Cartiva® Synthetic Cartilage Implant and Instrumentation
Instructions for Use

CAUTION: Federal (United States) law restricts this device to sale by or on the order of a physician.

HOW SUPPLIED
Cartiva® Synthetic Cartilage Implants – ***Sterile***
Cartiva® SCI Instrumentation – ***Non-sterile***

DEVICE DESCRIPTION
The Cartiva® SCI device is comprised of an organic hydrogel polymer made of polyvinyl alcohol and saline. Cartiva® SCI has a high water content, and its elastic and compressive mechanical properties are similar to articular cartilage. The device is intended to replacing focal areas of painful damaged cartilage thereby reducing pain and maintaining range of motion in the MTP joint.

The Cartiva® SCI, a molded cylindrical implant, is placed into the metatarsal head in the first metatarsophalangeal (MTP) joint via press-fit implantation.

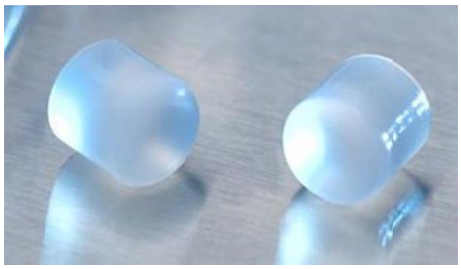

Figure 1 Cartiva® Synthetic Cartilage Implant

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

Cartiva SCI Implant Sizes	
8 mm	10 mm
(8 mm diameter x 8 mm depth)	(10 mm diameter x 10 mm depth)

The Cartiva® SCI device is implanted using instruments specifically designed for placement of the device. The Cartiva® instrumentation is used to drill an appropriately sized cavity in the metatarsal head and deploy the Cartiva® SCI device into the prepared cavity.

INDICATIONS
The Cartiva® Synthetic Cartilage Implant (SCI) 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 (MTP) joint.

CONTRAINDICATIONS
The Cartiva 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

WARNINGS
The safety and effectiveness of this device has not been established in subjects with the following conditions:
- Skeletally immature subjects, pediatric or adolescent (< 21 years old)
- Subjects on chronic anticoagulation due to a bleeding disorder or has taken anticoagulants within 10 days prior to surgery
- Subjects with osteonecrosis of the first metatarsophalangeal joint

- Grade 0 or 1 osteoarthritis

PRECAUTIONS
The Cartiva® SCI should only be used by surgeons who are experienced with orthopaedic procedures of the foot and have undergone training in the use of this device. Only surgeons who are familiar with the implant, instruments, procedure, clinical applications, biomechanics, adverse events, and risks associated with the Cartiva® SCI should use this device. A lack of adequate experience and/or training may lead to a higher incidence of adverse events.

Preoperative planning should be performed by the surgeon to estimate the required implant size. Prior to surgery, assure that the appropriate implant sizes are available for surgery.

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

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

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

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

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

Surgical implants must never be re-used or re-implanted. Ensure proper alignment and placement of device components as misalignment may cause excessive wear and/or early failure of the device.

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 hemi-arthroplasty 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 clinical study of the Cartiva SCI device, please see the Safety Results in the CLINICAL STUDIES section below.

SUMMARY OF CLINICAL STUDIES
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 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 Activities of Daily Living (FAAM ADL) score 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 patients 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.

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 Sport subscale (FAAM Sport), active MTP dorsiflexion, Revised Foot Function Index (FFI-R), and SF-36 Physical Function Scores. A radiographic assessment was performed by an independent radiologist.

Upon confirmation of eligibility, patients 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.

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 1 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); • Preoperative 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); • Preoperative 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 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; • 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 Activities of Daily Living (FAAM ADL) 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 2 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 using a composite definition of study success as compared to treatment with fusion.

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) and secondary surgical procedures.

The primary endpoint of the investigation was individual patient success, which required the patient to meet all of the following criteria at 24 months:

- Improvement in pain (VAS of ≥30%)
- Maintenance or improvement in function based on the Foot and Ankle Ability Measure Activities of Daily Living (FAAM ADL) (inclusive of decrease <8)
- Freedom from safety events defined by radiographic and subsequent secondary surgery measures

Secondary endpoints, measured in both treatment groups, included VAS Pain scores, FAAM Sports Subscale and Activities of Daily Living, Active MTP peak dorsiflexion, Patient Global Assessment, SF-36 Physical Functioning Scale, and Foot Function Index Revised (FFI-R), and general health.

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.

Accountability of PMA Cohort
A total of 236 subjects were enrolled in Cartiva's pivotal MOTION study. Seventeen (17) subjects withdrew prior to randomization, leaving 219 subjects who were either assigned to the non-randomized roll-in cohort (n=22) or who were randomized (n=197). Of the 197 randomized subjects, 17 withdrew prior to treatment, yielding 180 randomized subjects who received their assigned treatment. Thus, the safety population comprised 202 treated subjects, including 152 subjects treated with Cartiva (130 randomized and 22 non-randomized roll-in) and 50 fusion treated subjects. At the time of database lock, of the 180 randomized subjects who were treated, complete 24 month data were available for 176 subjects (98%), including 129 Cartiva subjects (99%) and 47 fusion control subjects (94%).

For the mITT cohort at 24 months, there were 130 Cartiva subjects and 50 fusion subjects who were theoretically available for follow-up. In this cohort, there were 13 Cartiva subjects and 6 fusion subjects who had an SSSI that deemed them as terminal failures and excluded them from assessment of success via FAAM and VAS, leaving 117 Cartiva and 44 fusion subjects expected due for these measurements. Of these subjects, clinical success data was available for 116 Cartiva and 41 fusion subjects. When considering all components of the primary endpoint, there were 129 Cartiva subjects and 47 fusion subjects with composite data available, indicating an overall clinical follow-up for primary endpoint of 97.8% (99.2% for Cartiva and 94.0% for fusion). The high rate of follow-up in the MOTION study allows for great confidence in clinical study results due to the limited amount of missing data.

Table 3 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.

The following terms are used to describe the populations used for analysis:

Throughout this discussion of the clinical data, the following terms describe the populations used for analysis:

Table 4 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.

Study Population Demographics and Baseline Parameters
Subject demographics are summarized in Table 5. These data show that the treatment groups were well-balanced and no statistically significant differences were noted. The baseline demographics of the study population are consistent with baseline demographics reported in the literature for hallux rigidus subjects treated with cheilectomy, hemi-arthroplasty and/or fusion.

Table 5 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**
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

Perioperative Information
A detailed retrospective review of source documents was performed to collect the requested data. 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.

Table 6 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 (Table 8-11**)**. 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.

SAFETY AND EFFECTIVENESS RESULTS
Safety Results
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 7 Summary of Adverse Event Experiences Safety Analysis Set

	Cartiva (N = 152)			Fusion (N = 50)		
	Events	n	%	Events	n	%
Any adverse event	245	105	69.1%	72	36	72.0%
Treatment Emergent Event	102	67	44.1%	32	21	42.0%
Device Related Event	31	23	15.1%	4	4	8.0%
Operative Procedure Related Event	71	51	33.6%	28	18	36.0%
Non-Treatment Emergent Event	143	73	48.0%	40	26	52.0%
Any Serious adverse event	37	30	19.7%	12	9	18.0%
Treatment Emergent Event	17	17	11.2%	4	4	8.0%
Device Related Event	11	11	7.2%	2	2	4.0%
Operative Procedure Related Event	6	6	3.9%	2	2	4.0%
Non-Treatment Emergent Event	20	14	9.2%	8	5	10.0%
AE by Severity						
Mild	110	70	46.1%	41	25	50.0%
Moderate	114	61	40.1%	26	14	28.0%
Severe	21	16	10.5%	5	5	10.0%

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 8 . 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 8 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 serious adverse events is shown in Table 9. 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 9 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.

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).

The incidence of serious treatment emergent adverse events 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 (implant site, medical device pain, or procedure). The majority (75%; 3/4) of the fusion events were for complications (medical device or post procedural). Of the 17 serious Cartiva® events, 15 (15/17; 88%) resolved without sequelae and of the 4 fusion events, 3 (3/4; 75%) resolved without sequelae. 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 10.

Table 10 Treatment Emergent Events by System Organ Class, Preferred Term, and Treatment Group

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 secondary surgical intervention. Secondary surgical interventions, classified as revisions, removals, reoperations or supplemental fixations, qualified as study failures pursuant to 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 11 Secondary Subsequent Surgical Interventions through 24 months (Safety Cohort)

SSSI	Cartiva (n=152)	Fusion (n=50)
Removal	14 (9.2%)[1]	4 (8%)
Reoperation	1 (0.7%)	0
Revision	1 (0.7%)	3 (6%)[3]
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.
[3]For the fusion control, a revision procedure consisted of partial removal of the hardware.

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 12**.**

Table 12 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 Safety population is included in Table 13.

Table 13 Primary Endpoint Radiographic Failures (Safety)

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.

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 14. The results of the primary analysis in the ITT demonstrated non-inferiority of Cartiva to fusion on the multi-pronged primary composite endpoint which captures 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. These analyses demonstrate that the finding of non-inferiority of Cartiva to fusion is robust.

Table 14 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 Analysis

Following review of the PMA data, the Agency requested a revised composite primary endpoint (Table 8-13) assessment to further understand the safety and effectiveness of Cartiva. The Sponsor concurs with FDA's requested endpoint modifications, which will be the focus of the analyses presented in this Executive Summary.

Table 15 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 fusion group.

Table 16 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 16 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 endpoint analysis continue to demonstrate non-inferiority of the Cartiva SCI relative to fusion control based on the lower bound of the one-sided 95% confidence interval being -0.1029 which is greater than the pre-specified non-inferiority margin (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

[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.

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 in the primary analysis (mITT) cohort. Through a subgroup analysis there was no significant difference in clinical outcomes by OA grade, age, or BMI.

SECONDARY EFFECTIVENESS ANALYSIS

In addition to the components of the primary endpoint presented above, secondary effectiveness variables were also assessed for the Primary Analysis population: VAS, FAAM Activities of Daily Living, FAAM Sport, Active MTP Dorsiflexion, Foot Function Index-Revised, and SF-36 Physical Function.

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. Subject satisfaction surveys at 24 months 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.

CONCLUSIONS DRAWN FROM THE STUDY

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

Table 17 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 demonstrate 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.

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.

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.

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 (15.1%) as compared to 4 fusion subjects (8%). All Cartiva device-related events were considered anticipated. A slightly 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.

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.

REFERENCES

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DIRECTIONS FOR USE

Reference the *Cartiva Synthetic Cartilage Surgical Implantation Technique Guide* for further information.

Cartiva SCI is implanted through the use of dedicated accompanying instrumentation designed to provide the surgeon and subject with an implant that is well-seated through a press fit implantation. The implantation procedure is similar to that used for osteochondral autograft or allograft transplantation, where a defect area is removed and resurfaced.

Implantation of Cartiva SCI device has been validated for use with surgical instrumentation distributed by Cartiva, Inc. The instruments are provided non-sterile and require sterilization prior to use. The Cartiva SCI Instrumentation have been validated for their intended function and use with a cannulated drill, and are specific to the size of the device being implanted. The following table references optimal dimensions for successful implantation of Cartiva SCI implants slightly proud (~0.5-1.5mm) with the surrounding cartilage:

Table 18 Cartiva SCI Specifications of Implant Site

Lesion size	Implant	Drill Part	Hole Diameter	Hole Depth
Up to 8 mm	CAR-08	MTD-08	7.9 mm	8.3 mm
8 mm to 10 mm	CAR-10	MTD-10	9.5 mm	10.0 mm

Using standard surgical technique, access the affected joint as necessitated by the size and location of the lesion. Care should be taken to avoid nerve damage along the dorso-medial aspect of the joint. Expose the entire joint to gain access to the central metatarsal head. Resect any osteophytes from the proximal phalanx and/or metatarsal head, ensuring adequate dorsal bone stock is preserved for insertion and stability of the implant. The ability to attain over 40 degrees of motion of dorsiflexion prior to insertion of the Cartiva SCI device is preferred. Confirm the appropriate size implant to be used by using the concave end of the appropriate Placer size on the metatarsal head.

Once the appropriate size is determined, use the concave end of the Placer, ensuring it is centered in the medial/lateral plane, to determine proper placement of the Guide Pin. Insert the Guide Pin into the center of the defect ensuring it is securely seated within the defect and is perpendicular to the central aspect of the metatarsal head. The placer should be positioned relatively central but can be slightly asymmetrical so as to address the worst area of arthritic involvement.

Select the appropriate Drill bit (MTD-08 or MTD-10) to drill a hole into the subchondral bone to the proper depth (recommendations can be found in the table above). The drill bit should match the selected implant size to achieve a tight fit with the implant. Drilling should be conducted with the Drill bit perpendicular to the articular cartilage surface with the Drill bit centered on the repair area. Insert the Drill bit over the Guide Pin, and advance the drill until the stop reaches the level of the adjacent tissue, to ensure appropriate depth is achieved. Note the Guide Pins are single use.

If necessary, remove any cartilage and/or bone debris from the recipient implant site.

Remove implant from packaging using smooth forceps. Moisten the Introducer tube with sterile saline. Place the Cartiva SCI implant into the wide end of the Introducer with the flat end first (curved portion anterior) so that the flat side of the implant will be placed in the bottom of the joint cavity. Insert the smaller, flat end of the Placer into the wide end of the Introducer. Rest the distal end of the Introducer on a flat, non-shedding, sterile surface and slowly advance the implant to the distal end of the Introducer using the Placer. Place the distal end of the Introducer at (but not into) the target implant site. Advance the Cartiva SCI implant into the implant site using the Placer. Remove the Introducer and Placer.

Confirm that the final placement of implant is tight in the implant site. The implant should be slightly proud (~0.5 to 1.5 mm) in the implant site.

PACKAGING

The Cartiva® Synthetic Cartilage Implant (SCI) is provided in two sizes (8mm and 10mm). The device is provided pre-packaged and sterile. It is intended for single use only. Before presentation to the operative field, inspect the package to ensure sterility has not been compromised during transportation. Do not use the Cartiva SCI if the package is opened or damaged. Before use, ensure that the temperature-sensitive indicator on the outer box is light gray. The Cartiva SCI device is not compatible with storage or shipment temperatures in excess of 49°C (120°F). If the temperature indicator has turned dark gray to black, do NOT use the device. The Cartiva SCI is sterilized using E-beam radiation at a minimum dose of 25 kGy. The contents of the outer pouch, including the tray and implant are sterile. Aseptic technique must be used while opening the packaging. The shelf box and exterior of the container are not sterile. Do NOT present the shelf box or outer pouch to the operative field. Inspect the Cartiva SCI to ensure it is not hard, brittle, torn, or otherwise damaged. The shelf life of the Cartiva SCI device is two years. The use-before-date of the sterile device is provided on the shelf box, external package label, and inner foil label. Re-sterilization of the device is strictly prohibited.

The Cartiva SCI sterilization tray and associated surgical instruments are supplied non-sterile and must be cleaned and sterilized prior to use according to the instructions in this document. The instruments and tray are shipped and stored in packaging that is labeled according to its contents. Store the sterilization tray in normal hospital environmental conditions. Store the instruments in the original packaging. Do not remove an instrument from the packaging until it is ready to be placed in the sterilization tray.

HANDLING

All instruments and implants should be treated with care. Improper use or handling may lead to damage and/or possible malfunction. Instruments should be checked to ensure that they are in working order prior to surgery. All instruments should be

inspected prior to use and at all stages of handling to ensure that there is no unacceptable deterioration such as damage, wear, nicks or corrosion. Cutting edges should be free of nicks and present a continuous edge. Long slender instruments should be inspected for any distortion. If any damage is detected, do not use the instrumentation. Non-working or damaged instruments should be returned to Cartiva, Inc. USA.

INSTRUMENTATION CLEANING
Instrumentation must be sterilized by the user prior to use in surgery. Implants are provided sterile and are not to be sterilized.

Precautions
- Failure to properly clean instruments prior to sterilization may lead to inadequate sterilization.
- Surgical instruments are used with or on subjects who may harbor both recognized and unrecognized infections. To prevent the spread of infection, all reusable instruments must be thoroughly cleaned and sterilized prior to initial use and after each patient use.
- Instruments may have sharp edges or features. Users and reprocessors must be cautious when handling instruments.

Limitations on Reprocessing
- Repeated processing, according to these instructions, has minimal effect on and should not compromise the performance of reusable Cartiva SCI instruments. End of life is normally determined by wear and damage due to use.
- In addition to the Cartiva SCI Instrumentation that is labeled for re-use, Cartiva, Inc. provides single-use guide pins for use during the Cartiva SCI implantation procedure. Re-use of the single-use guide pins is strictly prohibited. The material properties and reliability of these devices in a multi-use scenario have not been explicitly tested or demonstrated. Re-use of a single-use guide pin could result in improper device placement (depth, alignment, etc.) and undesired clinical outcomes.
- Guide Pins must be discarded after one use.

Damage Inspection
- Inspect the instruments for damage, wear, and corrosion at all stages of handling.
- Cutting edges should be free of nicks and present a continuous edge.
- Check instruments with long slender features for distortion.
- If damage is detected, do not use instrument but consult Cartiva, Inc. for guidance.

Instrument Description
The Cartiva SCI Instrumentation supplied by Cartiva, Inc. is not designed, sold or intended for use other than as indicated within the Cartiva SCI Instructions for Use. The Cartiva SCI instruments are constructed of surgical grade stainless steel types 17-4SS H900 and 455SS H900 (as referenced in ASTM F899 “Wrought Stainless Steel for Surgical Instruments”).

Table 19 Non-Sterile Instrumentation

Part Description	Instrumentation Reference	Classification
Drill Bit (Fabricated from 455 H900 Stainless Steel) ***Note: All drill bits (part numbers MTD-##) are designed for use with drills having a chuck size of at least 0.25". The drill bits are not compatible with a 6 mm chuck.***	MTD-08 MTD-10	Reusable
Introducer (Fabricated from 17-4 H900 Stainless Steel)	INT-08 INT-10	Reusable
Placer (Fabricated from 17-4 H900 Stainless Steel)	PLC-08 PLC-10	Reusable
Guide Pin (Fabricated from 316L Stainless Steel)	PNN-02	Single Use Only
Instrumentation Sterilization Tray	TRA-00	Reusable

Manual Cleaning Instructions
Automated cleaning may not be effective at removing debris from inner lumens or crevices and is not validated or recommended.

Table 20 Manual Cleaning Instructions

Post-use	• Remove excess soil with disposable non-shedding wipe. • Instruments should be covered with a damp cloth to prevent drying of soil prior to cleaning.
Containment and Transportation	• Observe universal precautions for handling contaminated/biohazardous materials. • Instruments should be cleaned within 30 minutes of use to minimize the potential for drying prior to cleaning.
Preparation for Cleaning	• No assembly/disassembly of Cartiva SCI instruments is required. • For initial and subsequent uses, follow all cleaning and sterilization instructions. • Prepare a neutral pH or nearly neutral pH enzymatic detergent at the use-dilution and temperature recommended by the agent's manufacturer. • Cleaning agents with chlorine or chloride as the active ingredient are corrosive to stainless steel and must not be used. Acidic cleaning agents should be avoided. • Saline solution has a corrosive effect on stainless steel and should not be used to rinse, soak, or clean instruments.
Cleaning Instructions	• Submerge the instruments in enzymatic detergent and soak for 20 minutes. • While submerged in enzymatic detergent, scrub each instrument with a soft-bristled brush, paying special attention to areas where debris might accumulate. Lumens and crevices should be cleaned with a long, narrow, soft-bristled brush. Avoid any harsh materials or cleaning motions that can scratch the surface of the instruments. • Remove the instruments from the enzymatic detergent and rinse each instrument thoroughly in purified water (such as distilled or deionized water) for a minimum of 3 minutes. Thoroughly flush lumens and other difficult to reach areas. • Sonicate instruments for a minimum of 10 minutes in an ultrasonic cleaner containing fresh enzymatic detergent, preferably at 45-50 kHz (according to the ultrasonic unit's directions). • Remove the instruments from the enzymatic detergent and rinse each instrument thoroughly with purified water (such as distilled or deionized water) for at least 3 minutes and until there is no sign of soil in the rinse stream. Thoroughly flush lumens and other difficult to reach areas.
Verifying Cleaning	• Check instruments for visible soil. All exterior surfaces as well as inner lumens should be inspected to ensure no visual contamination. • Repeat cleaning if soil or contamination is visible, and re-inspect.
Drying	• Instruments with inner lumens should be agitated or positioned so that liquid inside the lumens may drain. • Dry the exterior of the instruments with a clean, disposable, non-shedding wipe.

TRAY CLEANING

The sterilization tray should be cleaned and inspected between uses. Do not use broken or damaged trays. To clean, remove lids, trays, and liners and wish with a mild detergent. A sponge or soft bristle brush may be used if necessary. Do not use solvents, metal brushes or abrasives that may damage materials or coatings. After washing, rinse with clean water and dry with a lint free towel.

Warnings

Do not stack cases on top of one another. Be sure that ventilation holes are not obstructed, and that mats are correctly installed. For effective sterilization cases must have adequate steam circulation around all surfaces. They must also be placed upright on shelves in order for proper ventilation. Condensation can pool on non-absorbent surfaces. Do no place cases on their sides or at vertical angles in chamber, in order to ensure that proper drainage can occur during the cycle.

Small baskets, trays, or other accessories with covers or lids should only be used in trays specifically designed and labeled for the purpose. Do no overload cases. Overloading may inhibit steam flow, cause excessive drying times, and make cases too heavy to safely handle. Load and sterilize instruments in trays in accordance with the instructions provided within this IFU.

INSTRUMENTATION STERILIZATION

Packaging

Instruments may be loaded into dedicated instrument trays or general-purpose sterilization trays. The maximum load configuration, regardless of instrument size, is as follows using standard medical-grade steam sterilization wrap to double-wrap the tray.

Table 21 Sterilization Tray Loading Configuration

Sterilization Maximum Load Configuration
1 x Drill Bit (MTD-##) 1 x Introducer (INT-##) 1 x Placer (PLC-##) 3 x Guide Pins (PNN-02)

Sterilization Parameters

Steam-sterilize using one of the two validated steam cycles listed below. Each has been found to demonstrate a sterilization assurance level (SAL) of 10^{-6} for the maximum load configurations described above (AAMI TIR12):

Table 22 Cartiva SCI Instrumentation Sterilization Parameters

Gravity	
Sterilization Temperature	270°F / 132°C
Exposure Time	25 minutes
Minimum Drying Time	30 minutes

Pre-Vacuum	
Sterilization Temperature	270°F / 132°C
Exposure Time	4 minutes
Minimum Drying Time	20 minutes

Sterilizers vary in design and performance characteristics, so cycle parameters should be verified against the sterilizer manufacturer's instructions for the specific sterilizer and load configuration being used. When sterilizing multiple instruments in one steam sterilization cycle, ensure that the sterilizer manufacturer's maximum load is not exceeded. Drying time may vary according to load size (larger loads require longer drying times). Instruments must be adequately cooled after removal from the sterilizer. Do not touch instruments during the cooling process.

Storage
Sterilized, packaged instruments should be stored in a designated, limited access area that is well ventilated and provides protection from dust, moisture, insects, vermin, and temperature/humidity extremes. Sterilized instrument packages should be examined closely prior to opening to ensure that there has been no loss of package integrity.

PRODUCT COMPLAINTS
Any health care professional (e.g., customer or user of this system), who has complaints or who has experienced any dissatisfaction in the product quality, identity, durability, reliability, safety, effectiveness and/or performance, should notify Cartiva, Inc. USA. Further, if any of the implanted system ever "malfunctions," (i.e. does not meet any of its performance specifications or otherwise does not perform as intended), or may have caused or contributed to the death or serious injury of a patient, Cartiva, Inc. should be notified immediately by telephone, fax or written correspondence. When filing a complaint, please provide the device size, part number, lot number(s), your name and address, and the nature of the complaint. Complaints may also be reported directly to Medwatch at http://www.fda.gov/medwatch.

DEVICE RETRIEVAL
Should it be necessary to explant a Cartiva SCI device, please contact Cartiva, Inc. to receive instructions for device return. All explanted devices should be returned to Cartiva, Inc. for investigational analysis, in a leakproof container, with the date of explantation, explanting surgeon, and any known information regarding initial implantation, reasons for removal, and adverse event information. Also, please provide descriptive information about the gross appearance of the device in situ, as well as descriptions of the removal methods, i.e., intact or in pieces.

WARRANTY
The manufacturer does not take responsibility for any effects on safety, reliability or performance of the product if the product is not used in conformity with the instructions for use. Limited warranty and disclaimer: Cartiva, Inc. products are sold with a limited warranty to the original purchaser against defects in workmanship and materials. To the maximum extent permitted by applicable law any other express or implied warranties, including warranties of merchantability or fitness, are hereby disclaimed.

CAUTION
Federal (U.S.A.) Law Restricts this Device to Sale by or on the order of a Physician.

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A complete Summary of Safety and Effectiveness (SSED), surgical technique, and labeling information for the Cartiva® Synthetic Cartilage Implant may be obtained at www.fda.gov by searching PMA number P150017.