Matrix-Applied Characterized Autologous Cultured Chondrocytes Versus Microfracture

Five-Year Follow-up of a Prospective Randomized Trial

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Investigation performed by the SUMMIT Extension Study Group based on the multicenter study performed at 14 sites across 7 European countries

Background: Matrix-based cell therapy improves surgical handling, increases patient comfort, and allows for expanded indications with better reliability within the knee joint. Five-year efficacy and safety of autologous cultured chondrocytes on porcine collagen membrane (MACI) versus microfracture for treating cartilage defects have not yet been reported from any randomized controlled clinical trial.

Purpose: To examine the clinical efficacy and safety results at 5 years after treatment with MACI and compare these with the efficacy and safety of microfracture treatment for symptomatic cartilage defects of the knee.

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

Methods: This article describes the 5-year follow-up of the SUMMIT (Superiority of MACI Implant Versus Microfracture Treatment) clinical trial conducted at 14 study sites in Europe. All 144 patients who participated in SUMMIT were eligible to enroll; analyses of the 5-year data were performed with data from patients who signed informed consent and continued in the Extension study.

Results: Of the 144 patients randomized in the SUMMIT trial, 128 signed informed consent and continued observation in the Extension study: 65 MACI (90.3%) and 63 microfracture (87.5%). The improvements in Knee injury and Osteoarthritis Outcome Score (KOOS) Pain and Function domains previously described were maintained over the 5-year follow-up. Five years after treatment, the improvement in MACI over microfracture in the co-primary endpoint of KOOS pain and function was maintained and was clinically and statistically significant (P = .022). Improvements in activities of daily living remained statistically significantly better (P = .007) in MACI patients, with quality of life and other symptoms remaining numerically higher in MACI patients but losing statistical significance relative to the results of the SUMMIT 2-year analysis. Magnetic resonance imaging (MRI) evaluation of structural repair was performed in 120 patients at year 5. As in the 2-year SUMMIT (MACI00206) results, the MRI evaluation showed improvement in defect filling for both treatments; however, no statistically significant differences were noted between treatment groups.

Conclusion: Symptomatic cartilage knee defects 3 cm^2 or larger treated with MACI were clinically and statistically significantly improved at 5 years compared with microfracture treatment. No remarkable adverse events or safety issues were noted in this heterogeneous patient population.

Keywords: cartilage repair; clinical outcomes; knee; matrix-applied characterized autologous cultured chondrocytes (MACI) implant; microfracture

Patients with full-thickness cartilage defects of the knee experience considerable pain and impairment of activity. Focal chondral lesions left untreated may progress to clinically relevant joint pain with dysfunction, osteoarthritis, and detrimental influence on quality of life.[10,15] Several approaches exist to manage symptomatic chondral and osteochondral defects in the knee, including nonsurgical and nonreparative approaches (eg, lifestyle changes, pain medication, debridement, and knee joint lavage), reparative procedures (marrow stimulation techniques including microfracture), and restorative procedures (mosaicplasty, osteochondral allografts, allograft surface treatments, and autologous chondrocyte implantation [ACI]).

First-generation ACI was limited due to the need for open surgery, risk of uneven distribution of cells, and postoperative complications such as periosteal hypertrophy. An improvement was the use of a bioabsorbable collagen membrane cover, known as collagen-covered ACI, instead of an

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autologous periosteal membrane. Initial studies of this second-generation ACI reported similar clinical results as with first-generation ACI but with fewer complications such as hypertrophy. However, the second-generation ACI still required an open surgical technique with sutures.[1-3,6,7]

MACI (autologous cultured chondrocytes on a porcine collagen membrane) was developed to address the unmet medical need for a safer and more efficient ACI to ensure consistency of the product as well as the method of application. The viability, identity, and potency cell assays are critical quality assessments of seeded cells used to measure their chondrogenic potential and to assess process consistency over time through use of a characterized strain of chondrocytes.[26,27] The MACI membrane is a cell carrier with the chondrocytes seeded on the rough side facing the bony defect area, while the smooth, denser side is placed facing the articular cavity. Because of the membrane's elastic properties, the membrane can conform to differently shaped defects and is easy to introduce into the joint via mini-arthrotomy or transarthroscopic procedure to be fixed in the cartilage lesion with fibrin glue. After 48 hours, most of the cells have migrated away from the type I/III collagen membrane and are spread throughout the fibrin glue matrix.

In the previously published short-term follow-up of the SUMMIT (Superiority of MACI Implant Versus Microfracture Treatment) randomized controlled clinical trial, we showed the safety of MACI and the clinically better outcomes of MACI versus microfracture for symptomatic cartilage knee defects 3 cm^2 or larger; the improvement in outcomes was statistically significant ($P = .001$), and structural repair tissue and safety were similar.[28]

Here, using data for 5 years total, we report the efficacy and safety results after treatment with MACI or microfracture treatment for cartilage defect of the knee.

METHODS

Overview of SUMMIT

Extensive method description has been previously provided for the 2-year SUMMIT trial.[28] Briefly, the SUMMIT trial was a prospective randomized, open-label, parallel-group, multicenter study conducted at 16 sites in Europe (NCT00719576; EudraCT 2006-004817-16). Patients eligible for inclusion in SUMMIT were male and female patients aged 18 to 55 years with 1 or more symptomatic cartilage defects and a moderate to severe Knee injury and Osteoarthritis Outcome Score (KOOS) pain value (<55) at baseline. Index defects were Outerbridge grade III or IV focal cartilage defects on the medial femoral condyle (MFC), lateral femoral condyle (LFC), and/or trochlea that were 3 cm^2 or larger. Cartilage defects were treated with MACI or arthroscopic microfracture.

All patients who met the eligibility criteria and whom the surgeon considered suitable for treatment in the study had a cartilage biopsy specimen taken before randomization to study treatment. Eligible patients were randomized during the index arthroscopy procedure to receive either MACI or microfracture. Patients randomized to microfracture underwent the procedure during the initial arthroscopy. Microfracture was performed at the time of arthroscopic surgery strictly according to the technique described by Steadman et al.[30] All patients were provided a recommended postoperative rehabilitation program.[18] Patients randomized to treatment with MACI returned within approximately 4 to 8 weeks to undergo the MACI chondrocyte implantation procedure via mini-arthrotomy. The final MACI product was a 20-cm^2 membrane seeded at a density of at least 500,000 cells/cm^2 and up to 1 million cells/cm^2.

Overview of SUMMIT Extension Study Design

The SUMMIT Extension study (NCT01251588; EudraCT 2009-016970-33) was a 3-year follow-up of the SUMMIT clinical trial, entailing up to 5 years of observation after surgery (Figure 1). The Extension study was conducted between December 2010 and March 2015. All 144 patients who received study treatment in SUMMIT had the option to enroll in the Extension study. In the Extension study, efficacy and safety assessments were performed at scheduled visits 3, 4, and 5 years after treatment with MACI or microfracture in the SUMMIT trial. The Extension study was conducted at 14 study sites across 7 countries in Europe. The protocol and informed consent form were approved by the appropriate national and local ethics committees at each site. The study was conducted according to

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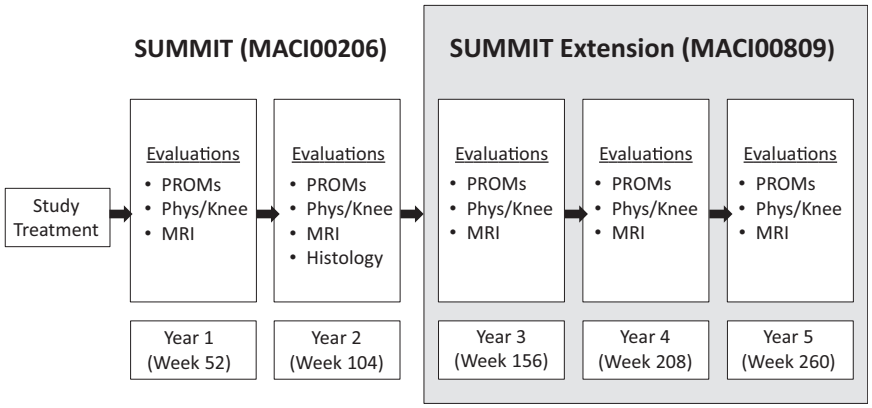

Figure 1. Overall study design for SUMMIT and SUMMIT Extension. MRI, magnetic resonance imaging; Phys, physical; PROM, patient-reported outcome measures.

TABLE 1
SUMMIT Extension Study Endpoints[a]

	Description
Efficacy	Change from baseline in KOOS Pain and Function subscales
	Response rate based on KOOS Pain and Function scores; a responder was defined as a patient with at least a 10-point improvement in both the KOOS Pain and Function scores from baseline
	Change from baseline in the remaining KOOS subscales (ADL, Knee-Related QOL, Other Symptoms)
	Mean reported (observed) KOOS scores (Pain, Function, ADL, QOL, and Other Symptoms)
	Mean reported (observed) other patient-reported outcome scores (modified Cincinnati Knee Rating System, IKDC, SF-12 Physical, SF-12 Mental, EQ-5D VAS)
	Assessment of treatment failure
Safety	Treatment-emergent adverse events, serious adverse events, subsequent surgical procedures (procedures performed on the target knee during the study)

[a]ADL, activities of daily living; EQ-5D VAS, EuroQol 5 Dimensions Visual Analog Scale; IKDC, International Knee Documentation Committee; KOOS, Knee injury and Osteoarthritis Outcome Score; QOL, Quality of Life; SF-12, 12-Item Short Form Health Survey.

Good Clinical Practice (GCP) guidelines and principles of the Declaration of Helsinki. Two study sites that enrolled patients in the initial randomized controlled trial elected not to participate in the Extension study; patients at the 2 sites did not want to continue in the study and refused transfer to other sites. All patients provided written informed consent before participating.

Study Endpoints

The prespecified primary endpoint of the Extension study was the change from baseline to week 156 (year 3) in KOOS Pain and Function (Sports and Recreational Activities) scores. The clinically and statistically significant results of the analyses of the co-primary endpoint at year 3 of the Extension study were presented previously by Brittberg et al[8] and are not described further in the 5-year analysis provided here. Study endpoints presented in this 5-year analysis are shown in Table 1.

Statistical Analysis

Planned Analyses. All analyses of the 5-year data were performed by use of data from patients who signed informed consent and enrolled in the Extension study (modified full analysis set [mFAS]). No patients were excluded from the analyses, including those patients with treatment failure or subsequent surgical procedures. Per the statistical analysis plan, the evaluation of efficacy at 5 years was planned to be descriptive in nature.

Post Hoc Analysis of Treatment Effect. To evaluate the effect of treatment at 5 years for those patients continuing in the Extension study, a post hoc analysis was conducted with the same method as used in the 2-year SUMMIT trial. For patients enrolled in the Extension study (mFAS), the 5-year analysis for the co-primary endpoint of KOOS Pain and Function was performed by evaluation of the change from baseline at each yearly scheduled postbaseline KOOS evaluation visit by multivariate analysis of covariance (MANCOVA) model and last observation carried forward (LOCF) for missing data. All analyses were performed with SAS v9.2 (SAS Institute). The final MANCOVA model included treatment, study site, index knee location, and baseline KOOS values. The Wilks lambda test statistic and associated single P value from the MANCOVA model were used to test the statistical significance of the difference in the co-primary endpoint between MACI and microfracture. All other changes in the KOOS subscales at all other time points were analyzed and compared between MACI and microfracture by use of analysis

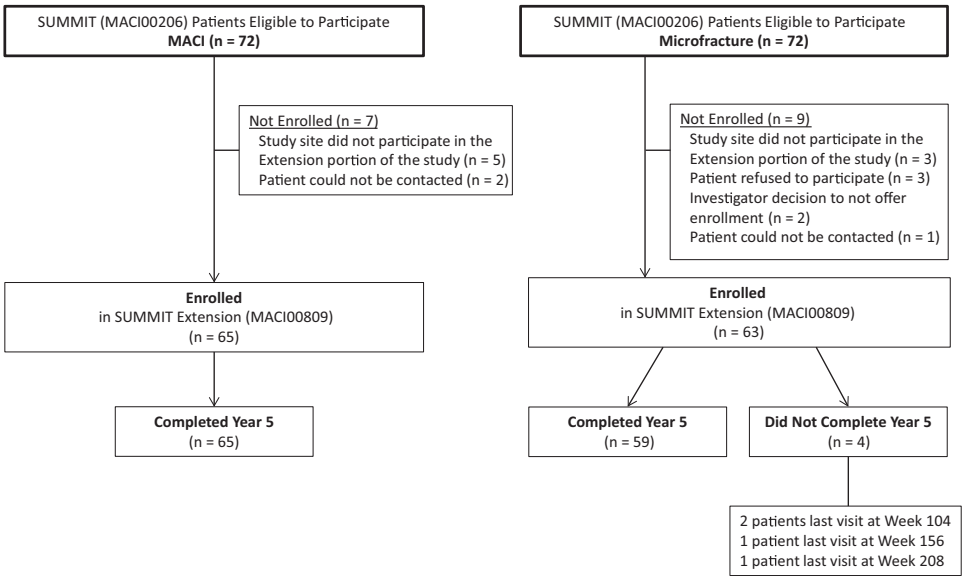

Figure 2. Patient disposition for patients enrolled in SUMMIT Extension. MACI, matrix-applied characterized autologous cultured chondrocytes.

of variance and LOCF with terms for treatment, study site, and baseline.

RESULTS

Patient Disposition and Characteristics

Of the 144 patients randomized in the SUMMIT trial, 128 were enrolled in the Extension study: 65 patients (90.3%) from the MACI group and 63 patients (87.5%) from the microfracture group (Figure 2). Whereas all patients in the MACI group who entered the Extension completed the study, 4 patients in the microfracture group were lost to follow-up early in the study and did not complete evaluations. Overall, 90% of MACI (65/72) and 82% of microfracture (59/72) patients were evaluated over a 5-year time period.

Evaluation of Patients Enrolled Versus Not Enrolled in SUMMIT Extension

Due to the loss of follow-up for patients going into the Extension study (as a result of patient choice or investigator nonparticipation), the differences between enrolled and not enrolled patients in baseline characteristics (patient and lesion) and 2-year KOOS response were evaluated. In general, patient and lesion characteristics between enrolled and not enrolled patients were similar with respect to age, sex, race, defect location, and Outerbridge grade (Table 2). The majority of patients in both populations were male, and the median age was 34 years (microfracture) to 38 years (MACI). The majority of patients had the index lesion on the MFC, classified as grade IV on the Outerbridge scale. The mean index lesion size was smaller in patients not enrolled in the Extension.

As shown in Figure 3, for those patients enrolled in the Extension, mean KOOS Pain and Function scores at the final SUMMIT visit (2 years; week 104) differed relative to those who did not enroll; that is, in the Extension study there was a loss of higher responding MACI patients. Of the 7 MACI patients not enrolled in the Extension, 6 patients were responders and 1 patient missed an assessment. Of the 13 microfracture patients who did not enroll or dropped out early from the Extension, 8 were responders, 3 were nonresponders, and 2 missed assessments. The difference between the two groups (enrolled vs not enrolled) was statistically significant in regard to change from baseline in KOOS Function score for MACI-treated patients (44.6 vs 68.3, respectively; $P = .042$; post hoc t test); the change in KOOS pain was not significant (45.0 vs 57.9; $P = .132$). No adjustments for differences were made in the 5-year analysis presented in this article.

Five-Year KOOS Subscale Results

Post Hoc Analysis of Treatment Effect at 5-Year LOCF Analysis (KOOS Subscales). Five years after treatment, the improvement seen in MACI over microfracture with regard to the co-primary endpoint of KOOS Pain and Function was maintained and was clinically and statistically significant ($P = .022$). Changes at year 5 in KOOS Pain and Function, Activities of Daily Living (ADL), Quality of Life (QOL), and Other Symptoms scores are shown in Figure 4. Improvements in ADL remained statistically significantly better ($P = .007$) in MACI versus microfracture patients, with QOL and Other Symptoms scores remaining numerically better in MACI patients but losing statistical significance relative to the results of the SUMMIT 2-year analysis.

TABLE 2
Patient and Lesion Characteristics (Enrolled vs Not Enrolled in Extension)[a]

	Patients Enrolled		Patients Not Enrolled	
Baseline Variables	MACI (n = 65)	Microfracture (n = 63)	MACI (n = 7)	Microfracture (n = 9)
Patient age, median (min, max), y	35.0 (18, 54)	34.0 (18, 54)	38.0 (23, 53)	34.0 (21, 50)
Male sex, n (%)	40 (62)	42 (67)	5 (71)	6 (67)
Location of lesion, n (%)				
Medial femoral condyle	48 (74)	44 (70)	6 (86)	9 (100)
Lateral femoral condyle	13 (20)	15 (24)	0	0
Trochlea	4 (6)	4 (6)	1 (14)	0
Outerbridge grade, n (%)				
Grade III	19 (29)	12 (19)	2 (29)	3 (33)
Grade IV	46 (71)	51 (81)	5 (71)	6 (67)
Lesion size, mean (SD), cm^2	5.1 (3)	4.9 (2)	3.4 (0.6)	3.5 (0.6)

[a]MACI, autologous cultured chondrocytes on porcine collagen membrane.

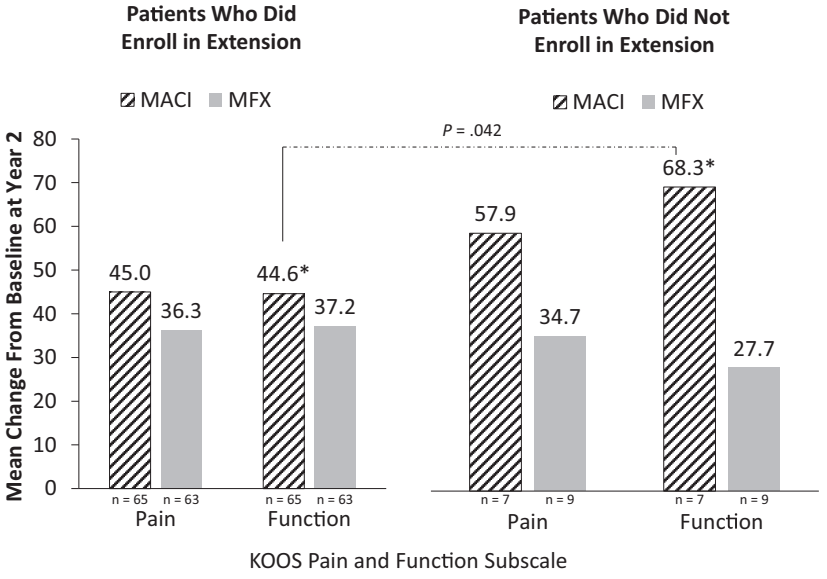

Figure 3. Comparison of 2-year (SUMMIT) Knee injury and Osteoarthritis Outcome Score (KOOS) Pain and Function scores for patients enrolled in the SUMMIT Extension versus those not enrolled. MACI, autologous cultured chondrocytes on porcine collagen membrane; MFX, microfracture.

Descriptive Summary of Observed Data. Change from baseline in KOOS Pain and Function scores over time is shown in Figure 5. The improvements in KOOS Pain and Function scores were maintained over 5 years total of our current follow-up. As shown in the figure, the improvements in MACI and microfracture were consistent, with separation of the 2 curves maintained over time.

As shown in Table 3, when analyzed by defect location subgroup (MFC, LFC, or trochlea), improvements in KOOS Pain and Function scores were greater in each subgroup in MACI compared with microfracture patients; however, with the exception of MFC, the numbers of patients in each subgroup were small.

Mean scores for all KOOS subscales at baseline and year 2 (SUMMIT) and year 5 (Extension study) are shown in Table 4. Across all subscales, mean observed scores were consistent over time. A summary of KOOS responders is also shown in Table 4.

Other Clinical Outcomes. Supportive of the KOOS subscale MANCOVA analysis, improvements in other patient-reported scores were maintained from year 2 to year 5 (Table 5). Significantly better improvements from baseline to year 5 favoring MACI were observed for the modified Cincinnati Knee Rating System score (P = .035), the 12-Item Short Form Health Survey (SF-12) Physical (P = .025), and the EuroQol 5 Dimensions Visual Analog Scale (EQ-5D VAS) score (P = .043). Note that the EQ-5D VAS was not significant in the analysis at 2 years.[28] As in the 2-year analysis, no significant differences were seen in the International Knee Documentation Committee (IKDC) or SF-12 Mental scores.

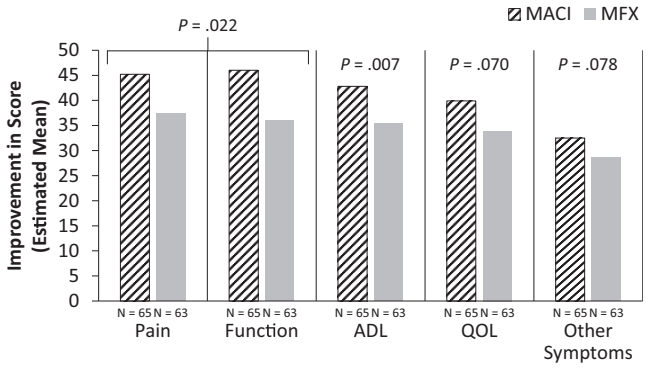

Figure 4. Changes from baseline to year 5 in all Knee injury and Osteoarthritis Outcome Score subscales: post hoc analysis of treatment effect. ADL, activities of daily living; MACI, autologous cultured chondrocytes on porcine collagen membrane; MFX, microfracture; QOL, quality of life.

Magnetic resonance imaging (MRI) evaluation of structural repair was performed in 120 patients at year 5. As in the 2-year SUMMIT (MACI00206) results,[28] the MRI evaluation showed improvement in defect filling for both treatments; however, no statistically significant differences were noted between treatment groups.

Treatment Failures. As in the 2-year SUMMIT (MACI00206) study,[28] no analyses were conducted on treatment failure rates because of the small number of treatment failures in both treatment groups. Four patients (1 MACI and 3 microfracture) were considered to have treatment failures by an adjudication committee over the 5-year period.

Safety. No unexpected safety events were reported over the 5 years of observation. Analysis of adverse events showed that the frequency of adverse events was similar in both treatment groups and was consistent with our previous publication.[28] Arthralgia remained the most frequently reported event in both treatment groups. The proportion of patients with subsequent surgical procedures was similar in MACI and microfracture treatment groups (10.8% in MACI and 9.5% in microfracture).

DISCUSSION

We have previously reported that 2 years after treatment, MACI resulted in statistically significantly better improvements than microfracture in treating symptomatic cartilage defects of the knee, meeting the SUMMIT study predefined co-primary endpoint of KOOS Pain and Function subscale scores.[28] Evaluation of data up to 5 years after initial surgery showed sustained efficacy across the full follow-up period as demonstrated by better KOOS subscale scores in MACI-treated patients for all 5 subscales compared with microfracture-treated patients.

A post hoc evaluation of treatment effect at 5 years showed that statistically significant improvement of MACI compared with microfracture was maintained over the 5 years of evaluation in the KOOS Pain and Function subscales (co-primary endpoint) and the ADL subscale. In addition, analysis of safety showed the frequency of adverse events and subsequent surgical procedures to be similar in both treatment groups. Supportive of the KOOS subscale MANCOVA analysis, significantly better improvements from baseline to year 5 favoring MACI were observed for the modified Cincinnati, the SF-12 Physical (P = .025), and the EQ-5D VAS scores. In addition, a subgroup analysis of KOOS Pain and Function scores by defect location (MFC, LFC, or trochlea) showed greater improvements in MACI compared with microfracture patients in each subgroup although the numbers of patients in each subgroup, with the exception of MFC, were small.

Good clinical outcomes (sustained improvements from baseline) at 5 years reported with MACI in our study are similar to those reported in case series and review studies. In a 5-year study of outcomes by Marlovits et al,[22] MACI-treated patients had significant improvements on all KOOS subscales, few complications, and low treatment failures. Gikas et al[16] reported on a prospective, single-center study evaluating MACI (n = 231) versus collagen-covered autologous chondrocyte implantation (C-ACI; n = 101). Significant improvements from baseline in VAS and Bentley functional rating scores were observed with both treatments each year ($P <$ .0001), with improvements maintained over time (1-9 years of follow-up; mean 32 months). Ebert et al[12] published

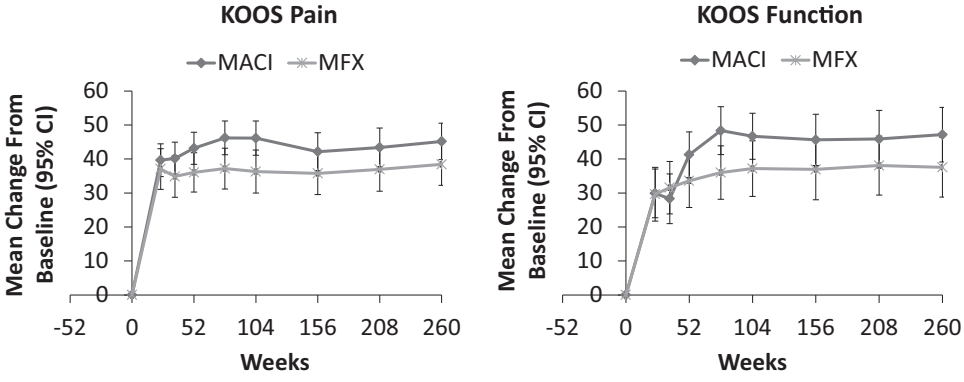

Figure 5. Clinical improvement from baseline in Knee injury and Osteoarthritis Outcome Score (KOOS) Pain and Function scores for autologous cultured chondrocytes on porcine collagen membrane (MACI) and microfracture (MFX) groups at 2 years was maintained up to 5 years (observed data).

TABLE 3
Clinical Improvements Compared With Baseline
in KOOS Pain and Function Scores by Defect Location at Year 2 and Year 5[a]

	MACI Group				Microfracture Group			
	Year 2		Year 5		Year 2		Year 5	
	n[b]	Change[c]	n[b]	Change[c]	n[b]	Change[c]	n[b]	Change[c]
KOOS Pain								
All	63	45.0 ± 20.0	64	45.2 ± 21.6	60	36.3 ± 24.5	59	38.4 ± 23.6
MFC	47	42.8 ± 20.9	47	40.7 ± 21.8	42	32.4 ± 21.2	42	34.8 ± 20.8
LFC	12	50.9 ± 16.4	14	58.1 ± 17.7	13	48.2 ± 28.8	13	55.1 ± 22.3
Trochlea	4	52.8 ± 14.9	4	56.9 ± 8.6	4	35.4 ± 34.1	4	22.2 ± 33.4
KOOS Function								
All	63	44.6 ± 26.8	64	47.2 ± 32.2	60	37.2 ± 31.7	59	37.6 ± 33.6
MFC	47	42.9 ± 27.5	47	44.0 ± 32.8	42	34.4 ± 27.6	42	34.3 ± 31.0
LFC	12	49.2 ± 25.7	14	61.2 ± 30.5	14	47.2 ± 41.8	13	55.9 ± 37.1
Trochlea	4	51.3 ± 26.6	4	38.8 ± 18.9	4	31.3 ± 33.0	4	12.5 ± 29.0

[a]KOOS, Knee Injury and Osteoarthritis Outcome Score; LFC, lateral femoral condyle; MACI, autologous cultured chondrocytes on porcine collagen membrane; MFC, medial femoral condyle.
[b]Observed data: some patients may have remained in the study but did not complete an evaluation for a study visit; therefore, the number of patients may be different at each visit.
[c]Values are changes in KOOS subscale score from baseline, expressed as mean ± SD.

TABLE 4
Mean Patient-Reported Scores (Observed Data) at Baseline, Year 2, and Year 5[a]

	MACI Group			Microfracture Group		
	Baseline (n = 65)[b]	Year 2 (n = 63)[b]	Year 5 (n = 65)[b]	Baseline (n = 63)[b]	Year 2 (n = 60)[b]	Year 5 (n = 59)[b]
KOOS subscales						
Pain	37.1 ± 13.1	82.2 ± 15.8	82.2 ± 20.1	35.2 ± 12.3	71.8 ± 23.9	74.8 ± 21.7
Function	15.4 ± 14.8	60.5 ± 26.5	61.9 ± 30.9	11.9 ± 16.2	48.9 ± 30.6	50.3 ± 32.3
ADL	43.6 ± 18.6	87.3 ± 16.2	86.4 ± 17.6	42.6 ± 18.2	77.0 ± 23.6	80.0 ± 21.2
QOL	19.9 ± 14.6	55.4 ± 22.3	59.8 ± 24.6	17.1 ± 13.2	47.8 ± 26.8	52.4 ± 26.6
Other Symptoms	48.4 ± 17.0	83.5 ± 13.2	80.9 ± 18.0	44.4 ± 18.3	72.1 ± 20.0	74.8 ± 18.5
KOOS responders[c]	NA	86%	78%	NA	68%	73%

[a]Scores expressed as mean ± SD. ADL, Activities of Daily Living; KOOS, Knee injury and Osteoarthritis Outcome Score; MACI, autologous cultured chondrocytes on porcine collagen membrane; NA, not applicable; QOL, Quality of Life.
[b]Observed data: some patients may have remained in the study but did not complete an evaluation for a study visit; therefore, the number of patients may be different at each visit.
[c]KOOS responder: A KOOS responder was defined as a patient who responded to treatment at the particular scheduled visit with at least a 10-point improvement from baseline in both KOOS Pain and KOOS Function (Sports and Recreational Activities) scores.

a prospective, single-center case series that evaluated clinical outcomes of MACI in 35 patients who were followed to 5 years. Significant improvements from baseline were observed for all KOOS ($P < .0001$) and 36-Item Short Form Health Survey subscales (all $P < .05$). Most patients were satisfied with pain relief (98%), daily activities (86%), sports participation (73%), and overall surgery results (86%) at 5 years. In a study by Behrens et al,[5] 38 patients with localized cartilage defects were treated with MACI. Five years after treatment, 8 of 11 patients rated the function of their knee as much better or better than before. Gille et al[17] reported the clinical outcomes of 14 patients with a mean follow-up of 16 years. Overall, the MACI procedure resulted in significant clinical improvements from baseline to 5 years and up to 15 years for Lysholm-Gilquist, IKDC, and Tegner scores (*P* values not reported). The primary findings of a review by Oussedik et al[25] of 1622 lesions (146 MACI; 313 C-ACI; 580 periosteum-ACI (P-ACI); 583 microfracture) was used for an evidence-based appraisal by the National Institute for Health and Care Excellence.[23] Treatment failure rates ranged from 10% to 23% for microfracture, 7% to 26% for P-ACI, 9% to 13% for C-ACI, and 10% for MACI. Overall, P-ACI was shown to be associated with symptomatic cartilage hypertrophy more frequently than C-ACI.[25]

Although useful to assess biological activity, improvements on histological or MRI assessment have not been shown to be validated surrogates of clinical effect in patients with cartilage defects. The association between clinical and structural outcomes is variable, as reported in a systematic review of controlled ACI studies that evaluated clinical, histological, and MRI assessment results.[11] Comparing ACI with microfracture, Knutsen et al[19,20] reported a lack of

TABLE 5
Other Patient-Reported Outcome Scores (Observed Data) at Baseline, Year 2, and Year 5[a]

	MACI Group			Microfracture Group			
Scale	Baseline (n = 65)	Year 2 (n = 63)	Year 5 (n = 65)	Baseline (n = 63)	Year 2 (n = 60)	Year 5 (n = 59)	P^b
Modified Cincinnati Knee Rating System	3.0 ± 1.2	6.3 ± 1.9	6.6 ± 2.1	3.0 ± 1.2	5.5 ± 2.3	5.8 ± 2.2	.035
IKDC	33.1 ± 13.5	65.3 ± 18.1	68.5 ± 21.2	29.3 ± 12.0	60.1 ± 22.7	61.8 ± 21.5	.113
SF-12 Physical	–1.7 ± 0.8	–0.35 ± 0.9	–0.20 ± 0.95	–2.0 ± 0.8	–0.79 ± 1.1	–0.67 ± 1.1	.025
SF-12 Mental	0.04 ± 1.2	0.44 ± 0.9	0.41 ± 0.9	–0.07 ± 1.3	0.52 ± 0.9	0.46 ± 1.0	.740
EQ-5D VAS	60.3 ± 21.1	76.5 ± 15.2	80.4 ± 13.7	54.7 ± 21.7	74.1 ± 18.5	73.8 ± 19.1	.043

[a]EQ-5D VAS, EuroQol 5 Dimensions Visual Analog Scale; IKDC, International Knee Documentation Committee; MACI, autologous cultured chondrocytes on porcine collagen membrane; SF-12, 12-Item Short Form Health Survey.
[b]*P* value for difference between treatments in estimated means for change from baseline to year 5 using analysis of covariance.

association between histology scores and clinical outcome at 2 and 5 years after treatment. Similarly, in the SUMMIT study there was no association between clinical and structural outcomes, regardless of treatment group.

Kraeutler et al[21] published a systematic review of 5-year outcomes comparing microfracture and ACI, showing no significant difference in clinical outcomes between the two treatment options. This systematic review did not include any MACI studies, nor were the selected ACI studies designed to show clinical superiority over microfracture. The significance of our 5-year report is that it is the first and only randomized trial to demonstrate that cultured chondrocytes at 5 years maintained clinical efficacy and statistical significance over microfracture.

In our study, for those patients observed over 5 years, sustained improvements were found from baseline in the microfracture groups. The data for long-term studies of microfracture are limited,[23] although the sustained efficacy in our patients is in agreement with publications of several other clinical trials with longer term data that included microfracture as a comparator.[29,31,33] Other studies showed some deterioration of effect in the microfracture group over 2 years[4] to 5 years.[32] The reported differences in longer term microfracture outcomes may be due to a number or combination of factors, including the reporting from prospective multicenter randomized clinical trials versus retrospective analyses or systematic analysis of existing literature, or differences in rehabilitation protocols.

The goal of extension studies is often to confirm maintenance of the treatment effect from a shorter term study over an extended period of time. However, the voluntary nature of most extension studies can present issues regarding missing data and loss of power to detect differences between treatment groups as well as introduce bias through the self-selection of patients to enter into a follow-up study.[9] In our study, 20 patients did not enroll in the Extension study or dropped out early, including 8 patients from 2 sites who chose not to participate. Despite this limitation, significant improvements with MACI versus microfracture were maintained at 5 years as shown in post hoc analysis using the same statistical method as in the 2-year study.

The limitation of the analysis of data over 5 years is that the SUMMIT Extension study was designed in a way that provided opportunity for patients and sites to self-select for continued observation, thus introducing potential bias and reduced power to test treatment effect if patients or sites elected not to continue into the Extension study. Ideally, this type of study in the future would be designed as a single study with 5 years of follow-up. In addition, neither SUMMIT nor the Extension studies could be blinded. The comparison of MACI with microfracture may be considered a limitation because of the larger lesion size (entry criteria of $\geq$3 cm^2) in this study. However, microfracture is considered the standard treatment against which other cartilage repair treatments are compared for studies conducted in both the United States and the European Union[24] and is consistent with Food and Drug Administration (FDA)[14] and European Medicines Agency[13] guidance for design of studies in cartilage repair of the knee. Additionally, a study by the Steadman group[6] found that patient-centered outcomes were the same for a contained chondral lesion of the knee regardless of lesion size (138 patients had lesions >4.0 cm^2 compared with lesion size <1.0 cm^2 [123 patients], 1-3 cm^2 [138 patients], or 3.1-4 cm^2 [161 patients]).

This study is among the very few GCP-conducted, prospective, multicenter, controlled studies of cell-based cartilage repair to date, and MACI is the first FDA-approved product that applies the process of tissue engineering to grow cells on scaffolds using healthy cartilage tissue from the patient's own knee. Strengths of the study included standardized surgical and rehabilitation procedures, validated clinical outcome instruments, and multiple investigators with consistent outcomes.

In this post hoc analysis using the same statistical methods as used in the 2-year analysis of SUMMIT data, we have demonstrated that at 5 years of follow-up, MACI provides clinically relevant and statistically significantly better improvements in the co-primary endpoint of pain and function when compared with microfracture treatment in this heterogeneous population when treating symptomatic articular cartilage defects of the knee that are 3 cm^2 or larger.

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