Matrix-Applied Characterized Autologous Cultured Chondrocytes Versus Microfracture

Two-Year Follow-up of a Prospective Randomized Trial

Daniel Saris, MD, PhD, Andrew Price, MD, Wojciech Widuchowski, MD, PhD, Marion Bertrand-Marchand, MD, Jacob Caron, MD, Jon Olav Drogset, MD, PhD, Pieter Emans, MD, PhD, Ales Podskubka, MD, PhD, Anika Tsuchida, MD, Sven Kili, MD, David Levine, MD, MPH, and Mats Brittberg, MD, PhD, on behalf of the SUMMIT study group

Investigation performed at several sites sponsored by Sanofi

The American Journal of Sports Medicine. 2014;42:1384-1394.

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

SUMMIT (Demonstrate the Superiority of MACI implant to Microfracture Treatment) trial overview

Study design	Purpose
Two-year, prospective, Phase 3, multicenter, randomized, open-label, parallel-group clinical trial	Compare clinical efficacy (reduce pain, improve function) and safety of MACI vs arthroscopic microfracture in patients with symptomatic knee cartilage defects
	Co-primary endpoints: Improvement in KOOS (Knee Injury Osteoarthritis Outcome Score) pain and function SRA (sports and recreational activities) subscores from baseline to Week 104 (Year 2)

Patient characteristics	Inclusion criteria	Materials and methods
Enrolled/randomized population 144 patients	At least one symptomatic knee cartilage defect ≥3 cm^2 (medial femoral condyle, lateral femoral condyle, and/or trochlea)	**Baseline arthroscopy** Performed <8 weeks from screening to assess cartilage/obtain biopsy from minor or non–weight-bearing healthy area of femoral condyle (approximately 200 mg)
Mean age 33.8 years (range 18–55 years)	Outerbridge Grade III or IV	**Surgical procedures** MACI performed via mini-arthrotomy 4 to 8 weeks after baseline arthroscopy Microfracture performed at baseline arthroscopy
Male sex 62.5% (MACI) 66.7% (microfracture)	KOOS pain value <55 at baseline	**Post-surgical follow-up** 6 weeks after MACI or microfracture Second-look arthroscopy 2 years' post-surgery
Mean lesion size 4.8 cm^2 (range 3–20 cm^2)	Stable knee with intact or partial meniscus (≥50%)	

Patient withdrawals

- **MACI group:** 2 withdrawals (1 due to adverse events; 1 wished to withdraw)
- **Microfracture group:** 5 withdrawals (1 due to adverse events; 1 wished to withdraw; 3 withdrew for lack of efficacy)

Please see Important Safety Information on Page 6 and full Prescribing Information for MACI.

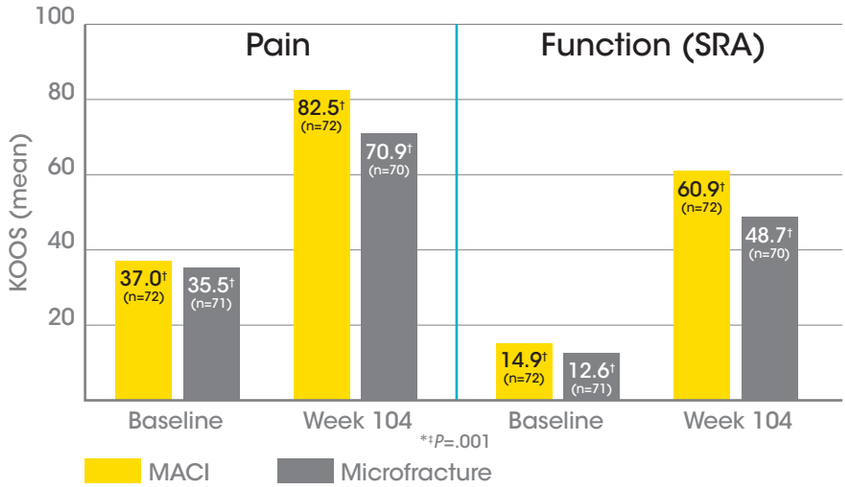
Autologous cellularized scaffold for the repair of cartilage defects of the knee

MACI statistically significantly improved pain and function better than microfracture*

Co-primary endpoints: improvement in pain and function from baseline to Year 2

- Estimated mean difference in the KOOS pain and function subscores between MACI and microfracture was 11.76 (*P*<.001) and 11.41 (*P*=.016), respectively

Improvement in pain and function (baseline and Week 104 [Year 2])*

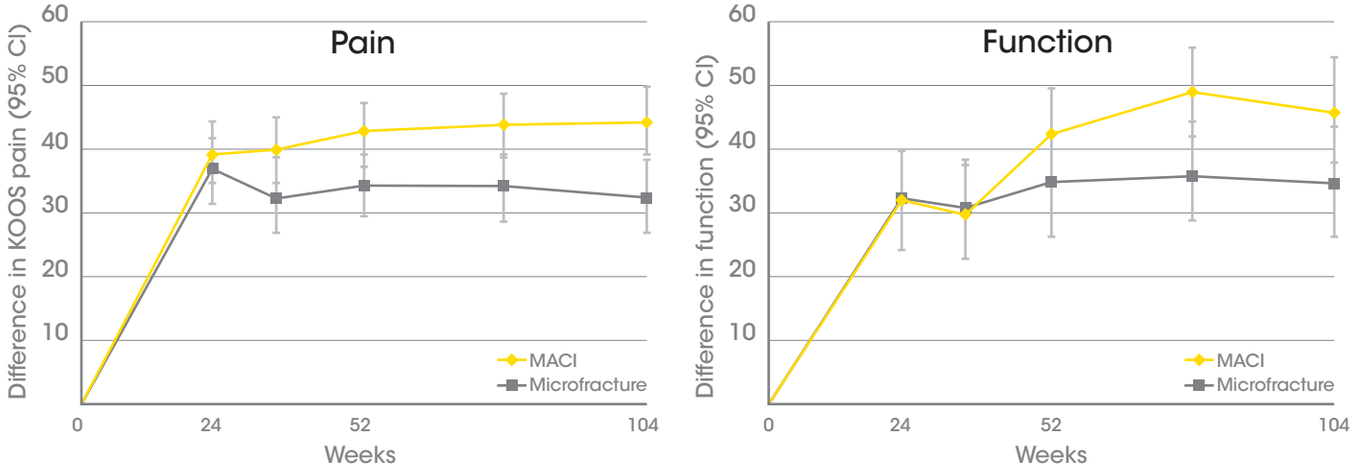


†Absolute scores.
‡*P* value for co-primary endpoint (KOOS pain and KOOS function) for difference between treatments in estimated means for change from baseline to Year 2.

Post hoc analysis: improvement in MACI over microfracture observed early on in treatment

- Improvement in pain and function occurred as early as 36 weeks and was maintained at 52 weeks and out to 104 weeks (Year 2)

KOOS pain and function subscales (mean improvement) over time



Please see Important Safety Information on Page 6 and full Prescribing Information for MACI.

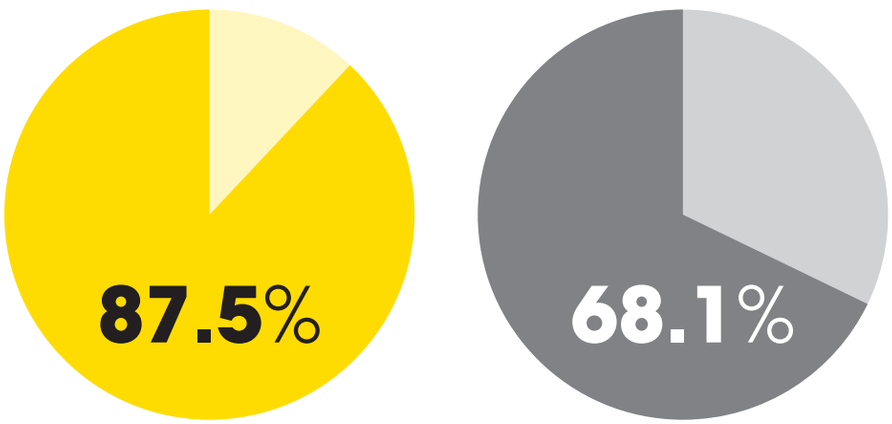
maci autologous cultured chondrocytes on porcine collagen membrane

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

Greater percentage of patients responded to MACI than microfracture

Clinical response

Patient responders (%) to treatment at Week 104 (Year 2)*



MACI (n=72) | Microfracture (n=72)

*Responders were defined as a patient with at least a 10-point improvement in both KOOS pain and function scores from baseline to Week 104 (Year 2).

Predictor subanalysis

Patients with the following characteristics were more likely to respond to MACI than microfracture:

- Male sex
- Younger (median age <34.5 years)
- Only one lesion (lesions most commonly from acute trauma)
- Lesion size >4 cm^2
- Lesion location, medial femoral condyle
- Had one prior knee surgery
- Symptom duration >3 years

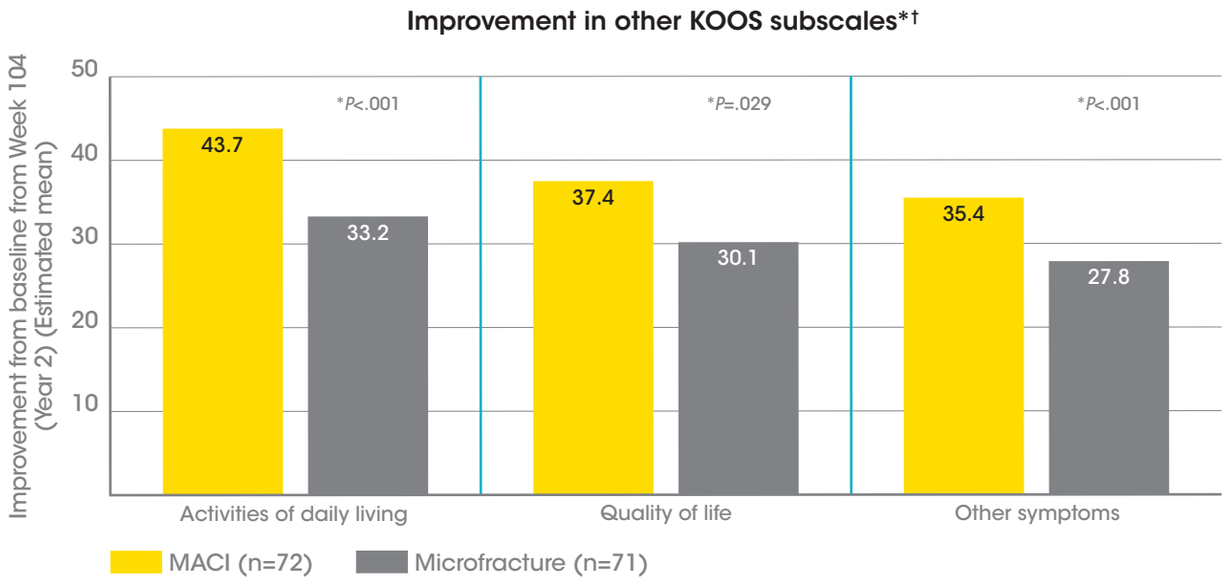
Structural endpoints: cartilage repair assessment

- MRI evaluation of structural repair at Year 1 and Year 2 showed comparable improvement in defect fill for both treatment groups (*P*=NS)
- Histology findings at Week 104 were similar between MACI and microfracture groups: mean microscopic ICRS II overall assessment score 63.8 vs 62.3, respectively (*P*=.717)
- Repair tissue assessment at Year 2, measured with macroscopic ICRS II cartilage repair scores, showed similar results between groups in overall repair assessment (*P*=.145), degree of defect repair (*P*=.430), graft integration to border zones (*P*=.519), and macroscopic appearance (*P*=.164)

Please see Important Safety Information on Page 6
and full Prescribing Information for MACI.

MACI statistically significantly improved other knee-related health areas, with comparable safety*

Secondary endpoint: other KOOS subscales (baseline to Year 2)



†Change in other KOOS subscales measured at Weeks 24, 36, 52, and 78.

MACI demonstrated a safety profile comparable to microfracture

- Most common treatment-emergent adverse events (TEAs) (≥5%) among patients in both groups were arthralgia (57.6%), headache (23.6%), and nasopharyngitis (11.8%)
- Most TEAEs were mild or moderate
- More patients in the microfracture group (n=5) withdrew from the study than in the MACI group (n=2) — The number of withdrawals due to adverse events was the same in both groups (n=1)
- The MACI group had no treatment failures, while the microfracture group had 2 treatment failures

Please see Important Safety Information on Page 6 and full Prescribing Information for MACI.

maci® autologous cultured chondrocytes on porcine collagen membrane

Important Safety Information

Indication for use

- 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^2) 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 in pocket.

64 Sidney Street, Cambridge, MA 02139 | **800.453.6948** | MACI.com

VERICEL

maci autologous cultured chondrocytes on porcine collagen membrane

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

Daniel Saris, Andrew Price, Wojciech Widuchowski, Marion Bertrand-Marchand, Jacob Caron, Jon Olav Drogset, Pieter Emans, Ales Podskubka, Anika Tsuchida, Sven Kili, David Levine, Mats Brittberg and on behalf of the SUMMIT study group

Am J Sports Med published online April 8, 2014
DOI: 10.1177/0363546514528093

AJSM PreView, published on April 8, 2014 as doi:10.1177/0363546514528093

Matrix-Applied Characterized Autologous Cultured Chondrocytes Versus Microfracture

Two-Year Follow-up of a Prospective Randomized Trial

Daniel Saris,*†‡ MD, PhD, Andrew Price,§ MD, Wojciech Widuchowski,‖ MD, PhD, Marion Bertrand-Marchand,¶ MD, Jacob Caron,# MD, Jon Olav Drogset,** MD, PhD, Pieter Emans,†† MD, PhD, Ales Podskubka,‡‡ MD, PhD, Anika Tsuchida,† MD, Sven Kili,§§ MD, David Levine,‖‖ MD, MPH, and Mats Brittberg,¶¶ MD, PhD, on behalf of the SUMMIT study group##
Investigation performed at several sites sponsored by Sanofi

Background: Randomized controlled trials studying the efficacy and safety of matrix-applied characterized autologous cultured chondrocytes (MACI) versus microfracture (MFX) for treating cartilage defects are limited.

Purpose: To compare the clinical efficacy and safety of MACI versus MFX in the treatment of patients with symptomatic cartilage defects of the knee.

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

Methods: Patients enrolled in the SUMMIT (Demonstrate the Superiority of MACI implant to Microfracture Treatment) trial had $\geq$1 symptomatic focal cartilage defect (Outerbridge grade III or IV; $\geq$3 cm^2) of the femoral condyles or trochlea, with a baseline Knee Injury and Osteoarthritis Outcome Score (KOOS) pain value <55. The co–primary efficacy endpoint was the change in the KOOS pain and function subscores from baseline to 2 years. Histological evaluation and magnetic resonance imaging (MRI) assessments of structural repair tissue, treatment failure, the remaining 3 KOOS subscales, and safety were also assessed.

Results: Of the 144 patients treated, 137 (95%) completed the 2-year assessment. Patients had a mean age of 33.8 years and a mean lesion size of 4.8 cm^2. The mean KOOS pain and function subscores from baseline to 2 years were significantly more improved with MACI than with MFX (pain: MACI, 37.0 to 82.5 vs MFX, 35.5 to 70.9; function: MACI, 14.9 to 60.9 vs MFX, 12.6 to 48.7; P = .001). A significant improvement in scores was also observed on the KOOS subscales of activities of daily living (MACI, 43.5 to 87.2 vs MFX, 42.6 to 75.8; $P < .001$), knee-related quality of life (MACI, 18.8 to 56.2 vs MFX, 17.2 to 47.3; P = .029), and other symptoms (MACI, 48.3 to 83.7 vs MFX, 44.4 to 72.2; $P < .001$) for patients treated with MACI compared with MFX. Repair tissue quality was good as assessed by histology/MRI, but no difference was shown between treatments. A low number of treatment failures (nonresponders: MACI, 12.5% vs MFX, 31.9%; P = .016) and no unexpected safety findings were reported.

Conclusion: The treatment of symptomatic cartilage knee defects $\geq$3 cm^2 in size using MACI was clinically and statistically significantly better than with MFX, with similar structural repair tissue and safety, in this heterogeneous patient population. Moreover, MACI offers a more efficacious alternative than MFX with a similar safety profile for the treatment of symptomatic articular cartilage defects of the knee.

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

Cell therapy has been an integral part of the technovolution[20] in cartilage repair, utilizing autologous chondrocytes to generate effective repair tissue. Treating cartilage lesions is important as cartilage injuries are prevalent and can lead to significant pain and reduced function.[39] If left untreated, cartilage lesions can become symptomatic and may progress to osteoarthritis.[38]

The first autologous chondrocyte implantation (ACI) procedure for cartilage repair was performed 25 years ago.[4] Over time, the procedure has advanced to collagen-covered ACI (second-generation technology)[13] and then to matrix-applied characterized autologous cultured chondrocytes (MACI; Genzyme Biosurgery, Cambridge, Massachusetts, USA) implantation, which is third-generation technology. Progression to third-generation technology

The American Journal of Sports Medicine, Vol. XX, No. X
DOI: 10.1177/0363546514528093

resulted in added benefits to patients including shorter procedure time, better surgical consistency, a smaller incision, more consistent cell seeding, less periosteal hypertrophy, and fewer adverse events.[3,7,18,31] For MACI, cultured chondrocytes are seeded in a collagen membrane, which is implanted in the defect. Culturing cells in the membrane allows for their redifferentiation to a more chondrogenic phenotype after monolayer culture; cells are better fixed and distributed in the defect.[3,10,11,40] Physical properties of the type I/III collagen membrane (ACI-Maix, Matricel GmbH, Herzogenrath, Germany) make it tear resistant and durable and thus permit the implant to be easily trimmed and handled.[3,10,11] Overall, good clinical outcomes and repair tissue have been shown with MACI with a good safety profile and especially less periosteal hypertrophy than with the ACI procedure.[3,6,7,18]

Microfracture (MFX), a bone marrow stimulating procedure,[34] is frequently used to repair specific cartilage injuries. While MFX provides good clinical outcomes, these are not always sustained.[15,16,23,25] Previous studies show that patients with smaller lesions have better clinical outcomes with MFX than patients with larger lesions,[21] whereas lesions on the trochlea do not improve as well as those on the femoral condyle.[16] Repair tissue with MFX has been shown to be fibrous in nature[30] compared with more hyaline-like repair tissue reported with MACI.[3] In addition, intralesional osteophytes may result from MFX and could compromise any successful clinical outcomes with the procedure.[22] Also, MFX may negatively affect outcomes of subsequent cell-based cartilage repair treatment.[22,27]

We have conducted the largest randomized controlled trial with the highest power to date in cartilage repair, consistent with the guidance of regulatory agencies, comparing MACI with MFX. Although MFX is traditionally used for the treatment of smaller lesions, clinicians also treat larger defects with MFX[23] because there are few established or acceptable alternative treatment options. The primary objective of our study was to compare the clinical efficacy and safety of MACI with MFX in the treatment of patients with symptomatic knee cartilage defects $\geq$3 cm^2 in size.

MATERIALS AND METHODS

Study Design

The SUMMIT (Demonstrate the Superiority of MACI implant to Microfracture Treatment) trial (in patients with symptomatic articular cartilage defects in the knee) was a prospective, randomized, open-label, parallel-group, multicenter study conducted at 16 European sites (NCT00719576), with enrollment beginning in May 2008. Cartilage defects of the medial femoral condyle (MFC), lateral femoral condyle (LFC), and/or trochlea were treated with MACI or arthroscopic MFX. The protocol and informed consent form were approved by the appropriate national/local ethics committee at each site. The study was conducted according to Good Clinical Practice (GCP) guidelines and principles of the Declaration of Helsinki. All patients provided written informed consent before participating. All surgeons were trained on all surgical procedures, which were standardized.

Patient Population

Male and female patients aged 18 to 55 years with $\geq$1 symptomatic cartilage defects and a moderate to severe Knee Injury and Osteoarthritis Outcome Score (KOOS) pain value (<55) at baseline were included. Index defects

Note: MACI was recently registered as the name of the medicinal product (matrix applied characterised autologous cultured chondrocytes) licensed for cartilage cell therapy use in Europe and manufactured by Sanofi Biosurgery (formerly Genzyme Biosurgery).

*Address correspondence to Daniel Saris, MD, PhD, University Medical Center Utrecht, Postbus 85500, 3508 GA Utrecht, the Netherlands (e-mail: d.saris@umcutrecht.nl).

†University Medical Center Utrecht, Utrecht, the Netherlands.

‡Reconstructive Medicine, Tissue Regeneration, MIRA Institute, University of Twente, Enschede, the Netherlands.

§NIHR Biomedical Research Unit, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK.

‖District Hospital of Orthopedics and Trauma Surgery, Department of Knee Surgery, Arthroscopy and Sports Traumatology, Piekary Slaskie, Poland.

¶Chirurgie Arthrose, Sport et Arthroscopie, Polyclinique Saint Roch, Montpellier, France.

#St Elisabeth Ziekenhuis, Afdeling Orthopedie, Tilburg, the Netherlands.

**Department of Orthopaedics, Trondheim University Hospital, Trondheim, Norway.

††Academisch Ziekenhuis Maastricht, Afdeling Orthopedie, Maastricht, the Netherlands.

‡‡First Faculty of Medicine, Charles University in Prague, Hospital Bulovka, Prague, Czech Republic.

§§Genzyme Biosurgery (now Sanofi Biosurgery), Oxford, UK.

‖‖Genzyme Biosurgery (now Sanofi Biosurgery), Cambridge, Massachusetts, USA.

¶¶Region Halland Orthopedics, Kungsbacka Hospital, Kungsbacka, Sweden.

##Additional authors are listed in the Contributing Authors section at the end of this article.

Drs Saris and Price are first coauthors.

One or more of the authors has declared the following potential conflict of interest or source of funding: Genzyme Biosurgery (now Sanofi Biosurgery) sponsored this study, and Sanofi provided support for medical writing assistance to Precise Publications LLC. D.S. is a consultant for Smith & Nephew, TiGenix, and Regentis; has received grant support for research activity from Genzyme Biosurgery (now Sanofi); has developed educational presentations for Sanofi, TiGenix, and Smith & Nephew; and is an executive committee member of the International Cartilage Repair Society. A. Price is on the speakers' bureau for Biomet; has received grant support for research activity from Biomet, Genzyme Biosurgery (now Sanofi), Smith & Nephew, and Zimmer; and is an advisory board member of the British Orthopaedic Association and International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine. W.W., M.B.-M., J.C., J.O.D., A. Podskubka, L.P., T.T., and K.S. have received grant support for research activity from Genzyme Biosurgery (now Sanofi). P.E. is a consultant at Medtronic; has developed educational presentations for Biomet, Stryker, Smith & Nephew, and Zimmer; and has received grant support for research activity from Genzyme Biosurgery (now Sanofi). S.K. and B.-J.S. are employees of Sanofi Biosurgery and are stockholders of Sanofi. D.L. and M. Bezuidenhoudt are former employees of Genzyme Biosurgery (now Sanofi) and are stockholders of Sanofi. M. Brittberg is a consultant for Sanofi and Piramal Healthcare and has received grant support for research activity from Genzyme Biosurgery (now Sanofi).

were Outerbridge grade III or IV focal cartilage defects[26] on the MFC, LFC, and/or trochlea and were $\geq$3 cm^2 in size. Osteochondritis dissecans (OCD) lesions were allowed if no bone graft was required. A stable knee was required; ligament reconstruction procedures were allowed before or concurrently with the study treatment. An intact or partial meniscus ($\geq$50%) was also required; meniscal repair or resection was allowed before or concurrently with the cartilage repair procedure if $\geq$50% of the functional meniscus remained.

Major exclusion criteria included any knee joint surgery within 6 months before screening; modified Outerbridge grade III or IV defect(s)[26] on the patella or tibia; a symptomatic musculoskeletal condition in the lower limbs that could impede efficacy measures in the target knee; total meniscectomy, meniscal allograft, or bucket-handle tear or displaced tear requiring >50% removal of the meniscus in the target knee; malalignment requiring osteotomy to correct tibial-femoral or patella-femoral alignment; Kellgren-Lawrence grade 3 or 4 osteoarthritis; inflammatory disease or other condition affecting the joints; or septic arthritis within 1 year before screening.

Surgical Procedures

The control selected for efficacy comparison was MFX as recommended by the United States Food and Drug Administration (FDA) and European Medicines Agengy (EMA) in their guidances.[9,35] Microfracture is still considered by some as first-line therapy for cartilage repair, is easily available, and is widely used clinically, thus reflecting a pragmatic "real-world" experience.

At baseline arthroscopic surgery (performed <8 weeks from screening) to assess the cartilage lesion and surrounding cartilage, a cartilage biopsy specimen (~200 mg) was harvested from a minor or nonweightbearing healthy area of the femoral condyle from all patients. After biopsies, patients were intraoperatively randomized, using an interactive voice response system and computer-generated 1:1 randomization scheme, to MACI or arthroscopic MFX.

For patients randomized to the MACI procedure, the biopsy specimens were sent to Genzyme Biosurgery (Cambridge, Massachusetts, USA), where autologous chondrocytes were isolated, cultured, and seeded onto a purified, resorbable, porcine-derived collagen type I/III membrane (ACI-Maix, Matricel GmbH). The final MACI product was a 20-cm^2 (5 $\times$ 4 cm) membrane seeded with 500,000 to 1 million cells/cm^2.

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

Microfracture was performed at the time of arthroscopic surgery strictly according to the technique described by Steadman et al.[34] Briefly, after debridement (as above), multiple holes (centers 3-4 mm apart and 4 mm deep) were made in the subchondral bone with a sharp surgical awl. The cartilage specimens obtained during biopsy were cryopreserved in the laboratory in the event that any patient required later MACI treatment. The patients' first follow-up visit was 6 weeks after MFX or MACI implantation (second stage).

Second-look arthroscopic surgery was used to assess the knee joint according to the International Cartilage Repair Society (ICRS) macroscopic evaluation criteria and obtain a biopsy specimen of repair tissue at year 2.

Rehabilitation

The 4-phase standardized rehabilitation program was based on a report by Steadman et al[33] and was the same for both treatments but individualized for each patient. On the basis of physical therapists' assessments, patients progressed through the program at different rates dependent on lesion size, lesion location, preoperative duration of symptoms, physical condition, patient motivation, and the expected course of healing for the procedure employed. Only when certain goals were reached at the end of each rehabilitation stage were the patients allowed to progress to the next stage. Rehabilitation phases are described in the Appendix (available in the online version of this article at http://ajsm.sagepub.com/supplemental).

Study Endpoints

The primary efficacy analysis was based on the co–primary endpoint of change from baseline to year 2 for the patient's KOOS pain and function (sports and recreational activities) subscores. One of the secondary endpoints was the patient's response rate to treatment based on the KOOS pain and function subscores at year 2. A responder was defined as having at least a 10-point improvement in both the KOOS pain and function subscales, whereas anyone not meeting both criteria was regarded as a nonresponder. Other endpoints are listed in Table 1.

Other predefined endpoints included the histological evaluation of structural repair biopsy specimens, as measured by the microscopic ICRS II overall assessment; magnetic resonance imaging (MRI) assessment of the degree of defect fill, as measured by the scale of the Whole Organ MRI Score (WORMS: 0%-25%, 26%-50%, 51%-75%, 76%-100%)[28] (the Magnetic Resonance Observation of Cartilage Repair Tissue [MOCART] scoring system[19] was not available at the time of study design); and treatment failure rate. Histology and MRI measures were evaluated in a blinded fashion by independent experts in pathology and radiology, respectively. Patients were defined as having a treatment failure if, at any time after week 24, they had a patient and physician global assessment result that was the same or worse than at baseline, a <10% improvement in the KOOS pain subscale, physician-diagnosed failure ruling out all other potential causes,

TABLE 1
SUMMIT Trial Endpoints[a]

Endpoint	Description
Co-primary (month 24)	Change from baseline in KOOS pain and function (sports and recreational activities) subscores
Secondary (month 24)	Histology (ICRS II)[17]
	Assessment of defect fill by magnetic resonance imaging
	Responder rate based on KOOS pain and function (≥10-point improvement) subscales
	Treatment failure rate
	Other KOOS subscales (activities of daily living, knee-related quality of life, and other symptoms)
Tertiary	At weeks 24, 36, 52, and 78:
	Change in all KOOS subscales
	Response rate
	Treatment failure
	Other clinical assessments:
	Modified Cincinnati Knee Rating System[26]
	International Knee Documentation (IKDC)[14]
	Quality of life assessments (months 24 and 48):
	12-Item Short Form Health Survey (SF-12)[37]
	European Quality of Life (EuroQol)–5 dimensions questionnaire (EQ-5D)
	Macroscopic ICRS "Cartilage Repair Assessment" (month 48)
Safety	Treatment-emergent adverse events
	Serious adverse events
	Subsequent surgical procedures

[a]ICRS, International Cartilage Repair Society; KOOS, Knee Injury and Osteoarthritis Outcome Score; SUMMIT, Demonstrate the Superiority of MACI implant to Microfracture Treatment.

and the physician deciding that surgical retreatment was needed. Physician-identified treatment failure cases were further evaluated by an independent treatment failure evaluation committee that reassessed whether each case met the treatment failure criteria.

Patients were evaluated for adverse events at each study visit. An adverse event was defined as any undesirable physical, psychological, or behavioral effect experienced by a patient, independent of treatment relatedness. Adverse events were categorized using the Medical Dictionary for Regulatory Activities, recorded by severity, duration, and treatment relationship. Subsequent surgical procedures were those performed on the target knee during the study; subsequent surgical procedures were not necessarily considered treatment failure but were classified as a serious adverse event. Planned second-look arthroscopic surgeries performed at the 2-year follow-up were not identified as subsequent surgical procedures.

Statistical Analysis

To power the study at 85% to detect a difference between groups, a total sample size of 144 patients (72 patients per arm) was estimated based on the change from baseline to year 2 in the co–primary efficacy endpoint of the KOOS pain and function subscales with an α of .05 (and accounting for patient discontinuation), assuming a difference of 12 points each for the KOOS pain and function subscores with standard deviations of 20 and 30, respectively, and a correlation coefficient of 0.56 between the co–primary variables.

All randomized and treated patients were analyzed. The co–primary endpoint of change in the KOOS pain and function subscales from baseline to year 2 was analyzed with SAS (SAS Institute, Cary, North Carolina, USA) using a multivariate analysis of variance (MANOVA) model and last observation carried forward (LOCF) for missing data imputation. The final MANOVA model included treatment, study site, and baseline KOOS values. The Wilks λ test statistic and associated single P value from the MANOVA model were used to test the statistical significance of the difference in the co–primary endpoint between MACI and MFX. All other changes in the KOOS subscales at all other time points were analyzed and compared between MACI and MFX using analysis of variance (ANOVA) and LOCF. Individual P values for the change from baseline to 2 years for pain and function were also reported; however, that analysis was not part of the a priori statistical analysis plan. Differences between groups were tested by MANOVA and the Cochran-Mantel-Haenszel χ^2 test for histology and by the Cochran-Mantel-Haenszel χ^2 test for responders and defect fill. The Cochran-Mantel-Haenszel χ^2 test was also used to analyze differences in response rates between groups by lesion size, lesion location, and OCD origin.

Predictor variables were also tested post hoc on the co–primary endpoint changes from baseline using multivariate analysis of covariance (MANCOVA), with treatment and center as fixed effects and baseline KOOS pain and function subscores, age, total defect size, occurrence of previous surgery, duration of symptoms, and index lesion location as covariates. Only significant covariates at a .05 level were included in the final model. The Wilks λ test statistic and associated P value were used to test the statistical significance for the co–primary endpoint between MACI and MFX.

TABLE 2
Patient and Lesion Characteristics[a]

	MACI (n = 72)	Microfracture (n = 72)
Patients		
Age, mean ± SD, y	34.8 ± 9.2	32.9 ± 8.8
Male sex, %	62.5	66.7
Body mass index, mean ± SD, kg/m^2	26.2 ± 4.3	26.4 ± 4.0
Duration of symptoms, mean (range), y	5.8 (0.05-28.0)	3.7 (0.1-15.4)
Baseline KOOS pain, mean ± SD	37.0 ± 13.5	35.5 ± 12.1
Baseline KOOS function, mean ± SD	14.9 ± 14.7	12.6 ± 16.7
Lesions		
Index lesion size, mean ± SD, cm^2	4.9 ± 2.8	4.7 ± 1.8
Total defect surface area, mean ± SD, cm^2	5.8 ± 5.1	5.3 ± 2.5
Location, n (%)		
MFC	54 (75.0)	53 (73.6)
LFC	13 (18.1)	15 (20.8)
Trochlea	5 (6.9)	4 (5.6)
Origin, n (%)		
Acute trauma	33 (45.8)	45 (62.5)
Chronic degeneration	18 (25.0)	9 (12.5)
Osteochondritis dissecans	8 (11.1)	12 (16.7)
Unknown	9 (12.5)	6 (8.3)
Other	4 (5.6)	0
Outerbridge grade, n (%)		
III	21 (29.2)	15 (20.8)
IV	51 (70.8)	57 (79.2)
Lesion containment, n (%)		
Completely contained	50 (69.4)	46 (63.9)
Partially contained	22 (30.6)	26 (36.1)

[a]KOOS, Knee Injury and Osteoarthritis Outcome Score; LFC, lateral femoral condyle; MACI, matrix-applied characterized autologous cultured chondrocytes; MFC, medial femoral condyle.

RESULTS

Patient and Lesion Characteristics

A total of 144 patients were enrolled and treated with MACI (n = 72) or MFX (n = 72) (Figure 1). Most of the patients (95%; 137/144) completed a full 2 years of the study. No patients treated with MACI discontinued because of a lack of efficacy compared with 3 patients treated with MFX (Figure 1). Patients had a mean age of 33.8 years and a mean body mass index of 26 kg/m^2, and 65% were male (Table 2). The mean baseline values for the KOOS pain and function subscales were 37.0 and 14.9 in the MACI arm and 35.5 and 12.6 in the MFX arm, respectively.

Lesions had a mean size of 4.8 cm^2 (range, 3-20 cm^2), and most were located on the MFC or LFC and were completely contained (Table 2). Acute trauma was the most common underlying cause of the lesions (54.2%), followed by chronic degeneration (18.8%) and OCD (13.9%).

The most common prior procedures were diagnostic arthroscopic surgery (50.3%), marrow stimulation techniques (34.6%), debridement of the lesion (26.3%), and loose body removal (23.2%) (see Appendix Table A1, available online). The most common concomitant procedures during the index biopsy or implantation were loose body removal, partial medial meniscectomy, and synovectomy/synovial plica excision (see Appendix Table A1).

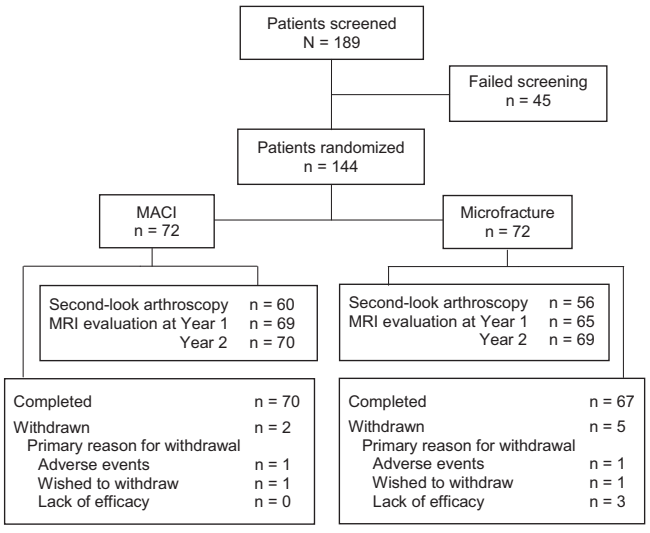


Figure 1. Patient characterisitics.

KOOS Pain and Function

Two years after treatment, the improvement seen in MACI over MFX with regard to the co–primary endpoint was clinically and statistically significant (P = .001), with the

TABLE 3
Scores for Patient-Reported Outcomes With MACI and Microfracture at Baseline and Year 2[a]

	MACI				Microfracture					
	n	Baseline	n	Year 2	n	Baseline	n	Year 2	Estimated Mean Difference	P^b
KOOS subscales										
Pain	72	37.0 ± 13.5	72	82.5 ± 16.2	71	35.5 ± 12.1	70	70.9 ± 24.2	11.76	.001[c]
Function	72	14.9 ± 14.7	72	60.9 ± 27.8	71	12.6 ± 16.7	70	48.7 ± 30.3	11.41	
Activities of daily living	72	43.5 ± 18.2	72	87.2 ± 16.5	72	42.6 ± 19.6	71	75.8 ± 24.2	12.01	<.001
Knee-related quality of life	72	18.8 ± 14.7	72	56.2 ± 23.9	72	17.2 ± 14.1	71	47.3 ± 27.0	8.98	.029
Other symptoms	72	48.3 ± 16.9	72	83.7 ± 14.0	72	44.4 ± 18.6	71	72.2 ± 19.5	11.61	<.001
Modified Cincinnati Knee Rating System	72	3.0 ± 1.2	72	6.4 ± 2.1	72	3.0 ± 1.2	71	5.4 ± 2.2	1.05	.002
IKDC subjective knee evaluation	71	32.9 ± 13.3	72	65.7 ± 18.5	72	29.3 ± 13.4	71	58.8 ± 22.3	5.94	.069
SF-12 physical component score	72	–1.77 ± 0.86	72	–0.32 ± 0.89	69	–1.93 ± 0.82	71	–0.82 ± 1.12	0.51	.001
SF-12 mental component score	72	0.04 ± 1.2	72	0.45 ± 0.9	69	–0.17 ± 1.3	71	0.49 ± 1.0	–0.09	.523
EQ-5D visual analog scale	72	60.8 ± 20.9	72	77.5 ± 15.3	72	56.2 ± 22.1	70	73.4 ± 18.4	3.75	.148

[a]Values are expressed as mean ± standard deviation unless otherwise specified. EQ-5D, European Quality of Life (EuroQol)–5 dimensions questionnaire; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; MACI, matrix-applied characterized autologous cultured chondrocytes; SF-12, 12-Item Short Form Health Survey.

[b]*P* value for difference between treatments in estimated means for change from baseline to year 2.

[c]Wilk λ *P* value for co–primary endpoint (KOOS pain and KOOS function) for difference between treatments in estimated means for change from baseline to year 2.

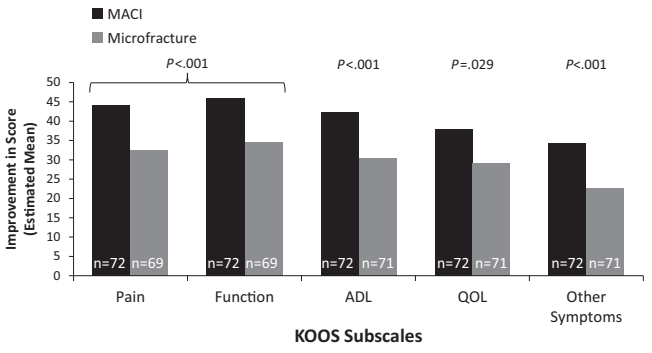


Figure 2. Changes from baseline to year 2 in all Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales for patients treated with the matrix-applied characterized autologous cultured chondrocytes (MACI) implant or microfracture.

estimated mean difference in the KOOS pain subscore being 11.76 ($P < .001$) and function subscore being 11.41 ($P = .016$) (Table 3). Changes in the KOOS pain and function subscales at year 2 are shown in Figure 2. The significant improvement for MACI over MFX was observed for the KOOS pain and function subscales as early as 36 weeks ($P < .03$) and was maintained at 52 weeks ($P < .025$) (Figure 3) and out to 104 weeks.

The percentage of patients who responded to treatment at year 2 (Figure 4) was significantly greater ($P = .016$) with MACI (87.5%) than with MFX (68.1%). Also, MACI and MFX nonresponders comprised 12.5% and 31.9%, respectively.

The predictors' subanalysis of the response rates by patient characteristics showed that significantly more patients responded with MACI than with MFX when patients were male, had a median age <34.5 years, only had 1 lesion, had lesions resulting from acute trauma, underwent 1 prior surgery, or had a duration of symptoms lasting >3 years (see Appendix Table A2). Response rates between patients with or without prior cartilage surgeries were similar. When analyzed by lesion characteristics, significantly more patients responded with MACI compared with MFX when their lesions were >4 cm^2 in size and located on the MFC.

Other Clinical Outcomes

In year 2, the mean improvements from baseline in the other KOOS subscales (activities of daily living, knee-related quality of life, and other symptoms) were significantly better for patients treated with MACI versus MFX ($P < .001$, $P = .029$, and $P < .001$, respectively) (Figure 2). At 52 and 78 weeks, mean improvements were significantly better for all KOOS subscales for MACI versus MFX. Improvements from baseline were significantly better for the modified Cincinnati Knee Rating System scores at years 1 and 2 ($P = .018$ and $P = .002$, respectively) and for the IKDC score at year 1 ($P = .009$), favoring MACI over MFX (Table 3).

Significantly better improvements from baseline to year 1 and 2 ($P = .029$ and $P = .001$, respectively) were observed for the 12-Item Short Form Health Survey (SF-12) physical component score but not the mental component score (Table 3). Increases in the European Quality of Life (EuroQol)–5 dimensions questionnaire (EQ-5D) visual analog scale scores from baseline to year 2 were similar for both groups. No significant difference in the mean improvement of the overall health status was seen at year 1 or at year 2 from baseline.

No analyses were conducted for treatment failure rates between treatment groups because of the small number of treatment failures. Only 2 patients in the MFX group were

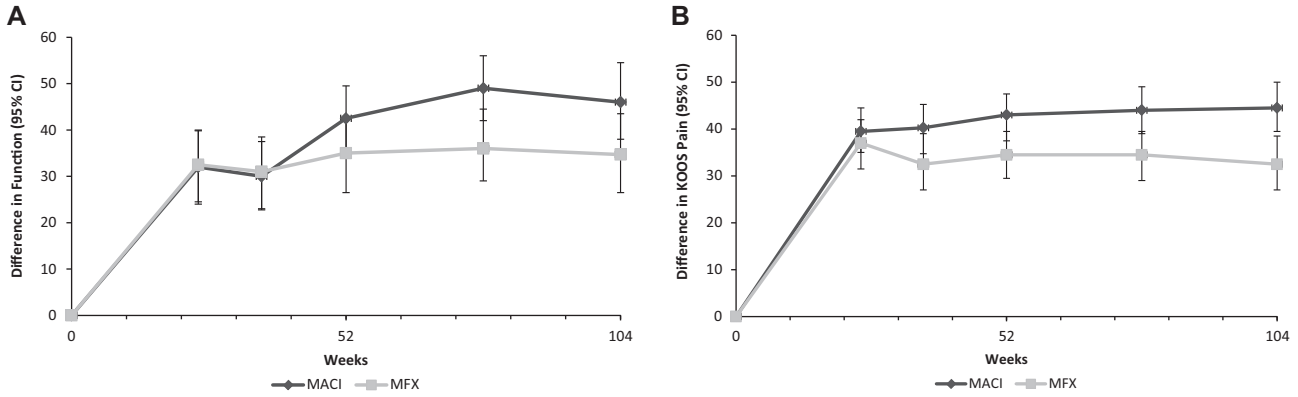


Figure 3. Mean (95% CI) improvement in the Knee Injury and Osteoarthritis Outcome Score (KOOS) function (A) and pain (B) subscales over time for patients treated with the matrix-applied characterized autologous cultured chondrocytes (MACI) implant or microfracture. A significant improvement ($P < .030$) was observed with MACI compared with microfracture for the KOOS function and pain subscales at year 1, which was maintained to year 2 ($P < .025$).

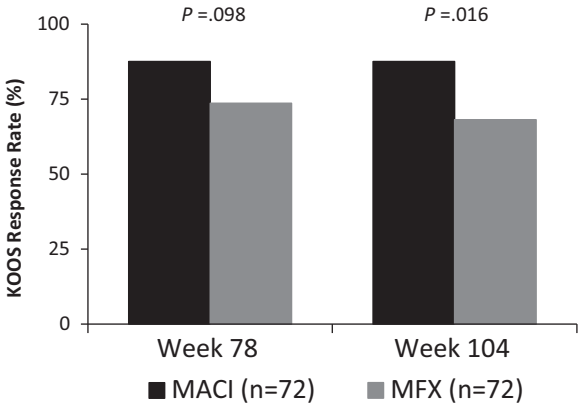


Figure 4. Percentage of patients who responded (≥10-point improvement in the Knee Injury and Osteoarthritis Outcome Score [KOOS] pain and function subscales at year 2).

deemed treatment failures, and no patients in the MACI group were considered treatment failures.

Repair Tissue Assessment

One hundred sixteen patients (MACI, n = 60; MFX, n = 56) underwent second-look arthroscopic surgery and biopsy (Figure 1). Overall, structural repair tissue was very good for both treatments. The mean microscopic ICRS II overall assessment score between groups (63.8 vs 62.3, respectively; estimated mean difference, 1.52) was not significantly different ($P = .717$).

Repair tissue assessment at year 2 with the macroscopic ICRS II cartilage repair scores showed similar results between groups, with no significant difference in the overall repair assessment, degree of defect repair, graft integration to border zones, and macroscopic appearance (Table 4). Approximately 76% of patients in the MACI group had normal or nearly normal (grade I/II) results for the overall repair assessment versus 60% of patients in the MFX group. The majority of patients had a degree of defect repair that was in line with the surrounding cartilage, showed graft integration to border zones that was either complete or with a <1-mm demarcating border, and had repair tissue with an intact smooth or fibrillated surface.

The MRI evaluation of structural repair was performed in 134 patients at year 1 and in 139 patients at year 2 (Figure 1). The MRI evaluation of structural repair at year 1 and 2 showed improvement in defect filling for both treatments but with no statistically significant differences. At year 2, 83% of patients who had MACI and 77% of patients who had MFX showed a degree of defect fill that was >50% of the defect depth.

Safety

No unexpected safety events were reported. Treatment-emergent adverse events (TEAEs) were observed in 55 patients (76.4%) in the MACI group and 60 patients (83.3%) in the MFX group. Most TEAEs were of moderate or mild intensity. The most common TEAEs (Table 5) were arthralgia (57.6%), headache (23.6%), and nasopharyngitis (11.8%). The incidence of TEAEs considered to be related to the study treatment was comparable between treatments (MACI: 34.7% and MFX: 38.9%). The most common related TEAEs were treatment failure, arthralgia, and joint swelling. In each group, 1 patient (1.4%) discontinued because of TEAEs.

Serious TEAEs were reported more frequently in the MFX group (26.4%) than in the MACI group (15.3%), which were attributed to treatment failure, cartilage injury, and arthralgia in the MFX group. No deaths occurred in this study.

The number of patients with at least 1 subsequent surgical procedure was not significantly different ($P = .427$) between the MACI group (8.3%) and the MFX group (9.7%). Two subsequent surgical procedures were experienced by 2 patients in the MFX group but by no patient in the MACI group. Increasing age significantly decreased

TABLE 4
Macroscopic ICRS Cartilage Repair Assessment Scores[a]

	MACI (n = 72)	Microfracture (n = 72)	*P*
Overall repair assessment			.145
Grade I (normal)	14 (19.4)	8 (11.1)	
Grade II (nearly normal)	41 (56.9)	35 (48.6)	
Grade III (abnormal)	4 (5.6)	12 (16.7)	
Grade IV (severely abnormal)	5 (6.9)	4 (5.6)	
Missing	8 (11.1)	13 (18.1)	
Degree of defect repair			.430
In line with surrounding cartilage	45 (62.5)	38 (52.8)	
75% repair of defect depth	10 (13.9)	9 (12.5)	
50% repair of defect depth	4 (5.6)	7 (9.7)	
25% repair of defect depth	4 (5.6)	3 (4.2)	
0% repair of defect depth	1 (1.4)	2 (2.8)	
Missing	8 (11.1)	13 (18.1)	
Graft integration to border zones			.519
Complete integration	21 (29.2)	15 (20.8)	
Demarcating border <1 mm	20 (27.8)	20 (27.8)	
3/4 integrated, 1/4 with border >1 mm	14 (19.4)	13 (18.1)	
1/2 integrated, 1/2 with border >1 mm	3 (4.2)	7 (9.7)	
No contact to 1/4 integrated	6 (8.3)	4 (5.6)	
Missing	8 (11.1)	13 (18.1)	
Macroscopic appearance			.164
Intact smooth surface	25 (34.7)	16 (22.2)	
Fibrillated surface	21 (29.2)	22 (30.6)	
Small, scattered fissures	13 (18.1)	13 (18.1)	
Several small or few but large fissures	3 (4.2)	5 (6.9)	
Total degeneration of grafted areas	2 (2.8)	3 (4.2)	
Missing	8 (11.1)	13 (18.1)	

[a]Values are expressed as n (%). ICRS, International Cartilage Repair Society; MACI, matrix-applied characterized autologous cultured chondrocytes.

the likelihood of at least 1 subsequent surgical procedure occurring (P = .038).

DISCUSSION

Our study demonstrates that MACI is clinically and statistically significantly better than MFX for treating symptomatic cartilage defects of the knee, meeting our study's predefined co–primary endpoint. Overall, patients treated with MACI had superior KOOS subscores for all 5 subscales than patients treated with MFX after 2 years. Additionally, significantly more patients in the MACI group had ≥10-point improvement in their KOOS pain and function subscores versus those in the MFX group. Scores for the modified Cincinnati Knee Rating System and SF-12 physical component scores also improved significantly more with MACI than with MFX. In addition, no treatment failures were reported for the MACI group compared with 2 in the MFX group. Further, repair tissue with MACI also showed good structural outcomes, although not statistically different than with MFX. Finally, the safety profile was similar between the groups, and no unexpected safety issues were encountered.

Our better clinical outcomes with MACI versus MFX are consistent with the results from a recent smaller randomized trial in which treated symptomatic chondral defects of the femoral condyle or patella (N = 60) showed that the Lysholm, Tegner, and patient and surgeon ICRS scores improved significantly more with MACI than with MFX after 2 years.[2] In a case series (N = 34), the

TABLE 5
Most Frequently Reported (>5%) TEAEs[a]

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

[a]Values are expressed as n (%). MACI, matrix-applied characterized autologous cultured chondrocytes; TEAE, treatment-emergent adverse event.

Lysholm-Gillquist score also improved by more points with MACI than with MFX (48 vs 29, respectively).[1]

Good clinical outcomes reported with MACI in our study are also similar to those reported in previous MACI implant case series.[6-8,18] Marlovits and colleagues[18] reported good clinical outcomes with few complications and a low rate of treatment failure in a 5-year follow-up study of patients treated with MACI. Consistent with our study, the patients had significant improvements from baseline on all KOOS subscales, modified Cincinnati Knee Rating System, and IKDC as well as significant improvements in the Tegner-Lysholm scores as early as 1 year after treatment.[18]

In the previous studies described above that reported safety, MACI provided a good safety profile, similar to our study.[2,7,18] In one study, typical postoperative swelling and effusion were observed in patients but resolved within 4 weeks of the MACI procedure.[18] In another study, 2 patients developed deep vein thrombosis early after treatment, while 1 patient developed a postoperative hematoma; all patients recovered without sequelae.[7] In all of the studies, no deaths occurred.[2,7,18]

Beneficial results with MFX here are also consistent with those of previous MFX studies showing good clinical outcomes[12,32]; however, some reports showed that such improvements with MFX are not always sustained past 18 to 24 months.[15,16,23,25]

Our analysis of predictors by the response rate showed that more patients with a longer duration of symptoms (>3 years) or younger age (median, <34.5 years) improved with MACI when compared with MFX. However, Vanlauwe and colleagues[36] found that patients with less time since symptom onset (<3 years vs ≥3 years) did better with characterized chondrocyte implantation (CCI) than with MFX, while cell therapy in older defects did not seem to have an added benefit. Furthermore, no discernible difference was observed between younger (<35 years) and older (≥35 years) patients.[36] In another study, younger patients (<30 years) had better clinical outcomes than older patients, regardless of treatment with MACI or MFX.[15] The reasons for the inconsistencies in our results compared with findings in these previous studies are unknown but may pertain to patient population, lack of statistical power among the subgroups, or technique differences.

Structural endpoints assessed by MRI and repair tissue histology assessed by the ICRS II score demonstrated good quality repair tissue with MACI. However, good quality repair tissue with MACI was not different than that found with MFX, even given the clinical results favoring MACI. These findings were unexpected in that MFX structural scores were better than anticipated, as previous studies showed better repair tissue with autologous cell therapies than with MFX. However, it should be noted that the study's power was based on the primary clinical endpoint, and the study was not powered to show a statistical difference on secondary structural endpoints. In a study by Bachmann and colleagues,[1] the MRI-evaluated repair tissue was of better quality, with the defect fill being more consistent, and better integrated with the adjacent cartilage with MACI (n = 27) than with MFX (n = 7). These authors also found that the MRI signal intensity of the repair tissue with MACI was close to that of the surrounding native cartilage, whereas the signal intensity was different than that of adjacent normal cartilage with MFX.

Other studies showed better repair tissue with other cell therapy technologies than with MFX. One year after CCI, structural repair tissue was better than with MFX,[30] as shown by better mean histology assessment (blinded) scores (P = .012) and more intense safranin O and collagen II stainings (P = .03).[30] However, MRI assessment showed similar repair tissue after 3 years,[29] with no report on repair tissue at year 5.[36]

The reasons for our unanticipated similar results in structural repair tissue between MACI and MFX are currently unknown. The clinical relevance, reproducibility, and applicability to long-term clinical outcomes of the ICRS II, a recently developed histology grading system for cartilage repair, still need to be established.[17] Further, one cannot ensure that biopsy specimens taken were the best representative sample of the total repair tissue especially because the samples were taken by individual surgeons and not by 1 dedicated sampling person, although this would apply equally to both groups.[24] Evidence for the "overperformance" of MFX in the present study can be found in a study comparing MFX with CCI, as our overall ICRS II score with MFX (62.3) was numerically higher than that in the MFX-CCI comparison (~44).[30] Finally, the study protocol was designed so that all MRI readings, including preoperative reads, were blinded from a treatment and temporal perspective to minimize reader bias.

Additional longer term comparative studies are needed to further understand the relationship between clinical outcomes and integrity of the structural cartilage tissue. A systematic review and meta-analysis reported by de Windt et al[5] found that the majority of articular cartilage repairs in knee studies showed limited or no correlation between clinical outcomes and MRI parameters; only 28% of studies (9/32) showed a correlation between clinical outcomes and MOCART or Henderson scores. This is in line with guidance from regulatory agencies (EMA and FDA) that suggests that MRI data, as well as histology data, are not predictive of outcomes and that clinical outcomes assessing pain and function are the most important parameters in determining the efficacy of cell-based therapies.[9,35] Nevertheless, an extension of our study is currently underway in which 3- and 5-year outcomes will be assessed.

Some of the limitations of this study include the fact that the procedures were performed by many surgeons and that it was not a blinded study. However, all surgeons were trained on standardized surgical procedures, and their training was audited by the sponsor. In addition, given that the surgical techniques for MACI (2 surgeries) and MFX (1 surgery) are different, the study could not be blinded; however, histological and MRI evaluations were assessor blinded. Because of the inherent heterogeneity of cartilage repair tissue, one limitation of the histological evaluation is the inability to ensure that the biopsy specimen acquired was representative of the total cartilage repair tissue.[24] Also, it is possible that the favorable results

observed for patients in both treatment groups could have been positively influenced by the rigorous patient education and follow-up inherent in the study protocol.

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

Overall, improvements in clinically relevant endpoints such as pain and function, as opposed to those of structural repair, remain the more important endpoints for the study of cartilage defects with regard to patient care.[24] This trial demonstrated that at 2-year follow-up, MACI provides significantly better pain relief and functional improvement when compared with MFX in this heterogeneous population, with similarities in repair and safety profiles, when treating symptomatic articular cartilage defects ≥ 3 cm^2 of the knee.

CONTRIBUTING AUTHORS

Libor Paša, MD, PhD (Trauma Department, Medical Faculty, Masaryk University Brno, Trauma Hospital, Brno, Czech Republic); Tomas Trc, MD (Fakultni Nemocnice v Motole, Ortopedická Klinika UK 2.LF a FN Motol, Prague, Czech Republic); Konrad Slynarski, MD, PhD (Center for Sports Medicine CMS, Warsaw, Poland); Bernd-Jan Sanson, MD, PhD (Genzyme Europe, Naarden, the Netherlands); and Mauritz Bezuidenhoudt, MSc (Genzyme Europe, Naarden, the Netherlands).

ACKNOWLEDGMENT

The authors acknowledge the following investigators of the study: Michel Allizard, MD, PhD (Hopital d'Instruction des Armées, Cedex, France); Wojciech Banach, MD (Orthopedics and Traumatology Clinic, Bydgoszcz, Poland); Julien Chouteau, MD (Centre Hospitalier Lyon Sud, Cedex, France); and Pierre Hamon, MD (Maussins-Nollet Clinic, Paris, France). The authors also acknowledge Thomas Bauer, MD, PhD (Cleveland Clinic, Cleveland, Ohio, USA) and Michael L. Hawes, DVM, DACVP (Charter Preclinical Services, Hudson, Massachusetts, USA) for blinded histology reading; Charles Peterfy, MD, PhD and Yan Chen, MD (Spire Sciences, Oakland, California, USA) for blinded MRI reading; Qifeng Yu, PhD (Sanofi, Cambridge, Massachusetts, USA) for statistical analysis; Sarah J. Fritchley, PhD (Covance, Cambridge, UK) for study oversight and coordination; and Geary MacQuiddy, MBA (Sanofi, Cambridge, Massachusetts, USA) for study oversight. In addition, the authors acknowledge Astrid Diemeer for study management, Duncan McKay for regulatory strategy, Shalu Ramrakha for regulatory management, and Veronika Kunert for study oversight and coordination; all are former employees of Genzyme/Sanofi. Further acknowledgment goes to the medical writing support of Kathleen Ohleth, PhD, and Dominique Verlaan, PhD (Precise Publications), which was funded by Sanofi (formerly Genzyme Biosurgery).

REFERENCES

1. Bachmann G, Basad E, Lommel D, Steinmeyer J. MRT in the follow-up of matrix-guided autologous chondrocyte implantation (MACI®) and microfracture. *Radiologe*. 2004;44(8):773-782.
2. Basad E, Ishaque B, Bachmann G, Sturz H, Steinmeyer J. Matrix-induced autologous chondrocyte implantation versus microfracture in the treatment of cartilage defects of the knee: a 2-year randomised study. *Knee Surg Sports Traumatol Arthrosc*. 2010;18(4):519-527.
3. Brittberg M. Cell carriers as the next generation of cell therapy for cartilage repair: a review of the matrix-induced autologous chondrocyte implantation procedure. *Am J Sports Med*. 2010;38(6):1259-1271.
4. Brittberg M, Lindahl A, Nilsson A, Ohlsson C, Isaksson O, Peterson L. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. *N Engl J Med*. 1994;331(14):889-895.
5. de Windt TS, Welsch GH, Brittberg M, et al. Is magnetic resonance imaging reliable in predicting clinical outcome after articular cartilage repair of the knee? A systematic review and meta-analysis. *Am J Sports Med*. 2013;41(7):1695-1702.
6. Ebert JR, Robertson WB, Lloyd DG, Zheng MH, Wood DJ, Ackland T. A prospective, randomized comparison of traditional and accelerated approaches to postoperative rehabilitation following autologous chondrocyte implantation: 2-year clinical outcomes. *Cartilage*. 2010;1(3):180-187.
7. Ebert JR, Robertson WB, Woodhouse J, et al. Clinical and magnetic resonance imaging-based outcomes to 5 years after matrix-induced autologous chondrocyte implantation to address articular cartilage defects in the knee. *Am J Sports Med*. 2011;39(4):753-763.
8. Ebert JR, Smith A, Edwards PK, Hambly K, Wood DJ, Ackland TR. Factors predictive of outcome 5 years after matrix-induced autologous chondrocyte implantation in the tibiofemoral joint. *Am J Sports Med*. 2013;41(6):1245-1254.
9. European Medicines Agency. Reflection paper on in-vitro cultured chondrocyte containing products for cartilage repair of the knee. April 8, 2010. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/05/WC500090887.pdf. Accessed March 21, 2014.
10. Gavénis K, Schmidt-Rohlfing B, Mueller-Rath R, Andereya S, Schneider U. In vitro comparison of six different matrix systems for the cultivation of human chondrocytes. *In Vitro Cell Dev Biol Anim*. 2006;42(5-6):159-167.
11. Gigante A, Bevilacqua C, Ricevuto A, Mattioli-Belmonte M, Greco F. Membrane-seeded autologous chondrocytes: cell viability and characterization at surgery. *Knee Surg Sports Traumatol Arthrosc*. 2007;15:88-92.
12. Gill TJ. The treatment of articular cartilage defects using microfracture and debridement. *Am J Knee Surg*. 2000;13(1):33-40.
13. Gomoll AH, Probst C, Farr J, Cole BJ, Minas T. Use of a type I/III bilayer collagen membrane decreases reoperation rates for symptomatic hypertrophy after autologous chondrocyte implantation. *Am J Sports Med*. 2009;37(Suppl 1):20S-23S.
14. Irrgang JJ, Anderson AF, Boland AL, et al. Development and validation of the International Knee Documentation Committee subjective knee form. *Am J Sports Med*. 2001;29(5):600-613.
15. Knutsen G, Drogset JO, Engebretsen L, et al. A randomized trial comparing autologous chondrocyte implantation with microfracture: findings at five years. *J Bone Joint Surg Am*. 2007;89(10):2105-2112.
16. Kreuz PC, Steinwachs MR, Erggelet C, et al. Results after microfracture of full-thickness chondral defects in different compartments in the knee. *Osteoarthritis Cartilage*. 2006;14(11):1119-1125.
17. Mainil-Varlet P, Van DB, Nesic D, Knutsen G, Kandel R, Roberts S. A new histology scoring system for the assessment of the quality of

human cartilage repair: ICRS II. *Am J Sports Med*. 2010;38(5):880-890.
18. Marlovits S, Aldrian S, Wondrasch B, et al. Clinical and radiological outcomes 5 years after matrix-induced autologous chondrocyte implantation in patients with symptomatic, traumatic chondral defects. *Am J Sports Med*. 2012;40(10):2273-2280.
19. Marlovits S, Striessnig G, Resinger CT, et al. Definition of pertinent parameters for the evaluation of articular cartilage repair tissue with high-resolution magnetic resonance imaging. *Eur J Radiol*. 2004;52(3):310-319.
20. Mastbergen SC, Saris DB, Lafeber FP. Functional articular cartilage repair: here, near, or is the best approach not yet clear? *Nat Rev Rheumatol*. 2013;9(5):277-290.
21. Miller BS, Joseph TA, Barry EM, Rich VJ, Sterett WI. Patient satisfaction after medial opening high tibial osteotomy and microfracture. *J Knee Surg*. 2007;20(2):129-133.
22. Minas T, Gomoll AH, Rosenberger R, Royce RO, Bryant T. Increased failure rate of autologous chondrocyte implantation after previous treatment with marrow stimulation techniques. *Am J Sports Med*. 2009;37(5):902-908.
23. Mithoefer K, McAdams T, Williams RJ, Kreuz PC, Mandelbaum BR. Clinical efficacy of the microfracture technique for articular cartilage repair in the knee: an evidence-based systematic analysis. *Am J Sports Med*. 2009;37:2053-2063.
24. Mithoefer K, Saris DBF, Farr J, et al. Guidelines for the design and conduct of clinical studies in knee articular cartilage repair: International Cartilage Repair Society recommendations based on current scientific evidence and standards of clinical care. *Cartilage*. 2011;2(2):100-121.
25. Mithoefer K, Williams RJ III, Warren RF, et al. The microfracture technique for the treatment of articular cartilage lesions in the knee: a prospective cohort study. *J Bone Joint Surg Am*. 2005;87(9):1911-1920.
26. Noyes FR, Barber SD, Mooar LA. A rationale for assessing sports activity levels and limitations in knee disorders. *Clin Orthop Relat Res*. 1989;246:238-249.
27. Pestka JM, Bode G, Salzmann G, Sudkamp NP, Niemeyer P. Clinical outcome of autologous chondrocyte implantation for failed microfracture treatment of full-thickness cartilage defects of the knee joint. *Am J Sports Med*. 2012;40(2):325-331.
28. Peterfy CG, Guermazi A, Zaim S, et al. Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee in osteoarthritis. *Osteoarthritis Cartilage*. 2004;12(3):177-190.
29. Saris DB, Vanlauwe J, Victor J, et al. Treatment of symptomatic cartilage defects of the knee: characterized chondrocyte implantation results in better clinical outcome at 36 months in a randomized trial compared to microfracture. *Am J Sports Med*. 2009;37(Suppl 1):10S-19S.
30. Saris DB, Vanlauwe J, Victor J, et al. Characterized chondrocyte implantation results in better structural repair when treating symptomatic cartilage defects of the knee in a randomized controlled trial versus microfracture. *Am J Sports Med*. 2008;36(2):235-246.
31. Sohn DH, Lottman LM, Lum LY, et al. Effect of gravity on localization of chondrocytes implanted in cartilage defects. *Clin Orthop Relat Res*. 2002;394:254-262.
32. Steadman JR, Briggs KK, Rodrigo JJ, Kocher MS, Gill TJ, Rodkey WG. Outcomes of microfracture for traumatic chondral defects of the knee: average 11-year follow-up. *Arthroscopy*. 2003;19(5):477-484.
33. Steadman JR, Rodkey WG, Briggs KK. Microfracture to treat full-thickness chondral defects: surgical technique, rehabilitation, and outcomes. *J Knee Surg*. 2002;15(3):170-176.
34. Steadman JR, Rodkey WG, Singleton SB, Briggs KK. Microfracture techinique for full-thickness chondral defects: technique and clinical results. *Oper Tech Orthop*. 1997;7(4):300-304.
35. US Department of Health and Human Services, Food and Drug Administration. Guidance for Industry: preparation of IDEs and INDs for products intended to repair or replace knee cartilage. December 2011. Available at: http://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/cellularandgenetherapy/ucm288011.pdf. Accessed March 21, 2014.
36. Vanlauwe J, Saris DB, Victor J, Almqvist KF, Bellemans J, Luyten FP. Five-year outcome of characterized chondrocyte implantation versus microfracture for symptomatic cartilage defects of the knee: early treatment matters. *Am J Sports Med*. 2011;39(12):2566-2574.
37. Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care*. 1996;34(3):220-233.
38. Widuchowski W, Widuchowski J, Faltus R, et al. Long-term clinical and radiological assessment of untreated severe cartilage damage in the knee: a natural history study. *Scand J Med Sci Sports*. 2011;21(1):106-110.
39. Widuchowski W, Widuchowski J, Trzaska T. Articular cartilage defects: study of 25,124 knee arthroscopies. *Knee*. 2007;14(3):177-182.
40. Zheng M-H, Willers C, Kirilak L, et al. Matrix-induced autologous chondrocyte implantation (MACI®): biological and histological assessment. *Tissue Eng*. 2007;13(4):737-746.

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

----------RECENT MAJOR CHANGES----------

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

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.

DOSAGE AND ADMINISTRATION

For autologous implantation only.

- Contact Vericel at 1-800-453-6948 or 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^2) 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)

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^2. (3)

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)

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)

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* for voluntary reporting of adverse reactions.

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

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

MACI® (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 regarding training materials for surgical implantation of MACI.

2.1 Dosage

- The amount of MACI implanted depends on the size (surface area in cm^2) 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

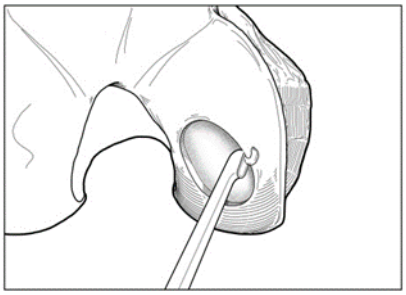
- Perform implantation procedure during arthrotomy using sterile surgical techniques.

- 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

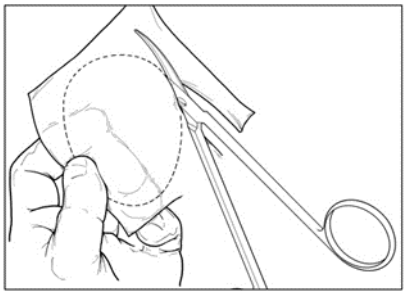


- For osteochondral defects, debride the defect bed back to stable cartilage with vertical walls down to healthy stable bone.
- Avoid bleeding through the subchondral plate. If bleeding occurs, use a suitable hemostatic agent to control the bleeding.

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.

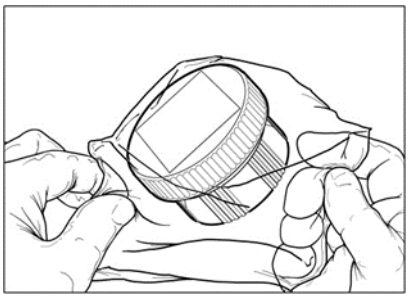
Preparing MACI Implant

- 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

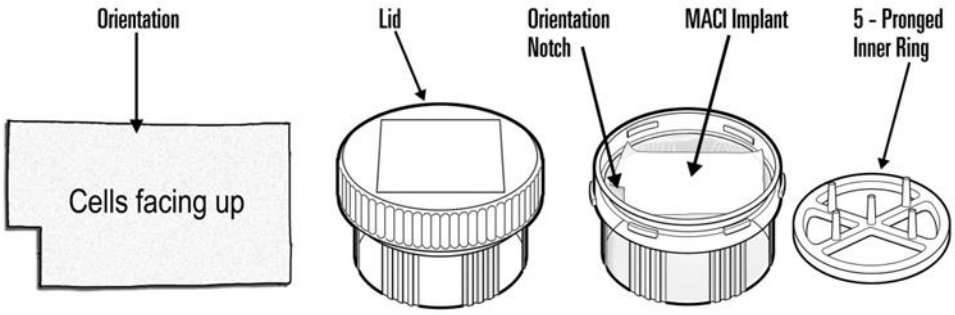


– Tear notches on the self-seal pouch to open the pouch and remove the covered dish.

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^2.

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^2 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^2.

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 (≥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[1], 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 ≥5% of patients in either treatment group in the 2-year clinical trial are provided in Table 1.

Table 1. Adverse Reactions in ≥5% of Patients in Any Treatment Group in the 2-Year Clinical Trial

System Organ Class	MACI n = 72 n (%)	Microfracture n = 72 n (%)
Musculoskeletal and Connective Tissue Disorders		
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)
Injury, Poisoning and Procedural Complications		
Cartilage injury	3 (4.2)	9 (12.5)
Ligament sprain	3 (4.2)	5 (6.9)
Procedural pain	3 (4.2)	4 (5.6)
General Disorders and Administration Site Conditions		
Treatment failure	1 (1.4)	4 (5.6)

In the 3-year extension study, adverse reactions reported in ≥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 n = 72 n (%)	Microfracture n = 72 n (%)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	1 (1.4)	7 (9.7)
Joint Lock	0	3 (4.2)
Meniscus Injury	3 (4.2)	0
Osteoarthritis	3 (4.2)	0
Injury, Poisoning and Procedural Complications		
Cartilage injury	3 (4.2)	8 (11.1)
General Disorders and Administration Site Conditions		
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^2. The final MACI implant contains at least 500,000 cells per cm^2 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),[1] 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])[2]. 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 Mean (SD)			Microfracture 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 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
Difference * [MACI – Microfracture]		11.8	11.4			
p-value **	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 mean (SD)**	**Function mean (SD)**	**N**	**Pain mean (SD)**	**Function 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^2 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^2 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

MACI® is a registered trademark of Vericel Corporation.

65617.A