SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Synthetic Cartilage Implant
Device Trade Name:	Cartiva® Synthetic Cartilage Implant (SCI)
Device Product Code	PNW
Applicant's Name/Address:	Cartiva, Incorporated 6120 Windward Parkway, Suite 220 Alpharetta, GA 30005
Date of Panel Recommendation:	April 20, 2016
Premarket Approval Application: (PMA Number)	P150017
Date of Notice of Approval to the Applicant:	July 1, 2016

II. INDICATIONS FOR USE

The Cartiva Synthetic Cartilage Implant is intended for use in the treatment of patients with painful degenerative or post-traumatic arthritis (hallux limitus or hallux rigidus) in the first metatarsophalangeal joint with or without the presence of mild hallux valgus[1]

III. CONTRAINDICATIONS

The Cartiva SCI device should not be implanted in subjects with the following conditions:

- Active infection of the foot
- Known allergy to polyvinyl alcohol
- Inadequate bone stock due to significant bone loss, avascular necrosis, and/or large osteochondral cyst (> 1cm) of the first metatarsophalangeal joint
- Lesions of the first metatarsal head greater than 10 mm in size
- Diagnosis of gout with tophi
- Physical conditions that would tend to eliminate adequate implant support (*e.g.*, insufficient quality or quantity of bone resulting from cancer, congenital dislocation, or osteoporosis), systemic and metabolic disorders leading to progressive deterioration of

[1] A hallux valgus angle less than or equal to 20º (greater than 20º was an exclusion criteria in the clinical study).

bone (*e.g.*, cortisone therapies or immunosuppressive therapies), and/or tumors of the supporting bone structures

IV. PRECAUTIONS

The safety and effectiveness of this device have not been established in subjects with the following conditions:

- Pediatric patients (< 22 years of age)
- Subjects with osteonecrosis of the first metatarsal
  Osteoarthritis involving the first metatarsophalangeal joint with grade 0 or 1 hallux rigidus per the Coughlin Scale[2]

The safety and effectiveness of the Cartiva SCI device for treatment in the presence of hallux varus to any degree or hallux valgus >20° is unknown.

The safety and effectiveness of using more than one Cartiva SCI device per joint is unknown.

The safety and effectiveness of the Cartiva SCI device at anatomic locations other than the first metatarsophalangeal joint is unknown.

The Cartiva SCI device should only be used by experienced surgeons who have undergone training in the use of this device. A lack of adequate experience and/or training may lead to a higher incidence of adverse events.

Examine all instruments prior to surgery for wear or damage. Replace any worn or damaged instruments.

Use aseptic technique when removing the Cartiva SCI device from the innermost packaging.

Carefully inspect the device and its packaging for any signs of damage, including damage to the sterile barrier. Do not use Cartiva SCI devices if the packaging is damaged or the implant shows signs of damage.

Use care when handling the Cartiva device to ensure that it does not come in contact with objects that could damage the implant. Damaged implants are no longer functionally reliable.

The Cartiva SCI device should not be used with components or instruments from other manufacturers.

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[2] Coughlin MJ, Shurnas PS. Hallux rigidus. Grading and long-term results of operative treatment. American Journal of Bone Joint Surgery. 85-A(11):2072-88. November 2003

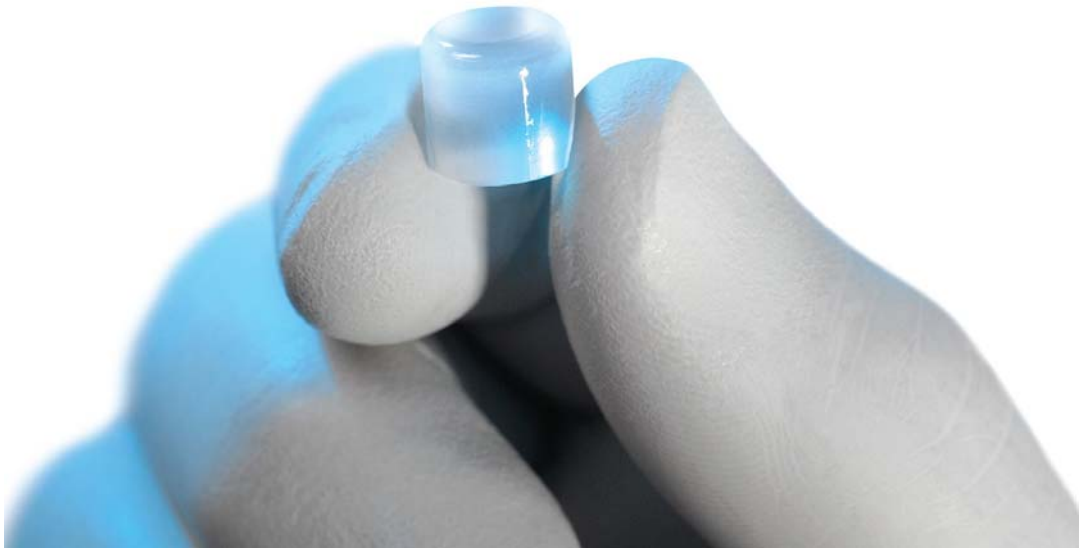
Cartiva SCI device should not be re-used or re-implanted. Ensure proper alignment and placement of device components as misalignment may cause excessive wear and/or early failure of the device.

V. DEVICE DESCRIPTION

The Cartiva SCI device is a polymer-based biomaterial implant for treatment of first metatarsophalangeal joint osteoarthritis. The viscoelastic hydrogel implant's material properties are conducive to replacing focal areas of damaged cartilage, providing pain reduction, and maintaining range of motion. The Cartiva SCI device does not regrow or replace cartilage. The device is intended as an alternative to fusion procedures, hereafter referred to as arthrodesis.

The device is a molded cylindrical implant composed of polyvinyl alcohol and saline that is placed into the metatarsal head in the first metatarsophalangeal (MTP) joint via press-fit implantation. This biocompatible material is widely used in other FDA cleared and approved medical devices, such as contact lenses, permanently implanted injectable embolic spheres, and nerve cuffs. The Cartiva SCI device is implanted during a short and minimally invasive implantation procedure that allows for faster recovery, preservation of joint function compared to the surgical fusion of the MTP joint, and preserves the option for future surgical treatment in the event of complications.

Figure 1: Cartiva Synthetic Cartilage Implant



The Cartiva SCI device is manufactured in two sizes for treatment of first metatarsophalangeal joint osteoarthritis:

Catalog Number	Size
CAR-08	8 mm (8 mm diameter x 8 mm depth)
CAR-10	10 mm (10 mm diameter x 10 mm depth

The Cartiva SCI device is placed into the first MTP using dedicated instrumentation in a straightforward and bone-preserving surgical procedure. The Cartiva SCI instrumentation includes the Placer, Introducer, Metatarsal Drill Bit, guide pins (off the shelf), and sterilization tray. Each piece of instrumentation is made of surgical grade stainless steel and is provided to the user non-sterile. All instrumentation, with the exception of the guide pins are reusable and are provided with cleaning and sterilization instructions. The guide pins are provided with sterilization instructions and are disposed of after a single use.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative treatment options for first metatarsophalangeal osteoarthritis depend upon the severity of a patient's symptoms and may include non-operative and operative treatments.

- Non-operative treatment options include the use of orthotics or accommodative footwear, use of a stiff-soled shoe, use of pain relievers and anti-inflammatory medicines, injections, hot/cold temperature baths, and limitation of activities.
- Surgical treatment options for metatarsophalangeal osteoarthritis include: cheilectomy, a joint salvage procedure that involves resection of the dorsal osteophytes from both the metatarsal and proximal phalanx and removal of the degenerative portion of the metatarsal head; hemiarthroplasty, a joint sparing procedure that involves the implantation of a device to resurface the first metatarsophalangeal head; total joint replacement, a procedure which involves replacing the entire metatarsophalangeal joint with an implant; or, arthrodesis, a procedure in which the two sides of the metatarsophalangeal joint are debrided of cartilage, and the bones are held together with plates and/or screws so that the bones grow together.

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

VII. MARKETING HISTORY

The Cartiva SCI device has been commercially distributed since 2002 with approvals in Europe, Canada and Brazil. Through the international market, the Cartiva SCI device has been used in over 4,000 procedures in various joint including the first metatarsophalangeal joint. The Cartiva SCI device has not been withdrawn from marketing for any reason.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications). In addition to the risks listed below, there is also the risk that surgery may not be effective in relieving symptoms, or may cause worsening of symptoms. Additional surgery may be required to correct some of the adverse effects.

1. Risks associated with surgical procedures involving the foot include: infection, blood clots, blood loss, damage to adjacent nerves, arteries, or veins, anesthesia-related problems, allergic reaction, numbness in the toes, painful scars, pain when wearing shoes or walking, incomplete correction, recurrence of the deformity, heart attack, stroke, nerve damage, deep vein thrombosis (DVT), pulmonary embolus (PE), and death.

2. Risks associated with implantation of the Cartiva Synthetic Cartilage Implant include infection, inflammation, pain, swelling, effusion, joint irritation, fibrosis, joint instability, joint malalignment, periarticular cyst, bone cyst, bone loss, sesamoid bone(s) irritation, sesamoid bone(s) fracture, metatarsal bone fracture, osteonecrosis, avascular necrosis, implant fracture, implant loosening, implant dislocation, implant dislodgement, implant subsidence, revision or conversion to arthrodesis, allergic reaction to polyvinyl alcohol (PVA), progressive osteoarthritis (OA), incorrect implant placement, and damage to adjacent or surrounding tissues.

For the specific adverse events that occurred in the MOTION clinical study, please see Section X.

IX. SUMMARY OF PRE-CLINICAL STUDIES

A variety of mechanical and other non-clinical tests were conducted to characterize the mechanical properties and performance of the Cartiva SCI device, as outlined below. This testing included biocompatibility testing, long-term implant compatibility testing, wear testing, and testing to evaluate that the device provides a sufficient loading surface for the first MTP joint. Testing met all predefined requirements.

A. BIOCOMPATIBILITY

The Cartiva SCI device and instrumentation are designed to be biocompatible for their respective intended use and duration of contact with the body. As summarized in Table 1 below, the Cartiva SCI device was assessed for biocompatibility per the testing guidelines outlined in ISO 10993.

Table 1: Biocompatibility Testing of the Cartiva SCI Device

Study	Test Method	Results
Cytotoxicity	L929 MEM Elution	Non-cytotoxic
Cytotoxicity	Direct Contact	Non-cytotoxic
Sensitization	Kligman Maximization	Non-sensitizer
Irritation/Intracutaneous	IC Injection	Negligible irritant
Acute Systemic Toxicity	Systemic Injection	Negative
Subchronic Toxicity	Femoral Condyle Implantation	Non-toxic
Chronic Toxicity	Femoral Condyle Implantation	Non-toxic
Genotoxicity	Ames Reverse Mutation	Non-mutagenic
Genotoxicity	Chromosomal Aberration Assay	Non-clastogenic
Genotoxicity	Rodent Bone Marrow Micronucleus	Non-clastogenic
Implantation	Bone Implantation in Femoral Condyle	Negative/no reaction
Pyrogenicity	Rabbit Pyrogen Test	Non-pyrogenic

The Cartiva SCI device is placed into its implant position using dedicated instrumentation. As summarized in Table 2 below, the Cartiva SCI instruments were assessed for biocompatibility per the testing guidelines outlined in ISO 10993.

Table 2: Biocompatibility Testing of the Cartiva SCI Instrumentation

Study	Test Method	Results
Cytotoxicity	L929 MEM Elution	Non-cytotoxic
Sensitization	Kligman Maximization	Non-sensitizer
Irritation/Intracutaneous	IC Injection	Negligible irritant

B. MECHANICAL CHARACTERIZATION TESTING

A summary of the mechanical characterization testing of the Cartiva SCI device is presented below in Table 3.

Table 3: Mechanical Characterization Testing of the Cartiva SCI Device

Test	Purpose	Results
Confined Compression (aggregate modulus)	To characterize the aggregate moduli or stiffness at equilibrium.	The mean aggregate modulus for the Cartiva SCI device was 6.7 ±1.0 MPa. This value supported selection of wear test parameters.

Test	Purpose	Results
Unconfined Compression (Young's modulus)	To characterize the deformation resistance of the device to an applied load and determine the compatibility with surrounding native tissues.	The compressive moduli and equilibrium elastic moduli observed for the Cartiva SCI device was (0.31 to 0.80 unconfined compression moduli[3]; equilibrium elastic moduli mean .677 ± .223 MPa[4]), which is less than traditional hard joint replacement materials.
Shear	To obtain a baseline characterization of the simple shear properties as the device functions as a cartilage replacement material.	Fatigued devices exhibited no change in shear properties and resistance to mechanically induced degradation properties. All devices exhibited full 100% lateral shear strain without tearing or showing shear fracture.
Creep	To characterize the creep and creep recovery responses of the device under clinical loading conditions.	The compressive creep observed was due to water loss with compressive loading, which resulted in an average mass loss of 21% across all samples. Under clinical loading, the device still had sufficient mass to serve as a bearing surface for the joint. All samples demonstrated significant recovery swelling upon the removal of the compressive load, as anticipated for a porelastic hydrogel material and thus is expected to tolerate clinical loading and unloading of the joint.
Dynamic Axial Compression (S-N Analysis)	To determine the fatigue endurance limit of the device (the maximum axial compression stress amplitude that will not cause fatigue failure in 5,000,000 cycles).	This study demonstrates that catastrophic failure of the Cartiva SCI device does not occur even when the device is subjected to stresses approximately 6 times greater than the 4 MPa anticipated peak load for the first MTP.
Particulate Implant Testing	To assess the bioreactivity of device-generated wear debris.	Wear debris representing 5 years of expected debris was implanted in a rabbit model. There were no complications on injection. No test article-related adverse changes occurred. No significant findings on clinical observation, gross pathology, histomorphometry, or histopathology of localized tissue. Systemic tissues showed no microscopic changes related to the treatment. Overall, no local or systemic response was evident.

[3] Korhonen RK, Laasanen MS, Toyras J, Rieppo J, Hirvonen J, Helminen JF, Jurvelin JS, Comparison of the Equilibrium Response of Articular Cartilage in Unconfined Compression, Confined Compression and Indentation, J Biomech. 2002 Jul;35(7):903-909.

[4] Jurvelin JS, Buschmann MD, Hunziker EB, Optical and Mechanical Determination of Poisson's Ratio, J Biomechanics. 1997;30(3):235-241.

C. PERFORMANCE TESTING

Performance testing was conducted to evaluate the device in simulated clinical use conditions or under simulated worst-case conditions. These are described below:

Fatigue Testing

The purpose of dynamic fatigue testing of the Cartiva SCI device was to assess if the device has adequate compressive strength to survive the repetitive, compressive loads that occur clinically in the first metatarsophalangeal joint. Mechanical fatigue was carried out utilizing the anticipated clinical loading. Cartiva SCI devices withstood the equivalent of 5 years of continual cyclic loading without fracturing, indicating a mechanical durability representing 5 years of continuous use.

Wear Testing

Cartiva SCI devices were subjected to loading parameters reflecting the normal gait cycle and opposing surfaces that were intended to simulate the wear environment of the first metatarsophalangeal joint. The Cartiva SCI devices sustained only minor damage during the 5,000,000 cycles under worst-case wear conditions under maximum loading that simulated 5 years of continuous walking.

To assess the long-term effect of the material and possible wear debris, a worst-case 5-year amount of Cartiva SCI device particulate was injected intra-articularly into the rabbit knee in amounts 9 times greater than that identified during wear testing. The test conditions applied incorporated the use of excessive quantities of potential wear debris in a bolus application. The rabbit particulate implant study demonstrated a lack of local or systemic toxicity to the Cartiva SCI device particulate at both 3-months and 6-months. The particulate implant testing results demonstrated no toxic or adverse reactions to the wear debris from the hydrogel material.

The average total mass of debris collected per specimen over the 5 million cycles was 1.64 mg (0.18% of average initial mass of the test articles) based on the worst-case assumption that all of the debris was of Cartiva device origin. The morphology of the particulate recovered was generally granular, oval in shape and with average aspect ratios < 1.8. The associated volumetric wear rate was determined to be 0.53 mm^3/yr. The amount of wear produced under these testing parameters indicates a low rate of wear compared with other polymers utilized in bearing surfaces of orthopedic implants. However, the threshold wear rate to induce osteolysis in the vicinity of the first metatarsophalangeal joint is unknown.

One-Year Animal Implant Study

A one-year animal implant study was conducted in accordance with Good Laboratory Practices (GLP) in a load-bearing large animal model (goat). The intent of the study was to evaluate the integrity of the implanted device after 1 year and to assess local and systemic toxicity of the Cartiva SCI device, as well as to, determine whether the implants elicit any inflammatory

reaction in a load-bearing environment. The test animals received Cartiva SCI devices while the controls received empty defects. Both groups were followed out to one year with an interim assessment at six months. The surgical procedure was well tolerated by all animals. There were no obvious differences observed between the two groups following necropsy. There were no instances of device failure, such as dislodgement or fragmentation. There were non-significant changes to the opposing tibial surface in both groups. No differences in presence of subarticular cysts between test animals that received Cartiva SCI device, as compared to the control, were observed. No implant wear and no particulate migration were observed. The results of the study demonstrated that there was no local or systemic toxicity, no ongoing chronic inflammatory reaction around the implant, and no osteolytic bone loss.

Conclusion

These data fully characterize the mechanical properties and performance of the device in simulated clinical use conditions or under simulated worst-case conditions.

D. STERILIZATION AND CLEANING

The Cartiva SCI device is provided sterile within a tray-in-pouch configuration that allows for aseptic introduction into the sterile field. The primary packaging (the tray) holds the Cartiva SCI device and saline and is sealed with a foil lid. The sealed tray is packaged in a secondary outer Tyvek pouch. The Cartiva SCI device is implanted using dedicated instrumentation. All instruments outside of the guide pins are reusable. All instrumentation, including guide pins and the sterilization tray are provided with cleaning and sterilization instructions. The guide pins are disposed of after a single use.

The final, packaged Cartiva SCI device is terminally sterilized to a sterility assurance level of 10^{-6} using E-beam radiation per a validated method in accordance with industry standard ISO 11137-2 Third Edition 2013, Sterilization of Health Care Products – Radiation – Part 2: Establishing the Sterilization Dose –Sterility.

The Cartiva SCI instrumentation's cleaning and sterilization cycle specifications are validated and consistent with cycle specifications outlined in AAMI TIR 12:2010 Designing, testing and labeling reusable medical devices for reprocessing in health care facilities: A guide for medical device manufacturers; AAMI TIR 30:2011 A Compendium of Processes, Materials, Test Methods, and Acceptance Criteria for Cleaning Reusable Medical Devices, and ANSI/AAMI ST79 Comprehensive Guide to Steam Sterilization and Sterility Assurance in Health Care Facilities, including a Pre-Vacuum 132°C 4-minute cycle and a Gravity 132° 25-minute cycle.

E. PACKAGING AND SHELF LIFE

The Cartiva SCI device is provided in sterile packaging and ready for use. The Cartiva SCI device packaging, a tray-in-pouch configuration, has been qualified to maintain device functionality and sterility and tested in accordance with *ASTM F1929-98 Standard Test Method*

for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration and *ASTM D4169 Standard Practice for Performance Testing of Shipping and Containers and Systems.*

The Cartiva SCI instrumentation is provided non-sterile. The Cartiva SCI instrumentation packaging has been qualified to maintain device functionality through simulated distribution conditions in accordance with *ASTM D4169 Standard Practice for Performance Testing of Shipping and Containers and Systems.*

The Cartiva SCI device has a labeled shelf life of 24 months. This duration was qualified by direct testing of real-time aged product to confirm retention of critical physical and mechanical characteristics of the device and to ensure the tray-in-pouch packaging retained integrity of both the outer and inner packaging seals.

The Cartiva SCI instrumentation is provided non-sterile, is reusable, and does not carry a labeled shelf life.

X. SUMMARY OF CLINICAL STUDIES

This PMA presents data from a prospective, randomized, controlled multi-center clinical trial performed to evaluate the safety and effectiveness of the Cartiva SCI device compared to arthrodesis for the treatment of subjects with painful degenerative or post-traumatic arthritis (hallux limitus or hallux rigidus) involving the first metatarsophalangeal joint, with or without the presence of mild hallux valgus. A summary of the clinical trial is presented below.

A. STUDY DESIGN

The pivotal clinical study (the "MOTION" Study) compared the Cartiva SCI device to the control treatment, arthrodesis. The study was a prospective, randomized (2:1), multi-center, two arm, unmasked, concurrently controlled, non-inferiority clinical study in 202 subjects treated at 12 sites in the United Kingdom and Canada. The study was conducted in compliance with ICH guidelines and Good Clinical Practice (GCP) guidelines. All sites had Ethics Approval and subjects were required to sign an Informed Consent in compliance with 21 CFR Part 50 and ICH guidelines. Subjects were treated between October 2009 and February 2013. The database for this PMA reflected data collected through February 2015 and was updated with a retrospective analysis of peri-operative data in October 2015.

The study employed a composite primary endpoint that reflected three outcomes (pain, function, and safety). The individual components of the primary outcome measures were a Visual Analog Scale (VAS) to assess pain, the Foot and Ankle Ability Measure (FAAM) to assess function, and the absence of major complications and subsequent surgical interventions to assess safety.

This was a frequentist, non-inferiority study with a pre-specified endpoint of the proportion of subjects achieving success (i.e., meeting all criteria of the primary composite endpoint) and a non-inferiority margin of 15%. The statistical model for this endpoint was two independent binomial proportions.

Letting $p_{Cartiva}$ and p_{Fusion} represent the proportions with 24-month success for the Cartiva SCI device and arthrodesis groups, respectively, and $\delta = 0.15$ being the non-inferiority margin, the statistical hypotheses for the pre-specified primary endpoint were:

$$H_0 : p_{Cartiva} - p_{Fusion} \leq -\delta$$
$$H_a : p_{Cartiva} - p_{Fusion} > -\delta$$

These statistical hypotheses were assessed via one-sided 95% confidence intervals on the difference in the proportion of responders in the Cartiva group minus the proportion of responders in the arthrodesis group, see Table 27 for details regarding the definition of a "responder".

In addition to the outcomes comprising the primary composite endpoint, other functional and quality-of-life outcomes scores were studied, and included active MTP dorsiflexion, Revised Foot Function Index (FFI-R), and SF-36 Physical Function Scores. Fisher's Exact test was used to calculate all p-values.

The initial two subjects enrolled and treated at each site were not randomized to ensure surgeons were adequately familiar with the procedure.

Upon confirmation of eligibility, subjects were randomized into one of two treatment groups: (1) Cartiva SCI device into the MTP joint, or (2) arthrodesis, a procedure in which the two sides of the MTP joint are held together with plates and/or screws so that the bones grow together and no longer move.

The investigators, who were fellowship-trained and board-certified orthopedic foot and ankle surgeons, performed clinical and radiographic assessments in accordance with the protocol to monitor subject outcomes. A radiographic assessment was performed by an independent core lab with an independent radiologist who assessed subjects in both treatment arms according to a pre-specified protocol.

Clinical Inclusion/Exclusion Criteria

To be eligible for the MOTION study, subjects were required to be eligible for an arthrodesis procedure and meet all of the inclusion criteria and none of the exclusion criteria, which are presented below in Table 4.

Table 4: MOTION Study Inclusion/Exclusion Criteria

Study Inclusion Criteria	Study Exclusion Criteria
• ≥18 years of age; • Degenerative or post-traumatic arthritis of the first metatarsophalangeal joint and is a candidate for arthrodesis with Grade 2, 3, or 4[2]; • Pre-operative VAS Pain score of ≥40; • Presence of good bone stock, with <1cm osteochondral cyst and without need for bone graft; • Capable of completing self-administered questionnaires; • Be willing and able to return for all study-related follow-up procedures; • Have not participated in any other research protocol within the last 30 days, and will not participate in any other research protocol during this study; • If female, is either using contraception or is postmenopausal, or male partner is using contraception; and • Have been informed of the nature of the study, agreeing to its requirements, and have signed the informed consent approved by the IRB/Ethics Committee.	• <18 years of age; • Degenerative or post-traumatic arthritis of the first metatarsophalangeal joint and is not a candidate for arthrodesis with Grade 0 or 1[2]; • Pre-operative VAS Pain score <40; • Active bacterial infection of the foot; • Additional ipsilateral lower limb (hip, knee, ankle, or foot) pathology that requires active treatment (*i.e.,* surgery, brace); • Bilateral degenerative or post-traumatic arthritis of the first metatarsophalangeal joints that would require simultaneous treatment of both MTP joints; • Previous cheilectomy resulting in inadequate bone stock; • Inflammatory arthropathy; • Diagnosis of gout; • Any significant bone loss, avascular necrosis, and/or large osteochondral cyst (>1cm) of the first metatarsophalangeal joint; • Lesions greater than 10 mm in size; • Hallux varus to any degree or hallux valgus >20°; • Physical conditions that would tend to eliminate adequate implant support (*e.g.*, insufficient quality or quantity of bone resulting from cancer, congenital dislocation, or osteoporosis), systemic and metabolic disorders leading to progressive deterioration of bone (*e.g.*, cortisone therapies or immunosuppressive therapies), and/or tumors and/or cysts >1cm of the supporting bone structures; • Patient is on chronic anticoagulation due to a bleeding disorder or has taken anticoagulants within 10 days prior to surgery; • Patient was diagnosed with cancer in the last two (2) years and received treatment with chemotherapy or received radiation to the lower extremity to be treated with Cartiva SCI device or arthrodesis; • Suspected allergic reaction to polyvinyl alcohol; • Muscular imbalance, peripheral vascular disease that prohibits adequate healing, or a poor soft-tissue envelope in the surgical field, absence of musculoligamentous supporting structures, or

[2]Coughlin MJ, Shurnas PS. Hallux rigidus. Grading and long-term results of operative treatment. American Journal of Bone Joint Surgery. 85-A(11):2072-88. November 2003

Study Inclusion Criteria	Study Exclusion Criteria
	peripheral neuropathy; • In the opinion of the Investigator, any medical condition that makes the subject unsuitable for inclusion in the study, including, but not limited to subjects with a diagnosis of concomitant injury that may interfere with healing; subjects with clinically significant renal, hepatic, cardiac, endocrine, hematologic, autoimmune or any systemic disease or systemic infection which may make interpretation of the results difficult; subjects who have undergone systemic administration within 30 days prior to implantation of any type of corticosteroid, antineoplastic, immunostimulating or immunosuppressive agents; • Co-morbidity that reduces life expectancy to less than 36 months; • If female, be pregnant, planning to become pregnant during the course of the study, breast-feeding, or if childbearing age, is not using contraception; • History of substance abuse (e.g. recreational drugs, narcotics, or alcohol); • Is a prisoner or ward of the state; • Are unable to meet the treatment and follow-up protocol requirements; or • Are being compensated under workers' compensation or are currently involved in litigation.

Follow-up Schedule

All subjects were evaluated pre-operatively, intra-operatively, post-operatively prior to discharge, and post-operatively at 2 weeks, 6 weeks, and at 3, 6, 12, and 24 months. This included the evaluation of pain as measured by the Visual Analog Scale (VAS), function as assessed by the Foot and Ankle Ability Measure (FAAM) Score, and the assessment of major complications and subsequent secondary surgical interventions. In addition, range of motion and radiographic outcomes were assessed, and subject and investigator questionnaires were completed. Subjects were required to have discontinued all pain medications (NSAIDs, narcotics, and any other analgesics) for a minimum of 8 hours prior to competing any of the study assessments. All complications and adverse events, device-related or not, were evaluated over the course of the study. The schedule for the various assessments is shown below in Table 5:

Table 5: MOTION Study Assessments

	Baseline	Operative/ Discharge (Day 0)	2w	6w	3m	6m	12m	18m	24m	Unscheduled
Window Days			**±7**	**±14**	**±14**	**±14**	**±60**	**±14**	**±60**	
Eligibility/Informed Consent	✓									
Medical History	✓									
Foot Exam	✓		✓	✓	✓	✓	✓		✓	✓
Foot X-ray	✓		✓	✓	✓	✓	✓		✓	✓
General Health	✓		✓	✓	✓	✓	✓		✓	✓
VAS Pain	✓		✓	✓	✓	✓	✓		✓	✓
Foot Function Index Revised (FFI-R)	✓		✓	✓	✓	✓	✓		✓	✓
Foot & Ankle Ability Measure (FAAM)	✓		✓	✓	✓	✓	✓		✓	✓
SF-36 Health Survey	✓			✓	✓	✓	✓		✓	✓
Global Assessment (Subject & Site PI)			✓	✓	✓	✓	✓		✓	✓
Operative/ Discharge Form		✓								
Follow-up Visit Form			✓	✓	✓	✓	✓		✓	✓
Telephone Follow-up								✓		
AE Reporting		✓	✓	✓	✓	✓	✓	✓	✓	✓

Clinical Endpoints

The effectiveness of the Cartiva SCI device was assessed and compared to treatment with arthrodesis using a composite clinical endpoint. Success required freedom from subsequent secondary surgical interventions (SSSI), a clinically meaningful reduction in pain (≥30% based on VAS), maintenance in function (FAAM), and a safety component defined as presence versus absence of any of an *a priori* selected set of device-specific radiographic findings.

The safety of the Cartiva SCI device was assessed by comparison to the arthrodesis control group with respect to the nature and frequency of adverse events (overall and in terms of seriousness and relationship to the implant/procedure), the need for subsequent secondary surgical intervention, and presence versus absence of any of an *a priori* selected set of radiographic findings.

Study Protocol Pre-specified Endpoint

The pre-specified primary endpoint of the study was individual subject success defined as follows:

- Improvement (decrease) from baseline in VAS Pain of ≥30% at 12 months;[5]
- Maintenance of function from baseline in FAAM Sports score (inclusive of decrease <9) at 12 months; and,[6]
- Freedom from major complications[7] and SSSIs through 24 months.
- No radiographic failure, which for each arm is defined separately:
    - Cartiva SCI - device displacement, device fragmentation, and/or development of avascular necrosis
    - Arthrodesis - mal-union, non-union, and/or hardware failure. The radiographic assessment for non-union and mal-union will only be included from 3 months to 24 months after surgery.

Revised Primary Endpoint

After review of the data submitted in the PMA, FDA requested additional analysis using a revised primary endpoint. The FDA requested revised endpoint is similar to the pre-specified composite endpoint with the following differences: 1) evaluate all efficacy outcomes at 24 months and 2) evaluate the FAAM ADL subscale instead of the FAAM Sports subscale. There were no changes to the definition of the safety prong.

The revised composite endpoint was defined as follows:

- Improvement (decrease) from baseline in VAS Pain of ≥30% at 24 months;
- Maintenance in function from baseline in FAAM ADL score (inclusive of decrease <8) at 24 months; and,
- Freedom from major complications[8] and SSSIs through 24 months
- No radiographic failure, which for each arm was defined separately as:
    - Cartiva SCI: device displacement, device fragmentation, and/or development of avascular necrosis

[5] The criterion for the success for pain was based on the work conducted by Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) consensus group. Dworkin and the IMMPACT consensus group evaluated the level of improvement in pain reported in clinical studies and recommended that a decrease in pain of ≥ 30% be reported in future clinical trials. This level of response was defined as a clinically important change and represented a moderate level of improvement.

[6] Martin et al. reported in the validation of the Foot and Ankle Mobility Scale (FAAM) that 9 points was the minimal clinically important difference in the Sports subscale and 8 points in the ADL subscale. The individual success criterion for the function component ensures there is no clinically significant worsening in function in order for subjects to be considered a responder in the primary endpoint.

[7] Major complications were defined from radiographic findings and were assessed by an independent radiographic reviewer. These included absence of device displacement, device fragmentation, and avascular necrosis in the Cartiva group and the absence of mal-union, non-union, and hardware fractures in the control (arthrodesis) group.

- Arthrodesis: mal-union, non-union, and/or hardware failure. The radiographic assessment for non-union and mal-union will only be included from 3 months to 24 months after surgery.

The proportion of successes in each group was determined and the difference (Cartiva minus arthrodesis) and one-sided 95% confidence interval for the difference between treatment groups was calculated. If the one-sided 95% lower confidence interval is greater than the equivalence limit (-15%), the primary endpoint will have been met.

Secondary Endpoints and Assessments

Secondary endpoints, measured in both treatment groups, included VAS Pain scores, FAAM Sports and ADL scores, range of motion as assessed by active MTP peak dorsiflexion, subject satisfaction, SF-36 Physical Functioning Scale, and FFI-R.

Other radiographic findings beyond the assessments included in the primary endpoint analysis were evaluated to determine their effect on subject outcomes.

B. ACCOUNTABILITY OF PMA COHORT

A total of 236 subjects were enrolled including n=17 subjects who withdrew prior to randomization, n=22 non-randomized roll-in subjects, and 197 randomized subjects (132 to Cartiva SCI device and 65 to arthrodesis). Among randomized subjects, 2 of 132 (1.5%) subjects randomized to the Cartiva SCI device withdrew prior to receiving treatment, as did 15 of 65 (23.1%) subjects randomized to arthrodesis, leaving 130 and 50 subjects, respectively, included in the Cartiva SCI device and arthrodesis mITT analysis set. The primary reason associated with withdrawal prior to treatment (66.7%) were subjects randomized to arthrodesis who wanted the Cartiva SCI device. The total number of treated Cartiva SCI device subjects included in the Safety Analysis was 152 including 22 non-randomized roll-in subjects. A summary of subject accountability data is provided in Figure 2 and Table 6 below.

Figure 2: Subject Accountability Tree

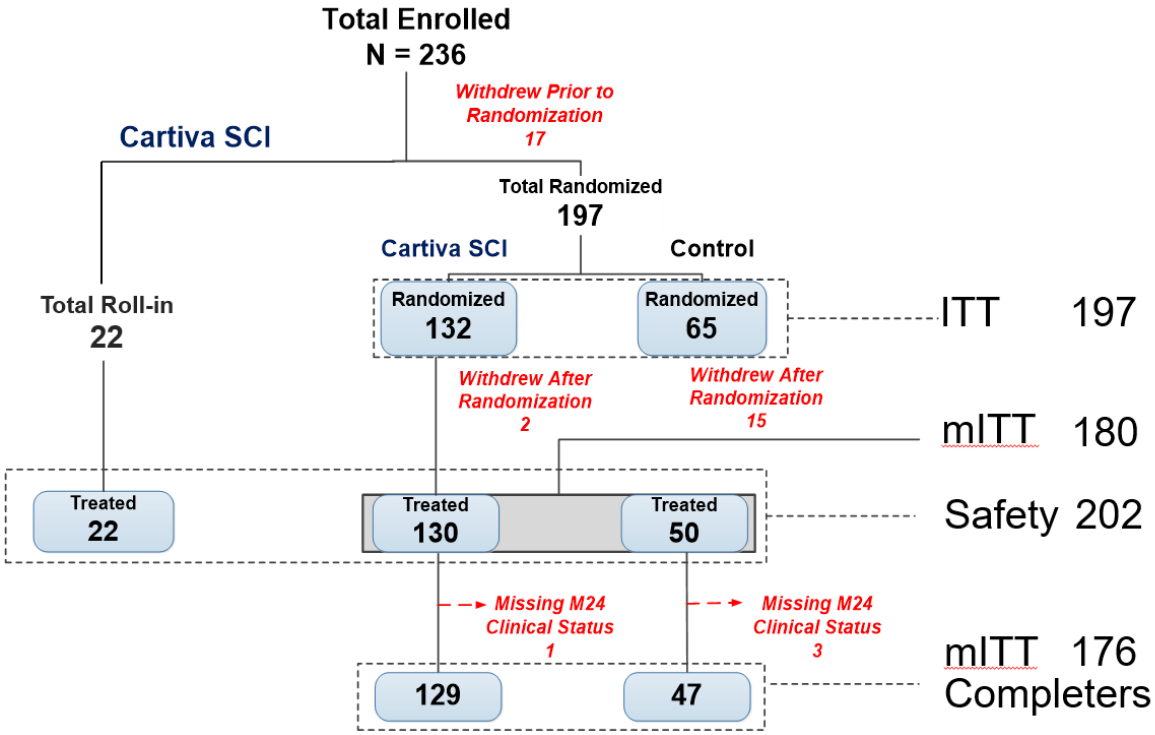


Table 6: MOTION Study Cumulative Randomized Implanted Subjects Accountability by Visit (mITT Cohort)

	Pre-Op		Week 6		Month 3		Month 6		Month 12		Month 24	
	I	C	I	C	I	C	I	C	I	C	I	C
(1) Theoretical follow-up	130	50	130	50	130	50	130	50	130	50	130	50
(2) Cumulative deaths	0	0	0	0	0	0	0	0	0	0	0	0
(3) Cumulative (Terminal) Failures	0	0	1	0	2	2	2	3	7	4	13	6
(4) Deaths+Failures among theoretical due	0	0	1	0	2	2	2	3	7	4	13	6
(5) Expected due for clinic visit	130	50	129	50	128	48	128	47	123	46	117	44
(6) Failures among theoretical due	0	0	1	0	2	2	2	3	7	4	13	6
(7) Expected due+Failures among theoretical due	130	50	130	50	130	50	130	50	130	50	130	50
All Evaluated Accounting (Actual[1]) Among Expected Due Procedures												
	I	C	I	C	I	C	I	C	I	C	I	C
(8) FAAM ADL Follow-up (9) / (5) (%)	99.2%	100%	96.90%	96.00%	97.70%	95.80%	95.30%	91.50%	99.20%	93.50%	98.30%	93.20%
(9) Change from baseline in FAAM ADL available	129	50	125	48	125	46	122	43	122	43	115	41
(10) Change from baseline in VAS Pain available	130	50	128	48	128	46	124	43	123	43	116	41
(11) Radiography endpoint									130	50	130	50
(12) CCS at Month 12 and Month 24 available									130	47	129	47
(13) Actual[1] % Follow-up for CCS (12) / (7)									100.00%	94.00%	99.20%	94.00%

[1]Subjects with any follow-up data reviewed or evaluated by investigator.

Analysis Populations

Throughout this summary, the following terms are used to describe the populations used for analysis:

Table 7: MOTION Study Analysis Populations

Analysis Population	Cartiva *Randomized*	Arthrodesis	Cartiva *Roll-In*	Total Subjects
Safety[1]	130	50	22	202
ITT[2]	132	65	-	197
mITT[3]	130	50	-	180
mITT Completers[4]	129	47	-	176
Per Protocol (PP)[5]	127	47	-	174

[1]The Safety population includes all treated subjects.

[2]The ITT population includes all randomized subjects. Subjects who dropped out prior to treatment are considered study failures.

[3]The mITT population includes all randomized subjects who received the treatment to which they were randomized.

[4]The mITT completers population includes all randomized subjects who received the treatment to which they were randomized and have 24M data available.

[5]The PP population includes all randomized subjects who received the treatment to which they were randomized with subjects having major inclusion/exclusion deviations excluded.

C. STUDY POPULATION DEMOGRAPHICS AND BASELINE PARAMETERS

Subject demographics are summarized below in Table 8. These data show that the treatment groups were well balanced and no statistically significant differences were noted. The baseline demographics of the study population are consistent with baseline demographics reported in the literature for hallux rigidus subjects treated with cheilectomy, hemiarthroplasty, and/or arthrodesis. The majority (80%) of the subjects enrolled in the study were females, consistent with the literature that shows that women have a higher incidence of MTP osteoarthritis compared to men. The majority of MOTION subjects treated (77%) presented with angular alignment of the first metatarsophalangeal joint, within a normal range (less than 15°) and 23% presented with angular deformity of the first metatarsophalangeal joint between 15°-20° (mild hallux valgus) Table 11.

Table 8: MOTION Study Subject Baseline Characteristics (Continuous Variables, mITT Cohort)

	Cartiva (N=130)			Arthrodesis (N=50)			t-test
Demographics - All	**Mean**	**SD**	**Med**	**Mean**	**SD**	**Med**	**p-value[1]**
Age at surgery (yrs)	57.4	8.8	57.9	54.9	10.5	55.1	0.115
Height (cm)	165.9	7.8	165.0	167.4	9.4	165.6	0.293
Weight (kg)	75.1	14.5	72.7	73.7	15.5	71.0	0.591
BMI (k/m^2)	27.2	4.4	26.5	26.3	4.7	25.7	0.222
Baseline Functional Status							
FAAM ADL	59.4	16.9	58.3	56.0	16.8	54.9	0.222
FAAM Sports	36.9	20.9	34.4	35.6	20.5	31.3	0.694
SF36	52.4	22.8	50.0	49.8	23.6	40.0	0.499
VAS	68.0	13.9	68.3	69.3	14.3	70.0	0.571

[1]Two sample Pooled t-test p-value.

Table 9: MOTION Study Subject Baseline Characteristics (Categorical Variables, mITT Cohort)

	Cartiva		Arthrodesis		p-value[1]
Gender	**n**	**%**	**N**	**%**	
Male	26	20.0%	12	24.0%	0.547
Female	104	80.0%	38	76.0%	

[1]Two sample Pooled t-test p-value.

Table 10: MOTION Study Subject Baseline Characteristics - Grade of Hallux Rigidus[2] (ITT)

Categorical Variables	Cartiva (N=132)		Arthrodesis (N=65)[2]		p-value[1]
	n	**%**	**n**	**%**	
Grade					0.3418
2	37	28.03	21	32.81	
3	74	56.06	29	45.31	
4	21	15.91	14	21.88	

[1]Two-sided Fisher's exact test.

[2]One arthrodesis patient did not have a baseline OA grade

Table 11: MOTION Study Subjects Baseline Characteristics – Angular Deformities Involving the First Metatarsophalangeal Joint (Normal and Mild Hallux Valgus)

Angular Deformity	n	N	%
0 to 15° Normal	155	202	77%
≥ 15 to 20° Mild Hallux Valgus	47	202	23%

D. PERI-OPERATIVE INFORMATION

Surgical timing information was available for 112 (74% of treated) Cartiva SCI device subjects and 39 (78% of treated) arthrodesis subjects, and length of anesthesia information was available for 137 (90%) Cartiva SCI device subjects and 44 (88%) arthrodesis subjects (Table 12).

Table 12: Length of Surgical Procedure and Anesthesia (minutes) for the Safety Cohort

	Cartiva			Arthrodesis			p-value
	N	Mean	SD	N	Mean	SD	
Procedure Time (minutes)	112	34.7	12.3	39	57.8	21.5	<0.001
Length of Anesthesia (minutes)	137	67.0	27.8	44	95.3	41.1	<0.001

The Cartiva SCI device surgical implantation procedure time is, on average, 40% shorter (23 minutes) than arthrodesis. Due to the shorter surgical procedure, as expected, the length of anesthesia administration for Cartiva SCI device subjects was, on average, 28 minutes shorter than that for arthrodesis subjects ($p<0.001$).

There were no significant differences observed in the type of anesthesia regimen with 92% of subjects in both treatment arms receiving general IV sedation combined with a regional ankle nerve block anesthetic.

E. SAFETY AND EFFECTIVENESS RESULTS

Safety

The analysis of safety was based on the Safety Cohort of 202 total subjects treated (22 Cartiva SCI device roll-in subjects, 130 randomized and treated Cartiva SCI device subjects, and 50 arthrodesis control subjects).

Adverse events were classified by the Investigator for relationship to the device, severity, and for seriousness of the event. The overall adverse event rate was similar for the Cartiva SCI device group (69.1%) and the arthrodesis control group (72.0%). The majority of the events were mild or moderate in nature as classified by the Investigator for the Cartiva SCI device subjects (86.2%) and arthrodesis control group (78.0%).

Table 13: Summary of Adverse Event Experiences - Safety Analysis Set

	Cartiva (N = 152)			Fusion (N = 50)			Cartiva vs Fusion			
	Events	n	%	Events	n	%	Diff	LB[1]	UB[1]	p-value[2]
Any adverse event	245	105	69.1%	72	36	72.0%	-2.9%	-18.8%	12.9%	0.727
Treatment Emergent Event	102	67	44.1%	32	21	42.0%	2.1%	-14.0%	18.1%	0.870
Device Related Event	31	23	15.1%	4	4	8.0%	7.1%	-9.0%	23.0%	0.238
Operative Procedure Related Event	71	51	33.6%	28	18	36.0%	-2.4%	-18.2%	13.5%	0.864
Non-Treatment Emergent Event	143	73	48.0%	40	26	52.0%	-4.0%	-20.0%	12.2%	0.745
Any Serious adverse event	37	30	19.7%	12	9	18.0%	1.7%	-14.2%	17.5%	0.999
Treatment Emergent Event	17	17	11.2%	4	4	8.0%	3.2%	-12.9%	19.2%	0.605
Device Related Event	11	11	7.2%	2	2	4.0%	3.2%	-12.9%	19.3%	0.526
Operative Procedure Related Event	6	6	3.9%	2	2	4.0%	-0.1%	-16.2%	16.1%	0.999
Non-Treatment Emergent Event	20	14	9.2%	8	5	10.0%	-0.8%	-16.8%	15.2%	0.999
AE by Severity										
Mild	110	70	46.1%	41	25	50.0%	-3.9%	-20.0%	12.2%	0.744
Moderate	114	61	40.1%	26	14	28.0%	12.1%	-3.7%	27.8%	0.133
Severe	21	16	10.5%	5	5	10.0%	0.5%	-15.5%	16.5%	0.999
AE Resolution Status										
Resolved without Sequelae	145	76	50.0%	48	26	52.0%	-2.0%	-18.1%	14.2%	0.871
Resolved with Sequelae	9	8	5.3%	3	2	4.0%	1.3%	-14.9%	17.4%	0.999
Unresolved at Study Exit / Completion	87	55	36.2%	21	17	34.0%	2.2%	-13.5%	18.1%	0.865
Unknown	1	1	0.7%	0	0	0.0%	0.7%	-15.5%	16.8%	0.999
Other	2	2	1.3%	0	0	0.0%	1.3%	-14.8%	17.4%	0.999
Anticipated Events	100	66	43.4%	28	19	38.0%	5.4%	-10.6%	21.3%	0.515
Unanticipated Events	145	73	48.0%	44	27	54.0%	-6.0%	-22.0%	10.2%	0.516

Notes:
[1] Lower and upper bounds of exact 95% confidence interval for the group difference in percentages experiencing the event.
[2] Fisher's Exact Test

There were no statistically significant differences with respect to total adverse events, treatment emergent (device and operative related) adverse events (AEs), or Serious Adverse Events (SAEs).

All Adverse Events

All adverse events, as shown in Table 14 below, are reported from the "Safety Population", which included 152 Cartiva patients and 50 arthrodesis patients enrolled in the multi-center clinical study. Adverse event rates presented are based on the number of patients having at least one occurrence for a particular adverse event divided by the total number of patients in that treatment group.

A total of 105 Cartiva patients (69.1%) had at least one adverse event within 24 months versus 36 arthrodesis patients (72.0%). A total of 245 events were reported in 105 Cartiva patients and 72 events were reported in 36 arthrodesis patients. The summary of AEs by System Organ Class (SOC) and Preferred Term (PT) in either treatment group is provided in the table below reported as number of events and number of patients in the safety population.

Table 14: Adverse Events by System Organ Class, Preferred Term, and Treatment Group

	Cartiva (N = 152)			**Fusion (N = 50)**		
	Events	**Subj.**	**%**	**Events**	**Subj.**	**%**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1	1	0.7%	0	0	0.0%
Splenomegaly	1	1	0.7%	0	0	0.0%
CARDIAC DISORDERS	2	2	1.3%	0	0	0.0%
Aortic valve stenosis	1	1	0.7%	0	0	0.0%
Aortic valve disease	1	1	0.7%	0	0	0.0%
CONGENITAL, FAMILIAL, AND GENETIC DISORDERS	1	1	0.7%	0	0	0.0%
Congenital foot malformation	1	1	0.7%	0	0	0.0%
EAR AND LABYRINTH DISORDERS	2	1	0.7%	0	0	0.0%
Eustachian tube patulous	2	1	0.7%	0	0	0.0%
ENDOCRINE DISORDERS	1	1	0.7%	0	0	0.0%
Hypothyroidism	1	1	0.7%	0	0	0.0%
GASTROINTESTINAL DISORDERS	6	6	3.9%	1	1	2.0%
Abdominal pain upper	2	2	1.3%	0	0	0.0%
Diverticulum	1	1	0.7%	0	0	0.0%
Gastrointestinal pain	1	1	0.7%	0	0	0.0%
Salivary gland calculus	1	1	0.7%	0	0	0.0%
Small intestinal obstruction	1	1	0.7%	0	0	0.0%
Tongue oedema	0	0	0.0%	1	1	2.0%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	28	23	15.1%	2	2	4.0%
Fibrosis	1	1	0.7%	0	0	0.0%
Gait disturbance	3	2	1.3%	0	0	0.0%
Impaired healing	1	1	0.7%	1	1	2.0%

	Cartiva (N = 152)			Fusion (N = 50)		
	Events	Subj.	%	Events	Subj.	%
Oedema peripheral	1	1	0.7%	0	0	0.0%
Non-cardiac chest pain	0	0	0.0%	1	1	2.0%
Implant site pain	18	16	10.5%	0	0	0.0%
Implant site cyst	1	1	0.7%	0	0	0.0%
Implant site induration	1	1	0.7%	0	0	0.0%
Implant site swelling	2	2	1.3%	0	0	0.0%
HEPATOBILIARY DISORDERS	3	3	2.0%	0	0	0.0%
Cholecystitis	1	1	0.7%	0	0	0.0%
Cholecystitis acute	1	1	0.7%	0	0	0.0%
Hepatomegaly	1	1	0.7%	0	0	0.0%
INFECTIONS AND INFESTATIONS	13	12	7.9%	7	5	10.0%
Arthritis viral	1	1	0.7%	0	0	0.0%
Bronchitis	1	1	0.7%	0	0	0.0%
Clostridium difficile colitis	1	1	0.7%	0	0	0.0%
Cystitis	1	1	0.7%	0	0	0.0%
Herpes zoster	1	1	0.7%	0	0	0.0%
Influenza	1	1	0.7%	0	0	0.0%
Nasopharyngitis	2	2	1.3%	0	0	0.0%
Onychomycosis	0	0	0.0%	1	1	2.0%
Pneumonia	1	1	0.7%	1	1	2.0%
Postoperative wound infection	1	1	0.7%	0	0	0.0%
Sepsis	0	0	0.0%	1	1	2.0%
Sinusitis	1	1	0.7%	1	1	2.0%
Stitch abscess	1	1	0.7%	0	0	0.0%
Urinary tract infection	1	1	0.7%	3	2	4.0%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	86	57	37.5%	31	21	42.0%
Ankle fracture	2	2	1.3%	0	0	0.0%
Back injury	1	1	0.7%	0	0	0.0%
Device breakage	0	0	0.0%	1	1	2.0%
Device migration	1	1	0.7%	0	0	0.0%
Fall	1	1	0.7%	0	0	0.0%
Foot fracture	6	5	3.3%	1	1	2.0%
Hand fracture	1	1	0.7%	0	0	0.0%
Humerus fracture	1	1	0.7%	0	0	0.0%
Joint sprain	2	2	1.3%	0	0	0.0%
Road traffic accident	1	1	0.7%	0	0	0.0%
Spinal cord injury	1	1	0.7%	0	0	0.0%
Tendon rupture	1	1	0.7%	0	0	0.0%

	Cartiva (N = 152)			Fusion (N = 50)		
	Events	Subj.	%	Events	Subj.	%
Muscle strain	1	1	0.7%	0	0	0.0%
Contusion	1	1	0.7%	1	1	2.0%
Comminuted fracture	1	1	0.7%	0	0	0.0%
Meniscus lesion	1	1	0.7%	0	0	0.0%
Medical device complication	0	0	0.0%	4	4	8.0%
Post procedural bile leak	1	1	0.7%	0	0	0.0%
Post procedural discharge	1	1	0.7%	0	0	0.0%
Post procedural complication	1	1	0.7%	1	1	2.0%
Medical device pain	6	6	3.9%	2	2	4.0%
Joint injury	5	4	2.6%	2	1	2.0%
Limb injury	2	1	0.7%	3	2	4.0%
Skeletal injury	2	1	0.7%	0	0	0.0%
Postoperative wound complication	0	0	0.0%	1	1	2.0%
Post procedural oedema	3	3	2.0%	2	2	4.0%
Limb crushing injury	0	0	0.0%	1	1	2.0%
Procedural pain	31	29	19.1%	9	9	18.0%
Avulsion fracture	1	1	0.7%	0	0	0.0%
Post procedural swelling	11	10	6.6%	3	3	6.0%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	68	46	30.3%	20	16	32.0%
Arthralgia	16	15	9.9%	3	3	6.0%
Arthritis	4	4	2.6%	3	2	4.0%
Arthropathy	2	1	0.7%	0	0	0.0%
Back pain	1	1	0.7%	2	2	4.0%
Bone cyst	1	1	0.7%	0	0	0.0%
Bunion	2	2	1.3%	1	1	2.0%
Bursitis	1	1	0.7%	0	0	0.0%
Cervical spinal stenosis	0	0	0.0%	1	1	2.0%
Exostosis	1	1	0.7%	0	0	0.0%
Fracture nonunion	0	0	0.0%	2	2	4.0%
Joint stiffness	2	2	1.3%	0	0	0.0%
Metatarsalgia	0	0	0.0%	1	1	2.0%
Monarthritis	1	1	0.7%	0	0	0.0%
Muscle spasms	1	1	0.7%	0	0	0.0%
Musculoskeletal pain	0	0	0.0%	1	1	2.0%
Osteoarthritis	7	4	2.6%	1	1	2.0%
Pain in extremity	11	10	6.6%	1	1	2.0%
Palindromic rheumatism	1	1	0.7%	0	0	0.0%

	Cartiva (N = 152)			Fusion (N = 50)		
	Events	Subj.	%	Events	Subj.	%
Plantar fasciitis	2	2	1.3%	1	1	2.0%
Spinal column stenosis	1	1	0.7%	0	0	0.0%
Tendonitis	3	2	1.3%	1	1	2.0%
Fibromyalgia	2	2	1.3%	0	0	0.0%
Muscle tightness	1	1	0.7%	0	0	0.0%
Joint crepitation	1	1	0.7%	0	0	0.0%
Foot deformity	7	6	3.9%	1	1	2.0%
Limb discomfort	0	0	0.0%	1	1	2.0%
NEOPLASMS BENIGN, MALIGNANT, AND UNSPECIFIED (INCL CYSTS AND POLYPS)	6	5	3.3%	2	2	4.0%
B-cell lymphoma	1	1	0.7%	0	0	0.0%
Neuroma	1	1	0.7%	0	0	0.0%
Throat cancer	1	1	0.7%	0	0	0.0%
Gastrointestinal stromal tumor	0	0	0.0%	1	1	2.0%
Prostate cancer	2	2	1.3%	0	0	0.0%
Benign soft tissue neoplasm	0	0	0.0%	1	1	2.0%
Benign muscle neoplasm	1	1	0.7%	0	0	0.0%
NERVOUS SYSTEM DISORDERS	5	5	3.3%	2	1	2.0%
Carpal tunnel syndrome	1	1	0.7%	0	0	0.0%
Dysaesthesia	0	0	0.0%	1	1	2.0%
Hypoaesthesia	0	0	0.0%	1	1	2.0%
Neuralgia	1	1	0.7%	0	0	0.0%
Neuropathy peripheral	1	1	0.7%	0	0	0.0%
Syncope	1	1	0.7%	0	0	0.0%
Cognitive disorder	1	1	0.7%	0	0	0.0%
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	1	1	0.7%	1	1	2.0%
Pregnancy	1	1	0.7%	1	1	2.0%
PSYCHIATRIC DISORDERS	5	5	3.3%	1	1	2.0%
Anxiety	2	2	1.3%	0	0	0.0%
Depression	2	2	1.3%	1	1	2.0%
Insomnia	1	1	0.7%	0	0	0.0%
RENAL AND URINARY DISORDERS	0	0	0.0%	1	1	2.0%
Nephrolithiasis	0	0	0.0%	1	1	2.0%
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1	1	0.7%	1	1	2.0%
Metrorrhagia	0	0	0.0%	1	1	2.0%
Postmenopausal hemorrhage	1	1	0.7%	0	0	0.0%

	Cartiva (N = 152)			Fusion (N = 50)		
	Events	Subj.	%	Events	Subj.	%
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	4	3	2.0%	0	0	0.0%
Dysphonia	1	1	0.7%	0	0	0.0%
Dyspnoea	1	1	0.7%	0	0	0.0%
Nasal septum deviation	1	1	0.7%	0	0	0.0%
Sleep apnoea syndrome	1	1	0.7%	0	0	0.0%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	6	5	3.3%	2	2	4.0%
Dyshidrosis	1	1	0.7%	0	0	0.0%
Ingrowing nail	1	1	0.7%	0	0	0.0%
Rash	2	2	1.3%	0	0	0.0%
Scar	1	1	0.7%	0	0	0.0%
Skin disorder	0	0	0.0%	1	1	2.0%
Skin lesion	1	1	0.7%	0	0	0.0%
Skin ulcer	0	0	0.0%	1	1	2.0%
SURGICAL AND MEDICAL PROCEDURES	3	3	2.0%	1	1	2.0%
Bunion operation	1	1	0.7%	0	0	0.0%
Hip Arthroplasty	1	1	0.7%	0	0	0.0%
Hysterectomy	0	0	0.0%	1	1	2.0%
Muscle operation	1	1	0.7%	0	0	0.0%
VASCULAR DISORDERS	3	3	2.0%	0	0	0.0%
Hypertension	3	3	2.0%	0	0	0.0%

From the table above, there are three categories of adverse events for Preferred Term in which the Cartiva SCI device group is greater than or equal to approximately 4% points higher for the number of subjects in the study experiencing these adverse events than compared to the arthrodesis group. These PT categories include: Implant site pain (10.5% vs 0%); Arthralgia (9.9% vs 6.0%); and Pain in the Extremity (6.6% vs 2.0%). Specifically, a higher percentage of Cartiva SCI device subjects had adverse events involving pain. The correlation between subjects with high rates of pain adverse events and primary outcome measures for device effectiveness were seen in 8 out of 16 subjects with device related pain events that were counted as overall successes.

There were two PT categories where the number of subjects experiencing an adverse event was greater in the arthrodesis group: Fracture Non-union (4.0% vs 0%), Medical Device Breakage (2.0% vs 0%), and Medical Device Complications (8.0% vs 0%), which also is defined as including non-union and delayed union for the arthrodesis group.

Among the SOC categories, there are a greater percentage of Cartiva SCI device subjects (15.1% vs 4.0%) who experienced "General Disorders and Administration Site Conditions." The PT

categories under this SOC category shows that there were a greater percentage of Cartiva SCI device subject were observed with Implant Site Pain (10.5% vs 0%), Gait Disturbance (1.3% vs 0 %), and Implant Site Swelling (1.3% vs 0%).

Table 15 below provides all Adverse Events by time course.

Table 15: Counts of Adverse Events by Time Interval in Cartiva (I) and Arthrodesis (C) Safety Analysis Sets

	Immed Post-Op		1 mo		3 mo		6 mo		12 mo		24 mo		24+mo		Total Events	
	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Splenomegaly	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
CARDIAC DISORDERS	0	0	0	0	0	0	1	0	1	0	0	0	0	0	2	0
Aortic valve stenosis	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
Aortic valve disease	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0
CONGENITAL, FAMILIAL, AND GENETIC DISORDERS	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
Congenital foot malformation	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
EAR AND LABYRINTH DISORDERS	0	0	0	0	0	0	0	0	0	0	1	0	1	0	2	0
Eustachian tube patulous	0	0	0	0	0	0	0	0	0	0	1	0	1	0	2	0
ENDOCRINE DISORDERS	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Hypothyroidism	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
GASTROINTESTINAL DISORDERS	0	0	0	0	1	0	0	0	3	0	1	1	1	0	6	1
Abdominal pain upper	0	0	0	0	0	0	0	0	1	0	1	0	0	0	2	0
Diverticulum	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0
Gastrointestinal pain	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0
Salivary gland calculus	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
Small intestinal obstruction	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
Tongue oedema	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1	0	2	1	7	0	7	0	7	1	2	0	2	0	28	2
Fibrosis	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
Gait disturbance	0	0	0	0	0	0	0	0	2	0	1	0	0	0	3	0
Impaired healing	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1
Oedema peripheral	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0
Non-cardiac chest pain	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1
Implant site pain	0	0	1	0	6	0	6	0	4	0	1	0	0	0	18	0
Implant site cyst	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0
Implant site induration	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0
Implant site swelling	1	0	0	0	0	0	1	0	0	0	0	0	0	0	2	0

	Immed Post-Op		1 mo		3 mo		6 mo		12 mo		24 mo		24+mo		Total Events	
	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C
HEPATOBILIARY DISORDERS	0	0	0	0	0	0	0	0	0	0	2	0	1	0	3	0
Cholecystitis	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Cholecystitis acute	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0
Hepatomegaly	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
INFECTIONS AND INFESTATIONS	0	0	1	1	5	3	1	2	3	1	3	0	0	0	13	7
Arthritis viral	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Bronchitis	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Clostridium difficile colitis	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
Cystitis	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
Herpes zoster	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0
Influenza	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0
Nasopharyngitis	0	0	0	0	1	0	0	0	0	0	1	0	0	0	2	0
Onychomycosis	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1
Pneumonia	0	0	0	0	0	0	0	1	1	0	0	0	0	0	1	1
Postoperative wound infection	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0
Sepsis	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Sinusitis	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1
Stitch abscess	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0
Urinary tract infection	0	0	0	0	0	2	1	0	0	1	0	0	0	0	1	3
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	3	0	1	2	17	11	16	9	23	6	24	3	2	0	86	31
Ankle fracture	0	0	0	0	1	0	0	0	1	0	0	0	0	0	2	0
Back injury	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0
Device breakage	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Device migration	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Fall	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0
Foot fracture	1	0	0	0	0	0	1	0	2	1	1	0	1	0	6	1
Hand fracture	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Humerus fracture	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
Joint sprain	0	0	0	0	0	0	0	0	2	0	0	0	0	0	2	0
Road traffic accident	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
Spinal cord injury	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Tendon rupture	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Muscle strain	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0
Contusion	0	0	0	0	1	0	0	0	0	0	0	1	0	0	1	1
Comminuted fracture	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Meniscus lesion	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0

	Immed Post-Op		1 mo		3 mo		6 mo		12 mo		24 mo		24+mo		Total Events	
	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C
Medical device complication	0	0	0	0	0	2	0	1	0	1	0	0	0	0	0	4
Post procedural bile leak	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0
Post procedural discharge	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0
Post procedural complication	0	0	0	0	0	0	0	1	0	0	1	0	0	0	1	1
Medical device pain	1	0	0	0	0	0	0	0	2	2	2	0	1	0	6	2
Joint injury	0	0	0	0	0	0	0	2	2	0	3	0	0	0	5	2
Limb injury	0	0	0	0	0	1	0	2	2	0	0	0	0	0	2	3
Skeletal injury	0	0	0	0	0	0	2	0	0	0	0	0	0	0	2	0
Postoperative wound complication	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Post procedural oedema	0	0	0	0	1	2	1	0	1	0	0	0	0	0	3	2
Limb crushing injury	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1
Procedural pain	0	0	0	1	8	4	6	2	8	1	9	1	0	0	31	9
Avulsion fracture	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Post procedural swelling	0	0	0	0	3	2	5	0	1	1	2	0	0	0	11	3
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	3	0	3	0	9	2	4	0	22	4	20	11	7	3	68	20
Arthralgia	1	0	2	0	1	0	1	0	7	0	4	3	0	0	16	3
Arthritis	1	0	0	0	1	0	0	0	2	1	0	0	0	2	4	3
Arthropathy	0	0	0	0	0	0	0	0	2	0	0	0	0	0	2	0
Back pain	0	0	0	0	0	0	0	0	1	0	0	2	0	0	1	2
Bone cyst	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0
Bunion	0	0	0	0	0	0	1	0	0	1	1	0	0	0	2	1
Bursitis	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
Cervical spinal stenosis	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Exostosis	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0
Fracture nonunion	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	2
Joint stiffness	0	0	0	0	2	0	0	0	0	0	0	0	0	0	2	0
Metatarsalgia	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Monarthritis	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
Muscle spasms	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0
Musculoskeletal pain	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Osteoarthritis	0	0	0	0	0	0	0	0	0	0	7	0	0	1	7	1
Pain in extremity	0	0	0	0	0	0	2	0	4	0	3	1	2	0	11	1
Palindromic rheumatism	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0
Plantar fasciitis	0	0	0	0	1	0	0	0	0	0	1	1	0	0	2	1
Spinal column stenosis	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Tendonitis	1	0	0	0	1	0	0	0	1	1	0	0	0	0	3	1

	Immed Post-Op		1 mo		3 mo		6 mo		12 mo		24 mo		24+mo		Total Events	
	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C
Fibromyalgia	0	0	0	0	1	0	0	0	1	0	0	0	0	0	2	0
Muscle tightness	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0
Joint crepitation	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Foot deformity	0	0	1	0	1	0	0	0	2	0	2	1	1	0	7	1
Limb discomfort	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
NEOPLASMS BENIGN, MALIGNANT, AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	0	0	0	0	0	1	1	1	0	4	1	0	0	6	2
B-cell lymphoma	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Neuroma	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Throat cancer	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
Gastrointestinal stromal tumour	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1
Prostate cancer	0	0	0	0	0	0	1	0	0	0	1	0	0	0	2	0
Benign soft tissue neoplasm	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Benign muscle neoplasm	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
NERVOUS SYSTEM DISORDERS	0	0	1	1	0	1	0	0	3	0	1	0	0	0	5	2
Carpal tunnel syndrome	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Dysaesthesia	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Hypoaesthesia	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Neuralgia	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0
Neuropathy peripheral	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
Syncope	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
Cognitive disorder	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0	0	0	0	0	0	0	0	1	0	0	1	0	0	1	1
Pregnancy	0	0	0	0	0	0	0	0	1	0	0	1	0	0	1	1
PSYCHIATRIC DISORDERS	0	0	0	0	1	0	0	0	2	1	2	0	0	0	5	1
Anxiety	0	0	0	0	0	0	0	0	2	0	0	0	0	0	2	0
Depression	0	0	0	0	1	0	0	0	0	1	1	0	0	0	2	1
Insomnia	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
RENAL AND URINARY DISORDERS	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
Nephrolithiasis	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	0	0	0	0	0	0	0	1	0	0	1	0	0	1	1
Metrorrhagia	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Postmenopausal haemorrhage	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	0	0	0	0	2	0	1	0	1	0	0	0	4	0
Dysphonia	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0

	Immed Post-Op		1 mo		3 mo		6 mo		12 mo		24 mo		24+mo		Total Events	
	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C
Dyspnoea	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
Nasal septum deviation	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0
Sleep apnoea syndrome	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	0	0	0	1	0	1	0	2	1	2	1	0	0	6	2
Dyshidrosis	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
Ingrowing nail	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0
Rash	0	0	0	0	0	0	1	0	0	0	1	0	0	0	2	0
Scar	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Skin disorder	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1
Skin lesion	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
Skin ulcer	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
SURGICAL AND MEDICAL PROCEDURES	0	0	0	0	1	0	0	0	1	0	1	1	0	0	3	1
Bunion operation	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Hip Arthroplasty	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
Hysterectomy	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Muscle operation	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0
VASCULAR DISORDERS	0	0	0	0	0	0	0	0	1	0	1	0	1	0	3	0
Hypertension	0	0	0	0	0	0	0	0	1	0	1	0	1	0	3	0

[1]The verbatim event term for the event device migration in the Cartiva group indicated the device shifted within the implant cavity. The device did not migrate outside of the cavity or dislodge the cavity or joint. This event was not observed by the independent radiographic reviewer and did not correlate to any independent radiographic findings.

Serious Adverse Events

A summary of the total number of Serious Adverse Events (SAE) is shown in Table 16. To evaluate that Cartiva SCI device is safe, the company collected all adverse event data and had safety data reviewed by the Medical Monitor. A SAE was defined as follows: 1) death or threat to life; or, 2) permanent impairment of a body function or permanent damage to a body structure; or, 3) an event requiring medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. During the MOTION study, there were a total of 37 SAEs in 30 subjects (19.7%) in the Cartiva SCI device arm and 12 serious adverse events in 9 subjects (18.0%) in the arthrodesis arm.

Table 16: Serious Adverse Events by System Organ Class, Preferred Term, and Treatment Group - Safety Analysis Set

	Cartiva (N = 152)			Fusion (N = 50)		
	Events	**Subj.**	**%**	**Events**	**Subj.**	**%**
CARDIAC DISORDERS	1	1	0.7%	0	0	0.0%
Aortic valve stenosis	1	1	0.7%	0	0	0.0%
CONGENITAL, FAMILIAL, AND GENETIC DISORDERS	1	1	0.7%	0	0	0.0%
Congenital foot malformation	1	1	0.7%	0	0	0.0%
EAR AND LABYRINTH DISORDERS	1	1	0.7%	0	0	0.0%
Eustachian tube patulous	1	1	0.7%	0	0	0.0%
GASTROINTESTINAL DISORDERS	1	1	0.7%	0	0	0.0%
Small intestinal obstruction	1	1	0.7%	0	0	0.0%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	9	9	5.9%	0	0	0.0%
Fibrosis	1	1	0.7%	0	0	0.0%
Implant site pain	8	8	5.3%	0	0	0.0%
HEPATOBILIARY DISORDERS	2	2	1.3%	0	0	0.0%
Cholecystitis	1	1	0.7%	0	0	0.0%
Cholecystitis acute	1	1	0.7%	0	0	0.0%
INFECTIONS AND INFESTATIONS	1	1	0.7%	3	1	2.0%
Postoperative wound infection	1	1	0.7%	0	0	0.0%
Sepsis	0	0	0.0%	1	1	2.0%
Urinary tract infection	0	0	0.0%	2	1	2.0%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	8	8	5.3%	4	4	8.0%
Ankle fracture	1	1	0.7%	0	0	0.0%
Tendon rupture	1	1	0.7%	0	0	0.0%
Medical device complication	0	0	0.0%	2	2	4.0%
Post procedural bile leak	1	1	0.7%	0	0	0.0%
Post procedural complication	0	0	0.0%	1	1	2.0%
Medical device pain	3	3	2.0%	1	1	2.0%
Procedural pain	2	2	1.3%	0	0	0.0%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	7	5	3.3%	3	3	6.0%
Arthralgia	1	1	0.7%	1	1	2.0%
Arthritis	3	3	2.0%	1	1	2.0%
Joint stiffness	1	1	0.7%	0	0	0.0%
Osteoarthritis	1	1	0.7%	0	0	0.0%
Foot deformity	1	1	0.7%	1	1	2.0%

	Cartiva (N = 152)			Fusion (N = 50)		
	Events	**Subj.**	**%**	**Events**	**Subj.**	**%**
NEOPLASMS BENIGN, MALIGNANT, AND UNSPECIFIED (INCL CYSTS AND POLYPS)	2	1	0.7%	1	1	2.0%
Throat cancer	1	1	0.7%	0	0	0.0%
Gastrointestinal stromal **tumor**	0	0	0.0%	1	1	2.0%
Prostate cancer	1	1	0.7%	0	0	0.0%
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2	2	1.3%	0	0	0.0%
Dysphonia	1	1	0.7%	0	0	0.0%
Nasal septum deviation	1	1	0.7%	0	0	0.0%
SURGICAL AND MEDICAL PROCEDURES	2	2	1.3%	1	1	2.0%
Hip Arthroplasty	1	1	0.7%	0	0	0.0%
Hysterectomy	0	0	0.0%	1	1	2.0%
Muscle operation	1	1	0.7%	0	0	0.0%
Any Serious adverse event	37	30	19.7%	12	9	18.0%

Serious Treatment Emergent Adverse Events

The incidence of as Treatment-Emergent Adverse Events (TEAE) among subjects was similar between the groups (44% Cartiva and 42% Arthrodesis). TEAEs were defined by the sponsor as events that were either operative site related or device related.

There was an overall total of 134 TEAEs reported within the safety population. A total of 102 events (76.1% of total events) in 67 subjects (44.1% of Cartiva SCI device subjects) were reported in the Cartiva SCI device patients and 32 events (23.8% of total events) in 21 subjects (42.0% of arthrodesis subjects) were reported in the arthrodesis group. Therefore, the numbers of subjects experiencing adverse events were similar between groups. The summary of TEAEs by SOC and PT in either treatment group is provided in Table 17 below, reported as number of events and number of patients in the safety population.

Table 17: Treatment Emergent Events by System Organ Class, Preferred Term & Treatment

Treatment Emergent	Cartiva (N = 152)			Fusion (N = 50)		
	Events	**Subjects**	**%**	**Events**	**Subjects**	**%**
All Treatment Emergent Events	**102**	**67**	**44.1%**	**32**	**21**	**42.0%**
CONGENITAL, FAMILIAL, AND GENETIC DISORDERS	1	1	0.7%	0	0	0.0%
Congenital foot malformation	1	1	0.7%	0	0	0.0%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	25	21	13.8%	1	1	2.0%

Treatment Emergent	Cartiva (N = 152)			Fusion (N = 50)		
	Events	Subjects	%	Events	Subjects	%
Fibrosis	1	1	0.7%	0	0	0.0%
Gait disturbance	1	1	0.7%	0	0	0.0%
Impaired healing	1	1	0.7%	1	1	2.0%
Implant site pain	18	16	10.5%	0	0	0.0%
Implant site cyst	1	1	0.7%	0	0	0.0%
Implant site induration	1	1	0.7%	0	0	0.0%
Implant site swelling	2	2	1.3%	0	0	0.0%
INFECTIONS AND INFESTATIONS	1	1	0.7%	0	0	0.0%
Stitch abscess	1	1	0.7%	0	0	0.0%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	57	43	28.3%	24	18	36.0%
Device breakage	0	0	0.0%	1	1	2.0%
Device migration	1	1	0.7%	0	0	0.0%
Foot fracture	2	2	1.3%	1	1	2.0%
Comminuted fracture	1	1	0.7%	0	0	0.0%
Medical device complication	0	0	0.0%	4	4	8.0%
Post procedural discharge	1	1	0.7%	0	0	0.0%
Post procedural complication	1	1	0.7%	1	1	2.0%
Medical device pain	6	6	3.9%	2	2	4.0%
Postoperative wound complication	0	0	0.0%	1	1	2.0%
Post procedural oedema	3	3	2.0%	2	2	4.0%
Procedural pain	31	29	19.1%	9	9	18.0%
Post procedural swelling	11	10	6.6%	3	3	6.0%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	14	9	5.9%	3	3	6.0%
Arthritis	1	1	0.7%	0	0	0.0%
Arthropathy	2	1	0.7%	0	0	0.0%
Bone cyst	1	1	0.7%	0	0	0.0%
Bunion	1	1	0.7%	0	0	0.0%
Exostosis	1	1	0.7%	0	0	0.0%
Fracture nonunion	0	0	0.0%	2	2	4.0%
Joint stiffness	2	2	1.3%	0	0	0.0%
Tendonitis	2	1	0.7%	1	1	2.0%
Foot deformity	4	3	2.0%	0	0	0.0%
NERVOUS SYSTEM DISORDERS	2	2	1.3%	2	1	2.0%
Dysaesthesia	0	0	0.0%	1	1	2.0%
Hypoaesthesia	0	0	0.0%	1	1	2.0%
Neuralgia	1	1	0.7%	0	0	0.0%

Treatment Emergent	Cartiva (N = 152)			Fusion (N = 50)		
	Events	Subjects	%	Events	Subjects	%
Neuropathy peripheral	1	1	0.7%	0	0	0.0%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1	1	0.7%	2	2	4.0%
Scar	1	1	0.7%	0	0	0.0%
Skin disorder	0	0	0.0%	1	1	2.0%
Skin ulcer	0	0	0.0%	1	1	2.0%
SURGICAL AND MEDICAL PROCEDURES	1	1	0.7%	0	0	0.0%
Bunion operation	1	1	0.7%	0	0	0.0%

Note: The verbatim event term for the event device migration in the Cartiva group indicated the device shifted within the implant cavity. The device did not migrate outside of the cavity or dislodge the cavity or joint. This event was not observed by the independent radiographic reviewer and did not correlate to any independent radiographic findings.

Similar to the All Adverse Events table, in the TEAE table there is one category (Implant Site Pain) in which the Cartiva group is greater than four percentage points higher for the number of subjects experiencing such events compared to the arthrodesis group. This PT category is Implant Site Pain (10.5% vs 0%). Specifically, a higher percentage of Cartiva SCI device subjects had treatment emergent adverse events considered as serious and involved pain. As stated previously, the correlation between subjects with high rates of pain measured as SAEs and primary outcome measures for device effectiveness were seen in 8 out of 16 subjects with device related pain events that were counted as overall successes.

Similar to the All Adverse Events table (Table 14), there were two PT categories where the number of subjects experiencing a TEAE was greater in the control group: Fracture Non-union (4.0% vs 0%) and Medical Device Complications (8.0% vs 0%).

For the SOC category "General Disorders and Administration Site Conditions", there was a greater percentage of Cartiva SCI device subjects (13.8% vs 2.0%) who experienced "General Disorders and Administration Site Conditions" TEAEs. The PT categories under this SOC category shows that there are a greater percentage of Cartiva SCI device subjects whom experienced Implant Site Pain (10.5% vs 0%), and Implant Site Swelling (1.3% vs 0%).

Adverse Events Requiring Secondary Surgical Intervention

Secondary surgical procedures (SSSIs) were defined in the protocol and were considered any operation at the treated joint. SSSIs were documented to include revisions, removals, reoperation, and/or supplemental fixations over a 24 month follow-up period. The definitions for SSSIs were applied as outlined in the FDA's Guidance document, "Guidance for Industry and FDA Staff: Clinical Data Presentations for Orthopedic Device Applications".

SSSIs were analyzed as to whether or not, for example, a secondary surgical procedure was required to treat non-unions and to remove broken hardware in arthrodesis subjects or to address mechanical failure, device fracture, or device dislodgement in Cartiva SCI device subjects.

There was a total of 23 (23/202; 11%) subjects who underwent an SSSI, with a similar incidence between groups (11% Cartiva and 12% arthrodesis). A total of 14 (9.2%) Cartiva subjects and 4 (8%) arthrodesis subjects had the implant and/or hardware removed during the course of the study. A total of 17 Cartiva subjects and 6 arthrodesis subjects had an SSSI defined by the protocol.

Table 18: Secondary Subsequent Surgical Interventions through 24 months

SSSI	**Cartiva Roll-In (n=22)**	**Cartiva Randomized (n=130)**	**Cartiva Total (n=152)**	**Arthrodesis (n=50)**
Removal	4 (18.2%)	10 (7.7%)	14 (9.2%)	4 (8%)
Reoperation	0	1 (0.8%)	1 (0.7%)	0
Revision	0	1 (0.8%)	1 (0.7%)	3 (6%)
Supplemental Fixation	0	1 (0.8%)	1 (0.7%)	0
Overall	**4 (18.2%)**	**13 (10.0%)**	**17 (11.2%)**	**6[1] (12.0%)**

[1]One arthrodesis subject had a revision at 6 weeks and a removal of the remaining hardware at 1 year.

The median time to SSSI was 157 days in the arthrodesis group and 364 days in the Cartiva SCI device group, or approximately 6 months and 1 year respectively.

Among subjects that underwent SSSI, arthrodesis subjects had less pain and greater function. For three arthrodesis subjects, all at site 2, the reason for the procedure was listed as "Hardware removed as an elective procedure, no failure or dislocation." While the two groups experienced similar rates of SSSI, the types of procedures differed between the Cartiva SCI device and arthrodesis subjects. In the Cartiva SCI group, device removal and conversion to arthrodesis was the predominant SSSI, whereas arthrodesis subjects having an SSSI were either revision of the fusion construct or removal of prominent hardware.

Table 19: Pain and Function Scores for Subjects That Had SSSI Events

Time point	**Cartiva (n=13)**		**Arthrodesis (n=6)**	
	VAS	**FAAM ADL**	**VAS**	**FAAM ADL**
Baseline	71	59	72	56
3 months	39	65	9	84
6 months	50	70	4	85
1 year	40	70	7	94
2 years	12	87	4	96

Device Related Adverse Events

From the analysis, there were a 7% greater number of Cartiva SCI device patients who experienced device-related events than control subjects (15.1% Cartiva SCI device vs 8% arthrodesis). The majority of these events were attributed to device pain (Implant Site Pain 10.5% vs 0%). Implant site pain by PT as a TEAE was 10% greater in the Cartiva SCI device group than in the control group.

As shown in the table below, there were 31 Cartiva SCI device patients and 4 arthrodesis patients who had adverse events classified as device-related adverse event over 24 months. Table 20 below outlines those serious adverse events further considered by the sponsor as device related. The majority of these serious device related adverse event are attributed to the Cartiva device under the PT of Implant Site Pain (10.5% vs 0%).

Table 20: Device Related Adverse Events by Treatment Group

Device Related	Cartiva (N = 152)			Fusion (N = 50)		
	Events	**Subjects**	**%**	**Events**	**Subjects**	**%**
All Device Related Events	31	23	15.1%	4	4	8.0%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	22	18	11.8%	0	0	0.0%
Implant site pain	18	16	10.5%	0	0	0.0%
Implant site cyst	1	1	0.7%	0	0	0.0%
Implant site induration	1	1	0.7%	0	0	0.0%
Implant site swelling	2	2	1.3%	0	0	0.0%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	7	7	4.6%	4	4	8.0%
Device breakage	0	0	0.0%	1	1	2.0%
Device migration	1	1	0.7%	0	0	0.0%
Medical device complication	0	0	0.0%	1	1	2.0%
Medical device pain	6	6	3.9%	2	2	4.0%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2	2	1.3%	0	0	0.0%
Joint stiffness	1	1	0.7%	0	0	0.0%
Tendonitis	1	1	0.7%	0	0	0.0%

Note: The verbatim event term for the event device migration in the Cartiva group indicated the device shifted within the implant cavity. The device did not migrate outside of the cavity or dislodge the cavity or joint. This event was not observed by the independent radiographic reviewer and did not correlate to any independent radiographic findings.

Table 21 provides the actual counts of specific events by time of onset. The reported adverse events were distributed throughout the course of the study up to 24 months. No additional clinically important trends in adverse event occurrence were demonstrated by the data.

Table 21: Device Related Adverse Events by Time of Occurrence and Treatment Group

TEAE Related	Preferred Term	Op		Discharge-2 wks		2-6 wks		6 wks - 3 mo		3 mo – 6 mo		6 mo – 12 mo		12 mo – 24 mo	
		C N=152 x (%)	A N=50 x (%)	C N=152 x (%)	A N=50 x (%)	C N=152 x (%)	A N=50 x (%)	C N=152 x (%)	A N=50 x (%)	C N=151 x (%)	A N=50 x (%)	C N=151 x (%)	A N=50 x (%)	C N=151 x (%)	A N=50 x (%)
Device	Implant Site swelling	1 (0.66)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.66)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
	Med. Device Complication	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1[1] (2.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
	Med. Device Pain	1 (0.66)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1[1] (0.66)	0 (0.00)	2[2] (1.32)	2[2] (4.00)	2 (1.32)	0 (0.00)
	Implant Site Pain	0 (0.00)	0 (0.00)	1 (0.66)	0 (0.00)	2[2] (1.32)	0 (0.00)	4[2] (1.97)	0 (0.00)	6[2] (3.97)	0 (0.00)	5[2] (3.31)	0 (0.00)	0 (0.00)	0 (0.00)
	Joint Stiffness	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.66)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
	Device Breakage	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (2.00)	0 (0.00)	0 (0.00)
	Device Migration	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1[3] (0.66)	0 (0.00)	0 (0.00)	0 (0.00)
	Tendonitis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.66)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
	Implant Site Cyst	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.66)	0 (0.00)
	Implant Site Induration	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.66)	0 (0.00)
	Total	**2 (1.32)**	**0 (0.00)**	**1 (0.66)**	**0 (0.00)**	**2 (1.32)**	**1 (2.00)**	**5 (3.29)**	**0 (0.00)**	**9 (5.96)**	**0 (0.00)**	**8 (5.30)**	**3 (6.00)**	**4 (2.65)**	**0 (0.00)**

[1]Event led to or was a Safety Secondary Surgical Intervention (SSSI).
[2]At least one event led to a Safety Secondary Surgical Intervention (SSSI).
[3]This isolated local radiographic finding after revision surgery was not correlated with any additional clinical presentation or symptomatology. The subject continued the study without incident.

Effectiveness

The primary efficacy of the Cartiva SCI device, which is based on the primary endpoint of the MOTION study, is discussed below. As shown in the following sections, Cartiva SCI device was shown to be statistically non-inferior compared to arthrodesis when using a 15% non-inferiority margin.

Pre-Specified Analysis Primary Composite Endpoint

The pre-specified analysis of effectiveness defined in the protocol was based on the ITT cohort which was comprised of all 197 randomized subjects (132 Cartiva SCI device subjects, and 65 arthrodesis subjects), but there were a large number of subjects that were randomized but not treated. Using the pre-specified method of analyzing missing data would have considered all randomized but not treated subjects, which includes 23% of control subjects and 2% of treatment subjects, as failures. It was agreed with the sponsor that this was inappropriate. While multiple imputation and other analyses were explored, it was agreed to focus on the mITT analysis for the primary analysis.

Assessment of the primary endpoint in the mITT cohort demonstrated a lower bound for the 95% one-sided confidence bound of the composite success rate of -10.50%, which supported the non-inferiority determination. Assessments in the per protocol cohort, multiple imputation analysis to address missing data, and tipping point assessment of missing data also demonstrated non-inferiority using a 15% margin. Subjects enrolled at all sites were comparable and a statistical analysis of the efficacy results for the primary endpoint demonstrated the results were poolable across the 12 study sites and across the two countries.

Table 22: Primary Endpoint Analysis

	Cartiva			Arthrodesis			Non-inferiority LB 95% CI[1]
	N	n	%	N	n	%	
mITT	130	104	80.0%	50	40	80.0%	-0.1050

[1]The lower 95% one-sided confidence interval of the difference must be greater than -15%.

Revised, FDA Requested Analysis Primary Composite Endpoint

Following review of the PMA data, FDA requested a revised composite primary endpoint assessment to further understand the safety and effectiveness of the Cartiva SCI device (Table 23). The sponsor concurred with FDA's requested endpoint modifications, which are the focus of the primary endpoint analyses presented in this SSED.

Table 23: Revisions to the MOTION Study Pre-Specified Primary Endpoint

Composite Prong	Pre-specified Primary Endpoint	Revised Primary Endpoint
Pain	Improvement (decrease) from baseline in VAS Pain of ≥30% at 12 months	Improvement (decrease) from baseline in VAS Pain of ≥30% at 24 months
Function	Maintenance of function from baseline based on the FAAM Sports score (inclusive of decrease <9) at 12 months	Maintenance of function from baseline based on the FAAM ADL score (inclusive of decrease <8) at 24 months
Safety	Freedom from major complications and SSSIs through 24 months	Freedom from major complications and SSSIs through 24 months

Table 24 presents a summary of the Cartiva SCI device and arthrodesis subjects who met the FDA-requested, revised primary composite endpoint at the 24-month time point. As requested by the FDA, the mITT cohort was designated to be the primary analysis cohort for this assessment due to an imbalance between treatment groups of subjects who dropped out of the study following randomization.

Table 24: Revised Primary Composite Endpoint at 24-Months

	Cartiva			Arthrodesis			Non-Inferiority LB 95% CI[1]
	N	n	%	N	n	%	
mITT Completers	129	103	79.8%	47	37	78.7%	-0.1029

[1]The lower 95% one-sided confidence interval of the difference must be greater than -15%.

The results of the revised primary composite endpoint in the mITT population demonstrate non-inferiority of Cartiva SCI device to arthrodesis based on this multi-pronged endpoint which includes clinically significant measures of pain, function, and safety (noting that the lower bound of the one-sided 95% Confidence Interval (CI) being greater than the pre-specified non-inferiority margin of 0.15). Nearly 80% of the Cartiva SCI device subjects and nearly 79% of the arthrodesis subjects met the revised primary composite endpoint at 24 months in the primary analysis (mITT) cohort.

Primary Endpoint Missing Data Analysis

At the 24-month follow-up visit, there were only 4 subjects in the mITT cohort who had an endpoint assessment missing at this time point (1 Cartiva SCI device and 3 arthrodesis). An assessment of missing data is presented in Table 25.

Table 25: Missing Data Assessment for Revised Primary Composite Endpoint

Analysis	Number and Percentage Achieving Month 24 Composite Clinical Success						Non-Inferiority LB 95% CI
	Cartiva			Arthrodesis			
	N	n	%	N	n	%	
Primary Analysis (mITT)	129	103	79.8%	47	37	78.7%	-0.1029
All Missing Data = Failures	130	103	79.2%	50	37	74.0%	-0.0653
All Missing Data = Successes	130	104	80.0%	50	40	80.0%	-0.1158
"Best Case" for Cartiva	130	104	80.0%	50	37	74.0%	-0.0572
"Worst Case" for Cartiva	130	103	79.2%	50	40	80.0%	-0.1176

Note: The lower 95% one-sided confidence interval of the difference must be greater than -15%.

As the amount of data missing in the MOTION study is low, the results of the revised primary endpoint are robust with regard to missing data. All missing data assessments meet the *a priori* analysis criteria of the lower bound of the 95% confidence interval (including the worst case for the Cartiva SCI device), indicating that the non-inferiority assessment is robust with regard to missing data.

With the worst case for the Cartiva SCI device (all three missing arthrodesis subjects as successes and the single missing Cartiva SCI device subject as a failure), the lower bound of the 95% confidence interval is -0.1176, which meets the pre-specified non-inferiority margin.

Primary Endpoint per Protocol Analysis

Per Protocol (PP)

The MOTION study per protocol analysis is an assessment of the primary safety and efficacy analysis taking into consideration disqualifying protocol deviations. The Medical Monitor, blinded to the study data, evaluated the types of protocol deviations that could have an impact on the primary endpoint per ICH guidelines and determined which type of protocol deviations would be minor or major. The Medical Monitor considered major protocol deviations to be only those events that would have an impact on the assessment of safety and effectiveness at the 24-month endpoint. Only two of the deviations were considered major deviations and were for patients who had their 24-month follow-up visit outside of the 2-month window in FDA guidance. As the data for these subjects would not satisfactorily represent a 24-month time point, they were excluded in the per protocol analysis (PP) that was conducted as part of the PMA submission.

In this analysis, the overall success of the Cartiva SCI device was 101/127 (79.5%) and arthrodesis was 37/47 (78.7%). These results indicate non-inferiority of the Cartiva SCI device to arthrodesis on the composite endpoint. Following a supplemental review of protocol violations by the Agency, the use of a revised definition of a protocol violation for exclusion from the per protocol cohort did not lead to a substantial change in the overall analysis result.

Table 26: Revised Primary Endpoint at 24-Months (PP*)

Population	Cartiva			Arthrodesis			LB 95% CI
	N	n	%	N	n	%	
PP1 Analysis	127	101	79.5%	47	37	78.7%	-0.1065

* Per Protocol = all randomized subjects who received the treatment to which they were randomized with subjects having major inclusion/exclusion deviations excluded. Excludes two Cartiva subjects.

Individual Components of the Revised Primary Composite Endpoint

A composite endpoint allows the comparison of a combination of clinically meaningful assessments between two treatment groups in a single endpoint. All components of the MOTION study primary endpoint were based on categories widely accepted in the literature as clinically meaningful improvements/differences between pre and post-

treatment. Each component is valid for what it measured, and subjects were required to demonstrate clinically meaningful performance in all categories to be ruled as a success.

An evaluation of the individual components of the revised endpoint was also performed. Pain success is defined as Pain VAS improvement of at least 30% relative to baseline. Function success was defined as maintenance of function per Foot and Ankle Ability Measure (FAAM) ADL that was defined as no more than an 8-point reduction relative to baseline. Success regarding the freedom from SSSI was defined as the absence of revisions, removals, reoperations, or supplemental fixations. Assessment of the radiographic component of the composite endpoint is necessarily different between groups to allow for capturing information regarding the distinct potential failure modes of the Cartiva SCI device and arthrodesis treatments. However, both definitions of radiographic success are consistent with the types of radiographic events observed for these types of devices that demonstrate a need for future intervention or device malfunction.

Table 27 demonstrates that both treatments had very high responder rates for each component of the primary composite endpoint.

Table 27: Revised Endpoint Components at 24 Months (mITT Cohort)

	Cartiva			**Arthrodesis**		
	N	**n**	**%**	**N**	**n**	**%**
Pain VAS Improvement of ≥ 30 % compared to baseline	116	103	**88.8%**	41	40	**97.6%**
FAAM ADL Maintenance of function from baseline	115	113	**98.3%**	41	40	**97.6%**
Radiographic • For Cartiva: absence of displacement, fragmentation, AVN • For arthrodesis: absence of malunion, nonunion, or hardware fracture	130	130	**100.0%**	50	45	**90.0%**
Freedom from SSSI Absence of revisions, removals, reoperations, supplemental fixation	130	117	**90.0%**	50	44	**88.0%**
Revised Composite Endpoint	129	103	**79.8%**	47	37	**78.7%**

Note: Variations in subject numbers per line item are based on subjects with available data at 24 months. Clinical outcomes (Pain VAS and FAAM ADL) are censored for subjects having any SSSI of reoperation, revision, removal or supplemental fixation.

When each component of the revised composite endpoint is considered separately, the results demonstrate both clinical and radiographic success for the Cartiva SCI device subjects through 24 months post-operatively. With regard to pain relief, nearly 89% of the Cartiva SCI device population experienced a clinically significant decrease in their pain, compared to 97% of the arthrodesis population, for those subjects reaching the 24-month endpoint without an SSSI. In the arthrodesis population, subjects experienced significantly better pain reduction, even though the overall composite endpoint results were non-inferior. However, in the arthrodesis population pain relief required sacrifice of first metatarsophalangeal joint motion. In contrast, the Cartiva SCI device population maintained first metatarsophalangeal joint motion and over 98% of the Cartiva SCI device population maintained or improved their function (as measured by FAAM ADL scores).

Radiographic Endpoints

Radiographic assessments, as utilized in the safety component of the composite primary endpoint, were performed at 24 months by an independent review of plain radiographs. Plain radiographs allowed for the assessment of abnormal bone formation at the arthrodesis site, no bone formation, or hardware fracture in arthrodesis subjects and loss of implant integrity with the Cartiva SCI device.

Qualitative evaluations included heterotopic ossification (HO), radiolucency, bony fractures, avascular necrosis (AVN), adverse bony reactions, device displacement, arthrodesis status, device integrity, and additional observations.

Due to the differences in the intended mechanism of action of the Cartiva SCI device and arthrodesis, the two groups were examined for different radiographic outcomes as part of a safety endpoint that also served as one component of the single composite primary endpoint. The Cartiva SCI device subjects were deemed as failures if there was device displacement, device fragmentation, and/or development of avascular necrosis, whereas the arthrodesis subjects were deemed as failures if there was mal-union, non-union, and/or hardware failure.

The independent examination of the radiographs did not determine any Cartiva SCI device subjects to be radiographic failures, and the independent examination determined that 5 (10%) of the arthrodesis subjects were radiographic failures. Table 28 below summarizes the radiographic findings.

Table 28: All Radiographic Findings

Radiographic Finding	Cartiva® SCI mITT (n=130)		Cartiva SCI Safety (n=152)		Arthrodesis (n=50)	
	n	%	n	%	n	%
Radiographic Failure Modalities in Primary Endpoint						
Avascular Necrosis	0	0.0%	0	0.0%	0	0.0%
Device Displacement	0	0.0%	0	0.0%	--	--
Device Fragmentation	0	0.0%	0	0.0%	--	--
Non Union	--	--	--	--	4	8.0%
Mal Union	--	--	--	--	0	0.0%
Fractured Hardware	--	--	--	--	1	2.0%
Other Radiographic Findings						
Radiolucency (any)	5	3.8%	6	3.9%	6	12.0%
Bony Fracture	1	0.8%	1	0.7%	1	2.0%
Bony Reaction	64	49.2%	75	49.3%	3	6.0%
Heterotopic Ossification	75	57.7%	89	58.6%	24	48.0%
Bony Reactions and/or Heterotopic Ossification						
Bony Reaction Only	25	19.2%	28	18.4%	1	2.0%
Heterotopic Ossification Only	36	27.7%	42	27.6%	22	44.0%
Bony Reaction + Heterotopic Ossification	39	30.0%	47	30.9%	2	4.0%
Any Bony Reaction or Heterotopic Ossification	100	76.9%	117	77.0%	25	50.0%
No Bony Reaction or Heterotopic	30	23.1%	35	23.0%	25	50.0%

The Cartiva group had higher rates of bony reactions (Cartiva, 49%; arthrodesis, 6%) and Class 1-3 Heterotopic Ossification (Cartiva, 53%, and arthrodesis, 4%). Note that Class 4 Heterotopic Ossification is not unexpected in arthrodesis subjects. There is no evidence within the study that the radiographic findings cited above led to poor outcomes. These observations were explored, as reported below.

Types of Bony Reactions

In Table 28 above, various types and severities of bony reactions are grouped together. However, only the most extreme bony reactions represent a concern. The Agency is specifically concerned with osteolysis.

Table 29: Incidence of Bony Reactions

Bony Reaction	Cartiva SCI MITT (n=130)		Cartiva SCI Safety (n=152)		Arthrodesis (n=50)	
	n	%	n	%	n	%
Erosion	2	1.5%	3	2.0%	0	0.0%
Cystic Changes	26	20.0%	30	19.7%	0	0.0%
Loss of Cortical White	35	26.9%	40	26.3%	0	0.0%
Osteolysis	2	1.5%	3	2.0%	3	6.0%
Any Bony Reaction[1]	**64**	**49.2%**	**75**	**49.3%**	**3**	**6.0%**
No Bony Reaction	**66**	**50.8%**	**77**	**50.7%**	**47**	**94.0%**

[1]Subject had both loss of cortical white and osteolysis at different time points.

If all osteolysis subjects are considered failures, then two Cartiva successes would be considered failures. As two of the arthrodesis subjects were already failures, then only one additional arthrodesis subject would be considered a failure. This would lead to a lower bound of the non-inferiority confidence interval of -10.1% for the analysis of bony reactions.

Heterotopic Ossification

The independent core lab, Medical Metrics, Inc., provided qualitative measurements of heterotopic ossification via independent radiographic review using the following categories:

- **None**: No evidence heterotopic bone formation
- **Class 1**: Islands of bone within the soft tissue about the MTP joint
- **Class 2**: Bone spurs contiguous with the distal first metatarsal, proximal phalanx of the great toe or sesamoid bones which do not contact or nearly contact adjacent bones or bone spurs.
- **Class 3**: Bone spurs from the distal first metatarsal, proximal phalanx of the great toe or sesamoid bones which contact or nearly contact each other but do not appear fused
- **Class 4**: Apparent bone ankylosis of the MTP joint

The Agency was concerned with classes 3 and 4 of heterotopic ossification. An analysis was performed to assess the impact of heterotopic ossification on success. The presence of heterotopic ossification did not demonstrate a correlation with success or failure.

Table 30: Incidence of Heterotopic Ossification

Heterotopic Ossification	Cartiva SCI Randomized (n=130)		Cartiva SCI Safety (n=152)		Fusion (n=50)	
	n	%	n	%	n	%
Class 1	21	16.2%	29	19.1%	1	2.0%
Class 2	63	48.5%	70	46.1%	1	2.0%
Class 3	11	8.5%	13	8.6%	0	0.0%
Class 4	0	0.0%	0	0.0%	22	44.0%
Any Heterotopic Ossification	**75***	**57.7%**	**89***	**58.6%**	**23**	**46.0%**
No Heterotopic Ossification	**55**	**42.3%**	**63**	**41.4%**	**27**	**54.0%**

*19 Cartiva subjects had different grades of heterotopic ossification at different time points.

Subjects Considered as Study Failures Based on Radiographic Findings

Table 31: Pain and Function scores for Control (Arthrodesis) subjects that were radiographic failures only

Subject*	Reason for Failure	VAS			FAAM ADL		
		6 months	1 year	2 year	6 months	1 year	2 years
1	Non-union	75	2	0	56	81	95
2	Device fracture	0	0	0	100	100	100
3	Non-union	17	31	9	90	90	96

* Subject IDs were redacted throughout in order to protect patient privacy

There was no evidence within the 24-month study that the above radiographic findings led to poor overall outcomes, as they were not correlated with increases in pain or loss of function. Accordingly, the clinical relevance of the radiographic assessment criteria is uncertain.

The radiographic component of the primary endpoint was pre-specified, and it is typical in orthopedic studies to include this type of endpoint. Still, because of the difference in the application of this part of the composite endpoint, it is reasonable to look at a sensitivity analysis where this is not part of the primary endpoint.

Table 32: Sensitivity Analysis When Radiographic Criteria Are Removed From Primary Endpoint

Analysis Group	Cartiva	Arthrodesis	Lower Bound of one-sided 95% Confidence Interval
Primary - Completers	103/129 (79.8%)	40/47 (85.1%)	-15.6%

Secondary Effectiveness Analyses

Assessment of secondary effectiveness endpoints was done by a repeated measures analysis of variance with independent variables of treatment, study visit, and treatment by visit interaction. If either the treatment or treatment by visit interaction were statistically significant, this would provide evidence of a treatment effect. Each secondary variable was tested in order with additional analyses of the means at each follow-up visit by two-sample unpaired t-test of the difference from baseline. The pre-specified order of the secondary endpoints was as follows:

1. VAS Pain Scores
2. FAAM Activities of Daily Living Scores
3. Active MTP Peak Dorsiflexion
4. Patient Global Assessment
5. Investigator Global Assessment
6. SF-36 Physical Functioning Scale
7. Foot Function Index-Revised (FFI-R)

In addition to complying with the pre-specified order, all hypotheses were tested with P-values ranked, and statistical significance was assessed using the Hochberg step down approach[8].

Since statistical significance was not demonstrated (P>0.9999) for superiority of the Cartiva treatment group to arthrodesis for the first secondary endpoint to be assessed, VAS pain scores, all remaining tests of secondary hypotheses were considered exploratory.

VAS Pain

Both Cartiva and arthrodesis cohorts demonstrated a decrease (improvement) in VAS Pain scores at Week 2 which continued to decline through Month 24. The box plot below shows the median (middle line), mean (diamond), and range (top and bottom lines) of pain scores for both groups (Figure 3).

[8] Hochberg Y, A Sharper Bonferroni Procedure for Multiple Tests of Significance. Biometrika. 1988; 75; 4; 800-802

Figure 3: Cartiva and Arthrodesis mITT Completers- VAS Pain Scores over Time[9]

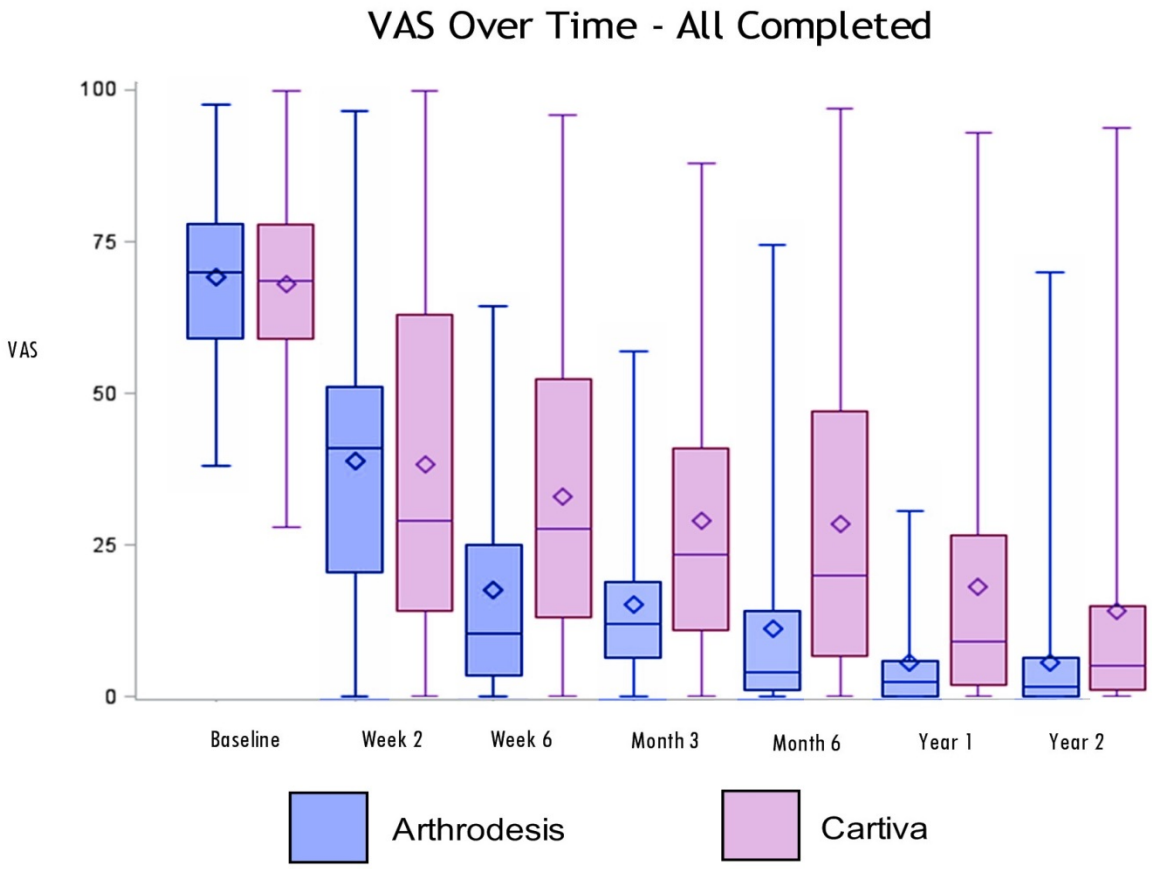


Table 33 shows the responder rate for VAS, where a responder is defined as a 30% reduction in pain. By 3 months, the arthrodesis group has a responder rate of 94%, which it maintains through 2 years. The Cartiva SCI device group nears a 90% responder rate at 1 and 2 years. On the right is the confidence interval for the difference between the two groups, where a negative difference means the arthrodesis group had a greater reduction in pain than the Cartiva SCI device group. If the confidence interval does not include 0, this represents a significant difference. At the pre-specified time point of 1 year, there is a significant difference. Also, please note that some subjects may continue to experience pain, in spite of being responders in this analysis. For example, one responder at 24-months had a VAS of 60. There were 6 Cartiva subjects and 0 arthrodesis subjects that were VAS responders and overall successes but had 24-month VAS rates over 30.

[9] median (middle line), mean (diamond), and range (top and bottom lines)

Table 33: VAS Responder Analysis for Pain over Time – mITT Completers

Time Point	Cartiva	Arthrodesis	Difference (C-A)	95% Conf. Interval
2 weeks	84/130 (65%)	32/49 (65%)	-0.7	(-14%, 12%)
6 weeks	90/129 (70%)	44/48 (92%)	-22%	(-31%, -13%)
3 months	102/130 (78%)	46/48 (96%)	-17%	(-25%, -10%)
6 months	91/126 (72%)	44/46 (96%)	-24%	(-32%, -15%)
1 year	115/130 (88%)	47/47 (100%)	-12%	(-16%, -7%)
2 years	114/128 (89%)	46/47 (98%)	-9%	(-15%, -3%)

Table 34 shows the change from baseline in Pain VAS. Both groups experienced large improvements in pain from baseline. The improvement from baseline was higher in the arthrodesis group at every time point. Cartiva failed to show a statistically significant improvement in comparison to arthrodesis at the pre-specified time point of 1 year. Instead, the improvement from baseline in the arthrodesis group was significantly greater than the improvement in the Cartiva group.

Table 34: Mean Improvement from Baseline over Time – mITT Completers

Time Point	Cartiva	Arthrodesis	Difference (C-A)	95% Conf. Interval
2 weeks	30	30	-0.8	(-11, 9)
6 weeks	35	52	-17	(-26, -8)
3 months	39	54	-15	(-24, -7)
6 months	39	58	-19	(-28, -9)
1 year	50	63	-13	(-21, -5)
2 years	53	63	-10	(-18, -1)

Foot and Ankle Ability (FAAM)

To be a responder for this endpoint the requirement was not to get worse by either 8 or 9 points, depending on which scale is used. The reason that improvement was not necessary to be a responder is that some subjects began the study with quite high functional scores. Given these definitions of a responder, the responder rates were near 100% for both groups at both 1 and 2 years.

The confidence intervals at the primary time point of 1 year do not include 0, but the differences in the responder rates are small and are similar for both measures of function

Table 35: FAAM Sports and ADL at 1 and 2 years

FAAM	Time Point	Cartiva	Arthrodesis	Difference (C-A)	95% Conf. Interval
Sports	1 year	122/126 (97%)	47/47 (100%)	-3%	(-6%, -0.01%)
	2 years	117/123 (95%)	46/47 (98%)	-3%	(-7%, 2%)
ADL	1 year	124/128 (97%)	47/47 (100%)	-3%	(-6%, -0.01%)
	2 years	124/127 (98%)	46/47 (98%)	-0.2%	(-4%, 4%)

The results, as seen in the next two sections, are similar for both measures of function.

Foot and Ankle Ability Measure Activities of Daily Living Score (FAAM ADL)
Both the Cartiva SCI device and arthrodesis subjects exhibited a marked functional improvement, as measured by FAAM ADL. Figure 4 presents box plots for FAAM ADL over time, with higher functional scores indicating improvement in patient function, with a maximum score of 100. The functional scores in both groups are lower at Week 2, while at Week 6, the Cartiva SCI device group demonstrated higher functional scores. Arthrodesis subjects were required to wear a boot through about Week 6. The functional benefit of Cartiva compared to arthrodesis is limited to this initial 2-month period. By month 3, both two groups demonstrate similar functional scores, and at Month 6 and Year 1, the arthrodesis group demonstrated higher functional scores.

Figure 4 Cartiva and Arthrodesis mITT Completers - FAAM ADL Scores over Time[9]

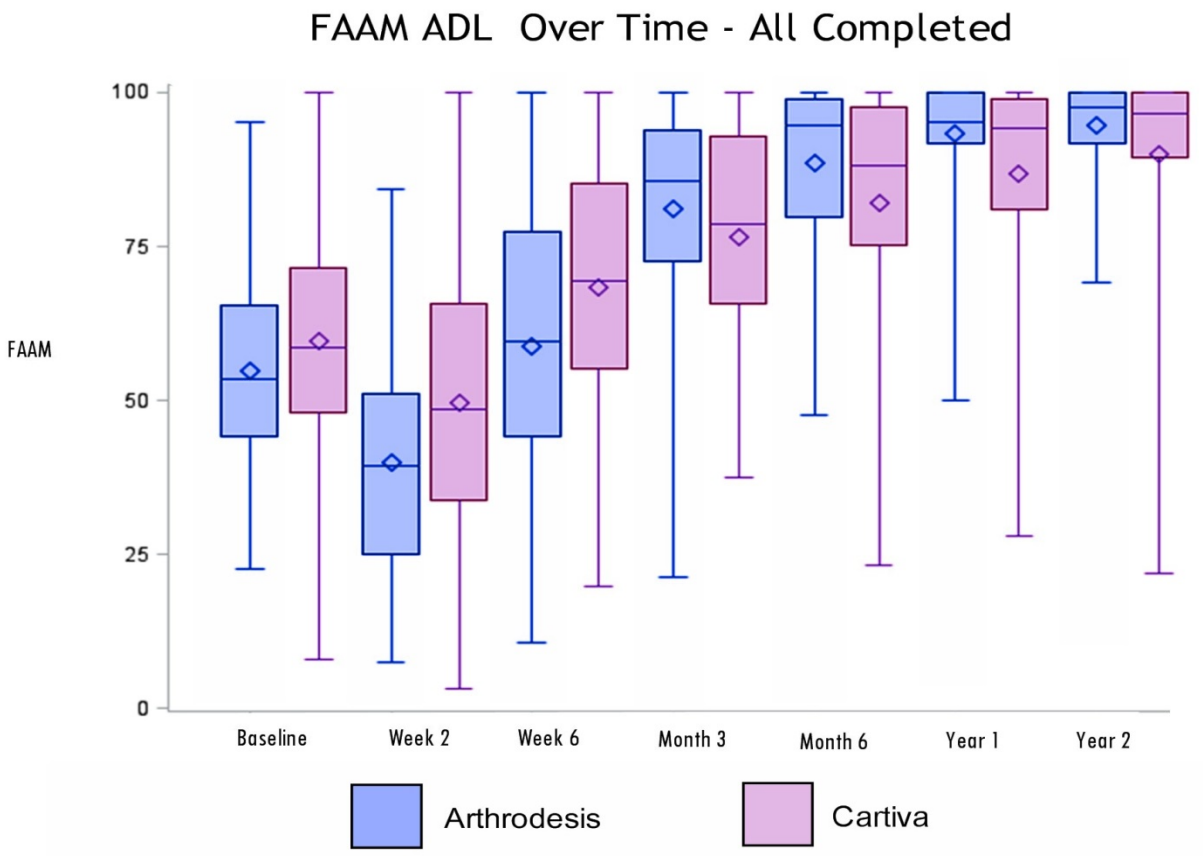


Table 36 shows the change from baseline for FAAM ADL. Again, both groups saw large improvements from baseline. The Cartiva SCI device group demonstrated higher functional scores compared to arthrodesis through 6 weeks, while arthrodesis demonstrated higher functional scores compared to the Cartiva SCI device group at 3 months to 2 years.

Table 36 Cartiva and Arthrodesis mITT Completers – Change in FAAM ADL over Time

Time Point	Cartiva	Arthrodesis	Difference (C-A)	95% Conf. Interval
2 weeks	-11	-16	5	(-2, 13)
6 weeks	10	3	6	(-0.6, 13)
3 months	17	26	-9	(-14, -3)
6 months	23	32	-9	(-15, -2)
1 year	28	38	-10	(-16, -3)
2 years	31	38	-7	(-14, -1)

The FAAM ADL questionnaire is made up of 21 questions, many of which are only slightly different from the questions included below in Table 37 (i.e. walking for 10 minutes, walking uphill, etc.). Of the 21 activities in the survey, only for "Up on Toes" was there a higher percentage of subjects that had "No Difficulty" in the Cartiva SCI device group than in the arthrodesis group.

Table 37: FAAM ADL Questionnaire Excerpt

Question	Group	No Difficulty	Slight Difficulty	Moderate Difficulty	Extreme Difficulty	Unable to Do
Daily Activities	Arth.	94%	6%	0%	0%	0%
	Cart.	88%	10%	0%	2%	0%
Walk 15 Min	Arth.	85%	13%	0%	0%	0%
	Cart.	67%	17%	9%	5%	2%
Upstairs	Arth.	87%	13%	0%	0%	0%
	Cart.	83%	10%	4%	2%	0%
Up on Toes	Arth.	36%	28%	17%	9%	11%
	Cart.	37%	33%	15%	7%	9%
Squat	Arth.	70%	21%	6%	2%	0%
	Cart.	57%	18%	11%	6%	2%

Foot and Ankle Ability Measure (FAAM) Sports Score

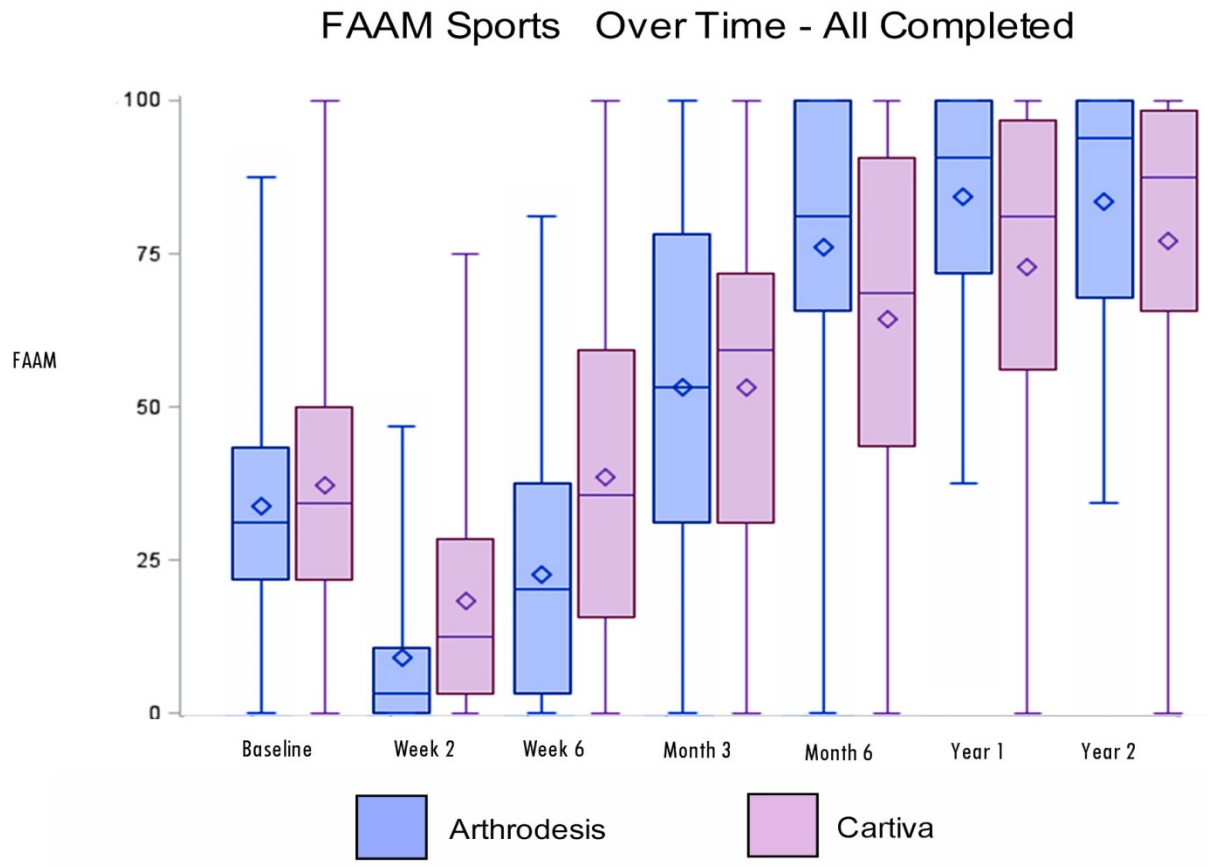
The FAAM Sports subscale was used to assess functional outcomes related to a subject's ability to perform sports activities, such as running, jumping, cutting/lateral movements, and ability to participate in desired sports. For FAAM Sports, functional improvement in

sports activities was based on the clinically meaningful difference (9 points), with higher FAAM Sports scores indicating an increase in function.

The median FAAM Sports scores for the Cartiva SCI device and arthrodesis mITT subjects show both cohorts experienced improved function.

Figure 5 presents the box plots for FAAM Sports Scores over time. Again, higher functional scores represent improved function. For this endpoint, baseline scores ranged from 0 to 100. There is a very similar pattern for FAAM Sports Scores over time as compared to FAAM ADL Scores. Function initially decreases in both groups, with the Cartiva SCI device demonstrating higher scores at early time points. Then both groups improve with arthrodesis demonstrating higher scores at the later time points.

Figure 5: Cartiva and Arthrodesis mITT Completers - FAAM Sports Scores over Time[9]



The change from baseline of FAAM Sports scores over time for mITT subjects is represented in Table 38. Both groups experienced initial declines in function followed by improvements from baseline. The Cartiva SCI device group demonstrated higher scores

than arthrodesis at 2 and 6 weeks while arthrodesis demonstrated higher scores than the Cartiva SCI device group at later time points, including the pre-specified time point of 1 year.

Table 38: Cartiva and Arthrodesis mITT Completers– Change in FAAM Sports over Time

Time Point	Cartiva	Arthrodesis	Difference (C-A)	95% Conf. Interval
2 weeks	-19	-28	9	(1.5, 16.6)
6 weeks	2	-13	15	(6, 24)
3 months	17	19	-1	(-9, 7)
6 months	28	41	-12	(-21, -3)
1 year	37	49	-12	(-21, -4)
2 years	41	48	-7	(-17, 2)

The FAAM Sports questionnaire is made up of 8 questions, of which 5 are shown in Table 39 below. None of these activities had a higher percentage of subjects that had "No Difficulty" in the Cartiva SCI device group compared to the arthrodesis group.

Table 39: FAAM Sports Questionnaire Excerpt

Question	Group	No Difficulty	Slight Difficulty	Moderate Difficulty	Extreme Difficulty	Unable to Do
Jumping	Arth.	45%	25%	21%	6%	2%
	Cart.	37%	21%	17%	10%	13%
Running	Arth.	45%	28%	15%	10%	2%
	Cart.	33%	25%	15%	12%	12%
Participate in Sport	Arth.	57%	19%	11%	6%	2%
	Cart.	40%	22%	19%	6%	8%
Normal Technique	Arth.	64%	32%	4%	0%	0%
	Cart.	58%	22%	13%	4%	2%
Low Impact	Arth.	89%	6%	4%	0%	0%
	Cart.	63%	21%	10%	5%	1%

Active Metatarsophalangeal (MTP) Joint Dorsiflexion

The sponsor also collected joint motion data for the Cartiva SCI device subjects and the angle at which the toe was fused for arthrodesis subjects over time. Active MTP dorsiflexion measurements were taken at all clinic visits using a goniometer. Measurements were taken with subjects standing and in a weight bearing position.

Both groups had a baseline peak dorsiflexion of about 23 degrees. The table shows the peak dorsiflexion change from baseline for all subjects. When subjects that were converted to arthrodesis are excluded, the Cartiva SCI device group increased their range of motion from baseline from 23 degrees to about 29 degrees, while arthrodesis subjects' had no range of motion, as was intended, because the joint was fused..

Table 40: Cartiva and Arthrodesis mITT Completers– Change from Baseline for Active MTP Dorsiflexion over Time

Time Point	Cartiva	Arthrodesis	Difference (C-A)	95% Conf. Interval
2 weeks	-2	-10	8	(5, 12)
6 weeks	2	-10	12	(8, 16)
3 months	4	-9	13	(9, 17)
6 months	5	-7	12	(8, 17)
1 year	6	-7	12	(8, 17)
2 years	5	-7	12	(8, 17)

Note that arthrodesis subjects did not have range of motion and the angle dorsiflexion reported is the fixed angle at which the joint was fused.

Arthrodesis is designed to eliminate range of motion, so it was expected that there would be differences in peak dorsiflexion. Not all the Cartiva SCI device subjects saw an increase in motion. In 26% of the Cartiva SCI device group, subjects experienced a decrease in range of motion over 2 years.

Revised Foot Function Index (FFI-R)

Outcomes were also assessed with the FFI-R. The FFI-R short-form includes a 34-item global assessment of foot functioning. It has sections asking about pain, stiffness, difficulty, activity limitation, and social issues.

There was a nominal difference in favor of arthrodesis from Week 2 to Month 24.

Table 41: Cartiva and Arthrodesis mITT Completers – Change from Baseline for FFI-R over Time

Time point	Cartiva	Arthrodesis	Difference (C-A)	95% Conf. Interval
2 weeks	9	15	-6	(-13, -2)
6 weeks	18	28	-9.4	(-16, -3)
3 months	22	30	-8	(-14, -2)
6 months	24	36	-12	(-19, -6)
1 year	30	40	-10	(-16, -4)
2 years	34	40	-6	(-12, -1)

Based on literature[10], a clinically important difference in the FFI-R total score was considered to be 5 points (with lower FFI-R scores indicating an increase in function).

Using this value, the strata for this assessment were defined as follows:

- Improvement: ≥5 point decrease from baseline
- Maintenance: <5 point decrease to <5 point increase from baseline
- Worsened: ≥5 point increase from baseline

The MOTION study results demonstrate functional improvements in a significant proportion of both the Cartiva SCI device and arthrodesis arms of the MOTION study. For the Cartiva SCI device arm, 94.8% achieved a clinically significant improvement in function as measured by FFI-R. Cartiva SCI device's outcomes compare favorably to the arthrodesis arm, which experienced a 95.1% improvement in FFI-R function.

SF-36 Physical Function Scores

The 10-item Physical Functioning (PF) scale captures both the presence and extent of physical limitations using a three-level response continuum. The Cartiva SCI device subjects performed much better at Week 6, but the later time points favored arthrodesis.

[10] Rao et al. Shoe Inserts Alter Plantar Loading and Function in Patients With Midfoot Arthritis. Journal of Orthopaedic & Sports Physical Therapy. 2009; 39; 7; 522-531

Table 42: Cartiva and Arthrodesis mITT Completers– Change from Baseline for SF-36 over Time

Time point	Cartiva	Arthrodesis	Difference (C-A)	95% Conf. Interval
6 weeks	8	-6	14	(5, 22)
3 months	15	21	-6	(-13, 2)
6 months	20	30	-10	(-19, -2)
1 year	25	33	-9	(-18, 0.4)
2 years	31	34	-3	(-11, 5)

The SF-36 physical function scores from the MOTION Study were also stratified by degree of improvement, with improvement, maintenance, slight declines, and deterioration in SF-36 scores defined as follows:

- Improvement ≥10 point increase from baseline
- Maintenance: ≥0 point increase from baseline.
- Slight Decline: 0-10 point decrease from baseline
- Deteriorated: ≥ 10 point decrease from baseline

These results demonstrate that a significant proportion of subjects in both the Cartiva SCI arm and arthrodesis arm maintained or improved their function as measured by the SF-36 physical function score. For the Cartiva SCI device arm, 94.0% maintained or improved their SF-36 score. Cartiva SCI device's outcomes compare favorably to the arthrodesis arm, which experienced a 92.7% rate of maintenance or improvement in SF-36 physical function score.

Patient Satisfaction and Overall Well Being

The subject global assessment asked the subject to consider his/her overall well-being since the beginning of the study and whether it has improved. Possible responses include: strongly agree, agree, neither agree nor disagree, disagree, and strongly disagree. Table 43 shows the percent of subjects that either agreed or strongly agreed. The percentage of subjects indicating strongly agree or agree in the arthrodesis group was higher at every time point from 6 weeks on.

Table 43: Patients' assessments of if their overall well-being has improved at each time point– Percent Agreed or Strongly Agreed – mITT Completers

Time point	Cartiva	Arthrodesis	Difference (C-A)	95% Conf. Interval
2 weeks	53/130 (41%)	15/48 (31%)	10%	(-4%, 34%)
6 weeks	68/129 (53%)	31/49 (63%)	-11%	(-24%, 3%)
3 months	86/130 (66%)	37/48 (77%)	-11%	(-23%, 1%)
6 months	85/126 (67%)	38/46 (83%)	-15%	(-27%, -4%)
1 year	97/130 (75%)	37/47 (79%)	-4%	(-16%, 8%)
2 years	94/128 (73%)	40/47 (85%)	-12%	(-22%, -1%)

The difference between the two groups was largest if looking at those that strongly agree.

- Strongly Agree at 12 months – Cartiva 33%, arthrodesis 53%
- Strongly Agree at 24 months – Cartiva 39%, arthrodesis 55%

The Investigators were also asked to rate the subject's overall well-being since the beginning of the study, and whether it has improved. They felt that more arthrodesis subjects had improved at 3 months, 6 months and 1 year, but the Investigators felt that there was little difference in the two groups at the early time points or at 2 years.

Table 44: Investigators' assessments of if their overall well-being has improved at each time point– Percent Agreed or Strongly Agreed – mITT Completers

Time point	Cartiva	Arthrodesis	Difference (C-A)	95% Conf. Interval
2 weeks	31/130 (24%)	11/50 (22%)	2%	(-10%, 13%)
6 weeks	57/129 (44%)	23/50 (46%)	-2%	(-16%, 12%)
3 months	70/130 (54%)	39/49 (80%)	-26%	(-38%,-14%)
6 months	79/126 (62%)	38/47 (81%)	-19%	(-30%,-6%)
1 year	98/130 (75%)	39/47 (83%)	-8%	(-19%, 3%)
2 years	107/127 (84%)	39/47 (83%)	1%	(-9%, 12%)

XI. 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 regulations. The pivotal clinical study included 49 investigators and/or sub-investigators of which none were full-time or part-time employees of the sponsor and 3 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None
- Significant payment of other sorts: 3
- Proprietary interest in the product tested held by the investigator: None
- Significant equity interest held by investigator in applicant of covered study: None

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XII. PANEL RECOMMENDATIONS

A. Panel Meeting Recommendation

At an advisory meeting held on April 20, 2016, the Orthopaedic and Rehabilitation Devices Panel voted 10-2 that there is reasonable assurance the device is safe, 9-3 that there is reasonable assurance that the device is effective, and 8-2 (2 abstentions) that the benefits of the device do outweigh the risks in subjects who meet the criteria specified in the proposed indication. The 24-hour Panel Summary is located at the following link:
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/OrthopaedicandRehabilitationDevicesPanel/UCM497187.pdf

B. FDA's Post Panel Meeting Action

Following the Panel meeting, the applicant worked with FDA to (1) develop a post-approval study to address the outstanding issues highlighted by the Panel, namely, the need for longer-term follow-up; and (2) to revise the indications for use statement to reflect the Panel's input regarding use of the device in patients with mild hallux valgus deformity and the absence of instability.

The applicant has adequately addressed the outstanding issues raised by the Panel relating to continued follow-up and modification of the Indications for Use of the device. FDA agrees with the applicant's response and has determined that the information the applicant has submitted to address the Panel's concerns is acceptable.

XIII. CONCLUSIONS DRAWN FROM THE PRECLINICAL AND CLINICAL STUDIES

The scientific evidence presented in the preceding sections provides reasonable assurance that the Cartiva SCI device is safe and effective for the treatment of painful degenerative or post-traumatic arthritis (hallux limitus or hallux rigidus) in the first metatarsophalangeal joint with or without the presence of mild hallux valgus.

A. SAFETY CONCLUSIONS

The risks of the Cartiva SCI device were evaluated with nonclinical laboratory studies as well as data collected in the randomized, controlled MOTION study conducted to support PMA approval as described above.

Preclinical testing performed on the device demonstrated that the Cartiva SCI device should withstand the expected physiologic loads in the first metatarsophalangeal joint, and the clinical study supports these findings; there were no occurrences or evidence of device breakages or fragmentation observed throughout the study population.

In the MOTION Study, the investigational Cartiva SCI device implanted in the first metatarsophalangeal joint was found to have a reasonable assurance of safety and to be at least as safe as the control treatment while preserving first metatarsophalangeal joint motion. Overall adverse event rates were similar between treatment groups, as were the rates of treatment-emergent adverse events. Device-related events occurred in 23 subjects in the Cartiva SCI device group (event rate of 15.1%) as compared to 4 arthrodesis subjects (8%). All Cartiva SCI device-related events were considered anticipated. A higher rate of procedure-related adverse events occurred in the arthrodesis group (36.0%) compared to the Cartiva SCI device group (33.6%). The overall serious device-related event rate was 7% for Cartiva SCI device and 4% for arthrodesis. Non-serious procedure or device-related events were well tolerated by Cartiva SCI device subjects. There were no Cartiva SCI device failures.

The rate of secondary surgeries in the Cartiva SCI device group and the arthrodesis control group were comparable. A total of 9.2% (14/152) Cartiva SCI device subjects and 10% (5/50) arthrodesis subjects had the implant and/or hardware removed during the course of the study. All Cartiva SCI device subjects that had the device removed were successfully converted to arthrodesis without event.

In conclusion, the safety profile of the Cartiva SCI device implanted in the first metatarsophalangeal joint demonstrates that the device has a reasonable assurance of safety and is at least as safe as the control in regards to adverse event rates and secondary surgeries.

B. EFFECTIVENESS CONCLUSIONS

In this study, subjects were enrolled, treated, and followed up through the 24-month post-operative visit. The sponsor had a satisfactory follow-up, with 99.2% of the Cartiva SCI device cohort and 94.0% of the control cohort having data available for analysis at the completion of the study for those subjects who were randomized and treated. Assessment of effectiveness was performed using the mITT and the per protocol populations. Statistical analysis demonstrated that the results from all sites were poolable to determine safety and effectiveness. Analysis of patient demographic and baseline data showed the Cartiva SCI device and arthrodesis groups to be comparable, and the sponsor demonstrated that the OUS study patients were generalizable to the US patient population.

To meet the primary effectiveness endpoint, individual subjects were considered a success if they 1) demonstrated a clinically significant (≥30%) reduction in pain; 2) demonstrated a maintenance of foot and ankle function from preoperative state; 3) experienced no subsequent secondary surgical interventions at the treated joint; and 4) experienced no pre-specified radiographic failure outcomes, defined differently for each treatment group (Cartiva SCI device subjects: avascular necrosis, device dislodgement, device fragmentation; arthrodesis subjects: non-union, malunion, hardware fracture).

For overall success, the proportion of success subjects in each group was determined and the difference (Cartiva SCI device minus arthrodesis) and one-sided 95% confidence interval for the difference between treatment groups was calculated. If the one-sided 95% lower confidence interval is greater than the equivalence limit (-15%), the primary endpoint will have been met. As expressed by the sponsor during pre-submission meetings, the ITT population would inherently favor the Cartiva arm given the number of subjects who withdrew after being randomized to arthrodesis. The ITT analysis was reviewed by the FDA, and, based on the same premise, FDA requested that all further analyses be based on the revised mITT cohort.

Table 45 presents a summary of the Cartiva SCI device and arthrodesis subjects who met the pre-specified and revised primary composite endpoint.

Table 45: MOTION Study Primary Composite Endpoint Analyses

	Cartiva		Arthrodesis		Non-inferiority LB 95% CI
	N	%	N	%	
Pre-Specified (VAS 12M+FAAM Sports 12 M + Safety 24 M)					
mITT[1]	130	**80.0%**	50	**80.0%**	**-0.1050**
FDA Requested (VAS 24M + FAAM ADL 24M + Safety 24M)					
mITT Completers[2]	129	**79.8%**	47	**78.7%**	**-0.1029**

[1]mITT cohort prospectively defined in the pre-specified endpoint analysis.
[2] All randomized subjects who received the treatment to which they were randomized and have 24M data available.

Results indicate non-inferiority of the composite endpoint based on the lower bound of the one-sided 95% confidence interval being greater than the pre-specified non-inferiority margin of -0.15 for the ITT, mITT, and Per Protocol populations. Nearly 80% of the Cartiva SCI device subjects and nearly 79% of the arthrodesis subjects met the revised primary composite endpoint at 24 months.

When each component of the composite endpoint is considered separately, the results demonstrate both clinical and radiographic success for the Cartiva subjects through 24 months post-operatively:

- **Pain:** Nearly 89% of the Cartiva SCI device population experienced a significant decrease in their pain. The control population experienced greater pain reduction in a larger percentage of subjects.
- **Function:** Over 98% of the Cartiva SCI device population maintained or improved their function (as demonstrated by FAAM ADL). Furthermore, 87.7% of the Cartiva SCI device subjects had a clinically significant increase in function (as demonstrated by FAAM ADL).
- **Radiographic outcomes:** 100% of the Cartiva SCI device subjects were radiographic successes. Specifically, none experienced device displacement, device fragmentation, or avascular necrosis. In addition to the pre-specified radiographic failure modes, other radiographic observations such as bony reactions and heterotopic ossification were collected to allow for assessment other radiographic findings that could possibly be indicative of device complications or treatment failure. These findings were compiled and reviewed and none were found to be clinically symptomatic in the first 24 months of follow-up.
- **Freedom from Subsequent Secondary Surgical Interventions (SSSI):** 90% of the Cartiva population did not need to undergo an SSSI.

Secondary endpoints measuring pain, function, and overall quality of life demonstrate that a large portion of the Cartiva SCI device subjects achieve a clinically significant improvement at 6 weeks to 3 months that persists to 24 months following surgery, although the improvement was larger for the arthrodesis group.

Through a subgroup analysis, there were no significant differences in clinical outcome.

This multi-center study used the same eligibility criteria at all sites and all sites followed the same study protocol. Subjects enrolled at all sites were comparable and a statistical analysis of the efficacy results for the primary endpoint demonstrated the results were poolable across the 12 study sites and across the two countries.

In conclusion, the clinical study data indicate that, at 24 months post-operatively, the Cartiva SCI device has a reasonable assurance of effectiveness for the treatment of arthritis of the first metatarsal phalangeal joint.

C. BENEFIT-RISK DETERMINATION

The probable benefits of the Cartiva SCI device are based on data collected in the clinical study conducted to support PMA approval as described above. The results of the study demonstrating these benefits are summarized below:

Summary of Benefits

Over the course of the study, the following benefits were considered with use of the Cartiva device when compared to the arthrodesis control group:

1. Improvement in VAS pain scores, with 88% and 89% responders in the Cartiva SCI device group at 12 and 24 months respectively, where a responder is defined as having a 30% or greater decrease in VAS. The responder rate in the arthrodesis control group was 100% and 98% at 12 and 24 months.

2. Maintenance of function as measured by FAAM Sports scores, with 98% and 96% responders at 12 and 24 months in the Cartiva device group, where a responder is defined as not having worsened by more than 9 points from baseline. The responder rate in the arthrodesis control group was 100% and 98% at 12 and 24 months. The Cartiva SCI device group was better than the arthrodesis group at Week 6 for this assessment.

3. Maintenance of function as measured by FAAM ADL scores, with 99% and 98% responders at 12 and 24 months in the Cartiva SCI group, where a responder is defined as not having worsened by more than 8 points from baseline. The responder

rate in the arthrodesis control group was 100% and 98% at 12 and 24 months. The responder rate in the Cartiva SCI device group was higher than the arthrodesis group at Week 6 for this assessment.

4. Improvement in quality of life as measured by SF-36, with 89% and 94% responders at 12 and 24 months, where a responder is defined as having improved by 10 points from baseline. The responder rate in the arthrodesis control group was 93% and 93% at 12 and 24 months. The Cartiva SCI device group was better than the arthrodesis group at Week 6 for this assessment.

5. Improvement in function as measured by FFI-R, with 94% and 95% responders in the Cartiva SCI device group at 12 and 24 months, where a responder is defined as having improved by 5 points from baseline. The responder rate in the arthrodesis control group was 100% and 95% at 12 and 24 months.

6. General agreement at 12 and 24 months post-treatment with the patient satisfaction question, "My overall well-being has improved since the beginning of the study?" The proportion of subjects in the primary analysis dataset responding with answers of "strongly agree" or "agree" at 12 months was 76% for the Cartiva SCI device treatment group and 79% for the arthrodesis group. At 24 months, 74% of Cartiva subjects and 85% of arthrodesis subjects responded with answers of "strongly agree" or "agree".

7. General agreement at 12 and 24 months post-treatment with the investigator's assessment of the satisfaction question, "My overall well-being has improved since the beginning of the study?" The proportion of subjects in the primary analysis dataset responding with answers of "strongly agree", or "agree" at 12 months was 75% for the Cartiva SCI device treatment group and 83% for the arthrodesis group. At 24 months, 84% of the Cartiva SCI device subjects and 83% of arthrodesis subjects responded with answers of "strongly agree" or "agree".

8. Maintenance of range of motion as measured by active MTP dorsiflexion. The Cartiva SCI device group showed greater range of motion than the arthrodesis group at all time points. However, as discussed in Section 10.3.1, this greater range of motion for Cartiva subjects did not appear to correlate with function assessment scores, which were nominally higher for arthrodesis subjects at longer time points.

9. Shorter surgery times, as the average procedure time was 23 minutes less in the Cartiva SCI device group. Data were not available for all subjects. Data was available for 112 (74%) Cartiva SCI device subjects and 39 (78%) arthrodesis control subjects.

10. Lower rates of certain radiographic endpoints, such as non-union in the Cartiva SCI group. However, such radiographic endpoints are not the goal of the Cartiva SCI device procedure.

Summary of Risks

Over the course of the study, the following risks were identified, with use of the Cartiva SCI device when compared to the arthrodesis control group:

1. The overall rate of any device related adverse event at 24 months was numerically higher in the Cartiva SCI device as compared to the arthrodesis control (Cartiva SCI device, 15.1%; arthrodesis, 8.0%). The overall rate of any serious device related adverse event at 24 months was numerically higher in the Cartiva SCI device as compared to the arthrodesis control (Cartiva SCI device, 7.2%; arthrodesis, 4.0%).

2. The rates subjects experiencing any of Bony Reaction, 49% Cartiva SCI device and 6% arthrodesis, and Class 1-3 Heterotopic Ossification, 59% Cartiva SCI device and 4% arthrodesis (Class 4 is expected in arthrodesis subjects) are higher in the Cartiva SCI device group as compared to the arthrodesis control.

3. Subjects may require a secondary surgery if the Cartiva SCI device procedure is unsuccessful. The estimated rate of secondary surgeries is 11.2% at 24 months and 13.8% if all known SSSI events are included.

4. Reductions from baseline VAS pain scores were less for the Cartiva SCI device group as compared to the arthrodesis control at every time point from Week 6 to Month 24. Serious pain related adverse events were higher in the Cartiva SCI device group compared to arthrodesis control. See Table 34: Improvement from Baseline over Time.

5. The FAAM Sports function scores measured as a change from baseline were lower in the Cartiva SCI device group as compared to the arthrodesis control at Month 6 and Month 12.

6. The FAAM ADL function scores measured as a change from baseline were lower in the Cartiva SCI device group as compared to the arthrodesis control at Month 6 and Month 12.

7. The FFI-R function scores as a change from baseline were lower in the Cartiva SCI device group as compared to the arthrodesis control at every time point from Week 6 to Month 24.

8. The SF-36 quality of life scores were lower in the Cartiva SCI device group as compared to the arthrodesis control group at Month 6.

9. The patient global assessment where subjects responded to the question "My overall well-being has improved since the beginning of the study?" showed lower rates of patients answering "Strongly Agree" at Month 6 (Cartiva SCI device 29% arthrodesis 47%), Month 12 (Cartiva SCI device 33%, arthrodesis 53%) and Month 24 (Cartiva SCI device 39%, arthrodesis 55%).

Patient Perspectives

The sponsor cited certain patient preferences associated with retaining range of motion. The sponsor notes that arthrodesis subjects are often dissatisfied with the outcome of a fusion procedure due to the alterations in gait, shorter step length, and loss of toe step off. Furthermore, many subjects complain of the restrictive rehabilitation including the time to return to work, the limitations of shoe wear (ski boots, cowboy boots and high heels) and the lack of joint motion following a fusion procedure. The lower degree at longer time points (up to two years) of pain reduction, as well as the lower degree at longer time points of maintenance or improvement in functional capability, achieved by treatment with the Cartiva device as compared to arthrodesis may be an acceptable trade-off for patients who feel strongly about such preferences.

In addition, for patients treated with the Cartiva SCI device in the study, there was general agreement at 12 and 24 months post-treatment with the patient satisfaction question, "My overall well-being has improved since the beginning of the study?" The proportion of subjects in the primary analysis dataset responding with answers of "strongly agree" or "agree" was 76% and 74% at 12 and 24 months respectively for the Cartiva SCI device treatment group and 79% and 85% at 12 and 24 months respectively for the arthrodesis group

D. OVERALL CONCLUSIONS

The MOTION study has demonstrated safety and effectiveness of the Cartiva SCI device for the treatment of painful first metatarsophalangeal joint osteoarthritis with conclusive evidence of a therapeutic effect and an acceptable safety profile. The risks of implantation of the Cartiva SCI device are balanced by the benefits of improved function and decreased pain that the Cartiva SCI device provides for subjects.

In conclusion, given the available information above, the data support that for the Cartiva Synthetic Cartilage Implant, which is intended for use in the treatment of patients with painful degenerative or post-traumatic arthritis (hallux limitus or hallux rigidus) in the first metatarsophalangeal joint with or without the presence of mild hallux valgus, the probable benefits outweigh the probable risks.

XIV. CDRH DECISION

CDRH issued an approval order on July 1, 2016.

The sponsor will conduct a post-approval study as described below:

ODE Lead PMA Post-Approval Study – Metatarsophalangeal Joint Osteoarthritis as Compared to a Control: Long-Term Follow-up (MOTION Extend Study): The Office of Device Evaluation (ODE) will have the lead for this clinical study, which was initiated prior to device approval. The MOTION Extend Study is as follows:

Based on the study plan received on May 16, 2016, and amended on June 23, 2016, the sponsor will perform a PAS to extend the duration of follow-up to 60 months of patients treated with the Cartiva device in the original MOTION study. The study will evaluate the long-term safety and effectiveness of the Cartiva SCI device by following all available Cartiva patients from the Canada and United Kingdom pivotal study. The sponsor states that its sample size will include 135 Cartiva subjects (119 randomized and 16 roll-in) eligible for study participation. Assuming a 15% lost to follow-up rate, the sponsor estimates that 115 subjects will have 5-year device status determined. Thus, the post-approval study duration will be approximately 36 months as all the patients have reached 24 months prior to the start of this study.

The sponsor will collect data to assess the following primary and secondary study endpoints:

Primary Study Endpoints
The primary endpoint will evaluate the long-term safety of the Cartiva implant by demonstrating the following:

1. Durability of the implant over the longer term.
2. Assessment of no unanticipated safety concerns that arise after Month 24 up to 5 years. Addressed by:
    a. determining the incidence of serious device-related adverse events per year and overall from Month 24 to Year 5; and
    b. summarizing device-related radiographic major complications[11] over time from Month 24 to Year 5.

Secondary Study Endpoints
1. Evaluation of maintenance of range of motion
2. Wear characteristics or device degradation for any Cartiva implant removed
3. Pain and function over time (VAS, FAAM ADL and Sports)
4. Evaluation of radiographic findings (radiolucency, bony reactions, and heterotopic ossification) looking at presence or progression from 24 months to 5+ years as well as correlation with the 5+ years clinical outcomes (effectiveness and safety).

[11] Major complications are radiographic findings assessed by an independent radiographic reviewer. These include absence of device displacement, device fragmentation, and avascular necrosis in the Cartiva group.

The primary hypothesis of this extended follow-up post approval study is that the performance of the Cartiva SCI device implant removal rate at 5 years post-op is non-inferior to the rate expected assuming the same exponential removal rate observed during the first 24 months of follow up. The hypothesis test will be performed based on the 2-5 year data collected in this post-approval study, with expected cumulative event rate from 2 to 5 based on exponential survival equal to 13.5%. The hypothesis stated is:

H_0: $\pi_A > \pi_0 + \delta$
H_A: $\pi_A \leq \pi_0 + \delta$

where π_A is the true proportion of subjects expected to have revision in the 2-5 year period, π_0 is exponential removal rate from 2 to 5 years estimated based on the 24 month data, ($\pi_0 = 0.135$), and a non-inferiority $\delta = 0.10$.

In addition, the rates of Cartiva SCI device removal and conversion to arthrodesis over time will be computed and presented to assess device survivorship.

FDA will expect at least 85% follow-up at the 60-month time point to provide sufficient data to evaluate safety and effectiveness as well as the sensitivity analyses to address missing data.

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

XV. APPROVAL SPECIFICATIONS

Directions for Use: See labeling.

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

Post Approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

See Footnotes throughout document.