SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

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

II. INDICATIONS FOR USE

The Cartiva® Synthetic Cartilage Implant is intended for use in the treatment of patients with degenerative or post-traumatic arthritis in the first metatarsophalangeal joint in the presence of good bone stock along with the following clinical conditions: hallux valgus or hallux limitus, hallux rigidus, and an unstable or painful metatarsophalangeal joint.

III. CONTRAINDICATIONS

The Cartiva Synthetic Cartilage Implant (SCI) should not be implanted in subjects with the following conditions:

- Active infection of the foot
- Known allergy to polyvinyl alcohol
- Inadequate bone stock
- Diagnosis of gout with Tophi
- Any 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
- 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

IV. WARNINGS AND PRECAUTIONS

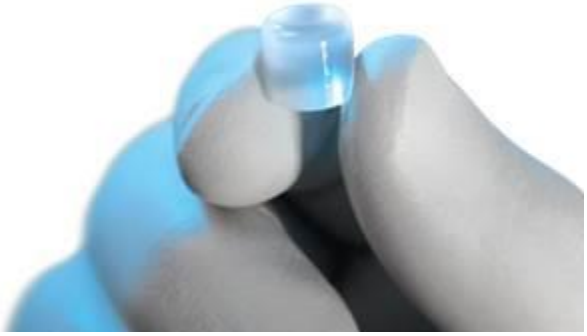
The warnings and precautions can be found in the Cartiva Synthetic Cartilage Implant labeling.

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 does not regrow or replace cartilage. The device is intended as an alternative to fusion procedures which result in a total loss of joint movement.

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 a number of FDA cleared and approved permanently implanted medical devices, such as injectable embolic spheres, nerve cuffs, and contact lenses. The Cartiva SCI is implanted during a short and minimally invasive implantation procedure that allows for faster recovery, preservation of joint function compared to the standard of care treatment options, and preserves the option for future surgical treatment in the event of complications.

Figure 1 Cartiva Synthetic Cartilage Implant



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 implant 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 outside 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 a patient's severity of symptoms and may include non-operative and operative treatments.

- Conservative non-operative treatment includes the use of orthotics or accommodative footwear, use of a stiff-soled shoe, the use of pain relievers and anti-inflammatory medicines, injections, hot/cold temperature baths, and limitations in activities.
- Surgical treatments 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 replacing the entire metatarsophalangeal joint; or, fusion (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 fully discuss the available alternatives with his or her physician to select the option that best meets their clinical condition, lifestyle and expectations.

VII. MARKETING HISTORY

The Cartiva 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. 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 foot surgical procedures 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 of the problem, recurrence of the deformity, heart attack, stroke, nerve damage, deep vein thrombosis (DVT), pulmonary embolus (PE), and death.

2. Risks associated with implantation of hemiarthroplasty devices or 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 fusion, 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, as outlined below. This testing included biocompatibility, long term implant compatibility, 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 implant and instrumentation are designed to be biocompatible for their respective intended use and duration of contact with the body. The Cartiva SCI device was assessed for biocompatibility per the testing guidelines outlined in ISO 10993.

Table 1 Biocompatibility of 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 through the use of dedicated instrumentation. The Cartiva SCI Instruments were assessed for biocompatibility per the testing guidelines outlined in ISO 10993.

Table 2 Biocompatibility of 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 device is presented in Table 3.

Table 3 Mechanical Characterization Testing of 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.
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 was (0.31 to 0.80 unconfined compression moduli[1]; equilibrium elastic moduli mean .677 ± .223 MPa[2]), 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.

C. PERFORMANCE TESTING

Performance testing was conducted to evaluate the device in simulated clinical scenarios act as a surrogate for potential clinical results or reactions. These are described below:

Fatigue Testing

The purpose of dynamic fatigue testing of the Cartiva SCI device is to assess if the device has adequate compressive strength to survive the repetitive, compressive loads that occur clinically in the 1st 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 in excess of 5 years of continuous use.

Wear Testing

Cartiva SCI devices were subjected to loading parameters reflecting the normal gait cycle and opposing surfaces identified to best simulate the wear environment of the 1st metatarsophalangeal joint. The Cartiva SCI devices sustained only minor damage during the 5,000,000 cycles under worst case wear conditions which simulates years. In particular, the implants were tested under maximum loads throughout the entire walking cycle unlike what is observed clinically

In order to assess the long term effect of the material and possible wear debris, a worst case 5-year amount of Cartiva SCI particulate was injected intra-articularly into the rabbit knee in amounts 9x 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 9-fold factor increase of injected quantities establishes a significant safety factor for the intended patient population. The particulate implant testing results demonstrate 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 the debris was of Cartiva 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, which is considerably lower than the threshold wear rate reported to induce osteolysis for UHMWPE which is 80 mm^3/yr (or a linear penetration rate of 0.1 mm/yr).[3] The amount of wear produced under these testing parameters indicate a low rate of wear compared with other polymers utilized in bearing surfaces of orthopedic implants.

1-Year Animal Implant Study

The 1-year animal implant study 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 implant, as well as, determine whether the implants illicit any inflammatory reaction in a load-bearing environment. The test animals received Cartiva SCI devices while the controls received empty defects and 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 on necropsy between the two groups. 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 difference in presence of subarticular cysts as compared to the control, no implant wear observed, and no particulate migration. 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. These data provided sufficient evidence to initiate clinical trials.

Conclusion

These data fully characterize the mechanical properties and performance of the device in simulated clinical use conditions or under worst case conditions. FDA has concluded its review of this preclinical material with no outstanding comments.

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 immediate container, the tray, holds the device and saline, and is sealed with a foil lid. The sealed tray is sealed 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, and the tray-in-pouch packaging to ensure 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 as non-inferior compared to fusion for the treatment of subjects with degenerative or post-traumatic arthritis in the first metatarsophalangeal (MTP) joint in the presence of good bone stock along with the following clinical conditions: hallux valgus or hallux limitus, hallux rigidus, or an unstable or painful metatarsophalangeal joint. A total of 236 subjects were enrolled, and 202 subjects were treated at 12 sites in the United Kingdom and Canada. To date, this is the largest randomized study performed for the treatment of osteoarthritis of the great toe.

A. STUDY DESIGN

The pivotal clinical study (the "MOTION" Study) compared the Cartiva SCI device to the control treatment, fusion (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. Subjects were treated between October 2009 and February 2013. The database for this PMA reflected data collected through February 2015 and updated with retrospective analysis of peri-operative data in October 2015.

The MOTION study design was generalizable to the United States patient population.

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

This was a frequentist, non-inferiority study with a pre-specified endpoint of 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 and fusion 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 fusion group.

In addition to the outcomes comprising the primary composite endpoint, other functional and quality-of-life outcomes scores were studied and included Foot and Ankle Ability Measure scale (FAAM), 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 2 subjects enrolled at each site were not randomized; they were implanted with Cartiva for the purpose of site training.

Upon confirmation of eligibility, subjects were randomized into one of two treatment groups: (1) Cartiva SCI implanted into the MTP joint, or (2) fusion, 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 ankle surgeons, performed clinical and radiographic assessments in accordance with the protocol to monitor subject outcomes. A radiographic assessment was performed by an independent radiologist who assessed subjects in both treatment arms.

Clinical Inclusion/Exclusion Criteria

To be eligible for the MOTION study, subjects had to meet all of the inclusion criteria and none of the exclusion criteria:

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 (Coughlin et al., 2003); • 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(Coughlin et al., 2003); • 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 10mm 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 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 peripheral neuropathy;

Study Inclusion Criteria	Study Exclusion Criteria
	• 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. The primary efficacy parameters assessed during follow-up included 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) 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.

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 (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 fusion using a composite clinical endpoint. Success required freedom from 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 fusion 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;
- Maintenance of function from baseline in FAAM Sports score (inclusive of decrease <9) at 12 months; and,
- Freedom from major complications[1] and SSSIs through 24 months.

[1]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 (fusion) group.

Revised Primary Endpoint

After review of the data submitted in the PMA, FDA made a number of requests for changes to the primary endpoint, including a revision to require the subject to meet all of the following criteria at 24 months to be considered an individual subject success:

- 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[1] and SSSIs through 24 months

[1]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 (fusion) group.

Thus, this changed the pre-specified primary endpoint by substituting the FAAM ADL for FAAM Sports and by requiring all prongs of the endpoint to be evaluated at 24 months. In addition, the following requests by FDA were made with respect to the analysis and statistical methods:

- mITT analysis defined as the primary analysis cohort;
- ITT analysis should not be the primary analysis (due to LOCF imputation for fusion subjects who withdrew prior to treatment); and,
- An additional per protocol analysis focusing on a more stringent criteria for evaluating eligibility deviations.

The proportion of successes in each group was determined and the difference (Cartiva minus fusion) 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 in order to determine their effect on subject outcomes

After review of the data submitted in the PMA, FDA made a number of requests for changes to the primary endpoint.

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-ins and 197 randomized subjects (132 to Cartiva SCI and 65 to fusion). Among randomized subjects 2 of 132 (1.5%) subjects randomized to Cartiva withdrew prior to receiving treatment as did 15 of 65 (23.1%) subjects randomized to fusion leaving 130 and 50 subjects, respectively, included in the Cartiva SCI and fusion mITT analysis set. The primary reason associated with withdrawal prior to treatment was subject choice not to have the fusion procedure. The total number of treated Cartiva SCI subjects included in the Safety Analysis was 152 including the 22 non-randomized roll-ins. A summary of subject accountability data is provided in the figure and table below.

Figure 2 Subject Accountability Tree

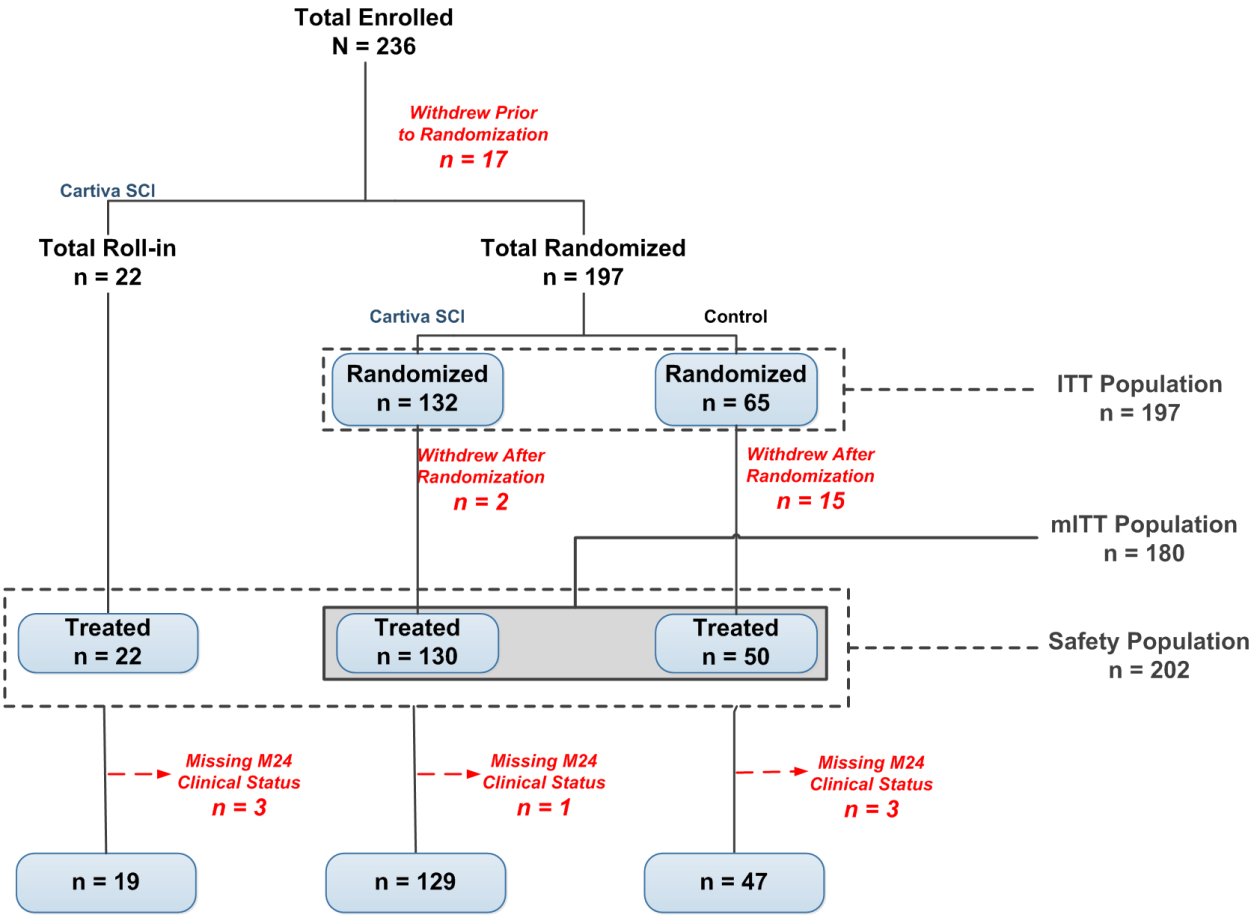


Table 6 MOTION Study Cumulative Randomized Implanted Subjects Accountability by Visit (mITT Cohort)

	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[B]) 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%	100.0%	96.9%	96.0%	97.7%	95.8%	95.3%	91.5%	99.2%	93.5%	98.3%	93.2%
(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[B] % Follow-up for CCS (12) / (7)									100.0%	94.0%	99.2%	94.0%

Actual[B] = 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*	Fusion	Cartiva *Roll-In*	Total Subjects
Safety[1]	130	50	22	202
ITT[2]	132	65	-	197
mITT[3]	130	50	-	180
Per Protocol 1 (PP1)[4]	127	47	-	174
Per Protocol 2 (PP2)[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 PP1 population includes all mITT subjects who did not have a major deviation.

[5]The PP2 population includes all mITT subjects who did not have a major deviation related to eligibility criteria.

C. STUDY POPULATION DEMOGRAPHICS AND BASELINE PARAMETERS

Subject demographics are summarized in Table 8. These data show that the treatment groups in the ITT and mITT populations 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 fusion. 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.

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

	Cartiva (n=130)			Fusion (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

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

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

D. PERI-OPERATIVE INFORMATION

Surgical timing information was available for 112 (74% of treated) Cartiva subjects and 39 (78% of treated) fusion subjects, and length of anesthesia information was available for 137 (90%) Cartiva subjects and 44 (88%) fusion subjects (refer to Table 10).

Table 10 Length of Surgical Procedure and Anesthesia (minutes) for the Safety Cohort

	Cartiva			Fusion			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 surgical implantation procedure is, on average, 40% faster (23 minutes) than fusion. Due to the nature of the faster surgical procedure, as expected, the length of anesthesia administration for Cartiva subjects was, on average, 28 minutes shorter than that for fusion subjects ($p<0.001$).

There were no significant differences observed in the type of anesthesia with 92% of subjects in both treatment arms receiving general anesthesia. This is consistent with the typical anesthesia for foot surgery which usually consists of general IV sedation combined with a regional ankle nerve block anesthetic

E. SAFETY AND EFFECTIVENESS RESULTS

Safety Results

The analysis of safety was based on the Safety Cohort of 202 total subjects treated (22 Cartiva roll-in subjects, 130 randomized and treated Cartiva subjects, 22 non-randomized Cartiva subjects, and 50 fusion 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 group (69.1%) and the fusion control group (72.0%). The majority of the events were mild or moderate in nature as classified by the Investigator for the Cartiva subjects (86.2%) and fusion control group (78.0%).

Table 11 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

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 complications, treatment emergent (device and operative related) adverse events (AEs), or Serious Adverse Events (SAEs).

The adverse events reported in the PMA from all 202 treated subjects (130 randomized Cartiva subjects, 22 non-randomized Cartiva subjects, and 50 fusion control subjects) are shown in Table 12. This table includes adverse events from all subjects, randomized and non-randomized, to study completion (24 months). Adverse events are listed in alphabetical order according to adverse event categories by System Organ Class.

Table 12 Adverse Events by System Organ Class, Preferred Term, and Treatment Group

All Adverse Events	Cartiva (N = 152)			Fusion (N = 50)		
	Events	Subjects	%	Events	Subjects	%
All Adverse Events	245	105	69.1%	72	36	72.0%
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%
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%
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%
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 tumour	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%

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%

A summary of the total number of serious adverse events is shown in Table 13. To demonstrate that Cartiva is safe, the company collected all adverse event data and had safety data reviewed by the Medical Monitor. The data herein establishes that the Cartiva device does not pose any unreasonable risk to the subject and demonstrates a comparable safety profile compared to the control treatment through valid scientific data.

Table 13 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						
Aortic valve stenosis	1	1	0.7%	0	0	0.0%
CONGENITAL, FAMILIAL, AND GENETIC DISORDERS						
Congenital foot malformation	1	1	0.7%	0	0	0.0%
EAR AND LABYRINTH DISORDERS						
Eustachian tube patulous	1	1	0.7%	0	0	0.0%
GASTROINTESTINAL DISORDERS						
Small intestinal obstruction	1	1	0.7%	0	0	0.0%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
Fibrosis	1	1	0.7%	0	0	0.0%
Implant site pain	8	8	5.3%	0	0	0.0%
HEPATOBILIARY DISORDERS						
Cholecystitis	1	1	0.7%	0	0	0.0%
Cholecystitis acute	1	1	0.7%	0	0	0.0%
INFECTIONS AND INFESTATIONS						
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						
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						
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%
NEOPLASMS BENIGN, MALIGNANT, AND UNSPECIFIED (INCL CYSTS AND POLYPS)						
Throat cancer	1	1	0.7%	0	0	0.0%
Gastrointestinal stromal tumour	0	0	0.0%	1	1	2.0%
Prostate cancer	1	1	0.7%	0	0	0.0%
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS						
Dysphonia	1	1	0.7%	0	0	0.0%
Nasal septum deviation	1	1	0.7%	0	0	0.0%
SURGICAL AND MEDICAL PROCEDURES						
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%

During the MOTION study, there were a total of 37 serious adverse events in 30 subjects (19.7%) in the Cartiva arm and 12 serious adverse events in 9 subjects (18.0%) in the fusion arm. For the events of implant site pain and medical device pain in the Cartiva arm, all of these events were due to on-going joint pain not attributable to the normal course of recovery. These pain events all resulted in a return to the operating room for removal of the implant and conversion to fusion. All of these subjects were followed after implant removal and all subjects went on to

achieve a successful joint fusion. All implant site pain and medical device pain SAEs were reported as resolved without sequelae immediately following the implant removal procedure.

The incidence of serious treatment emergent adverse events (i.e., those events defined as either device or procedure-related) was 11% and 8% for the Cartiva and fusion groups, respectively. The majority (76%; 13/17) of the Cartiva serious adverse events were for pain (coded in the preferred terns of implant site pain, medical device pain, or procedure pain). The majority (75%; 3/4) of the fusion events were for complications (medical device or post procedural). Of these events, only 11 (7.2%) and 2 (4.0%) subjects experienced device related events for the Cartiva and fusion groups, respectively. All the serious treatment emergent events resulted in a secondary surgical intervention. The treatment emergent events by System Organ Class and preferred term are provided in Table 14.

Table 14 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%
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%
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 the independent radiographic reviewer and did not correlate to any independent radiographic findings

Adverse Events Requiring Secondary Surgical Intervention

Some adverse events resulted in subsequent surgical intervention. Secondary surgical interventions, classified as revisions, removals, reoperations or supplemental fixations, qualified as study failures in concert with FDA's Guidance Document, *Clinical Data Presentations for Orthopedic Device Applications* (2004). There were comparable secondary surgeries in the Cartiva SCI group compared to the fusion control group. A total of 14 (9.2%) Cartiva subjects and 6 (12%) fusion subjects had the implant and/or hardware removed during the course of the study. All Cartiva subjects that had the device removed were successfully converted to fusion without event. Of the 17 Cartiva subjects having an SSSI, 13 were in the randomized cohort and 4 were in the roll-in cohort.

Table 15 Secondary Subsequent Surgical Interventions through 24 months (Safety Cohort)

SSSI	Cartiva Total (n=152)	Fusion (n=50)
Removal	14 (9.2%)[1]	4 (8%)
Reoperation	1 (0.7%)	0
Revision	1 (0.7%)	3 (6%)
Supplemental Fixation	1 (0.7%)	0
All	17 (11.2%)	6[2] (12.0%)

[1]All Cartiva removal subjects were successfully converted to fusion without incident .

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

Device Related Adverse Events

The relationship between adverse events and the implant was assessed by the Investigators from data coded according to Preferred Terms (PT) of the MedRA (Medical Dictionary for Regulatory Activities) Classification. Throughout the study, AEs were collected during the course of subject follow-up visits by the Investigators, and relationship was recorded. Events classified as device related were grouped together and analyze. The type and time of occurrence of subjects with device related events is presented in Table 16.

Table 16 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 the independent radiographic reviewer and did not correlate to any independent radiographic findings.

Radiographic Measurements

With the exception of the radiographic endpoint, success with respect to the individual components of the composite endpoint is defined identically for the Cartiva and fusion populations. Assessment of the radiographic component of the composite endpoint is necessarily different in the two study arms to allow for capturing information regarding the distinct potential failure modes of the Cartiva and fusion treatments.

Radiographic success for the Cartiva arm was defined *a priori* as the absence of device displacement, device fragmentation, and avascular necrosis (AVN). These events are relevant to the Cartiva population, yet not the fusion population. For the fusion arm, radiographic success is defined as the absence of mal-union, non-union, or hardware fracture. These failure modes are specific to treatment with fusion. While there are differences between how radiographic success is defined for the two study populations, both definitions capture the meaningful radiographic events specific to the treatment the subject received, and relevant to a determination of safety and effectiveness specific to device malfunction or a need for re-intervention. Therefore, the composite primary endpoint is valid for evaluating and comparing the clinical and radiographic outcomes of the Cartiva and fusion populations. The differences in the radiographic component are necessary and appropriate to ensure that events specific to the treatment are being captured to demonstrate where the device and/or procedure were not performing as intended.

A summary of the radiographic failures per the primary endpoint observed in the mITT population is included in Table 17.

Table 17 Primary Endpoint Radiographic Failures (mITT)

Radiographic Failure Modalities	Cartiva N=152 [x (%)]	Fusion N=50 [x (%)]
Any	0 (0.0)	5 (10.0)
Avascular Necrosis – Present	0 (0.0)	N/A
Device Displacement – Present	0 (0.0)	N/A
Device Integrity – Fragmentation	0 (0.0)	N/A
Device Integrity – Fractured Hardware	N/A	1 (2.0)
Fusion Status – Mal-Union or Non-Union	N/A	4 (8.0)

Based on these findings, the overall radiographic success rate was 100% for the Cartiva group and 90% for the fusion group.

Safety Conclusions

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 a subject's natural motion at the joint. 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 group (event rate of 15.1%) as compared to 4 fusion subjects (8%). All Cartiva device-related events were considered anticipated. A higher rate of procedure-related adverse events occurred in the fusion group (36.0%) compared to the Cartiva group (33.6%). The overall serious device-related event rate was 7% for Cartiva and 4% for fusion. Non-serious procedure or device-related events were well tolerated by Cartiva subjects. There were no Cartiva SCI device failures.

There were comparable secondary surgeries in the Cartiva SCI group compared to the fusion control group. A total of 9.2% (14/152) Cartiva subjects and 12% (6/50) fusion subjects had the implant and/or hardware removed during the course of the study. All Cartiva subjects that had the device removed were successfully converted to fusion without event.

Based on the overall radiographic findings, 0% of the Cartiva safety population and 10% of the control group had a radiographic event contributing to failure. The instances of radiographic failure in the control arm due to non-union and fractured hardware indicate that the goal of the fusion procedure was not met. None of the Cartiva subjects experienced avascular necrosis, device displacement, or device fragmentation demonstrating device durability and no inflammatory response to the device material.

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.

Primary Efficacy Analysis

Pre-Specified Analysis

The pre-specified analysis of effectiveness defined in the protocol was based on the ITT cohort comprising all 197 randomized subjects (132 Cartiva subjects, and 65 fusion subjects).

All analyses of the pre-specified primary composite endpoint demonstrated non-inferiority of Cartiva compared to the fusion control as summarized in Table 18. The results of the primary analysis in the ITT demonstrated non-inferiority of Cartiva to fusion on the multi-pronged primary composite endpoint which capture information on pain, function, and safety (adverse events, subsequent surgical interventions and radiographic failures). 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%, and was supported by the non-inferiority determination as well as the per protocol and multiple imputation analyses. In addition, a tipping point analysis was performed and demonstrated that 94.3% of the comparisons support non-inferiority. 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. These analyses demonstrate that the finding of non-inferiority of Cartiva to fusion is robust.

Table 18 Pre-Specified Primary Endpoint Analysis

	Cartiva			Fusion			LB 95% CI[1]
	N	n	%	N	n	%	
ITT	132	104	78.8%	65	40	61.5%	0.0552
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

Following review of the PMA data, the Agency requested a revised composite primary endpoint assessment to further understand the safety and effectiveness of Cartiva (reference Table 19). The Sponsor concurs with FDA's requested endpoint modifications, which will be the focus of the analyses presented in this Executive Summary.

Table 19 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%[1] at 12 months	Improvement (decrease) from baseline in VAS Pain of ≥30%[1] at 24 months
Function	Maintenance of function from baseline based on the FAAM Sports score (inclusive of decrease <9)[2] at 12 months	Maintenance of function from baseline based on the FAAM ADL score (inclusive of decrease <8)[2] at 24 months
Safety	Freedom from major complications[1] and SSSIs through 24 months	Freedom from major complications[1] and SSSIs through 24 months

[1]Major complications were determined as the presence versus absence of specific radiographic findings that were assessed by an independent radiographic reviewer, including 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 (fusion) group.

Table 20 presents a summary of the Cartiva and fusion subjects who met the FDA-requested, revised primary composite endpoint at the 24-month time point. As requested by the FDA, the mITT cohort is the primary analysis cohort for this assessment due to an imbalance between treatment groups in subjects who dropped out of the study following randomization.

Table 20 Revised Primary Composite Endpoint at 24-Months

	Cartiva			Fusion			LB 95% CI[1]
	N	n	%	N	n	%	
mITT	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 again demonstrate non-inferiority of Cartiva to fusion on this multi-pronged endpoint reflecting clinically significant measures of pain, function and safety (noting that the lower bound of the one-sided 95% CI being greater than the pre-specified non-inferiority margin of 0.15). While having multiple components in a composite endpoint can often result in a low rate of overall success, (since subjects need to be considered a success on all prongs to be considered an overall success), the above results demonstrate a high rate of success for both the Cartiva and fusion

[1] 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 $\geq$ 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.

[2] 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.

subjects. Nearly 80% of the Cartiva subjects and nearly 79% of the fusion subjects met the revised primary composite endpoint at 24 months in the primary analysis (mITT) cohort.

Missing Data Analysis

At the 24 month follow-up visit, in the mITT cohort there were only 4 subjects who had an endpoint assessment missing at that time point (1 Cartiva and 3 fusion). An assessment of missing data is presented in Table 21.

Table 21 Missing Data Assessment for Revised Primary Composite Endpoint

Analysis	Number and Percentage Achieving Month 24 Composite Clinical Success						LB 95% CI
	Cartiva			Fusion			
	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

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 Cartiva), indicating that the non-inferiority assessment is robust with regards to missing data.

A tipping point analysis was conducted in order to further assess the effect of missing data (1 Cartiva and 3 fusion subjects) on the revised primary endpoint. This analysis is presented in Table 22.

Table 22 Tipping Point Analysis of MOTION Study (mITT)

LB of 95% Confidence Interval

Number of Cartiva Successes	Number of Fusion Successes: 0	1	2	3
1	-0.0572	-0.0749	-0.0923	-0.1158
0	-0.0653	-0.0830	-0.1004	-0.1176

The results of the tipping point analysis further demonstrate that the non-inferiority result of the revised primary endpoint is robust with respect to missing data. With the "worst case for Cartiva (all three missing fusion subjects as successes and the single missing Cartiva subject as a failure), the lower bound of the 95% confidence interval is -0.1176, which meets the pre-specified non-inferiority margin.

Per Protocol Analysis

Per Protocol 1 (PP1)

In this analysis, the overall success of Cartiva was 101/127 (79.5%) and fusion was 37/47 (78.7%).

Table 23 Revised Primary Endpoint at 24-Months (PP1*)

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

* Per Protocol 1 = all randomized subjects who received the treatment to which they were randomized with subjects having major inclusion/exclusion deviations excluded. Excludes two Cartiva subjects.

Results indicate non-inferiority of Cartiva to fusion on the composite endpoint.

Per Protocol 2 (PP2)

In this analysis, the overall success of Cartiva was 103/127 (81.1%) and fusion was 37/47 (78.7%).

Table 24 Revised Primary Endpoint at 24-Months (PP2*)

Population	Cartiva			Fusion			LB 95% CI
	N	n	%	N	n	%	
PP2 Analysis	127	103	81.1%	47	37	78.7%	-0.0898

* Per Protocol 2 = all randomized subjects who received the treatment to which they were randomized with subjects having major eligibility deviations excluded. Excludes two Cartiva subjects.

Results again indicate non-inferiority of Cartiva to fusion on the composite endpoint.

Individual Components of the Revised Composite Endpoint

An evaluation of the 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 is defined as maintenance of function per FAAM ADL defined as no more than an 8 point reduction relative to baseline; and success regarding the freedom from subsequent secondary surgical interventions (SSSI) 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 and fusion 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 25 demonstrates that both treatments had very high responder rates for each component of the primary composite endpoint.

Table 25 Revised Endpoint Components at 24-Months (mITT Cohort)

	Cartiva			Fusion		
	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 fusion: 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 subjects through 24 months post-operatively. With regard to pain relief, nearly 89% of the Cartiva population experienced a clinically significant decrease in their pain, compared to 97% of the fusion population, for those subjects reaching the 24 month endpoint without an SSSI. As anticipated, pain relief was slightly better in the fusion cohort as these subjects underwent a procedure that requires elimination and removal of the first MTP joint. By eliminating the joint, the opportunity for pain during joint motion is also completely voided. This pain relief is accomplished, however, at the expense of maintaining the anatomy and motion of the first MTP joint. It should be noted that while the great majority of fusion subjects obtain substantial pain relief, some 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.[4] Furthermore, subjects want to avoid the long rehabilitation associated with the fusion procedure and the limitations of shoe wear, such as ski boots, cowboy boots and high heels.

Over 98% of the Cartiva population maintained or improved their function (as measured by FAAM ADL). While subjects were not required to have a functional impairment for enrollment in the study, 87.7% of Cartiva subjects had a clinically significant increase (≥8 point improvement) in function. Similar rates of function success were noted in the fusion cohort.

Effectiveness Discussion

The Cartiva device demonstrated non-inferiority to the fusion control using a primary endpoint that consisted of pain, function, radiographic, and safety outcomes, with nearly 80% of the Cartiva subjects and nearly 79% of the fusion subjects meeting the revised primary composite endpoint at 24 months in the primary analysis cohort (mITT). This determination is supported by analysis of the per protocol cohort and is statistically robust when considering the impact of subjects having missing data, as follow-up was 98% at 24 months post-operatively. Specific endpoints related to pain relief, functional improvement, and quality of life improvement further accentuate the effectiveness of the Cartiva device for the treatment of osteoarthritis of the first metatarsophalangeal joint.

In conclusion, the study data indicate that the Cartiva SCI device implanted in the first metatarsophalangeal joint is at least as effective as the control treatment (fusion), for the subject population and indications studied in this investigation, in terms of the overall success according to the protocol-specified composite primary endpoint and revised alternative primary endpoint, sensitivity analyses, and secondary endpoints.

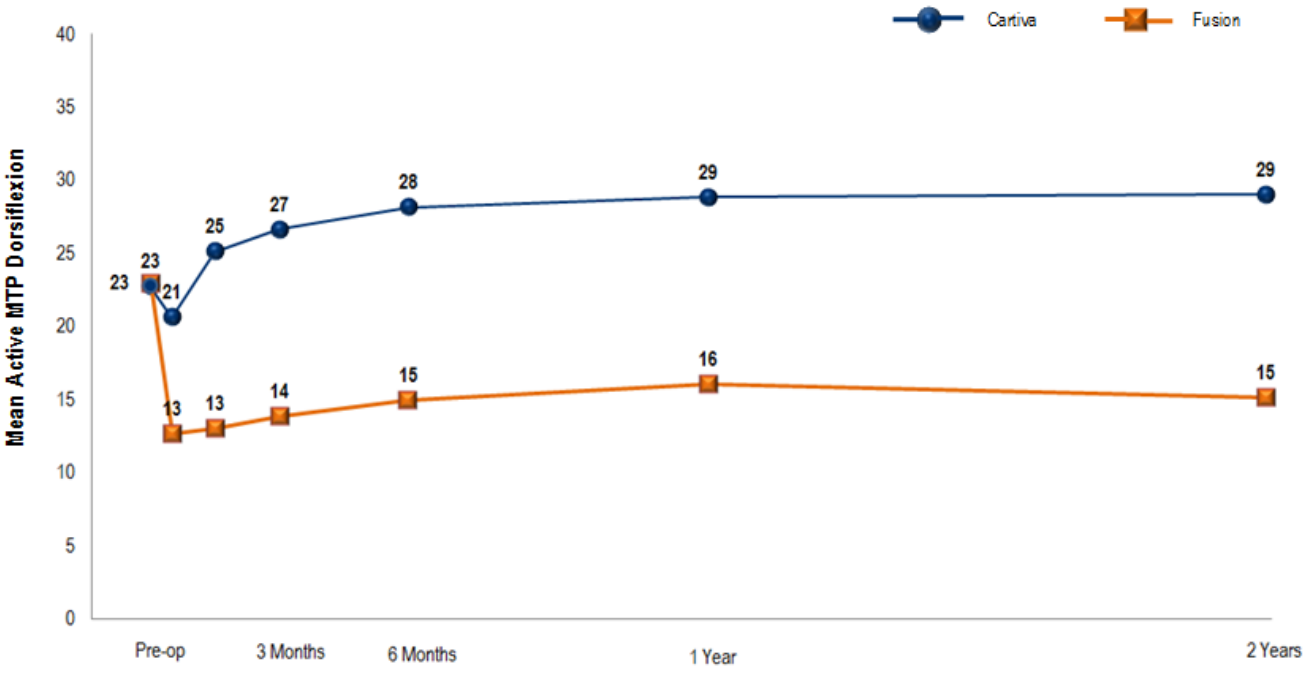
Secondary Effectiveness Analysis

Results for secondary endpoints measuring function (FAAM Sports, FAAM ADL, and FFI-R) demonstrate that a large proportion of Cartiva subjects achieved a clinically significant improvement at 6 weeks to 3 months that persists to 24 months following surgery, where the improvement was at least comparable to that in the fusion group. However, the Cartiva cohort exhibited a substantial improvement in joint dorsiflexion over the course of 24 months compared to baseline while the fusion group exhibited an overall decrease in dorsiflexion given that the position of the great toe was fused. The improvements in foot, ankle and joint function were reflected in overall quality of life measurements (SF-36) where a large proportion of Cartiva subjects demonstrated an improvement in satisfaction with physical function. Following completion of the study at 24 months, additional subject satisfaction surveys reported that over 86% of the Cartiva subjects would have the procedure again, in contrast to only 78% of fusion subjects, indicative of a positive outcome for a large proportion of subjects.

Active MTP Dorsiflexion

Cartiva also collected joint motion data on both Cartiva SCI and fusion 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. Mean Active MTP Dorsiflexion scores for Cartiva and fusion mITT subjects are presented in Figure 3

Figure 3 Cartiva and Fusion mITT Cohort – Mean Active MTP Dorsiflexion Over Time



The Cartiva cohort exhibited an improvement in Active MTP Dorsiflexion over the course of 24 months compared to baseline (from 22.7° to 29.0°) while the fusion group exhibited an overall decrease in Active MTP Dorsiflexion through Month 24 (from 22.9° to 15.1°) given that the position of the great toe was fused at the maximum level of dorsiflexion, while the Cartiva SCI subject still retained range of motion of the joint with the dorsiflexion measurement reflecting the maximum. Active MTP Dorsiflexion was statistically significantly different between the two groups at Week 2 through Month 24 in favor of the Cartiva cohort ($p<0.0001$).

VAS Pain

The mean VAS pain score over time is presented in Table 26.

Table 26 Cartiva and Fusion mITT Cohort – Descriptive Statistics for VAS Pain Over Time

	Cartiva Total Score				Arthrodesis Total Score				t-test
	N	Mean	SD	Med	N	Mean	SD	Med	p-value
Baseline	130	68.0	13.9	68.3	50	69.3	14.3	70.0	0.571
Week 2	130	38.5	28.7	29.5	49	39.2	23.8	40.5	0.874
Week 6	128	33.2	24.7	27.4	48	17.2	17.6	10.6	<.0001
Month 3	128	29.4	23.2	23.8	46	15.5	13.1	12.0	0.000
Month 6	124	28.9	27.5	20.5	43	11.7	18.3	4.0	0.000
Month 12	123	17.8	23.0	9.0	43	5.7	8.5	2.3	0.001
Month 24	116	14.5	22.1	5.0	41	5.9	12.1	1.5	0.020

Both Cartiva and fusion cohorts demonstrated a substantial decrease (improvement) in VAS Pain scores at Week 2 which continued to decline through Month 24. The median pain decreased dramatically in both groups from baseline to 24 months (Cartiva – 68.3 to 5.0; fusion 70.0 to 1.5) demonstrating that there was very little residual pain in most subjects in both groups at 24 months. Similar decreases in mean pain were also observed in both groups (reference Figure 4 and Figure 5).

Figure 4 Cartiva and Fusion mITT Cohort - Mean VAS Pain Scores Over Time

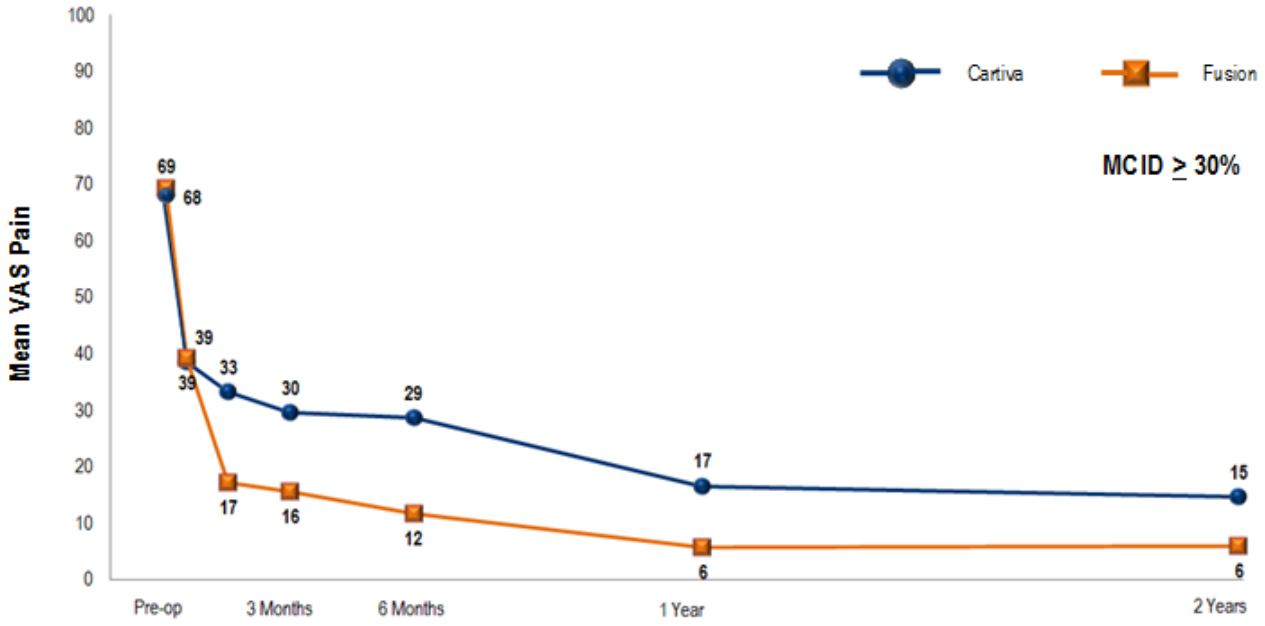
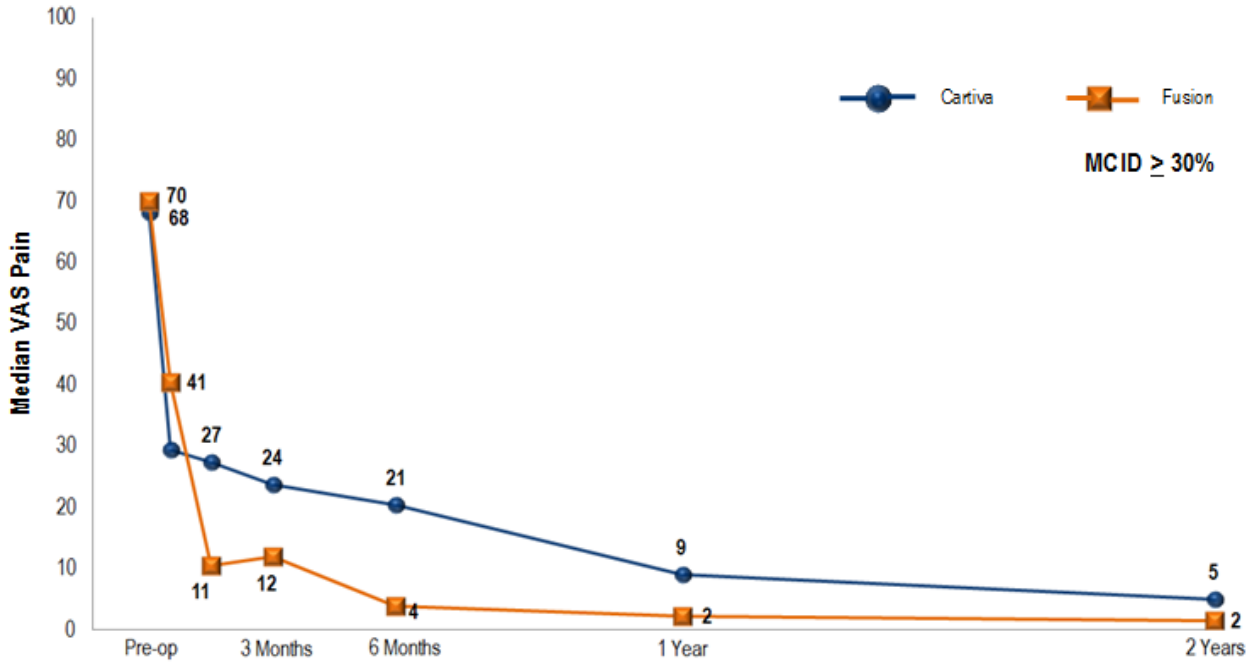


Figure 5 Cartiva and Fusion mITT Cohort - Median VAS Pain Scores Over Time



Individual subject success on pain relief was based on the clinically meaningful difference (30%) indicated as part of the primary endpoint (with lower VAS scores indicating lower levels of pain). Table 27 reports the percentage of subjects experiencing a clinically significant improvement in pain, a minor improvement in pain, maintenance of pain outcome, and those who worsened post-operatively.

These results demonstrate excellent pain reduction for both the Cartiva and fusion arms of the study through 24 months. For the Cartiva arm, 88.8% achieved a clinically significant improvement in pain, with a 94.0% overall rate of improvement. Although pain relief in the Cartiva group is numerically slightly less than fusion, the two outcomes compare favorably in terms of pain reduction while maintaining joint preservation.

FAAM ADL

The mean FAAM ADL score over time is presented in Table 27.

Table 27 Cartiva and Fusion mITT Cohort – Descriptive Statistics for FAAM ADL Over Time

	Cartiva Total Score				Arthrodesis Total Score				t-test
	N	Mean	SD	Med	N	Mean	SD	Med	p-value
Baseline	129	59.4	16.9	58.3	50	56.0	16.8	54.9	0.222
Week 2	126	48.8	21.6	47.6	47	40.3	20.7	39.3	0.021
Week 6	126	69.0	19.0	69.6	48	59.6	24.8	63.1	0.008
Month 3	125	77.3	17.7	80.0	46	82.5	14.9	86.9	0.079
Month 6	123	82.7	17.5	88.1	43	89.9	12.4	95.2	0.014
Month 12	123	88.6	14.4	95.0	43	94.1	6.8	95.2	0.017
Month 24	116	90.4	15.0	96.4	41	94.6	7.1	96.4	0.082

Both cohorts exhibited a decline in FAAM ADL at Week 2 attributed to surgical recovery, with a significantly lesser decline in function in the Cartiva group (p=0.021) and a significantly greater FAAM ADL score at 6 weeks (p=0.008), indicative of a shorter and less severe recovery period. Similarly, the Cartiva and fusion groups demonstrated an increase in FAAM ADL at Week 6 with continued improvement through Month 24.

Nearly 100% of the Cartiva population maintained or improved their function (as measured by FAAM ADL). As there was not an inclusion criterion related to functional impairment, some subjects entered the study with relatively high FAAM ADL scores. Nonetheless, 88.7% of Cartiva subjects achieved a clinically significant improvement in function (as measured by FAAM ADL).

The functional component of the primary composite endpoint required maintenance in a subject's FAAM ADL score. Per this definition, 98.3% of Cartiva subjects and 97.6% of fusion subjects met the endpoint. Therefore, there is no appreciable difference between the functional outcomes of the Cartiva and fusion populations.

Both Cartiva and fusion subjects exhibited a marked functional improvement, as measured by FAAM ADL. The median score of >90 (out of 100) at 12 and 24 months in both treatment groups indicates a high level of overall function of activities of daily life as measured by FAAM (reference Figure 6 and Figure 7).

Figure 6 Cartiva and Fusion mITT Cohort - Mean FAAM ADL Scores Over Time

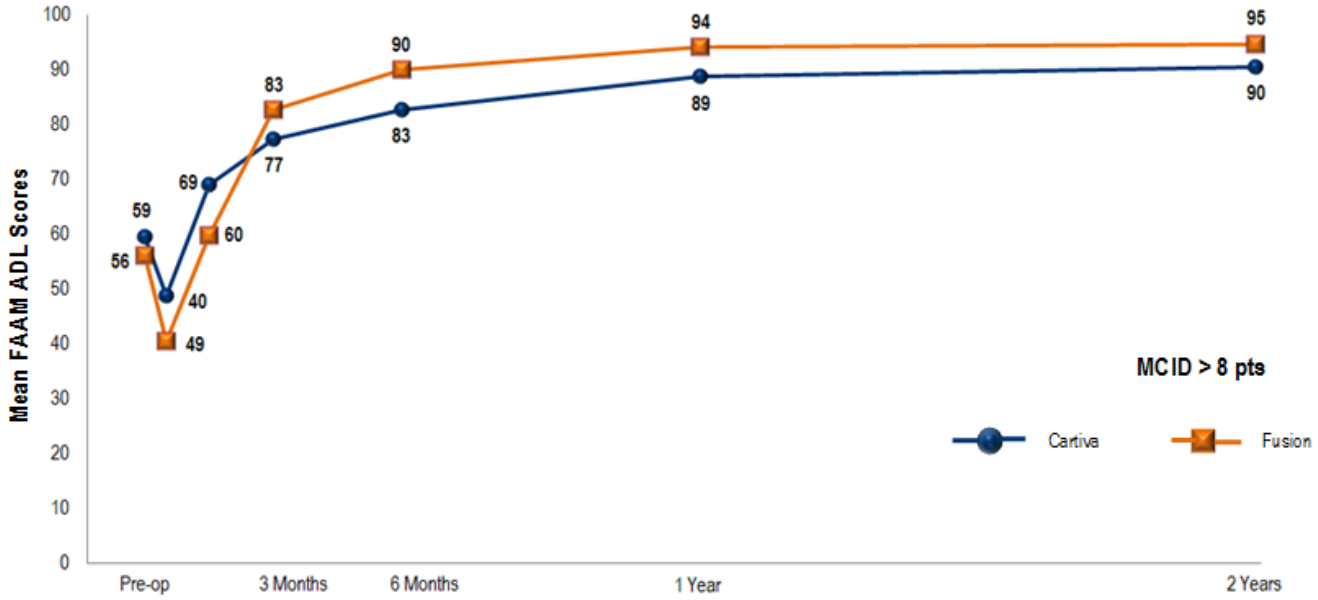
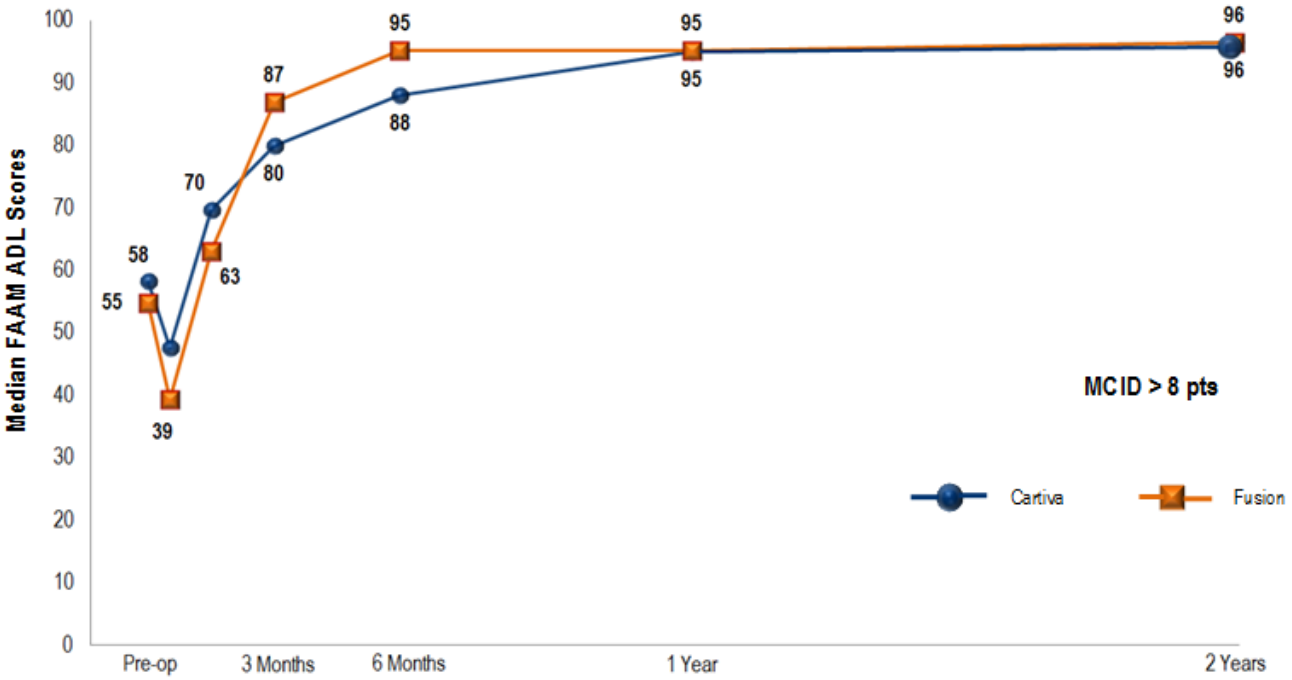


Figure 7 Cartiva and Fusion mITT Cohort - Median FAAM ADL Scores Over Time



Success in the form of functional improvement in activities of daily life (measured via FAAM ADL) was based on the clinically meaningful difference (8 points) indicated as part of the revised primary endpoint (with higher FAAM ADL scores indicating an increase in function). Table 29 reports the percentage of subjects experiencing a clinically significant improvement in function, maintenance of function, and those who worsened post-operatively.

These results demonstrate functional improvements in a significant proportion of both the Cartiva and fusion arms of the MOTION study. At the 24-month time point, 88.7% of the Cartiva arm achieved a clinically significant improvement in function as measured by the FAAM ADL score, and over 98% maintained or improved their function. Cartiva's outcomes compare favorably to the fusion arm which experienced a 92.7% improvement in FAAM ADL score, and a 97.6% rate of maintenance or improvement. These robust results in subjects implanted with the Cartiva SCI demonstrate sustained functional improvement at 24 months post-operative. The slight differences between the Cartiva and fusion results for FAAM ADL were not statistically significant.

FAAM Sports

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, were also assessed (measured via FAAM Sports subscale). The mean FAAM Sports scores over time for mITT subjects is represented in Table 28.

Table 28 Cartiva and Fusion mITT Cohort – Descriptive Statistics for FAAM Sports Over Time

	Cartiva Total Score				Arthrodesis Total Score				t-test
	N	Mean	SD	Med	N	Mean	SD	Med	p-value
Baseline	127	36.9	20.9	34.4	50	35.6	20.5	31.3	0.694
Week 2	127	18.4	18.3	12.5	47	7.8	12.4	3.1	0.000
Week 6	126	39.5	26.3	37.5	49	22.4	22.5	18.8	<.0001
Month 3	123	55.1	26.5	59.4	46	53.9	29.5	56.3	0.804
Month 6	120	66.6	26.3	71.9	42	78.6	23.8	87.5	0.010
Month 12	120	75.8	24.8	81.3	43	84.1	16.9	90.6	0.043
Month 24	113	79.5	24.6	90.6	41	82.7	20.5	90.6	0.461

Both cohorts exhibited a decline in FAAM Sports at Week 2, with a significantly lesser decline in function in the Cartiva group (p=0.000) indicative of a less difficult recovery period. The Cartiva group demonstrated an increase in FAAM Sports at Week 6 with continued improvement through Month 24. The fusion group demonstrated an increase in FAAM Sports later than the Cartiva group, at Month 3, with continued improvement through Month 24. A statistically significant difference in mean FAAM Sports scores exists between groups at Week 2 and Week 6 ($p<0.0001$) in favor of the Cartiva cohort, indicative of a faster rehabilitation period.

Nearly 96% of the Cartiva population maintained or improved their function (as demonstrated by FAAM Sports). Furthermore, 86.6% of Cartiva subjects had a clinically significant increase in function (as demonstrated by FAAM Sports). These data demonstrate that treatment with Cartiva® SCI results in a similar increase in subject function compared with fusion.

These results demonstrate functional improvements in a significant proportion of both the Cartiva® and fusion arms of the MOTION study. For the Cartiva arm, 86.6% achieved a clinically significant improvement in function as measured by the FAAM Sports score. Cartiva's outcomes compare favorably to the fusion arm which experienced a 95.1% improvement in function.

Therefore, functional success required maintenance in a subject's FAAM Sports score. Per this definition, 95.5% of Cartiva subjects and 97.5% of fusion subjects met the endpoint. Again, there is no appreciable difference between the functional outcomes of the Cartiva and fusion populations when measured by FAAM Sports (reference Figure 8 and Figure 9).

Figure 8 Cartiva and Fusion mITT Cohort - Mean FAAM Sports Scores Over Time

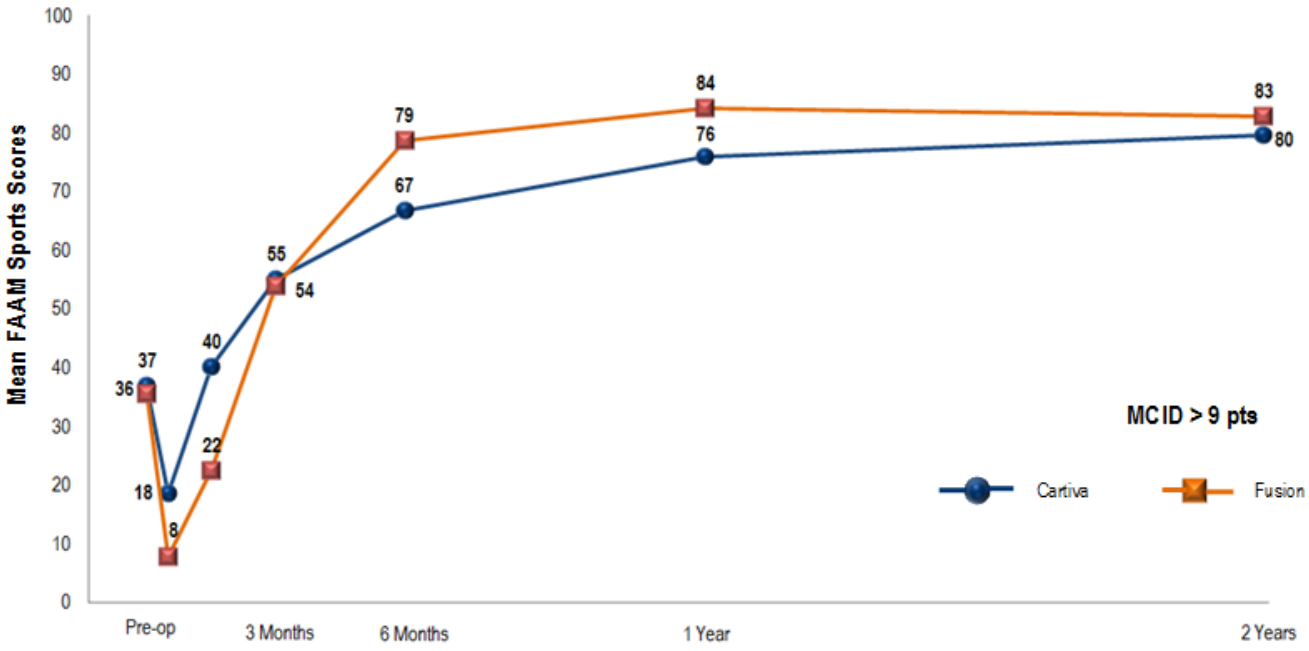
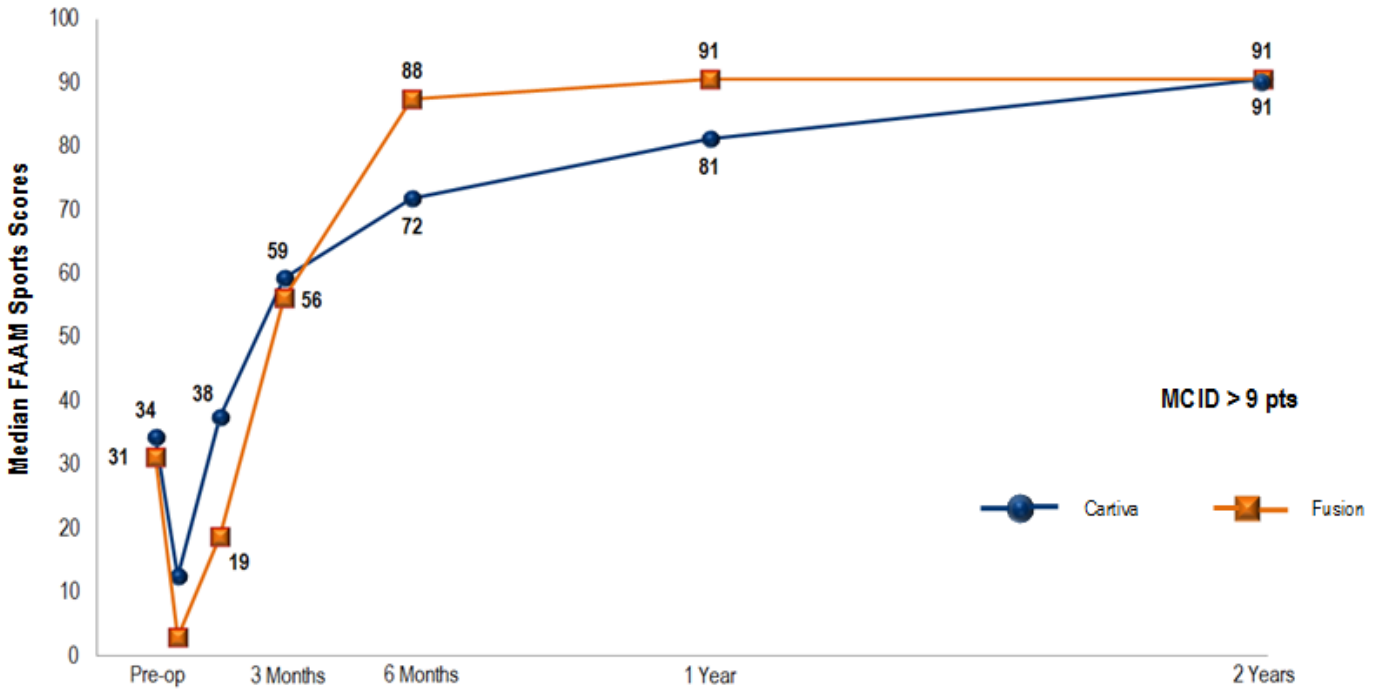


Figure 9 Cartiva and Fusion mITT Cohort - Median FAAM Sports Scores Over Time



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 percentages of Cartiva and fusion mITT subjects achieving improvement, maintenance or worsening in FAAM Sports score are presented in Table 31.

These results demonstrate functional improvements in a significant proportion of both the Cartiva and fusion arms of the MOTION study. For the Cartiva arm, 86.6% achieved a clinically significant improvement in function as measured by the FAAM Sports score. Cartiva's outcomes compare favorably to the fusion arm which experienced a 95.1% improvement in function.

Revised Foot Function Index (FFI-R)

Outcomes were also assessed with the FFI-R. Based on literature, 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

Table 29 Cartiva and Fusion mITT Subjects – Descriptive Comparisons of the Percentages of Subjects Achieving Degrees of Improvement in FFI-R

	Month 12				Month 24			
	Cartiva		Fusion		Cartiva		Fusion	
	n	%	n	%	n	%	n	%
Improved (>= 5pt decrease)	115	93.5%	43	100.0%	110	94.8%	39	95.1%
Maintained (<5pt to <5pt)	3	2.4%	0	0.0%	1	0.9%	1	2.4%
Worsened (>= 5pt increase)	5	4.1%	0	0.0%	5	4.3%	1	2.4%

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

SF-36 Physical Function Scores

The SF-36 physical function scores from the MOTION Study were also stratified by degree of improvement.

The categorization for SF-36 physical function was:

- 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

The percentages of Cartiva and fusion mITT subjects achieving maintenance or improvement, slight decline or deterioration in SF-36 physical function score are presented in Table 30**.**

Table 30 Cartiva and Fusion mITT Cohort – Percentages of Subjects Achieving Degrees of Improvement in SF-36 Physical Function

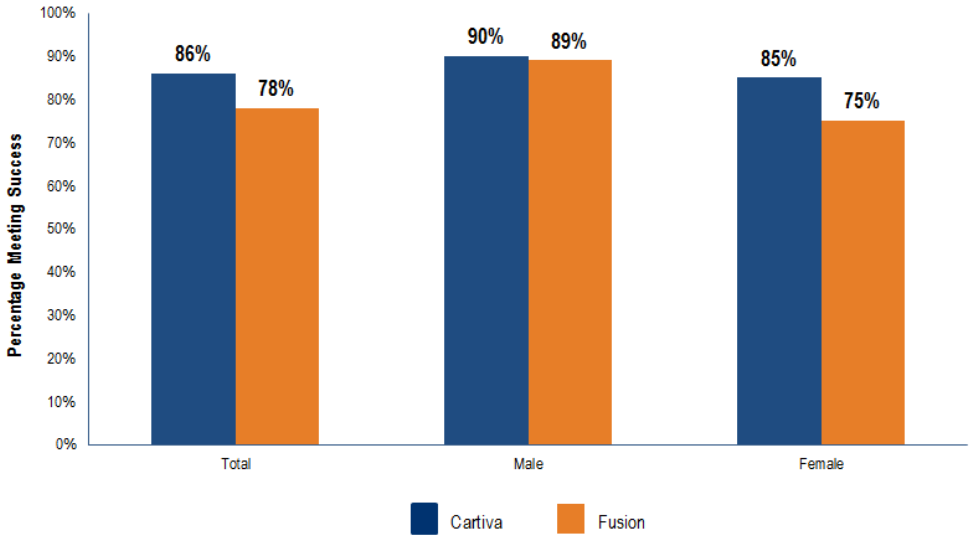
	Month 12				Month 24			
	Cartiva		Fusion		Cartiva		Fusion	
	n	%	n	%	n	%	n	%
Improvement (>=10pt increase)	96	78.0%	35	81.4%	95	81.9%	35	85.4%
Maintenance (>=0pt to 10pt increase)	14	11.4%	5	11.6%	14	12.1%	3	7.3%
Slight Decline (0pt to 10pt decrease)	3	2.4%	0	0.0%	2	1.7%	0	0.0%
Deteriorated (>=10pt decrease)	10	8.1%	3	7.0%	5	4.3%	3	7.3%

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

Patient Satisfaction

In the MOTION study, subjects were asked whether they would have the procedure again and at 24 months, 86.3% of Cartiva subjects would have the procedure again versus 78.0% of the fusion subjects.

Figure 10 Would you Have the Procedure Again? (24 months) (Safety Cohort)



This difference is even greater in female subjects compared to the male subjects where only 75% of female subjects in the fusion arm would have the procedure again at 24 months compared to 85% of the female subjects in the Cartiva group, as shown in Figure 10.

This is further supported by the literature where the choice of shoe wear was noted as the next most important factor in female subjects following pain relief.[3] The factors of difficulty fitting into shoes and foot and/or ankle weakness were significantly different between men and women, as women thought that fitting into shoes was a very important issue. This is of further relevance as female subjects represented 80% of MOTION study subjects overall, consistent with literature that female subjects represent the majority of MTP arthritis surgeries.

Radiographic Observations

[3] Baumhauer, JB et al. Age and Sex Differences Between Patient and Physician-Derived Outcome Measures in the Foot and Ankle. J Bone Joint Surg Am. 2013;95:209-14.

In addition to the radiographic outcomes which were assessed as part of the primary composite endpoint and discussed in detail above, each subject's radiographs were reviewed for observations. Events such as radiolucency, bony reactions, and heterotopic ossification are common when a medical device comes into contact with bone and is subject to loading. While these assessments were not pre-specified as radiographic failure modalities, a review of all radiographic observations was conducted to discern if a correlation exists between the incidence of these observations and the subject's clinical outcome in order to determine if any Cartiva subjects should be categorized as radiographic failures.

The analysis perfromed demonstrate that the incidence of radiographic findings, namely radiolucency, bony reactions, and heterotopic ossification, had no correlation with individual subject success according to the primary composite endpoint or with the pain, function or incidence of SSSI.

Secondary Endpoint and Assessment Summary

Secondary endpoints measuring function and overall quality of life demonstrate that a large proportion of Cartiva subjects achieved a clinically significant improvement at 6 weeks to 3 months that persists to 24 months following surgery. These results were demonstrated using validated measurements of foot function (FAAM Sports, FFI-R) and overall quality of life measurements (SF-36). Following completion of the study at 24 months, over 85% of the Cartiva subjects would have the procedure again, indicative of a positive subject outcome for a large proportion of subjects.

Furthermore, the Cartiva device provides an increase in the range of motion of the first MTP joint of 28% at 24 months post-operative compared to baseline measurement. The amount of active motion of the Cartiva subjects observed at 24 months (29˚) compares favorably to 31˚ of dorsiflexion of the MTP joint observed during walking in subjects with no history of foot and ankle pathology as reported by Nawoczenski, et al.[5] In contrast, fusion subjects lost 31% of their range of motion (to fused position at 15˚), which significantly alters a subject's foot biomechanics. MTP joint fusion can lead to gait abnormalities, arthritis in adjacent joints, and shoe-fit problems. Specifically, reduction in range of motion of the first MTP joint has been linked to differences in gait and walking speed. Zhang et al. (2014) found a slight reduction in walking speed and gait with a simulated fusion of the first MTP joint in healthy volunteers, as well as differences in walking kinematics of the ankle, knee, and hip.[6] These alterations of other joint kinematics in order to compensate for first MTP fusion could introduce the potential for degeneration in these joints due to altered loading patterns. Laroche et al. (2006) found similar results in subjects with rheumatoid arthritis, where a decreased range of motion of the joint led to decreases in walking speed and gait, independent of whether or not the subject reported pain while walking.[7] As such, return of a subject's natural range of motion is an important benefit of the Cartiva device.

Changes to the joint and foot mechanics subsequent to fusion can severely impair the function of the foot and lead to complications (such as painful plantar and interphalangeal pressure points, transfer metatarsalgia, and shoe-fit problems) and puts subjects at an increased risk for slips and falls.[8] Additionally, when considering outcomes following treatment for foot and ankle disorders, the most important factor to subjects is limitations to walking and, of significant importance to women, is the ability to fit into desired choice of shoe wear.[9]

Overall, the radiographic finding of bony reactions, heterotopic ossification, and device loosening did not have a clinical impact on the safety and effectiveness of the Cartiva SCI device. Clinical outcome measurements indicate that subjects having these radiographic findings experienced similar rates of success as those subjects who did not have any radiographic findings. From a safety perspective, these findings did not lead to an increase in SSSIs or adverse events. Furthermore, these findings were not defined *a priori* as part of the success criteria for the MOTION study. Although it is important to assess these radiographic data for monitoring purposes, bony reactions, heterotopic ossification, and device loosening (as defined in the radiographic protocol) were not of clinical concern to subjects receiving the Cartiva SCI device.

There is overlap between subjects exhibiting bony reactions and heterotopic ossification. This finding is not surprising, as both measurements are indicative of local bone remodeling that occurs due to manipulation and stimulation of bony surfaces as part of surgery in the joint. This is evidenced by bone production (heterotopic ossification) and bony reactions that occur with an isolated dorsal cheilectomy procedure in which bone is removed and no implant is placed. These radiographic findings have been observed in other anatomical locations following surgery (e.g., ankle, spine) and are similarly asymptomatic.

F. CONCLUSIONS

The pivotal clinical study (the "MOTION" Study) compared the Cartiva SCI device to the control treatment, fusion (fusion), for treatment of symptoms associated with osteoarthritis of the first metatarsophalangeal joint. The Cartiva cohort experienced a high rate of success while benefitting from a shorter surgery, maintenance of motion in the subject's first MTP joint, and avoidance of the risks of non-union and hardware fracture observed in the fusion cohort.

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

B. FDA's Post Panel Meeting Action

XIII. CONCLUSIONS DRAWN FROM THE STUDIES

The pivotal clinical study (the "MOTION" Study) compared the Cartiva SCI device to the control treatment, fusion (fusion), for treatment of symptoms associated with osteoarthritis of the first metatarsophalangeal joint. The Cartiva cohort experienced a high rate of success while benefitting from a shorter surgery, maintenance of motion in the subject's first MTP joint, and avoidance of the risks of non-union and hardware fracture observed in the fusion cohort.

A. EFFICACY CONCLUSIONS

For overall success, the proportion of success subjects in each group was determined and the difference (Cartiva minus fusion) 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 fusion. The ITT analysis was reviewed by the FDA, and based on the same premise, requested that all further analyses be based on the revised mITT cohort.

Table 38 presents a summary of the Cartiva and fusion subjects who met the pre-specified and revised primary composite endpoint.

Table 31 MOTION Study Primary Composite Endpoint Analysis

	Cartiva			Fusion			LB 95% CI
	N	n	%	N	n	%	
ITT[1]	132	104	**78.8%**	65	40	**61.5%**	**0.0552**
mITT[2]	130	104	**80.0%**	50	40	**80.0%**	**-0.1050**
mITT[3]	129	103	**79.8%**	47	37	**78.7%**	**-0.1029**
PP1 Analysis[4]	127	101	**79.5%**	47	37	**78.7%**	**-0.1065**
PP2 Analysis[5]	127	103	**81.1%**	47	37	**78.7%**	**-0.0898**

[1]Prospectively defined as the primary; however, impacted by fusion dropout rate.
[2]mITT cohort prospectively defined in the pre-specified endpoint analysis.
[3]Requested for purposes of primary composite analysis.
[4]Per Protocol 1 = all randomized subjects who received the treatment to which they were randomized with subjects having major inclusion/exclusion deviations excluded. Excludes two Cartiva subjects.
[5]Per Protocol 2 = all randomized subjects who received the treatment to which they were randomized with subjects having major eligibility deviations excluded. Excludes two Cartiva subjects.

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, e mITT, and Per Protocol populations. While having multiple components in a composite endpoint can often result in a low rate of overall success, the observed results demonstrated a high rate of success for both the Cartiva and fusion subjects. Nearly 80% of the Cartiva subjects and nearly 79% of the fusion 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 population experienced a significant decrease in their pain. Although the control population experienced greater pain reduction in a larger percentage of subjects, this difference in the pain prong of the composite endpoint was expected.
- **Function:** Over 98% of the Cartiva population maintained or improved their function (as demonstrated by FAAM ADL). Furthermore, 87.7% of Cartiva subjects had a clinically significant increase in function (as demonstrated by FAAM ADL).
- **Radiographic outcomes:** 100% of Cartiva 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. Additionally, analyses were conducted and are included herein that demonstrate none of the bony reaction or heterotopic ossification findings had any correlation with efficacy or safety or were determinates of a subject's success or failure per the primary endpoint.

- **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 Cartiva subjects achieve a clinically significant improvement at 6 weeks to 3 months that persists to 24 months following surgery.

Through a subgroup analysis there was no significant difference in clinical outcome by OA grade, age, or BMI.

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 study data indicate that the Cartiva SCI device implanted in the first metatarsophalangeal joint is as effective as the control treatment (fusion) for the subject population and indications studied in this investigation. These results are notable given the motion-preserving nature of Cartiva compared to fusion.

B. SAFETY CONCLUSIONS

The risks of the Cartiva Synthetic Cartilage (SCI) device are based on 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 a subject's natural motion at the joint. 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 group

(event rate of 15.1%) as compared to 4 fusion subjects (8%). All Cartiva device-related events were considered anticipated. A higher rate of procedure-related adverse events occurred in the fusion group (36.0%) compared to the Cartiva group (33.6%). The overall serious device-related event rate was 7% for Cartiva and 4% for fusion. Non-serious procedure or device-related events were well tolerated by Cartiva subjects. There were no Cartiva SCI device failures.

There were comparable secondary surgeries in the Cartiva SCI group compared to the fusion control group. A total of 9.2% (14/152) Cartiva subjects and 10% (5/50) fusion subjects had the implant and/or hardware removed during the course of the study. All Cartiva subjects that had the device removed were successfully converted to fusion 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.

C. BENEFIT-RISK CONCLUSIONS

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 in Table 32.

Table 32 Summary MOTION Study Results (mITT)

	Cartiva	Fusion
Revised Primary Composite Endpoint (mITT)	79.8%	78.7%
Components of Primary Endpoint (24 mo.)		
- Pain: VAS Improvement ≥30%	88.8%	97.6%
- Function: FAAM ADL maintain	98.3%	97.6%
- Safety: Freedom from SSSI	90.0%	88.0%
- Safety: Freedom from radiographic failure	100.0%	90.0%
Other Results		
Procedure time	35 min.	58 min.
Pain: VAS at 24 mo. (median)	5.0 mm	1.5 mm
Function: FAAM ADL at 24 mo. (median)	96.4	96.4
Function: FAAM Sports at 24 mo. (median)	90.6	90.6
Function: FFI-R improved at 24 mo.	94.8%	95.1%
Radiographic failures	0.0%	10.0%
Active Peak Dorsiflexion	29°	Joint fixed at 15°
Subject Satisfaction at 24 Months (would repeat surgery)	86%	78%

The clinical study demonstrated several benefits of the Cartiva SCI device in the first metatarsophalangeal joint over the duration of the study. Among all Cartiva study subjects that received treatment, approximately 80% met the pre-specified criteria for reduction of VAS pain (≥ 30%), improved or maintained function, and freedom major safety events over the 24 month follow-up period. These results were similar to those seen in the fusion control group, considered the standard of care for treatment of pain associated with osteoarthritis of the first metatarsophalangeal joint.

The clinical function and pain improvement outcomes of the Cartiva group well exceeded the threshold for a minimal clinically important difference (MCID) and are non-inferior to the standard of care, fusion, using this composite endpoint. In particular, subjects exhibited a large reduction in pain that was maintained through 24 months of follow-up, along with associated increases in function (measured by FAAM ADL, FAAM Sports, and FFI-R) as well as overall quality of life (measured by SF-36).

Additional benefits include:

- ***Maintenance of Natural Foot Biomechanics***: Study data demonstrate that the Cartiva device increases the subject's range of motion at the MTP joint which can help to maintain the subject's natural foot biomechanics, allowing for a more natural gait and not restricting subject activities. Specifically, Cartiva subjects demonstrated a 27.3% improvement in range of motion in the MTP joint following surgery. The degree of active motion of the Cartiva subjects observed at 24 months of 29 degrees compares favorably to 31 degrees of dorsiflexion of the metatarsophalangeal joint observed during walking in subjects with no history of foot and ankle pathology as reported by Nawoczenski, et al. In contrast, fusion subjects lost 31% of their range of motion, which significantly alters a subject's foot biomechanics. The fusion of the MTP joint sacrifices motion which can lead to gait abnormalities, arthritis in adjacent joints, and shoe-fit problems.
- ***Avoidance of the Risks Associated with Fusion Procedures***: This study demonstrated that 12% of the fusion subjects required a subsequent secondary surgical intervention (SSSI) to treat non-unions and to remove broken hardware. These procedures introduce a risk of infection, nerve injury, and wound healing problems. Further, revision of a failed fusion can be difficult due to bone shortening from the original procedure. This has been noted in the literature. "The incidence of malunion [6.1%] and hardware removal [8.5%] is inappropriately high, and efforts to determine effective methods of decreasing their incidence should be undertaken."[10]
- ***Quicker Rehabilitation***: Cartiva presents significant advantages over fusion with respect to the rehabilitation protocol. The faster recovery period was demonstrated in increased FAAM scores at week 2 and 6 for Cartiva subjects.

Cartiva SCI Rehab	Fusion Rehab
• Subject allowed to immediately weight bear as tolerated. • Range of motion (ROM) exercises are encouraged to begin immediately. • Dressing removed in 8-10 days • Significantly shorter recovery time with less limitations	• Non-weight bearing for 2 weeks (must use crutches or walker) o Crutch use can be challenging for subjects in the typical age range undergoing MTP fusion. Getting up and down stairs, in and out of cars, and even standing to cook a meal can be very difficult. • Limited weight bearing for 4-6 more weeks • Bandage with hard cast for 6-8 weeks o When wearing a cast, the subject often has difficulty bathing, and sleeping. • Air cast or boot for 6-12 weeks or until fusion • Driving not safe for 8-10 weeks o These subjects will need to depend on others to shop and help with daily needs

- ***Simple Surgical Procedure***: The Cartiva SCI's implantation is a short, out-subject procedure resulting in significant clinical benefits for the vast majority of treated subjects. On average, the Cartiva implantation procedure was 23 minutes shorter than for fusion. The short procedure length helps to minimize the risks of anesthesia to the subject as well as intraoperative complications.
- ***Straightforward Revision Procedure (if needed)***: Of the Cartiva subjects who underwent device removal and a subsequent fusion procedure, the study data demonstrate that all underwent a successful fusion procedure. The original Cartiva procedure does not require a significant bone resection, and, therefore, there is a lower likelihood of bone shortening allowing for preservation of other treatment options, as necessary.

The MOTION study has demonstrated safety and effectiveness of the Cartiva SCI device for the treatment of first metatarsophalangeal joint osteoarthritis with conclusive evidence of a therapeutic effect and an acceptable safety profile. Based on the treatment options currently available to first metatarsophalangeal joint osteoarthritis subjects (i.e., joint-sacrificing fusion or bone-sacrificing arthroplasty procedures), the minor risks of implantation of the Cartiva SCI device are tremendously outweighed by the benefits of improved function and decreased pain that the Cartiva SCI device provides for subjects.

XIV. CDRH DECISION

CDRH issued an approval order on _____.

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

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

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

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