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 Reusable Instrumentation – ***Non-sterile***

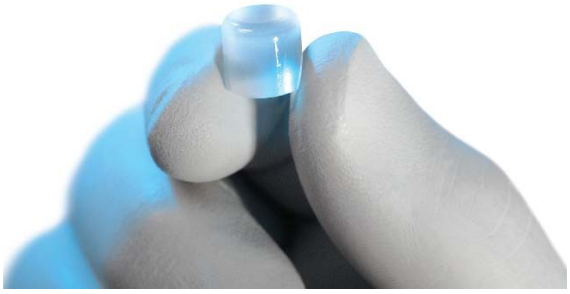
Cartiva® SCI Disposable Instrumentation – ***Sterile, Single-use***

DEVICE DESCRIPTION

The Cartiva Synthetic Cartilage Implant ("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 replace focal areas of painful damaged cartilage thereby reducing pain and maintaining range of motion in the first metatarsophalangeal (MTP) joint.

The Cartiva SCI, a molded cylindrical implant, is placed into the metatarsal head in the first metatarsophalangeal 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 is intended for use in the treatment of patients with painful degenerative or post-traumatic arthritis (hallux limitus or hallux rigidus) in the first metatarsophalangeal joint with or without the presence of mild hallux valgus.

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

PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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. The study was conducted in compliance with ICH guidelines and Good Clinical Practice (GCP)s. All sites had Ethics Approval and subject's signed an Informed Consent in compliance with 21 CFR Part 50 and ICH guidelines. Subjects were treated between October 2009 and February 2013. The database for this PMA reflected data collected through February 2015 and 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 (FAAM) for function, and the absence of major complications and subsequent surgical interventions.

In addition to the outcomes comprising the primary composite endpoint, other functional and quality-of-life outcomes scores were studied and included active MTP dorsiflexion, Revised Foot Function Index (FFI-R), and SF-36 Physical Function Scores.

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

The initial 2 subjects enrolled and treated at each site were not randomized to ensure they were adequately familiar with the procedure.

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.

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. This included the evaluation of pain as measured by the Visual Analog Scale (VAS), function as assessed by the Foot and Ankle Ability Measure (FAAM) Score, and the assessment of major complications and subsequent secondary surgical interventions. In addition, range of motion and radiographic outcomes were assessed, and subject and investigator questionnaires were completed. Subjects were required to have discontinued all pain medications (NSAIDs, narcotics, and any other analgesics) 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 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 Primary 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;[2]
- Maintenance of function from baseline in FAAM Sports score (inclusive of decrease <9) at 12 months; and,[3]
- Freedom from major complications[4] and SSSIs through 24 months.

Revised Primary Endpoint

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

The revised composite endpoint is defined as follows:

- Improvement (decrease) from baseline in VAS Pain of ≥30% at 24 months2;
- Maintenance in function from baseline in FAAM ADL score (inclusive of decrease <8) at 24 months3; and,
- Freedom from major complications4 and SSSIs through 24 months

In addition, the following requests by FDA were made with respect to the analysis and statistical methods:

- Modified Intent-to-treat (mITT) analysis defined as the primary analysis cohort.

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.

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

[3] 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.

[4] 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.

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.

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 (66.7%) were subject's randomized to fusion who wanted Cartiva. 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 table below.

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	100.00%	96.90%	96.00%	97.70%	95.80%	95.30%	91.50%	99.20%	93.50%	98.30%	93.20%
(9) Change from baseline in FAAM ADL available	129	50	125	48	125	46	122	43	122	43	115	41
(10) Change from baseline in VAS Pain available	130	50	128	48	128	46	124	43	123	43	116	41
(11) Radiography endpoint									130	50	130	50
(12) CCS at Month 12 and Month 24 available									130	47	129	47
(13) Actual[B] % Follow-up for CCS (12) / (7)									100.00%	94.00%	99.20%	94.00%

Actual[B] = Patients 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 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
mITT Completers[4]	129	47	-	176
Per Protocol (PP)[5]	127	47	-	174

[1]The Safety population includes all treated subjects.
[2]The ITT population includes all randomized subjects. Subjects who dropped out prior to treatment are considered study failures.
[3]The mITT population includes all randomized subjects who received the treatment to which they were randomized.

[4]The mITT completers population includes all randomized subjects who received the treatment to which they were randomized and have 24M data available.
[5]The PP population includes all randomized subjects who received the treatment to which they were randomized with subjects having major inclusion/exclusion deviations excluded.

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. 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 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[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	**Mean**	**SD**	**Med**	**Mean**	**SD**	**Med**	**t-test p-value[1]**
FAAM ADL	59.4	16.9	58.3	56.0	16.8	54.9	0.222
FAAM Sports	36.9	20.9	34.4	35.6	20.5	31.3	0.694
SF36	52.4	22.8	50.0	49.8	23.6	40.0	0.499
VAS	68.0	13.9	68.3	69.3	14.3	70.0	0.571

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

Table 6 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%	

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

Table 7 MOTION Study Subject Baseline Characteristics – OA Grade (ITT)

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

[1]Two-sided Fisher's exact test.
[2]One arthrodesis patient did not have a baseline OA grade

Table 8 MOTION Study Subjects Baseline Characteristics – Angular Deformities Involving the First Metatarsophalangeal Joint (Normal and Mild Hallux Valgus)

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

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 9).

Table 9 Length of Surgical Procedure and Anesthesia (minutes) for the Safety Cohort

	Cartiva			Fusion			p-value
	N	Mean	SD	N	Mean	SD	
Procedure Time[1]	112	34.7	12.3	39	57.8	21.5	<0.001
Length of Anesthesia[1]	137	67.0	27.8	44	95.3	41.1	<0.001

[1]Measured in minutes.

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.

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, and 50 fusion control subjects).

The overall adverse event rate was similar for 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%).

Table 10 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 (22 roll-in subjects, 130 randomized Cartiva subjects, and 50 fusion control subjects) are shown in Table 11. 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 11 Adverse Events by System Organ Class, Preferred Term, and Treatment Group

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

	Cartiva (N = 152)			Fusion (N = 50)		
	Events	Subj.	%	Events	Subj.	%
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 tumor	0	0	0.0%	1	1	2.0%
Prostate cancer	2	2	1.3%	0	0	0.0%
Benign soft tissue neoplasm	0	0	0.0%	1	1	2.0%

	Cartiva (N = 152)			Fusion (N = 50)		
	Events	Subj.	%	Events	Subj.	%
Benign muscle neoplasm	1	1	0.7%	0	0	0.0%
NERVOUS SYSTEM DISORDERS	5	5	3.3%	2	1	2.0%
Carpal tunnel syndrome	1	1	0.7%	0	0	0.0%
Dysaesthesia	0	0	0.0%	1	1	2.0%
Hypoaesthesia	0	0	0.0%	1	1	2.0%
Neuralgia	1	1	0.7%	0	0	0.0%
Neuropathy peripheral	1	1	0.7%	0	0	0.0%
Syncope	1	1	0.7%	0	0	0.0%
Cognitive disorder	1	1	0.7%	0	0	0.0%
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	1	1	0.7%	1	1	2.0%
Pregnancy	1	1	0.7%	1	1	2.0%
PSYCHIATRIC DISORDERS	5	5	3.3%	1	1	2.0%
Anxiety	2	2	1.3%	0	0	0.0%
Depression	2	2	1.3%	1	1	2.0%
Insomnia	1	1	0.7%	0	0	0.0%
RENAL AND URINARY DISORDERS	0	0	0.0%	1	1	2.0%
Nephrolithiasis	0	0	0.0%	1	1	2.0%
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1	1	0.7%	1	1	2.0%
Metrorrhagia	0	0	0.0%	1	1	2.0%
Postmenopausal hemorrhage	1	1	0.7%	0	0	0.0%
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%

The data presented demonstrate a reasonable assurance of the safety of the Cartiva device compared to fusion for the treatment of pain associated with arthritis of the first MTP joint.

Table 12 Serious Adverse Events by System Organ Class, Preferred Term, and Treatment Group - Safety Analysis Set

	Cartiva (N = 152)			Fusion (N = 50)		
	Events	Subj.	%	Events	Subj.	%
CARDIAC DISORDERS	1	1	0.7%	0	0	0.0%
Aortic valve stenosis	1	1	0.7%	0	0	0.0%
CONGENITAL, FAMILIAL, AND GENETIC DISORDERS	1	1	0.7%	0	0	0.0%
Congenital foot malformation	1	1	0.7%	0	0	0.0%
EAR AND LABYRINTH DISORDERS	1	1	0.7%	0	0	0.0%
Eustachian tube patulous	1	1	0.7%	0	0	0.0%
GASTROINTESTINAL DISORDERS	1	1	0.7%	0	0	0.0%

	Cartiva (N = 152)			Fusion (N = 50)		
	Events	Subj.	%	Events	Subj.	%
Small intestinal obstruction	1	1	0.7%	0	0	0.0%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	9	9	5.9%	0	0	0.0%
Fibrosis	1	1	0.7%	0	0	0.0%
Implant site pain	8	8	5.3%	0	0	0.0%
HEPATOBILIARY DISORDERS	2	2	1.3%	0	0	0.0%
Cholecystitis	1	1	0.7%	0	0	0.0%
Cholecystitis acute	1	1	0.7%	0	0	0.0%
INFECTIONS AND INFESTATIONS	1	1	0.7%	3	1	2.0%
Postoperative wound infection	1	1	0.7%	0	0	0.0%
Sepsis	0	0	0.0%	1	1	2.0%
Urinary tract infection	0	0	0.0%	2	1	2.0%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	8	8	5.3%	4	4	8.0%
Ankle fracture	1	1	0.7%	0	0	0.0%
Tendon rupture	1	1	0.7%	0	0	0.0%
Medical device complication	0	0	0.0%	2	2	4.0%
Post procedural bile leak	1	1	0.7%	0	0	0.0%
Post procedural complication	0	0	0.0%	1	1	2.0%
Medical device pain	3	3	2.0%	1	1	2.0%
Procedural pain	2	2	1.3%	0	0	0.0%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	7	5	3.3%	3	3	6.0%
Arthralgia	1	1	0.7%	1	1	2.0%
Arthritis	3	3	2.0%	1	1	2.0%
Joint stiffness	1	1	0.7%	0	0	0.0%
Osteoarthritis	1	1	0.7%	0	0	0.0%
Foot deformity	1	1	0.7%	1	1	2.0%
NEOPLASMS BENIGN, MALIGNANT, AND UNSPECIFIED (INCL CYSTS AND POLYPS)	2	1	0.7%	1	1	2.0%
Throat cancer	1	1	0.7%	0	0	0.0%
Gastrointestinal stromal **tumor**	0	0	0.0%	1	1	2.0%
Prostate cancer	1	1	0.7%	0	0	0.0%
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2	2	1.3%	0	0	0.0%
Dysphonia	1	1	0.7%	0	0	0.0%
Nasal septum deviation	1	1	0.7%	0	0	0.0%
SURGICAL AND MEDICAL PROCEDURES	2	2	1.3%	1	1	2.0%
Hip Arthroplasty	1	1	0.7%	0	0	0.0%
Hysterectomy	0	0	0.0%	1	1	2.0%
Muscle operation	1	1	0.7%	0	0	0.0%
Any Serious adverse event	37	30	19.7%	12	9	18.0%

During the MOTION study, there were a total of 37 serious adverse events (SAE) 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 terms of implant site pain, medical device pain, or procedure pain). For the serious 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 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 13.

Table 13 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 surgical intervention. Secondary surgical interventions were prospectively classified as revisions, removals, reoperations or supplemental fixations 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 14 Secondary Subsequent Surgical Interventions

SSSI	Cartiva (N=152)	Arthrodesis (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
Overall	**17 (11.2%)**	**6 (12%)**[2]

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

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

Device Related Adverse Events

Events classified as device related are presented in Table 15.

Table 15 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 Failures

A summary of the radiographic failures per the protocol specified primary endpoint that were observed in the mITT population is included in Table 16.

Table 16 Primary Endpoint Radiographic Failures (mITT)

Radiographic Failures (mITT)	Cartiva N=130	Fusion N=50
None	100%	90% (45)
Avascular Necrosis	0	N/A
Device Displacement	0	N/A
Device Fragmentation	0	N/A
Mal-union or Non-union	N/A	8% (4)
Fractured Hardware	N/A	2% (1)

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

Overall Conclusions from Review of Adverse Events

The overall adverse event rates of the Cartiva SCI and fusion cohorts were similar, but there were differences in the types of adverse events. While the cohorts each had different associated adverse events, the balance of these evets, either serious or non-serious, and overall adverse event rate, were not preferential to one cohort or another. More specifically, Cartiva subjects experienced more device-related adverse events; as compared with fusion subjects who experienced more procedure-related adverse events, although the differences were similar between the two groups. The data presented demonstrate a reasonable assurance of the safety of the Cartiva device compared to fusion for the treatment of pain associated with arthritis of the first MTP joint.

Radiographic Observations

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.

Radiolucency

Analyses of radiolucency in Cartiva subjects demonstrated that there was no impact on clinical outcomes or incidence of SSSIs. The presence of radiolucency in fusion subjects primarily resulted in study failures for non-union or fractured hardware.

Table 17 MOTION Study Radiolucency Observations (Safety)

	Cartiva (N=152)		Fusion (N=50)	
≤ 2 mm	2	1.3%	2	4.0%
> 2 mm	5	3.3%	4	8.0%
Any Radiolucency	**6[1]**	**3.9%**	**6**	**12.0%**

[1] One subject had a different classification of radiolucency at different time points

Bony Reactions

Radiographic findings of bony reactions were assessed and divided into erosion, cystic changes, loss of cortical white line and osteolysis. Bony reactions in general can be caused by bone remodeling typical to variations in increases or decreases in loading or surgical stimulation of the bone surface. Where observed, they were non-specific and not related to the implant. These radiographic observations were not correlated to clinical symptoms nor an indicator of success or failure in the study when assessing the composite endpoint.

Table 18 MOTION Study Bony Reaction Observations (Safety)

	Cartiva (N=152)		Fusion (N=50)	
Erosion	2	1.4%	0	0.0%
Cystic Changes	25	17.1%	0	0.0%
Loss of Cortical White Line	33	22.6%	0	0.0%
Osteolysis	2	1.4%	3	6.4%

For the composite endpoint and each individual assessment of pain, function and subsequent secondary surgical intervention, all subjects (with and without observation of bony reaction) experienced very similar rates of success.

Heterotopic Ossification

There was no radiographic evidence that the heterotopic ossification observations are related to the Cartiva device. The observations were assessed to be capsular in nature and similar to reactions noted in other surgical procedures involving surgical stimulation of the bone and the surrounding tissues.

Table 19 MOTION Study Heterotopic Ossification Observations (Safety)

	Cartiva (N=152)		Fusion (N=50)	
Class 1	12	8.2%	1	2.1%
Class 2	54	37.0%	1	2.1%
Class 3	12	8.2%	0	0.0%
Class 4	0	0.0%	20	42.6%

From a safety perspective, the observation of heterotopic ossification did not lead to an increase in Subsequent Secondary Surgical Interventions or adverse events. Further, heterotopic ossification was not correlated to clinical symptoms or lack of success.

EFFECTIVENESS

The primary efficacy of the Cartiva SCI device, which is based on the primary endpoint of the MOTION study, are discussed below. As shown in the following sections, Cartiva SCI was shown to be statistically non-inferior compared to fusion.

Pre-Specified Analysis Primary Composite Endpoint

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 20. 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%, which supported the non-inferiority determination along with the endpoint assessments in the per protocol cohort, multiple imputation analysis to address missing data, and tipping point assessment of missing data. 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 20 Pre-Specified Primary Endpoint Analysis

Population	Cartiva			Fusion			Non-inferiority 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 Primary Composite Endpoint

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 21) as well as indicated that the primary analysis population be the mITT population. The Sponsor concurs with FDA's requested endpoint modifications, which will be the focus of the analyses presented herein.

Table 21 Revisions to the MOTION Study Pre-Specified Primary Endpoint

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

Table 22 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 22 Revised Primary Composite Endpoint at 24-Months

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

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

The results of the revised primary composite endpoint in the mITT population 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 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.

Primary Endpoint 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 23.

Table 23 Missing Data Assessment for Revised Primary Composite Endpoint

Analysis	Number and Percentage Achieving Month 24 Composite Clinical Success						Non-Inferiority LB 95% CI[1]
	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

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

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

Primary Endpoint Per Protocol Analysis

Per Protocol (PP)

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

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

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

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

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

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

Individual Components of the Revised Primary Composite Endpoint

A composite endpoint allows for a combination of clinically meaningful assessments to be compared between two treatment groups in a single endpoint. All components of the MOTION study primary endpoint were based on categories widely accepted in the literature as clinically meaningful improvements/differences between pre and post-treatment. Each component is valid for what it measured, and subjects had to have a clinically meaningful performance in all categories to be ruled as a success. When looking at individual prongs of the composite, they should be evaluated using the pre-specified analysis (dichotomous) approach as an analysis of mean values within each prong does not capture whether individual subjects had clinically meaningful improvement.

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 or improvement of function	**115**	**113**	**98.3%**	**41**	**40**	**97.6%**
Radiographic • For Cartiva: absence of displacement, fragmentation, AVN • For fusion: absence of malunion, nonunion, or hardware failure	**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%**
Composite	**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 a removal, reoperation, revision, or supplemental fixation.

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:

SECONDARY EFFECTIVENESS ANALYSIS
Results for secondary endpoints measuring pain (VAS pain) and 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 assessment of active MTP dorsiflexion demonstrated that 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 great toe was fused at 15° of standing natural dorsiflexion.

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.

A two-sided alpha 0.05 statistical test was carried out such that if either the treatment effect or the treatment by visit interaction is statistically significant, a significant treatment effect could be declared. Since the VAS analysis by this method favored the Arthrodesis group, statistical significance did not demonstrate superiority for the Cartiva group (P>0.9999) all remaining tests of secondary hypotheses were considered exploratory.

VAS Pain
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 decreased from 68.3 to 5.0; fusion decreased from 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. 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			
	N	Mean	SD	Med	N	Mean	SD	Med
Baseline	130	68.0	13.9	68.3	50	69.3	14.3	70.0
Week 2	130	38.5	28.7	29.5	49	39.2	23.8	40.5
Week 6	128	33.2	24.7	27.4	48	17.2	17.6	10.6
Month 3	128	29.4	23.2	23.8	46	15.5	13.1	12.0
Month 6	124	28.9	27.5	20.5	43	11.7	18.3	4.0
Month 12	123	17.8	23.0	9.0	43	5.7	8.5	2.3
Month 24	116	14.5	22.1	5.0	41	5.9	12.1	1.5

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).

These results demonstrate 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
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. The mean FAAM ADL 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			
	N	Mean	SD	Med	N	Mean	SD	Med
Baseline	129	59.4	16.9	58.3	50	56.0	16.8	54.9
Week 2	126	48.8	21.6	47.6	47	40.3	20.7	39.3
Week 6	126	69.0	19.0	69.6	48	59.6	24.8	63.1
Month 3	125	77.3	17.7	80.0	46	82.5	14.9	86.9
Month 6	123	82.7	17.5	88.1	43	89.9	12.4	95.2
Month 12	123	88.6	14.4	95.0	43	94.1	6.8	95.2
Month 24	116	90.4	15.0	96.4	41	94.6	7.1	96.4

Both cohorts exhibited a decline in FAAM ADL at Week 2 attributed to surgical recovery. 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.

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.

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).

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.

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

The median FAAM Sports scores for Cartiva and fusion mITT subjects show both cohorts experienced significantly improved function with no appreciable difference at 24 months. The mean FAAM Sports scores for Cartiva and fusion mITT subjects show both cohorts exhibited a decline in FAAM Sports at Week 2. 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.

Again, there is no appreciable difference between the functional outcomes of the Cartiva and fusion populations when measured by FAAM Sports. 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			
	N	Mean	SD	Med	N	Mean	SD	Med
Baseline	127	36.9	20.9	34.4	50	35.6	20.5	31.3
Week 2	127	18.4	18.3	12.5	47	7.8	12.4	3.1
Week 6	126	39.5	26.3	37.5	49	22.4	22.5	18.8
Month 3	123	55.1	26.5	59.4	46	53.9	29.5	56.3
Month 6	120	66.6	26.3	71.9	42	78.6	23.8	87.5
Month 12	120	75.8	24.8	81.3	43	84.1	16.9	90.6
Month 24	113	79.5	24.6	90.6	41	82.7	20.5	90.6

Nearly 96% of the Cartiva population maintained or improved their 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. Cartiva's outcomes compare favorably to the fusion arm which experienced a 95.1% improvement in function.

Active MTP Dorsiflexion

Cartiva also collected joint motion data on both Cartiva 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 Table 29. Note: The angles reported for the fusion subjects reflect the angle at which the MTP joint is rigidly fixed in a natural standing (rest position) during the fusion procedure.

Table 29 Cartiva and Fusion mITT Cohort – Descriptive Statistics for Active MTP Dorsiflexion Over Time

	Cartiva Total Score				Arthrodesis Total Score			
	N	Mean	SD	Med	N	Mean	SD	Med
Baseline	130	22.7	11.2	20.0	50	22.9	11.2	20.0
Week 2	129	20.6	10.1	20.0	49	12.6	8.1	10.0
Week 6	127	25.1	10.8	25.0	48	13.0	9.0	14.5
Month 3	128	26.6	11.7	26.0	45	13.8	9.7	15.0
Month 6	124	28.1	9.8	30.0	44	14.9	8.6	15.0
Month 12	123	28.8	11.2	30.0	43	16.0	7.3	15.0
Month 24	114	29.0	11.9	30.0	41	15.1	8.4	16.0

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 (rigid fixation at 15° of standing natural dorsiflexion), while the Cartiva SCI subject still retained range of motion of the joint with the dorsiflexion measurement reflecting the maximum.

Revised Foot Function Index (FFI-R)

Outcomes were also assessed with the FFI-R.

Table 30 Cartiva and Fusion mITT Cohort – Descriptive Statistics for FFI-R Over Time

	Cartiva Total Score				Arthrodesis Total Score			
	N	Mean	SD	Med	N	Mean	SD	Med
Baseline	130	42.5	15.3	40.0	50	45.4	16.8	43.4
Week 2	129	33.2	20.3	32.0	49	30.5	19.0	30.0
Week 6	128	24.2	15.8	22.9	48	17.1	15.6	14.7
Month 3	128	20.5	13.2	20.0	46	14.3	11.5	11.7
Month 6	124	18.5	15.6	16.0	43	7.6	9.6	4.0
Month 12	123	11.3	14.4	8.0	43	4.2	6.2	2.9
Month 24	116	8.7	13.5	2.9	41	3.9	7.8	0.0

SF-36 – Physical Function Scores
The SF-36 physical function scores from the MOTION Study were also evaluate. The 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.

Table 31 Cartiva and Fusion mITT Cohort – Descriptive Statistics for SF-36 Over Time

	Cartiva Total Score				Arthrodesis Total Score			
	N	Mean	SD	Med	N	Mean	SD	Med
Baseline	130	52.4	22.8	50.0	50	49.8	23.6	40.0
Week 6	128	60.7	23.7	60.0	49	44.7	26.8	40.0
Month 3	128	68.1	25.2	75.0	46	71.7	25.5	80.0
Month 6	124	72.3	26.3	80.0	43	82.8	22.4	90.0
Month 12	123	78.9	22.7	90.0	43	83.7	24.9	95.0
Month 24	116	83.2	20.9	95.0	41	85.1	19.5	95.0

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

Patient Satisfaction
In the MOTION study, subjects that had completed their 24 months follow- 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. When considering subject gender, 85% of female subjects in the Cartiva group would have the procedure again at 24 months compared to 75% of the female subjects in the fusion arm.

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. 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.

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

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

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

Table 32 MOTION Study Primary Composite Endpoint Analyses

	Cartiva		Fusion		Non-inferiority LB 95% CI	Non-inferiority P-value (15%Δ)
	N	%	N	%		
Pre-Specified (VAS 12M+FAAM Sports 12 M + Safety 24 M)						
ITT[1]	132	**78.8%**	65	**61.5%**	**0.0552**	**<.0001**
mITT[2]	130	**80.0%**	50	**80.0%**	**-0.1050**	**0.0121**
FDA Requested (VAS 24M + FAAM ADL 24M + Safety 24M)						
mITT Completers[3]	129	**79.8%**	47	**78.7%**	**-0.1029**	**0.0101**
PP Analysis[4]	127	**79.5%**	47	**78.7%**	**-0.1065**	**0.0116**

[1]Prospectively defined as the primary; however, impacted by fusion dropout rate.
[2]mITT cohort prospectively defined in the pre-specified endpoint analysis.
[3] All randomized subjects who received the treatment to which they were randomized and have 24M data available.
[4]Per Protocol = all randomized subjects who received the treatment to which they were randomized with subjects having major inclusion/exclusion deviations excluded. Excludes two Cartiva subjects.

Results indicate non-inferiority of the composite endpoint based on the lower bound of the one-sided 95% confidence interval being greater than the pre-specified non-inferiority margin of -0.15 for the ITT, mITT, and Per Protocol population. 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.

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.

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

Safety Conclusions
Overall adverse event rates were similar between treatment groups, as were the rates of treatment-emergent adverse events. All Cartiva device-related events were considered anticipated. 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.

Benefit/Risk Conclusions

The MOTION 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).

Nearly the same percent of patients in both groups experienced any adverse event as well as any treatment emergent event (device or operative related). The majority of adverse events were classified as minor or moderate by the investigator. There were no unanticipated treatment emergent events. There were no reports of device migration, synovitis, bone destruction or device fragmentation.

The MOTION study has demonstrated a reasonable assurance of 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 outweighed by the benefits of improved function and decreased pain that the Cartiva SCI device provides for subjects.

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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 Cartiva SCI Instrumentation are available in both REUSABLE and DISPOSABLE configurations which 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 33 Cartiva SCI Implant Site Specifications

Lesion size	Implant	REUSABLE Drill Part	DISPOSABLE Instrument Set	Hole Diameter	Hole Depth
Up to 8 mm	CAR-08-US	MTD-08	MTK-08	7.9 mm	8.3 mm
8 mm to 10 mm	CAR-10-US	MTD-10	MTK-10	9.5 mm	10 mm

REUSABLE Instrumentation

The REUSABLE instruments are provided non-sterile and require sterilization prior to use.

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. 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 Placement Guide Pin. Insert the Placement 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 Placement Guide Pin, and advance the drill until the stop reaches the level of the adjacent tissue, to ensure appropriate depth is achieved. Note the Placement 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.

DISPOSABLE Instrumentation

The DISPOSABLE instrumentation is provided sterile and may only be used once.

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. Select the disposable instrument set based on the size of the lesion. 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 Placement Guide Pin. Remove the protective caps from the Placement Guide Pin and beware of the sharp tip under the metal protective cap. Insert the Placement 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 instrument set (8 mm or 10 mm), and remove the protective caps from the included Drill Bit. Beware of the Drill Bit's sharp blades. Utilize the Drill Bit to drill a hole into the subchondral bone to the proper depth

(recommendations can be found in the table above). The set and included 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 Placement Guide Pin, and advance the drill until the stop reaches the level of the adjacent tissue, to ensure appropriate depth is achieved. Confirm the cavity depth using the depth mark near the flat end of the Placer.

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. Markings on the Introducer depict the proper orientation of the implant in the Introducer. 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 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 (~1.5 mm) in the implant site.

PACKAGING

All instruments and implants are provided with dedicated packaging that has been qualified and validated for its particular use.

Cartiva Implant

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.

REUSABLE Instrumentation

The Cartiva SCI reusable sterilization tray and associated reusable surgical instruments are supplied non-sterile and must be cleaned and sterilized prior to use according to the instructions in this document. The reusable 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 a reusable instrument from the packaging until it is ready to be placed in the sterilization tray

DISPOSABLE Instrumentation

The Cartiva SCI disposable instrument sets are provided pre-packaged and sterile. They are intended for single use only. Before presentation to the operative field, inspect the package to ensure sterility has not been compromised during transportation. The shelf life of the disposable instrument set is five years. The use-before-date is provided on the shelf box and inner tray labels. Re-sterilization of the disposable instruments is strictly prohibited.

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.

CLEANING OF REUSABLE INSTRUMENTATION

The reusable instrumentation must be sterilized by the user prior to use in surgery. Implants and disposable instrumentation are provided sterile and are not to be sterilized or reprocessed.

Precautions

- Failure to properly clean reusable 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 placement guide pins for use during the Cartiva SCI implantation procedure. Re-use of the single-use placement guide pins or disposable instrumentation 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 instrument could result in improper device placement (depth, alignment, etc.) and undesired clinical outcomes.
- Placement Guide Pins must be discarded after one use.

Damage Inspection

- Inspect the reusable 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 reusable 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"). The disposable Cartiva SCI instruments are constructed of 316 and 316LVM stainless steel and medical grade Makrolon.

Table 34 Reusable 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
Placement Guide Pin (Fabricated from 316L Stainless Steel)	PNN-02	Single Use Only
Instrumentation Sterilization Tray	TRA-05-US	Reusable

Table 35 Disposable Instrumentation

Instrumentation Reference	Component Description	Classification
8 mm or 10 mm Metatarsal Instrument Set (MTK-08 or MTK-10)	Drill Bit (Fabricated from 316 Stainless Steel)	Single Use Only
	Introducer (Fabricated from Makrolon)	Single Use Only
	Placer (Fabricated from Makrolon)	Single Use Only
	Placement Guide Pin (Fabricated from 316LVM Stainless Steel)	Single Use Only

Manual Cleaning Instructions for REUSABLE INSTRUMENTATION

Only reusable instrumentation undergoes cleaning. Implants and DISPOSABLE instrumentation are provided sterile and are not to be sterilized or reprocessed.

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

Table 36 Manual Cleaning Instructions for REUSABLE INSTRUMENTATION

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.

Do not clean disposable instrumentation.

CLEANING of REUSABLE TRAY
The REUSABLE sterilization tray provided with REUSABLE instrumentation should be cleaned, sterilized and inspected prior use in accordance with the tray's Instructions for Use.

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.

STERILIZATION of REUSABLE INSTRUMENTATION
The REUSABLE instrumentation must be sterilized by the user prior to use in surgery. Implants and DISPOSABLE instrumentation are provided sterile and are not to be sterilized or reprocessed.

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

Table 37 Sterilization Tray Loading Configuration for REUSABLE INSTRUMENTATION

Sterilization Maximum Load Configuration
1 x Drill Bit (MTD-##) 1 x Introducer (INT-##) 1 x Placer (PLC-##) 3 x Placement 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 38 Sterilization Parameters for REUSABLE INSTRUMENTATION

Gravity	
Sterilization Temperature[1]	270°F / 132°C (+5°F / +3°C)
Exposure Time	25 minutes
Minimum Drying Time	30 minutes

Pre-Vacuum	
Sterilization Temperature[1]	270°F / 132°C (+5°F / +3°C)
Exposure Time	4 minutes
Minimum Drying Time	20 minutes

[1]Sterilization Validation Temperature Range

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 REUSABLE instruments and DISPOSABLE 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. 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.