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# Prospective, Randomized, Multi-centered Clinical Trial Assessing Safety and Efficacy of a Synthetic Cartilage Implant Versus First Metatarsophalangeal Arthrodesis in Advanced Hallux Rigidus


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**Abstract**

**Background:** Although a variety of great toe implants have been tried in an attempt to maintain toe motion, the majority have failed with loosening, malalignment/dislocation, implant fragmentation and bone loss. In these cases, salvage to arthrodesis is more complicated and results in shortening of the ray or requires structural bone graft to reestablish length. This prospective study compared the efficacy and safety of this small (8/10 mm) hydrogel implant to the gold standard of a great toe arthrodesis for advanced-stage hallux rigidus.

**Methods:** In this prospective, randomized non-inferiority study, patients from 12 centers in Canada and the United Kingdom were randomized (2:1) to a synthetic cartilage implant or first metatarsophalangeal (MTP) joint arthrodesis. VAS pain scale, validated outcome measures (Foot and Ankle Ability Measure [FAAM] sport scale), great toe active dorsiflexion motion, secondary procedures, radiographic assessment, and safety parameters were evaluated. Analysis was performed using intent-to-treat (ITT) and modified ITT (mITT) methodology. The primary endpoint for the study consisted of a single composite endpoint using the 3 primary study outcomes (pain, function, and safety). The individual subject's outcome was considered a success if all of the following criteria were met: (1) improvement (decrease) from baseline in VAS pain of ≥30% at 12 months; (2) maintenance of function from baseline in FAAM sports subscore at 12 months; and (3) absence of major safety events at 2 years. The proportion of successes in each group was determined and 1-sided 95% confidence interval for the difference between treatment groups was calculated. Noninferiority of the implant to arthrodesis was considered statistically significant if the 1-sided 95% lower confidence interval was greater than the equivalence limit (<15%). A total of 236 patients were initially enrolled; 17 patients withdrew prior to randomization, 17 patients withdrew after randomization, and 22 were nonrandomized training patients, leaving 152 implant and 50 arthrodesis patients. Standard demographics and baseline outcomes were similar for both groups.

**Results:** VAS pain scores decreased significantly in both the implant and arthrodesis groups from baseline at 12 and 24 months. Similarly, the FAAM sports and activity of daily living subscores improved significantly at 12 and 24 months in both groups. First MTP active dorsiflexion motion improvement was 6.2 degrees (27.3%) after implant placement and was maintained at 24 months. Subsequent secondary surgeries occurred in 17 (11.2%) implant patients (17 procedures) and 6 (12.0%) arthrodesis patients (7 procedures). Fourteen (9.2%) implants were removed and converted to arthrodesis, and 6 (12.0%) arthrodesis patients (7 procedures [14%]) had isolated screws or plate and screw removal. There were no cases of implant fragmentation, wear, or bone loss. When analyzing the ITT and mITT population for the primary composite outcome of VAS pain, function (FAAM sports), and safety, there was statistical equivalence between the implant and arthrodesis groups.

**Conclusion:** A prospective, randomized (2:1), controlled, noninferiority clinical trial was performed to compare the safety and efficacy of a small synthetic cartilage bone implant to first MTP arthrodesis in patients with advanced-stage hallux rigidus. This study showed equivalent pain relief and functional outcomes. The synthetic implant was an excellent

alternative to arthrodesis in patients who wished to maintain first MTP motion. The percentage of secondary surgical procedures was similar between groups. Less than 10% of the implant group required revision to arthrodesis at 2 years.
**Level of Evidence:** Level I, prospective randomized study.

**Keywords:** arthritis, forefoot disorders, hallux disorders, clinical trial, implant, arthrodesis

## Introduction

Great toe arthritis or hallux rigidus is a common problem and affects 1 in 40 people over the age of 50.[9] Individuals with hallux rigidus have joint pain and demonstrate a restriction in dorsiflexion at the first metatarsophalangeal (MTP) joint. This progressive pain from osteophyte formation and degeneration of the cartilage begins dorsally in the early stages of the disease and progresses to involve the entire first metatarsophalangeal joint, resulting in cartilage loss, with resultant pain and limitation of functional activities. The first MTP joint plays a functional role during gait, carrying approximately 119% of an individual's body weight with each step.[12] With advancing arthritis, the current surgical options include a partial or total joint replacement, or first MTP arthrodesis. Many joint replacement surgeries have experienced higher than average complications from bone loss, wear debris, implant fragmentation and loosening, transfer metatarsalgia, lack of predictability with implants,[3] and limited clinical data. After implant failure, a salvage of the problem by conversion to a first MTP fusion has been shown to have more complications and worse functional results.[11] Based on these challenges, primary first MTP arthrodesis is considered the most reliable surgical option for advanced arthritis of the great toe. A successful fusion decreases pain, maintains toe length, and provides stability of the first ray while sacrificing first MTP joint motion. Loss of first MTP joint motion can interfere with activities requiring great toe motion such as running and jumping and also influences the choice of footwear. Consequently, there are benefits of joint-salvaging procedures that would allow for reduced great toe pain, improved function, and maintenance of motion without excessive bone resection or shortening, thus maintaining the option of a fusion if needed. The purpose of this prospective, randomized trial was to examine the function, pain, and safety parameters in patients with advanced great toe arthritis treated with a synthetic cartilage implant compared to first MTP arthrodesis.

## Methods

A prospective, randomized, multicenter, noninferiority study was designed to examine patients with advanced great toe arthritis treated with arthrodesis versus a small synthetic cartilage (hydrogel) implant of the first metatarsal head. After study approval from each site's institutional review board (IRB), patients 18 years and older diagnosed with hallux rigidus grade II, III, or IV[4] assessed through a foot and ankle orthopaedic clinic and considered surgical candidates for arthrodesis were invited to participate in this study. A power analysis was performed a priori to calculate the minimum sample size required to detect an 80% effect size at a 1-sided significance level of $P < .05$ (N = 210). Inclusion and exclusion criteria are listed in Tables 1 and 2. After informed consent was completed, initial demographic

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**Table 1.** Study Inclusion 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;[4]
- Preoperative visual analog scale pain score of ≥40;
- Presence of good bone stock, with <1 cm osteochondral cyst and without need for bone graft;
- Capable of completing self-administered questionnaires;
- Be willing and able to return for all study-related follow-up procedures;
- Have not participated in any other research protocol within the last 30 days, and will not participate in any other research protocol during this study;
- If female, is either using contraception or is postmenopausal, or male partner is using contraception; and
- Have been informed of the nature of the study, agreeing to its requirements, and have signed the informed consent approved by the institutional review board/ethics committee.

**Table 2.** Study Exclusion Criteria.

- <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 visual analog scale pain score <40;
- Active bacterial infection of the foot;
- Additional ipsilateral lower limb (hip, knee, ankle, or foot) pathology that requires active treatment (ie, surgery, brace);
- Bilateral degenerative or post-traumatic arthritis of the first metatarsophalangeal (MTP) 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 (>1 cm) of the first MTP joint;
- Lesions greater than 10 mm in size;
- Hallux varus to any degree or hallux valgus >20°;
- Physical conditions that would tend to eliminate adequate implant support (eg, insufficient quality or quantity of bone resulting from cancer, congenital dislocation, or osteoporosis), systemic and metabolic disorders leading to progressive deterioration of bone (eg, cortisone therapies or immunosuppressive therapies), and/or tumors and/or cysts >1 cm of the supporting bone structures;
- Subject is on chronic anticoagulation due to a bleeding disorder or has taken anticoagulants within 10 days prior to surgery;
- Subject was diagnosed with cancer in the last 2 years and received treatment with chemotherapy or received radiation to the lower extremity to be treated with synthetic implant 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 that 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;
- Comorbidity 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 (eg, 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.

information was obtained and the patients were randomized 72 hours or less prior to surgery in a 2:1 allotment of either a synthetic implant (Cartiva Synthetic Cartilage Implant; Cartiva, Inc, Alpharetta, GA) or first MTP arthrodesis respectively. Primary outcomes included the Foot and Ankle Ability Measure (FAAM) sports score, visual analog scale (VAS), and safety parameters and were obtained pre-operatively; 2 and 6 weeks; and 3, 6, 12, and 24 months after surgery (Table 3). The FAAM instrument is a validated outcome measure made up of sports and activity of daily

**Table 3.** Study Assessments.

| Follow-up Visit | Window (d) | Eligibility/ informed consent | Medical history | Foot examination | Foot radiograph | General health | VAS pain | Foot Function Index –Revised (FFI-R) | Foot and Ankle Ability (FAAM) | SF-36 Health Survey | Operative/ discharge form | Follow-up visit form | Telephone follow-up | Adverse event reporting |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline visit/pre-implant screening | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | | |
| Operative/ discharge (day 0) | | | | | | | | | | | ✓ | | | ✓ |
| 2-wk follow-up | ±7 | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | ✓ | | ✓ |
| 6-wk follow-up | ±14 | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | | ✓ |
| 3-mo follow-up | ±14 | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | | ✓ |
| 6-mo follow-up | ±14 | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | | ✓ |
| 12-mo follow-up | ±60 | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | | ✓ |
| 18-mo follow-up | ±14 | | | | | | | | | | | | ✓ | ✓ |
| 24-mo follow-up | ±60 | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | | ✓ |
| Unscheduled visit | | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | | ✓ |

Abbreviations: VAS, visual analog scale.

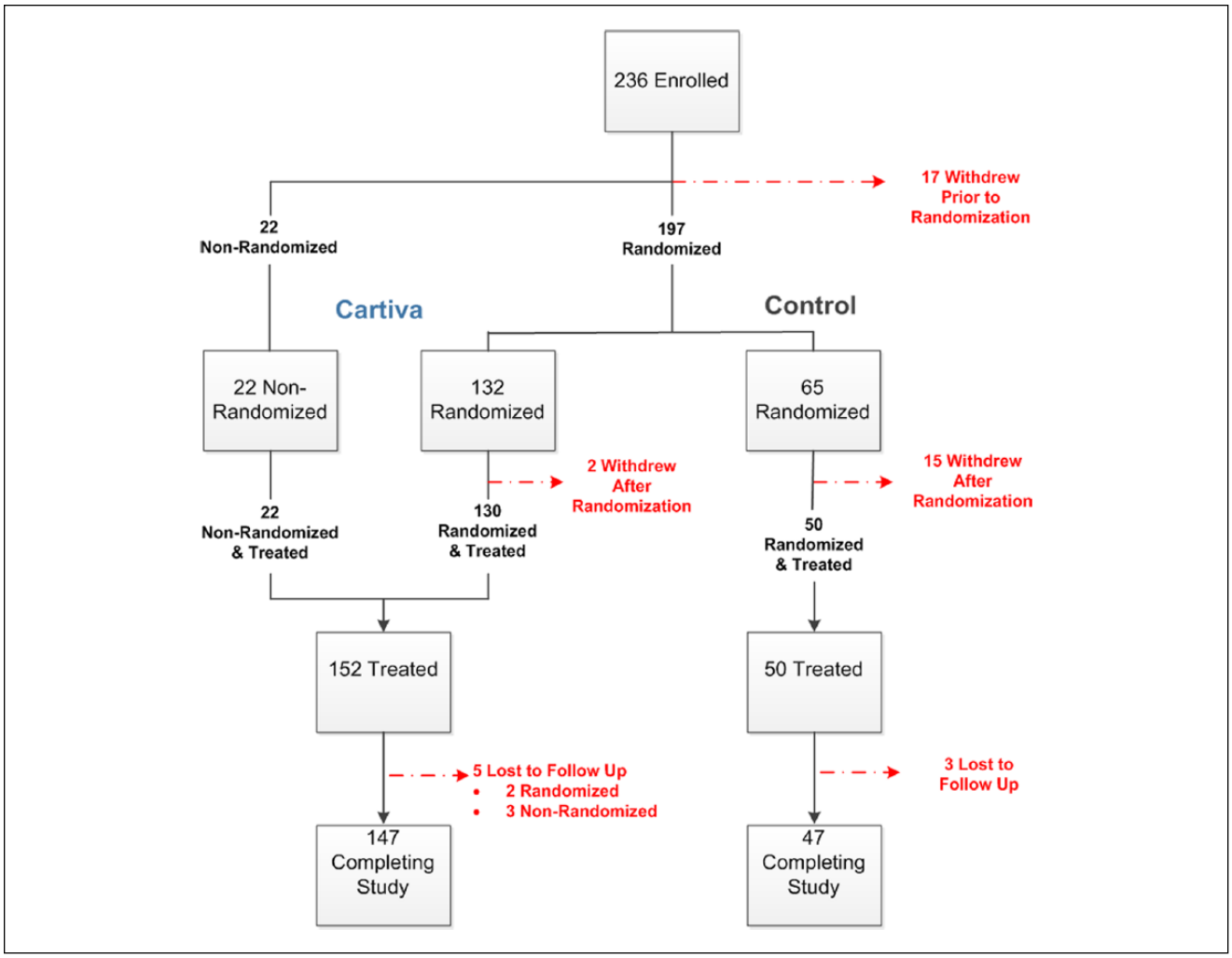


**Figure 1.** Study enrollment.

living (ADL) subscores. Each subscore has been independently validated and found responsive to change with a reported minimal clinically important difference (MCID) value assigned the Sports score of a 9-point difference and ADL score of an 8-point difference. VAS also has an assigned value for MCID (≥30% difference). Safety parameters included revisions, removals, reoperations and/or supplemental fixations, device displacement, device fragmentation, development of avascular necrosis, malunion, nonunion of arthrodesis, and/or hardware failures. A secondary outcome included the validated Short Form-36 physical functioning (SF-36 PF) score.

Between October 2009 and July 2012, a total of 12 clinical sites enrolled 236 subjects into the study. Of the 236 enrolled, 22 patients were implant training patients and were not randomized, 17 patients withdrew prior to randomization, and another 17 withdrew after randomization, leaving 152 patients in the implant arm and 50 in the arthrodesis arm (Figure 1). A total of only 8 patients (4%) were lost to follow-up (5 implant and 3 arthrodesis patients). Demographics and baseline variables for the study groups are listed in Tables 4 and 5. There were no significant differences in the baseline characteristics of age, gender, height, weight, BMI, VAS, FAAM sports, FAAM ADL, SF-36 PF, or hallux rigidus grade between treatment groups.

The primary endpoint for the study consisted of a single composite endpoint utilizing the 3 primary study outcomes (pain, function, and safety). The individual subject's outcome was considered a success if all of the following criteria were met: (1) improvement (decrease) from baseline in VAS pain of ≥30% at 12 months; (2) maintenance of function from baseline in FAAM sports subscore at 12 months; and (3) absence of major safety events. The proportion of successes in each group was determined, and 1-sided 95% confidence interval for the difference between treatment groups was calculated. Noninferiority of the implant to arthrodesis was considered statistically significant if the 1-sided 95% lower confidence interval was greater than the

**Table 4.** Summary of Demographic and Baseline Characteristics of Implant and Arthrodesis Modified Intent-to-Treat Cohorts.

| | Implant | | | | | | Fusion | | | | | | *t*-test | Wilcoxon |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | SD | Med | Min | Max | n | Mean | SD | Med | Min | Max | *P* value[a] | *P* value[b] |
| Demographics: all | | | | | | | | | | | | | | |
| Age at surgery (y) | 130 | 57.4 | 8.8 | 57.9 | 30.5 | 79.2 | 50 | 54.9 | 10.5 | 55.1 | 32.4 | 78.2 | .115 | .097 |
| Height (cm) | 130 | 165.9 | 7.8 | 165.0 | 147.3 | 182.9 | 50 | 167.4 | 9.4 | 165.6 | 154.0 | 190.5 | .293 | .519 |
| Weight (kg) | 130 | 75.1 | 14.5 | 72.7 | 47.5 | 116.0 | 50 | 73.7 | 15.5 | 71.0 | 50.0 | 131.2 | .591 | .473 |
| BMI | 130 | 27.2 | 4.4 | 26.5 | 19.1 | 37.1 | 50 | 26.3 | 4.7 | 25.7 | 19.1 | 41.6 | .222 | .175 |
| Demographics: Male | | | | | | | | | | | | | | |
| Age at surgery (y) | 26 | 56.9 | 11.2 | 58.1 | 30.5 | 72.5 | 12 | 55.2 | 11.2 | 57.6 | 32.4 | 70.6 | .653 | .683 |
| Height (cm) | 26 | 176.3 | 4.4 | 177.0 | 166.0 | 182.9 | 12 | 178.3 | 5.7 | 178.9 | 170.0 | 190.5 | .241 | .270 |
| Weight (kg) | 26 | 91.5 | 11.8 | 89.7 | 70.0 | 116.0 | 12 | 88.2 | 17.9 | 85.0 | 65.2 | 131.2 | .505 | .285 |
| BMI | 26 | 29.5 | 3.7 | 29.5 | 23.7 | 37.1 | 12 | 27.8 | 5.5 | 27.4 | 21.6 | 41.6 | .266 | .079 |
| Demographics: Female | | | | | | | | | | | | | | |
| Age at surgery (y) | 104 | 57.5 | 8.2 | 57.9 | 35.2 | 79.2 | 38 | 54.8 | 10.4 | 53.9 | 35.6 | 78.2 | .117 | .090 |
| Height (cm) | 104 | 163.3 | 6.1 | 162.8 | 147.3 | 180.3 | 38 | 163.9 | 7.4 | 162.8 | 154.0 | 188.0 | .633 | .996 |
| Weight (kg) | 104 | 71.0 | 12.0 | 68.9 | 47.5 | 99.0 | 38 | 69.2 | 11.6 | 68.4 | 50.0 | 99.3 | .430 | .465 |
| BMI | 104 | 26.7 | 4.4 | 25.8 | 19.1 | 36.8 | 38 | 25.9 | 4.4 | 25.5 | 19.1 | 37.5 | .332 | .341 |
| Baseline functional status | | | | | | | | | | | | | | |
| FAAM ADL | 129 | 59.4 | 16.9 | 58.3 | 7.1 | 100.0 | 50 | 56.0 | 16.8 | 54.9 | 22.6 | 95.2 | .222 | .152 |
| FAAM sports | 127 | 36.9 | 20.9 | 34.4 | 0.0 | 100.0 | 50 | 35.6 | 20.5 | 31.3 | 0.0 | 87.5 | .694 | .505 |
| SF-36 | 130 | 52.4 | 22.8 | 50.0 | 0.0 | 100.0 | 50 | 49.8 | 23.6 | 40.0 | 15.0 | 100.0 | .499 | .352 |
| VAS | 130 | 68.0 | 13.9 | 68.3 | 27.8 | 100.0 | 50 | 69.3 | 14.3 | 70.0 | 38.0 | 97.5 | .571 | .529 |

Abbreviations: ADL, activity of daily living subscore; BMI, body and mass index; FAAM, Foot and Ankle Ability Measure; Max, maxima, Min, minima; Med, median; SD, standard deviation; SF-36, Short Form–36 Item Health Survey.
[a]Two-sample pooled *t*-test *P* value.
[b]Two-sample Wilcoxon rank-sum test *P* value.

**Table 5.** Summary of Baseline and Demographic Characteristics of Implant and Arthrodesis Modified Intent-to-Treat Cohorts—OA Grade.

| Categorical Variables | Implant (n = 130) x/n (%) | Arthrodesis (n = 50) x/n (%) | Overall (n = 180) x/n (%) |
|---|---|---|---|
| OA grade | | | |
| 2 | 36/130 (27.7) | 18/50 (36.0) | 54/180 (30.0) |
| 3 | 74/130 (56.9) | 23/50 (46.0) | 97/180 (53.9) |
| 4 | 20/130 (15.4) | 9/50 (18.0) | 29/180 (16.1) |

Abbreviation: OA, osteoarthritis.

equivalence limit (<15%). In addition, an analysis of the primary endpoint was performed that looked at success using the FAAM ADL scores at 12 and 24 months. Fisher exact test was used to assess any differences between the primary outcome measures. Two-sample pooled *t*-test and 2-sample Wilcoxon rank-sum test were used to assess any differences between the baseline and demographic variables in the 2 cohorts and to assess any differences between FAAM subscores, pain VAS, SF-36 physical functioning, and dorsiflexion motion over time between groups. A probability value (*P* value) of <.05 was considered significant.

## Surgical Techniques and Postoperative Protocol

The detailed surgical technique for the synthetic cartilage implant has been standardized and published previously.[17,18] A straight dorsal incision was placed centered over the medial edge of the extensor hallucis longus tendon to access to the first MTP joint. Alternatively, a standard mid-medial approach to the first MTP joint was used. The dorsal, medial, and lateral osteophytes were removed preserving the cortical rim of the metatarsal head. Flexion of the proximal phalanx was performed to allow for visualization of the metatarsal head. A central guide wire was placed in the metatarsal head and extended into the shaft. An 8- or 10-mm implant was selected based on the sizing guide and the step drill was placed over the guide wire and the metatarsal head was drilled. The appropriately sized synthetic cartilage hydrogel implant (Cartiva, Inc) was placed with the implant delivery tube and seated to allow for 1 to 2 millimeters of the implant to extend beyond the adjacent native cartilage of the metatarsal head (Figure 2). Layered closure of capsule and subsequently the skin was performed. A soft dressing was used, along with a postoperative shoe. The patient could bear weight immediately and begin range-of-motion exercises at 1 week as tolerated. Skin sutures were removed at 2 to 3 weeks,

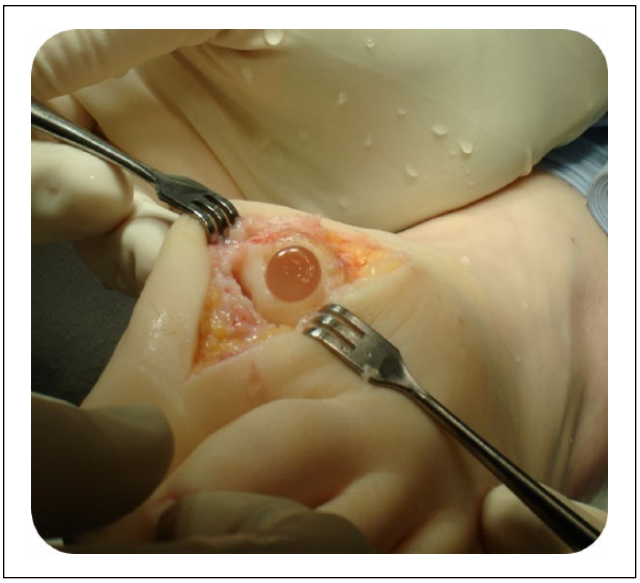

**Figure 2.** Intraoperative clinical photograph of 10-mm implant in first metatarsal head.

at which time the patient could return to wearing his or her regular shoes.

First MTP arthrodesis technique has been well described in the literature.[3,5,7,8,14,16] The proximal phalanx was positioned in slight dorsiflexion / valgus and stabilized with crossed screws or plate and screws. The patient was placed in a sterile dressing and immobilized in a cast or boot. Weight bearing was delayed in all arthrodesis cases and begun at 2 to 6 weeks at the discretion of the surgeon.

## Results

Intent-to-treat (ITT; all randomized patients utilizing last observation carried forward [LOCF] for missing data) and modified ITT (mITT; all randomized and treated patients utilizing LOCF for missing data) were performed for the composite endpoint and results listed in Table 6. All analyses were statistically significant, demonstrating noninferiority of the synthetic cartilage implant to arthrodesis for the primary composite outcome measure. Composite endpoint results utilizing FAAM ADL at 12 months and VAS pain score, FAAM sports, FAAM ADL, and safety at 24 months are listed in Table 7.

The means and standard deviations for the FAAM sports, FAAM ADL, SF-36 PF, VAS pain, and first MTP range of motion at each study time point are listed in Tables 8 to 12. For all FAAM subscores and VAS pain score, both the implant and arthrodesis groups improved significantly over time. In the early postoperative period (weeks 2 and 6), the implant group had higher mean FAAM Sport subscores, which were greater than 9 points, demonstrating clinically and statistically significant improvement over the arthrodesis group. However, at 2 years, the functional improvement was equivalent between the groups. The FAAM ADL subscore demonstrated a similar pattern of early clinically significant difference favoring the implant group (value >8 points). However, at 2 years, the 2 groups improved to a similar level. The SF-36 PF similarly improved to a greater degree earlier in the implant group at week 6 compared to the arthrodesis group. Nonetheless, the 2-year values were similar. The mean SF-36 PF scores seemed to show a trend toward continued improvement at 2 years in the implant group, whereas the arthrodesis group remained stable. The VAS pain scores improved in each group over time.

Dorsiflexion range of motion was significantly different between the implant and arthrodesis groups. The implant group had improvement in dorsiflexion motion of 6.2 degrees (27.3%) that was maintained at 2 years.

The secondary surgery data are listed in Table 13. A total of 14 (9.2%) implant subjects (14 procedures) and 6 (12%) arthrodesis subjects (7 procedures) had secondary surgeries consisting of implant and/or hardware removed during the course of the study. All implant patients that had the device removed were successfully converted to arthrodesis as a result of persistent or recurrent pain without any additional complications. The 6 secondary surgery arthrodesis patients (7 procedures) had isolated screws or plate and screw removal. The mean time was 390 days (54-737) for the implant patients and 220 days (45-476) for the arthrodesis patients. Inspection of the retrieval implants did not demonstrate any implant wear. The root cause for the implant failure was not determined. Figure 3 depicts the survivorship curve for implant (removal and conversion to fusion) compared to the arthrodesis (hardware revision or removal). The comparison of complication rates between the Cartiva and fusion safety analysis cohorts is provided in Table 14. There were no statistically significant differences with respect to total complications, treatment emergent events (which includes device-related adverse events [AEs] and procedure-related AEs), or serious adverse events (SAEs). In the MOTION Study, the investigational Cartiva SCI device implanted in the first metatarsophalangeal joint was found to have a reasonable assurance of safety and to be at least as safe as the control treatment. There were no Cartiva SCI device failures.

An independent radiographic review was performed on all foot radiographs at all time periods throughout the study. There were 5 arthrodesis patients who had 6 radiographic findings: 5 non-unions and 1 broken screw. Of these non-unions, 2 revision arthrodesis procedures were performed. Of the remaining non-unions, a revision was not performed as they were not felt to have clinical symptoms warranting revision (fibrous non-union).

## Discussion

Great toe arthritis is a common problem that leads to pain and activity limitation. In advanced-stage arthritis, first MTP

**Table 6.** Summary Table of Primary Effectiveness Endpoint Analyses.

| Analysis population (n) | Implant (%) | Arthrodesis (%) | One-sided 95% lower bound (%)[a] | Noninferiority *P* value |
|---|---|---|---|---|
| ITT[b] (I: 132; A: 65) | 79 | 62 | 5.52 | **<.0001** |
| mITT (I: 130; A: 50) | 80 | 80 | −10.50 | **<.0075** |

Abbreviations: A, arthrodesis; I, implant; ITT, intent to treat; mITT, modified intent to treat.
[a]The lower 1-sided 95% confidence limit, which must be greater than −15.
[b]Primary endpoint analysis.

**Table 7.** Summary Table of Alternate Primary Effectiveness Endpoint Analyses in mITT Population.

| Effectiveness endpoint components | Implant (%) | Arthrodesis (%) | One-sided 95% lower bound (%)[a] | Noninferiority *P* value |
|---|---|---|---|---|
| VAS, FAAM ADL, and safety—12 mo | 84.5 | 85.1 | −10.63 | 1.000 |
| VAS, FAAM sports, and safety—24 mo | 80.0 | 78.7 | −10.17 | .835 |
| VAS, FAAM ADL, and safety—24 mo | 80.5 | 78.7 | −9.64 | .832 |

Abbreviations: ADL, activity of daily living; FAAM, Foot and Ankle Ability Measure; mITT, modified intent to treat; VAS, visual analog scale.
[a]Fisher exact test.

**Table 8.** FAAM Sports Scores by Treatment Group Over Time in the Modified Intent-to-Treat Population.

| Visit | Implant Mean (SD) n Med (min, max) | Arthrodesis Mean (SD) n Med (min, max) | *t*-test *P* value[a] | Wilcoxon *P* value[b] |
|---|---|---|---|---|
| Baseline | 36.9 (20.9) 127<br>34.4 (0, 100.0) | 35.6 (20.5) 50<br>31.3 (0, 87.5) | .694 | .505 |
| 2 wk | 18.4 (18.3) 127<br>12.5 (0, 75) | 7.8 (12.4) 47<br>3.1 (0, 46.9) | .000 | .000 |
| 6 wk | 39.5 (26.3) 126<br>35.7 (0, 100) | 22.4 (22.5) 49<br>20.3 (0, 81.3) | <.0001 | .000 |
| 3 mo | 55.1 (26.5) 123<br>59.4 (0, 100) | 53.9 (29.5) 46<br>54.7 (0, 100) | .804 | .853 |
| 6 mo | 66.6 (26.3) 120<br>65.6 (0, 100) | 78.6 (23.8) 42<br>79.7 (0, 100) | .010 | .005 |
| 1 y | 75.8 (24.8) 120<br>81.2 (0, 100) | 84.1 (16.9) 43<br>90.6 (28.1, 100) | .043 | .098 |
| 2 y | 79.5 (24.6) 113<br>87.5 (0, 100) | 82.7 (20.5) 41<br>90.6 (28.1, 100) | .461 | .437 |

Abbreviation: FAAM, Foot and Ankle Ability Measure; max, maxima; Med, median; min, minima; SD, standard deviation.
[a]Two-sample pooled *t*-test *P* value.
[b]Two-sample Wilcoxon rank-sum test *P* value.

joint arthrodesis is a reliable operation for pain relief and improvement in some functional activities; however, the loss of dorsiflexion motion limits running and jumping sports as well as shoe and boot choice. In an attempt to maintain first MTP joint motion and relieve pain, joint replacement implants were designed. The early silicone implants had a high failure rate because of excessive wear debris and loosening. This silicone material failure led to the advancement of metal, ceramic, and plastic products that either resurfaced the first metatarsal head or the proximal phalangeal base, or both. As a result of the complex motion of the great toe, the sesamoid articulation and the large loads carried through this joint, these implants were also found to be inferior compared with the outcomes obtained by arthrodesis. The failure mode was due to implant loosening, resultant malalignment, and transfer loading to the lesser metatarsals. With the excessive bone resection required for the technique, salvage of this surgery to a fusion is more difficult and

**Table 9.** FAAM ADL Scores by Treatment Group Over Time in the Modified Intent-to-Treat Population.

| Visit | Implant<br>Mean (SD) n<br>Med (min, max) | Arthrodesis<br>Mean (SD) n<br>Med (min, max) | *t*-test<br>*P* value[a] | Wilcoxon<br>*P* value[b] |
|---|---|---|---|---|
| Baseline | 59.4 (16.9) 129<br>58 3 (7.1, 100.0) | 56.0 (16.8) 50<br>54.9 (22.6, 95.2) | .222 | .152 |
| 2 wk | 48.8 (21.6) 126<br>47.6 (2.4, 100.0) | 40.3 (20.7) 47<br>39.3 (7.5, 84.2) | .021 | .023 |
| 6 wk | 69.0 (19.0) 126<br>69.6 (19.0, 100.0) | 59.6 (24.8) 48<br>63.1 (10.7, 100.0) | .008 | .032 |
| 3 mo | 77.3 (17.7) 125<br>80.0 (36.9, 100.0) | 82.5 (14.9) 46<br>86.9 (41.7, 100.0) | .079 | .110 |
| 6 mo | 82.7 (17.5) 123<br>88.1 (22.6, 100.0) | 89.9 (12.4) 43<br>95.2 (50.0, 100.0) | .014 | .010 |
| 1 y | 88.6 (14.4) 123<br>95.0 (27.4, 100.0) | 94.1 (6.8) 43<br>95.2 (71.4, 100.0) | .0176 | .066 |
| 2 y | 90.4 (15.0) 116<br>96.4 (29.8, 100.0) | 94.6 (7.1) 41<br>96.4 (69.0, 100.0) | .082 | .524 |

Abbreviations: ADL, activity of daily living; FAAM, Foot and Ankle Ability Measure; max, maxima; Med, median; min, minima; SD, standard deviation.
[a]Two-sample pooled *t*-test *P* value.
[b]Two-sample Wilcoxon rank-sum test *P* value.

**Table 10.** Short Form–36 Physical Functioning Scores by Treatment Group Over Time in the Modified Intent-to-Treat Population.

| Visit | Implant<br>Mean (SD) n<br>Med (min, max) | Arthrodesis<br>Mean (SD) n<br>Med (min, max) | *t*-test<br>*P* value[a] | Wilcoxon<br>*P* value[b] |
|---|---|---|---|---|
| Baseline | 52.4 (22.8) 130<br>50 (0, 100) | 49.8 (23.6) 50<br>40 (15, 100) | .499 | .352 |
| 6 wk | 60.7 (23.7) 128<br>60 (10, 100) | 44.7 (26.8) 49<br>45 (0, 100) | .000 | .000 |
| 3 mo | 68.1 (25.2) 128<br>75 (5, 100) | 71.7 (25.5) 46<br>80 (0, 100) | .405 | .353 |
| 6 mo | 72.3 (26.3) 124<br>80 (0, 100) | 82.8 (22.4) 43<br>90 (5, 100) | .021 | .014 |
| 1 y | 78.9 (22.7) 123<br>90 (5, 100) | 83.7 (24.9) 43<br>95 (0, 100) | .247 | .064 |
| 2 y | 83.2 (20.9) 116<br>95 (25, 100) | 85.1 (19.5) 41<br>95 (5, 100) | .613 | .597 |

Abbreviations: max, maxima; Med, median; min, minima; SD, standard deviation.
[a]Two-sample pooled *t*-test *P* value.
[b]Two-sample Wilcoxon rank-sum test *P* value.

results in poorer functional outcomes for the patients than primary arthrodesis. The current synthetic cartilage implant made of hydrogel has had extensive biomechanical testing[1] and has been proven to withstand shear and axial load force beyond those required for the great toe without fragmentation. The implant is small (8 or 10 mm) and requires limited joint dissection and bone resection for implantation. With this limited dissection, the joint kinematics and kinetics are left undisturbed. There were no cases of transfer metatarsalgia within the implant group as the joint relationship and ray length were maintained.

This randomized, prospective, multicentered study of great toe arthritis utilized validated outcome measures and rigorous standardized surgical techniques and follow-up. The synthetic cartilage implant (Cartiva, Inc) outcomes of pain relief, function, and safety were equivalent to those of arthrodesis while providing the additional benefit of maintaining and often improving first MTP joint motion. Although approximately 9% of patients required removal because of persistent or recurrent pain and an additional 2% had revision surgery with maintenance of the implant, this was equivalent to the secondary procedures for the arthrodesis group (12%). Most

**Table 11.** Visual Analog Scale Scores by Treatment Group Over Time in the Modified Intent-to-Treat Population.

| Visit | Implant<br>Mean (SD) n<br>Med (min, max) | Arthrodesis<br>Mean (SD) n<br>Med (min, max) | *t*-test<br>*P* value[a] | Wilcoxon<br>*P* value[b] |
|---|---|---|---|---|
| Baseline | 68.00 (13.9) 130<br>68.3 (27.8, 100.0) | 69.3 (143) 50<br>70 (38, 97.5) | .571 | .529 |
| 6 wk | 33.2 (24.7) 128<br>27.4 (0, 96) | 17.2 (17.6) 48<br>11.5 (0, 71.75) | <.0001 | .000 |
| 3 mo | 29.4 (23.2) 128<br>23.8 (0, 88) | 15.5 (13.1) 46<br>12 (0, 56.75) | .000 | .000 |
| 6 mo | 28.9 (27.75) 124<br>20.5 (0, 97) | 11.7 (18.3) 43<br>4.25 (0, 74.75) | .000 | .000 |
| 1 y | 17.8 (23.0) 123<br>9.0 (0, 91) | 5.7 (8.5) 43<br>2.5 (0, 56.5) | .0011 | .000 |
| 2 y | 14.5 (22.1) 116<br>5.0 (0, 94) | 5.9 (12.1) 41<br>1.5 (0, 70) | .002 | .005 |

Abbreviations: max, maxima; Med, median; min, minima; SD, standard deviation.
[a]Two-sample pooled *t*-test *P* value.
[b]Two-sample Wilcoxon rank-sum test *P* value.

**Table 12.** Active Peak Dorsiflexion Angles by Treatment Group Over Time in the Modified Intent-to-Treat Population.

| Visit | Implant<br>Mean (SD) n<br>Med (min, max) | Arthrodesis<br>Mean (SD) n<br>Med (min, max) | *t*-test<br>*P* value[a] | Wilcoxon<br>*P* value[b] |
|---|---|---|---|---|
| Baseline | 22.7 (11.2) 130<br>20 (0, 58) | 22.9 (11.2) 50<br>20 (5, 50) | .910 | .965 |
| 2 wk | 20.6 (10.1) 129<br>20 (0, 40) | 12.6 (8.1) 49<br>10 (0, 30) | <.0001 | .000 |
| 6 wk | 25.1 (10.8) 127<br>25 (5, 55) | 13.0 (9.0) 48<br>14.5 (0, 26) | <.0001 | .000 |
| 3 mo | 26.6 (11.7) 128<br>26 (0, 60) | 13.8 (9.7) 45<br>15 (0, 30) | <.0001 | .000 |
| 6 mo | 28.1 (9.8) 124<br>30 (5, 60) | 14.9 (8.6) 44<br>15 (0, 30) | <.0001 | .000 |
| 1 y | 28.8 (11.2) 123<br>30 (5, 60) | 16.0 (7.3) 43<br>15 (0, 35) | <.0001 | .000 |
| 2 y | 29 (11.9) 114<br>30 (5, 60) | 15.1 (8.4) 41<br>16 (0, 35) | <.0001 | .000 |

Abbreviations: max, maxima; Med, median; min, minima; SD, standard deviation.
[a]Two-sample pooled *t*-test *P* value.
[b]Two-sample Wilcoxon rank-sum test *P* value.

**Table 13.** Secondary Surgeries in Safety Population.

| Secondary surgery | Implant (n = 152) | Arthrodesis (n = 50) |
|---|---|---|
| Removal by number of procedures (%) | 14 (9.2%), implant removal and conversion to arthrodesis | 7 (14%), hardware removal[a] |
| Reoperation by number of procedures (%) | 1 (0.7%), joint manipulation for motion<br>1 (0.7%), debridement of the joint for scar and synovitis and implant repositioning<br>1 (0.7%), Moberg osteotomy of the proximal phalanx for improved toe positioning, motion, and pain relief | 0 |
| Overall (procedures) | 17 (11.2%) | 7 (14%) |

[a]One arthrodesis patient had 2 secondary surgeries for initial removal of 1 screw at 6 weeks and the remaining hardware at 1 year.

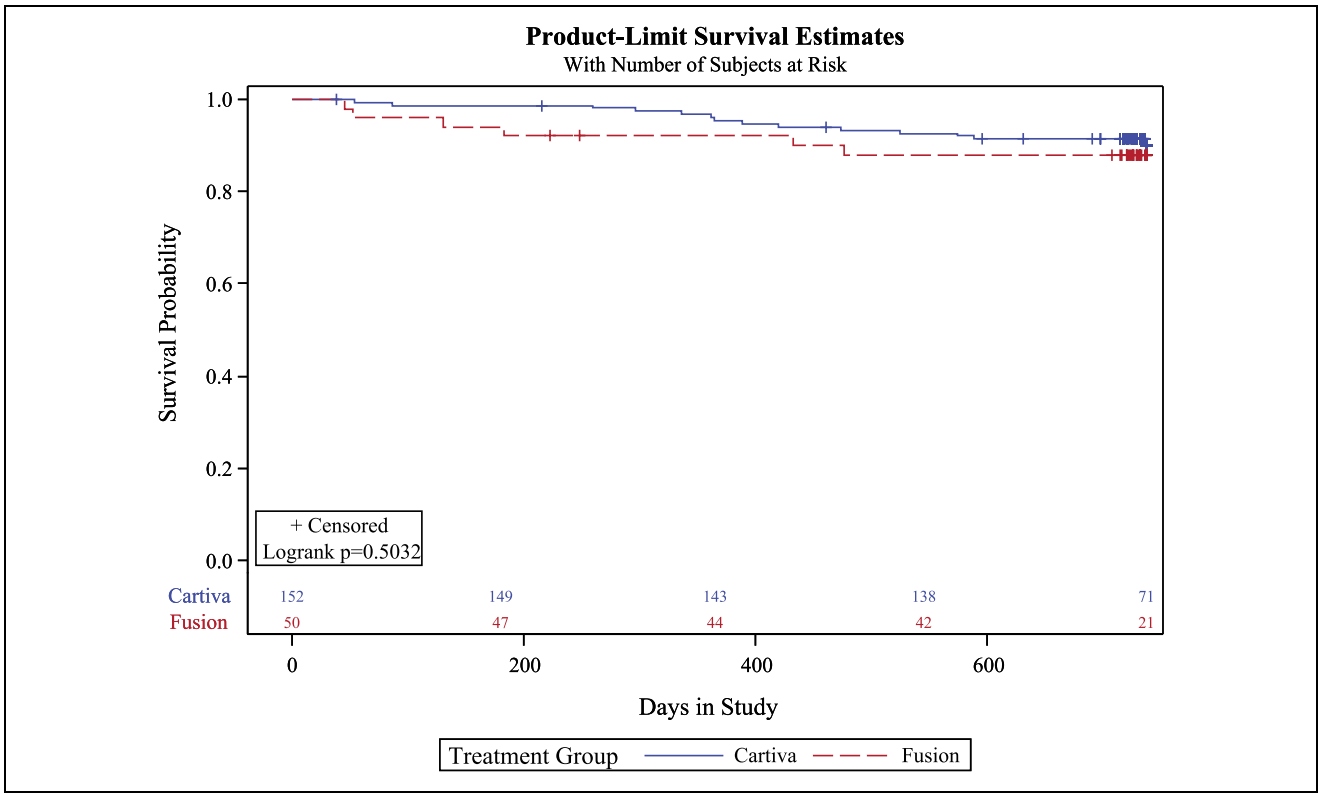


**Figure 3.** Survivorship curves for implant or arthrodesis.
Implant (Cartiva) removal and conversion to fusion.

**Table 14.** Adverse Events in Safety Population.

| | Implant (n = 152) | | | Arthrodesis (n = 50) | | | |
|---|---|---|---|---|---|---|---|
| | Events | n | % | Events | n | % | *P* value |
| Any adverse event | 245 | 105 | 69.1 | 72 | 36 | 72.0 | .727 |
| Treatment emergent event | 102 | 67 | 44.1 | 32 | 21 | 42.0 | .870 |
| Nontreatment emergent event | 143 | 73 | 48.0 | 40 | 26 | 52.0 | .745 |
| Any serious adverse event | 37 | 30 | 19.7 | 12 | 9 | 18.0 | .999 |
| Treatment emergent event | 17 | 17 | 11.2 | 4 | 4 | 8.0 | .605 |
| Nontreatment emergent event | 20 | 14 | 9.2 | 8 | 5 | 10.0 | .999 |

importantly, with failure of the implant, conversion of the implant to arthrodesis was considered straightforward because of the maintenance of bone stock and resultant improvement in pain (86.4% reduction) and function (39.0 point increase) outcomes for these 14 patients with implants.

Prior synthetic cartilage implant (Cartiva, Inc) outcomes are available from one case series of patients with hallux rigidus.[15] This study reported improved American Orthopaedic Foot & Ankle Society hallux scores in 100% patients at 1 year. No additional clinical studies are available in the literature using this implant for this indication. The outcomes from case series of great toe arthrodeses show similar improvement in pain and function using a variety of outcome measures. These studies also report the complications of this procedure, with prominent hardware, non-union, transfer metatarsalgia, and malunion representing some of the complications seen in this study.[2,3,6,8,10,13,14] This supportive documentation from prior published work on great toe arthrodesis supports the current study methodology and assessment.

The data from this prospective, randomized study is generalizable to a broad group as it traversed continents, was multicentered, well controlled with comparative demographic characteristics, and enlisted 49 surgeons. A study of this magnitude demonstrates how foot and ankle orthopedists can work together globally to explore unsolved clinical problems and answer important questions with tremendous benefit to our patients.

The limitations of this study include the loss of 23% of the arthrodesis patients who initially consented to randomization and withdrew from the study. This emphasizes the importance patients place on maintaining their great toe motion.

This problem, nonetheless, led to 15 patients being included in the ITT analysis when this treatment was not provided. This could bias the results in favor of the implant. To address this bias, the mITT analysis was performed. Regardless of how the analyses were performed, the outcomes from the arthrodesis group and implant group were similar, illustrating the robustness of the findings. Other limitations inherent to any clinical study include the loss of data, data that were collected outside of the predetermined windows and protocol deviations. In this study, 99% of the patients in the implant arm and 94% of patients in the arthrodesis arm had data eligible for the per protocol analysis, demonstrating the strength of the adherence to the protocol. In addition, there was a high degree of study compliance, with only 4% of patients lost to follow-up at 2 years. The follow-up duration was set at 2 years, and a potential limitation is the lack of data beyond this time frame. Plans to continue to follow these patients out to 5 years are under way.

In conclusion, the synthetic cartilage implant (Cartiva, Inc) decreased pain, improved function, had few safety concerns, and was equivalent to the gold standard, great toe arthrodesis, for advanced great toe arthritis (hallux rigidus). The implant had the added benefit of maintaining and often improving dorsiflexion motion. Less than 10% of implant cases had pain that resulted in conversion to a successful arthrodesis. The safety profile of the implant device demonstrated a reasonable assurance of safety and was at least as safe as an arthrodesis with regard to adverse event rates and secondary surgeries.

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