



Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Epidemiology

Pharmacovigilance Plan Review Memorandum
MACI™ (BLA 125603/0)

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To: John Thomas, PhD
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Office of Tissues and Advanced Therapies (OTAT)

STN: Original BLA 125603/0

Product: *Proposed brand name:* MACI™ (autologous cultured chondrocytes on porcine collagen membrane)

Proposed indication: MACI is indicated for the repair of symptomatic, full-thickness cartilage defects (single or multiple) of the knee, with or without bone involvement (b) (4) in adults.

Sponsor: Vericel Corporation

Action Due Date: January 3, 2017

1. INTRODUCTION

1.1 Objectives and Scope

The sponsor, Vericel, submitted an original BLA 125603/0 seeking initial licensure for the product MACI (autologous cultured chondrocytes on porcine collagen membrane) to treat cartilage defects of the knee in adults. The purpose of this review memorandum is to evaluate Vericel's plan for postmarketing safety monitoring and to identify potential safety concerns associated with the use of MACI that may need to be addressed through additional postmarketing safety surveillance, studies, or other pharmacovigilance activities, should the product be approved.

1.2 Product Description

MACI is a *combination product* consisting of autologous cultured chondrocytes (*biological component*) seeded onto a bioresorbable Type I/III porcine-derived collagen membrane (*device component*). Each MACI implant contains 500,000 to 1,000,000 autologous cells per cm².

Reviewer comment: Of note, the autologous cellular component of MACI is (b) (4)

The device component of MACI has also been previously licensed as ACI-Maix™.

Proposed indication: *the repair of symptomatic, full-thickness cartilage defects (single or multiple) of the knee, with or without bone involvement (b) (4) in adults.*

Proposed mechanism of action: *Once implanted into a full-thickness articular cartilage defect, the delivered cells initiate a reparative response that fills the defect with hyaline-like repair tissue, which has been shown clinically to reduce pain and allow many patients to resume normal activities.*

Treatment with MACI requires a two-stage procedure: (i.) biopsy of cartilage, followed by (ii.) implantation of MACI. MACI implantation is performed by a surgeon during arthrotomy and requires preparation of the defect bed and application of a fibrin sealant to secure the MACI implant; multiple defects may be treated. The amount of MACI to be administered is determined by the size of the cartilage defect being treated; the MACI implant needs to completely cover the defect, and multiple implants may be used to treat large defects. Vericel will distribute the MACI product from its manufacturing facility directly to the surgeon at the hospital.

1.3 Regulatory History

MACI has been available in some European markets since 1998, as well as in Australia and parts of Asia since 2000. In 2005, MACI was acquired by Genzyme Corporation. In 2006, the European Union passed the Advanced Therapies Medicinal Products (ATMP) Regulation that required formal approval of MACI implant and all other cell therapy products through the centralized European Medicines Agency (EMA) process. Under the new EU regulations, MACI implant could continue to be commercialized in the EU markets until the ATMP regulations became effective in December 2012, after which EMA approval was required. In 2008, Genzyme initiated the phase 3 SUMMIT clinical trial.

MACI received European Union (EU) Marketing Authorization Approval on June 27, 2013. In August 2014, Vericel became the Marketing Authorisation Holder for MACI. The license and marketing of MACI

¹ BLA 125603\0; module 2.7.3 Summary of Clinical Efficacy, p9

in the EU has been temporarily suspended (September 2014) for commercial reasons, but the sponsor is continuing ongoing routine postmarketing surveillance.

On January 4, 2016, Vericel submitted original BLA 125603/0 to FDA seeking initial approval for MACI.

2. MATERIALS REVIEWED

Materials reviewed in support of this pharmacovigilance plan assessment are listed below.

- Manufacturer's Submissions
 - Original BLA submission 125603\0
 - Module 1.16: Pharmacovigilance Plan (Revised June 30, 2016)
 - Module 2.5: Clinical Overview
 - Module 2.7.4: Summary of Clinical Safety
 - Module 2.7.3 Summary of Clinical Efficacy.
- Input from BLA review team, including FDA Clinical Memorandum (DRAFT); OTAT Clinical Reviewer: Dr. Michael Yao.

3. CLINICAL STUDIES

Clinical trial overview

The clinical trial data submitted in support of this BLA is based on a single pivotal 2-year study (SUMMIT study; N = 144 subjects) and its 3-year long-term safety follow-up extension study (SUMMIT Extension study; N = 128 subjects). Data was collected over a 5-year period. We defer to the OTAT clinical review for a detailed discussion of study design and efficacy results.

SUMMIT study: The primary evidence of effectiveness comes from this 2-year prospective phase 3 trial.²

Study title: SUMMIT study (MACI00206)		
Study objective: Evaluate safety and efficacy of MACI compared with microfracture		
Study design: Randomized, controlled, open-label, multicenter, single dose pivotal phase 3 study		
Region: European Union		
Study population: Adult patients with symptomatic, full-thickness cartilage defects of the knee. 100% Caucasian study population. Other demographics presented below.		
	MACI	Microfracture
Sex	45 male; 27 female	48 male; 24 female
Mean Age (range)	34.8 years (18-54)	32.9 years (18-54)
Study size: N = 144; 72 subjects treated with MACI; 72 subjects treated with microfracture (control).		
Study design [Source: 2.7.3 Summary of Clinical Efficacy, p.40]		


² Adapted from BLA 125603; Module 2.7.3 Summary of Clinical Efficacy.

Primary Endpoint: Co-primary endpoints of Knee injury and Osteoarthritis Outcome Scores (KOOS) Pain and KOOS Function (Sports and Recreational Activities (SRA)) scores from baseline to week 104. The treatment comparison used a superiority hypothesis (MACI vs microfracture).
Study duration: 2 years
Efficacy results: The treatment-group differences (MACI vs microfracture) in changes of subjects' KOOS Pain and KOOS Function (SRA) scores were statistically significant (p = 0.001). Although both treatment groups showed substantial improvement from baseline, the mean differences between treatment groups (over 10 points on each rating scale) are considered clinically meaningful and were statistically significant. [FDA Clinical Memorandum (DRAFT); OTAT Clinical Reviewer: Dr. Michael Yao]

SUMMIT Extension study: Long term follow-up on subjects who completed the SUMMIT study³.

Study title: SUMMIT Extension study (MACI00809)
Study objective: Evaluate safety and exploratory efficacy in patients who received treatment with MACI or microfracture in SUMMIT study.
Study design: open-label, multicenter, 3-year extension study to follow-up on long-term safety and efficacy
Region: European Union
Study population: Patients who completed the SUMMIT study were eligible
Study size: N = 128; 65 patients treated with MACI; 63 patients treated with microfracture
Intervention: Only patients who failed initial treatment from SUMMIT during the extension study received re-treatment, which could have been MACI
Primary Endpoint: Co-primary endpoints of KOOS Pain and KOOS Function
Study duration: 3-year extension study
Efficacy results: primary efficacy outcomes remained stable in both treatment groups over 5-year follow-up from initial treatment in SUMMIT study. [FDA Clinical Memorandum (DRAFT); OTAT Clinical Reviewer: Dr. Michael Yao]

(b) (4)



³ Adapted from BLA 125603; Module 2.7.3 Summary of Clinical Efficacy.

4. SAFETY DATABASE

4.1 Clinical Trial Safety Data from the SUMMIT and SUMMIT Extension studies

Treatment-Emergent Adverse Events (TEAEs): In the SUMMIT Study, the proportion of subjects with at least one TEAE was 76.4% in the MACI group v. 83.3% in the control (microfracture) group. In the Extension study, the proportion of subjects with at least one TEAE was 75.4% in the MACI group and 74.6% in the microfracture group.

The most common TEAEs in >10% of subjects reported for MACI in the SUMMIT and the SUMMIT Extension trials (combined) by preferred term (PT): arthralgia, headache, nasopharyngitis, and back pain, influenza, cartilage injury, ligament sprain. TEAEs with MACI were most frequently reported within the SOC, *musculoskeletal and connective tissue disorders*, (60.0% in the MACI group).

Treatment-Emergent Serious Adverse Events (TESAEs): TESAEs were reported more frequently in the microfracture group (26.4%) than in the MACI group (15.3%). The most common TESAEs occurring in ≥3% of subjects reported for MACI in SUMMIT and the SUMMIT Extension trial (combined) were cartilage injury, meniscus injury, treatment failure, and osteoarthritis. Each TESAE was reported in 3 or fewer patients (<5%) in the MACI group.

Deaths: No deaths occurred in the clinical trials.

Adverse Events of Special Interest (AESIs): The following perioperative and/or implant-related AEs were reported – hemarthrosis (2 subjects) and graft delamination (1 subjects) in the MACI arm of the trial.

Reviewer Comment: The overall frequency of TEAEs and SAEs was comparable in both groups for all categories. Majority of TEAEs were non-serious. Overall, TEAEs were consistent with the known safety profile of this product class, the underlying condition and consistent with the study population of patients with knee cartilage defects and surgery. The most frequently reported SOC was *musculoskeletal and connective tissue disorders*. Treatment failure is often seen with cartilage repair products, due to extensive underlying cartilage injury. Many patients with knee cartilage defects remain symptomatic even after interventions.

4.2 120-Day Safety Update

As per the sponsor, currently MACI is not marketed in any country and there are no ongoing clinical investigations. *“During the 120-day period following the BLA submission, there have been no emerging safety concerns or adverse event reports in any ICH region. The safety information and risk-benefit profile described in the original BLA application remains unchanged.”*⁴

4.3 Foreign Postlicensure Safety Data

MACI has been commercially available outside US since 1998. In 2005, MACI was acquired by Genzyme and a pharmacovigilance monitoring system was instituted. Thus postmarketing surveillance has been ongoing for MACI since 2005. From 2005 – 2015, 6032 patients have been exposed to MACI (this includes patients treated under the clinical development program and postmarketing use). European postmarketing surveillance data (2005 – 2015: There were total 196 spontaneous AE reports (Table 1 below)

⁴ 120-day Safety Update, STN 125603/0.8 (Amendment); Received 5/3/2016

Table 1: Summary of Foreign Postmarketing Surveillance data⁵

Preferred Term (MedDRA v18.0)	Total Events N = 196 n (%)
Graft complication	27 (13.8)
Treatment failure	12 (6.1)
Tendonitis	11 (5.6)
Graft delamination	11 (5.6)
Arthralgia	10 (5.1)
Joint swelling	7 (3.6)
Deep vein thrombosis	5 (2.6)
Pain	5 (2.6)
Synovitis	5 (2.6)
Transplant failure	5 (2.6)
Joint effusion	5 (2.6)
Cartilage injury	4 (2.0)
Bone marrow oedema	4 (2.0)
Wound infection	4 (2.0)

- Of spontaneously reported AEs, common PTs included: graft complication, treatment failure/transplant failure, tendonitis, graft delamination, and arthralgia.
- There were 4 reports involving PT “*wound infection*” (of which only 1 was a serious report; 3 were non-serious reports). There were 3 serious reports of PT “*arthritis infective*” and 1 serious report of “*arthritis bacterial*.”
- There was 1 report of medication error in which a patient was implanted with another patient’s MACI

Reviewer Comment: There is a single foreign report of a medication error involving administration of a different patient’s implant. Of note, should the product be approved in the U.S., Vericel will have restricted distribution of this autologous product under the controlled distribution system (further discussed in section 5). As per the proposed PVP, Vericel will also conduct root-cause investigation of any medication errors.

4.4 Conclusion

The sponsor provided an integrated summary of identified risks associated with MACI from clinical trial data, postmarketing use and literature (Table 1).

Reviewer Comment: In conjunction with the clinical review, discussions with the review team, and overall assessment of the safety database, there are no new clinically significant safety issues that would require additional pharmacovigilance measures, should the product be approved in the US.

⁵ BLA 125603, module 5.3.5.3 Integrated Summary of Safety, p95

Table 2: Summary of Safety Concerns from Clinical Trial Data and Postmarketing Use of MACI⁶

Source of Information	Risk	Frequency ^a
Clinical Trials MACI00206 and MACI00809 (AEs considered related to study treatment by the Investigator)	Arthralgia Joint swelling Joint effusion Treatment failure Joint range of motion decreased Graft delamination Joint lock Impaired healing	Very common (22/72) Common (5/72) Common (3/72) Common (3/72) Common (2/72) Common (2/72) Common (1/72) Common (1/72)
Pharmacovigilance Database (AEs and SAEs from commercial experience and literature surveillance) ^b	Graft complication Treatment failure Tendonitis Graft delamination Arthralgia Joint swelling Deep vein thrombosis Pain Synovitis Transplant failure Joint effusion Cartilage injury Bone marrow edema Wound infection	Uncommon (27/6032) Uncommon (12/6032) Uncommon (11/6032) Uncommon (11/6032) Uncommon (10/6032) Uncommon (7/6032) Rare (5/6032) Rare (5/6032) Rare (5/6032) Rare (5/6032) Rare (5/6032) Rare (4/6032) Rare (4/6032) Rare (4/6032)

^a Council for International Organizations of Medical Sciences (CIOMS) definitions of frequency of adverse drug reactions: very common $\geq 1/10$; common $< 1/10$ and $\geq 1/100$; uncommon $< 1/100$ and $\geq 1/1000$; rare $< 1/1000$ and $\geq 1/10,000$.

^b Includes AEs reported in $\geq 2\%$ of MACI pharmacovigilance database cases as of 31 August 2015. Cases reported in the clinical trials are not included in this summary.

Source: ISS Table 14.3.1.10.4; ISS in-text Table 44: Summary of Adverse Events Reported in $\geq 2\%$ of Nonstudy MACI Cases.

5. PHARMACOVIGILANCE PLAN⁷

5.1 Proposed Pharmacovigilance Plan

The Pharmacovigilance Plan (PVP) includes the sponsor's assessment of identified and potential risks and missing information based on pre-licensure clinical trial data, published literature, known product-class effects, and other relevant sources of safety information. Overview of the PVP is described in Table 3.

⁶ BLA 125603, module 1.16 RMP Risk Evaluation and Mitigation Strategy (REMS), p4

⁷ Pharmacovigilance Plan, Revised June 30, 2016 submitted in BLA 125603, module 1.16

Table 3: Summary of Safety Concerns and Proposed Actions⁸

Safety Concern	Planned Action(s)
Important identified risks related to MACI or the surgical procedure	
Graft hypertrophy (including graft complication) Graft delamination (complete or partial, possibly leading to loose bodies in the joint or graft [treatment] failure) Thromboembolic events Deep infection Medication errors	Routine PV Root-cause investigation in the case of graft (treatment) failure, infection, or medication errors
Important potential risks related to cellular therapy	
Carcinogenicity Immunogenicity Systemic inflammation	Routine PV
Important missing information	
Safety in children	Pediatric Study Plan (PSP) in place Routine PV
Safety in patients >65 years of age	Routine PV

5.2 Safety concerns and Proposed Actions

Complications of surgery and treatment failure are important identified risks for MACI.

- Proposed actions: The sponsor proposes routine passive surveillance and labeling. At this time, Vericel is not planning any additional postmarketing studies for long term safety follow-up.

Reviewer comment: Procedural complications, treatment failure, and AEs related to musculoskeletal and connective tissue disorders are known risks of autologous chondrocyte implants. AEs related to cartilage injury may also be related to the patient's underlying knee pathology (confounded by indication). At this time, routine pharmacovigilance is acceptable. The sponsor also proposes to conduct additional clinical follow-up of spontaneously reported serious adverse events. Since this is an autologous product, additional clinical follow-up with the treating physician will likely be feasible. Vericel will also conduct root cause investigation for graft failure, infections and medication errors.

Safety concerns related to administration of MACI: During the BLA review, the clinical review team consulted with Dr. Neil J. Barkin, orthopedic surgeon at CDRH. As a subject matter expert (SME), he provided the following comment regarding training for the MACI implantation procedure: *Although most components of both MACI and microfracture procedures are well within the technical ability of an arthroscopically trained orthopedic surgeon, the MACI procedure is effectively 3 operations spaced widely apart. To ensure that the initial arthroscopic cell harvesting is properly performed, that the microfracture or MACI procedures are accurately completed, and the week 104 biopsy is done correctly, in my opinion, a hands-on training session for prospective surgeons would be appropriate. I would*

⁸ BLA 125603, module 1.16 PVP, p17

estimate this could be readily achieved in a half to a full day session utilizing cadaver and simulated joint models.

- Proposed actions: The sponsor has *voluntarily* proposed the following measures to provide training for the MACI implantation procedure.
 - Healthcare provider (HCP) training: Vericel has developed a Surgical Manual to provide specific guidance on the surgical procedures for index arthroscopy, cartilage biopsy and MACI implantation. Vericel's Cell Therapy Specialist will also train the surgical support staff. Vericel's training platform will require that a knowledge check be completed by the HCP prior to confirmation that the training has been successfully completed. For the first treated patient, intraoperative monitoring by a trained cell therapy specialist from Vericel will be provided as needed.
 - Controlled distribution: MACI is an autologous cellular product for which Vericel plans to limit distribution to HCPs trained in cartilage biopsy collection and MACI implantation. As per Vericel, the HCP will not be able to order MACI for an implantation until they have fulfilled their training requirements.
 - (b) (4)

Reviewer comment: MACI is similar to the first generation autologous chondrocyte product, Carticel, which was approved by FDA in 1997. Carticel is administered surgically during arthrotomy via direct injection of expanded autologous chondrocytes into the cartilage defect and secured using a harvested autologous periosteal flap. Carticel has a Surgeon Training Program, also provided voluntarily by Vericel. MACI uses autologous chondrocytes seeded on a collagen membrane which enables delivery of the cell product to the cartilage defect, and has the advantage of not requiring a periosteal flap. As per Vericel, *"compared to Carticel, MACI can be implanted with less invasive techniques. These surgical advantages reduce the duration of surgery, and have the potential to reduce surgical site morbidity and postoperative complications."*

The reviewer agrees with the measures proposed voluntarily by the sponsor to train the healthcare provider administering MACI. Orthopedic surgeons, with specialized training in cartilage repair procedures, will administer this product, and as per the SME consult, *"most components of both MACI and microfracture procedures are well within the technical ability of an arthroscopically trained orthopedic surgeon."* This autologous product will be available under a controlled distribution system and will be restricted to surgeons who receive additional MACI-specific training provided by Vericel. As per the SME consult, MACI-specific training for *"prospective surgeons would be appropriate."* Please note that the training materials and the communication plan are *voluntary* actions undertaken by the sponsor. As per FDA guidance⁹, *"If FDA determines that a REMS is not required, an applicant may undertake voluntary risk management measures that would be performed outside of REMS."* The available data demonstrates a similar safety profile to the licensed first generation autologous chondrocyte implant product, Carticel, and as described above, MACI implantation techniques are less invasive than those for Carticel. The training for Carticel is also provided voluntarily by Vericel. There is no new safety concern that would require a Risk Evaluation and Mitigation Strategy (REMS) under Title IX of the Food and Drug Administration Amendments Act of 2007 (FDAAA), to be necessary to ensure that the benefits of MACI outweigh its risks.

⁹ Guidance for Industry Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications. September 2009.

Potential risks associated with cellular therapy: No events relating to carcinogenicity, immunogenicity or systemic inflammation occurred in any subject during the clinical trials or during postmarketing use.

- Proposed actions: The sponsor proposes routine passive surveillance and labeling.

Reviewer comment: At this time, the proposed PVP is acceptable.

Missing information

- Proposed actions
 - The sponsor proposes routine passive surveillance and labeling
 - The sponsor has submitted a Pediatric Study Plan (PSP).

Reviewer comment: Clinical safety database is limited and there is no safety data on the use of MACI in select under-represented patient populations: children, geriatric patients, pregnant or lactating women. In the SUMMIT Study, the mean age was 34.8 years (age range 18 – 54 years). Additionally, the safety data from the SUMMIT Study was derived from a population that was 100% Caucasian, and may not be applicable to the broad US population.

At this time, the proposed PVP is acceptable. OBE/DE will defer to OTAT regarding review of the PSP. Evaluation of the safety and efficacy of MACI in pediatric patients aged 10 – 17 years is planned. Children <10 years of age are not expected to be treated with MACI.

6. OTHER MANAGED REVIEW INFORMATION

- There are no outstanding safety issues, based on results of the SUMMIT Study and its extension study that were identified by the clinical reviewer (primary clinical reviewer: Dr. Michael Yao/OTAT).
- Healthcare training for MACI administration was discussed with OTAT review team, and OTAT agreed with OBE/DE that the training materials and the communication plan will be *voluntary* actions undertaken by the sponsor. The available data do not suggest a safety concern that would require a REMS under Title IX of FDAAA. OBE/DE will defer to OTAT clinical review team and Advertising and Promotional Labeling Branch (APLB) to review the content and format of the healthcare provider training materials.
- Postmarketing requirement (PMR) pediatric study under PREA: The sponsor submitted a pediatric study plan (PSP). Based upon recommendations from FDA Pediatric Research Committee (PeRC), OTAT agrees with a partial waiver for pediatric patients <10 years and deferral of studies in patients aged 10 – 17 years who have knee cartilage defects due to (b) (4) and acute trauma.

7. DE ASSESSMENT AND RECOMMENDATIONS

Final determination of the benefit/risk profile of MACI is pending the clinical, statistical and product reviews. Safety-related data and the proposed pharmacovigilance plan (Revised June 30, 2016) submitted in BLA 125603/0 have been reviewed. The available data do not suggest a safety concern that would necessitate a Risk Evaluation and Mitigation Strategy (REMS), a postmarketing commitment (PMC) or a required postmarketing (PMR) study that is specifically designed to evaluate safety as a primary endpoint. A pediatric study plan was submitted by the sponsor to evaluate the safety and efficacy of MACI in children aged 10 – 17 years (this will be a PMR pediatric study under PREA).

Of note, Vericel *voluntarily* proposes to provide healthcare training for MACI implantation procedure via the following measures:

- Vericel developed surgeon training manual for MACI procedures
- Communication plan
- Controlled distribution system to limit product distribution to healthcare providers who have been trained in surgical procedures specific to MACI

At this time, routine pharmacovigilance is recommended to monitor the identified and potential risks and missing information associated with MACI, should the product be licensed. Postmarketing adverse experiences should be reported to CBER in accordance with 21 CFR 600.80. Routine surveillance includes 15-day expedited reports for serious, unlabeled (unexpected) adverse events, and quarterly periodic safety reports for 3 years (annual thereafter). Distribution reports should be provided to CBER in accordance with 21 CFR 600.81.