NDI is scored on a 50-point scale (10 questions with a score of 0-5 for each) that is then normalized to a scale of 100%. Higher NDI is representative of greater symptomatology. The following outcomes reflect NDI percentage-points out of 100%. NDI data are censored following intra-operative deviation or SSI.

Table 29: NDI percentage-points over time (Primary Analysis Population)

	Simplify Disc						ACDF						Group Difference*			
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p	Δ	LB	UB
Pre-Op	150	63.3	12.5	61.0	40.0	94.0	117	62.4	12.6	64.0	40.0	90.0	0.950	0.1	-3.3	3.5
Week 06	146	23.1	17.8	20.0	0.0	86.0	112	33.7	19.5	32.0	0.0	78.0	<.001	-11.3	-16.5	-6.2
Month 03	145	17.3	16.7	14.0	0.0	84.0	111	25.9	19.5	24.0	0.0	74.0	<.001	-9.5	-14.5	-4.5
Month 06	144	16.8	16.6	12.0	0.0	86.0	101	23.0	20.3	22.0	0.0	78.0	0.009	-7.0	-12.2	-1.8
Month 12	143	16.5	17.4	14.0	0.0	88.0	100	22.8	21.3	17.0	0.0	78.0	0.022	-6.4	-11.9	-0.9
Month 24	138	13.6	14.3	10.0	0.0	84.0	96	23.0	19.8	19.0	0.0	72.0	<.001	-11.0	-15.9	-6.1

Subjects censored at Index level secondary surgical interventions.
*Device group mean differences and 95% CI adjusting for propensity score (PS) subclass using two-way analysis of variance.
Source: Table Clinical Follow-up.sas; Analyzed: 14MAY2020

Table 29 shows the mean NDI percentage-points for the Primary Analysis Population at pre-operative, 6-week, 3-month, 6-month, 12-month, and 24-month time points for both the Simplify® Cervical Artificial Disc and historical ACDF control groups. Pre-operative percentage-point was numerically greater in the Simplify® Cervical Artificial Disc group; however, the difference in percentage-points was not statistically significant (p=0.950). The mean pre-op NDI score for the Simplify® Cervical Artificial Disc cohort was 63.3, which improved to a mean NDI score of 13.6 at Month 24. Similarly, the mean pre-op NDI score for the historical ACDF control cohort was 62.4, which improved to a mean NDI score of 23.0 at Month 24. The difference in NDI percentage-points between groups was statistically significant at Week 6 through Month 24, in favor of the Simplify® Cervical Artificial Disc group ($p<0.05$).

Table 30: NDI change in percentage-points from pre-operative (Primary Analysis Population)

	Simplify Disc						ACDF						Group Difference*			
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p	Δ	LB	UB
Week 06	146	-40.3	20.0	-43.0	-78.0	14.0	112	-28.5	19.4	-28.0	-78.0	8.0	<.001	-11.7	-17.2	-6.2
Month 03	145	-46.3	18.6	-50.0	-86.0	6.0	111	-36.5	19.8	-36.0	-76.0	6.0	<.001	-9.8	-15.1	-4.6
Month 06	144	-46.6	17.8	-48.0	-86.0	8.0	101	-39.1	19.8	-40.0	-82.0	6.0	0.005	-7.6	-12.9	-2.3
Month 12	143	-47.2	19.2	-50.0	-94.0	8.0	100	-39.3	20.5	-40.0	-78.0	8.0	0.011	-7.4	-13.0	-1.7
Month 24	138	-49.4	16.8	-50.0	-92.0	4.0	96	-38.9	20.6	-38.0	-78.0	10.0	<.001	-11.9	-17.3	-6.5

Subjects censored at Index level secondary surgical interventions.
*Device group mean differences and 95% CI adjusting for propensity score (PS) subclass using two-way analysis of variance.
Source: Table Clinical Follow-up.sas; Analyzed: 14MAY2020

Table 30 presents the mean change in NDI percentage-points from pre-operative for the Primary Analysis Population at Week 6, Month 3, Month 6, Month 12, and Month 24 time points for both the Simplify® Cervical Artificial Disc and historical ACDF control groups. Similar to the trends seen in mean score, the difference in NDI percentage-points change from pre-operative was statistically significant at all time points, in favor of the Simplify® Cervical Artificial Disc group ($p<0.05$). Of interest, there was a greater change at the Week 6 visit (-40.3 vs. -28.5, $p<0.001$) in the Simplify® Cervical Artificial Disc group that was sustained through the study. The historical ACDF control group mean change was significantly smaller with the plateau seen at the Month 6 visit, presumably when the fusion was generally healed. This speaks to the clinical meaning of the acute response seen with reconstructing the disc space with a motion-permitting device versus a fusion that requires months to heal.

Table 31: NDI Improved/ Stable/ Deteriorated Status (Primary Analysis Population)

	Week 06				Month 03				Month 06				Month 12				Month 24			
	Simplify Disc		ACDF		Simplify Disc		ACDF		Simplify Disc		ACDF		Simplify Disc		ACDF		Simplify Disc		ACDF	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Improved [-100, -15]	127	87%	86	77%	139	96%	90	81%	138	96%	92	91%	133	93%	84	84%	135	98%	83	86%
Stable (-15, 0]	14	10%	18	16%	3	2%	18	16%	3	2%	7	7%	6	4%	13	13%	2	1%	10	10%
Deteriorated (0, 100]	5	3%	8	7%	3	2%	3	3%	3	2%	2	2%	4	3%	3	3%	1	1%	3	3%

Subjects censored at Index level secondary surgical interventions.
Source: Table Clinical Follow-up.sas; Analyzed: 14MAY2020

Table 31 presents the number and percentage of subjects who demonstrated improvement (NDI decrease >15 percent), number and percentage of subjects who were stable (NDI decrease 0-15 percent), and number and percentage of subjects who deteriorated (any increase) relative to pre-operative at Week 6, Month 3, Month 6, Month 12, and Month 24 time points. As shown above, majority of subjects demonstrated improvement in both groups.

Table 32: NDI 15 Percentage-Point Responder (Primary Analysis Population)

	Simplify Disc			ACDF			Group Difference*			
	N	n	%	N	n	%	p	Δ	LB	UB
Week 06	146	127	87.0%	112	86	76.8%	0.080	9.4%	-0.8%	19.7%
Month 03	145	139	95.9%	111	90	81.1%	0.002	14.0%	5.3%	22.6%
Month 06	144	138	95.8%	101	92	91.1%	0.283	3.7%	-3.1%	10.4%
Month 12	143	133	93.0%	100	84	84.0%	0.064	8.4%	-0.4%	17.3%
Month 24	138	135	97.8%	96	83	86.5%	0.009	9.9%	1.9%	17.9%

Subjects censored at Index level secondary surgical interventions.
*Device group differences and 95% CI adjusting for propensity score (PS) subclass using two-way generalized linear model.
Source: Table Clinical Follow-up.sas; Analyzed: 14MAY2020

Table 32 presents the number and percentage of subjects showing an improvement in NDI greater than 15 percentage-points as compared to all subjects in the study at Week 6, Month 3, Month 6, Month 12, and Month 24 time points for both the Simplify® Cervical Artificial Disc and historical ACDF control groups. A numerically greater percentage of Simplify® Cervical Artificial Disc subjects achieved 15 percentage-point improvement in NDI at all time points as compared to the historical ACDF control group, with 97.8% (135/138) of subjects in the Simplify® Cervical Artificial Disc Group meeting achieving this level of improvement in NDI at Month 24. This difference was statistically significant at Month 3 and Month 24 ($p<0.05$).

VAS Neck and Arm

Table 33 shows the VAS score for combined Neck and Arm pain for the Primary Analysis Population at pre-operative, postoperative, Week 6, Month 3, Month 6, Month 12, and Month 24 time points for both the Simplify® Cervical Artificial Disc and historical ACDF control groups.

Table 33: VAS (Neck, Arm) values over time (Primary Analysis Population)

	Simplify Disc						ACDF						Group Difference*			
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p	Δ	LB	UB
Pre-Op	150	81.6	12.4	84.0	41.0	100.0	117	77.6	13.5	79.0	42.0	100.0	0.717	0.6	-2.7	4.0
Post-Op	146	32.6	28.6	23.5	0.0	100.0	114	37.8	27.4	30.5	0.0	100.0	0.269	-4.3	-12.0	3.4
Week 06	146	22.9	24.5	13.0	0.0	99.0	113	27.6	24.9	19.0	0.0	100.0	0.052	-6.7	-13.4	0.1
Month 03	144	18.2	21.5	10.0	0.0	90.0	111	25.0	25.0	15.0	0.0	91.0	0.024	-7.4	-13.8	-1.0
Month 06	144	17.9	22.2	7.5	0.0	93.0	101	23.9	23.4	15.0	0.0	79.0	0.028	-7.3	-13.8	-0.8
Month 12	142	17.7	21.3	9.0	0.0	81.0	100	22.3	23.6	13.0	0.0	88.0	0.169	-4.5	-10.8	1.9
Month 24	139	15.6	20.2	7.0	0.0	90.0	95	23.3	24.3	15.0	0.0	92.0	<.001	-11.9	-18.1	-5.6

Subjects censored at Index level secondary surgical interventions.
*Device group mean differences and 95% CI adjusting for propensity score (PS) subclass using two-way analysis of variance.
Source: Table Clinical Follow-up.sas; Analyzed: 14MAY2020

As demonstrated in **Table 33**, mean pre-operative score was numerically greater in the Simplify® Cervical Artificial Disc group (81.6) as compared to the historical ACDF control group (77.6), though the difference was not statistically significant (p=0.717). The difference in mean VAS score for combined Neck and Arm pain between groups was statistically significant at Months 3, 6, and 24, in favor of the Simplify® Cervical Artificial Disc group ($p<0.05$), with a mean VAS score of 15.6 for the Simplify® Cervical Artificial Disc group at Month 24, as compared to a mean VAS score of 23.3 for the historical ACDF control group at Month 24.

Table 34 presents the change in VAS score from pre-operative for combined Neck and Arm pain for the Primary Analysis Population at postoperative, Week 6, Month 3, Month 6, Month 12, and Month 24 time points for both the Simplify® Cervical Artificial Disc and historical ACDF control groups.

Table 34: VAS (Neck, Arm) change from pre-operative (Primary Analysis Population)

	Simplify Disc						ACDF						Group Difference*			
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p	Δ	LB	UB
Post-Op	146	-49.1	29.6	-52.0	-96.0	26.0	114	-39.7	31.3	-46.5	-100.0	39.0	0.235	-5.0	-13.2	3.3
Week 06	146	-58.8	25.5	-63.5	-99.0	19.0	113	-49.8	27.5	-52.0	-100.0	55.0	0.041	-7.5	-14.8	-0.3
Month 03	144	-63.7	22.7	-68.5	-97.0	14.0	111	-52.7	26.6	-59.0	-100.0	13.0	0.015	-8.4	-15.1	-1.6
Month 06	144	-64.0	24.2	-71.5	-100.0	17.0	101	-53.6	25.0	-57.0	-99.0	4.0	0.016	-8.6	-15.6	-1.6
Month 12	142	-64.5	23.1	-70.5	-99.0	0.0	100	-54.8	26.9	-59.5	-100.0	14.0	0.066	-6.6	-13.6	0.5
Month 24	139	-66.4	21.8	-71.0	-100.0	14.0	95	-53.7	26.6	-56.0	-100.0	16.0	<.001	-13.9	-20.9	-6.9

Subjects censored at Index level secondary surgical interventions.
*Device group mean differences and 95% CI adjusting for propensity score (PS) subclass using two-way analysis of variance.
Source: Table Clinical Follow-up.sas; Analyzed: 14MAY2020

Similar to the trends seen in mean score presented in **Table 34**, the mean difference in VAS combined Neck and Arm pain score change compared to pre-operative was statistically significant at 6-week, 3-month, 6-month, and 24-month time points ($p<0.05$), in favor of the Simplify® Cervical Artificial Disc group. At Month 24, the change in mean VAS score as compared to pre-

op was -66.4 for the Simplify® Cervical Artificial Disc group. For the historical ACDF control group, the change in mean VAS score at Month 24 as compared to pre-op was -53.7.

Table 35 presents the number and percentage of subjects showing an improvement in VAS combined Neck and Arm pain greater than 20 points as compared to baseline at Week 6, Month 3, Month 6, Month 12, and Month 24 time points for both the Simplify® Cervical Artificial Disc and historical ACDF control groups.

Table 35: VAS Neck and Arm 20-Point Responder (Primary Analysis Population)

	Simplify Disc			ACDF			Group Difference*			
	N	n	%	N	n	%	p	Δ	LB	UB
Post-Op	146	114	78.1%	114	82	71.9%	0.577	3.3%	-7.9%	14.6%
Week 06	146	133	91.1%	113	97	85.8%	0.073	8.0%	-0.6%	16.7%
Month 03	144	136	94.4%	111	94	84.7%	0.059	7.3%	-0.5%	15.2%
Month 06	144	136	94.4%	101	91	90.1%	0.268	4.2%	-3.2%	11.5%
Month 12	142	132	93.0%	100	87	87.0%	0.300	4.2%	-3.8%	12.3%
Month 24	139	134	96.4%	95	83	87.4%	0.008	10.9%	2.6%	19.1%

Subjects censored at Index level secondary surgical interventions.
*Device group differences and 95% CI adjusting for propensity score (PS) subclass using two-way generalized linear model.
Source: Table Clinical Follow-up.sas; Analyzed: 14MAY2020

As demonstrated in **Table 35**, a numerically greater percentage of Simplify® Cervical Artificial Disc subjects achieved 20-point improvement at VAS combined Neck and Arm pain as compared to the historical ACDF control group at all time points with a statistically significant difference at Month 24 in favor of the Simplify® Cervical Artificial Disc group (p=0.008). A total of 96.4% (134/139) of the Simplify® Cervical Artificial Disc subjects achieved at least a 20-point improvement in VAS combined Neck and Arm pain at Month 24, as compared to 87.4% (83/95) of the historical ACDF control subjects at the same evaluation time point.

Short-Form 12 (SF-12) – Physical Component Score (PCS)

Table 36 includes the PCS of the SF-12 for all subjects in the Simplify® Cervical Artificial Disc group at pre-operative, Month 6, Month 12, and Month 24 time points. SF-12 scores are normalized to the US general population (not age/gender based). At pre-op, the mean PCS of the

Simplify® Cervical Artificial Disc subjects was 31.1, which improved to a mean PCS of 50.7 at Month 24.

Table 36: SF-12 (Physical Component Score – PCS) values over time (Primary Analysis Population)

	Simplify Disc					
	N	Mean	SD	Med	Min	Max
Pre-Op	150	31.1	7.4	30.3	11.2	56.1
Month 06	143	48.7	9.0	50.3	17.4	64.4
Month 12	143	49.7	8.6	51.8	16.5	62.2
Month 24	138	50.7	8.7	53.5	16.5	66.3

Subjects censored at Index level secondary surgical interventions.
Source: Table Clinical Follow-up.sas; Analyzed: 14MAY2020

As demonstrated in **Table 36**, the mean SF-12 PCS score increased from the pre-operative time point through the Month 24 time point, indicating continued improvement in SF-12 PCS.

Table 37 includes the change in PCS from pre-operative for all subjects in the Simplify® Cervical Artificial Disc group at 6-month, 12-month, and 24-month time points. At Month 6, the mean PCS improvement of the Simplify® Cervical Artificial Disc subjects was 17.5, which increased to a mean PCS improvement of 19.3 at Month 24.

Table 37: SF-12 (Physical Component Score - PCS) change from pre-operative (Primary Analysis Population)

	Simplify Disc					
	N	Mean	SD	Med	Min	Max
Month 06	143	17.5	9.3	18.7	-20.7	35.3
Month 12	143	18.4	9.9	19.2	-7.8	40.9
Month 24	138	19.3	10.4	21.6	-10.1	43.6

Subjects censored at Index level secondary surgical interventions.
Source: Table Clinical Follow-up.sas; Analyzed: 14MAY2020

As demonstrated in **Table 37**, the magnitude of change in SF-12 PCS increased through Month 24.

Table 38 includes the number and percentage of subjects achieving maintenance or improvement in SF-12 PCS score.

Table 38: SF-12 PCS – Subjects Achieving Maintenance or Improvement (Primary Analysis Population)

	Simplify Disc		
	N	n	%
Month 06	143	138	96.5%
Month 12	143	134	93.7%
Month 24	138	129	93.5%

Subjects censored at Index level secondary surgical interventions.
Source: Table Clinical Follow-up.sas; Analyzed: 14MAY2020

As shown above, a high rate of subjects achieved maintenance or improvement in SF-12 PCS at all postoperative time points.

Short-Form 12 (SF-12) – Mental Component Score (MCS)

Table 39 includes the MCS of the SF-12 for all subjects in the Simplify® Cervical Artificial Disc group at pre-operative, 6-month, 12-month, and 24-month time points. SF-12 scores are normalized to the US general population (not age/ gender based). At pre-op, the mean MCS of the Simplify® Cervical Artificial Disc subjects was 42.4, which increased to a mean MCS of 52.2 at Month 24.

Table 39: SF-12 (Mental Component Score – MCS) values over time (Primary Analysis Population)

	Simplify Disc					
	N	Mean	SD	Med	Min	Max
Pre-Op	150	42.4	12.2	42.3	15.6	67.5
Month 06	143	52.5	9.4	56.4	18.9	67.0
Month 12	143	52.3	9.1	55.6	14.5	67.5
Month 24	138	52.2	8.8	54.9	23.1	63.5

Subjects censored at Index level secondary surgical interventions.
Source: Table Clinical Follow-up.sas; Analyzed: 14MAY2020

As demonstrated in **Table 39**, the mean SF-12 MCS increased postoperatively and was maintained through Month 24, indicating continued improvement in SF-12 MCS.

Table 40 includes the change in MCS from pre-operative for all subjects in the Simplify® Cervical Artificial Disc group in the study at 6-month, 12-month, and 24-month time points. At Month 6, the mean MCS improvement of the Simplify® Cervical Artificial Disc subjects was 10.1, which decreased to a mean MCS improvement of 9.5 at Month 24.

Table 40: SF-12 (Mental Component Score - MCS) change from pre-operative (Primary Analysis Population)

	Simplify Disc					
	N	Mean	SD	Med	Min	Max
Month 06	143	10.1	12.2	10.0	-17.4	44.5
Month 12	143	10.0	12.1	9.5	-26.1	44.5
Month 24	138	9.5	12.1	8.4	-21.2	41.5

Subjects censored at Index level secondary surgical interventions.
Source: Table Clinical Follow-up.sas; Analyzed: 14MAY2020

As demonstrated in **Table 40**, the magnitude of change in SF-12 MCS was maintained through the Month 24 time point.

Table 41 includes the number and percentage of subjects achieving maintenance or improvement in SF-12 MCS score.

Table 41: SF-12 MCS – Subjects Achieving Maintenance or Improvement (Primary Analysis Population)

	Simplify Disc		
	N	n	%
Month 06	143	111	77.6%
Month 12	143	109	76.2%
Month 24	138	105	76.1%

Subjects censored at Index level secondary surgical interventions.
Source: Table Clinical Follow-up.sas; Analyzed: 14MAY2020

As shown above, a high rate of subjects achieved maintenance or improvement in SF-12 MCS at all postoperative time points. However, health-related quality of life data were not collected for the historical ACDF control group; therefore, no comparative analysis could be performed.

Treatment Satisfaction

Table 42 presents the subject responses for both the Simplify® Cervical Artificial Disc and historical ACDF control groups to the survey question, "How does the subject rate satisfaction with the treatment received?" The response options included "Very Satisfied," "Satisfied," "Somewhat Satisfied," "Somewhat Dissatisfied," "Dissatisfied," and "Very Dissatisfied." A total of 88% (122/138) of Simplify® Cervical Artificial Disc subjects reported that they were "Very Satisfied" at Month 24, as compared to a total of 70% (67/96) of this historical ACDF control subjects. Less than 1% of subjects in either group reported being "Dissatisfied" or "Very Dissatisfied" at Month 24.

Table 42: Treatment Satisfaction: "How does the subject rate satisfaction with the treatment received?" (Primary Analysis Population)

	Month 12				Month 24			
	Simplify Disc		ACDF		Simplify Disc		ACDF	
	n	%	n	%	n	%	n	%
Very Satisfied	118	83%	66	66%	122	88%	67	70%
Satisfied	17	12%	20	20%	12	9%	20	21%
Somewhat Satisfied	5	4%	11	11%	2	1%	5	5%
Somewhat Dissatisfied	0	0%	2	2%	2	1%	3	3%
Dissatisfied	1	1%	1	1%	0	0%	1	1%
Very Dissatisfied	1	1%	0	0%	0	0%	0	0%

Subjects censored at Index level secondary surgical interventions.
Source: Table Clinical Follow-up.sas; Analyzed: 14MAY2020

As demonstrated in **Table 42**, a greater percentage of subjects in the Simplify® Cervical Artificial Disc group reported "Very Satisfied" in terms of treatment satisfaction at Month 12 and Month 24 than the historical ACDF control group.

Table 43 presents the subject responses to the survey question, "If you could go back in time, would you choose to have the same treatment that you received for your neck condition?" The response options included "Definitely Yes," "Probably Yes," "Maybe," "Probably Not," and "Definitely Not." A total of 90% (124/138) of Simplify® Cervical Artificial Disc subject indicated that they would have the same procedure again when asked at Month 24, as compared to 70% (67/96) of historical ACDF control subjects.

Table 43: Treatment Satisfaction: "If you could go back in time, would you choose to have the same treatment that you received for your neck condition?" (Primary Analysis Population)

	Month 12				Month 24			
	Simplify Disc		ACDF		Simplify Disc		ACDF	
	n	%	n	%	n	%	n	%
Definitely Yes	122	86%	66	67%	124	90%	67	70%
Probably Yes	10	7%	16	16%	6	4%	16	17%
Maybe	8	6%	10	10%	7	5%	7	7%
Probably Not	2	1%	5	5%	1	1%	4	4%
Definitely Not	0	0%	2	2%	0	0%	2	2%

Subjects censored at Index level secondary surgical interventions.
Source: Table Clinical Follow-up.sas; Analyzed: 14MAY2020

As demonstrated in **Table 43**, a greater percentage of subjects in the Simplify® Cervical Artificial Disc group reported "Definitely Yes" when asked if the subject would choose the same treatment for their neck condition again after treatment at Month 12 and Month 24 than the historical ACDF control group.

Odom's Criteria

Odom's criteria data are censored following intra-operative deviation or SSI. Simplify® Cervical Artificial Disc and historical ACDF control subjects were categorized by the physician according to Odom's criteria as described below.

Excellent	Improvement in most (at least 80%) of the preoperative signs and symptoms, with little deterioration (not more than 10%)
Good	Improvement in some (at least 70%) of the preoperative signs and symptoms, with some deterioration (not more than 15%)
Fair	Improvement in half (at least 50%) of the preoperative signs and symptoms, with some deterioration (not more than 20%)
Poor	Improvement in few (less than 50%) of the preoperative signs and symptoms, or significant deterioration (more than 20%)

Table 44. Odom's Criteria (Primary Analysis Population)

	Post-Op				Week 06				Month 03			
	Simplify Disc		ACDF		Simplify Disc		ACDF		Simplify Disc		ACDF	
	n	%	n	%	n	%	n	%	n	%	n	%
Excellent	92	62%	55	49%	100	69%	66	58%	113	78%	66	59%
Good	38	26%	38	34%	37	26%	35	31%	24	17%	27	24%
Fair	15	10%	15	13%	5	3%	12	11%	6	4%	13	12%
Poor	3	2%	4	4%	3	2%	1	1%	1	1%	6	5%
	Month 06				Month 12				Month 24			
	Simplify Disc		ACDF		Simplify Disc		ACDF		Simplify Disc		ACDF	
	n	%	n	%	n	%	n	%	n	%	n	%
Excellent	124	86%	65	63%	118	83%	62	63%	121	87%	64	67%
Good	17	12%	25	24%	17	12%	19	19%	12	9%	18	19%
Fair	3	2%	8	8%	7	5%	14	14%	5	4%	8	8%
Poor	1	1%	5	5%	1	1%	4	4%	1	1%	5	5%

Subjects censored at Index level secondary surgical interventions.
Source: Table Clinical Follow-up.sas; Analyzed: 14MAY2020

As shown above in **Table 44**, a greater percentage of Simplify® Cervical Artificial Disc subjects were classified as 'Excellent' at all follow-up time points. At Month 24, 87% (121/139) of Simplify® Cervical Artificial Disc subjects were classified as "Excellent", as compared to 67% (64/95) of historical ACDF control subjects.

Medication Usage

Table 45 presents self-reported narcotic use at baseline and follow-up time points. As shown below, the PS adjusted group difference is not statistically significant at baseline; however, the difference between groups is statistically significant at all follow-up time points with a greater percentage of historical ACDF control subjects using narcotics.

Table 45: Narcotic Use (Primary Analysis Population)

	Simplify Disc			ACDF			Group Difference*			
	N	n	%	N	n	%	p	Δ	LB	UB
Pre-Op	147	61	41.5%	117	64	54.7%	0.838	-1.5%	-14.9%	12.0%
Month 06	145	28	19.3%	103	42	40.8%	0.010	-16.8%	-29.0%	-4.5%
Month 12	144	22	15.3%	100	39	39.0%	0.002	-19.6%	-31.6%	-7.5%
Month 24	139	15	10.8%	95	35	36.8%	<.001	-25.8%	-37.8%	-13.9%

Subjects censored at Index level secondary surgical interventions.
*Device group differences and 95% CI adjusting for propensity score (PS) subclass using two-way generalized linear model.
Source: Tables Medication and Cons Therapy.sas; Analyzed: 23JUN2020

Other Performance Outcomes

Other evaluations of effectiveness included dysphagia handicap index (DHI), return to work status, and time to recovery.

Dysphagia Handicap Index (DHI)

Table 46 includes the DHI score for all subjects in the Simplify® Cervical Artificial Disc group at pre-operative, postoperative, 6-month, 12-month, and 24-month time points. At pre-op, the mean DHI score for subjects in the Simplify® Cervical Artificial Disc group was 6.2, which increased to 7.0 at week 6, and then gradually fell to 3.8 at Month 6, where it appeared to plateau thereafter (4.1 at Month 12; 4.0 at Month 24).

Table 46: DHI scores over time (Primary Analysis Population)

	Simplify Disc					
	N	Mean	SD	Med	Min	Max
Pre-Op	150	6.2	8.8	3.0	0.0	50.0
Week 06	146	7.0	11.0	2.0	0.0	78.0
Month 03	145	4.2	7.6	2.0	0.0	50.0
Month 06	144	3.8	7.4	0.0	0.0	44.0
Month 12	143	4.1	8.3	0.0	0.0	72.0
Month 24	138	4.0	7.6	2.0	0.0	58.0

Subjects censored at Index level secondary surgical interventions.
Source: Table Clinical Follow-up.sas; Analyzed: 14MAY2020

As demonstrated in **Table 46**, there was an increase in mean DHI at Week 6, followed by a decrease at Month 3 that was maintained through Month 24.

Table 47 includes the change in DHI score from pre-operative for all subjects in the Simplify® Cervical Artificial Disc group at 6-week, 3-month, 6-month, 12-month, and 24-month time points.

Table 47: DHI score change from pre-operative (Primary Analysis Population)

	Simplify Disc					
	N	Mean	SD	Med	Min	Max
Week 06	146	0.7	10.9	0.0	-50.0	70.0
Month 03	145	-2.2	8.9	-2.0	-50.0	28.0
Month 06	144	-2.6	8.6	-2.0	-42.0	36.0
Month 12	143	-2.3	9.2	-2.0	-48.0	42.0
Month 24	138	-2.3	8.6	-2.0	-48.0	28.0

Subjects censored at Index level secondary surgical interventions.
Source: Table Clinical Follow-up.sas; Analyzed: 14MAY2020

As demonstrated in **Table 47**, there was an increase in mean change in DHI from pre-operative at Week 6, followed by a maintained decrease Month 3 through Month 24.

The incidence and severity of dysphagia as evaluated during neurologic exam over time is presented in **Table 48**. No incidences of dysphagia were categorized as severe at any evaluation time point. The highest incidences of mild dysphagia occurred at week 6 (26% - 38/110) and Month 3 (29% - 34/77), but these events gradually declined over time, with only 3% (4/139) of subjects observed to have mild dysphagia at Month 24.

Table 48. Dysphagia Over Time – Safety Analysis Set

	Pre-Op		Post-Op		Week 06		Month 03		Month 06		Month 12		Month 24	
	I		I		I		I		I		I		I	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Absent	149	99%	113	97%	110	74%	77	66%	129	89%	97	84%	139	97%
Mild	1	1%	4	3%	38	26%	34	29%	14	10%	16	14%	4	3%
Moderate	0	0%	0	0%	0	0%	5	4%	2	1%	2	2%	1	1%
Severe	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%

Subjects censored at Index level SSIs.
Source: Tables Neurological.sas; Analyzed: 14MAY2020

DHI scores are provided below by timepoint for the eight (8) Simplify® Cervical Artificial Disc subjects who reported dysphagia AEs. DHI was not collected in the historical study; therefore, these data are not available for the three (3) historical ACDF control subjects reporting dysphagia AEs.

Table 49. DHI Scores in Simplify® Cervical Artificial Disc Subjects Reporting Dysphagia

Subject	Pre-Op	Week 6	Month 3	Month 6	Month 12	Month 24
01	0	2	14	14	0	0
02	0	12	6	0	0	0
03	10	18	12	14	8	6
04	4	6	4	12	6	22
05	2	6	0	0	26	26
06	0	2	4	0	4	4
07	4	2	14	8	12	4
08	2	28	30	16	4	2

According to Silbergleit et al., patient perceived severity of dysphagia correlated to the following DHI scores: normal = 7.89 ± 7.75, mild = 15.69 ± 9.77, moderate = 34.86 ± 16.02, and severe =

63.20 ± 23.38.[5] As shown in **Table 49**, majority of Simplify® Cervical Artificial Disc subjects reported DHI scores corresponding to normal to mild severity. DHI scores were not collected for the historical ACDF control group; therefore, no comparative analysis could be performed.

Work Status

Work status data are censored following intra-operative deviation or SSI. As shown in **Table 50**, 80% of the Simplify® Cervical Artificial Disc group was employed pre-operatively and 89% were employed at Month 24. 70% of the historical ACDF control group was employed pre-operatively and 68% were employed at Month 24. Please note: the one (1) subject reporting 'N/A' at Month 6 is a stay-at-home mom. 'Other' employment included student and homemaker.

Table 50: Work Status (Primary Analysis Population)

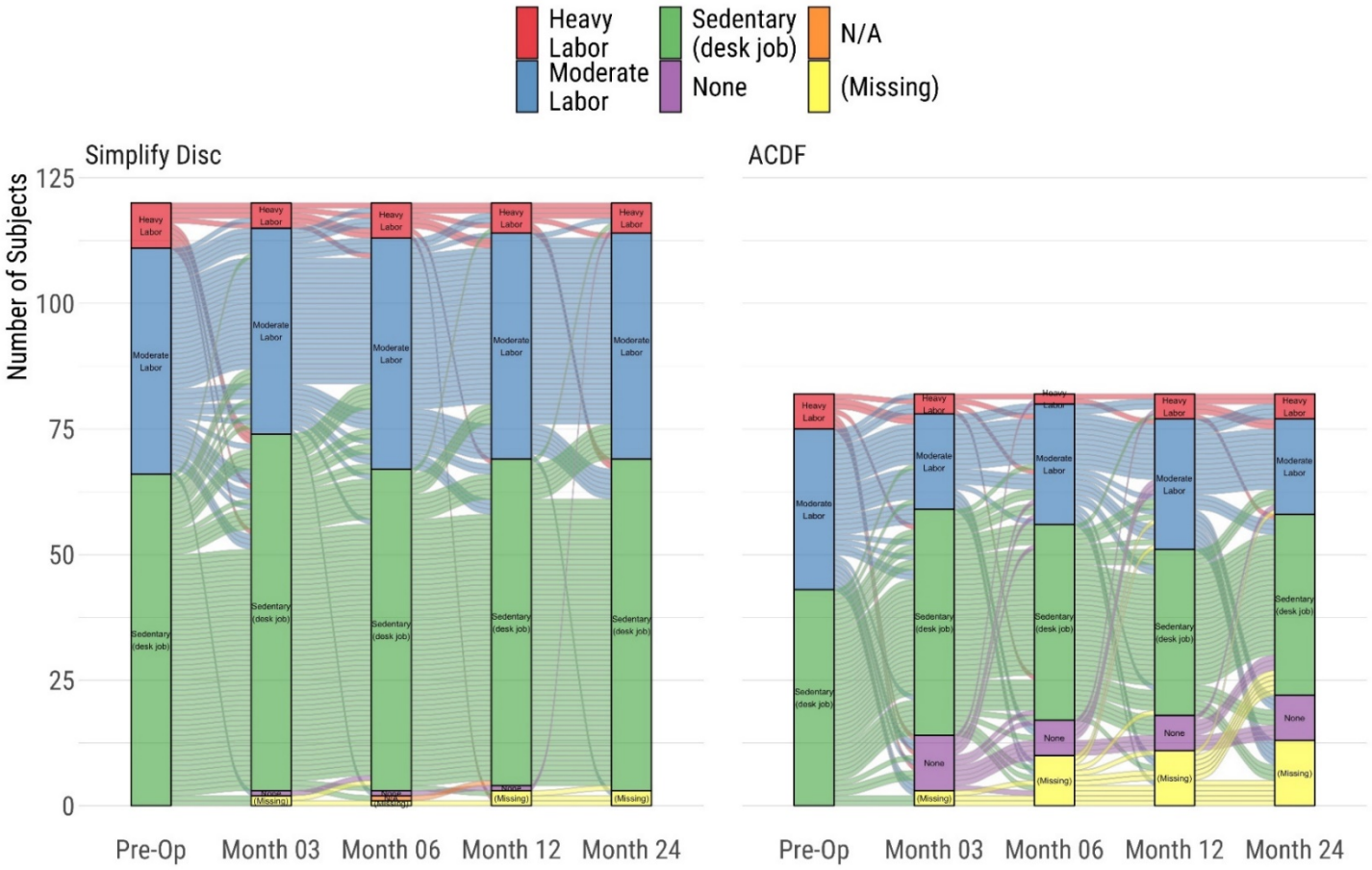
	Pre-Op				Month 03				Month 06				Month 12				Month 24			
	Simplify Disc		ACDF		Simplify Disc		ACDF		Simplify Disc		ACDF		Simplify Disc		ACDF		Simplify Disc		ACDF	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Employed	120	80%	82	70%	117	81%	74	66%	123	85%	74	72%	124	86%	69	69%	124	89%	65	68%
Short-term disability	4	3%	6	5%	7	5%	12	11%	3	2%	4	4%	3	2%	3	3%	1	1%	4	4%
Long-term disability	3	2%	9	8%	2	1%	8	7%	2	1%	9	9%	2	1%	10	10%	2	1%	11	11%
Unemployed	10	7%	8	7%	10	7%	8	7%	8	6%	6	6%	4	3%	11	11%	6	4%	6	6%
Retired	0	0%	0	0%	0	0%	0	0%	0	0%	2	2%	0	0%	0	0%	0	0%	3	3%
Other	13	9%	12	10%	9	6%	10	9%	8	6%	8	8%	11	8%	7	7%	6	4%	7	7%
N/A	0	0%	0	0%	0	0%	0	0%	1	1%	0	0%	0	0%	0	0%	0	0%	0	0%

Subjects censored at Index level secondary surgical interventions.
Source: Table Clinical Follow-up.sas; Analyzed: 14MAY2020

Figure 5 is an Alluvial plot showing the Normal employment type at Pre-Op through Month 24 in all subjects who were Employed at baseline. The lines within each plot denote one subject's longitudinal Normal employment journey following their index procedure. In general, in the Simplify® Cervical Artificial Disc arm, it is observed that large proportions of subjects maintained their previous Normal employment type, with only one subject reporting None as their Normal employment type at Month 3 to Month 6, and none by Month 24. In the ACDF arm, 14% of those previously employed subjects reported "None" as their Normal employment at Month 3, with fractions not returning to Normal employment through Month 24 and another fraction restarting and re-stopping previous employment types.

[5] Silbergleit, A.K., Schultz, L., Jacobson, B., Beardsley, T. and Johnson, A. (2012) The Dysphagia Handicap Index: Development and Validation. Dysphagia, 27, 46-52.

Figure 5: Alluvial Diagram of Employment status among subjects employed at baseline



Note: These data are not censored after SSI to show the entire trajectory of subjects. Therefore, a fraction the "(Missing)" in ACDF is made up of previously re-operated subjects. Please note: Table 50 above reports Work Status and the Figure 5 reports Employment type.

Time to Recovery

Time to recovery data are censored following intra-operative deviation or SSI. Time to recovery is defined as time to first 15-point improvement in NDI. At Week 6, 87.0% (127/146) of the Simplify® Cervical Artificial Disc subjects and 76.8% (86/112) of historical ACDF control subjects achieved recovery defined as an improvement of at least 15 percentage-points. By Month 3, 95.9% (139/145) of Simplify® Cervical Artificial Disc and 81.1% (90/111) of historical ACDF control subjects achieved recovery.

Radiographic Assessments

Average Disc Height – Superior Adjacent Level

Table 51 describes the average disc height above the index level at pre-operative, postoperative, 6-week, 3-month, 6-month, 12-month and 24-month time point.

Table 51: Average Disc Height (Above the Index Level) [mm] (Primary Analysis Population)

	Simplify Disc						ACDF						Group Difference*			
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p	Δ	LB	UB
Pre-Op	150	3.82	0.75	3.80	1.70	6.20	115	3.89	0.71	3.80	2.30	6.10	0.519	-0.07	-0.27	0.14
Post-Op	147	3.82	0.77	3.80	1.60	6.40	112	3.86	0.70	3.85	2.30	5.40	0.815	-0.02	-0.23	0.18
Week 06	144	3.79	0.77	3.80	1.60	6.20	112	3.86	0.72	3.80	2.20	6.20	0.505	-0.07	-0.28	0.14
Month 03	144	3.80	0.77	3.75	1.60	6.20	107	3.87	0.71	3.90	2.20	5.80	0.661	-0.05	-0.26	0.16
Month 06	143	3.83	0.82	3.80	1.50	6.60	100	3.89	0.68	3.90	1.90	5.40	0.689	-0.04	-0.27	0.18
Month 12	142	3.82	0.78	3.80	1.60	6.30	95	3.94	0.66	4.00	2.40	5.70	0.231	-0.13	-0.35	0.08
Month 24	137	3.82	0.77	3.80	1.70	6.30	92	3.83	0.75	3.85	1.30	6.20	0.773	-0.03	-0.26	0.19

Subjects censored at Index level secondary surgical interventions.
*Device group mean differences and 95% CI adjusting for propensity score (PS) subclass using two-way analysis of variance.
Source: Tables Radiography - Quantitative.sas; Analyzed: 14MAY2020

Mean disc height at the level above the index level was relatively unchanged as compared to pre-operative in both arms of the study. There were no statistically significant differences in adjacent (above) disc height at any time point.

Table 52 describes the change in average disc height above the index level at postoperative, 6-week, 3-month, 6-month, 12-month and 24-month time point as compared to pre-operative.

Table 52: Average Disc Height (Above the Index Level) [mm] Change from Pre-operative (Primary Analysis Population)

	Simplify Disc						ACDF						Group Difference*			
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p	Δ	LB	UB
Post-Op	147	0.01	0.16	0.00	-0.50	0.40	111	-0.01	0.16	0.00	-0.50	0.40	0.587	0.01	-0.03	0.06
Week 06	144	-0.02	0.15	0.00	-0.40	0.40	111	-0.04	0.13	0.00	-0.50	0.30	0.475	0.01	-0.03	0.05
Month 03	144	-0.02	0.15	0.00	-0.70	0.40	106	-0.03	0.14	0.00	-0.50	0.30	0.289	0.02	-0.02	0.06
Month 06	143	0.01	0.22	0.00	-0.50	1.70	99	-0.03	0.16	0.00	-0.80	0.20	0.147	0.04	-0.01	0.10
Month 12	142	0.01	0.22	0.00	-0.50	1.10	94	-0.03	0.20	0.00	-0.80	0.40	0.334	0.03	-0.03	0.09
Month 24	137	0.00	0.23	0.00	-0.90	1.10	91	-0.05	0.40	0.00	-1.40	2.80	0.638	0.02	-0.07	0.11

Subjects censored at Index level secondary surgical interventions.
*Device group mean differences and 95% CI adjusting for propensity score (PS) subclass using two-way analysis of variance.
Source: Tables Radiography - Quantitative.sas; Analyzed: 14MAY2020

There were no statistically significant differences in mean change in adjacent (above) disc height between groups at any time point.

Average Disc Height – Index Level

Table 53 describes the average disc height at the index level at pre-operative, postoperative, 6-week, 3-month, 6-month, 12-month and 24-month time point.

Table 53: Average Disc Height (Index Level) [mm] (Primary Analysis Population)

	Simplify Disc						ACDF						Group Difference*			
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p	Δ	LB	UB
Pre-Op	148	3.31	0.74	3.30	1.10	5.70	115	3.27	0.79	3.20	1.40	5.20	0.813	-0.03	-0.23	0.18
Post-Op	144	4.72	0.88	4.80	2.20	6.80	112	5.41	1.09	5.45	3.10	9.30	<.001	-0.63	-0.90	-0.36
Week 06	142	4.45	0.92	4.55	1.50	6.80	112	5.07	1.14	5.05	2.80	9.30	<.001	-0.56	-0.85	-0.28
Month 03	143	4.40	0.87	4.50	1.90	6.60	107	4.94	1.14	4.90	2.50	9.30	<.001	-0.48	-0.76	-0.21
Month 06	142	4.35	0.88	4.40	1.90	6.60	100	4.83	1.20	4.85	2.30	9.20	0.006	-0.42	-0.71	-0.12
Month 12	141	4.29	0.91	4.40	1.90	6.50	95	4.78	1.24	4.80	1.70	9.10	0.003	-0.47	-0.77	-0.16
Month 24	136	4.24	0.94	4.35	1.70	6.50	92	4.79	1.24	4.85	1.90	9.10	0.002	-0.50	-0.82	-0.19

Subjects censored at Index level secondary surgical interventions.
*Device group mean differences and 95% CI adjusting for propensity score (PS) subclass using two-way analysis of variance.
Source: Tables Radiography - Quantitative.sas; Analyzed: 14MAY2020

As shown in **Table 53**, mean index disc height increased in both groups postoperatively; however, there was a greater increase in disc height in the historical ACDF control group, resulting in a statistically significant difference in index disc height between groups postoperatively through Month 24.

Table 54 describes the change in average disc height at the index level at postoperative, 6-week, 3-month, 6-month, 12-month and 24-month time point as compared to pre-operative.

Table 54: Average Disc Height (Index Level) [mm] Change from Pre-operative (Primary Analysis Population)

	Simplify Disc						ACDF						Group Difference*			
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p	Δ	LB	UB
Post-Op	143	1.42	0.79	1.40	-0.70	3.10	111	2.15	1.08	2.20	-0.30	5.20	<.001	-0.62	-0.87	-0.36
Week 06	141	1.17	0.84	1.20	-1.70	3.00	111	1.82	1.16	1.80	-0.70	4.80	<.001	-0.53	-0.81	-0.26
Month 03	141	1.13	0.81	1.10	-1.30	2.90	106	1.68	1.16	1.70	-0.80	4.60	0.002	-0.44	-0.71	-0.17
Month 06	141	1.07	0.83	1.00	-1.30	3.00	99	1.54	1.19	1.60	-1.00	4.70	0.013	-0.36	-0.64	-0.08
Month 12	140	1.01	0.86	0.90	-1.30	3.10	94	1.45	1.19	1.50	-1.40	4.80	0.024	-0.34	-0.63	-0.05
Month 24	135	0.94	0.88	0.90	-1.30	3.10	91	1.46	1.24	1.50	-1.40	4.40	0.006	-0.44	-0.74	-0.13

Subjects censored at Index level secondary surgical interventions.
*Device group mean differences and 95% CI adjusting for propensity score (PS) subclass using two-way analysis of variance.
Source: Tables Radiography - Quantitative.sas; Analyzed: 14MAY2020

Similar to trends seen in mean scores, **Table 54** shows a statistically significant difference in mean change from pre-operative between groups at all time points with greater change in the historical ACDF control group.

Average Disc Height – Inferior Adjacent Level

Table 55 describes the average disc height below the index level at pre-operative, postoperative, 6-week, 3-month, 6-month, 12-month and 24-month time point.

Table 55: Average Disc Height (Below Index Level) [mm] (Primary Analysis Population)

	Simplify Disc						ACDF						Group Difference*			
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p	Δ	LB	UB
Pre-Op	119	3.93	0.70	4.00	2.00	6.00	75	4.24	0.69	4.30	2.80	6.60	<.001	-0.44	-0.66	-0.21
Post-Op	113	3.95	0.73	4.00	1.90	6.20	74	4.23	0.72	4.20	2.80	6.70	<.001	-0.42	-0.66	-0.18
Week 06	113	3.87	0.77	3.90	1.40	6.10	74	4.19	0.71	4.20	2.70	6.50	<.001	-0.50	-0.74	-0.25
Month 03	113	3.89	0.73	3.90	1.90	6.00	73	4.22	0.73	4.30	2.60	6.50	<.001	-0.46	-0.70	-0.22
Month 06	110	3.89	0.74	3.90	1.90	5.90	64	4.21	0.71	4.20	2.70	6.70	<.001	-0.46	-0.71	-0.21
Month 12	109	3.84	0.73	3.90	1.90	5.60	62	4.22	0.75	4.20	2.50	6.60	<.001	-0.57	-0.83	-0.32
Month 24	109	3.86	0.76	3.90	2.00	5.90	60	4.14	0.81	4.05	2.50	6.80	0.001	-0.45	-0.72	-0.19

Subjects censored at Index level secondary surgical interventions.
*Device group mean differences and 95% CI adjusting for propensity score (PS) subclass using two-way analysis of variance.
Source: Tables Radiography - Quantitative.sas; Analyzed: 14MAY2020

As shown in **Table 55**, the mean average disc height of the inferior adjacent level was significantly lower in the Simplify® Cervical Artificial Disc group at pre-operative and all follow-up time points as compared to the historical ACDF control group (p=0.001).

Table 56 describes the change in average disc height below the index level at postoperative, 6-week, 3-month, 6-month, 12-month and 24-month time point as compared to pre-operative.

Table 56: Average Disc Height (Below Index Level) [mm] Change from Pre-operative (Primary Analysis Population)

	Simplify Disc						ACDF						Group Difference*			
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p	Δ	LB	UB
Post-Op	112	0.02	0.16	0.00	-0.40	0.50	73	0.00	0.16	0.00	-0.30	0.50	0.538	0.02	-0.04	0.07
Week 06	110	-0.05	0.30	0.00	-2.60	0.50	73	-0.03	0.16	0.00	-0.40	0.30	0.302	-0.04	-0.13	0.04
Month 03	111	-0.03	0.23	0.00	-1.60	0.40	72	-0.01	0.20	0.00	-0.50	0.60	0.386	-0.03	-0.10	0.04
Month 06	106	-0.02	0.16	0.00	-0.50	0.50	63	-0.03	0.21	0.00	-0.60	0.50	0.848	0.01	-0.06	0.07
Month 12	105	-0.04	0.26	0.00	-1.60	0.50	61	-0.09	0.25	-0.10	-0.70	0.50	0.793	0.01	-0.08	0.10
Month 24	106	-0.08	0.31	-0.10	-1.60	0.50	59	-0.07	0.26	0.00	-0.70	0.40	0.344	-0.05	-0.15	0.05

Subjects censored at Index level secondary surgical interventions.
*Device group mean differences and 95% CI adjusting for propensity score (PS) subclass using two-way analysis of variance.
Source: Tables Radiography - Quantitative.sas; Analyzed: 14MAY2020

Differences in mean change from pre-operative were not statistically significant between groups at any follow-up time point.

Device Migration

Device migration assesses significant movement of the implant and was evaluated as follows:

0. None: No evidence of migration of the implant >3mm relative to the initial position of the implant at Post-Op.
1. Present: Presence of device migration >3mm relative to the initial position of the implant at Post-Op.
    a. Anterior: Device has migrated anteriorly.
    b. Posterior: Device has migrated posteriorly.
    c. Left: Device has migrated laterally to the left.
    d. Right: Device has migrated laterally to the right.

Migration was evaluated relative to the first available postoperative visit. A threshold of >3mm of implant motion was used to define significance. This represents approximately 20% of the AP

dimension of a typical cervical vertebra. If a notable implant slip occurs that does not meet the threshold, it may be documented in the reviewer's comments for subsequent evaluation. Presence of Left or Right migration was only evaluated in the Simplify® Cervical Artificial Disc group.

Table 57 presents the number and percentage of subjects with radiographic confirmation of device migration a 6-week, 3-month, 6-month, 12-month and 24-month time points.

Table 57: Device Migration (Primary Analysis Population)

	Week 06				Month 03				Month 06				Month 12				Month 24			
	Simplify Disc		ACDF		Simplify Disc		ACDF		Simplify Disc		ACDF		Simplify Disc		ACDF		Simplify Disc		ACDF	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
None	145	100%	109	96%	144	99%	108	97%	144	99%	95	94%	142	100%	90	92%	137	99%	90	95%
Anterior	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Posterior	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Left	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Right	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Unable to assess	0	0%	5	4%	1	1%	3	3%	1	1%	6	6%	0	0%	8	8%	2	1%	5	5%

Subjects censored at Index level secondary surgical interventions.
Source: Tables Radiography - Qualitative.sas; Analyzed: 14MAY2020

Device migration was not observed in Simplify® Cervical Artificial Disc or historical ACDF control subjects through Month 24.

Flexion/Extension Rotation

Table 58 describes the amount of rotation at the index level at pre-operative, postoperative, Month 3, Month 6, Month 12, and Month 24 time point.

Table 58: Rotation (Index Level) [degrees] (Primary Analysis Population)

	Simplify Disc						ACDF						Group Difference*			
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p	Δ	LB	UB
Pre-Op	143	7.29	4.22	6.40	0.00	21.40	110	7.27	4.36	6.75	-0.80	19.00	0.588	-0.33	-1.54	0.87
Month 03	139	8.64	5.06	8.20	0.30	22.10	107	1.74	1.21	1.40	0.00	5.10	<.001	7.11	6.01	8.21
Month 06	140	9.54	5.55	8.70	0.10	23.40	101	1.51	1.42	1.10	-0.20	6.80	<.001	8.15	6.89	9.41
Month 12	138	9.44	5.90	9.10	0.00	22.60	95	1.08	1.19	0.80	0.00	7.50	<.001	8.57	7.22	9.93
Month 24	134	9.61	6.30	9.15	0.00	23.60	95	0.72	0.75	0.50	-0.20	4.10	<.001	9.04	7.60	10.48

Subjects censored at Index level secondary surgical interventions.
*Device group mean differences and 95% CI adjusting for propensity score (PS) subclass using two-way analysis of variance.
Source: Tables Radiography - Quantitative.sas; Analyzed: 14MAY2020

The mean degree of rotation at the index level was not significantly different between groups at pre-operative. Postoperatively, rotation increased in the Simplify® Cervical Artificial Disc group and decreased in the historical ACDF control group. The mean rotation was significantly different between groups at all postoperative time points ($p<0.001$). This outcome is expected due to the motion sparing design of the Simplify® Cervical Artificial Disc treatment versus the ACDF treatment.

Table 59 describes the mean change in rotation at the index level over time at postoperative, Month 3, Month 6, Month 12, and Month 24 time points as compared to pre-operative.

Table 59: Rotation (Index Level) Change from Pre-operative [degrees] (Primary Analysis Population)

	Simplify Disc						ACDF						Group Difference*			
	N	Mean	SD	Med	Min	Max	N	Mean	SD	Med	Min	Max	p	Δ	LB	UB
Month 03	135	1.54	4.85	1.50	-16.70	11.20	100	-5.47	4.22	-4.65	-16.90	2.00	<.001	7.46	6.12	8.81
Month 06	137	2.33	5.18	1.90	-13.80	16.90	95	-5.82	4.30	-5.00	-17.60	0.60	<.001	8.63	7.19	10.08
Month 12	134	2.38	5.35	2.25	-12.00	13.30	89	-6.28	4.47	-5.70	-17.60	1.90	<.001	9.23	7.70	10.75
Month 24	130	2.41	6.00	2.05	-12.10	16.90	90	-6.76	4.35	-6.05	-18.40	0.80	<.001	9.68	8.03	11.32

Subjects censored at Index level secondary surgical interventions.
*Device group mean differences and 95% CI adjusting for propensity score (PS) subclass using two-way analysis of variance.
Source: Tables Radiography - Quantitative.sas; Analyzed: 14MAY2020

As expected, the mean change in rotation at the index level as compared to pre-operative was significantly greater in the Simplify® Cervical Artificial Disc group as compared to the historical ACDF control group ($p<0.001$).

Device Condition

Device Condition assesses the condition of the device using the following device specific grading scales:

Simplify® Cervical Artificial Disc Device

0. Intact: No evidence of dislocation or fracture of the device components.
1. Failed Superior Component: Fracture or deformation of the superior endplate.
2. Failed Core: Fracture or other failure of the core.
3. Failed Inferior Component: Fracture or deformation of the inferior endplate.
4. Disassembled: Dislocation or permanent subluxation of the articulating components of the implant. (Permanent subluxation is defined as severe (i.e. >50%) misalignment of the device components that does not reduce in flexion-extension or lateral bending.) There is little or no motion across the implant in the plane of the subluxation or dislocation.

ACDF:

0. Intact: No failed graft, loose screws or fractured hardware. The graft and hardware are intact and stable.
1. Failed Graft: Presence of visible gaps, fracture or disintegration of the graft material within the interbody space
2. Failed Screw: Fracture, deformation, migration, pull-out or loosening of one or more screws
3. Failed Plate: Fracture, deformation or disassembly of the plate from the screw(s)

Table 60 reports the number and percentage of subjects with radiographic confirmation of the condition of the device and the status of the Simplify® Cervical Artificial Disc device (Intact, Failed Superior Component, Failed Core, Failed Inferior Component, Disassembled, Indeterminate, or Unable to assess) at Week 6, Month 3, Month 6, Month 12, and Month 24 time points.

Table 60: Device Condition (Primary Analysis Population)

	Week 06		Month 03		Month 06		Month 12		Month 24	
	Simplify Disc		Simplify Disc		Simplify Disc		Simplify Disc		Simplify Disc	
	n	%	n	%	n	%	n	%	n	%
Intact	145	100%	144	99%	144	99%	142	100%	137	99%
Failed Superior Component	0	0%	0	0%	0	0%	0	0%	0	0%
Failed Core	0	0%	0	0%	0	0%	0	0%	0	0%
Failed Inferior Component	0	0%	0	0%	0	0%	0	0%	0	0%
Disassembled	0	0%	0	0%	0	0%	0	0%	0	0%
Unable to assess	0	0%	1	1%	1	1%	0	0%	2	1%

Subjects censored at Index level secondary surgical interventions.
Source: Tables Radiography - Qualitative.sas; Analyzed: 14MAY2020

As shown above, all evaluated Simplify® Cervical Artificial Discs were observed to be intact at Month 24. No device condition observations were reported at any time point.

Table 61 reports the number and percentage of subjects with radiographic confirmation of the condition of the device and the status of the device specific to fusion materials (Intact, Failed Graft, Failed Screw, Failed Plate, Disassembled, Indeterminate, or Unable to assess) at Week 6, Month 3, Month 6, Month 12, and Month 24 time points.

Table 61: Device Condition ACDF (Primary Analysis Population)

	Week 06		Month 03		Month 06		Month 12		Month 24	
	ACDF		ACDF		ACDF		ACDF		ACDF	
	n	%	n	%	n	%	n	%	n	%
Intact	106	93%	96	86%	75	74%	74	76%	83	87%
Failed Graft	0	0%	1	1%	13	13%	13	13%	7	7%
Failed Screw	1	1%	5	5%	1	1%	2	2%	1	1%
Failed Plate	0	0%	0	0%	0	0%	0	0%	0	0%
Unable to assess	7	6%	9	8%	12	12%	9	9%	4	4%

As shown in **Table 61**, 7% of subjects were reported to have a failed graft and 1% of subjects were reported to have a failed screw at the latest time point.

Device Failure

Device failure is defined as any device condition evaluation other than 'intact' and/or any device migration evaluation other than 'none' at any time through Month 24. Subsidence or failure of the allograft was not counted as a device failure in the historical ACDF control group. **Table 62** and **Figure 6** show a survival analysis and product-limit estimates of freedom from device failure.

The 'N Start', shown in **Table 62**, reports the number of subjects not yet terminal failures or censored and therefore are at risk for device failure in the current interval. That is, 'N Start' is the number of subjects at the end of the previous interval. 'N Start' is calculated based on prior interval 'N start' minus failures within the preceding interval ('F') and censored subjects ('C'). Subjects shown as 'censored' ('C') are unevaluable for the following interval but are not a failure (i.e., loss to follow-up, intraoperative deviation). One hundred forty-five (145) Simplify®

Cervical Artificial Disc subjects remain at risk for device failure at the start of the 24-month interval.

As shown below, no Simplify® Cervical Artificial Disc subjects exhibited postoperative device failure; therefore, there were no secondary surgeries related to a device performance issue. Seven (7) screw failures were identified in the historical ACDF control group.

Table 62. Device Failure Survival Analysis (Primary Analysis Population)

	Simplify® Cervical Artificial Disc (N= 150)								ACDF (N= 117)								Group Difference	
	N	Within Interval†			Cumulative*				N	Within Interval†			Cumulative*				Δ	Log-Rank
End Interval	Start	F	C	Surv.	F	%	LB	UB	Start	F	C	Surv.	F	%	LB	UB		p-value
Treatment	150	--	--	100.0%	0	--	--	--	117	--	--	100.0%	0	--	--	--	--	
Month 03	150	0	4	100.0%	0	100.0%	--	--	117	1	7	99.1%	1	99.1%	97.4%	100.0%	0.9%	
Month 06	146	0	0	100.0%	0	100.0%	--	--	109	4	10	96.3%	5	95.5%	91.6%	99.4%	4.5%	0.002
Month 12	146	0	1	100.0%	0	100.0%	--	--	95	1	4	98.9%	6	94.5%	90.2%	98.8%	5.5%	
Month 24	145	0	145	100.00	0	100.0%	--	--	90	1	89	98.9%	7	93.4%	88.7%	98.2%	6.6%	

Notes:
† Within Interval: F = failures within interval (visit), C = censored within interval, survival for that interval. These reflect within interval lifetable estimates;
* Cumulative: F = cumulative number of events, % is Kaplan-Meier (product-limit) estimate with 95% lower bound (LB) and upper bound (UB) based on log-log approach. The definitive product limit estimates cannot be recovered from lifetable estimates.

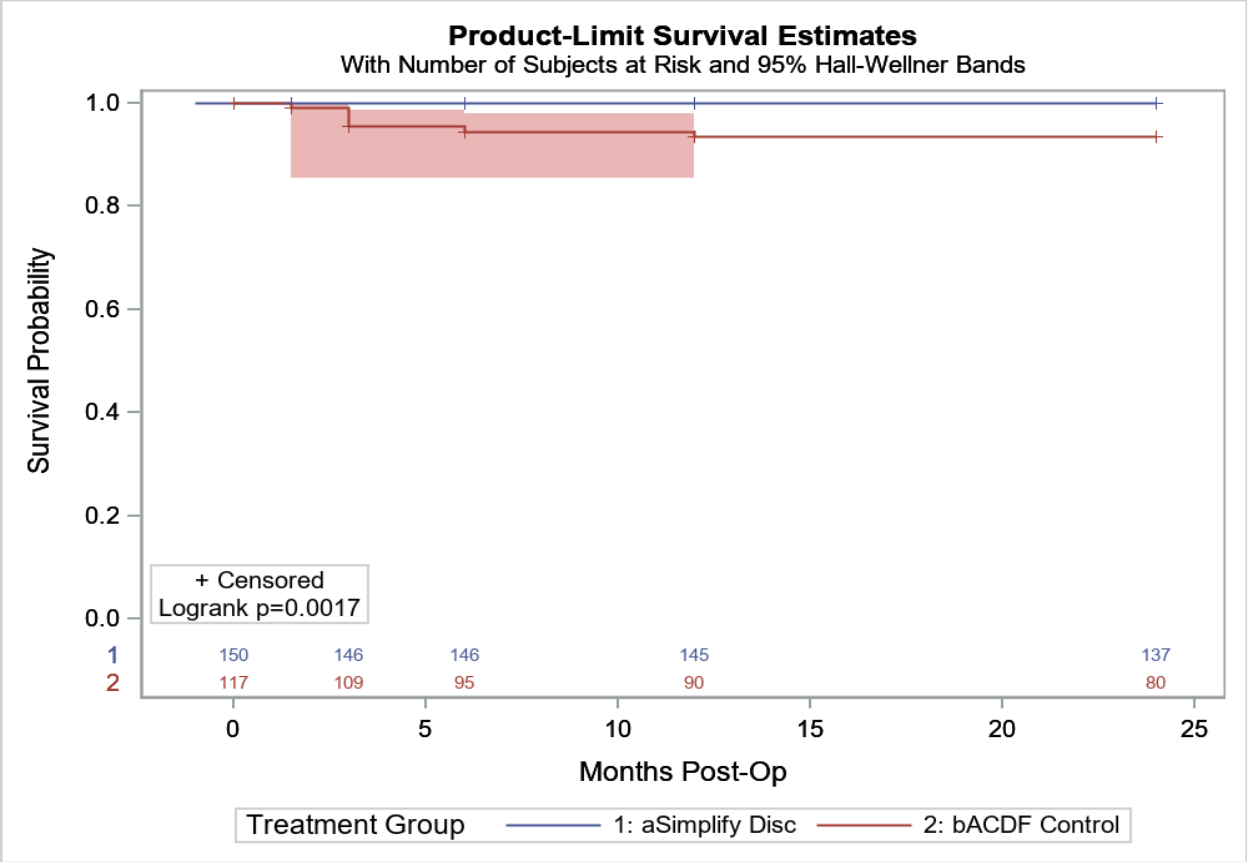


Figure 6: Device Failure Survival Analysis (Primary Analysis Population)

Adjacent Level Disc Degeneration (Derived)

Disc degeneration at the adjacent levels are graded in accordance with the following definitions:

1. None: Negligible disc space narrowing, no osteophyte formation, no endplate sclerosis.
2. Mild: <33% disc space narrowing, mild osteophyte formation, no endplate sclerosis.
3. Moderate: 33% - 66% disc space narrowing, moderate osteophyte formation, mild to moderate endplate sclerosis
4. Severe: >66% disc space narrowing, severe osteophyte formation or fusion, severe endplate sclerosis.

Superior Adjacent Level

Table 63 reports the number and percentage of subjects with adjacent level disc degeneration (ALDD) above the index level at pre-operative, Month 3, Month 6, Month 12 and Month 24 time points.

Table 63: Adjacent Level Disc Degeneration (Above Index Level) (Primary Analysis Population)

	Pre-Op				Month 03				Month 06				Month 12				Month 24			
	Simplify Disc		ACDF		Simplify Disc		ACDF		Simplify Disc		ACDF		Simplify Disc		ACDF		Simplify Disc		ACDF	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
None	104	69%	56	48%	100	69%	45	41%	99	68%	35	35%	92	65%	23	23%	87	63%	15	16%
Mild	28	19%	22	19%	26	18%	26	23%	26	18%	26	26%	29	20%	26	27%	26	19%	22	23%
Moderate	17	11%	27	23%	16	11%	29	26%	17	12%	30	30%	18	13%	32	33%	20	14%	36	38%
Severe	1	1%	9	8%	1	1%	10	9%	1	1%	10	10%	1	1%	15	15%	3	2%	20	21%
Unable to assess	0	0%	3	3%	2	1%	1	1%	2	1%	0	0%	2	1%	2	2%	3	2%	2	2%

Subjects censored at Index level secondary surgical interventions.
Source: Tables Radiography - Qualitative.sas; Analyzed: 14MAY2020

As shown in **Table 63**, the trend of ALDD at the superior adjacent level in the Simplify® Cervical Artificial Disc group was nearly constant from pre-op through 24 months. Conversely, adjacent level disc degeneration at the superior adjacent level continued to progress from pre-operative to 24 months in the historical ACDF control group.

Inferior Adjacent Level

Table 64 reports the number and percentage of subjects with ALDD below the index level at pre-operative, Month 3, Month 6, Month 12 and Month 24 time points.

Table 64: Adjacent Level Disc Degeneration (Below Index Level) (Primary Analysis Population)

	Pre-Op				Month 03				Month 06				Month 12				Month 24			
	Simplify Disc		ACDF		Simplify Disc		ACDF		Simplify Disc		ACDF		Simplify Disc		ACDF		Simplify Disc		ACDF	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
None	121	81%	39	33%	112	77%	32	29%	115	79%	30	30%	106	75%	20	20%	95	68%	14	15%
Mild	11	7%	12	10%	16	11%	13	12%	12	8%	10	10%	17	12%	15	15%	15	11%	15	16%
Moderate	7	5%	24	21%	8	6%	23	21%	9	6%	23	23%	10	7%	21	21%	16	12%	23	24%
Severe	1	1%	3	3%	0	0%	7	6%	0	0%	6	6%	1	1%	7	7%	2	1%	10	11%
Unable to assess	10	7%	39	33%	9	6%	36	32%	9	6%	32	32%	8	6%	35	36%	11	8%	33	35%

Subjects censored at Index level secondary surgical interventions.
Source: Tables Radiography - Qualitative.sas; Analyzed: 14MAY2020

As shown above, the progression of inferior ALDD was minimal in the Simplify® Cervical Artificial Disc group, with 78% of subjects with “None” or “Mild” at 24 months compared to 88% at pre-operative. In the historical ACDF control group, 43% had “None” to “Mild” at pre-op while 31% had the same categorization at 24 months.

Changes in Adjacent Level Disc Degeneration

Change in adjacent level disc degeneration (ALDD) was derived from the assessment of adjacent level disc degeneration relative to pre-operative and graded in accordance with the following definitions:

0. No change in derived ALDD since pre-operative.
1. One Grade Progression: One grade change in derived ALDD since pre-operative.
2. Two Grade Progression: Two grade change in derived ALDD since pre-operative
3. Three Grade Progression: Three grade change in derived ALDD since pre-operative
4. Decrease: One or more grade decrease in derived ALDD since pre-operative

Superior Adjacent Level

Table 65 reports the number and percentage of subjects with changes in ALDD above the index level at the Month 3, Month 6, Month 12, and Month 24 time points.

Table 65: Change in Adjacent Level Disc Degeneration (Above Index Level) (Primary Analysis Population)

	Month 03				Month 06				Month 12				Month 24			
	Simplify Disc		ACDF		Simplify Disc		ACDF		Simplify Disc		ACDF		Simplify Disc		ACDF	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
No Change	137	94%	94	85%	134	92%	82	81%	124	87%	64	65%	114	82%	49	52%
One Grade Progression	3	2%	10	9%	6	4%	12	12%	13	9%	21	21%	14	10%	25	26%
Two Grade Progression	0	0%	3	3%	0	0%	4	4%	0	0%	8	8%	6	4%	13	14%
Three Grade Progression	0	0%	1	1%	0	0%	1	1%	0	0%	2	2%	0	0%	6	6%
Decrease	3	2%	0	0%	3	2%	0	0%	3	2%	0	0%	2	1%	0	0%
Unable to assess	2	1%	3	3%	2	1%	2	2%	2	1%	3	3%	3	2%	2	2%

Subjects censored at Index level secondary surgical interventions.
Source: Tables Radiography - Qualitative.sas; Analyzed: 14MAY2020

A higher percentage of historical ACDF control subjects demonstrated progression in ALDD at the superior index level than Simplify® Cervical Artificial Disc subjects at Month 24 (14% of Simplify® Cervical Artificial Disc subjects had any grade progression vs 46% of historical ACDF control subjects), despite having less margin to progress since there was more pre-operative superior ALDD.

Inferior Adjacent Level

Table 66 reports the number and percentage of subjects with changes in ALDD below the index level at the Month 3, Month 6, Month 12, and Month 24 time points.

Table 66: Change in Adjacent Level Disc Degeneration (Below Index Level) (Primary Analysis Population)

	Month 03				Month 06				Month 12				Month 24			
	Simplify Disc		ACDF		Simplify Disc		ACDF		Simplify Disc		ACDF		Simplify Disc		ACDF	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
No Change	129	89%	65	59%	129	89%	54	53%	119	84%	41	42%	100	72%	32	34%
One Grade Progression	5	3%	4	4%	5	3%	5	5%	11	8%	15	15%	21	15%	16	17%
Two Grade Progression	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	3	2%	5	5%
Three Grade Progression	0	0%	2	2%	0	0%	2	2%	0	0%	2	2%	0	0%	2	2%
Decrease	1	1%	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%	0	0%
Unable to assess	10	7%	40	36%	11	8%	39	39%	11	8%	39	40%	14	10%	40	42%

Subjects censored at Index level secondary surgical interventions.
Source: Tables Radiography - Qualitative.sas; Analyzed: 14MAY2020

As shown in **Table 66**, "No Change" in inferior level ALDD progression was seen in 72% of the Simplify® Cervical Artificial Disc group versus 34% of the historical ACDF control group at Month 24.

Facet Degeneration

Facet degeneration was assessed using MRI and graded in accordance with the following definitions:[6,7]

0. None: Normal facet joint space.
1. Mild: Narrowing of the facet joint space and/or small osteophytes and/or mild hypertrophy of the articular process.
2. Moderate: Narrowing of the facet joint space and/or moderate osteophytes and/or moderate hypertrophy of the articular process and/or mild subarticular bone erosions.
3. Severe: Narrowing of the facet joint space and/or large osteophytes and/or sever hypertrophy of the articular process and/or severe subarticular bone erosions and/or subchondral cysts.

This measurement was performed in the Simplify® Cervical Artificial Disc group only.

Table 67 presents the number and percentage of subjects with evidence of facet degeneration at the index level at the pre-operative and 24-month time points. At pre-op, 36% (52/148) of Simplify® Cervical Artificial Disc subjects were identified to have some degree of facet degeneration, while similarly 37% (52/139) were found to have evidence of facet degeneration at Month 24.

[6] Weishaupt D, Zanetti M, Boos N, Hodler J. MR imaging and CT in osteoarthritis of the lumbar facet joints. Skeletal Radiology 28:215-219. (1999) 28:215-219. 1999.
[7] Fujiwara A, Tamai K, Yamato M, An HS, Yoshida H, Saotome K, Kurihashi A. The relationship between facet joint osteoarthritis and disc degeneration of the lumbar spine: an MRI study. Eur Spine J 8:396-401. 1999.

Table 67: Facet Degeneration over time (Primary Analysis Population)

	Pre-Op		Month 24	
	Simplify Disc		Simplify Disc	
	n	%	n	%
None	92	62%	80	58%
Mild	47	32%	42	30%
Moderate	4	3%	9	6%
Severe	1	1%	1	1%
Unable to Assess	4	3%	7	5%

Subjects censored at Index level secondary surgical interventions.
Source: Tables Radiography - Qualitative.sas; Analyzed: 14MAY2020

Similar percentages of facet degeneration were seen in the Simplify® Cervical Artificial Disc group at pre-operative and Month 24, indicating lack of progression of facet degeneration during the Month 24 follow-up.

Heterotopic Ossification

Heterotopic ossification was measured in the Simplify® Cervical Artificial Disc group using the following definitions:

0. None (Grade 0): No evidence of osteophyte formation or heterotopic ossification.

1. Mild (Grade 1): HO is detectable in the front or sides or the vertebral body, or as islands of bone in the adjacent soft tissue, but is not in the intervertebral disc space. Bone is not present between the planes formed by the two vertebral endplates.

2. Moderate (Grade 2): HO is growing into the disc space. Bone is present between the planes formed by the two adjacent endplates but is not significantly blocking or articulating between adjacent vertebral endplates or osteophytes.

3. Severe (Grade 3): The range of motion of the vertebral endplates is likely blocked by the formation of HO and/ or postoperative osteophytes on the radiographs, but some movement of the prosthesis may remain.

4. Bridging (Grade 4): HO is causing bony ankylosis. An apparent continuous connection of bridging bone exists between the adjacent vertebral endplates with little or no motion occurring across the treated segment.

Table 68 presents heterotopic ossification grades of the index level for all treated subjects at pre-operative, Month 3, Month 6, Month 12, and Month 24 time points.

Table 68: Heterotopic Ossification (Index Level) (Primary Analysis Population)

	Pre-Op		Month 03		Month 06		Month 12		Month 24	
	Simplify Disc		Simplify Disc		Simplify Disc		Simplify Disc		Simplify Disc	
	n	%	n	%	n	%	n	%	n	%
None (Grade 0)	100	68%	81	56%	58	40%	36	25%	20	14%
Mild (Grade 1)	26	18%	43	30%	41	28%	23	16%	16	12%
Moderate (Grade 2)	21	14%	18	12%	42	29%	74	52%	80	58%
Severe (Grade 3)	1	1%	2	1%	2	1%	7	5%	11	8%
Bridging (Grade 4)	0	0%	0	0%	1	1%	2	1%	10	7%
Unable to Assess	0	0%	1	1%	1	1%	0	0%	2	1%

Subjects censored at Index level secondary surgical interventions.
Source: Tables Radiography - Qualitative.sas; Analyzed: 14MAY2020

As shown above, "moderate" or lower grade heterotopic ossification was observed in the majority of subjects (58% - 80/139) at the latest time point. Few Simplify® Cervical Artificial Disc subjects experienced Grade 3 (11 subjects, 8% - 11/139) or Grade 4 (7% - 10/139) heterotopic ossification at Month 24.

All subjects with Grade 4 heterotopic ossification and bridging bone reached clinical success at 24 months according to the primary endpoint criteria (100% CCS).

Fusion

Fusion was assessed in the control subjects. Fusion was defined as:

- <3 mm translational motion;
- <5° angular motion;
- Evidence of bridging bone; and
- Radiolucent lines <50%

Fusion was observed in 88.4% (84/95) of the control subjects through 24 months.

3. Pediatric Extrapolation

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

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 47 investigators. None of the clinical

investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. PANEL RECOMMENDATIONS

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

XII. CONCLUSIONS DRAWN FROM THE PRECLINICAL AND CLINICAL STUDIES

The valid scientific evidence presented in the preceding sections provides reasonable assurance that the Simplify® Cervical Artificial Disc is a safe and effective disc replacement in skeletally mature patients for reconstruction of the disc from C3-C7 following discectomy at one level for intractable radiculopathy (arm pain and/or a neurological deficit) with or without neck pain, or myelopathy due to a single-level abnormality localized to the level of the disc space and manifested by at least one of the following conditions confirmed by radiographic imaging (e.g., X-rays, computed tomography (CT), magnetic resonance imaging (MRI)): herniated nucleus pulposus, spondylosis (defined by the presence of osteophytes), and/or visible loss of disc height as compared to adjacent levels.

A. Effectiveness Conclusions

One hundred sixty-six (166) subjects were enrolled in the Simplify® Cervical Artificial Disc population. Of these, 16 Simplify® Cervical Artificial Disc subjects were training subjects. The historical ACDF control population included 133 subjects. The 283 available subjects (150 Simplify® Cervical Artificial Disc (excluding training subjects) and 133 historical ACDF control) were assessed via the Propensity Score (PS) sub-classification process. After applying an established heuristic for 3 iterations (6 models), a total of 150 Simplify® Cervical Artificial Disc and 117 historical ACDF control subjects were retained in the final PS designed sample. Analysis of subject demographic and baseline data showed no meaningful differences between the treatment groups.

The success measurement was developed to measure safety and effectiveness of the Simplify® Cervical Artificial Disc when compared to anterior cervical discectomy and fusion (ACDF). A subject was considered a study success at two years follow-up if he/she met all of the following criteria:

- Improvement in NDI percentage of at least 15 points as compared to baseline at Month 24,
- Maintenance or improvement in neurologic status as compared to baseline at Month 24 (as determined by the CEC),
- No device failures within 24 months of index procedure,
- No SSI at the index level within 24 months of index procedure (as determined by the CEC), and
- No major AEs within 24 months of index procedure (as determined by the CEC).

For overall success, the proportion of subjects meeting the success criteria in each group was determined and the difference (Simplify® Cervical Artificial Disc minus ACDF) and the one-sided 90% confidence interval for the difference between treatment groups was calculated. The one-sided 90% lower confidence interval was greater than the non-inferiority margin (-10%) thus the primary endpoint was met. Additionally, the one-sided 95% confidence interval for the difference between treatment groups was calculated. The one-sided 95% lower confidence interval was greater than the superiority margin (0%) thus the Simplify® Cervical Artificial Disc group is confirmed to be superior to the historical ACDF control group.

Sensitivity analyses were performed to evaluate the composite success measurement using observed data only, best case evaluation and worst-case evaluation. All sensitivity analyses

demonstrate that the study success criterion for non-inferiority has been achieved. Further, the sensitivity analyses confirm the superiority of the Simplify® Cervical Artificial Disc group as compared to the historical ACDF control group.

Range of motion for the Simplify® Cervical Artificial Disc group was maintained through Month 24. Comparatively, the range of motion in the historical ACDF control group decreased. This is expected when comparing a motion-preserving device (artificial cervical disc) versus a motion-eliminating device (fusion).

In conclusion, the study data indicate that, at 24 months postoperatively, the Simplify® Cervical Artificial Disc is superior to the control treatment (ACDF), for the subject population and indications studied in this investigation, in terms of overall success according to the protocol-specified primary endpoint.

B. Safety Conclusions

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

Preclinical testing performed on the device demonstrated that the Simplify® Cervical Artificial Disc is designed to withstand the expected physiologic loads in the cervical spine.

In the clinical study conducted to support PMA approval, the investigational Simplify® Cervical Artificial Disc demonstrated a reasonable assurance of safety compared to the historical control ACDF. The observed AE rate for the Simplify® Cervical Artificial Disc group was 65.3% (98/150) compared with 59.0% (69/117) in the historical ACDF control group, with a SAE rate of 10.7% (16/150) in the Simplify® Cervical Artificial Disc group compared with 13.7% (16/117) in the historical ACDF control group. There were two definitely device-related events in one subject within the Simplify® Cervical Artificial Disc group (0.7% - 1/150) and one event definitely device-related event in the historical ACDF control (0.9% - 1/117).

A total of four (4) SSIs occurred in the Simplify® Cervical Artificial Disc group and six (6) SSIs occurred in the historical ACDF control group through post-operative day 790. The timecourse of these events demonstrates that majority of SSIs occurred between Month 12 and Month 24 in both groups; however, meaningful conclusions cannot be made with respect to timing due to the low number of SSI events in both groups.

The rate of SAEs that were considered device-related were similar between the two groups; 3.3% (5/150) of Simplify® Cervical Artificial Disc subjects and 4.3% (5/117) of historical ACDF control subjects had device-related SAEs. Of these, one Simplify® Cervical Artificial Disc subject (0.7%) (1/150) had a definitely device-related SAE.

In conclusion, the safety profile of the Simplify® Cervical Artificial Disc demonstrates that the device has a reasonable assurance of safety. The study results indicate that the Simplify® Cervical Artificial Disc is at least as safe as the historical ACDF control with regards to AE rates, neurologic status, and need for SSI.

C. Benefit-Risk Determination

The probable benefits of the Simplify® Cervical Artificial Disc are based on data collected in the clinical study conducted to support PMA approval as described above.

The clinical study demonstrated several benefits of the Simplify® Cervical Artificial Disc at a single cervical level over the 24-month time period studied. The table below also describes evaluation of risks.

Design Benefits	Restoration of Motion	Restoration of motion, restoring biomechanical function at the treated level, as well as the possibility to reduce subsequent degeneration of adjacent segments
	Optimized Materials	PEEK-on-ceramic design allows MRI visualization of the adjacent structures throughout the entire lifetime of the device, elimination of nickel allowing for use in population with nickel allergy, and minimizes metal wear debris. MRI visualization does not expose patients to ionizing radiation.
	Lower (4mm) Height	Only cervical disc replacement with 4mm height, more closely approximates native disc height in 39% of the population.
Treatment Benefits	Functional Improvement	97.8% of Simplify® Cervical Artificial Disc subjects experienced a clinically meaningful improvement from baseline (defined as a ≥15 percentage-point decrease on NDI) at Month 24 compared to 86.5% of ACDF subjects
	Pain Reduction (Neck and Arm)	96.4% of Simplify® Cervical Artificial Disc subjects experienced a clinically meaningful improvement from baseline (defined as ≥ 20 point decrease on VAS) at Month 24 compared to 87.4% of ACDF subjects, resulting in a statistically significant difference
	Restored Quality of Life	93.5% of Simplify® Cervical Artificial Disc subjects experienced maintenance or improvement in physical quality of life from baseline at Month 24 and 76.1% of subjects experienced maintenance or improvement in mental status from baseline at Month 24, demonstrating improvement in overall quality of life (SF-12)

	Treatment Satisfaction	At Month 24, a high rate of Simplify® Cervical Artificial Disc subjects were satisfied with treatment (97%) and would have treatment again (94%)
Risks	SSIs	Four (4) SSIs occurred in the Simplify® Cervical Artificial Disc group and six (6) SSIs occurred in the ACDF group through post-operative day 790
	Device Failure	Simplify® Cervical Artificial Disc subjects had no observations of failure of device integrity including device condition issues or device migration. These data demonstrate the Simplify® Cervical Artificial Disc design is robust and appropriate for the anatomical area.
	Device-Related Adverse Events	Simplify® Cervical Artificial Disc subjects experienced a lower rate of device-related adverse events than ACDF subjects (36.0% vs 39.3%) and lower rate of device-related SAEs (3.3% vs. 4.3%)
	Adjacent Segment Degeneration	Simplify® Cervical Artificial Disc subjects experienced a lower rate of progressive degeneration at adjacent disc levels than ACDF subjects (14% vs 46%) at the superior adjacent level, and (17% vs 24%) at the inferior adjacent level
	Radiographic Observations	Low observed rates of radiolucency, bridging bone and heterotopic ossification

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. At the Month 24 time-point, similar rates of any AE, any SAE, and definitely device-related AEs occurred in the two groups. The Simplify® Cervical Artificial Disc group experienced a higher adverse event rate than the historical ACDF control group (65.3% versus 59%), though this difference was not statistically significant. While the Simplify® Cervical Artificial Disc group had numerically greater definitely device-related AEs (two events in one subject versus one event in one subject), the rate was lower for the Simplify® Cervical Artificial Disc group (0.7% versus 0.9%). The historical ACDF control group experienced a higher rate of SAEs (13.7% versus 10.7%). In terms of SSIs, the historical ACDF control had a greater number of SSI than the Simplify® Cervical Artificial Disc group through Day 790 (6 events versus 4 events through day 790).

Additional factors that were considered in determining the probable benefits and risks for the Simplify® Cervical Artificial Disc included limitations of the clinical study design, including the inability to mask subjects to their treatment assignment, use of a historical control, reliance on subjective endpoints, and subjectivity in AE classification. Prospective investigational and

historical control studies were harmonized using subject level data for the historical control and adjudication by the CEC.

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

There are additional theoretical benefits of cervical total disc replacement devices, such as the Simplify® Cervical Artificial Disc, which include preservation of range of motion and decreased risk of adjacent segment degeneration. However, the clinical study conducted to support PMA approval of Simplify® Cervical Artificial Disc did not study these potential benefits. Further, long-term outcomes of implantation of Simplify® Cervical Artificial Disc, including long-term AE rates, will be the subject of a Post Approval Study (PAS).

Specific information on patient perspectives for this device was not directly measured. However, the subjects' perception of their benefit and risk was indirectly measured through a questionnaire. At 24 months following the index procedure, 94% (130/138) of Simplify® Cervical Artificial Disc and 87% (83/96) of historical ACDF control subjects reported that they would have the surgery again.

In conclusion, given the available information above, the data support that, for reconstruction of the disc at a single level from C3-C7 following discectomy for intractable radiculopathy (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 manifested by subject history and specific radiographic findings as outlined above in the Indications for Use, the probable benefits of the Simplify® Cervical Artificial Disc outweigh the probable risks through two years follow-up.

D. Overall Conclusions

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

XIII. CDRH DECISION

CDRH issued an approval order on September 18, 2020. The final clinical conditions of approval cited in the approval order are described below.

1. Based on the protocol synopsis received on September 10, 2020, the Extended Follow-up of IDE Subjects Treated with the Simplify® Cervical Artificial Disc: The primary study objective is to evaluate the long-term safety and effectiveness of the Simplify® Cervical

Artificial Disc at 5 years compared to a historical anterior cervical discectomy and fusion (ACDF) control. This study will consist of extended prospective follow-up of the IDE cohort for 5 years post-implantation. The study will follow all available Simplify® Cervical Artificial Disc subjects from the pivotal investigational device study. The annual visits will include the collection of the following data: assessment of neurologic function, Neck Disability Index (NDI), neck and arm pain Visual Analog Scale (VAS), subject satisfaction, quantitative and qualitative radiographic assessments, and all adverse event data including device-related and serious adverse events and information on all subsequent surgical procedures at the index level.

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

XIV. APPROVAL SPECIFICATIONS

Directions for Use: See device labeling.

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

Post Approval Requirements and Restrictions: See approval order.