

Summary Basis for Regulatory Action

Date: December 13, 2016

From: John Terrig Thomas, Ph.D., Chair of the Review Committee

BLA/ STN#: 125603/0

Applicant Name: Vericel Corp.

Date of Submission: January 4, 2016

PDUFA Goal Date: January 3, 2017

Proprietary Name: MACI

Proper Name: Autologous Cultured Chondrocytes on a Porcine Collagen Membrane

Indication: 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.

Recommended Action: Approval

Offices' Signatory Authorities:

Wilson W. Bryan, MD, Director, Office of Tissues and Advanced Therapies

- I concur with the summary review.
- I concur with the summary review and include a separate review to add further analysis.
- I do not concur with the summary review and include a separate review.

Mary Malarkey, Director, Office of Compliance and Biologics Quality

- I concur with the summary review.
- I concur with the summary review and include a separate review to add further analysis.
- I do not concur with the summary review and include a separate review.

Material Reviewed / Consulted/Specific Documentation Used in Developing the SBRA

CMC Review	12-Dec-2016 Malcolm Moos Jr, Carolyn Yong (DCGT) 29-Sept-2016 Joseph Nielsen (CDRH-ODE Consult) 21-Nov-2016 Latoya Oliver-Powell (CDRH-OC Consult) 29-Nov-2016 Hyesuk Kong (DBSQC)
Clinical Review	1-Dec-2016 Michael Yao, Bruce Schneider
Statistical Review	27-Sept-2016 Stan Lin
Nonclinical Pharmacology / Toxicology Review	21-Nov-2016 Allen Wensky
Facilities Review	12-Dec-2016 Pete Amin
Pharmacovigilance Review	14-Nov-2016 Meghna Alimchandani
Bioresearch Monitoring Review	30-Aug-2016 Anthony Hawkins
Advertising and Promotional Labeling Review	25-Aug-2016 Loan Nguyen
Advisory Committee Transcript	N/A
Establishment Inspection	09-May-2016 Pete Amin, John Stansberry, Terrig Thomas, Carolyn Yong
CBER Lot Release	19-Sept-2016 Karen Campbell
Environmental Assessment	10-25-2016 Terrig Thomas

Table of Contents

1. Introduction	pg. 4
2. Background	pg. 4
3. Chemistry, Manufacturing and Controls (CMC)	pg. 6
a) Product Quality	pg. 6
b) CBER Lot Release	pg. 9
c) Facilities Review/Inspection	pg. 9
d) Environmental Assessment	pg. 10
4. Nonclinical Pharmacology / Toxicology	pg. 10
5. Clinical Pharmacology.....	pg. 11
6. Clinical / Statistical	pg. 11
a) Clinical Program	pg. 11
b) Pediatrics	pg. 17
7. Safety.....	pg. 17
8. Advisory Committee Meeting	pg. 19
9. Other Relevant Regulatory Issues	pg. 19
10. Labeling	pg. 19
11. Recommendations and Risk / Benefit Assessment	pg. 19
a) Recommended Regulatory Action	pg. 19
b) Risk / Benefit Assessment.....	pg. 20
c) Recommendation for Postmarketing Risk Management Activities	pg. 20
d) Recommendation for Postmarketing Activities	pg. 20

1. Introduction

Biologics License Application (BLA) 125603 is for Autologous Cultured Chondrocytes on a Porcine Collagen Membrane, MACI, which is manufactured by Vericel Inc. MACI is an autologous cellular, biologic-device combination product indicated for the repair of single or multiple symptomatic, full-thickness cartilage defects of the knee with or without bone involvement in adults.

MACI consists of autologous cultured chondrocytes (biologic constituent) seeded onto a resorbable porcine Type I/III collagen membrane (device constituent). The cells are isolated from patient's cartilage biopsy taken from non-load-bearing regions of the knee, expanded in culture, and seeded onto the ACI-Maix Collagen membrane manufactured by Matricel GmbH. The assembled construct (b) (4) to yield the drug product, MACI, which is released based on predefined criteria for safety and quality.

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

This document summarizes the basis for approval for MACI, highlighting topics of key review discussions. The review team recommends approval of this BLA with one postmarketing requirement (PMR) for a PREA-related pediatric clinical study and three postmarketing commitments (PMC) related to CMC issues.

2. Background

Cartilage Defects

Articular cartilage defects of various sizes, often caused by traumatic injury, disrupt the normal anatomic relationship of cartilaginous surfaces between articulating joints. As knee articular cartilage has a limited capacity for self-repair, defects can cause severe pain, knee swelling, and reduction in mobility that affects quality of life. Arthroscopic microfracture is a common procedure performed in the US for treatment of symptomatic knee cartilage defects, where the defect is debrided and small holes are drilled into the subchondral bone to allow bleeding into the defect site. Stromal cells then effect a repair by producing a scar type tissue called fibrocartilage, which lacks the biomechanical properties of articular cartilage, but does provide an improvement in symptoms. The Autologous Chondrocyte Transplantation (ACT) product Carticel™, was licensed in 1997 for the treatment of focal articular cartilage defects of the knee. However, in addition to a cartilage biopsy obtained during initial arthroscopy, ACT requires a more complex surgical procedure, in which a periosteal flap is harvested from the tibia and then sutured over the defect site. MACI is proposed as an alternative to the current ACT procedure by seeding the expanded cells onto a resorbable porcine collagen membrane, eliminating the periosteal flap surgery.

Regulatory History and Considerations

It should be noted that manufacture of the MACI product and its use in the clinical trials in support of this BLA were conducted in Europe and were not subject to prior review under IND regulation.

The cellular product used in the clinical studies submitted to the BLA was manufactured using a process (b) (4)

and the name “MACI” is used to denote the product that is the subject of this BLA application. The applicant, Vericel, acquired both Carticel and MACI from Genzyme in 2014.

A Master File ((b) (4)) for the resorbable porcine Type I/III collagen membrane (ACI-Maix) device constituent, manufactured by Matricel GmbH (Herzogenrath Germany), was submitted and reviewed in support of this BLA. The chondrocyte Drug Substance, MACI Drug Product, and the review of the quality system of the MACI combination product were submitted and reviewed in the BLA.

One Phase 3 clinical trial (SUMMIT Study) and its extension were completed for MACI prior to submission of BLA 125603 on January 4, 2016. (b) (4)

These four studies are listed below:

- MACI00206 (SUMMIT Study): A Prospective, Randomized, Open-Label, Parallel-Group, Multicenter Study To Demonstrate The Superiority Of Matrix-induced Autologous Chondrocyte Implantation (Maci[®] Implant) Versus Arthroscopic Microfracture For The Treatment Of Symptomatic Articular Cartilage Defects Of The Femoral Condyle Including The Trochlea
- MACI00809 (SUMMIT Extension Study): An Extension Protocol for Participants of Genzyme-Sponsored Prospective, Randomized, Open-Label, Parallel-Group, Multicenter Study of Matrix-induced Autologous Chondrocyte Implantation (MACI implant) for the Treatment of Symptomatic Articular Cartilage Defects of the Femoral Condyle Including the Trochlea
- (b) (4)
- (b) (4)

3. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

Manufacturing Summary and Issues

MACI is manufactured by seeding cultured viable autologous human chondrocytes onto a porcine Type I/III collagen membrane.

The autologous chondrocytes are derived from a knee cartilage biopsy. They are expanded in culture and may be (b) (4) prior to assembly of the final MACI product.

The porcine Type I/III collagen membrane (ACI-Maix) is obtained by processing of porcine (b) (4) membranes by Matricel GmbH. The processing includes steps for microbial inactivation, and the resulting collagen is tested further for microbiological safety and physicochemical quality prior to shipment for use in manufacture of MACI.

The manufacturing process is approximately 6 weeks in duration. The critical production steps are described below:

- *Cartilage Biopsy* (b) (4)
A cartilage biopsy is (b) (4).
- *Expansion of Chondrocytes in Culture*
(b) (4)
- *Production of Porcine Collagen Membrane*
Porcine peritoneal membranes are processed to obtain a predominantly Type I/III collagen membrane, tested for (b) (4).
- *Final Product Assembly*
Upon final harvest the chondrocytes are tested for (b) (4), and seeded onto the porcine collagen membrane. (b) (4) the final MACI product is shipped to the clinical site when it meets the release criteria for safety and quality.

The stability data for MACI support a dating period of 6 days under the labeled storage conditions of storage at room temperature.

Control Strategy

Safety and quality testing for MACI is comprised of in-process and lot release tests per requirements of 21 CFR 610, including sterility, mycoplasma, endotoxin, identity, and potency.

Product Lot Release and In-Process Testing

The safety and quality of MACI is ensured by the testing strategy shown in Table 1. It is noted that lot release is required prior to the full evaluation of product sterility due to the limited shelf-life.

Table 1. MACI In-Process and Lot Release Testing

STAGE OF MANUFACTURE	ASSAY	METHOD	SPECIFICATION	
ACI-Maix Membrane	(b) (4)	(b) (4)	(b) (4)	
	(b) (4)	(b) (4)	(b) (4)	
Chondrocyte Drug Substance (prior to (b) (4))	Cell Count	(b) (4)	(b) (4)	
	(b) (4)	(b) (4)	(b) (4)	
	Sterility	(b) (4)	(b) (4)	
Final Drug Product	Final product integrity	Visual Inspection	Intact sheet and no detectable particles	
	Sterility	(b) (4)	(b) (4)	
	Mycoplasma	(b) (4)	(b) (4)	
	Endotoxin	(b) (4)	(b) (4)	
	Identity	(b) (4)	(b) (4)	
	Potency	Cell Number	(b) (4)	(b) (4)
		(b) (4)	(b) (4)	(b) (4)
(b) (4)		(b) (4)	(b) (4)	

(b) (4)

[Redacted text block]

Product Testing Review Issues

- Following the Center for Devices and Radiological Health (CDRH) consult review of (b) (4), a number of issues were identified related to the characterization, release testing, and Design Controls related to the ACI-Maix device constituent. These were communicated to the Master File holder (Matricel GmbH, Herzogenrath Germany) during the review cycle and the responses received were found to be acceptable. An agreement was reached that the acceptance criteria for (b) (4) testing of ACI-Maix will be updated after additional experience with manufactured lots. The CMC team recommends that this be documented as a postmarketing commitment.
- The initial validation of the (b) (4) sterility testing method was found to be unacceptable. Although the proposed sterility method (b) (4) [REDACTED]. Since MACI is the subject of a new Biologics License Application, Vericel was informed that the FDA's current standard for the validation of an alternate sterility test method is required. At the mid-cycle meeting on 23 June, 2016, Vericel was requested to perform a re-validation study to assess the Limit of Detection (LOD) using (b) (4) [REDACTED]. The results of the re-validation study were submitted on 04 October, 2016 and were found to be acceptable.

Manufacturing Risks, Potential Safety Concerns and Management

The greatest risks associated with the manufacture of MACI are product mix-ups and contamination introduced during the aseptic manufacturing process.

- To prevent product mix-ups the chain of identity of all in-process and final product manufacturing steps is maintained through the use of a lot-specific unique identification number, patient initials, and date of birth. Product labels and shipping carton labels are all labeled accordingly. The Prescribing Information includes instructions to confirm that the patient's identity matches the patient's identifiers on the MACI labels. In addition, during manufacturing, (b) (4) [REDACTED].
- To prevent operator-related contamination, MACI is manufactured using aseptic procedures (b) (4) [REDACTED]. Cleaning and change-over procedures are in place to further minimize the risk of cross-contamination. Assessments were based on review of documents submitted to the BLA and the direct observation of manufacturing processes and quality systems during the pre-license inspection (PLI) of the Cambridge, MA facility (see below *Facilities review/inspection*).
- To minimize the risk of microbiological or viral contaminants from critical reagents or raw materials, including those of human and animal origin, sourcing

and testing information were reviewed. Critical reagents included the porcine collagen membrane, bovine calf serum, (b) (4). All necessary information to address potential microbiological and adventitious viral contaminants was found to be acceptable. However, despite controls on sourcing of bovine materials to minimize the risk of the presence of the infectious agent of bovine spongiform encephalopathy (BSE), the theoretical risk cannot be dismissed. A statement regarding this risk has been included in the Warnings and Precautions section of the Prescribing Information.

b) CBER Lot Release

An exemption has been granted from CBER Lot Release testing, including no requirement for submission of product samples to CBER. The basis for this decision is the fact that MACI is an autologous product, so each lot will treat a single patient. Failure of a single lot will have a minimal potential impact on public health.

c) Facilities Review/Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of MACI (Autologous chondrocytes seeded on a porcine derived collagen membrane) are listed in the table below. The activities performed and inspectional histories are noted in the table and are further described in the paragraphs that follow.

Manufacturing Facilities Table for MACI

Name/Address	FEI Number	DUNS Number	Inspection/Waiver	Results/Justification
Drug Substance and Drug Product Manufacturing				
<i>Manufacturing of API (autologous cultured chondrocytes)</i> <i>Manufacturing of final product MACI</i> <i>Drug product release testing, product labeling.</i> Vericel Corporation 64 Sidney St Cambridge, MA 02139 USA	3002836339	079745570	Pre-license Inspection	CBER/ May 9 – 13, 2016 VAI
<i>ACI-Maix Membrane component manufacturing.</i>	3007113424	344166512	Not applicable	ACI- Maix membrane is a device

Matricel GmbH Kaiserstrasse 100 Harzogenrath, Germany 52134				component, not a finished device thus falls under Vericel's design controls and purchasing controls.
--	--	--	--	--

CBER conducted the pre-license inspection from May 9-13, 2016. The inspection was classified as VAI and all inspectional observations were satisfactorily resolved.

The ACI-Maix Membrane component of the MACI drug product is manufactured and supplied by Matricel GmbH, Germany. The ACI-Maix membrane is composed of processed porcine (b) (4). The membrane is a CE-marked Class III device in Europe and conforms to the European Medical Device Directive. ACI-Maix membranes are accepted by Vericel based on the Matricel Certificate of Analysis in addition to in-house testing.

Container Closure System

The drug product is filled into a clear polystyrene sterile container with a green polycarbonate cover that is sealed using an O-ring and helical lock closure. The drug product is held in place by a sterile green polycarbonate 5-point x-ring. (b) (4) fills the container and maintains the drug product in a suitable environment during transport. The dish, lid, and x-ring are custom products designed for Vericel with specifications developed by Vericel. Vericel conducted container closure integrity testing employing the (b) (4) test method; all acceptance criteria were met.

d) Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31 (c). The FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology / Toxicology

Implantation of ACI-Maix porcine membrane seeded with homologous (animal-derived) cultured chondrocytes and secured with a commercially available fibrin sealant resulted in improved repair of critical-sized defects in the knee/stifle of rabbits and horses, compared to implanted membrane alone or empty defect. There were no significant local or systemic safety signals identified in the animals. Mild inflammation was observed in the knees of both species, which resolved over time. The ACI-Maix membrane was still

present in both species at 6 months post-implant and microscopic fibers from the membrane were noted out to 53 weeks in the horses.

In the 53-week horse study, any observed lameness was mild in nature and occurred early (12 weeks) in approximately 50% of all animals in each group, with full gait recovery by 53 weeks in all animals. A trend towards improved cartilage repair for the defects implanted with chondrocyte-seeded ACI-Maix compared to the ACI-Maix-implanted defects and the empty defects was observed at 12 and 53 weeks. Improved biomechanical testing outcomes were observed in some of the defects implanted with chondrocyte-seeded ACI-Maix compared to defects implanted with ACI-Maix membrane alone or empty defects. However, the biomechanical properties of the cartilage defects implanted with chondrocyte-seeded ACI-Maix were not identical to native cartilage. Studies to evaluate the carcinogenicity, developmental / reproductive toxicity, or impairment of fertility potential of MACI were not performed. However, biocompatibility testing of the ACI-Maix porcine membrane showed that the collagen membrane was not toxic or incompatible with biological tissue. In addition, the expansion process for chondrocytes did not induce changes to the cellular karyotype.

5. Clinical Pharmacology

Drug Interactions

There have been no studies of drug interactions with MACI.

Mechanism of Action

The mechanism(s) by which implantation of MACI results in repair of knee cartilage is unknown.

6. Clinical / Statistical

a) Clinical Program

One clinical trial, referred to as the SUMMIT Study (MACI0020), and an extension study (MACI00809), referred to as the SUMMIT Extension Study, were completed for MACI prior to submission of the BLA. These studies evaluated the safety and effectiveness of MACI for the treatment of symptomatic articular cartilage defects of the femoral condyle including the trochlea.

The data supporting effectiveness claims were derived from the SUMMIT Study (72 subjects treated with MACI, 72 subjects treated with microfracture as control), which evaluated the effectiveness of MACI compared to microfracture over a two-year period. The SUMMIT Study was conducted at 16 sites across 7 countries in the European Union (EU) (Netherlands, France, Czech Republic, Norway, Poland, Sweden, and United Kingdom) from July, 2008 to March, 2012. Whereas the designs of both the SUMMIT Study and its extension study were in accordance with FDA and European Guidance, neither study was planned or conducted with FDA input.

The SUMMIT Extension study provides additional information on the safety and efficacy of MACI over a 3-year period following completion of the 2-year trial.

SUMMIT Study (n=144 for safety and efficacy analysis)

Design

SUMMIT was a 2-year, prospective, Phase 3, multicenter, randomized (1:1), open-label, parallel-group clinical trial designed to demonstrate the efficacy of MACI to reduce pain and improve function compared with arthroscopic microfracture in the treatment of subjects, ages 18 to 55 years, with at least 1 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 co-primary efficacy endpoints were changes from Baseline to Week 104 in the subject's Knee Injury and Osteoarthritis Outcome Score (KOOS) Pain and Function (Sports and Recreational Activities [SRA]) scores. Safety and secondary and tertiary efficacy variables were also evaluated through Week 104. The SUMMIT design, including choice of microfracture as comparator, and designation of specific pain and function outcomes measurements, was in keeping with FDA Guidance.

Results

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 efficacy). The demographic characteristics of subjects in the SUMMIT study were similar in both treatment groups. The majority of subjects were male (62% MACI, 67% microfracture), and the mean age was 35 (MACI) and 33 (microfracture) years.

At Week 104, pain and function scores (KOOS Pain and Function [SRA]) had improved substantially from baseline in both treatment groups, but the improvement was greater in the MACI group compared to that in the microfracture group. The between-group difference in the change from baseline to Week 104 for KOOS Pain scores (MANCOVA model) was 11.8 favoring MACI ($p < 0.001$). The between-group difference in least squares mean values for the change from baseline to Week 104 for KOOS Function (SRA) scores (MANCOVA model) was 11.4 favoring MACI ($p < 0.001$), in the intent-to-treat population. Outcomes for Pain and Function are shown in table 2 below:

Table 2: Changes from Baseline to Week 104 in KOOS Pain and KOOS Function scores

	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	70.8 (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	46.0		32.4	34.6
Difference * [MACI – Microfracture]	Difference in Pain Score: 11.8 Difference in Function Score: 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.

Secondary endpoints were listed in order “of importance” by the study sponsor and analyzed using a closed hierarchical testing procedure. The order of importance, listed below, with results for each analysis, was chosen by the sponsor without input from FDA:

- Histological evaluation at Week 104
 - 116 subjects (60 in MACI group and 56 in microfracture group) underwent a second-look arthroscopy and biopsy at Week 104
 - Result: The mean ICRS II Overall Assessment score was comparable in the 2 groups with no statistically significant difference between the groups ($p = 0.717$).
- MRI assessments of structural repair parameters at Weeks 52 and 104
 - 134 subjects (69 in MACI group and 65 in microfracture group) were evaluated at Baseline, Week 52, and Week 139 (70 subjects in MACI group and 69 subjects in microfracture group) at Week 104.
 - Result: Improvement in defect fill from baseline at both the 52-week and 104-week timepoints showed no statistically significant difference between the groups ($p = 0.717$ for the comparison at Week 52 and $p = 0.920$ for the comparison at Week 104).
- Response rate based on KOOS Pain and Function (SRA) scores at Week 104, using a pre-defined criterion of at least a 10-point improvement from Baseline in both Pain and Function (SRA), which is considered clinically meaningful by the developers of the KOOS rating scales and by the general orthopedic community
 - Result: The percentage of subjects who responded to treatment at Week 104 (had at least a 10-point improvement from Baseline in both Pain and Function [SRA]) was significantly greater ($p = 0.016$) for subjects in the MACI group compared to those in the microfracture group.
- Treatment failure requiring re-treatment Week 104

- Only 5 subjects (4 subjects in microfracture group and 1 subject in MACI group) were referred to the Independent Treatment Failure Evaluation Committee.
- Two were considered to be treatment failures by the Committee (both in the Microfracture group).
- There was no statistical testing of treatment failure rates due to the small numbers of subjects.
- Change from Baseline at Week 104 in KOOS other Symptoms, KOOS Knee-Related Quality of Life [QOL] and KOOS Activities of Daily Living [ADL]
 - Other Symptoms changes were significant ($p < 0.001$)
 - QOL changes were not significant ($p = 0.074$)
 - ADL changes were significant ($p = 0.002$)

However, as the first two secondary endpoints (histological evaluation and MRI assessment) failed to show statistical significance, the p-values for KOOS Pain and Function response rate, and the other KOOS subscales cannot be used to describe the outcomes and the results should be considered exploratory. Nonetheless, a comparison of response rates, in which each subject is evaluated for their response to intervention in both pain and function, is meaningful to providers and patients alike and should be conveyed in the product label, without presenting p-values or making mention of statistical significance. Furthermore, unlike the histology and imaging data, the responder analysis is viewed as a sensitivity analysis of the primary endpoint data, instead of a completely different and independent endpoint.

SUMMIT Extension Study (n=128 for efficacy and safety analysis)

Design

The SUMMIT Extension study was a three-year, long-term follow-up study, in which all subjects who completed the two-year SUMMIT trial were eligible to participate. Of the 144 original subjects, 137 subjects completed SUMMIT and were eligible to participate in the three-year extension study. Eight (5 MACI and 3 microfracture) subjects did not enroll because their two study sites elected not to participate. The other 8 did not enroll for other reasons. Thus 128 subjects entered the extension study. These subjects represented 89% of the initial SUMMIT trial population.

Results

Of the 128 subjects who participated in the SUMMIT Extension study, 65 subjects (65/65) in the MACI group and 59 subjects (59/63) in the microfracture group completed the long-term follow-up study (total retention = 97%). The mean Year 2 scores in KOOS pain and KOOS function remained fairly stable for an additional three years in both treatment groups (Figures 1 and 2). However, Vericel did not provide a formal hypothesis for the extension study. No formal statistical analysis of these outcomes was performed. Improvements in KOOS Pain and KOOS Function (SRA) Scores are shown in Figures 3 and 4 below, respectively.

Figure 1: Improvement of KOOS Pain Scores from Baseline over 5 Years +/- SE

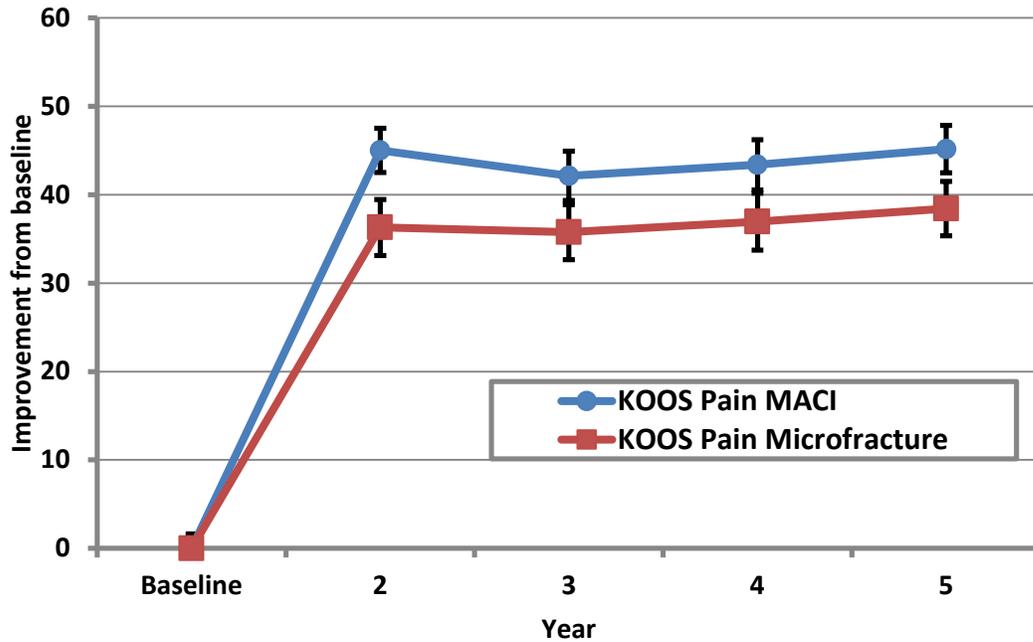
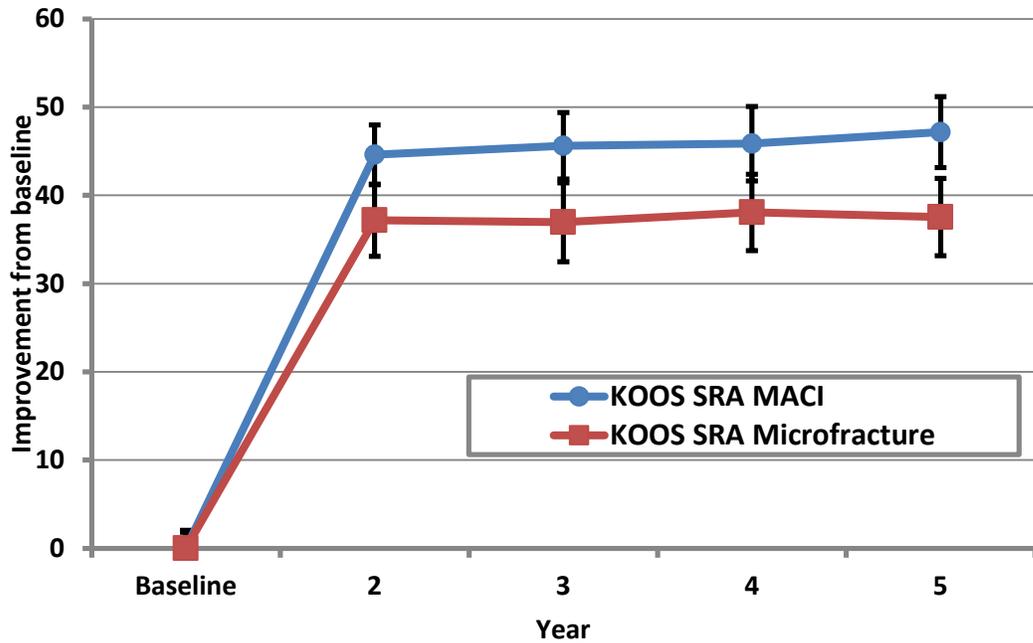
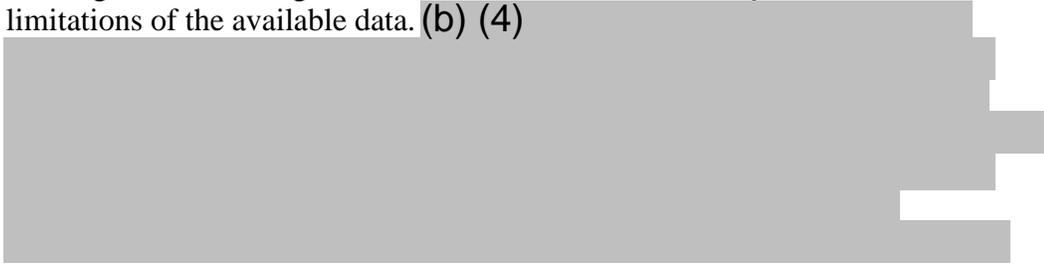


Figure 2: Improvement of KOOS SRA Scores from Baseline over 5 Years +/- SE



Effectiveness Review Issues

- The SUMMIT study population was 100% white, healthy, and relatively young (mean age was 35 years). Outcomes may not apply to an older group of subjects. In addition, the efficacy of MACI has not been evaluated in children and has not been evaluated in subjects over age 55 years. These issues have been addressed by revising the Prescribing Information to inform health care providers of the limitations of the available data. (b) (4)



See Section 6.b. *Pediatrics* regarding a required postmarketing study in adolescents.

Bioresearch Monitoring

Three European clinical investigator study sites under the Phase 3 study protocol MACI00206 (SUMMIT Study) were identified for Bioresearch Monitoring (BIMO) inspections. The sites were selected based upon number of study subjects enrolled, prior FDA inspection history, and the numbers and types of protocol deviations. The inspections were conducted in accordance with FDA’s Compliance Program 7348.811, Inspection Program for Clinical Investigators. Information submitted in the BLA was compared to source documents at each inspected site. The inspection assignment included specific questions concerning the clinical study.

Table 3. BIMO Results from the Three Clinical Investigator Inspections

Study Site	Site #	Location	FDA Form 483 Issued	Inspection Final Classification
Polyclinique Saint-Roch	5	Montpellier, France	No	VAI
University Medical Centre Utrecht	11	Utrecht, Netherlands	No	NAI
Wojewódzki Szpital	15	Piekary Śląskie, Poland	No	NAI

NAI: No Action Indicated VAI = Voluntary Action Indicated

The above BIMO inspections did not reveal substantive problems that impact the overall results of the data reviewed.

Efficacy Conclusion

The SUMMIT trial was adequate and well controlled. Based on the results of the SUMMIT and SUMMIT Extension studies, the review team concludes that the BLA contains substantial evidence of the effectiveness of MACI for the proposed indication.

b) Pediatrics

As MACI is unlikely to be used in children under the age of 10 years, Vericel submitted a request for a partial pediatric waiver for children less than 10 years of age. Vericel also submitted a request for a deferral to conduct a postmarketing study to evaluate the safety and efficacy of MACI in patients aged 10 to 17 years. The requests for a partial pediatric waiver and a deferral of a postmarketing study were reviewed by the FDA Pediatric Review Committee (PeRC) on October 12, 2016. The PeRC recommended a partial waiver in patients ages birth through 9 years because knee cartilage defects are rare or do not exist in children in this age group. The PeRC recommended a deferral of a postmarketing study in patients ages 10 to 17 years because the product is ready for approval in adults. The review team agrees with the PeRC recommendations.

Vericel submitted a protocol synopsis for the postmarketing pediatric study and estimates that enrollment of eligible patients will be a challenge. Over the past 10 years, approximately 96 pediatric patients were treated annually with Carticel in the US at a total of approximately 40 hospitals. If the proposed study includes 10 top-treating hospitals that treat a total of 20 patients/year, and approximately half of those patients were eligible and interested in the study, it will take approximately 5 years to recruit 45 patients for the study and 7 years total from first patient enrolled to last patient completed. Vericel proposed the following timeline for the completion of the clinical pediatric study: Protocol submission, by June 30, 2017; study initiation, by June 30, 2018; study completion by June 30, 2025; and submission of the final report by December 31, 2025.

7. Safety

Safety data are derived from the SUMMIT and SUMMIT Extension studies (b) (4)



The overall incidence of treatment-emergent adverse events (TEAEs) and SAEs was lower in the MACI group (76.4%) relative to the microfracture group (83.3%) for all categories with the exception of discontinuations from study due to TEAEs (1 patient in each treatment group discontinued due to AEs). No subjects died in the study.

In both treatment groups, most of the TEAEs were mild or moderate and the proportion of subjects with at least 1 TEAE of severe intensity was 9.7% in the MACI group and 13.9% in the microfracture group. The only severe TEAE reported in >5% of subjects in any treatment group was arthralgia (2 patients [2.8%] in the MACI group and 5 subjects [6.9%] in the microfracture group). Treatment-emergent AEs with moderate intensity reported in >5% of subjects in any treatment group were cartilage injury (1 patient [1.4%] in the MACI group and 6 subjects [8.3%] in the microfracture group) and arthralgia (12 subjects [16.7%] in the MACI group and 16 subjects [22.2%] in the microfracture group).

Nonfatal treatment-emergent SAEs (TESAEs), regardless of severity and relationship to study treatments, were reported more frequently in the microfracture group (26.4%) than in the MACI group (15.3%). The difference in incidence was due mainly to more serious cases of treatment failure, cartilage injury, and arthralgia in the microfracture group compared with the MACI group. The proportion of subjects with at least 1 subsequent surgical procedure (SSP) was comparable for the 2 treatment groups (8.3% in the MACI group and 9.7% in the microfracture group).

In the SUMMIT Extension study, which included the same subject population, TESAEs were reported at a similar rate in the MACI and microfracture groups (24.6% MACI, 27.0% microfracture). Within the 3 years of the extension study, no TESAEs had incidence >5% in the MACI treatment group, whereas 3 TESAEs (cartilage injury, treatment failure, and arthralgia) had incidence >5% in the microfracture group.

In conclusion, the overall safety profile of MACI was at least as good as that of microfracture and possibly better.

(b) (4) [Redacted]

[Redacted]

[Redacted]

8. Advisory Committee Meeting

This marketing application was not taken to an Advisory Committee meeting because the review of the application did not reveal new safety concerns, questions about the benefit / risk or postmarketing requirements that would warrant public discussion or outside expertise. The clinical study design was acceptable and in keeping with FDA guidance.

9. Other Relevant Regulatory Issues

Not applicable.

10. Labeling

The proposed Prescribing Information (PI) has been reviewed and revised by the BLA review team. The most significant changes made by the review team are summarized below:

- The proper name was determined to be “autologous cultured chondrocytes on porcine collagen membrane” by FDA.
- The Indication statement has been revised to “MACI[®] is an autologous cellularized scaffold product indicated for the repair of symptomatic, full-thickness cartilage defects (single or multiple defects) of the knee with or without bone involvement.” (b) (4).
- Sections on Contraindications, Warnings and Precautions, and Adverse Reactions were modified according to FDA labeling guidelines.
- The Clinical Studies section was revised to include efficacy results from the responder analysis and the SUMMIT Extension study.
- The Clinical Pharmacology section was revised to state that the mechanism by which MACI promotes cartilage repair is unknown.

The review team concludes that the proposed PI, following our modifications, provides adequate directions for the safe and effective use of MACI in the indicated population.

CBER’s Advertising and Promotional Labeling Branch (APLB) found the proprietary name, MACI to be acceptable. In addition to the proprietary name, APLB reviewed the PI and package and container labels from a promotional and comprehension perspective and found them acceptable.

11. Recommendations and Risk/Benefit Assessment

a) Recommended Regulatory Action

The FDA review team recommends approval of MACI with the revised indication statement, “MACI[®] is an autologous cellularized scaffold product indicated for the repair

of symptomatic, full-thickness cartilage defects (single or multiple defects) of the knee with or without bone involvement in adults.”

b) Risk / Benefit Assessment

The overall benefit / risk profile associated with MACI for implantation into cartilage defects in promoting cartilage repair is acceptable in adults. The quality, efficacy, and safety of MACI have been reviewed and have been determined to be acceptable for use as indicated in the label.

c) Recommendation for Postmarketing Risk Management Activities

No safety issues have been identified that would warrant a Risk Evaluation and Mitigation Strategy (REMS) for MACI. At this time, routine pharmacovigilance is adequate. Additionally, Vericel will have a voluntary communication plan, controlled distribution system, and provide healthcare provider training (including MACI-specific surgeon training), which the FDA considers adequate. (b) (4)

d) Recommendation for Postmarketing Activities

Routine pharmacovigilance includes adverse event reporting in accordance with 21 CFR 600.80: 15-day expedited reports for serious unlabeled adverse events and quarterly periodic safety reports for 3 years (annual thereafter). Distribution reports will be submitted as per 21 CFR 600.81.

PMR - Pediatric Clinical Study

The review team recommends a Postmarketing Requirement (PMR) under the Pediatric Research Equity Act (PREA) for Vericel Corporation to conduct a postmarketing study to evaluate the safety and effectiveness of MACI in pediatric patients 10 to 17 years of age. Vericel has agreed to conduct this postmarketing study and has agreed to submit the final study protocol by June 2017; to complete the study by June 2025; and submit the final report by December 2025.

PMC - CMC

The review team recommends the following three Postmarketing Commitments (PMCs) for MACI. In a letter received December 8, 2016 Vericel Corp. agreed to the following:

1. To perform the following to implement (b) (4) testing as an ACI-Maix collagen membrane quality inspection item:
 - a. Develop a quantitative method and provide appropriate validation of the method by June 30, 2017;

- b. Provide an initial release specification by June 30, 2017 based on assessment of statistical tolerance intervals constructed from results of at least (b) (4) samples of (b) (4) lots of ACI-Maix collagen membrane within expiry at the time of testing;
 - c. Provide in Annual Reports to the BLA, summary data for (b) (4) quantitation for all lots of ACI-Maix collagen membrane manufactured after BLA approval, until the acceptance criteria for (b) (4) content have been established, based upon the evaluation of a total of (b) (4) released lots;
 - d. Provide updated acceptance criteria for (b) (4) testing after analysis of a total of (b) (4) released manufactured lots;
 - e. Add (b) (4) testing to future validation studies for the ACI-Maix collagen membrane.
2. To perform the following to complete the implementation of (b) (4) testing as an ACI-Maix collagen membrane quality inspection item:
 - a. Develop a quantitative method and provide appropriate validation of the method by March 31, 2017;
 - b. Provide an initial release specification for (b) (4) by March 31, 2017 based on assessment of statistical tolerance intervals constructed from results of at least (b) (4) samples from (b) (4) lots of ACI-Maix collagen membrane within expiry at the time of testing;
 - c. Provide in Annual Reports to the BLA, summary data for (b) (4) testing on all lots of ACI-Maix collagen membrane manufactured after BLA approval, until the (b) (4) test acceptance criteria have been updated upon evaluation of an additional (b) (4) released lots after BLA approval;
 - d. Provide updated acceptance criteria for (b) (4) testing after analysis of an additional (b) (4) released lots after BLA approval;
 - e. Add (b) (4) testing to future validation studies for the ACI-Maix collagen membrane.
3. To complete updates to all standard operating procedure (SOP) documentation requiring revision due to obsoleted procedures and to implement the revised SOPs by February 28, 2017.