Matrix-Applied Characterized Autologous Cultured Chondrocytes Versus Microfracture Two-Year Follow-up of a Prospective Randomized Trial

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Matrix Applied Characterised Autologous Cultured Chondrocytes (MACI) Implant versus Microfracture: Two-Year Follow Up from a Prospective, Randomized Trial

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Abstract (Word limit 350, now 347)

Background: Evidence for the efficacy and safety of matrix applied characterised autologous cultured chondrocytes (MACI) implant versus microfracture for the treatment of cartilage defects was limited.

Purpose: To compare clinical efficacy and evaluate the safety profile of the MACI implant versus microfracture in the treatment of patients with symptomatic articular cartilage defects of the knee.

Study Design: Randomized, controlled clinical trial; Level of evidence, 1

Methods: Patients enrolled in the SUMMIT (Demonstrate the Superiority of MACI implant to Microfracture Treatment in patients with symptomatic articular cartilage defects in the knee) trial had ≥1 symptomatic focal articular cartilage defect (Outerbridge grade III or IV; ≥3 cm^2) of the femoral condyles and/or trochlea, with a baseline Knee Injury and Osteoarthritis Outcome Score (KOOS) pain score of <55. The co-primary efficacy endpoint was the change from baseline to 2 years for the KOOS pain and function (sports and recreational activities) subscales. Histological evaluation and MRI assessments of structural repair tissue, treatment failure, and the remaining 3 KOOS subscales were also assessed.

Results: Of the 144 patients who were treated, 95% completed the 2-year assessment. Patients had a mean age of 33.8 years and a mean lesion size of 4.8 cm^2. The co-primary endpoint, the KOOS pain and function subscales, was significantly better (pain LS mean: 11.76; function LS mean: 11.41; P=.001) for the MACI implant versus microfracture groups. Significantly better scores for the KOOS activities of daily living (P<.001), quality of life (P=.029) and other symptoms (P<.001) were also observed for patients treated with the MACI implant than with the

microfracture procedure. Repair tissue quality was good as assessed by histology/MRI but a difference could not be shown between treatments. A low number of treatment failures and no unexpected safety findings were reported.

Conclusions: Cartilage defect treatment using the MACI implant was clinically and significantly better than the microfracture group, with similar structural repair and safety, when used to treat symptomatic cartilage knee defects in this large, randomized controlled trial.

Clinical Relevance: The MACI implant procedure offers a more efficacious alternative than microfracture with a similar safety profile for the treatment of symptomatic articular cartilage defects of the knee.

Key Terms: cartilage repair, clinical outcomes, knee, matrix applied characterised autologous cultured chondrocytes (MACI) implant, microfracture.

What is known about the subject: Cartilage cell therapy has been an established treatment modality for certain indication and the MACI implant procedure has been shown to be a safe and efficacious treatment option for the management of symptomatic articular cartilage knee defects. However, there has only been cohorts, retrospective reports, and one other smaller randomized study comparing the efficacy of the MACI implant procedure versus that of microfracture, showing overall better outcomes with MACI versus microfracture.

What this study adds to existing knowledge: Randomized, controlled trials comparing the efficacy and safety of the MACI implant procedure versus microfracture for the treatment of patients with symptomatic articular cartilage defects of the knee are limited. The results of this GCP, GMP compliant study demonstrates that patients treated with the MACI implant procedure

show significantly better pain reduction and functional improvements than patients treated with microfracture, with a similar safety profile.

Note: These questions are only for reviewers and are not included in the word count.

Introduction

Cell therapy has been an integral part of the technovolution [28] of methods in cartilage repair, utilizing autologous chondrocytes to generate an effective repair tissue. Treating cartilage lesions is important as cartilage injury is prevalent and can lead to significant pain and reduced function. In Europe and the US, the incidence of chondral defects has been shown to be approximately 60% in those undergoing arthroscopy.[1,20,51,53] Articular cartilage has limited self-healing capacity due to its lack of access to blood stream[48] and dense matrix. If left untreated, cartilage lesions can become symptomatic and may progress to osteoarthritis.[7,19,29,52]

The first autologous chondrocyte implantation (ACI) for cartilage repair was performed 25 years ago.[5] Over time, the procedure has advanced to collagen-covered ACI (CACI; second-generation technology)[15,16,18] and then to the matrix applied characterised autologous cultured chondrocytes (MACI; Genzyme Biosurgery, Cambridge, MA, USA) implant, a third-generation technology. Progression from the first- to second- to third-generation technology occurred because of added benefits to the patients; these include shorter procedure time, smaller incision size, more consistent cell seeding, less pain from periosteal hypertrophy, and less AEs overall.[4,9,26,42,49] For the MACI implant, chondrocytes are cultured in monolayer and seeded on a collagen membrane, which is then implanted directly in the defect. Culturing cells on the membrane allows for their proliferation and phenotype redifferentiation to chondrocytes after monolayer culture, and the cells are better fixed and distributed in the defect.[4,12,13,54] Physical properties of the type I/III collagen membrane (ACI-Maix, Matricel GmbH, Germany) make it tear resistant and durable, but not self-adherent, and also permit the implant to be easily trimmed and handled.[4,12,13] Overall, good clinical outcomes and repair tissue have been shown with the

MACI implant with a good safety profile, especially less periosteal hypertrophy than with the ACI procedure.[4,8,9,26,39]

Microfracture (MFX), a bone marrow stimulating procedure developed before cell therapies,[45] is frequently used to repair specific cartilage injuries. While MFX provides good clinical outcomes, these are not always sustained.[24,32,34] Previous studies show that patients with smaller lesions have better clinical outcomes with MFX than patients with larger lesions,[30] whereas lesions on the trochlea do not improve as well as those on the femoral condyle.[24] Repair tissue with MFX has been shown to be fibrous in nature,[41] compared with more hyaline-like repair tissue reported with the MACI implant.[4] In addition, intralesional osteophytes may result from MFX and could compromise any successful clinical outcomes with the procedure. Microfracture may also negatively affect outcome of subsequent cell-based cartilage repair treatment.[31,37]

Conducting randomized controlled trials (RCTs) of surgical interventions in orthopedics is challenging. Most striking is the unethical nature of a control “placebo” or sham surgery. Establishing appropriate controls is difficult as different surgical procedures may create different-sized incisions or require a different number of steps, such that blinding is impossible. Another challenge is the large placebo effect seen with sham surgeries. Unblinded healthcare providers must also maintain clinical equipoise so patients will not perceive or have expectations around receiving a beneficial treatment. In our study, we attempt to address these issues in the largest, Good-Clinical-Practice randomized, controlled trial with the highest power to date in cartilage repair, as per the guidance of regulatory agencies.

Compared with most previous randomized trials of cell therapy versus MFX, this study uses a third generation technology, has higher statistical power with more patients, and includes

larger lesion sizes. Although MFX is traditionally used for the treatment of smaller lesions, clinicians also treat larger defects with MFX,[32] since there are few alternative treatment options. The primary objective of our study was to compare clinical efficacy and safety of the MACI implant with microfracture in the treatment of patients with symptomatic articular cartilage defects.

MATERIALS AND METHODS

Study Design

The SUMMIT (Demonstrate the Superiority of MACI implant to Microfracture Treatment [SUMMIT] in patients with symptomatic articular cartilage defects in the knee) trial was a Good Clinical Practices (GCP), prospective, randomized, open-label, parallel-group, multicenter study conducted at 16 European sites (NCT00719576), with enrollment beginning in May 2008. Articular cartilage defects of the medial femoral condyle (MFC), lateral femoral condyle (LFC) and/or trochlea were treated with the MACI implant procedure or arthroscopic MFX. The study protocol and informed consent form were approved by appropriate national or local ethics committee at each study site. The study was conducted according to GCP and principles of the Declaration of Helsinki.

Patient Population

Male and female patients aged 18 to 55 years old with ≥1 symptomatic cartilage defect and a baseline moderate to severe Knee Injury and Osteoarthritis Outcome Score (KOOS) pain score (<55) were included. Index defects were Outerbridge Grade III or IV focal cartilage defects on the MFC, LFC, and/or trochlea and were at least 3 cm^2 in size. Osteochondritis dissecans (OCD) lesions were allowed if no bone graft was required. A stable knee was required; ligament repair or reconstruction procedures were allowed before or concurrently with study treatment. An intact or partial meniscus (≥50%) was also required; meniscal repair or resection was allowed before or concurrently with the cartilage repair procedure if ≥50% of functional meniscus was retained. All patients provided written informed consent before participating in the study.

Major exclusion criteria included any knee joint surgery within 6 months prior to screening (not including diagnostic arthroscopy); modified Outerbridge Grade III or IV defect(s) on the patella or tibia; symptomatic musculoskeletal condition in the lower limbs that could impede efficacy measures in the target knee joint; total meniscectomy, meniscal allograft, or bucket handle tear or displaced tear requiring >50% removal of the meniscus in the target knee; malalignment requiring an osteotomy to correct tibial-femoral or patella-femoral alignment; Kellgren-Lawrence grade 3 or 4 osteoarthritis; inflammatory disease or other condition affecting the joints; or septic arthritis within 1 year prior to screening.

Surgical Procedures

The control selected for efficacy comparison was MFX as recommended by the FDA and EMA for this protocol and in their guidances.[11,46] MFX is also universally considered a standard first-line therapy for cartilage repair, is widely available, and is used clinically in larger lesions, thus, reflecting "real-world" experience.

At baseline arthroscopy (performed within 8 weeks of screening) to assess cartilage lesion and surrounding cartilage, biopsies were taken from all patients. Following biopsies, eligible patients were intra-operatively randomized, using an interactive voice response system and computer-generated 1:1 randomization scheme, to the MACI implant or arthroscopic microfracture. The same surgical procedure was performed on any additional Outerbridge grade III and IV lesions in the target knee; lesions grade I or II were not treated or debrided only.

For the MACI implant procedure, a cartilage biopsy (approximately 200 mg) was aseptically harvested from a minor or non-weightbearing, healthy area of the femoral condyle. The biopsy was sent to Genzyme Biosurgery (Cambridge, MA, USA) where autologous

chondrocytes were isolated, cultured and seeded onto a purified, resorbable, porcine-derived collagen type I/III membrane (ACI-Maix, Matricel GmbH, Germany). The final MACI product was a 20 cm^2 (5 x 4 cm) membrane seeded with 500,000 to 1 million cells per cm^2.

The MACI implant procedure was performed via mini-arthrotomy 4 to 8 weeks after baseline arthroscopy. Briefly, the lesions were debrided back to a vertical rim of stable, healthy cartilage without breaching the subchondral bone. The shape and size of the lesion(s) were assessed and a template for each lesion was created. The MACI implant was trimmed to the correct size and shape of the defect, and placed down into the debrided base of the defect with the cells facing the subchondral bone. The implant was then secured in place using a thin layer of fibrin sealant on the base and edges of the defect, and stability of the implant checked while fully extending and flexing the knee a number of times.

Microfracture was performed at the time of arthroscopy strictly according to the technique described by Steadman et al.[45] In brief, the lesion was debrided back to stable, healthy cartilage avoiding damage to the subchondral bone. Multiple fracture holes were made in the subchondral bone with a sharp surgical awl so that the centers of the holes were 3 to 4 mm apart and 4 mm deep. All surgeons were trained on all surgical procedures, which we standardized for the study.

Second-look arthroscopy was used to assess the knee joint according to the International Cartilage Repair Society (ICRS) macroscopic evaluation criteria and obtain a biopsy of repair tissue at year 2 to be scored independently and blinded to treatment origin using the ICRS II histological outcome score.

Rehabilitation

The 4-phase, standardized rehabilitation program was the same for both treatment groups, based on a report by Steadman et al.[44] but was individualized for each patient. Patients progressed through the program at different rates based on lesion size, lesion location, pre-operative duration of symptoms, physical condition, patient motivation, and the expected course of healing for the procedure employed. Only when certain goals were reached at the end of each rehabilitation stage were the patients allowed to progress to the next stage.

The 4 rehabilitation phases were designed to avoid deleterious forces to the repair site and to promote a gradual and safe return to function and activity. The focus of the early protection phase (Phase I: weeks 0-6) was to protect the new repair tissue and to restore joint homeostasis using restricted weight-bearing and range of motion exercises. Patients moved on to the transition phase (Phase II: weeks 6-12) when they attained full passive knee extension and knee flexion to 120° with minimal pain and swelling, and were able to perform quadriceps set exercises with good contraction and no lag. The focus of this second phase was to restore full range of knee motion and to begin to work on muscle strength using exercises that gradually increased in weight-bearing and range of motion.

The remodeling phase (Phase III: weeks 12-26) was started when patients attained a full range of motion with minimal pain and swelling, and when they reached 20% hamstring strength and 30% quadriceps strength of the contralateral leg, as well as being within 30% of balance testing of the contralateral leg. Patients also had to be able to walk 1-2 miles or ride a bike for 30 min. The focus of the remodeling phase was to improve muscle strength and endurance and to reintroduce activities, while monitoring the increase in activity. Finally, patients with full range of motion, achieving strength 80-90% of contralateral leg, and balance 75-80% of contralateral leg with no pain, inflammation or swelling moved on to the Maturation phase (Phase IV: weeks

26-52). In this this last phase, the patients were allowed to participate in full unrestricted activity by developing programs based on the patient needs and type of activity (low impact sports: 4-6 months; moderate impact sports: 8 months; high impact sports: 12-18 months).

Study Endpoints

The primary efficacy analysis was based on a co-primary endpoint of change from baseline to year 2 for the patient's KOOS pain and function (sports and recreational activities) scores. A response rate based on KOOS pain and function scores at year 2 and earlier time points was one of the secondary endpoints (responder defined as a ≥10-point improvement in both the KOOS Pain and Function subscales).

Other predefined secondary endpoints included the histological evaluation of structural repair biopsies harvested from the core of the index lesion (year 2), as measured by the macroscopic ICRS overall assessment; MRI assessments of structural repair parameters at baseline, and at years 1 and 2, and change from baseline to years 1 and 2 for degree of defect fill, degree of repair tissue integration with adjacent native cartilage, and signal intensity of the repair tissue relative to adjacent native cartilage as measured using the Whole Organ MRI (WORMS) score[38] (the Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) scoring system[27] was not available at the time of study design); treatment failure rate at year 2 and earlier time points; change from baseline in KOOS pain and function at earlier time points; and change from baseline in KOOS activities of daily living (ADLs), knee-related quality of life (QoL), and other symptoms at year 2. Both histology and MRI measures were evaluated in a blinded fashion. Patients were defined as a treatment failure if, at any time after week 24, they had a patient and physician global assessment the same or worse than baseline, a <10% improvement

in KOOS pain, physician-diagnosed failure ruling out all other potential etiologies, *and* the physician decided that surgical re-treatment was needed.

Other study endpoints included change from baseline in KOOS pain, symptoms, knee-related QoL, ADLs subscales at earlier time points (weeks 24, 36, 52, and 78); change from baseline to years 1 and 2 in the overall knee condition using the Modified Cincinnati Knee Rating System,[36] International Knee Documentation (IKDC),[21] 12-Item Short Form Health Survey (SF-12),[50] and European Quality of Life (EuroQOL) 5 dimensions questionnaire (EQ-5D); and Macroscopic ICRS cartilage repair assessment score in patients having a biopsy taken via arthroscopy at year 2.

Patients were evaluated for adverse events (AEs) at each study visit. An AE was defined as any undesirable physical, psychological or behavioral effect experienced by a patient during the study period, independent of treatment relatedness. Adverse events were fully described and recorded by severity, duration, and relationship to treatment, and were considered treatment emergent if the AE began or worsened after treatment. All AEs were categorized with the Medical Dictionary for Regulatory Activities (MeDRA). Adverse events were considered serious if they were life threatening, required in-patient hospitalization, resulted in significant disability, or might otherwise jeopardize the patient. Subsequent surgical procedures (SSPs) were those performed on the target knee during the study; SSPs were not considered treatment failure but were classified as a serious AE.

Statistical Analysis

To power the study at 85% to detect a difference between groups, a sample size was estimated at a total of 144 patients (72 patients per arm) based on the change from baseline to year 2 in the

co-primary efficacy endpoints of KOOS pain and function with an alpha of 0.05 (and accounting for patient study discontinuation), assuming a difference of 12 points each for KOOS pain and function with SDs of 20 and 30, respectively, and a correlation coefficient of 0.56 between the co-primary endpoints.

All patients who were randomized and treated were analyzed. The co-primary endpoint was analyzed with SAS® (Cary, NC, USA) using a multivariate analysis of variance (MANOVA) model and the last observation carried forward (LOCF) approach. The final MANOVA model included treatment, study site, and baseline KOOS scores. All other changes in the KOOS subscales at all other time points were analyzed using analysis of variance (ANOVA) and LOCF. Differences between groups were tested by MANOVA and the Cochran-Mantel-Haenszel χ^2 test for histology, and by Cochran-Mantel-Haenszel χ^2 test for the proportions of responders and defect fill. The Cochran-Mantel-Haenszel χ^2 was also used to analyze differences in response rates between groups by lesion size (>4 cm^2, >5 cm^2), lesion location (MFC/LFC/trochlea), and osteochondritis dissecans (OCD) etiology (yes/no).

Predictor variables were also tested posthoc on the co-primary endpoint changes from baseline using multivariate analysis of covariance (MANCOVA) with treatment and center as fixed effects and baseline KOOS pain and function, age, total defect size, occurrence of previous surgery, duration of symptoms and index lesion location as covariates. Only significant covariates at a 0.05 level were included in the final model. The Wilk's Lambda test statistic and associated p-value were used to test the statistical significance for the co-primary endpoints between MACI and microfracture.

Differences between treatment groups for treatment failure were not tested because of the low number of failures.

RESULTS

Patient and Lesion Characteristics

A total of 144 patients were enrolled in the study and treated with the MACI implant (n=72) or microfracture (n=72; Figure 1). Most of the patients (95%; 137/144) completed a full 2 years of the study (MACI implant [n=70], microfracture [n=67]). No patients treated with the MACI implant discontinued due to lack of efficacy compared with 3 patients treated with MFX. Patients had a mean age of 33.8 years and a mean BMI of 26 kg/m^2, and 65% were male and all were of Caucasian origin (Table 1). The onset of symptoms before current treatment was a mean of almost 6 years for the MACI implant group and almost 4 years for the MFX group. More patients in the MFX group (37.5%) than in the MACI implant group (23.6%) had a sports activity level rated as highly competitive prior to onset of symptoms; slightly more patients in the MACI implant group (55.6%) were at a recreational activity level than in the MFX group (44.4%). Mean baseline scores for KOOS pain and KOOS function were 37.0 and 14.9 in the MACI implant arm, and 35.5 and 12.6 in the microfracture arm, respectively.

Lesions had a mean size of 4.8 cm^2, and most were located on the MFC or LFC as opposed to the trochlea (Table 1); the majority of lesions (66.7%) were completely contained (Table 1). Acute trauma was the most common underlying etiology for the lesions (54.2%) followed by chronic degeneration and osteochondritis dissecans.

Prior and concurrent procedures are listed in Table 2. The most common prior surgical procedures were diagnostic arthroscopy, debridement of cartilage lesion, microfracture, and loose body removal. The most common concomitant procedures were loose body removal, partial medial meniscectomy, and graft reconstruction during cartilage biopsy or implantation;

and loose body removal and synovectomy/synovial plica excision during the core biopsy at year 2.

KOOS Pain and Function

Two years after treatment, the improvement with the MACI implant over MFX in the co-primary endpoint was clinically and statistically significant (*P*=.001), with the KOOS pain being 11.76 (LS mean) and KOOS function (sports and recreation) being 11.41 (Table 3). Changes in KOOS pain and function at year 2 are shown in Figure 2. The significant improvement for the MACI implant over MFX was observed for KOOS pain and function as early as 36 weeks (*P*<.03), and was maintained at 52 weeks (*P*<.025; Figure 3) and out to 104 weeks.

The percentage of patients who responded to treatment at year 2, with at least a 10-point improvement from baseline in both KOOS pain and function scores (Figure 4), was significantly greater (*P*=.016) for the MACI implant group (87.5%) than the MFX group (68.1%). The trend towards a significantly better response rate for the MACI implant compared with MFX was also evident at 78 weeks (*P*=.098).

Predictors' subanalysis of the response rates were performed using patient and lesion characteristics (Table 4). When response rates were analyzed by patient characteristics, significantly more patients responded with the MACI implant than with MFX when patients were male, younger than 34.5 years (median age), only had 1 lesion, had lesions resulting from acute trauma, had 1 prior surgery, or had duration of symptoms lasting more than 3 years. Response rates were not significantly different between patients with or without prior cartilage surgeries. When analyzed by lesions characteristics, significantly more patients responded with

the MACI implant compared with MFX when their lesions were >4 cm^2, on the MFC, and not of OCD origin.

Analysis of lesion size and etiology as response predictors based on mean change from baseline of the co-primary endpoint showed significant improvements with the MACI implant versus MFX in patients with lesions 3 to ≤6 cm^2 (*P*=0.002), with acute trauma (*P*=0.046), with no chronic degeneration (*P*=0.007), with no concurrent surgery (p=0.004), and with longer symptom duration (*P*=0.018), while improvements were not significantly different in patients with larger lesions (6-10 cm^2), without acute trauma, with chronic degeneration, with a concurrent surgery, or with shorter symptom duration. No difference in response predictors was observed when analyzed by days since last surgery between the treatments.

Other Clinical Outcomes

Year 2 mean improvements from baseline in the other KOOS subscales (ADL, QOL, and other symptoms) were significantly better for patients treated with the MACI implant versus MFX (*P*<.001, *P*=.029, and *P*<.001 respectively; Figure 3). At 24 weeks, mean improvement for the other symptoms subscale was already significantly better for the MACI implant group compared with the MFX group (*P*=.031) and a trend towards significantly greater improvement (*P*=.078) was seen for ADL. At 36 weeks, significant improvements from baseline were observed for ADL and other symptoms but not for QOL. At 52 and 78 weeks, mean improvements were significantly better for all KOOS subscales for the MACI implant group compared with the MFX group.

The improvements in the modified Cincinnati score from baseline to year 1 and 2 were significantly better with the MACI implant (*P*=.018 and *P*=.002, respectively) than with MFX

(Table 3). Similarly, the change from baseline in IKDC scores was significantly better in patients treated with the MACI implant at year 1 (*P*=.009) than patients treated with MFX, although this difference was no longer significant at year 2 (*P*=.069).

Significantly better SF-12 physical health scores from baseline to year 1 and 2 were observed for the MACI implant group (*P*=.029 and *P*=.001, respectively) compared with the MFX group, but no significant difference (*P*=.209 and *P*=.523, respectively) in mental health scores were observed between the 2 groups (Table 3). Increases in EQ-5D VAS scores from baseline to year 2 were similar for both groups. There was no significant difference in the mean improvement in overall health status at year 1 (*P*=.335) or at year 2 (*P*=.148) from baseline.

No analyses were conducted with regard to treatment failure rates and time to treatment failure between the 2 treatment groups because of the small number of treatment failure cases. Only 2 patients in the MFX group were deemed treatment failures and no patients in the MACI implant group were considered treatment failures.

Repair Tissue Assessment

One hundred sixteen patients (MACI implant n=60; MFX n=56) had a second-look arthroscopy and biopsy (Figure 1). Overall, structural repair tissue was very good; however, the mean microscopic ICRS II overall assessment score between the 2 groups (63.8 versus 62.3; LS mean difference 1.52) was not significantly different (*P*=.717). However, greater ICRS II overall assessment scores were observed at year 2 for patients treated with the MACI implant versus MFX if they had had >1 prior cartilage repair surgery, whereas patients treated with MFX versus the MACI implant did better if they had lesions located at the trochlea, osteochondritis dissecans lesions, and no prior cartilage repair surgery.

Repair tissue assessment at year 2 with the macroscopic ICRS II cartilage repair scores showed similar scores between the 2 groups, with no significant difference in overall repair assessment, degree of defect repair, graft integration to border zones, and macroscopic appearance (Table 5). Approximately 76% of patients in the MACI implant group had nearly normal (Grade II) or normal (Grade I) for the overall repair assessment versus 60% in the MFX group. Conversely, 22.2% of patients in the MFX group had an abnormal (Grade III) or severely abnormal (Grade IV) assessment compared with 12.5% in the MACI implant group, although the MFX group has more missing (18% versus 11%). The majority of patients had a degree of defect repair that was in line with the surrounding cartilage, showed graft integration to border zones that was either complete or with a smaller than 1 mm demarcating border, and had repair tissue with an intact smooth or fibrillated surface.

MRI evaluation of structural repair was performed in 134 patients at year 1 and in 139 patients at year 2 (Figure 1). MRI evaluation of structural repair at year 1 and 2 showed improvement in defect filling for both treatment groups but with no statistically significant differences. Two years after treatment, 83% of patients in the MACI group and 77% of patients in the MFX group showed a degree of defect fill that was more than 50% of the defect depth.

Safety

No unexpected safety events were reported. Treatment-emergent AEs (TEAEs) were observed in 55 patients (76.4%) in the MACI group and 60 patients (83.3%) in the MFX group. Most treatment-emergent AEs were of moderate or mild intensity. The most common TEAEs (Table 6) were arthralgia (57.6%), headache (23.6%) and nasopharyngitis (11.8%). The incidence of TEAEs considered related to study treatment was comparable between the 2 treatment groups

(MACI: 34.7% and MFX: 38.9%). The most common related TEAEs were treatment failure, arthralgia, and joint swelling. In each group, 1 patient (1.4%) discontinued the study prematurely because of treatment-emergent AEs.

Treatment-emergent serious AEs were reported more frequently in the MFX group (26.4%) than in the MACI group (15.3%), which was attributed to treatment failure, cartilage injury, and arthralgia in the MFX group. No deaths occurred in this study.

The number of patients with at least 1 SSP was not significantly different (P=.427) between the MACI group (8.3%) and the MFX group (9.7%). Two SSPs were experienced by 2 MFX patients, but by no MACI patient. Increasing age significantly decreased the likelihood of at least 1 SSP occurring (P=.038).

Discussion

Our study demonstrates that cartilage defect treatment using the MACI implant is clinically and statistically significantly better than MFX for treating symptomatic cartilage defects of the knee, meeting our study's predefined co-primary endpoint. Overall, patients treated with the MACI implant had superior KOOS scores covering all 5 subscales (Pain, Function, ADL, QoL, and Other Symptoms) than patients treated with MFX after 2 years. Additionally, significantly more patients in the MACI implant group had a 10-point improvement or more in both their KOOS pain and function scores versus those in the MFX group. More patients responded when treated with the MACI implant than with MFX if they were male, young, had symptoms for more than 3 years, had lesions resulting from trauma, larger than >4 cm^2, located on the MFC, and not of OCD in origin.

Scores for the modified Cincinnati Knee Rating System, and SF-12 physical component score also improved significantly more with the MACI implant than with MFX. In addition, no treatment failures were reported for the MACI group compared with 2 in the MFX group as per the failure protocol definition. Further, repair tissue with the MACI implant also showed good structural outcomes, although not statistically different than with MFX. Finally, the safety profile was similar between the groups and no unexpected safety issues were encountered.

Our better outcomes with the MACI implant versus MFX are consistent with the results from the recent smaller randomized trial of Basad et al.[3] In their study (N=60) treating single, isolated, symptomatic chondral defects of the femoral condyle or patella, the Lysholm, Tegner, and patient and surgeon ICRS scores improved significantly more with the MACI implant than with MFX after 2 years.[3] In a case series of 34 patients, the Lysholm-Gillquist score improved by more points with the MACI implant than with MFX (48 versus 29).[2] Unlike these comparator

studies, ours is a more rigorous, multicenter, pragmatic study with MRI and histology endpoints that may help change cartilage repair treatment policy.

Historical series and cohort studies have also shown good outcomes with cartilage cell therapy. However in randomized comparisons, patient-reported outcomes have been shown for the most part to be similar between earlier generation ACI technology and MFX.[22,47] Vanlauwe and colleagues, found no statistical difference in a combined KOOS score for the overall group of patients who were treated with characterized chondrocyte implantation (CCI) or microfracture after 5 years.[47] Similarly, in a study reported by Knutsen and colleagues, clinical outcomes were similar between ACI and MFX at 5 years; but at 2 years, the SF-36 physical component was better with MFX than with ACI.[22] While previous studies with MFX show good clinical outcomes,[14,43] some reports show that such improvements are not always sustained.[17,23,24,34,35] In 3-year studies by Kreuz et al., clinical results were shown to deteriorate between the 18- and 36-month time points, which depended on the age of the patient and/or location of the lesion.[23,24] In a 48-month study, Mithoefer and colleagues found that while various clinical outcomes improved up to 24 months after MFX, not all were maintained after 24 to 36 months.[34]

Good clinical outcomes reported with the MACI implant in our study are also similar to those reported in previous MACI implant case series. Marlovits and colleagues[26] reported good clinical outcomes with few complications, and a low rate of treatment failure in a 5-year follow-up study of patients treated with the MACI implant procedure. Consistent with our study, the patients had significant improvement from baseline on all KOOS subscales, modified Cincinnati, and IKDC, as well as significant improvements in the Tegner-Lysholm scores as early as 1 year after treatment.[26] In another 5-year follow up of MACI-implant−treated knee chondral defects,[9] patients demonstrated significant improvements from baseline 2 years later, which were

maintained to 5 years in all 5 KOOS subscales, both mental and physical component scores of SF-36, ROM knee extension, and a 6-minute walk test. Good clinical outcomes after MACI were also demonstrated in a 2-year study, also reported by Ebert and colleagues,[8] where patients who followed a traditional or an accelerated rehabilitation program had similar improvements from baseline in KOOS scores, SF-36, and VAS scores at 2 years, but significantly less pain over time was seen for those in the accelerated versus the more traditional rehabilitation program. In a follow-up study of these patients, significant improvements from baseline in the reported KOOS subscales (sports and recreation, and quality of life) were still evident at 5 years.[10]

Of the previous studies described above that reported safety, the MACI implant provided a good safety profile, similar to our study.[3,9,26] In one study, typical postoperative swelling and effusion was observed in patients but got resolved within 4 weeks of the MACI procedure. [26] In another study, 2 patients developed a deep vein thrombosis early after treatment while 1 patient developed a postoperative hematoma; all patients recovered without sequelae.[9] In all of the studies, no deaths occurred.[3,9,26]

Beneficial results with MFX here are also consistent with previous MFX studies showing good clinical outcomes[14,43]; however, some reports show that such improvements with MFX are not always sustained past 18-24 months, unlike what we found.[17,23,34]

Our analysis of predictors by response rate showed that more patients with longer duration of symptoms (>3 years) or younger age (< 34.5 median age) improved with MACI vs. MFX. However, Vanlauwe and colleagues found that patients with less time since symptom onset (<3 years versus ≥3 years) did better with CCI than with MFX, while cell therapy in older defects did not seem to have an added benefit.[47] Furthermore, no discernable difference was observed between younger (<35 years) and older (≥35 years) patients.[47] In another study,

younger patients (<30 years) had better clinical outcome than older patients but regardless of treatment with MACI or MFX.[22] The reasons for the inconsistencies in our results compared with these previous cell therapy studies are unknown but may pertain to patient population or technique differences.

Structural endpoints assessed by MRI and repair tissue histology assessed by the ICRS II score demonstrated good quality repair tissue with the MACI implant. However, the good quality repair tissue with the MACI implant was not numerically different than that found with MFX, even given the clinical results favoring the MACI implant. These findings were unexpected in that MFX performed better than anticipated, as previous studies show better repair tissue with autologous cell therapies than with MFX. In a study by Bachmann and colleagues, MRI-evaluated repair tissue was of better quality with the MACI implant than that with MFX.[2] For the 27 patients who received the MACI implant, defect fill was more consistent than with MFX (n=7), and 78% of patients' repair tissues was integrated with adjacent cartilage.[2] Further, the MRI signal indicated that the signal intensity of the repair tissue with the MACI implant was close to that of the surrounding native cartilage, but was not homogenous with a signal intensity different than that of adjacent normal cartilage with MFX.[2]

Other studies show better repair tissue with other cell-therapy technologies than with MFX. One year after characterized chondrocyte implantation (CCI), structural repair tissue was better than with MFX,[41] as shown by better mean histology assessment (blinded) score (P=.012), particularly in chondrocyte phenotype (P<.01) and tissue structure (P<.05) in CCI-treated patients than in MFX-treated patients.[41] Safranin O and collagen II stainings were also more intense as detected by the mean histomorphometry score with CCI than with MFX (P=0.03).[41]

However, MRI assessment showed similar repair tissue after 3 years,[40] with no report on repair tissue at year 5.[47]

The reasons for our unanticipated similar results in repair tissue between the MACI implant and MFX are unknown. The clinical relevance and applicability to long-term clinical outcome of the ICRS II, a recently developed grading system for cartilage repair, especially in terms of histology still needs to be established.[25] Further, one cannot ensure that biopsies taken were the best representative sample of the total repair tissue especially since the samples were taken by individual surgeons and not by one dedicated sampling person, although this would apply equally to both groups.[33] Evidence for the "overperformance" of MFX in the present study can be found in a study comparing MFX with CCI, as our overall ICRS II score with MFX (62.3) was numerically higher than that in the MFX-CCI comparison (approximately 44).[41] Finally, an error in the protocol that directed pre-operative MRI reads to be scored as post-operative reads may have contributed to these unexpected results. Further investigation of this scoring issue is currently underway.

Additional longer-term comparative studies are needed to further understand the relationship between clinical outcomes and integrity of the structural cartilage tissue. A systematic review and meta-analysis reported by de Windt et al. found that the majority of articular cartilage repair of the knee studies show limited or no correlation between clinical outcomes and MRI parameters; only 28% of studies (9 of 32) showed a correlation between clinical outcome and MOCART or Henderson scores.[6] This is in line with guidance from regulatory agencies (EMA and FDA) that suggests MRI data, as well as histology data, are not predictive of outcome, and that clinical outcomes assessing pain and function are the most important parameters in determining the efficacy of cell-based therapies.[11,46] Nevertheless, an

extension of our study is currently underway, where 3- and 5-year outcomes will be assessed, which may reveal a difference in MRI structural outcome between MACI and MFX treatments. Lastly, we did not examine biochemical properties of the repair tissue, which may help explain the better clinical outcome with the MACI implant.

Some of the limitations of this study include the fact that it was a multicenter study and therefore procedures were performed by many surgeons, and that it was not a blinded study. Procedures being performed by more than one physician may introduce investigator variability; although all surgeons were trained on standardized surgical procedures and their training was audited by the sponsor. In addition, given that the surgical techniques for the MACI implant (2 surgeries required) and microfracture (1 surgery) are different, the study could not be blinded; however, histologic and MRI evaluations were assessor blinded. Comparing 2- and 1-step surgeries is also a limitation, but the similar safety profile between the two demonstrates that the 2-step procedure is not more risky than the 1-step procedure, also reflected in our clinical experience. Due to the inherent heterogeneity of cartilage repair tissue, one limitation of the histological evaluation is the inability to ensure that the biopsy acquired was representative of the total cartilage repair tissue.[33] Also, it is possible that the favorable results observed for patients in both treatment groups could have been positively influenced by the rigorous patient education and follow-up inherent in the study protocol.

Our SUMMIT clinical trial is one of the very few Good Clinical Practice-conducted, prospective, multicenter, randomized, controlled study of cell-based cartilage repair to date. The study included stringent inclusion and exclusion criteria, standardized surgical and rehabilitation procedures, and ensured a comprehensive patient follow up. Other strengths of the study included the use of validated clinical outcomes and histology and MRI assessments.

Overall, improvements in clinically relevant endpoints such as pain and function, as opposed to those of structural repair, remain the more important endpoints for the study of cartilage defects with regard to patient care.[33] This trial demonstrated that the MACI implant provides more pain relief and functional improvement when compared with MFX, with a similar safety profile, when treating symptomatic articular cartilage defects of the knee based on significantly better outcomes for various patient-reported efficacy endpoints.

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TABLE 1
Patient and Lesion Characteristics

	MACI implant (n=72)	**Microfracture (n=72)**
Patients		
Age (years), mean ± SD	34.8 ± 9.2	32.9 ± 8.8
Gender, % male	62.5	66.7
Race, % White	100	100
BMI (kg/m^2), mean ± SD	26.2 ± 4.3	26.4 ± 4.0
Duration of symptoms (years)		
Mean (range)	5.8 (0.05 –28.0)	3.7 (0.1 – 15.4)
Baseline KOOS pain	37.0 ± 13.5	35.5 ± 12.1
Baseline KOOS function	14.9 ± 14.7	12.6 ± 16.7
Lesions		
Index lesion size (cm^2), mean ± SD	4.9 ± 2.8	4.7 ± 1.8
Total defect surface area (cm^2), mean ± SD	5.8 ± 5.1	5.3 ± 2.5
Location, n (%)		
MFC	54 (75.0)	53 (73.6)
LFC	13 (18.1)	15 (20.8)
Trochlea	5 (6.9)	4 (5.6)

	MACI implant (n=72)	**Microfracture (n=72)**
Etiology, n (%)		
Acute trauma	33 (45.8)	45 (62.5)
Chronic degeneration	18 (25.0)	9 (12.5)
Osteocondritis dissecans	8 (11.1)	12 (16.7)
Unknown	9 (12.5)	6 (8.3)
Other	4 (5.6)	0
Outerbridge grade, n (%)		
III	21 (29.2)	15 (20.8)
IV	51 (70.8)	57 (79.2)
Lesion Containment, n (%)		
Completely contained	50 (69.4)	46 (63.9)
Partially contained	22 (30.6)	26 (36.1)

KOOS: Knee Injury and Osteoarthritis Outcome Score; LFC: lateral femoral condyle; MACI: matrix applied characterised autologous cultured chondrocytes; MFC: medial femoral condyle; SD: standard deviation.

TABLE 2
Most Frequent Prior and Concomitant Procedures

	MACI implant (n=72)	**Microfracture (n=72)**
Patients with prior procedure, n (%)	65 (90.3)	60 (83.3)
Prior procedures		
Diagnostic arthroscopy	35 (53.8)	28 (46.7)
Debridement	20 (30.8)	13 (21.7)
Partial meniscectomy, medial	17 (26.2)	7 (11.7)
Loose body removal	16 (24.6)	13 (21.7)
Microfracture	12 (18.5)	18 (30.0)
Shaving	12 (18.5)	12 (20.0)
Other	11 (16.9)	10 (16.7)
ACL repair	9 (13.8)	5 (8.3)
Lavage	7 (10.8)	1 (1.7)
Subchondral drilling	7 (10.8)	4 (6.7)
Synovectomy/synovial plica excision	5 (7.7)	4 (6.7)
Partial meniscectomy, lateral	4 (6.2)	7 (11.7)
Fixation of OCD fragment	4 (6.2)	2 (3.3)
Hardware removal	4 (6.2)	3 (5.0)
Abrasion arthroplasty	2 (3.1)	0
Lateral release of patella retinaculum	2 (3.1)	2 (3.3)

	MACI implant (n=72)	Microfracture (n=72)
Osteochondral autograft	2 (3.1)	0
Biopsy harvest for ACI	1 (1.5)	0
Bone graft	1 (1.5)	0
Lateral meniscal repair	1 (1.5)	0
Patella tracking	0	1 (1.7)
Medial meniscal repair	0	1 (1.7)
Medial collateral ligament repair	0	1 (1.7)
Concomitant procedures		
During index biopsy or implantation	26 (36.1)	22 (30.6)
Loose body removal	7 (26.9)	9 (40.9)
Synovectomy/synovial plica excision	6 (23.1)	3 (13.6)
Partial medial meniscectomy	6 (23.1)	4 (18.2)
Graft reconstruction	4 (15.4)	6 (27.3)
Other	4 (15.4)	3 (13.6)
Partial lateral meniscectomy	2 (7.7)	4 (18.2)
Lateral release of patella retinaculum	0	1 (4.5)
During week 104 biopsy	19 (26.4)	17 (23.6)
Other	13 (68.4)	13 (76.5)
Loose body removal	6 (31.6)	5 (29.4)
Synovectomy/synovial plica excision	2 (10.5)	3 (17.6)
Partial medial meniscectomy	1 (5.3)	0

	MACI implant (n=72)	Microfracture (n=72)
Partial lateral menisectomy	0	1 (5.9)

ACI: autologous chondrocyte implantation; ACL: anterior cruciate ligament; MACI: matrix applied characterised autologous chondrocytes; OCD: osteochondritis dissecans.

TABLE 3
Mean Scores (± SD) for Patient-Reported Outcomes with the MACI Implant and Microfracture at Baseline and Year 2

	MACI implant				Microfracture					
	Baseline	**n**	**Year 2**	**n**	**Baseline**	**n**	**Year 2**	**n**	**LS Mean Difference**	***P*-Value***
KOOS subscales										
Pain	37.0 ± 13.5	72	82.5 ± 16.2	72	35.5 ± 12.1	71	70.9 ± 24.2	70	11.76	0.001†
Function	14.9 ± 14.7	72	60.9 ± 27.8	72	12.8 ± 16.7	71	48.7 ± 30.3	70	11.41	
Activities of Daily Living	43.5 ± 18.2	72	87.2 ± 16.5	72	42.6 ± 19.6	72	75.8 ± 24.2	71	12.01	<0.001
Knee Quality of Life	18.8 ± 14.7	72	56.2 ± 23.9	72	17.2 ± 14.1	72	47.3 ± 27.0	71	8.98	0.029
Other Symptoms	48.3 ± 16.9	72	83.7 ± 14.0	72	44.4 ± 18.6	72	72.2 ± 19.5	71	11.61	<0.001
Modified Cincinnati Knee Rating System	3.0 ± 1.2	72	6.4 ± 2.1	72	3.0 ± 1.2	72	5.4 ± 2.2	71	1.05	0.002
IKDC Subjective Knee Evaluation	32.9 ± 13.3	71	65.7 ± 18.5	72	29.3 ± 13.4	72	58.8 ± 22.3	71	5.94	0.069
SF-12 Physical Component Score	-1.77 ± 0.86	72	-0.32 ± 0.89	72	-1.93 ± 0.82	69	-0.82 ± 1.12	71	0.51	0.001
SF-12 Mental Component Score	0.04 ± 1.2	72	0.45 ± 0.9	72	-0.17 ± 1.3	69	0.49 ± 1.0	71	-0.09	0.523
EQ-5D Visual Analogue Scale Score	60.8 ± 20.9	72	77.5 ± 15.3	72	56.2 ± 22.1	72	73.4 ± 18.4	70	3.75	0.148

**P*-value for difference between treatment in LS means for change from baseline to year 2.
†*P*-value for co-primary endpoint (KOOS pain and function) for difference between treatment in LS means for change from baseline to year 2.
EQ-5D: European Quality of Life (EuroQOL) 5 dimensions questionnaire; IKDC: International Knee Documentation Committee, KOOS: Knee Injury and Osteoarthritis Outcome Score; MACI: matrix applied characterised autologous cultured chondrocytes; SF-12: 12-Item Short-Form Health Survey

TABLE 4
Response Rates* with MACI Implant and Microfracture at Year 2

		Response rates, % patients (n/N)		
		MACI implant	**MFX**	***P*-value**
Overall		87.5 (63/72)	68.1 (49/72)	0.016
Patient Characteristics				
Gender	Male	91.1 (41/45)	68.8 (33/48)	0.012
	Female	81.5 (22/27)	66.7 (16/24)	0.465
Median Age	<34.5 years	91.2 (31/34)	68.4 (26/38)	0.027
	≥34.5 years	84.2 (32/38)	71.9 (23/34)	0.210
Acute Trauma	Yes	87.9 (29/33)	55.8 (24/45)	0.004
	No	87.2 (34/39)	92.6 (25/27)	0.483
No. of Lesions	1	90.0 (45/50)	65.5 (36/55)	0.006
	>1	81.8 (18/22)	76.5 (13/17)	0.964
Prior Cartilage Surgeries	No	90.0 (27/30)	74.2 (23/31)	0.386
	1	87.0 (20/23)	67.9 (19/28)	0.110
	>1	84.2 (16/19)	53.9 (7/13)	0.061
Prior Surgeries	No	100 (11/11)	92.3 (12/13)	0.347
	1	100 (12/12)	62.5 (10/16)	0.027
	>1	81.6 (40/49)	62.8 (27/43)	0.087
Symptoms Duration	≤3 years	81.8 (27/33)	68.9 (21/45)	0.323
	>3 years	92.1 (35/38)	66.7 (18/27)	0.017

		Response rates, % patients (n/N)		
		MACI implant	**MFX**	***P*-value**
Lesion characteristics				
Size	>4 cm^2	97.1 (34/35)	77.4 (24/31)	0.014
	≤4 cm^2	78.4 (29/37)	60.9 (25/41)	0.225
	>5 cm^2	95.2 (20/21)	76.2 (16/21)	0.078
	≤5 cm^2	84.3 (43/51)	64.7 (33/41)	0.067
	>6 cm^2	100.0 (9/9)	86.7 (13/15)	0.253
	≤6 cm^2	85.7 (54/63)	63.2 (36/57)	0.015
Location	MFC	87.0 (47/54)	66.0 (35/53)	0.034
	LFC	92.3 (12/13)	73.3 (11/15)	0.191
	Trochlea	80.0 (4/5)	75.0 (3/4)	0.858
OCD	Yes	87.5 (7/8)	91.7 (11/12)	0.761
	No	87.5 (56/64)	63.3 (38/60)	0.006

*A patient was considered a responder if they had ≥10-point improvement over baseline in KOOS pain and function scores.

TABLE 5
Macroscopic ICRS Cartilage Repair Assessment Scores

n (%)	MACI implant (n=72)	Microfracture (n=72)
Overall Repair Assessment		
Grade I (Normal)	14 (19.4)	8 (11.1)
Grade II (Nearly normal)	41 (56.9)	35 (48.6)
Grade III (Abnormal)	4 (5.6)	12 (16.7)
Grade IV (Severely abnormal)	5 (6.9)	4 (5.6)
Missing	8 (11.1)	13 (18.1)
Degree of Defect Repair		
In Line With Surrounding Cartilage	45 (62.5)	38 (52.8)
75% Repair of Defect Depth	10 (13.9)	9 (12.5)
50% Repair of Defect Depth	4 (5.6)	7 (9.7)
25% Repair of Defect Depth	4 (5.6)	3 (4.2)
0% Repair of Defect Depth	1 (1.4)	2 (2.8)
Missing	8 (11.1)	13 (18.1)
Graft Integration to Border Zones		
Complete Integration	21 (29.2)	15 (20.8)
Demarcating Border <1 mm	20 (27.8)	20 (27.8)
¾ Integrated, ¼ With Border >1 mm	14 (19.4)	13 (18.1)
½ Integrated, ½ With Border >1 mm	3 (4.2)	7 (9.7)
No Contact to ¼ Integrated	6 (8.3)	4 (5.6)

n (%)	MACI implant (n=72)	Microfracture (n=72)
Missing	8 (11.1)	13 (18.1)
Macroscopic Appearance		
Intact Smooth Surface	25 (34.7)	16 (22.2)
Fibrillated Surface	21 (29.2)	22 (30.6)
Small, Scattered Fissures	13 (18.1)	13 (18.1)
Several Small or Few but Large Fissures	3 (4.2)	5 (6.9)
Total Degeneration of Grafted Areas	2 (2.8)	3 (4.2)
Missing	8 (11.1)	13 (18.1)

ICRS: International Cartilage Repair Society; MACI: matrix applied characterised autologous cultured chondrocytes

TABLE 6
Most Frequently Reported (>5%) Treatment-Emergent Adverse Events

Adverse event	**MACI implant**	**Microfracture**
n (%)	**n=72**	**n=72**
Any TEAE	55 (76.4)	60 (83.3)
Arthralgia	37 (51.4)	46 (63.9)
Headache	13 (18.1)	21 (29.2)
Nasopharyngitis	10 (13.9)	7 (9.7)
Back pain	8 (11.1)	7 (9.7)
Joint swelling	7 (9.7)	4 (5.6)
Joint effusion	5 (6.9)	4 (5.6)
Influenza	4 (5.6)	5 (6.9)
Pyrexia	4 (5.6)	2 (2.8)
Cartilage injury	3 (4.2)	9 (12.5)
Procedural pain	3 (4.2)	4 (5.6)
Ligament sprain	2 (2.8)	4 (5.6)
Abdominal pain	0 (0.0)	5 (6.9)

TEAE: treatment-emergent adverse event

Figure Legends

Figure 1: Patient Disposition

Figure 2: Changes from baseline to Year 2 in all Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales for patients treated with the matrix applied characterised autologous cultured chondrocytes (MACI) implant or microfracture

Figure 3: Mean (95% CI) Knee Injury and Osteoarthritis Outcome Score (KOOS) pain (A) and function (B) improvement over time for patients treated with the matrix applied characterised autologous cultured chondrocytes (MACI) implant or microfracture. A significant improvement ($P<0.030$) was observed for the MACI group compared with the MFX group for the KOOS Pain and Function at year 1, which was maintained to year 2 ($P<0.025$).

Figure 4: Percentage of patients who responded (≥10-point improvement in Knee Injury and Osteoarthritis Outcome Score (KOOS) pain and function at year 2)

Figures

Figure 1

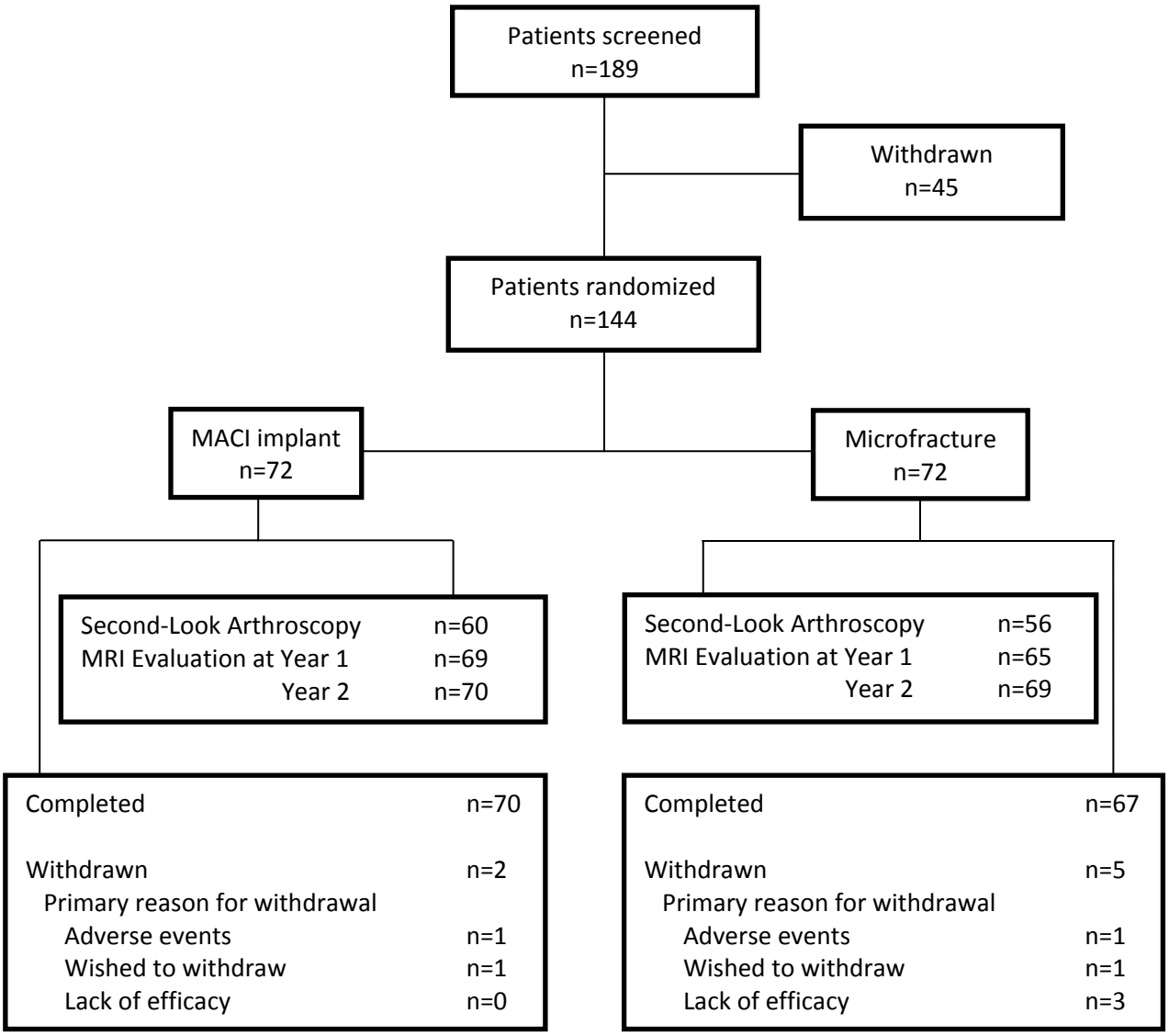


Figure 2

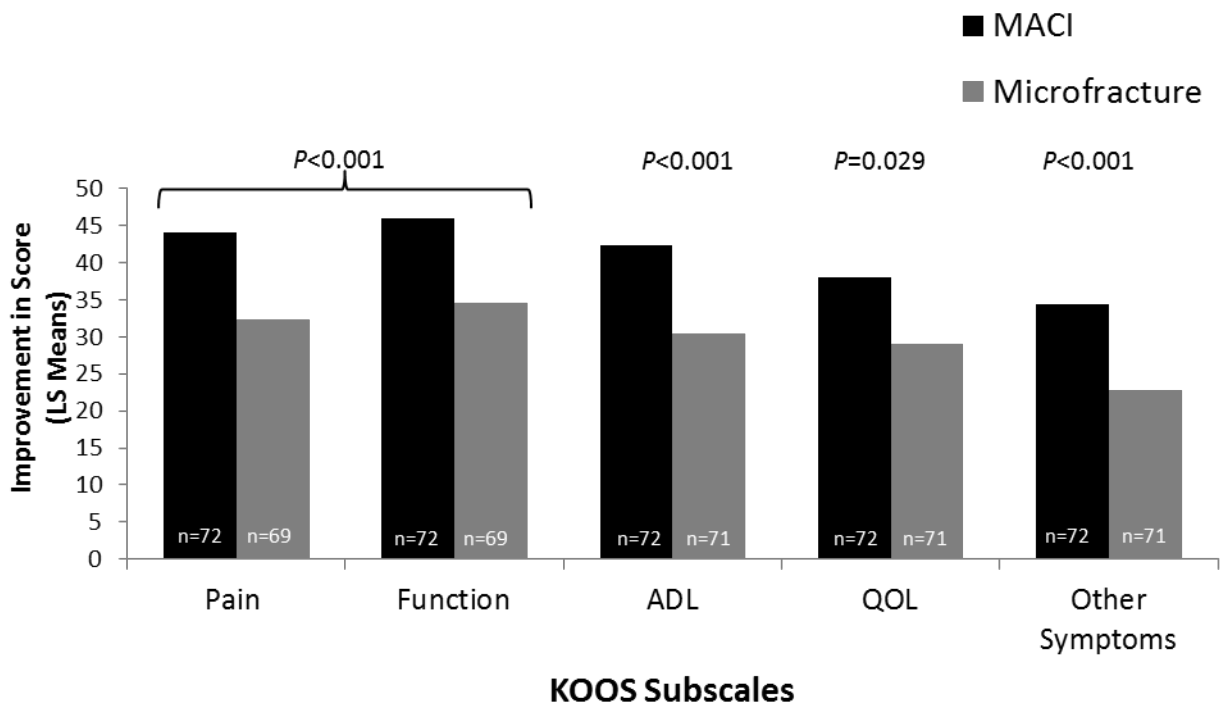
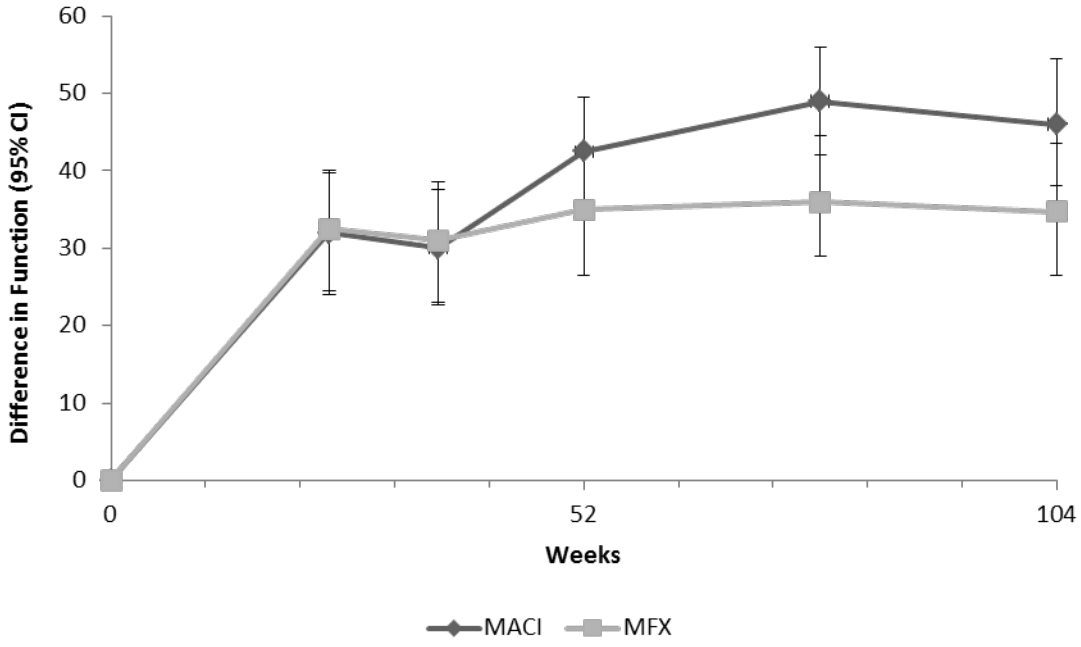

MACI
Microfracture
P<0.001
P<0.001
P=0.029
P<0.001
Improvement in Score (LS Means)
50
45
40
35
30
25
20
15
10
5
0
n=72
n=69
n=72
n=69
n=72
n=71
n=72
n=71
n=72
n=71
Pain
Function
ADL
QOL
Other Symptoms
KOOS Subscales

Figure 3

A. Pain



B. Function

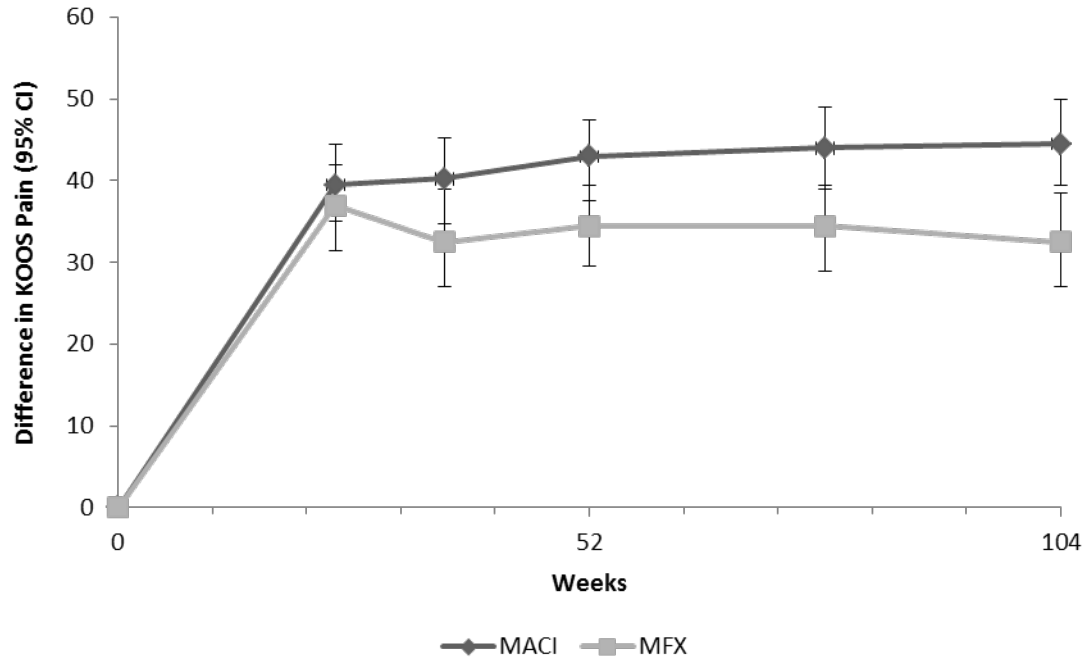


Figure 4