CARTIVA®
Synthetic Cartilage Implant

The Only PMA Approved Product for the Treatment of 1st MTP Osteoarthritis

PRODUCT MONOGRAPH
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I. INTRODUCTION

The following pages provide a detailed overview of osteoarthritis of the first metatarsophalangeal joint (big toe joint), including treatment options, and the Cartiva® Synthetic Cartilage Implant (Cartiva SCI). The content within this document has been extrapolated from peer-reviewed publications and data submitted to the FDA for the approval of use of the Cartiva SCI device.

The Cartiva SCI (CAR-08 and CAR-10) represents a novel technology for the treatment of osteoarthritis of the big toe joint. The Cartiva SCI device:

- CAN BE IMPLANTED THROUGH A SIMPLE SURGERY
- PROVIDES SUBSTANTIAL PAIN REDUCTION AND FUNCTIONAL IMPROVEMENT
- IMPROVES RANGE OF MOTION

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.

All claims are referenced.
II. OVERVIEW OF OSTEOARTHRITIS

A. EPIDEMIOLOGY AND COSTS

Osteoarthritis (OA) is the most widespread type of arthritis or joint disease, and is among the most frequent reported symptomatic health problems for middle aged and senior adults.\(^1\) OA is characterized by pain and dysfunction in the joint that is caused by progressive loss of articular cartilage, remodeling of the subchondral bone, and osteophyte formation. It is estimated that approximately 12.1% of the US population age 25-74 years have clinically defined OA, and the World Health Organization estimates that 10% of the world’s population >60 years of age suffer from OA. Of those individuals >60 years of age, 80% have limitation of movement and 25% are unable to perform daily activities. Furthermore, a third of the individuals over the age of 45, report symptoms, which range between occasional joint stiffness and pain, associated with normal activities, to constant pain and permanent loss of motion. The incidence of OA in each of the human joints escalates with age, and may affect any of the synovial joints, though is most commonly found in the hand, foot, knee, spine, and hip joints.\(^1\)

The pathology of OA encompasses the entire joint and includes focal defects with continuing hyaline articular cartilage loss, concomitant changes to the subchondral bone, as well as marginal outgrowths, osteophytes, and increased thickening. An osteoarthritic joint is scarred by permanent damage to the joint structures, including the cartilage, the bone, and the joint capsule.\(^3\) Excessive and repetitive loading of the joint can surpass the tolerance of the joint, resulting in degeneration. Symptoms of OA may slowly develop remaining relatively unchanged for many years, or can develop rapidly, rendering a patient completely disabled within a short period of time.\(^1\) Symptomatically, OA is characterized by joint pain, tenderness, restriction of movement, crepitus, effusion, and local inflammation.\(^4\)

B. DEFINITION OF OSTEO-ARTHRITIS OF THE FIRST METATARSOPHALANGEAL JOINT (MTP)

The first metatarsophalangeal joint (MTP), or hallux, is a modified hinge joint consisting of the metatarsal head and the proximal phalanx (Figure 1), which is intrinsically unstable, though it gains stability from an array of soft tissue structures that provide support.\(^5\) The first MTP joint plays a functional role during gait, carrying approximately 119% of an individual’s body weight with each step.\(^6\) The first MTP joint is also the most frequent site of OA in the forefoot, affecting 1 in 40 people over the age of 50.\(^7\) An array of disorders due to acquired orthopaedic abnormalities and traumatic injuries may contribute to the development of OA in the first MTP joint, including primary OA or OA development due to trauma, repetitive microtrauma, rheumatoid arthritis, severe bunion deformities (hallux valgus), and recurrent hallux deformity after surgery.\(^8,9\)

First MTP joint OA often presents with pain and limited range of motion due to the development of osteophytes on the dorsal aspect of the metatarsal head and the proximal phalanx.\(^10,11\) Patients complain of pain with push off and an inability to wear shoes, which can force the hallux
into dorsiflexion. This progressive pain form osteophyte formation and degeneration of the cartilage begins dorsally in the early stages of the disease and progresses to involve the entire first MTP joint, resulting in cartilage loss with resultant pain and limitation of functional activities.

Hallux limitus is a term used to describe the loss of motion in the first MTP joint resulting from early stage MTP joint OA. Hallux limitus is progressive in nature and primarily affects dorsiflexion (upward movement) of the great toe. Hallux rigidus is a term typically used to depict the symptoms associated with more advanced degenerative arthritis of the first MTP joint, characterized by more severe limitations in range of motion that can become progressive. The severity of degenerative changes is strikingly dependent upon the duration of symptoms.

C. RISK FACTORS

There is no unifying theory as to the cause of hallux rigidus. It can be traumatic, caused by inflammatory disorders such as rheumatoid arthritis or gout, congenital variations such as a long first ray, vascular (avascular necrosis of the first MTP head) or acquired by other factors such as obesity or restrictive foot wear. Coughlin et al. states that while the symptoms of hallux rigidus are similar, the underlying causes of first MTP osteoarthritis and hallux rigidus are contested. Subjects can present with multiple causative factors making it difficult to identify a singular and direct cause of the progressive nature of the disease(s).

Hallux rigidus often occurs in conjunction with hallux valgus. Hallux valgus is a static subluxation of the first MTP joint that has a lateral divergence of the hallux and medial divergence of the first metatarsal, and are often called bunions. Per the American Academy of Orthopaedic Surgeons (AAOS), more than half of the women in the US have hallux valgus, which is often the result of wearing tight, narrow, or high heeled shoes. It is believed that some individuals have predisposing factors, making their feet more prone to develop hallux valgus. In the progression of hallux valgus, the first MTP joint may become unbalanced, forcing the metatarsal head laterally, causing chronic inflammation and eroding the joint capsule.

D. GRADES OF OSTEOARTHRITIS OF THE FIRST MTP

Diagnosis of hallux rigidus is based on clinical signs and symptoms, joint range of motion measurement and radiographic appearance. Several classification systems for hallux rigidus have been proposed, based on radiographic criteria alone or based on a combination of radiographic and clinical features. Of these, the Coughlin grading scale (Table 1) developed by Coughlin, et al. is the most commonly utilized scale at present and is also the most widely applied grading system in recent US publications on hallux rigidus. The Coughlin grading scale was developed based on a retrospective review of US subjects with hallux rigidus who were treated surgically between 1981 and 1999. The scale incorporates clinical and radiographic features and provides first metatarsophalangeal joint dorsiflexion ranges of motion commonly observed with each grade of hallux rigidus severity. Due to its wide use and acceptance by the foot and ankle medical community and its considerations of range of motion, radiographic findings, and clinical symptomatology for determining Grade of OA, the Coughlin Grading scale was selected for preoperative grading of hallux rigidus in the MOTION study.

Scale on next page

Figure 3. First MTP joint hallux valgus angular deformity, with concomitant osteoarthritis.

II. OVERVIEW OF OSTEOARTHRITIS cont.
## II. OVERVIEW OF OSTEOARTHRITIS cont.

### COUGHLIN GRADING SCALE

<table>
<thead>
<tr>
<th>GRADE</th>
<th>DORSIFLEXION</th>
<th>RADIOGRAPHIC FINDINGS</th>
<th>CLINICAL FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>40°-60° and/or 10-20% loss compared w/ normal side</td>
<td>Normal</td>
<td>No pain; only stiffness &amp; loss of motion on examination</td>
</tr>
<tr>
<td>1</td>
<td>30°-40° and/or 20-50% loss compared w/ normal side</td>
<td>Dorsal osteophyte is main finding Minimal joint space narrowing Minimal periarticular sclerosis Minimal flattening of metatarsal head</td>
<td>Mild/occasional pain &amp; stiffness Pain at extremes of dorsiflexion and/or plantarflexion on examination</td>
</tr>
<tr>
<td>2</td>
<td>10°-30° and/or 50-75% loss compared w/ normal side</td>
<td>Dorsal, lateral, &amp; possibly medial osteophytes giving flattened appearance to MT head ≤¼ dorsal joint space involved on AP/lateral Mild to moderate joint space narrowing &amp; sclerosis Sesamoids not usually involved</td>
<td>Moderate to severe pain &amp; stiffness that may be constant Pain occurs just before maximum dorsiflexion &amp; maximum plantarflexion on examination</td>
</tr>
<tr>
<td>3</td>
<td>≤10° and/or 75-100% loss compared w/ normal side There is notable loss of metatarsophalangeal plantar flexion as well (often ≤10° of plantarflexion)</td>
<td>Dorsal, lateral, &amp; possibly medial osteophytes w/ substantial narrowing Possible periarticular cystic changes &gt;¼ dorsal joint space involved on AP/lateral Sesamoids enlarged and/or cystic and/or irregular</td>
<td>Nearly constant pain &amp; substantial stiffness at extremes ROM, but not at midrange</td>
</tr>
<tr>
<td>4</td>
<td>Same as Grade 3</td>
<td>Same as Grade 3</td>
<td>Nearly constant pain &amp; substantial stiffness at extremes &amp; definite pain at midrange passive ROM</td>
</tr>
</tbody>
</table>

*Table 1. Coughlin Clinical-Radiographic System for Grading Hallux Rigidus*
III. TREATMENT OF OSTEOARTHRITIS OF THE FIRST MTP

A. OVERVIEW AND OBJECTIVES

Treatment options for first MTP joint OA depend upon the severity of the disease and the patient’s symptoms. Conservative management of first MTP joint OA is typically the first line of treatment for patients, including the use of orthotics or accommodative footwear, using a stiff soled shoe, pain relievers and anti-inflammatory medicines, injections, hot/cold temperature baths, and limitations in activities. If conservative treatment fails to relieve symptoms, surgical treatment is recommended.5,33,35

B. TREATMENT OPTIONS

Surgical treatments for first MTP joint OA are often divided into joint salvage and joint destructive procedures.

1. CHEILECTOMY

Cheilectomy is a joint salvage procedure which involves resection of the dorsal osteophytes from both the metatarsal and proximal phalanx and removal of the degenerative portion of the metatarsal head. An advantage of cheilectomy is that it preserves or maintains motion, while sustaining joint stability and allows for additional future surgical procedures, if necessary. Cheilectomy is often used in patients with Grade 1 or early Grade 2 first MTP joint OA with successful outcomes ranging from 72%-100%. Less optimal results have been seen, with some authors reporting less pain relief with more advanced (Grade 3 or 4) first MTP OA.12,33 Cheilectomy can provide satisfactory results and relief of symptoms in early first MTP OA, though it does not address the underlying cause of disease and the natural progression of the degenerative joint.34 Coughlin, et al., evaluated the long term treatment effect of cheilectomy. At an average time point of follow-up of 9.6 years post-op, seven (8%) of the ninety-three cheilectomies followed had failed. At the time of final follow-up, the mean AOFAS score was significantly improved with cheilectomy patients demonstrating an improved mean of 45.7 points or a 95% increase.

2. HEMIARTHROPLASTY

Hemiarthroplasty initially began with implants for the proximal phalanx and have evolved to include implants for the metatarsal head portion of the joint. These implants are designed to resurface the first MTP joint, while maintaining or preserving motion.35 Hemiarthroplasty has been indicated in patients with Grade 2, 3, and 4 first MTP joint OA. Though several of these implants have been available for many years under 510(k) clearance (i.e., Class II medical devices), very few studies have been published investigating the effectiveness of these implants.33 Of the limited publications, Townley et al., reported on 279 procedures using the BioPro implant with follow ranging from 8-months to 33 years. Good to excellent results were reported in 95% of patients.34 Raikin et al., evaluated 20 patients treated with 21 implants, and a mean follow up time of 79-months.36 Five implants failed with 4 salvaged with a fusion. Stiffness and continued pain have been reported following the use of the available hemiarthroplasty implant in the proximal phalanx. Furthermore, the reports of implant loosening and the limited number of publications have provided clinicians contradictory and poor quality evidence to support the use of hemiarthroplasty implants in the proximal phalanx.33,37

With the incidence of complications with proximal phalanx implants and since the metatarsal head is more severely damaged and denuded of cartilage in advanced first MTP OA, devices were developed to resurface the metatarsal head. Metatarsal resurfacing implants currently available in the US include the Arthrosurface Hemi-CAP and the Wright Medical Metatarsal Decompression Implant (MDI). The only metatarsal resurfacing device with information published is the Arthrosurface Hemi-CAP Hasselman and Shields presented their clinical results using the Hemi-CAP in 60 patients with a mean follow up time of 10-months.38,39 The AOFAS score improved from a preoperative mean of 44.1 to a follow up mean of 82.1. The VAS score (scale 0-10) decreased from a preoperative mean of 6.8 to a mean of 1.4 at follow up. Only 1 complication was reported, which was a superficial wound breakdown. The authors concluded that the results indicate the metatarsal implant is as good as or better than other joint sparing procedures. Furthermore, it was concluded that the limited removal of the subchondral bone with a metatarsal implant, allows for future treatment options, should they be required.

3. TOTAL JOINT REPLACEMENT

The development of total joint replacements for the first MTP joint was initiated in an attempt to restore motion and joint stability, in addition to providing pain relief. Silastic joints were developed for the MTP joints in the 1970s. These implants were double stemmed, acting as a dynamic spacer for the joint. Initial implants failed in numerous patients due to the high shear forces seen on the hinge of the implant. Modifications were made to the design with the insertion of titanium grommets, which improved the durability of the implant, though the incidence of silicone debris became a larger problem. Foreign body reactions, synovitis, and bone erosion were seen in some patients.
III. TREATMENT OF OSTEOARTHRITIS OF THE FIRST MTP

Metal unconstrained implants have also been used in patients with first MTP joint OA. Of the limited published reports on these implants, unfavorable results have shown joint instability, implant loosening, and radiolucency around the implants. Furthermore, these implants have not been widely accepted and have been directed for use in older, less active, or sedentary patients.

4. ARTHRODESIS

Arthrodesis has been the primary surgical procedure in the treatment of later stage (Grade 2, 3, and 4) OA of the first MTP joint, and has been indicated in patients with hallux rigidus, hallux valgus, intractable metatarsalgia, and as a salvage treatment for failed procedures. In the literature, union rates have been reported with a range of 77% to 100%, and a mean of approximately 90%. Rigid fixation is a necessity for arthrodesis to increase the rate of union and maintain the desired position. Several publications have reported outcomes in patients with first MTP OA treated with arthrodesis, though only a limited number are prospective and even less are controlled. Raikin et al., reported results in 27 patients treated with arthrodesis, and compared the outcomes to 21 patients treated with hemiarthroplasty. All patients achieved fusion and the AOFAS scores improved from a preoperative mean of 36.1 to 83.8 at the mean follow up time of 30-months. Mean VAS pain score (scale 0-10) was 0.7 postoperatively, which was significantly lower than the hemiarthroplasty patients. Gibson et al., reported results of a randomized, controlled study comparing arthrodesis to total joint replacement. Twenty-two patients were treated with arthrodesis with a mean follow up time of 24-months. Mean preoperative VAS pain score (scale 0-100) was 61 and decreased to a mean of 11 at follow up. Seven patients developed wound infections around the hardware, and 6 patients (15%) experienced delayed union, which did not occur until 12-months postoperatively. Goucher et al., prospectively reviewed 50 patients treated with arthrodesis. The union rate was 92% and the AOFAS score improved from a preoperative mean of 51 to a mean of 82 at the 16-month mean follow time point. These outcomes are similar to other published reports. Literature reported complications primarily include non-union, progressive arthritis of surrounding joints, and lateral metatarsalgia.

Treatment of first MTP joint OA by fusion does result in good clinical outcomes as a primary procedure and as a salvage procedure, as noted by the publications presented above. Pain is reduced by eliminating motion in the arthritic joint through destruction of the articular surfaces, removal of the joint and fusion of the opposing bony surfaces. By eliminating the joint, the opportunity for pain during joint motion is also voided. It should be noted that patients are often dissatisfied with the outcome of a fusion procedure due to the alterations in gait, shorter step length, and loss of toe step off. Furthermore, many female patients complain of the inability to wear high heeled shoes due to the lack of joint motion following a fusion procedure.

5. RESURFACING/FOCAL CHONDRAL DEFECT REPAIR OF THE FIRST MTP JOINT

The limited clinical evidence supporting the use of an implant in the proximal phalanx, and the fact that most articular cartilage damage occurs on the metatarsal head in the joint, led to the eventual development of implants for the metatarsal head of the first MTP joint. To date, only limited data has been published on the use of the metatarsal head implant, and with the published reports on the complications seen with proximal phalanx implants, these may account for the slow adoption of these surgical options. Additionally, all of the available hemiarthroplasty implants are comprised of either cobalt chrome and/or titanium, which are significantly stiffer than native cartilage. An implant comprised of a material with properties more similar to that of native cartilage is more appealing to clinicians treating patients with more advanced first MTP joint OA.
A. INDICATIONS FOR USE

The Cartiva Synthetic Cartilage Implant is intended for use in the treatment of patients with painful degenerative or post-traumatic arthritis (hallux limitus or hallux rigidus) in the first metatarsophalangeal joint with or without the presence of mild hallux valgus, defined as a hallux valgus angle less than or equal to 20° (greater than 20° was an exclusion criteria in the clinical study).

B. DESIGN AND SPECIFICATIONS

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

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

C. MECHANISM OF ACTION

Cartiva SCI is made from a proprietary biomaterial. The device, which is classified as a hydrated polymer, consists of water in similar proportion to human tissue. This organic polymer-based biomaterial is capable of withstanding repetitive loading typical of normal walking conditions, and its mechanical properties are similar to articular cartilage.

D. MATERIAL AND WEAR TESTING

1. BACKGROUND

The function of articular cartilage is to provide a low-friction bearing surface enabling the joint to withstand weight bearing through the range of motion needed to perform activities of daily living. Various methods of repairing damaged articular cartilage surfaces have been proposed and a variety of implant materials have been tried in an attempt to decrease pain and improve function following cartilage repair. The majority of these techniques have significant limitations including with loosening, malalignment/dislocation, implant fragmentation and bone loss. A major cause of failure has been osteolysis and aseptic loosening due to wear. (Baker et al, 2012)

Cartiva SCI is a unique material that was developed to produce an artificial articular surface that has shock-absorbing ability, high wear resistance, and wear particulate...
IV. CARTIVA SYNTHETIC CARTILAGE IMPLANT cont.

biocompatibility, properties which are necessary for suitability as a biomaterial intended to replace damaged cartilage.

2. REGULATORY PATHWAY

The Food & Drug Administration (FDA) regulates medical devices in the United States with different levels of regulatory oversight depending upon the classification of the device. The two most common regulator pathways are the 510(k) premarket submission and the more rigorous Premarket Approval (PMA).

The Food and Drug Administration (FDA) evaluates medical devices including arthroplasty products by two main pathways, Premarket Notification or 510(k) and Premarket Approval (PMA). The former requires demonstration that the device is substantially equivalent to a predicate device. Submitted data typically involves laboratory testing demonstrating that the new device introduces no new safety risks. Any devices not substantially equivalent to existing products follow the more stringent PMA pathway, requiring evidence of device safety and effectiveness. For a PMA application, clinical data from a large randomized clinical study is required to demonstrate safety and effectiveness, in addition to comprehensive laboratory studies characterizing the device properties, functionality, and safety.

The majority of total joint replacement and hemiarthroplasty implants (utilizing materials already widely used such as titanium, ceramic, polyethylene and silicone) reach market via a 510(k) submission which, depending on availability of predicate device data, may or may not include wear testing simulating indication-specific in vivo conditions and animal implantation of wear particulate.

Because the Cartiva SCI represents the first use of a polyvinyl alcohol hydrogel material for cartilage repair, the FDA required the Premarket Approval (PMA) pathway, the most stringent type of device marketing application required by the FDA. In addition to the PMA requirement for large randomized clinical studies to prove safety and effectiveness of the device, a PMA requires extensive testing of the materials suitability as a cartilage replacement material.

3. OTHER HEMIARTHROPLASTY MATERIAL CONCERNS

Hemiarthroplasty initially began with implants into the proximal phalanx, and have evolved to include one implant for the metatarsal head side of the joint. These implants are designed to resurface the first metatarsophalangeal (MTP) joint while maintaining or preserving motion. Though some of these implants have been available for over 50 years, very few studies have been published investigating the effectiveness of these implants. Further, there have been a number of material concerns reported in literature, specifically with silicone implants. Unlike hydrogels, silicone elastomers are non-biphasic, hydrophobic, and not well-lubricated in the body.

Silicone orthopedic prostheses introduced in the early 1960s were initially believed to be durable and biocompatible with good initial clinical results. Occurrence of inflammatory responses is now well recognized with these types of implants and is attributed to foreign body giant cell reaction to silicone particles. Although the implant itself is inert, abrasion and fatigue fracture of the implants was found to produce microscopic particles that caused inflammatory synovitis, a complication not readily identifiable without laboratory wear testing modeling physiological load and articulation conditions as well as wear debris animal testing.

Figure 5. A1, B, A2, C1-3 – Silicone Implant Failure
Complications secondary to the silicone microfragmentation include peri-implant bone resorption, subchondral cyst formation, deformity, and silicone lymphadenopathy.\textsuperscript{47,48} The addition of silica (silicon dioxide) during the manufacture of silicone prostheses has also been identified as a potential material source known to induce inflammation and fibrosis. Wear may increase exposure to silica and may contribute to the cellular response.\textsuperscript{49}

Overall, from an engineering perspective, the two most relevant complications are device breakage and device wear. Specifically, the previously studied double-stemmed, hinged prosthesis spans both sides of the joint and is designed to allow the toe to continue to bend after implantation. This subjects the device to repetitive bending moments that cause device fracture at either the stems or at the hinge, which is a stress concentrator.

The hinged silicone prosthesis was initially believed to be durable and biocompatible. During the early 1980s, however, reports of premature wear and silicone synovitis began to appear in the literature. Although the implant itself is inert, abrasion of the implants was found to produce microscopic particles that caused an inflammatory synovitis. Implant wear was also found to cause a silicone particulate lymphadenitis and cystic osteolysis in cancellous bone adjacent to the implants.

4. CARTIVA SCI

The Cartiva Synthetic Cartilage Implant is a novel osteochondral defect repair implant of synthetic hydrogel polymer with properties similar to those of cartilage. The material is comprised of two components, a water-soluble synthetic polyvinyl alcohol polymer (PVA) and normal saline, which is formulated and device geometry fixed through a thermal-physical mixture. This PVA material structure mimics key properties of load bearing cartilage: permeability, shock absorption, and lubrication. During loading, fluid migration provides impact load damping and self-lubrication, reducing friction.\textsuperscript{50}

5. CARTIVA PRE-CLINICAL TESTING

Testing requirements include a broad range of studies to demonstrate the suitability of the material for its intended purpose, including biocompatibility, material properties testing, functional and fatigue testing, chemical characterization, animal testing, and extensive wear and in vivo wear particulate testing as illustrated in Table 1. Biocompatibility testing conducted in the implant and instrumentation utilizing ISO 10993 demonstrated the materials are biocompatible for the intended use and do not illicit a biologic reaction. Material testing included the evaluation of various properties such as confined compression (aggregate modulus), unconfined compression, creep, shear, hydration properties, and cyclic stress against the logarithmic of cycles to failure (S-N).

S-N analysis, as well as comparison of those values to that reported in the literature for articular cartilage. All materials testing demonstrated Cartiva’s suitability for use in the 1st MTP joint. Mechanical fatigue and wear testing were carried out utilizing the anticipated clinical loading as calculated through joint and gait modeling based on published literature. The fatigue and wear testing demonstrated the device can withstand a simulated 5 years of continual cyclic loading in excess of clinically relevant loading values, as well as withstand simulated 5-years of articulating wear. All benchtop testing values are indicative that the Cartiva device is designed to withstand the physiologic conditions of the 1st MTP joint. Pushout testing was conducted to quantify the fixation of Cartiva devices implanted into model tissue/bone constructs using the Cartiva instrumentation and the procedure that will be specified in the PMA product’s Instructions for Use (IFU) and demonstrated the implantation could easily be achieved and the implants were secure in the cavity. Results of the one-year goat implant study demonstrated that the study objectives were met in that there was no local or systemic toxicity, no inflammatory reaction around the implant, or osteolytic bone loss. In comparison to the controls (empty defect), there were non-significant changes to the opposing tibial surface and no difference in the occurrence of the presence of subarticular cysts. No device dislodgment was observed. There was no instance of device fragmentation and the device was retained in all instances.
# IV. **CARTIVA** SYNTHETIC CARTILAGE IMPLANT cont.

## EXTENSIVE PRECLINICAL TESTING COMPONENTS

<table>
<thead>
<tr>
<th>Biocompatibility</th>
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<tbody>
<tr>
<td>Cytotoxicity L929 MEM Elution</td>
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<tr>
<td>Cytotoxicity Direct</td>
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<tr>
<td>Sensitization Kligman Maximization</td>
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<tr>
<td>Irritation/Intracutaneous IC Injection</td>
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<tr>
<td>Acute Systemic Toxicity Systemic Injection Test</td>
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<td>Genotoxicity Ames Reverse Mutation</td>
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<td>Genotoxicity Rodent Bone Marrow Micronucleus Assay</td>
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<td>Implantation Bone Implantation in Femoral Condyle</td>
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<td>Pyrogenicity</td>
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<tr>
<th>Material Properties</th>
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</thead>
<tbody>
<tr>
<td>Unconfined Compression – Loading of unconfined devices to achieve 10%, 20%, 30% and 40% strain to measure deformation resistance of the matrix and determine compatibility of the device with surrounding native tissue</td>
</tr>
<tr>
<td>Confined Compression – Devices confined in compression fixture with 5%, 10%, 15%, 20% and 25% strain applied to assess matrix stiffness at equilibrium (i.e., when load-induced fluid flow has ceased)</td>
</tr>
<tr>
<td>Shear – Devices seated between test blocks that are moved apart perpendicularly until failure; thereby, providing a baseline understanding of the simple shear properties of the material.</td>
</tr>
<tr>
<td>Compressive Creep – Simulated use loading in confined compression fixture to elucidate structural changes since equilibrium swelling properties are sensitive to the nature and stability of the hydrogel crosslinks</td>
</tr>
<tr>
<td>Hydration Properties – Devices dehydrated at ambient conditions followed by rehydration</td>
</tr>
<tr>
<td><strong>S-N Analysis</strong> - Devices loaded in a confined fixture to 8, 12, 18, and 24 MPa out to 5,000,000 cycles</td>
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<tr>
<th>Functional Testing - Fatigue</th>
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<tr>
<td>Cycles – 5 Million</td>
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<td>Test Surface – Finished Cartiva Device vs. Stainless Steel</td>
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<td>Simulated Axial Load – 4 MPa</td>
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<th>Chemical Characterization</th>
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<td>Testing of PVA resin, non-sterile and sterile devices, as well as sterile devices following compressive fatigue cycling for characterization.</td>
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<td>Differential Scanning Calorimetry</td>
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<td>Fourier Transform Infrared Spectroscopy</td>
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<td>Density and Specific Gravity</td>
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<td>High Pressure Liquid Chromatography</td>
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<td>1 Yr. Goat – Implant in stifles of 8 mature goats; control defect in 4 goats</td>
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<td>High field strength MR imaging system for morphology and quantitative T2 and T1-rho parameters</td>
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<td>Histological Processing</td>
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<td>Biomechanical Testing</td>
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*Table 3. Preclinical Testing Summary*
IV. CARTIVA SYNTHETIC CARTILAGE IMPLANT cont.

EXTENSIVE PRECLINICAL TESTING COMPONENTS cont.

<table>
<thead>
<tr>
<th>Wear Testing</th>
<th>Articulation of Cartiva device vs cartilage to assess the propensity for wear</th>
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<tr>
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<td>Test Surface – Finished Cartiva device vs. cartilage</td>
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<td>Simulated Axial Load – 4 MPa</td>
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<td>Particulate Analysis – SEM Low Angle Light Scattering</td>
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<th>Wear Debris/Particulate Implant</th>
<th>6 Mos Particulate Implant Study in 16 rabbits</th>
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<td></td>
<td>Particulate injection in rabbit knee - particulate from 5 Million wear cycles replicated and injected via bolus in quantity 9x that generated during testing</td>
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<td></td>
<td>3 and 6 Mos – Histology and pathology per ISO standards show no bioreactivity</td>
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Table 3. Preclinical Testing Summary

6. CARTIVA WEAR AND PARTICULATE TESTING

6a. Wear Testing Methodology

Since the Cartiva implant involved a new material used in an orthopedic implant, there was considerable focus and attention to ensure that this material would be suitable for use in the MTP joint. This testing required the development of a new wear testing fixture and testing methodology to simulate the wear environment of the first metatarsophalangeal joint. Simulated wear under conditions more challenging than in the human first metatarsophalangeal was critical to demonstrate the long term durability of the Cartiva SCI device and to quantify the wear particles.

In order to achieve this wear environment in vitro, a six-station wear simulator was developed for MTP articulation to provide the degrees, loading and controls necessary to apply 5,000,000 cycles of a walking gait to multiple Cartiva SCI devices simultaneously. The Cartiva SCI devices were articulated against opposing wear surfaces (cartilage) that would most accurately simulate the environment of the first metatarsophalangeal joint.

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The individual test station set-up is depicted in Figure 8.

Figure 8. Cartiva (bottom) vs. Cartilage (top) Test Station

6b. Cartiva Wear Results

The Cartiva SCI devices demonstrated only minor wear during the 5,000,000 cycles of testing. This total number of cycles represents a wear scenario spanning 5 years under worst case wear conditions. The Cartiva SCI devices were tested under maximum loads throughout the entire walking cycle without interruption of loading, in excess of what is observed physiologically.

6c. Cartiva Wear Debris

The wear debris particulate collected during the Cartiva wear study was analyzed for size, total quantity and particle morphology using both laser light scattering (LALLS) and scanning electron microscopy (SEM) technology. The particles were round to oval or elongated in shape with an average aspect ratio of 1.7, but not excessively so and thus do not classify as fibers. The average particle equivalent circle diameter was 3.8 microns.
The average total mass of debris collected per device over 5 million cycles was 0.18% of the initial mass of the test articles, well below the acceptance criteria of 100 mg over 5 million cycles. The volumetric wear rate was determined to be 1.50 mm\(^3\)/yr. This is considerably lower than the threshold wear rate to induce osteolysis for UHMWPE which is 80 mm\(^3\)/yr (or a linear penetration rate of 0.1 mm/yr) (Jacobs et al, 2007). Not only is the wear rate of the Cartiva lower than that of UHMWPE, UHMWPE particulate cause intense inflammation as compared to PVA hydrogels.\(^{50}\)

To assess the biocompatibility of Cartiva hydrogel wear debris, particulate was generated for intra-articular implantation in the New Zealand white rabbit model. Particulate characteristics affecting the \textit{in vivo} biological response – particle size, morphology, and total amount of debris – were consistent with those of the debris generated during the wear study. The particulate was injected into the rabbit knees, a joint 6.5X smaller than the human first MTP joint as determined via synovial fluid volume comparison.\(^{51,52}\) The total mass per sample injected into each rabbit knee was 3.9 mg, a safety factor of approximately 9 fold the maximum mass of wear debris.

The animals were assessed via histological tissue processing and pathology per ISO 10993-6 \textit{Tests for Local Effects After Implantation} at 3 months and 6 months. Both time interval testing noted no complications. All animals survived to the scheduled 3-month and 6-month termination time points. There were no test article-related adverse changes in viabilities, physical examinations, clinical observations, administration site scores, body weight and gross or systemic pathology of animals assigned at the 3-month and 6-month intervals. Histomorphometry evaluations performed on RAM-11 stained knee joint sections indicated that intra-articular injection of Cartiva particulate did not elicit a significantly greater local reaction compared to the sodium chloride control treatment at either time point. There was a reduction in macrophage activity for both treated and control animals at the 6-month interval, but the differences were not statistically significant. Histopathology showed no microscopic changes related to the test article and no variations in scores were statistically significant. There were no treatment related changes in the morphology or integrity of the cartilage surfaces, synovium, joint capsule, or underlying bone. Treatment with the test article produced no evidence of arthritis at 3 or 6 months and there was no evidence of systemic toxicity. The test article was found to be a non-irritant in this model.

Overall, the Cartiva device demonstrated wear resistance under worst conditions of testing and provided an overall wear rate significantly lower than that published to induce osteolysis for UHMWPE devices.
CARTIVA®

IV. CARTIVA SYNTHETIC CARTILAGE IMPLANT cont.

E. SURGICAL TECHNIQUE

The Cartiva SCI device, a cylindrical device made from an elastic biomaterial, may be used as a replacement for damaged cartilage and bone without requiring the destruction or removal of a patient’s healthy tissue. It is intended for use during a single surgical procedure. The procedure is similar to that used for osteochondral autograft or allograft transplantation; a part is placed into a pre-drilled hole to resurface the damaged area of cartilage/bone.

Cartiva SCI provides an alternative to tissue-based treatments without exposing the patient to the risk of viral transmission or an inflammatory response because it does not contain substances derived from human or animal tissue.

Cartiva SCI is supplied in a range of sizes for selection by the physician. The device is supplied sterile and is packaged as a single unit.

The following procedure is furnished as an example for informational purposes only where Cartiva is used in the treatment of osteoarthritis of the first metatarsophalangeal joint. Each surgeon must evaluate the appropriateness of the procedure based on his or her own surgical training and experience.

SURGICAL TECHNIQUE – EXAMPLE FOR INFORMATIONAL PURPOSES ONLY

Make a small straight dorsal or straight medial incision approximately 4 cm long along the dorsal or medial aspect of the first MTP joint to provide exposure of the capsule. Care should be taken to avoid nerve damage along the dorso-medial aspect of the joint. The EHL tendon should also be protected during the dorsal approach.

Open the capsule with a “U” flap or other preferred surgical technique.

Expose the entire joint to gain access to the central metatarsal head, which may require release of the lateral and medial soft tissues, to ensure enough exposure to allow implantation perpendicular to the metatarsal head.

Resect any osteophytes from the proximal phalanx and/or metatarsal head. Care must be taken during osteophyte resection of the metatarsal head to ensure adequate dorsal bone stock is preserved for insertion and stability of implant. After osteophyte resection, check the 1st MTP range of motion.
IV. CARTIVA SYNTHETIC CARTILAGE IMPLANT cont.

Visualize any osteochondral defect(s) or cartilage degeneration of the metatarsal head.

Using the concave end of the Placer, ensuring it is centered in the medial/lateral plane, create a perpendicular angle to the metatarsal head to identify the target implantation site. The placer should be positioned relatively central but can be slightly asymmetrical so as to be placed over the worst area of arthritic involvement on the metatarsal head.

Insert the Guide Pin into drill and slide the Placer over the Guide Pin.

As noted above, the placer should be positioned relatively central but can be slightly asymmetrical so as to be placed over the worst area of arthritic involvement on the metatarsal head. With the Placer and Guide Pin in the drill, position the Guide Pin perpendicular to the central aspect of the metatarsal head. Advance the guide pin into the center of the defect such that it is securely seated within the defect before removing the Placer.

Remove the Placer, while leaving the Guide Pin in place in the metatarsal head. Fluoroscopic imaging can be used to confirm the correct angle of guide wire placement.

1. Slide the Drill bit over the Guide Pin.
Advance the drill until the post/stop is flush with the surrounding metatarsal head surface.

Carefully, remove the Drill bit and Guide Pin from the implant site.

Flush out and remove all debris from metatarsal head defect, to allow the implant to be appropriately seated within the bone.

Remove the Cartiva implant from the sterile packaging using smooth forceps. Moisten Introducer tube with sterile saline. Insert the implant into the Introducer tube at the “wide” end of the Introducer, with the flat end or bottom of the implant facing downward towards the floor, so that the “round” or “convex” portion of the implant is facing upwards towards the ceiling. The goal is for the flat side of the implant to be placed in the bottom of the joint cavity and the round or convex portion of the implant to be the bearing surface against the opposing proximal phalanx.

Firmly grasp the Introducer tube, with the “narrower” or “lip” end firmly placed against a hard flat non-shedding surface. Use the small flat end of the Placer to press the implant to the distal end of the Introducer tube.
IV. CARTIVA SYNTHETIC CARTILAGE IMPLANT cont.

Place the distal end of the Introducer tube at the implant site, but not into the defect, perpendicular to the metatarsal head.

Carefully, press down on the Placer, while maintaining the distal end at the implant site, to press fit the implant into the metatarsal head defect.

The implant will be clearly visible following implantation.

The implant will sit slightly proud (~0.5-1.5 mm) in the metatarsal head following implantation. No more than one implant should be used in the metatarsal head.

Resect any osteophytes from dorsal, lateral, and medial aspects of metatarsal head.

Confirm range of motion of the joint against the implant, ensuring there is no restriction or limitation of the joint. Ensure all bone debris is free and clear from the joint and the wound.
Procedures for the management of mild hallux valgus can be conducted if the concomitant procedure would not compromise the ability to properly place the Cartiva implant or compromise circumferential cortical bone stock in the metatarsal head. Repair as necessary any soft tissues transected to gain joint exposure, and close the capsule in standard fashion.

Close the skin incision using standard fashion and bandage joint appropriately.

Post-operative management:
Subjects receiving Cartiva should have their wound bandaged and placed in a stiff soled shoe. Weight bearing may begin immediately as tolerated by the subject, as there are no specific weight bearing restrictions for the device. Range of motion exercises should begin immediately to avoid stiffness.
IV. CARTIVA SYNTHETIC CARTILAGE IMPLANT cont.

F. CLINICAL TRIAL

1. MOTION 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.

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.
IV. CARTIVA SYNTHETIC CARTILAGE IMPLANT cont.

2. 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:

**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 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. |

Table 4. MOTION Study Inclusion/Exclusion Criteria
3. 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 completing any of the study assessments. All complications and adverse events, device-related or not, were evaluated over the course of the study.

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Table 5. MOTION Study Assessments
4. 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.

4a. 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;¹
- Maintenance of function from baseline in FAAM Sports score (inclusive of decrease <9) at 12 months; and,²
- Freedom from major complications and SSSIs through 24 months.

4b. 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 months¹;
- Maintenance in function from baseline in FAAM ADL score (inclusive of decrease <8) at 24 months²; and,
- Freedom from major complications³ and SSSIs through 24 months.

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

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

3 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.

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.

4c. 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.

4d. 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 on the next page.

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

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## IV. CARTIVA SYNTHETIC CARTILAGE IMPLANT cont.

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<td>(2) Cumulative deaths</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>(3) Cumulative (Terminal) Failures</td>
<td>0 0</td>
<td>1 0</td>
<td>2 2</td>
<td>2 3</td>
<td>7 4</td>
<td>13 6</td>
</tr>
<tr>
<td>(4) Deaths + Failures among theoretical due</td>
<td>0 0</td>
<td>1 0</td>
<td>2 2</td>
<td>2 3</td>
<td>7 4</td>
<td>13 6</td>
</tr>
<tr>
<td>(5) Expected due for clinic visit</td>
<td>130 50</td>
<td>129 50</td>
<td>128 48</td>
<td>128 47</td>
<td>123 46</td>
<td>117 44</td>
</tr>
<tr>
<td>(6) Failures among theoretical due</td>
<td>0 0</td>
<td>1 0</td>
<td>2 2</td>
<td>2 3</td>
<td>7 4</td>
<td>13 6</td>
</tr>
<tr>
<td>(7) Expected due + Failures among theoretical due</td>
<td>130 50</td>
<td>130 50</td>
<td>130 50</td>
<td>130 50</td>
<td>130 50</td>
<td>130 50</td>
</tr>
</tbody>
</table>

### ALL EVALUATED ACCOUNTING (ACTUAL) AMONG EXPECTED DUE PROCEDURES

<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th>C</th>
<th>I</th>
<th>C</th>
<th>I</th>
<th>C</th>
<th>I</th>
<th>C</th>
<th>I</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>(8) FAAM ADL Follow-up (9) / (5) [%]</td>
<td>99.2</td>
<td>100.00%</td>
<td>96.90%</td>
<td>96.00%</td>
<td>97.70%</td>
<td>95.80%</td>
<td>95.30%</td>
<td>91.50%</td>
<td>99.20%</td>
<td>93.50%</td>
</tr>
<tr>
<td>(9) Change from baseline in FAAM ADL available</td>
<td>129 50</td>
<td>125 48</td>
<td>125 46</td>
<td>122 43</td>
<td>122 43</td>
<td>115 41</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(10) Change from baseline in VAS Pain available</td>
<td>130 50</td>
<td>128 48</td>
<td>128 46</td>
<td>124 43</td>
<td>123 43</td>
<td>116 41</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(11) Radiography endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(12) CCS at Month 12 and Month 24 available</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>130 47</td>
<td>129 47</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(13) Actual® % Follow-up for CCS (12) / (7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100.00%</td>
<td>94.00%</td>
<td>99.20%</td>
<td>94.00%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Actual® = Patients with any follow-up data reviewed or evaluated by investigator.

*Table 6. MOTION Study Cumulative Randomized Implanted Subjects Accountability by Visit (mITT Cohort)*
4. Analysis Populations

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

<table>
<thead>
<tr>
<th>ANALYSIS POPULATION</th>
<th>CARTIVA RANDOMIZED</th>
<th>FUSION</th>
<th>CARTIVA ROLL-IN</th>
<th>TOTAL SUBJECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety¹</td>
<td>130</td>
<td>50</td>
<td>22</td>
<td>202</td>
</tr>
<tr>
<td>ITT¹</td>
<td>132</td>
<td>65</td>
<td>-</td>
<td>197</td>
</tr>
<tr>
<td>mITT²</td>
<td>130</td>
<td>50</td>
<td>-</td>
<td>180</td>
</tr>
<tr>
<td>mITT completers³</td>
<td>129</td>
<td>47</td>
<td>-</td>
<td>176</td>
</tr>
</tbody>
</table>

¹The Safety population includes all treated subjects.
²The ITT population includes all randomized subjects. Subjects who dropped out prior to treatment are considered study failures.
³The mITT population includes all randomized subjects who received the treatment to which they were randomized.
⁴The mITT completers population includes all randomized subjects who received the treatment to which they were randomized and have 24M data available.

Table 7. MOTION Study Analysis Populations

4f. Study Population Demographics and Baseline Parameters

Subject demographics are summarized in Table 8. These data show that the treatment groups were well-balanced and no statistically significant differences were noted. The baseline demographics of the study population are consistent with baseline demographics reported in the literature for hallux rigidus subjects treated with cheilectomy, 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 8. MOTION Study Subject Baseline Characteristics (Continuous Variables, mITT Cohort)

<table>
<thead>
<tr>
<th>CARTIVA (n=132)</th>
<th>FUSION (n=50)</th>
<th>t-test p-value¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics - All</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Age at surgery (yrs)</td>
<td>57.4</td>
<td>8.8</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165.9</td>
<td>7.8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75.1</td>
<td>14.5</td>
</tr>
<tr>
<td>BMI (k/m²)</td>
<td>27.2</td>
<td>4.4</td>
</tr>
<tr>
<td>Baseline Functional Status</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>FAAM ADL</td>
<td>59.4</td>
<td>16.9</td>
</tr>
<tr>
<td>FAAM Sports</td>
<td>36.9</td>
<td>20.9</td>
</tr>
<tr>
<td>SF36</td>
<td>52.4</td>
<td>22.8</td>
</tr>
<tr>
<td>VAS</td>
<td>68.0</td>
<td>13.9</td>
</tr>
</tbody>
</table>

¹Two sample Pooled t-test p-value.

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

<table>
<thead>
<tr>
<th>CARTIVA (n=132)</th>
<th>ARTHRODESIS (n=65)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>n</td>
</tr>
<tr>
<td>Male</td>
<td>26</td>
</tr>
<tr>
<td>Female</td>
<td>104</td>
</tr>
</tbody>
</table>

¹Two sample Pooled t-test p-value.

Table 10. MOTION Study Subject Baseline Characteristics – OA Grade (ITT)

<table>
<thead>
<tr>
<th>CARTIVA (n=132)</th>
<th>ARTHRODESIS (n=65)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>OA Grade</td>
<td>n</td>
</tr>
<tr>
<td>0 to 15° Normal</td>
<td>155</td>
</tr>
<tr>
<td>≥ 15 to 20° Mild Hallux Valgus</td>
<td>47</td>
</tr>
</tbody>
</table>

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

Table 11. MOTION Study Subjects Baseline Characteristics – Angular Deformities Involving the First Metatarsophalangeal Joint (Normal and Mild Hallux Valgus)
4g. 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 12).

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.

5. 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).

5a. Adverse Events

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>
<thead>
<tr>
<th>CARTIVA (n=152)</th>
<th>FUSION (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Events</strong></td>
<td><strong>n</strong></td>
</tr>
<tr>
<td>Any Adverse Effect</td>
<td>245</td>
</tr>
<tr>
<td>Treatment Emergent Event</td>
<td>102</td>
</tr>
<tr>
<td>Device Related Event</td>
<td>31</td>
</tr>
<tr>
<td>Operative Procedure Related Event</td>
<td>71</td>
</tr>
<tr>
<td>Non-Treatment Emergent Event</td>
<td>143</td>
</tr>
<tr>
<td><strong>Any Serious Adverse Event</strong></td>
<td>37</td>
</tr>
<tr>
<td>Treatment Emergent Event</td>
<td>17</td>
</tr>
<tr>
<td>Device Related Event</td>
<td>11</td>
</tr>
<tr>
<td>Operative Procedure Related Event</td>
<td>6</td>
</tr>
<tr>
<td>Non-Treatment Emergent Event</td>
<td>20</td>
</tr>
<tr>
<td><strong>AE by Severity</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Mild</strong></td>
<td>110</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>114</td>
</tr>
<tr>
<td><strong>Severe</strong></td>
<td>21</td>
</tr>
</tbody>
</table>

1Lower and upper bounds of exact 95% confidence interval for the group difference in percentages experiencing the event.

2Fisher’s Exact Test

Table 12. Summary of Adverse Event Experiences Safety Analysis Set

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 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.

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
IV. CARTIVA SYNTHETIC CARTILAGE IMPLANT cont.

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.

5b. 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 incident. Of the 17 Cartiva subjects having an SSSI, 13 were in the randomized cohort and 4 were in the roll-in cohort.

5c. 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 15.

5d. 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 events, 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.

6. EFFECTIVENESS RESULTS

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.
IV. CARTIVA SYNTHETIC CARTILAGE IMPLANT cont.

6a. 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 16. 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>
<thead>
<tr>
<th>POPULATION</th>
<th>CARTIVA</th>
<th>FUSION</th>
<th>NON-INFERIORITY LB 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>N</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>mITT</td>
<td>N</td>
<td>n</td>
<td>%</td>
</tr>
</tbody>
</table>

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

Table 16. Pre-Specified Primary Endpoint Analysis for the Safety Cohort

6b. 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 17) 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.

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 endpoint at 24 months in the primary analysis (mITT) cohort.

Table 17. Revisions to the MOTION Study Pre-Specified Primary Endpoint

Table 18 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>
<thead>
<tr>
<th>POPULATION</th>
<th>CARTIVA</th>
<th>FUSION</th>
<th>NON-INFERIORITY LB 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>mITT Completers</td>
<td>N</td>
<td>n</td>
<td>%</td>
</tr>
</tbody>
</table>

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

Table 18. Revised Primary Composite Endpoint at 24-Months
6c. 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 19.

<table>
<thead>
<tr>
<th>ANALYSIS</th>
<th>CARTIVA</th>
<th>FUSION</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>NON-INFERIORITY LB 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Analysis (mITT)</td>
<td>129</td>
<td>103</td>
<td>79.8%</td>
<td>47</td>
<td>37</td>
<td>78.7%</td>
<td>-0.1029</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Missing Data = Failures</td>
<td>130</td>
<td>103</td>
<td>79.2%</td>
<td>50</td>
<td>37</td>
<td>74.0%</td>
<td>-0.0653</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Missing Data = Successes</td>
<td>130</td>
<td>104</td>
<td>80.0%</td>
<td>50</td>
<td>40</td>
<td>80.0%</td>
<td>-0.1158</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Best Case” for Cartiva</td>
<td>130</td>
<td>104</td>
<td>80.0%</td>
<td>50</td>
<td>37</td>
<td>74.0%</td>
<td>-0.0572</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Worst Case” for Cartiva</td>
<td>130</td>
<td>103</td>
<td>79.2%</td>
<td>50</td>
<td>40</td>
<td>80.0%</td>
<td>-0.1176</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Table 19. Missing Data Assessment for Revised Primary Composite Endpoint

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.

6d. 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 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 20 demonstrates that both treatments had very high responder rates for each component of the primary composite endpoint.

<table>
<thead>
<tr>
<th>ANALYSIS</th>
<th>CARTIVA</th>
<th>FUSION</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>N</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain VAS Improvement of a 30% compared to baseline</td>
<td>116</td>
<td>103</td>
<td>88.8%</td>
<td>41</td>
<td>40</td>
<td>97.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAAM ADL Maintenance or improvement of function</td>
<td>115</td>
<td>113</td>
<td>98.3%</td>
<td>41</td>
<td>40</td>
<td>97.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiographic:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• For Cartiva: absence of displacement, fragmentation, AVN</td>
<td>130</td>
<td>130</td>
<td>100.0%</td>
<td>50</td>
<td>45</td>
<td>90.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• For fusion: absence of malunion, nonunion, or hardware failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Freedom from SSSI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence of revisions, removals, reoperations, supplemental fixation</td>
<td>130</td>
<td>117</td>
<td>90.0%</td>
<td>50</td>
<td>44</td>
<td>88.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite</td>
<td>129</td>
<td>103</td>
<td>79.8%</td>
<td>47</td>
<td>37</td>
<td>78.7%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

Table 20. Revised Endpoint Components at 24-Months (mITT Cohort)
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:

### 6e. 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.

### 6e.(1) 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 and median VAS pain scores over time is presented in Table 21 and illustrated in Figure 9.

<table>
<thead>
<tr>
<th>CARTIVA TOTAL SCORE</th>
<th>ARTHRODESIS TOTAL SCORE</th>
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<tr>
<td>N  Mean  SD  Med</td>
<td>N  Mean  SD  Med</td>
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<td>Baseline  130 68.0 13.9  68.3 50 69.3 14.3 70.0</td>
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<tr>
<td>Week 2  130 38.5 28.7  29.5 49 39.2 23.8 40.5</td>
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<tr>
<td>Week 6  128 33.2 24.7  27.4 48 17.2 17.6 10.6</td>
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<tr>
<td>Month 3 128 29.4 23.2  23.8 46 15.5 13.1 12.0</td>
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<td>Month 6 124 28.9 27.5  20.5 43 11.7 18.3  4.0</td>
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<tr>
<td>Month 12 123 17.8 23.0  9.0 43 5.7 8.5 2.3</td>
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<tr>
<td>Month 24 116 14.5 22.1  5.0 41 5.9 12.1  1.5</td>
<td></td>
</tr>
</tbody>
</table>

Table 21. Cartiva and Fusion mITT Cohort – Descriptive Statistics for VAS Pain Over Time

Figure 9. Median VAS Pain Scores

Substantial reduction in pain with demonstrated durability at 2 years

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.
6e.(2) FAAM ADL Pain

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 and median FAAM ADL over time is presented in Table 22 and Figure 10.

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.

6e.(3) 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 and median FAAM Sports scores over time for mITT subjects is represented in Table 23 and illustrated in Figure 11.
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.

**6e.(4) 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 are illustrated in Figure 12. Note: The fusion subject’s MTP joint is rigidly fixed in a natural standing (rest position) during the fusion procedure.

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°).

**6e.(5) Patient Satisfaction**

In the MOTION study, subjects that had completed their 24 months follow-up 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.

**7. 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.
IV. CARTIVA SYNTHETIC CARTILAGE IMPLANT cont.

At 2 years, more patients would opt to have the Cartiva procedure again (86.3% vs 78.0%)

Figure 13. Patient Satisfaction

7a. 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.

7b. 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 24 presents a summary of the Cartiva and fusion subjects who met the pre-specified and revised primary composite endpoint.

Table 24. MOTION Study Primary Composite Endpoint Analyses

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:
CARTIVA SYNTHETIC CARTILAGE IMPLANT cont.

7c. 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.

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 metatarsophalangeal joint.
IV. CARTIVA SYNTHETIC CARTILAGE IMPLANT cont.

G. COST EFFECTIVENESS

FASTER THAN FUSION
FAST & SIMPLE SURGICAL PROCEDURE

Cartiva surgeries are 40% (23 minutes) faster than fusion surgery.

In most operating rooms in the United States, the value of a minute can be as high as $100².
IV. CARTIVA SYNTHETIC CARTILAGE IMPLANT cont.

H. SUMMARY

1. INDICATIONS FOR USE
The Cartiva Synthetic Cartilage Implant is intended for use in the treatment of patients with painful degenerative or post-traumatic arthritis (hallux limitus or hallux rigidus) in the first metatarsophalangeal joint with or without the presence of mild hallux valgus, defined as a hallux valgus angle less than or equal to 20° (greater than 20° was an exclusion criteria in the clinical study).

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

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

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.

CAUTION: Federal law restricts this device to sale by, or on the order of, a physician. Please reference the Directions for Use labeling for a complete list of contraindications, warnings, precautions, and adverse events.

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

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

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.
V. CARTIVA REFERENCES

V. CARTIVA REFERENCES cont.


July 1, 2016

Cartiva, Incorporated
Ms. Deborah Moore
Vice President, Regulatory, Clinical, and Quality Affairs
6120 Windward Parkway, Suite 220
Alpharetta, Georgia 30005

Re: P150017
Trade/Device Name: Cartiva Synthetic Cartilage Implant
Filed: May 1, 2015
Amended: May 1, June 15, August 31, November 23, 2015; January 19, February 11, May 18, 2016 and May 19, 2016
Product Code: PNW

Dear Ms. Moore:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the Cartiva Synthetic Cartilage Implant. This device is indicated 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. We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). The device is further restricted under section 515(d)(1)(B)(ii) of the act insofar as the labeling must specify the specific training or experience practitioners need in order to use the device. FDA has determined that these restrictions on sale and distribution are necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

Expiration dating for this device has been established and approved at 2 years. This is to advise you that the protocol you used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(7).
Continued approval of this PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year from the date of approval of the original PMA. Two copies of this report, identified as "Annual Report" and bearing the applicable PMA reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84. This is a reminder that as of September 24, 2014, class III devices are subject to certain provisions of the final UDI rule. These provisions include the requirement to provide a UDI on the device label and packages (21 CFR 801.20), format dates on the device label in accordance with 21 CFR 801.18, and submit data to the Global Unique Device Identification Database (GUDID) (21 CFR 830 Subpart E). Additionally, 21 CFR 814.84 (b)(4) requires PMA annual reports submitted after September 24, 2014, to identify each device identifier currently in use for the subject device, and the device identifiers for devices that have been discontinued since the previous periodic report. It is not necessary to identify any device identifier discontinued prior to December 23, 2013. For more information on these requirements, please see the UDI website, http://www.fda.gov/udi.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the device, the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

In addition to the Annual Report requirements, you must provide the following data in post-approval study (PAS) reports for each PAS listed below. Separate PAS Progress Reports must be submitted for each study every six (6) months during the first two (2) years of the study and annually thereafter, unless otherwise specified by FDA. Two (2) copies of each report, identified as an "ODE Lead PMA Post-Approval Study Report" in accordance with how the study is identified below and bearing the applicable PMA reference number, should be submitted to the address below.

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

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

**Primary Study Endpoints**

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

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

**Secondary Study Endpoints**

1. Evaluation of maintenance of range of motion;
2. Wear characteristics or device degradation for any Cartiva implant removed;
3. Pain and function over time (Visual Analog Scale [VAS] pain scores, Foot and Ankle Ability Measure [FAAM] Activities of Daily Living [ADL] function scores and FAAM Sports function scores); and
4. Evaluation of radiographic findings (radiolucency, bony reactions, and heterotopic ossification) looking at presence or progression from 24 months to 5+ years as well as correlation with the 5+ years clinical outcomes (effectiveness and safety).

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

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\(^1\) Major complications are radiographic findings assessed by an independent radiographic reviewer. These include absence of device displacement, device fragmentation, and avascular necrosis in the Cartiva group.
A post-approval study, with expected cumulative event rate from 2 to 5 based on exponential survival equal to 13.5%. The hypothesis stated is:

H\(_0\): \( \pi_A > \pi_0 + \delta \)
H\(_A\): \( \pi_A \leq \pi_0 + \delta \)

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

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

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

Be advised that the failure to conduct any such study in compliance with the good clinical laboratory practices in 21 CFR part 58 (if a non-clinical study subject to part 58) or the institutional review board regulations in 21 CFR part 56 and the informed consent regulations in 21 CFR part 50 (if a clinical study involving human subjects) may be grounds for FDA withdrawal of approval of the PMA. In addition, the results from any post approval study should be included in the labeling as these data become available. Any updated labeling must be submitted to FDA in the form of a PMA Supplement. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order" ([http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm)).

Before making any change affecting the safety or effectiveness of the device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" ([http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm)).

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes
aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or

2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

In accordance with the recall requirements specified in 21 CFR 806.10, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at http://www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm.

CDRH does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm. Written requests for this information can also be made to the Food and Drug Administration, Dockets Management Branch, (HFA-305), 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all final labeling. Final labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final labeling is identical to the labeling approved in draft form. If the final labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in 6 copies, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.
If you have any questions concerning this approval order, please contact Jemin J. Dedania, MS, RAC at 301-769-6949 or jemin.dedania@fda.hhs.gov.

Sincerely,

William H. Maisel -S

William H. Maisel, MD, MPH
Deputy Center Director for Science
Center for Devices and Radiological Health
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# CARTIVA, INC. US PRODUCT CATALOG

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## Drill Bits

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<tr>
<th>Product</th>
<th>Description</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>INT-10</td>
<td>10 mm Introducer</td>
<td>$175</td>
</tr>
<tr>
<td>INT-8</td>
<td>8 mm Introducer</td>
<td>$175</td>
</tr>
</tbody>
</table>

## Placers

<table>
<thead>
<tr>
<th>Product</th>
<th>Description</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLC-10</td>
<td>10 mm Placer</td>
<td>$160</td>
</tr>
<tr>
<td>PLC-8</td>
<td>8 mm Placer</td>
<td>$160</td>
</tr>
</tbody>
</table>

## Delivery Tray

<table>
<thead>
<tr>
<th>Product</th>
<th>Description</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRA-05-US</td>
<td>Delivery Tray</td>
<td>$305</td>
</tr>
</tbody>
</table>

Clinical/Technical Support: 877-336-4616
## IMPLANTS

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRF-01</td>
<td>ProxiFuse Implant (includes bone awl)</td>
<td>$950</td>
</tr>
</tbody>
</table>

## RASPS

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAS-08</td>
<td>8 mm Rasp</td>
<td>$185</td>
</tr>
</tbody>
</table>
Form W-9

Request for Taxpayer Identification Number and Certification

Give Form to the requester. Do not send to the IRS.

1 Name (shown on your income tax return). Name is required on line 1, do not leave this line blank.
Cartiva, Inc.

2 Business name disregarded entity name, if different from above

3 Check appropriate box for federal tax classification; check only one of the following seven boxes:
   [ ] Individual/sole proprietor
   [ ] C Corporation
   [ ] S Corporation
   [ ] Partnership
   [ ] Trust/estate
   [ ] Limited liability company
   [ ] Single-member LLC
   [ ] Other (see instructions)

4 Preprinted codes (codes apply only to certain entities; see instructions on page 8)
   [ ] Exempt payee code (as set forth in section (c)(2)(A)(i)(v)(B) of the IRC)
   [ ] Exemption from FATCA reporting (as set forth in section (c)(2)(A)(i)(v)(B) of the IRC)

5 Address (number, street, and apt. or suite no.)
6120 Windward Parkway, Suite 220

6 City, state, and ZIP code
Alpharetta, GA 30005

7 List social security number here (optional)

Part I
Taxpayer Identification Number (TIN)
Enter your TIN in the appropriate box. The TIN provided must match the name given on line 1 to avoid backup withholding. For individuals, this is generally your social security number (SSN). However, for a resident alien, sole proprietor, or disregarded entity, see the Part I instructions on page 3. For other entities, it is your employer identification number (EIN). If you do not have a number, see How to get a TIN on page 3.

Note. If the account is in more than one name, see the instructions for line 1 and the chart on page 4 for guidelines on whose number to enter.

Social security number

Employer identification number
4 5 2 8 9 7 9 8 3

Part II
Certification
Under penalties of perjury, I certify that:
1. The number shown on this form is my correct taxpayer identification number (or I am waiting for a number to be issued to me), and
2. I am not subject to backup withholding because: (a) I am exempt from backup withholding, or (b) I have not been notified by the Internal Revenue Service (IRS) that I am subject to backup withholding as a result of a failure to report all interest or dividends, or (c) the IRS has notified me that I am no longer subject to backup withholding; and
3. I am a U.S. citizen or other U.S. person (as defined below); and
4. The FATCA code(s) entered on this form (if any) indicating that I am exempt from FATCA reporting is correct.

Certification instructions. You must cross out item 2 above if you have been notified by the IRS that you are currently subject to backup withholding because you have failed to report all interest and dividends on your tax return. For real estate transactions, item 2 does not apply. For mortgage interest paid, acquisition or abandonment of secured property, cancellation of debt, contributions to an individual retirement arrangement (IRA), and generally, payments other than interest and dividends, you are not required to sign the certification, but you must provide your correct TIN. See the instructions on page 3.

Sign Here
Signature of U.S. person

Date
3-29-16

General Instructions
Stationary references are to the Internal Revenue Code unless otherwise noted.

Purpose of Form
An individual or entity (Form W-9 requester) who is required to file an information return with the IRS must obtain your correct taxpayer identification number (TIN) which may be your social security number (SSN), individual taxpayer identification number (ITIN), adoption taxpayer identification number (ATIN), or employer identification number (EIN), to report on an information return the amount paid to you, or other amount reportable on an information return. Examples of information returns include, but are not limited to, the following:
- Form 1099-MISC (interest earned or paid)
- Form 1099-DIV (dividends, including those from stocks or mutual funds)
- Form 1098-MISC (various types of income, prizes, awards, or gross proceeds)
- Form 1099-B (stock or mutual fund sales and certain other transactions by brokers)
- Form 1099-F (proceeds from real estate transactions)
- Form 1099-K (merchandise and third party network transactions)

Cat. No. 10231X

Form W-9 (Rev. 12-2014)
The Only PMA Approved Product for the Treatment of 1st MTP Osteoarthritis

CARTIVA® Synthetic Cartilage Implant
The US Food and Drug Administration (FDA) has approved the Cartiva Synthetic Cartilage Implant for commercial use when used in accordance with the indications for use (P150017, date of approval July 1, 2016)