

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

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on behalf of the SUMMIT Extension Study Group

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

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## Important Safety Information

### Indication

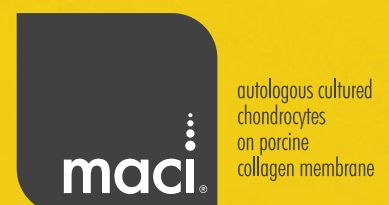
MACI® (autologous cultured chondrocytes on porcine collagen membrane) is an autologous cellularized scaffold product that is indicated for the repair of single or multiple symptomatic, full-thickness cartilage defects of the adult knee, with or without bone involvement.

### Limitations of Use

Effectiveness of MACI in joints other than the knee has not been established.

Safety and effectiveness of MACI in patients over the age of 55 years have not been established.

Please see additional Important Safety Information page 4 and accompanying [full Prescribing Information](#).



## SUMMIT (Superiority of MACI Implant versus Microfracture Treatment) 5-year follow-up extension study overview

| Study design                                   | Purpose  |
|--|--|
| Randomized controlled trial                    | The 3-year extension to the 2-year, multicenter, randomized study comparing MACI vs arthroscopic microfracture treatment was designed to provide efficacy and safety follow-up for the two treatment groups at 5 years after treatment |
| Level of evidence 1                            |  |
| Conducted between December 2010 and March 2015 |  |

| Patient characteristics  | Inclusion criteria  | Co-primary efficacy endpoints   |
|--|---|---|
| <b>Enrolled</b><br>128 patients<br>MACI: n=65<br>Microfracture: n=63                                     | All 144 subjects enrolled in the 2-year study had the option to enroll in the 3-year follow-up extension study, of which 128 subjects participated: <ul style="list-style-type: none"> <li>Two study sites that enrolled patients in the initial randomized controlled trial elected not to participate in the extension study</li> <li>In total, n=7 patients from the MACI group and n=9 patients from the microfracture group did not enroll in the extension study</li> </ul> | Change in KOOS* pain and function (SRA) <sup>†</sup> subscores from baseline to Years 3, 4, and 5 after treatment |
| <b>Median age</b><br>MACI: 35<br>Microfracture: 34<br>Range: 18–54                                       |   |   |
| <b>Male sex</b><br>MACI: 62%<br>Microfracture: 67%   |   |   |
| <b>Mean lesion size</b><br>MACI: 5.1 cm <sup>2</sup> (SD 3)<br>Microfracture: 4.9 cm <sup>2</sup> (SD 2) |   |   |

\*Knee Injury and Osteoarthritis Outcome Score.

<sup>†</sup>Sports and recreational activities.

### Patient withdrawals

- **MACI:** none
- **Microfracture:** 4 patients were lost to follow-up in the 3-year extension study

### Important Safety Information (continued)

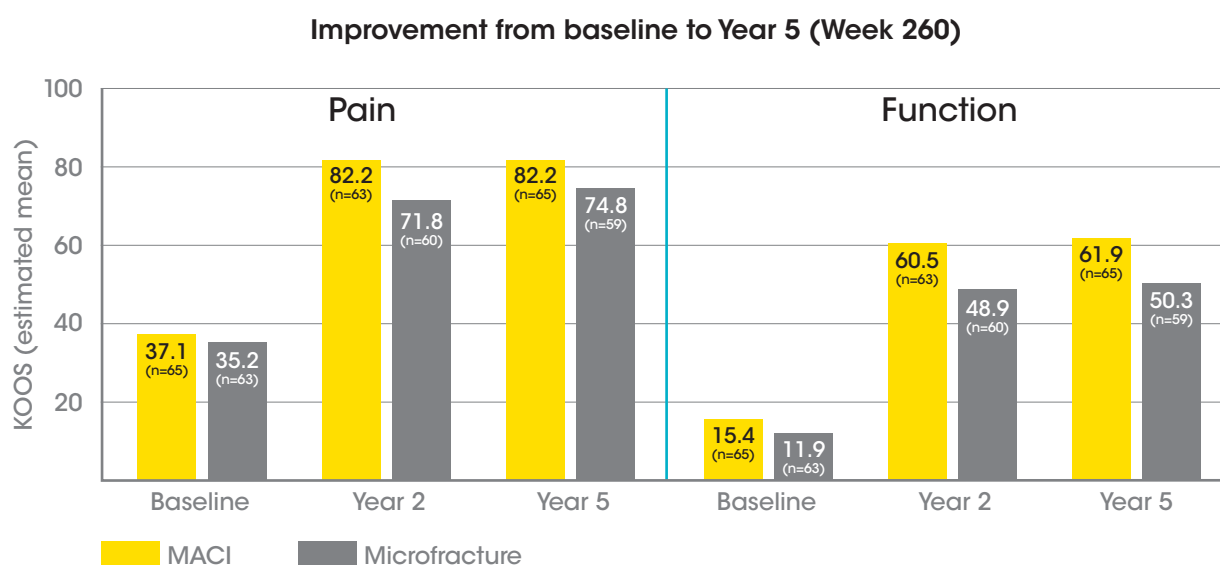
MACI is contraindicated in patients with a known history of hypersensitivity to gentamicin, other aminoglycosides, or products of porcine or bovine origin. MACI is also contraindicated for patients with severe osteoarthritis of the knee, inflammatory arthritis, inflammatory joint disease, or uncorrected congenital blood coagulation disorders. MACI is also not indicated for use in patients who have undergone prior knee surgery in the past 6 months, excluding surgery to procure a biopsy or a concomitant procedure to prepare the knee for a MACI implant.

**Please see additional Important Safety Information on page 4 and accompanying full Prescribing Information.**

Autologous cellularized scaffold for the repair of cartilage defects of the knee

## Improvements in KOOS pain, function were maintained with MACI at Year 5

Co-primary endpoints: improvement in pain and function from baseline to Year 5



- The mean 2-year KOOS pain and function scores remained consistent for the additional 3-year period in both treatment groups

### Adverse events

- Adverse events over 5 years were consistent with the SUMMIT trial at Year 2
- Similar adverse events were reported in both treatment groups, with arthralgia the most frequently reported

### Important Safety Information (continued)

MACI is contraindicated in patients who are unable to follow a physician-prescribed post-surgical rehabilitation program.

**Please see additional Important Safety Information on page 4 and accompanying [full Prescribing Information](#).**



## Important Safety Information

### Indication

- MACI® (autologous cultured chondrocytes on porcine collagen membrane) is an autologous cellularized scaffold product that is indicated for the repair of single or multiple symptomatic, full-thickness cartilage defects of the adult knee, with or without bone involvement.
- MACI is intended for autologous use and must only be administered to the patient for whom it was manufactured. The implantation of MACI is to be performed via an arthrotomy to the knee joint under sterile conditions.
- The amount of MACI administered is dependent upon the size (surface in cm<sup>2</sup>) of the cartilage defect. The implantation membrane is trimmed by the treating surgeon to the size and shape of the defect, to ensure the damaged area is completely covered, and implanted cell-side down.

### Limitations of Use

- Effectiveness of MACI in joints other than the knee has not been established.
- Safety and effectiveness of MACI in patients over the age of 55 years have not been established.

### Important Safety Information

- MACI is contraindicated in patients with a known history of hypersensitivity to gentamicin, other aminoglycosides, or products of porcine or bovine origin. MACI is also contraindicated for patients with severe osteoarthritis of the knee, inflammatory arthritis, inflammatory joint disease, or uncorrected congenital blood coagulation disorders. MACI is also not indicated for use in patients who have undergone prior knee surgery in the past 6 months, excluding surgery to procure a biopsy or a concomitant procedure to prepare the knee for a MACI implant.
- MACI is contraindicated in patients who are unable to follow a physician-prescribed post-surgical rehabilitation program.
- The safety of MACI in patients with malignancy in the area of cartilage biopsy or implant is unknown. Expansion of present malignant or dysplastic cells during the culturing process or implantation is possible.
- Patients undergoing procedures associated with MACI are not routinely tested for transmissible infectious diseases. A cartilage biopsy and MACI implant may carry the risk of transmitting infectious diseases to healthcare providers handling the tissue. Universal precautions should be employed when handling the biopsy samples and the MACI product.
- Final sterility test results are not available at the time of shipping. In the case of positive sterility results, health care provider(s) will be contacted.
- To create a favorable environment for healing, concomitant pathologies that include meniscal pathology, cruciate ligament instability and joint misalignment, must be addressed prior to or concurrent with the implantation of MACI.
- Local treatment guidelines regarding the use of thromboprophylaxis and antibiotic prophylaxis around orthopaedic surgery should be followed. Use in patients with local inflammations or active infections in the bone, joint, and surrounding soft tissue should be temporarily deferred until documented recovery.
- The MACI implant is not recommended during pregnancy. For implantations post-pregnancy, the safety of breast feeding to infant has not been determined.
- Use of MACI in pediatric patients (younger than 18 years of age) or patients over 65 years of age has not been established.
- The most frequently occurring adverse reactions reported for MACI (≥5%) were arthralgia, tendonitis, back pain, joint swelling, and joint effusion.
- Serious adverse reactions reported for MACI were arthralgia, cartilage injury, meniscus injury, treatment failure, and osteoarthritis.

**Please see accompanying full Prescribing Information.**

# Matrix-Applied Characterized Autologous Cultured Chondrocytes Versus Microfracture

## Five-Year Follow-up of a Prospective Randomized Trial

Mats Brittberg,<sup>\*†</sup> MD, PhD, David Recker,<sup>‡</sup> MD, John Ilgenfritz,<sup>§</sup> PhD, and Daniel B.F. Saris,<sup>\*||¶#</sup> MD, PhD, on behalf of the SUMMIT Extension Study Group\*\*  
*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<sup>2</sup> 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.<sup>10,15</sup> Several approaches exist to manage symptomatic chondral and

osteocondral 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 post-operative complications such as periosteal hypertrophy. An improvement was the use of a bioabsorbable collagen membrane cover, known as collagen-covered ACI, instead of an

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.<sup>1-3,6,7</sup>

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.<sup>26,27</sup> 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 trans-arthroscopic 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<sup>2</sup> or larger; the improvement in outcomes was statistically significant ( $P = .001$ ), and structural repair tissue and safety were similar.<sup>28</sup>

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.<sup>28</sup> 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<sup>2</sup> 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.<sup>30</sup> All patients were provided a recommended postoperative rehabilitation program.<sup>18</sup> 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<sup>2</sup> membrane seeded at a density of at least 500,000 cells/cm<sup>2</sup> and up to 1 million cells/cm<sup>2</sup>.

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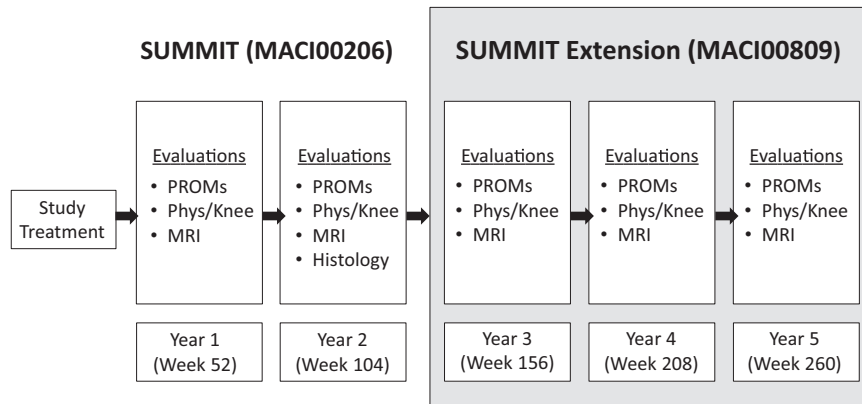
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**Figure 1.** Overall study design for SUMMIT and SUMMIT Extension. MRI, magnetic resonance imaging; Phys, physical; PROM, patient-reported outcome measures.

**TABLE 1**  
SUMMIT Extension Study Endpoints<sup>a</sup>

|          | Description  |
|----------|--|
| Efficacy | Change from baseline in KOOS Pain and Function subscales<br>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<br>Change from baseline in the remaining KOOS subscales (ADL, Knee-Related QOL, Other Symptoms)<br>Mean reported (observed) KOOS scores (Pain, Function, ADL, QOL, and Other Symptoms)<br>Mean reported (observed) other patient-reported outcome scores (modified Cincinnati Knee Rating System, IKDC, SF-12 Physical, SF-12 Mental, EQ-5D VAS) |
| Safety   | Assessment of treatment failure<br>Treatment-emergent adverse events, serious adverse events, subsequent surgical procedures (procedures performed on the target knee during the study)  |

<sup>a</sup>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**

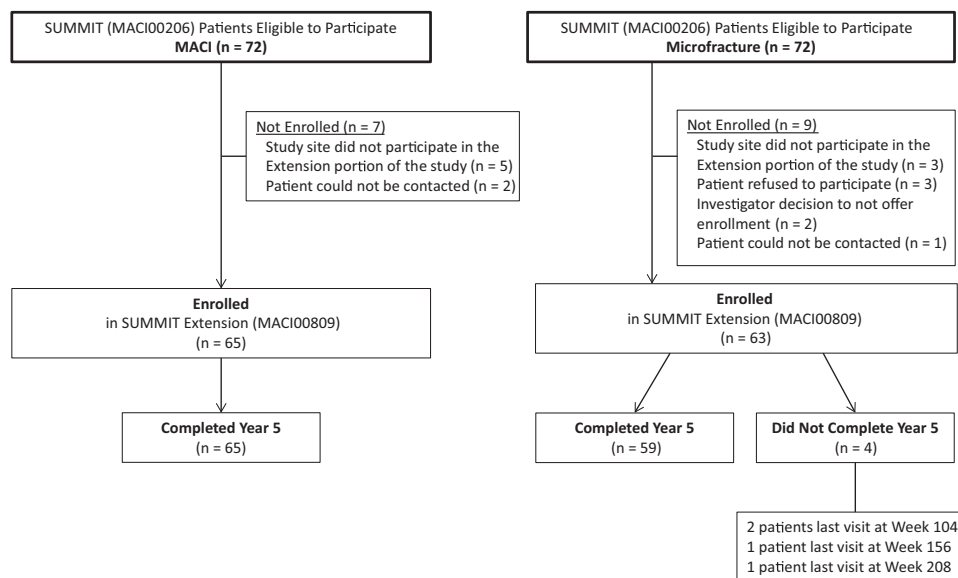
The prespecified primary endpoint of the Extension study was the change from baseline to week 156 (year 3) in KOOS Pain and Function (Sports and Recreational Activities) scores. The clinically and statistically significant results of the analyses of the co-primary endpoint at year 3 of the Extension study were presented previously by Brittberg et al<sup>8</sup> 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

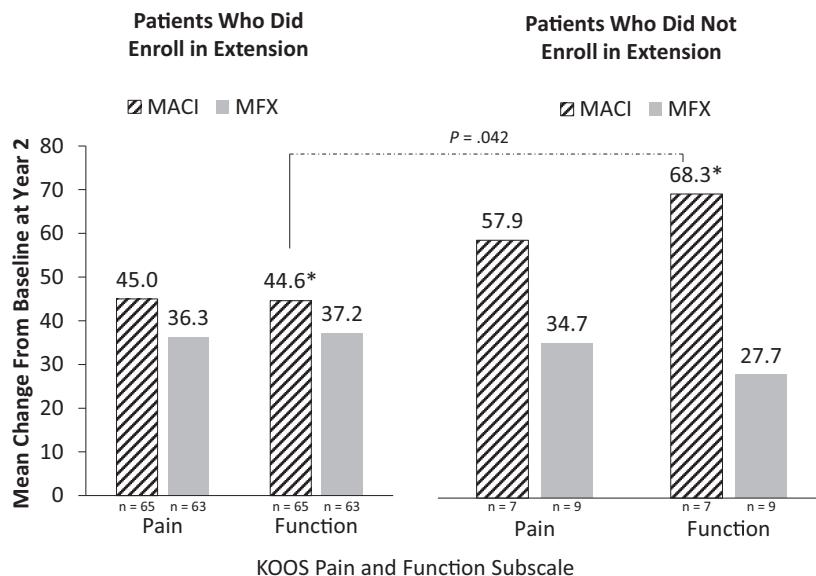
*Post Hoc Analysis of Treatment Effect at 5-Year LOCF Analysis (KOOS Subscales).* Five years after treatment, the improvement seen in MACI over microfracture with regard to the co-primary endpoint of KOOS Pain and Function was maintained and was clinically and statistically significant ( $P = .022$ ). 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)<sup>a</sup>

| Baseline Variables                      | Patients Enrolled |                        | Patients Not Enrolled |                       |
|---|-------------------|------------------------|-----------------------|-----------------------|
|   | 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 <sup>2</sup> | 5.1 (3)           | 4.9 (2)                | 3.4 (0.6)             | 3.5 (0.6)             |

<sup>a</sup>MACI, autologous cultured chondrocytes on porcine collagen membrane.



\*Statistically significant difference in KOOS function scores (MACI enrolling vs nonenrolling [ $P = .042$ ])

**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.

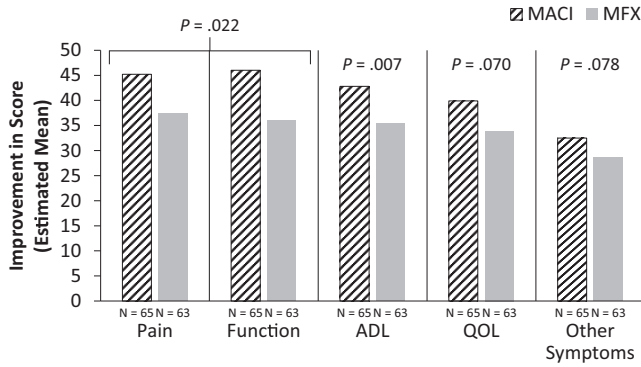
*Descriptive Summary of Observed Data.* Change from baseline in KOOS Pain and Function scores over time is shown in Figure 5. The improvements in KOOS Pain and Function scores were maintained over 5 years total of our current follow-up. As shown in the figure, the improvements in MACI and microfracture 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.<sup>28</sup> 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,<sup>28</sup> 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,<sup>28</sup> 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.

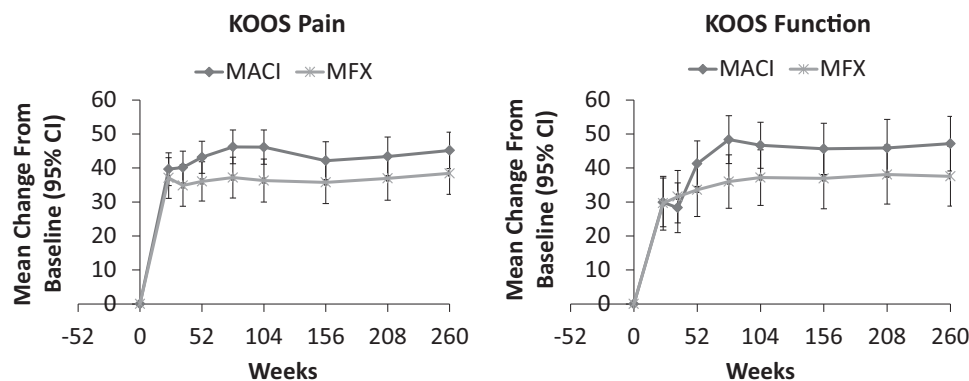
**Safety.** No unexpected safety events were reported over the 5 years of observation. Analysis of adverse events showed that the frequency of adverse events was similar in both treatment groups and was consistent with our previous publication.<sup>28</sup> Arthralgia remained the most frequently reported 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.<sup>28</sup> 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,<sup>22</sup> MACI-treated patients had significant improvements on all KOOS subscales, few complications, and low treatment failures. Gikas et al<sup>16</sup> 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<sup>12</sup> 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<sup>a</sup>

|               | MACI Group     |                     |                |                     | Microfracture Group |                     |                |                     |
|---------------|----------------|---------------------|----------------|---------------------|---------------------|---------------------|----------------|---------------------|
|               | Year 2         |                     | Year 5         |                     | Year 2              |                     | Year 5         |                     |
|               | n <sup>b</sup> | Change <sup>c</sup> | n <sup>b</sup> | Change <sup>c</sup> | n <sup>b</sup>      | Change <sup>c</sup> | n <sup>b</sup> | Change <sup>c</sup> |
| 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         |

<sup>a</sup>KOOS, Knee Injury and Osteoarthritis Outcome Score; LFC, lateral femoral condyle; MACI, autologous cultured chondrocytes on porcine collagen membrane; MFC, medial femoral condyle.

<sup>b</sup>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.

<sup>c</sup>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<sup>a</sup>

|                              | MACI Group                     |                              |                              | Microfracture Group            |                              |                              |
|------------------------------|--------------------------------|------------------------------|------------------------------|--------------------------------|------------------------------|------------------------------|
|                              | Baseline (n = 65) <sup>b</sup> | Year 2 (n = 63) <sup>b</sup> | Year 5 (n = 65) <sup>b</sup> | Baseline (n = 63) <sup>b</sup> | Year 2 (n = 60) <sup>b</sup> | Year 5 (n = 59) <sup>b</sup> |
| 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 <sup>c</sup> | NA                             | 86%                          | 78%                          | NA                             | 68%                          | 73%                          |

<sup>a</sup>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.

<sup>b</sup>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.

<sup>c</sup>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,<sup>5</sup> 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. Gillet et al<sup>17</sup> 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<sup>25</sup> 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.<sup>23</sup> 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.<sup>25</sup>

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.<sup>11</sup> Comparing ACI with microfracture, Knutsen et al<sup>19,20</sup> reported a lack of

TABLE 5  
Other Patient-Reported Outcome Scores (Observed Data) at Baseline, Year 2, and Year 5<sup>a</sup>

| Scale                                  | MACI Group        |                 |                 | Microfracture Group |                 |                 | <i>p</i> <sup>b</sup> |
|--|-------------------|-----------------|-----------------|---------------------|-----------------|-----------------|-----------------------|
|  | Baseline (n = 65) | Year 2 (n = 63) | Year 5 (n = 65) | Baseline (n = 63)   | Year 2 (n = 60) | Year 5 (n = 59) |                       |
| 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                  |

<sup>a</sup>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.

<sup>b</sup>*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<sup>21</sup> 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,<sup>23</sup> 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.<sup>29,31,33</sup> Other studies showed some deterioration of effect in the microfracture group over 2 years<sup>4</sup> to 5 years.<sup>32</sup> 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.<sup>9</sup> 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<sup>2</sup>) 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<sup>24</sup> and is consistent with Food and Drug Administration (FDA)<sup>14</sup> and European Medicines Agency<sup>13</sup> guidance for design of studies in cartilage repair of the knee. Additionally, a study by the Steadman group<sup>6</sup> 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<sup>2</sup> compared with lesion size  $<1.0$  cm<sup>2</sup> [123 patients], 1-3 cm<sup>2</sup> [138 patients], or 3.1-4 cm<sup>2</sup> [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<sup>2</sup> or larger.

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## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MACI safely and effectively. See full prescribing information for MACI.

**MACI® (autologous cultured chondrocytes on porcine collagen membrane)**

**Cellular sheet for autologous implantation**

**Initial U.S. Approval: 2016**

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### RECENT MAJOR CHANGES

Dosage and Administration, shaping the MACI implant (2.2) 06/2017

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### INDICATIONS AND USAGE

MACI® is an autologous cellularized scaffold product indicated for the repair of symptomatic, single or multiple full-thickness cartilage defects of the knee with or without bone involvement in adults. (1)

#### Limitations of Use

- Effectiveness of MACI in joints other than the knee has not been established.
- Safety and effectiveness of MACI in patients over the age of 55 years have not been established.

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### DOSAGE AND ADMINISTRATION

#### For autologous implantation only.

- Contact Vericel at 1-800-453-6948 or [www.MACI.com](http://www.MACI.com) regarding training materials for surgical implantation of MACI. (2)
- The amount of MACI implanted depends on the size (surface area in cm<sup>2</sup>) of the cartilage defect. (2.1)
- MACI should be trimmed to the size and shape of the defect and implanted with the cell-side down. (2.2)

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### DOSAGE FORMS AND STRENGTHS

Each 3 x 5 cm cellular sheet (MACI implant) consists of autologous cultured chondrocytes on a resorbable porcine Type I/III collagen membrane, at a density of at least 500,000 cells per cm<sup>2</sup>. (3)

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### CONTRAINDICATIONS

- Known history of hypersensitivity to gentamicin, other aminoglycosides, or products of porcine or bovine origin. (4)
- Severe osteoarthritis of the knee. (4)

- Inflammatory arthritis, inflammatory joint disease, or uncorrected congenital blood coagulation disorders. (4)
- Prior knee surgery (within 6 months), excluding surgery to procure a biopsy or a concomitant procedure to prepare the knee for a MACI implant. (4)
- Inability to cooperate with a physician-prescribed post-surgical rehabilitation program. (4)

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### WARNINGS AND PRECAUTIONS

- Safety of MACI in patients with malignancy in the area of cartilage biopsy or implant is unknown. Expansion of malignant or dysplastic cells present in biopsy tissue during manufacture and subsequent implantation may be possible. (5.1)
- Because patients undergoing procedures associated with MACI are not routinely tested for transmissible infectious diseases, cartilage biopsy and MACI implant may carry risk of transmitting infectious diseases. (5.2)
- Local inflammation or active infection in the bone, joint, and surrounding soft tissue, meniscal pathology, cruciate ligament instability, and misalignment should be assessed and treated prior to or concurrent with MACI implantation. (5.3)
- Final sterility test results are not available at the time of shipping. (5.4)

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### ADVERSE REACTIONS

The most frequently occurring adverse reactions (≥5%) reported for MACI were arthralgia, tendonitis, back pain, joint swelling, and joint effusion. (6)

Serious adverse reactions reported for MACI were arthralgia, cartilage injury, meniscus injury, treatment failure, and osteoarthritis. (6)

**To report SUSPECTED ADVERSE REACTIONS, contact Vericel at 1-800-453-6948 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch) for voluntary reporting of adverse reactions.**

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### USE IN SPECIFIC POPULATIONS

Pregnancy: Because MACI implantation requires invasive surgical procedures, use in pregnancy is not recommended. (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 06/2017

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## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

MACI<sup>®</sup> (autologous cultured chondrocytes on porcine collagen membrane) is an autologous cellularized scaffold product indicated for the repair of single or multiple symptomatic, full-thickness cartilage defects of the knee with or without bone involvement in adults.

#### Limitations of Use

- Effectiveness of MACI in joints other than the knee has not been established.
- Safety and effectiveness of MACI in patients over the age of 55 years have not been established.

### **2 DOSAGE AND ADMINISTRATION**

#### **For Autologous Implantation Only.**

Contact Vericel at 1-800-453-6948 or [www.MACI.com](http://www.MACI.com) regarding training materials for surgical implantation of MACI.

#### **2.1 Dosage**

- The amount of MACI implanted depends on the size (surface area in cm<sup>2</sup>) of the cartilage defect. The surgeon should trim the MACI implant to the size and shape of the defect, to ensure the damaged area is completely covered.
- MACI implant is for single-use. Multiple implants may be used if there is more than one defect. The size of MACI is adjusted for the size of each cartilage defect.

#### **2.2 Preparation and Implantation Procedure**

##### Preparation

- Confirm that the patient's identity matches the patient's identifiers on the MACI labels.
- Inspect the sealed MACI packaging for leaks and for any evidence of damage or contamination.
- DO NOT USE if the patient identifiers do not match, or there are signs of damage to the packaging. Contact MACI representative immediately or call Vericel Customer Care at 1-800-453-6948.
- Keep MACI at room temperature in its original packaging (outer shipping box). Do not unpack the MACI shipping box until the surgical site has been prepared.

##### Implantation Procedure

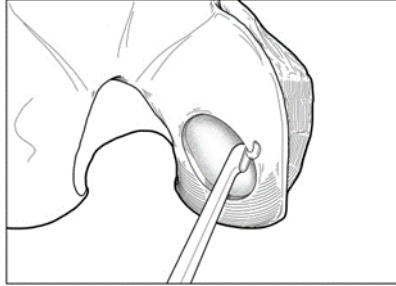
- Perform implantation procedure during arthrotomy using sterile surgical techniques.

- Follow the implantation with an appropriate, physician-prescribed rehabilitation program [see *Dosage and Administration (2.3)*].

*Preparing Defect*

- For chondral defects, remove all damaged and fibrous tissue on the defect bed. Debride the defect bed back to stable cartilage with vertical walls down to the subchondral bone by removing as little healthy cartilage as possible (Figure 1). Do not penetrate the subchondral bone.

**Figure 1: Preparing Defect Bed**

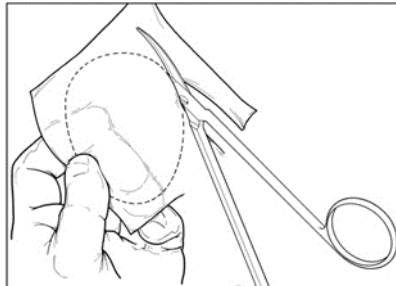


- For osteochondral defects, debride the defect bed back to stable cartilage with vertical walls down to healthy stable bone.
- Avoid bleeding through the subchondral plate. If bleeding occurs, use a suitable hemostatic agent to control the bleeding.

*Creating Defect Template*

- Create an exact template of the defect (Figure 2).

**Figure 2: Creating Defect Template**



- Create orientation markers on the template to assist with proper orientation of the MACI implant. Turn the marked template over to ensure that the cells will be properly placed into the defect.

*Preparing MACI Implant*

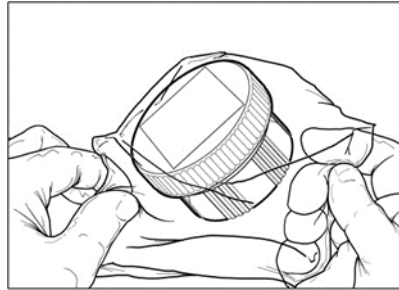
- Unpacking MACI implant box (outside sterile field).
  - Unpack MACI implant shipping box.
  - Remove the outer bag containing a covered dish holding the MACI implant.

Note: Keep the dish upright at all times.



- Remove the self-seal pouch containing the dish from the outer bag (Figure 3).

**Figure 3: Covered Dish in Self-Sealed Pouch**

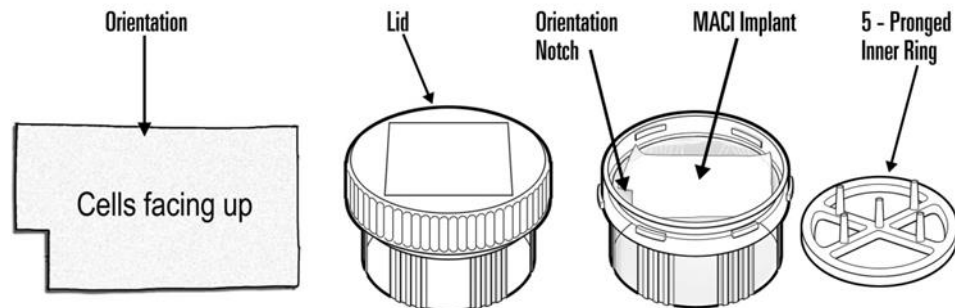


- Tear notches on the self-seal pouch to open the pouch and remove the covered dish.

Note: Do not remove the MACI implant from the dish until ready to be used.

- Unpacking the MACI implant dish (Figure 4)
  - When ready, a team member outside the sterile field but adjacent to the sterile prep table, will twist open and remove the lid from the dish.
  - Sterile field team member using sterile forceps will remove and discard the inner 5-pronged ring.
  - Sterile field team member will use 2 sterile non-tooth forceps to grasp the MACI implant corners and place the MACI implant onto the sterile work surface.

**Figure 4: Unpacking MACI Implant**



- The MACI implant has a rough side and a smooth side. The cells are seeded on the rough side and are facing up in the MACI dish. A notch in the lower left corner of the implant indicates that the cell-side is facing up. The cell-side of the MACI implant should remain facing up at all times until placement into the defect.

Note: The MACI implant must remain hydrated with the shipping media. Use the media from the dish to hydrate the implant if it ever starts to become dry after removal from the dish.

- Shaping the MACI implant
  - To maintain proper orientation, turn the template over and place it underneath the MACI implant, against the smooth, non-seeded side. The template should be visible through the translucent implant.

Note: Ensure minimal contact with the cell-seeded surface of the MACI implant.

- Using the template as a guide, cut the MACI implant to the correct size and shape.
- Place the custom-cut implant into a sterile intermediary dish, ensuring the cell-side up orientation and with adequate media from shipping dish to keep the implant hydrated.
- Place any remaining MACI implant into a separate intermediary dish with adequate media from the shipping dish to keep the implant hydrated. Discard if unused by the end of the implantation.

#### *Placing MACI Implant*

- Ensure defect area is dry and free of bleeding.
- Apply a thin layer of fibrin sealant to the entire base of the defect (bone) bed.
- Maintaining appropriate rotational orientation, place the custom-cut implant onto the defect bed cell-side down.
- Apply light digital pressure to the implant for approximately 3 minutes.
- Fibrin sealant may also be applied to the rim (periphery) of the implant. MACI implant fixation may also be supplemented with interrupted resorbable sutures if desired or if conditions warrant, particularly if the defect is uncontained (i.e, the cartilage defect is not 100% surrounded by a stable cartilage rim) or the lesion is larger than 10 cm<sup>2</sup>.

### **2.3 Postsurgical Rehabilitation**

A physician-prescribed rehabilitation program that includes early mobilization, joint range of motion, and weight bearing is recommended to promote graft maturation and reduce the risk of graft delamination, postoperative thromboembolic events, and joint stiffness. Stage this program to promote a progressive return to full joint range of motion and weight-bearing as well as muscle strengthening and conditioning. Return to recreational and sporting activity should be in consultation with healthcare professionals.

## **3 DOSAGE FORMS AND STRENGTHS**

MACI implant is available as a cellular sheet, 3 x 5 cm, with a 0.5-cm<sup>2</sup> section removed from the lower left-hand corner, consisting of autologous cultured chondrocytes on a resorbable Type I/III collagen membrane at a density of at least 500,000 cells per cm<sup>2</sup>.

## **4 CONTRAINDICATIONS**

MACI is contraindicated in patients with the following conditions:

- Known history of hypersensitivity to gentamicin, other aminoglycosides, or products of porcine or bovine origin. [*see Description (11)*]
- Severe osteoarthritis of the knee (Kellgren-Lawrence grade 3 or 4).
- Inflammatory arthritis, inflammatory joint disease, or uncorrected congenital blood coagulation disorders.
- Prior knee surgery (6 months), excluding surgery to procure a biopsy or a concomitant procedure to prepare the knee for a MACI implant.
- Inability to cooperate with a physician-prescribed post-surgical rehabilitation program [*See Dosage and Administration (2.3)*].

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Malignancy**

The safety of MACI used in patients with malignancy in the area of cartilage biopsy or implant is unknown. The potential exists for expansion of malignant or dysplastic cells present in biopsy tissue during manufacture and subsequent implantation. In addition, implantation of normal autologous chondrocytes could theoretically stimulate growth of malignant cells in the area of the implant, although there have been no such incidents reported in humans or animals.

### **5.2 Transmissible Infectious Diseases**

MACI is intended solely for autologous use. Patients undergoing the surgical procedures associated with MACI are not routinely tested for transmissible infectious diseases. Therefore, the cartilage biopsy and the MACI implant may carry the risk of transmitting infectious diseases to personnel handling these tissues. Accordingly, healthcare providers should employ universal precautions in handling the biopsy samples and the MACI product.

Product manufacture includes reagents derived from animal materials. All animal-derived reagents are tested for viruses, retroviruses, bacteria, fungi, yeast, and mycoplasma before use. Bovine materials are sourced to minimize the risk of transmitting a prion protein that causes bovine spongiform encephalopathy and may cause a rare fatal condition in humans called variant Creutzfeldt-Jakob disease.

These measures do not totally eliminate the risk of transmitting these or other transmissible infectious diseases and disease agents. Report the occurrence of a transmitted infection to Vericel Corporation at 1-888-453-6948.

### 5.3 Presurgical Assessment of Comorbidities

To create a favorable environment for healing, assess and treat the following conditions prior to or concurrent with implantation with MACI:

- Local inflammation or active infection in the bone, joint, and surrounding soft tissue: patients should be deferred until complete recovery.
- Meniscal pathology: presence of an unstable or torn meniscus requires partial resection, repair, or replacement prior to or concurrent with MACI implantation. MACI is not recommended in patients with a total meniscectomy.
- Cruciate ligament instability: the joint should not possess excessive laxity, which may create excessive shear and rotational forces across the joint. Both anterior and posterior cruciate ligaments should be stable or undergo reconstruction prior to or concurrent with MACI implantation.
- Misalignment: the tibio-femoral joint should be properly aligned, and patella tracking should be normalized. Varus or valgus misalignment of the tibio-femoral joint and abnormal patella tracking may abnormally load joint surfaces and jeopardize the implant. Misalignment and patella tracking should be addressed with a corrective osteotomy or similar corrective procedure prior to or concurrent with MACI implantation.

### 5.4 Product Sterility

MACI is shipped after passing preliminary test results from in-process microbial tests. A final sterility test is initiated prior to shipping, but the result will not be available prior to implantation. If microbial contamination is detected after the product has been shipped, Vericel will notify the healthcare provider(s) and recommend appropriate actions.

## 6 ADVERSE REACTIONS

The most frequently occurring adverse reactions ( $\geq 5\%$ ) reported for MACI were arthralgia, tendonitis, back pain, joint swelling, and joint effusion.

Serious adverse reactions reported for MACI were arthralgia, cartilage injury, meniscus injury, treatment failure, and osteoarthritis.

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a product cannot be directly compared to rates in the clinical trials of another product and may not reflect the rates observed in practice.

In a 2-year prospective, multicenter, randomized, open-label, parallel-group clinical trial<sup>1</sup>, 144 patients, ages 18 to 54 years, were randomized to receive a 1-time treatment with MACI or microfracture (1:1, 72 patients in each treatment group). Demographic characteristics of patients in the trial were similar in both treatment groups. The majority of patients were male (62.5% MACI, 66.7% microfracture), and the mean ages were 34.8 (MACI) and 32.9 (microfracture)

years. Overall, 70 patients in the MACI group and 67 patients in the microfracture group completed 2 years of follow-up.

In addition, all 144 subjects from the 2-year clinical trial had the option to enroll in a 3-year follow-up study (extension study). Safety and efficacy assessments were performed at yearly scheduled visits. The demographic characteristics of patients (N = 128) enrolled in the extension study were similar in both treatment groups and consistent with the overall population of the 2-year clinical trial.

The proportion of patients with at least 1 subsequent surgical procedure (any surgical procedure performed on the treated knee joint, including arthroscopy, arthrotomy, or manipulation under anesthesia) in the 2 years following study treatment was comparable between treatment groups (8.3% in the MACI group and 9.7% in the microfracture group).

Adverse reactions reported in  $\geq 5\%$  of patients in either treatment group in the 2-year clinical trial are provided in Table 1.

**Table 1. Adverse Reactions in  $\geq 5\%$  of Patients in Any Treatment Group in the 2-Year Clinical Trial**

| <b>System Organ Class</b>                                   | <b>MACI<br/>n = 72<br/>n (%)</b> | <b>Microfracture<br/>n = 72<br/>n (%)</b> |
|---|----------------------------------|---|
| <b>Musculoskeletal and Connective Tissue Disorders</b>      |                                  |   |
| Arthralgia  | 37 (51.4)                        | 46 (63.9)                                 |
| Back pain   | 8 (11.1)                         | 7 (9.7)                                   |
| Joint swelling  | 7 (9.7)                          | 4 (5.6)                                   |
| Joint effusion  | 5 (6.9)                          | 4 (5.6)                                   |
| <b>Injury, Poisoning and Procedural Complications</b>       |                                  |   |
| Cartilage injury  | 3 (4.2)                          | 9 (12.5)                                  |
| Ligament sprain   | 3 (4.2)                          | 5 (6.9)                                   |
| Procedural pain   | 3 (4.2)                          | 4 (5.6)                                   |
| <b>General Disorders and Administration Site Conditions</b> |                                  |   |
| Treatment failure   | 1 (1.4)                          | 4 (5.6)                                   |

In the 3-year extension study, adverse reactions reported in  $\geq 5\%$  of patients were (MACI vs microfracture): arthralgia (46.2% vs 50.8%), tendonitis (6.2% vs 1.6%), back pain (4.6% vs 6.3%), osteoarthritis (4.6% vs 7.9%), joint effusion (3.1% vs 7.9%), cartilage injury (6.2% vs 15.9%), procedural pain (3.1% vs 7.9%), ligament sprain (1.5% vs 7.9%), and treatment failure (4.6% vs 7.9%).

Serious adverse reactions reported in patients in either treatment group for integrated data across the 2-year clinical trial and the 3-year extension study are provided in Table 2.

**Table 2. Serious Adverse Reactions in Patients in Any Treatment Group Across the 2-Year Clinical Trial and the 3-Year Extension Study**

| System Organ Class  | MACI<br>n = 72<br>n (%) | Microfracture<br>n = 72<br>n (%) |
|---|-------------------------|----------------------------------|
| <b>Musculoskeletal and Connective Tissue Disorders</b>      |                         |                                  |
| Arthralgia  | 1 (1.4)                 | 7 (9.7)                          |
| Joint Lock  | 0                       | 3 (4.2)                          |
| Meniscus Injury   | 3 (4.2)                 | 0                                |
| Osteoarthritis  | 3 (4.2)                 | 0                                |
| <b>Injury, Poisoning and Procedural Complications</b>       |                         |                                  |
| Cartilage injury  | 3 (4.2)                 | 8 (11.1)                         |
| <b>General Disorders and Administration Site Conditions</b> |                         |                                  |
| Treatment failure   | 3 (4.2)                 | 7 (9.7)                          |

## 6.2 Postmarketing Experience

Graft complication (e.g., abnormalities to the repair graft that become symptomatic; this could include graft overgrowth [tissue hypertrophy], under-fill or damage to the repair tissue that has elicited a painful response, or mechanical symptoms), graft delamination (i.e., a dislodging of the repair graft from the underlying subchondral bone that has become symptomatic; this can be measured as marginal, partial, or a complete delaminated graft), and tendonitis have been reported during use of MACI outside the United States. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to MACI exposure.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

MACI implantation requires invasive surgical procedures; therefore use during pregnancy is not recommended. Limited clinical data on patients exposed to MACI during pregnancy are available. There are insufficient data with MACI use in pregnant women to inform a product-associated risk. Animal reproduction studies have not been conducted with MACI. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

## **8.2 Lactation**

### Risk Summary

There is no information regarding the presence of MACI in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MACI and any potential adverse effects on the breastfed infant from MACI or from the underlying maternal condition.

## **8.4 Pediatric Use**

The safety and effectiveness of MACI in pediatric patients have not been established.

## **8.5 Geriatric Use**

The safety and effectiveness of MACI in patients over 65 years of age have not been established. Clinical trials of MACI did not include subjects over the age of 55.

## **11 DESCRIPTION**

MACI, autologous cultured chondrocytes on porcine collagen membrane, is a cellular sheet that consists of autologous chondrocytes seeded on a 3 x 5 cm, resorbable porcine Type I/III collagen membrane, for implantation into cartilage defects of the knee. The active ingredients of MACI are the autologous cultured chondrocytes and porcine Type I/III collagen. The autologous chondrocytes are propagated in cell culture and are seeded on the collagen at a density of 500,000 to 1,000,000 cells per cm<sup>2</sup>. The final MACI implant contains at least 500,000 cells per cm<sup>2</sup> and does not contain any preservative.

The product manufacture also uses reagents derived from animal materials. The resorbable, Type I/III, collagen membrane, which is a component of MACI, is porcine-derived. Fetal bovine serum is a component in the culture medium used to propagate the autologous chondrocytes; therefore, trace quantities of bovine-derived proteins may be present in MACI. These animal-derived reagents are tested for viruses, retroviruses, bacteria, fungi, yeast, and mycoplasma before use.

MACI may contain residual gentamicin because it is included during manufacture. Gentamicin is not included in the transport medium used to maintain product stability. Studies determined an average of 9.2 µg residual gentamicin per MACI implant.

A final sterility test is initiated prior to shipping, but the result will not be available prior to implantation. Passing results from preliminary in-process microbial tests are required for release of MACI for shipping.

## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

No clinical pharmacology studies have been conducted with MACI and a mechanism of action has not been established.

### **12.3 Pharmacokinetics**

Clinical pharmacokinetic studies have not been performed with MACI. Studies in rabbits and horses indicated that the membrane is resorbed over a period of at least 6 months following implantation.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Studies to evaluate the carcinogenicity or impairment of fertility potential of MACI have not been performed. In vitro studies have shown that the expansion process for chondrocytes does not induce changes to the cellular karyotype.

Four studies (*in vitro* and *in vivo*) were conducted to assess the genotoxic potential of the collagen membrane. The results from these studies demonstrated that the collagen membrane was non-mutagenic.

### **13.2 Animal Toxicology and/or Pharmacology**

Implantation of analogous products in critical-size defects in the hind limbs of rabbits and horses did not reveal any serious safety concerns. The products consisted of the same membrane as MACI with rabbit or horse cells, respectively. Non-clinical testing has shown that the collagen membrane is not toxic and is compatible with biological tissue.

## **14 CLINICAL STUDIES**

The effectiveness of MACI implant was evaluated in a 2-year prospective, multicenter, randomized, open-label, parallel-group study, SUMMIT (Superiority of MACI implant versus Microfracture Treatment in patients with symptomatic articular cartilage defects in the knee),<sup>1</sup> which enrolled a total of 144 subjects, ages 18 to 54 years, with at least one symptomatic Outerbridge Grade III or IV focal cartilage defect on the medial femoral condyle, lateral femoral condyle, and/or the trochlea. Failure of a prior cartilage surgery was not required for study entry. The subjects were randomized to receive either a 1-time treatment with MACI or microfracture. The co-primary efficacy endpoint was change from baseline to Week 104 for the subject's Knee injury and Osteoarthritis Outcome Score (KOOS) in two subscales: Pain and Function (Sports and Recreational Activities [SRA])<sup>2</sup>. Safety also was evaluated through Week 104 [*see Adverse Reactions (6.1)*].

Of the 72 subjects randomized to MACI, 70 completed the study and 2 discontinued prematurely (1 due to an adverse event [AE] and 1 wished to withdraw). Of the 72 subjects randomized to microfracture, 67 completed the study and 5 discontinued prematurely (1 due to an AE, 1 wished to withdraw, and 3 due to lack of clinical benefit).

At Week 104, KOOS pain and function (SRA) had improved from baseline in both treatment groups, but the improvement was statistically significantly ( $p = 0.001$ ) greater in the MACI group compared with the microfracture group (Table 3).



**Table 3. Change in KOOS Pain and Function (SRA) Scores in the 2-Year Study**

|  | MACI<br>Mean (SD) |             |             | Microfracture<br>Mean (SD) |             |             |
|--|-------------------|-------------|-------------|----------------------------|-------------|-------------|
|  | N                 | Pain        | Function    | N                          | Pain        | Function    |
| Baseline                                       | 72                | 37.0 (13.5) | 14.9 (14.7) | 71                         | 35.4 (12.1) | 12.6 (16.7) |
| Week 104                                       | 72                | 82.4 (16.2) | 60.9 (27.8) | 70                         | 70.9 (24.2) | 48.7 (30.3) |
| Change From Baseline to<br>Week 104            | 72                | 45.4 (21.1) | 46.0 (28.4) | 69                         | 35.2 (23.9) | 35.8 (31.6) |
| LS Means (Week 104)                            |                   | 44.1        | 46.1        |                            | 32.4        | 34.6        |
| <b>Difference * [MACI –<br/>Microfracture]</b> |                   | 11.8        | 11.4        |                            |             |             |
| <b>p-value **</b>                              |                   | 0.001       |             |                            |             |             |

LS = least squares; KOOS = Knee injury and Osteoarthritis Outcome Score; SD = standard deviation; SRA = Sports and Recreational Activities.

\* Difference in least squares mean values at Week 104 [MACI – Microfracture].

\*\*p-value for difference in co-primary endpoints assessed jointly at Week 104 based on multivariate analysis of variance.

In a responder analysis, the proportion of subjects with at least a 10-point improvement in both KOOS pain and function (SRA) was greater in the MACI group (63/72=87.5%; 95% CI [77.6%, 94.1%]) compared with the microfracture group (49/72=68.1%; 95% CI [56.0%, 78.6%]).

All subjects from the 2-year study had the option to enroll in a 3 year follow-up study (extension study), in which 128 subjects participated. All 65 subjects (100%, 65/65) in the MACI group and 59 subjects (93.7%, 59/63) in the microfracture group completed the extension study. The mean 2-year KOOS pain and function scores remained stable for the additional 3-year period in both treatment groups (Table 4).

**Table 4. KOOS Pain and Function (SRA) Scores in the 3-Year Extension Study**

| Visit    | MACI  |                   |                       | Microfracture |                   |                       |
|----------|-------|-------------------|-----------------------|---------------|-------------------|-----------------------|
|          | N     | Pain<br>mean (SD) | Function<br>mean (SD) | N             | Pain<br>mean (SD) | Function<br>mean (SD) |
| Baseline | 65/65 | 37.1 (13.1)       | 15.4 (14.8)           | 63/63         | 35.2 (12.3)       | 11.9 (16.2)           |
| 2 Years  | 63/63 | 82.2 (15.8)       | 60.5 (26.5)           | 60/60         | 71.8 (23.9)       | 48.9 (30.6)           |
| 5 Years  | 65/64 | 82.2 (20.1)       | 61.9 (30.9)           | 59/59         | 74.8 (21.7)       | 50.3 (32.3)           |

## 15 REFERENCES

1. Saris D, Price A, Widuchowski W, Bertrand-Marchand M, Caron J, Drogset JO, et al. Matrix-applied characterized autologous cultured chondrocytes versus microfracture: two-year follow-up of a prospective randomized trial. Am J Sports Med. 2014 Jun;42(6):1384-94.
2. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. Health Qual Life Outcomes. 2003;1:64.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### How Supplied

- A single patient order may contain 1 or 2 implants, each in its own dish and shipper, depending on lesion size and number of lesions.
- MACI, NDC69866-1030-1, contains 1 implant supplied ready for use as a single cellular sheet approximately 3 x 5 cm, in a sterile, sealed, clear polystyrene dish. Each dish contains one 3 x 5 cm implant with a 0.5-cm<sup>2</sup> section removed from the lower left hand corner, held in place by a polycarbonate 5-pronged ring closed with a polycarbonate cover for shipment.
- MACI, NDC69866-1030-2, contains 2 implants supplied ready for use as cellular sheets approximately 3 x 5 cm, in a sterile, sealed, clear polystyrene dish. Each dish contains one 3 x 5 cm implant with a 0.5 cm<sup>2</sup> section removed from the lower left hand corner, held in place by a polycarbonate 5 pronged ring closed with a polycarbonate cover for shipment.
- Each dish is individually sealed in a clear plastic bag. The plastic bag(s) are placed into one 95kPa pouch (outer bag) with absorbent material. This pouch is enclosed in an outer carton insulated with ambient temperature gel packs.
- MACI is shipped cell-side up.

### Storage and Handling

- Store MACI at room temperature in its original packaging (outer carton) until ready to use.
- DO NOT REFRIGERATE or FREEZE, or sterilize MACI.
- Do not use if the dish is damaged or has been compromised.
- Use MACI prior to 11:59 PM ET on the date of expiration printed on the package.
- Dispose of unused MACI or waste material as surgical biohazardous waste in accordance with local requirements.

## 17 PATIENT COUNSELING INFORMATION

- Advise the patient that:

- A cartilage biopsy is needed to manufacture MACI. The biopsy is typically performed as an arthroscopic procedure at the time of diagnosis confirmation.
- The length of time between the biopsy and the implantation of MACI may vary depending on many factors, including the quality and number of cells obtained from the biopsy. On average this will take 6 weeks; however, cells can be held in storage until a convenient date for surgery is agreed upon between the patient and the surgeon.
- Even if the surgeon has taken a biopsy needed to produce MACI, it may be possible that the patient cannot be treated with MACI, (e.g., in case the biopsy is of insufficient quality to produce MACI, if the cells cannot be grown in the laboratory, or if the expanded cells do not meet all the quality requirements).
- Advise the patient on the risk of graft complications, subsequent surgical procedures, and treatment failure. [*See Adverse Reaction (6)*]
- Advise the patient on general complications related to knee surgery, which may include deep vein thrombosis and pulmonary embolism.
- Advise the patient to closely follow the physician-prescribed rehabilitation program, which will include limitations and allowances for beginning specific physical activities. [*See Dosage and Administration (2.3)*]

Manufactured by: Vericel Corporation, 64 Sidney Street, Cambridge, MA 02139

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