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T846.01: CBER BLA Clinical Review Memorandum

Effective date: Sept 1, 2016

POC: Jeff Roberts

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BLA Clinical Review Memorandum

Application Type	Original Application
STN	125603/000
CBER Received Date	01/04/2016
PDUFA Goal Date	01/03/2017
Division / Office	DCEPT/OTAT
Priority Review (Yes/No)	No
Reviewer Name(s)	Michael Yao, MD, Clinical Reviewer
Review Completion Date / Stamped Date	11-07-2016
Supervisory Concurrence	Bruce Schneider, MD, Team Leader Ilan Irony, MD, Branch Chief
Applicant	Vericel Corporation
Established Name	Matrix applied characterized autologous cultured chondrocytes
(Proposed) Trade Name	MACI™
Pharmacologic Class	Biologic
Formulation(s), including Adjuvants, etc.	Surgical Implant
Dosage Form(s) and Route(s) of Administration	Each MACI implant contains approximately 500,000 to 1,000,000 autologous cells per cm ² . The amount of MACI administered is dependent upon the size (surface area in cm ²) of the cartilage defect. Multiple implants may be used. The implant is trimmed by the surgeon to the size and shape of the defect, to ensure the damaged area is completely covered. Multiple defects may be treated. The implant is performed using sterile surgical techniques and requires both the preparation of the defect bed and the application of fibrin sealant to the base and rim of the defect in order to secure the implant.
Dosing Regimen	One time implantation
Indication(s) and Intended Population(s)	MACI™ is indicated for the repair of symptomatic, full-thickness cartilage defects (Single or multiple defects) of the knee, with or without bone involvement
Orphan Designated (Yes/No)	No

Table of Contents

Glossary5

1. Executive Summary6

 1.1 Demographic Information: Subgroup Demographics and Analysis Summary..... 9

2. Clinical and Regulatory Background..... 10

 2.1 Disease or Health-Related Condition(s) Studied 10

 2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)..... 11

 2.3 Safety and Efficacy of Pharmacologically Related Products 13

 2.4 Previous Human Experience with the Product (Including Foreign Experience) 13

 2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission .. 14

 2.6 Other Relevant Background Information..... 16

3. Submission Quality and Good Clinical Practices 16

 3.1 Submission Quality and Completeness 16

 3.2 Compliance with Good Clinical Practice and Submission Integrity 16

 3.3 Financial Disclosures 17

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines 18

 4.1 Chemistry, Manufacturing, and Controls 18

 4.2 Assay Validation..... 18

 4.3 Nonclinical Pharmacology/Toxicology 18

 4.4 Clinical Pharmacology..... 18

 4.4.1 Mechanism of Action 18

 4.4.2 Human Pharmacodynamics (PD)..... 18

 4.4.3 Human Pharmacokinetics (PK) 18

 4.5 Statistical..... 18

 4.6 Pharmacovigilance..... 18

5. Sources of Clinical Data and Other Information Considered in the Review..... 19

 5.1 Review Strategy 19

 5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review..... 22

 5.3 Table of Studies/Clinical Trials..... 22

 5.4 Consultations 22

 5.4.1 Advisory Committee Meeting (if applicable) 22

 5.4.2 External Consults/Collaborations 22

 5.5 Literature reviewed (if applicable) 23

6. Discussion of Individual Studies/Clinical Trials23

 6.1 Trial #1 23

 6.1.1 Objectives (Primary, Secondary, etc.) 24

 6.1.2 Design Overview 24

 6.1.3 Population..... 26

 6.1.4 Study Treatments or Agents Mandated by the Protocol 28

 6.1.5 Directions for Use 29

 6.1.6 Sites and Centers 30

 6.1.7 Surveillance/Monitoring 31

 6.1.8 Endpoints and Criteria for Study Success..... 34

 6.1.9 Statistical Considerations & Statistical Analysis Plan 38

 6.1.10 Study Population and Disposition..... 40

 6.1.11 Efficacy Analyses 45

 6.1.12 Safety Analyses 60

6.1.13 Study Summary and Conclusions	67
6.2 Trial #2	68
6.2.1 Objectives	68
6.2.2 Design Overview	69
6.2.3 Population	69
6.2.4 Study Treatments or Agents Mandated by the Protocol	69
6.2.5 Directions for Use	69
6.2.6 Sites and Centers	70
6.2.7 Surveillance/Monitoring	70
6.2.8 Endpoints and Criteria for Study Success.....	72
6.2.9 Statistical Considerations & Statistical Analysis Plan	73
6.2.10 Study Population and Disposition.....	74
6.2.11 Efficacy Analyses	75
6.2.12 Safety Analyses.....	82
7. Integrated Overview of Efficacy	90
7.1 Indication #1	90
7.1.1 Methods of Integration.....	90
7.1.2 Demographics and Baseline Characteristics.....	90
7.1.3 Subject Disposition	90
7.1.4 Analysis of Primary Endpoint(s)	90
7.1.5 Analysis of Secondary Endpoint(s)	90
7.1.6 Other Endpoints.....	90
7.1.7 Subpopulations.....	90
7.1.8 Persistence of Efficacy	90
7.1.9 Product-Product Interactions.....	90
7.1.10 Additional Efficacy Issues/Analyses	90
7.1.11 Efficacy Conclusions	91
8. Integrated Overview of Safety	91
8.1 Safety Assessment Methods	91
8.2 Safety Database.....	91
8.2.1 Studies/Clinical Trials Used to Evaluate Safety	91
8.2.2 Overall Exposure, Demographics of Pooled Safety Populations	91
8.2.3 Categorization of Adverse Events	91
8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials.....	91
8.4 Safety Results	91
8.4.1 Deaths	91
8.4.2 Nonfatal Serious Adverse Events.....	91
8.4.3 Study Dropouts/Discontinuations	91
8.4.4 Common Adverse Events.....	92
8.4.5 Clinical Test Results	92
8.4.6 Systemic Adverse Events.....	92
8.4.7 Local Reactogenicity	92
8.4.8 Adverse Events of Special Interest	92
8.5 Additional Safety Evaluations	92
8.5.1 Dose Dependency for Adverse Events	92
8.5.2 Time Dependency for Adverse Events	92
8.5.3 Product-Demographic Interactions.....	92
8.5.4 Product-Disease Interactions	92
8.5.5 Product-Product Interactions.....	92
8.5.6 Human Carcinogenicity	92
8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound	92
8.5.8 Immunogenicity (Safety).....	92

8.6 Safety Conclusions	93
9. Additional Clinical Issues.....	93
9.1 Special Populations.....	93
9.1.1 Human Reproduction and Pregnancy Data.....	93
9.1.2 Use During Lactation	93
9.1.3 Pediatric Use and Pediatric Research Equity Act (PREA) Considerations.....	93
9.1.4 Immunocompromised Patients	94
9.1.5 Geriatric Use.....	94
9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered	94
10. Conclusions.....	94
11. Risk-Benefit Considerations and Recommendations	96
11.1 Risk-Benefit Considerations.....	96
11.2 Risk-Benefit Summary and Assessment.....	99
11.3 Discussion of Regulatory Options.....	99
11.4 Recommendations on Regulatory Actions.....	99
11.5 Labeling Review and Recommendations	99
11.6 Recommendations on Post-marketing Actions.....	100
Appendix 1: Summary of Consultation with Dr. Phillip Posner (Patient Representative, SGE)	101
Appendix 2: Summary of Consultation to Dr. Neil, Barkin (Orthopedic Surgeon, CDRH)	104

Glossary

ACI	Autologous chondrocyte implantation
ADL	Activities of daily living
AE	Adverse event
BLA	Biologics License Application
BMI	Body mass index
CFR	Code of Federal Regulation
CRF	Case report form
CRR	Cartilage Repair Registry
CSR	Clinical study report
EMA	European Medicines Agency
EU	European Union
FAS	Full analysis set
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
ICRS	International Cartilage Repair Society
IKDC	International Knee Documentation Committee
IND	Investigational New Drug
ISE	Integrated Summary of Efficacy
ISO	International Organization for Standardization
ISS	Integrated Summary of Safety
ITT	Intention-to-treat
KOOS	Knee injury and osteoarthritis outcome score
LFC	Lateral femoral condyle
LOCF	Last observation carried forward
LS	Least squares
MACI	Matrix applied characterized autologous chondrocytes
MANOVA	Multivariate analysis of variance
MedDRA	Medical Dictionary for Regulatory Activities
MFC	Medial femoral condyle
MRI	Magnetic resonance imaging
OAT	Osteochondral autograft transplantation
OCTGT	Office of Cellular, Tissue and Gene Therapies
PBRER	Periodic Benefit-Risk Evaluation Report
PK	Pharmacokinetic
PRO	Patient-reported outcome
PT	Preferred term
PYE	Patient years of exposure
QOL	Quality of life
RBS	Registry-based study
REMS	Risk Evaluation and Mitigation Strategies
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SF-12	12-Item Short-Form Health Survey
SOC	System Organ Class
SRA	Sports and recreational activities
SSP	Subsequent surgical procedures
STAR	Study of Treatment of Articular Repair
TEAE	Treatment-emergent adverse event

1. Executive Summary

MACI consists of characterized autologous chondrocytes seeded onto 14.5 cm² of Type I/III purified, resorbable, porcine-derived collagen membrane, at a density of 500,000 to 1,000,000 cells per cm². The amount of MACI administered is dependent upon the size (surface area in cm²) of the cartilage defect. The implant is trimmed by the surgeon to the size and shape of the defect, to ensure the damaged area is completely covered. MACI implantation requires a two-stage procedure: biopsy of tissue followed by application of MACI in a second procedure.

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

The MACI implant has been commercially available in several European member states and Australia in accordance with their national laws and regulations since 1998. MACI received European Union (EU) Marketing Authorization Approval from the European Commission on 27 June 2013.

On 04 January 2016, Vericel Corporation submitted a full BLA application (BLA 125603) supported by clinical data from the SUMMIT study (Protocol: MACI00206) with its 3-year long-term safety follow-up data from the SUMMIT Extension study (Protocol; MACI00809) (b) (4)

SUMMIT is a 2-year prospective, Phase 3, multicenter, randomized, open-label, parallel-group clinical trial designed to evaluate efficacy and safety of MACI compared with arthroscopic microfracture in the treatment of subjects with at least one symptomatic Outerbridge Grade III or IV focal cartilage defect of the medial femoral condyle, lateral femoral condyle, and/or the trochlea (defect size ≥ 3.0 cm², irrespective of location). The SUMMIT study was conducted at 16 sites across 7 countries in the EU (Netherlands, France, Czech Republic, Norway, Poland, Sweden, and United Kingdom). The trial enrolled 144 subjects, 72 in each treatment group), ages 18 to 55 years.

The co-primary endpoints of SUMMIT were change in subjects' KOOS Pain and KOOS Sports and Recreational Activities (SRA) scores from baseline to Week 104. The treatment comparison used a superiority hypothesis (MACI vs microfracture).

The overall study design, including choice of co-primary endpoints, use of microfracture as comparator, and a superiority hypothesis, was in keeping with published FDA guidance (Guidance for Industry: Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage – December 2011), although the study itself was not conducted under FDA regulation and without input from FDA.

In this 2-year SUMMIT study, the treatment-group differences (MACI vs microfracture) in changes of subjects' KOOS Pain and KOOS Function (SRA) scores from baseline to Week 104 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. The co-primary efficacy endpoints were met in the SUMMIT study.

Secondary endpoints were listed in hierarchical order for the purpose of statistical analyses. The first two secondary endpoints – the mean of ICRS II Overall Assessment histology score at Week 104 from baseline and MRI evaluation of defect fill --- showed essentially no difference between the treatment groups. As a consequence, other secondary endpoints are viewed as exploratory.

Regarding the safety evaluation, the proportion of subjects with at least 1 TEAE was 76.4% in the MACI group and 83.3% in the microfracture group. All TEAEs were expected in this study population.

Treatment-emergent SAEs were reported more frequently in the microfracture group (26.4%) than in the MACI group (15.3%). The difference in incidence rates was mainly due 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 one subsequent surgical procedure (SSP) was comparable for the two treatment groups (8.3% in the MACI group and 9.7% in the microfracture group). No deaths occurred in this study.

The SUMMIT Extension was a 3-year, open-label, multicenter, elective enrollment study for subjects who were randomized and treated in SUMMIT. The objective of this study was to examine the 5-year efficacy and safety of MACI implant, as well as safety and efficacy of microfracture during the same period. The efficacy endpoints were the same as in the SUMMIT study. Safety and efficacy assessments were performed at scheduled visits 3, 4, and 5 years following treatment in SUMMIT. The SUMMIT Extension study enrolled 128 subjects from the SUMMIT study, 89% of the original trial population.

The Extension study showed that the mean 2-year primary efficacy outcomes remained essentially stable in both treatment groups over the following 3 years.

In the Extension Study, the proportion of subjects with at least 1 TEAE was 75.4% in the MACI group and 74.6% in the microfracture group over 3 years follow-up. The overall frequency of subjects with TEAEs and SAEs was comparable in both groups for all categories. No subjects in either treatment group discontinued the extension study prematurely due to a TEAE, and no patients died in the study.

Over the five years of both studies, there were 9 subjects with 18 subsequent surgical procedures (SSPs) in the MACI group compared to 10 subjects with 17 SSPs in microfracture group in SUMMIT/SUMMIT Extension studies. One subject in MACI group underwent microfracture procedure and 1 subject in microfracture group had a total knee replacement procedure.

(b) (4)



In conclusion, the co-primary efficacy endpoints were met in the 2-year SUMMIT study. All TEAEs and TESAEs were as expected in the SUMMIT study. There are no additional outstanding safety concerns identified in the safety database of the SUMMIT study.

The clinical data from the SUMMIT extension study indicate that KOOS pain and KOOS SRA remain relatively stable from Year 2 through Year 5 in the MACI group as well as in subjects treated with microfracture.

During this BLA review, a patient representative and an orthopedic surgeon have been consulted. Please see Appendix 1 and 2 for details.

The applicant submitted an agreed pediatric study plan (PSP) on 11-17-2015. Based upon recommendations from FDA PeRC, OCTGT agrees with a partial waiver for pediatric patients aged less than ten years and deferral of studies in patients aged 10 to 17 years, who have knee cartilage defects due to (b) (4) and acute trauma, as a PREA-related postmarketing requirement.

The review team from APLB/DCM agrees with the proposed proprietary name, MACI.

All inspections have been completed and received a classification of No Action Indicated (NAI), as per the Bioresearch Monitoring Branch (BIMO).

In this BLA submission, the applicant has submitted clinical data from only one randomized controlled clinical study (SUMMIT study) with its extension study to support MACI marketing application in the US. According to FDA guidance (Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products), FDA generally requires at least two adequate and well-controlled clinical trials to provide substantial evidence of effectiveness for submission of a marketing application. In addition, the SUMMIT study was open-label, with patient-reported outcomes as the primary effectiveness endpoint. Finally, there are no "hard" outcomes (e.g., histology or MRI) from SUMMIT or other studies to support the effectiveness of MACI over microfracture. These issues factored into our decision regarding approvability of MACI. However, we believe that the applicant has carried out a study in accordance with current clinical trial standards and scientific/technical ability to determine clinical benefit. Additionally, the design of the SUMMIT trial was in accordance with FDA regulatory guidance. Accordingly, our review is based on the cogency of the SUMMIT trial outcomes. These studies are difficult to conduct --- in fact, to our knowledge, SUMMIT is the only adequate randomized clinical trial of a biological cartilage replacement product for this indication that has been conducted in accordance with FDA guidelines. Based on the inability to blind subjects in a MACI trial with a microfracture comparator (2 procedures vs 1), the same open-label design problems would persist in a second trial, although a positive result would increase the persuasiveness of SUMMIT to some degree. A trial of MACI for a related indication or for an enriched subgroup would also potentially add cogency to the results of SUMMIT. The difficulty of performing these trials should also be taken into account. As noted, SUMMIT is the only randomized prospective trial of cellular therapy for knee cartilage injury that is in accordance with FDA guidance in a field that has been actively investigated for decades. This issue is discussed in detail in the body of this review.

SUMMIT and its extension study were conducted at 16 sites across 7 countries in the EU (Netherlands, France, Czech Republic, Norway, Poland, Sweden, and United Kingdom). Although critical aspects of the study are relevant and applicable to the US population, the review team believes there are some limitations. For example: 100% subjects participating in SUMMIT were white.

In order to minimize expected and unexpected TEAEs and TESAEs of MACI and its implantation procedure, the applicant voluntarily provided a detailed surgical training plan for MACI implantation and a rehabilitation program for post-MACI implant surgery if this product is approved by the FDA.

Clinical Reviewer’s Recommendations on Regulatory Action:

Based upon review of safety and efficacy information in this BLA, we recommend that BLA 125603 be approved with a Post-marketing Requirement (PMR) to conduct a pediatric study of MACI in subjects aged 10 to 17 years, who have knee cartilage defects due to (b) (4) and acute trauma.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Demographics of the 144 subjects enrolled in the SUMMIT study are presented in the following table (Table 1).

Table 1. Demographic characteristics of the SUMMIT Study participants

	Statistic	MACI (N= 72)	Microfracture (N= 72)	Total (N=144)
Age (Years)				
	n	72	72	144
	Mean (SD)	34.8 (9.16)	32.9 (8.78)	33.8 (9.00)
	Median	35.0	34.0	34.5
	Min, Max	18, 54	18, 54	18, 54
Gender				
Female	n (%)	27 (37.5)	24 (33.3)	51 (35.4)
Male	n (%)	45 (62.5)	48 (66.7)	93 (64.6)
Race				
White	n (%)	72 (100.0)	72 (100.0)	144 (100.0)
Black or African American	n (%)	0	0	0
Asian	n (%)	0	0	0
American Indian or Alaskan Native	n (%)	0	0	0
Native Hawaiian or Other Pacific Islander	n (%)	0	0	0
Other	n (%)	0	0	0
Ethnicity				
Hispanic or Latino	n (%)	0	0	0
Not Hispanic or Latino	n (%)	72 (100.0)	72 (100.0)	144 (100.0)

Source: Table 14.1.2.1 of the MACI00206 Study Report Body – page 151/946.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Articular (hyaline) cartilage matrix is mostly made up of type II collagen and chondroitin sulfate. This type of cartilage exists in several anatomical sites, including ribs, larynx, trachea, and bronchi, but is prominent on the articular surface of bones. Hyaline cartilage is synthesized by chondrocytes and is present inside the cavity of synovial joints; the matrix is bathed in synovial fluid. Of particular importance here, the structure of hyaline cartilage allows the knee joint to withstand shearing forces and absorb shock and loads up to 20 times body weight; damage to articular cartilage is quite common and can result from either acute or repetitive trauma. Cartilage defects can appear at any age. Cartilage injuries of the knee affect approximately 900,000 Americans annually, resulting in more than 200,000 surgical procedures.

The specific nature of knee cartilage defects can be readily identified during arthroscopic procedures. Articular defects can also be visualized noninvasively with advanced techniques of Magnetic Resonance Imaging (MRI).^{1,2} One study of 31,516 knee arthroscopies found that 63% of patients had chondral injury.³ In a collection of more than 35,000 arthroscopies performed by 136 surgeons between 1991 and 1995 using a "modified" Outerbridge Scale that is similar to the ICRS 2000 scale, Curl et. al. found that 41% of the patients had cartilage with grade III lesions and 19% of the patients had grade IV lesions. Grade III lesions are defined as: 1) by MRI: partial thickness cartilage loss with focal ulceration 2) arthroscopically: partial thickness cartilage loss with fibrillation. Grade IV lesions are defined as: 1) by MRI: full thickness cartilage loss with underlying bone reactive changes; 2) arthroscopically: cartilage destruction with exposed subchondral bone. Hjelle et al. found results similar to Curl in a prospective series of 1000 and 993 patients, respectively.⁴

The existence of cartilage defects in the knee joint is an important clinical finding because full-thickness defects do not heal spontaneously, causing pain and symptoms such as swelling, catching, and loss of knee function. Acute lesions are often diagnosed incidentally at the time of knee arthroscopy and are not necessarily initially symptomatic. For chronic lesions, patients usually have complaints about pain, dysfunction, catching, locking, and swelling, which may contribute to joint malalignment. Left untreated, such lesions may progress to degenerative joint conditions.

Any part of a joint can be injured and a common injury to the knee is a localized loss of articular cartilage (chondral defect) sometimes combined with an injury to the underlying supporting bone (osteochondral defect). Chondral and osteochondral defects of the knee occur along a spectrum of disease and severity, depending on the size, number, depth, and location of the lesions. These lesions can cause disabling symptoms such as pain,

1 Curl WW, Krome J, Gordon ES, Rushing J, Paterson Smith B, Poehling GG. Cartilage Injuries: A Review of 31,516 Knee Arthroscopies; *Arthroscopy* 1997; 19(4): 456-460.

2 Potter HG, Linklater JM, Allen AA, Hannafin JA, Haas SB. Magnetic Resonance Imaging of Articular Cartilage in the Knee. *J Bone Joint Surg Trauma Am* 1998 Sep; 80(9): 1276-84.

3 Cole BJ, Frederick RW, Levy AS, Zaslav KR. Management of a 37 year-old man with recurrent knee pain. *J Clin Outcomes Manag.* 1999;6:46-57.

4 Hjelle K, Solheim E, Strand T, Muri R, Brittberg M. Articular cartilage defects in 1000 knee arthroscopies. *Arthroscopy* Sep 2002; 18(7): 730-4.

dysfunction, catching, locking, and swelling. If left untreated, chondral lesions may progress to debilitating joint pain, dysfunction, and osteoarthritis

(b) (4)



2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Restoring articular cartilage can relieve pain and allow better function. The goal of cartilage restoration procedures is to stimulate new hyaline cartilage growth.

Patients with symptoms due to knee cartilage defects can be treated symptomatically with anti-inflammatory/analgesic medications, together with physical therapy, but the benefits of such non-invasive treatments (in terms of improvement in pain and function) are limited, and the underlying disease usually worsens over time and may progress to osteoarthritis.

Several more specific approaches have been used in the management of symptomatic chondral and osteochondral knee defects. These include both non-reparative methods, such as debridement and knee joint lavage procedures as well as surgical reparative methods, such as microfracture, mosaicplasty and autologous chondrocyte implantation (ACI).

Surgical techniques designed to repair damaged cartilage can relieve pain and restore knee function. Most importantly, surgery can delay or prevent the onset of arthritis. Most candidates for articular cartilage restoration are young adults with a single injury, or lesion. Older patients, or those with many lesions in one joint, are less likely to benefit from available surgical approaches. The most common procedures for knee cartilage repair and/or restoration are:

- 1) Microfracture
- 2) Drilling
- 3) Abrasion Arthroplasty
- 4) Autologous Chondrocyte Implantation (ACI)
- 5) Osteochondral Autograft Transplantation
- 6) Osteochondral Allograft Transplantation

The microfracture procedure has been described in detail by Steadman.⁵ Microfracture is intended to stimulate the marrow to provide "an enriched environment for tissue regeneration." Microfracture begins with debridement of the cartilage defect down to the subchondral bone including the calcified layer of cartilage. The procedure is then taken a step further, whereby an awl is used to pierce the subchondral bone at regular

⁵ Steadman JR, Rodkey WG, Rodrigo JJ. Microfracture: Surgical technique and rehabilitation to treat chondral defects. Clin Orthop Relat Res 2001 Oct; 391 Suppl:S362-9.

anatomical intervals. The prepared lesion provides a pool that helps hold the marrow clot.

Microfracture results in the development of fibrocartilage at the site of the procedure. Fibrocartilage is a mixture of fibrous and cartilaginous tissue, the latter consisting of both type I and type II collagen. Fibrocartilage is tough and has some elasticity, but is not an adequate replacement for the smooth hyaline cartilage normally present in joint surfaces. Fibrocartilage is less durable, less resilient and less able to withstand shock and shearing forces, compared to native articular hyaline cartilage. Retrospective MRI analysis of 80 patients showed that microfracture led to bony overgrowth in nearly 50% of the patients reviewed.⁶ Mithoefer, reporting on the analysis of data obtained in a prospective registry, described bony overgrowth in 25% of patients. Slightly more than half of the defects demonstrated filling of more than 67%; there was also a gap of more than 2 mm in the native cartilage in 42% of the defects.⁷

Moreover, clinical improvement after microfracture is not consistently observed: about 25% of patients treated with microfracture reported no or minimal relief in pain and symptoms within the first 12-24 months of treatment⁸ and clinical improvement can wane after 24 months.⁹

Drilling, like microfracture, stimulates the production of a mixture of smooth hyaline cartilage and fibrous scar-like tissue. Multiple holes are made through the injured area in the subchondral bone with a surgical drill or wire. The subchondral bone is penetrated to create a healing response. Drilling can be done with an arthroscope. It is less precise than microfracture and the heat of the drill may cause injury to some of the tissues.

Abrasion arthroplasty is similar to drilling. Instead of drills or wires, high speed burrs are used to remove the damaged cartilage and reach the subchondral bone. Abrasion arthroplasty can be done with an arthroscope.

Autologous chondrocyte implantation (ACI) is a two-step procedure. First, healthy cartilage tissue is removed from a non-weight-bearing area of the bone. The chondrocytes from cartilage tissue are cultured and increase in number over a 3- to 5-week period. An open surgical procedure, or arthrotomy, is then done to implant the newly grown cells. First, the cartilage defect is prepared for debridement. A layer of periosteum is sewn over the area. This cover is sealed with fibrin glue. The newly grown cells are then injected into the defect under the periosteal cover. ACI is most useful for younger patients who have single defects larger than 2 cm in diameter. In the US, ACI is marketed as Carticel.

6 Brown WE, Potter HG, Marx RG, Wickiewicz 'IL, Warren RF. Magnetic resonance imaging appearance of cartilage repair in the knee. Clin Orthop Relat Res 2004 May; 422 214-23.

7 MithoeferX, Wtlliams ill RJ, Warren RK, Potter HG, Spock CR. Jones EC, Wickiewicz TI., Marx RG. The micro:fracture technique for the treatment of articular cartilage lesions in the knee. A prospective cohort study. J Bone Joint Surg Am 2005.; 87: 1911"1920

8 Knutsen G, Engebretsen L, Ludvigsen TC, Drogset JO, Grontvedt T, Solheim E, Strand T, Roberts S, Isaksen V, Johansen O. Autologous chondrocyte implantation compared with microfracture in the knee. A randomized trial. J Bone Joint Surg Am. 2004 Mar;86-A(3):455-64.

9 Kreuz PC, Steinwachs MR. Erggelet C, Krause SJ, Konrad G, Uhl M, Siidkamp N. Results after microfracture of full-thickness chondral defects in different compartments in the knee. Osteoarthritis and Cartilage (2006) 14, 1119" 1125.

The surgical procedure was described by Petersen, showing functional improvement at two years and further improvement at long term follow-up between five and 11 years following implantation for 44 patients with osteochondritis dissecans or with defects on the femoral condyle alone or with ACL reconstruction.¹⁰ The modified Cincinnati Knee Score was significantly higher both at two years and at long term follow-up when compared to the baseline score. Of note, there were 10 treatment failures (16%) of the 61 patients enrolled.

Knutsen et.al. described a randomized trial of 80 subjects that compared ACI to microfracture.⁸ Both treatment groups had significantly higher Lysholm scores and reduced pain at one- and two-year follow-up when compared to the baseline measurements, but there was no statistical difference between the groups. The improvement in the SF-36 score in the first two years was significantly higher for the microfracture group. All other clinical results from the two treatment methods were similar.

In osteochondral autograft transplantation, cartilage (and bone) tissue is transferred from one part of the joint to another (non-weight-bearing). The graft is taken as a cylindrical plug of cartilage and subchondral bone. It is then matched to the surface area of the defect and impacted into place. Osteochondral autograft is used for smaller cartilage defects. This is because the healthy graft tissue can be taken only from a limited area of the same joint. The procedure can be performed arthroscopically.

If a cartilage defect is too large for an autograft, a cadaveric allograft may be considered. Like an autograft, it is a block of cartilage and bone. In the laboratory it is sterilized and prepared. It is tested for any possible disease transmission. Allografts are typically implanted through an open incision.

The long-term outcomes of osteochondral autograft and allograft procedures are not known precisely, as there are no clinical data from randomized and well controlled studies.

2.3 Safety and Efficacy of Pharmacologically Related Products

Autologous chondrocyte implants were approved in the US under the proprietary name Carticel. Please refer to Section 6 of this review for additional information on this product.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

The MACI implant has been commercially available in several European member states and Australia in accordance with their national laws and regulations since 1998. Please see section 2.5 for details.

¹⁰ Peterson L, Minas T, Brittberg M, Lindahl A treatment of osteochondritis dissecans of the knee with autologous chondrocyte transplantation: results of two to ten years. J Bone Joint Surg Am.85:17-24, 2003.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

The following summarizes the most important regulatory issues and history associated with BLA 125603. A summary of details of the regulatory history of MACI, including regulatory interactions with FDA, appears in sections 2.5.2 and 2.5.3.

Vericel Corporation (formerly Aastrom Biosciences, Inc.) obtained Carticel (BLA STN 103661) and matrix applied characterized autologous chondrocytes (MACI) through the acquisition of the Cell Therapy and Regenerative Medicine (CTRM) business from Genzyme Corporation, a Sanofi Company, on 30 May 2014.

Carticel is autologous cultured chondrocytes; the product was approved by FDA in 1997 (BLA STN 103661) for the repair of symptomatic cartilage defects of the femoral condyle. To date, more than 20,000 patients have been treated with Carticel in the US. As described above in Section 2.3, the Carticel product, autologous expanded chondrocytes, is injected directly into the cartilage defect and secured using an autologous periosteal flap. This procedure may lead to the development of graft overgrowth and arthrofibrosis, which may result in a need for additional surgery. Many surgeons in the US try to approach this problem by applying the autologous chondrocytes (supplied as Carticel) to a marketed Type I/III collagen membrane. However, this use is not standardized (or FDA-approved), in terms of application of the cells or the type of membrane used. To address this problem, MACI (a combination product consisting of (b) (4) autologous chondrocytes seeded on a resorbable Type I/III collagen membrane, ACI Maix™) was developed to provide a standardized approach (cells plus scaffold) that will eliminate the need for the harvest, placement, and suture of a periosteal flap to retain the chondrocyte suspension in the cartilage defect. During the implantation procedure, the MACI implant is trimmed to the size and shape of the cartilage defect and is implanted cell-side down into the defect. The MACI is sealed into place using fibrin sealant. This reduction from a two-step to a one-step operative procedure results in shorter operating time with MACI, compared to Carticel. The applicant suggests that this will reduce postoperative symptoms of pain, swelling and graft overgrowth, the last often requiring additional surgery.^{10,11,12,13.}

MACI received European Union (EU) Marketing Authorization Approval from the European Commission on 27 June 2013, based on data from the SUMMIT Study. To date, over 8,000 patients have received the MACI implant in the EU.

For marketing of MACI in the US, Vericel Corporation has submitted a BLA application (January 3, 2016, accepted for filing March 2016), which is supported by clinical data from the SUMMIT study (Protocol: MACI00206) with its three-year long-term safety

11 Gomoll AH, Probst C, Farr J et al Use of a Type I/III Bilayer Collagen Membrane Decreases Reoperation Rates for Symptomatic Hypertrophy After Autologous Chondrocyte Implantation. Am J Sports Med 37:21S-23S, 2009

12 Zaslav K, Cole B, Brewster, R et al. A prospective Study of Autologous Chondrocyte Implantation in Patients With Failed Prior Treatment for Articular Cartilage Defect of the Knee. Am J Sports Med 37: 42-55, 2009

13 Harris JD, Siston RA, Brophy, RH et al. Failures, re-operations, and complications after autologous chondrocyte implantation – a systematic review. Osteoarthritis and Cartilage 19 (2011) 779-791, 2011

follow-up data (Protocol; MACI00809), (b) (4)

European Regulatory Activity

The MACI implant has been commercially available in several European member states (and Australia) in accordance with their national laws and regulations since 1998. The previous sponsor, Genzyme Corporation, a Sanofi Company, acquired MACI in February 2005 from Verigen AG, a German-based company. Over 6,000 patients received MACI implant from 1998 to 2008.

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 in 2006.

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 EMEA approval was required. In order to assure continued commercial availability of MACI in Europe through the 2012 compliance deadline, Genzyme re-focused efforts in 2006 toward developing and initiating a MACI implant phase 3 clinical trial (SUMMIT, Protocol ID MACI00206, ClinTrial.gov Identifier: NCT00719576) under the DG Enterprise, Clinical Trials Directive 2001/20/EC to support formal marketing authorization. The SUMMIT study was initiated in early 2008. It was designed to be a GCP, well-controlled, scientific evaluation of the safety and effectiveness of MACI implants. The study design incorporates both the earlier FDA guidance (cited above) and the subsequent EMEA scientific advice Genzyme received to assess both clinical and structural cartilage repair outcomes.

MACI received European Union (EU) Marketing Authorisation Approval from the European Commission on 27 June 2013. Aastrom Biosciences DK, Aps (an EU subsidiary of Vericel Corporation) became the Marketing Authorisation Holder in August 2014. The license and marketing of MACI in the EU has been temporarily suspended (September 2014) for commercial reasons.

On 30 May 2014, Vericel Corporation (formerly Aastrom Biosciences, Inc.) obtained Carticel (BLA No. 103661) and MACI through the acquisition of the Cell Therapy and Regenerative Medicine (CTRM) business from Genzyme Corporation, a Sanofi Company. To date, over 8,000 patients have received MACI implant in these countries.

US FDA Regulatory History

In 2006, following the Verigen acquisition, Genzyme initiated Pre-IND discussions with FDA regarding MACI implant development plans for US marketing approval. FDA held multiple meetings with Genzyme to provide guidance, recommendation and comments regarding MACI development in US market. A summary of the most important pre-BLA interactions with FDA is provided in Table 2.

Table 2. Summary of Regulatory History the FDA Regarding MACI Development

Date/ Tracking number	Type Interaction	Sponsor	Purpose
14 Dec 2012 PTS PS000826 Meeting ID: 8714	Type B Meeting	Genzyme (Sanofi)	Pre-BLA meeting to address clinical and preclinical questions for a future BLA submission.
10 Oct 2013 PTS PS000826 Meeting ID 9088	Pre-BLA Teleconference	Genzyme (Sanofi)	Pre-BLA. Discussion of format and content of the anticipated BLA application including labeling and REMS.
(b) (4)			
07 May 2015 PTS PS 002661 Meeting ID 9727	Pre-BLA Meeting	Vericel Corporation	Discuss data requirements, content and format of MACI BLA.
18 September 2015 PTS PS 002661 Meeting ID 9886	Written Response	Vericel Corporation	Follow up meeting to discuss format of the BLA submission
24 September 2015 PTS PS 002261	OCTGT Email communication	Vericel Corporation	Clarification FDA Written Reponses for PS002661 – 18 September 2015
29 September 2015 PTS PS 002661	OCTGT Email communication	Vericel Corporation	Clarification FDA Written Reponses for PS002661 – 18 September 2015

BLA = Biologics License Application, FDA = Food and Drug Administration, OCTGT = Office of Cellular, Tissue and Gene Therapies; REMS = Risk Evaluation and Mitigation Strategies..

2.6 Other Relevant Background Information

N/A

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

This BLA submission contains all content parameters as FDA required, which is electronic CTD submission. The submission was adequately formatted and integrated to accommodate the conduct of a complete clinical review.

3.2 Compliance with Good Clinical Practice and Submission Integrity

The applicant provided sufficient information that the clinical studies were conducted according to Good Clinical Practice.

All inspections have been completed and received a classification of No Action Indicated (NAI), as per the Bioresearch Monitoring Branch (BIMO).

3.3 Financial Disclosures

Table 3-1: Financial Disclosure Form

Covered clinical study (name and/or number): SUMMIT study (MACI00206), SUMMIT Extension study (MACI00809), [REDACTED]		
Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: 108		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 108		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>108</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in sponsor of covered study: <u>0</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>N/A</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

A total of 64 investigators at 16 study sites across 7 countries in Europe (3 in the Czech Republic, 4 in France, 3 in the Netherlands, 1 in Norway, 3 in Poland, 1 in Sweden, and 1 in the United Kingdom) were involved in SUMMIT and SUMMIT Extension study including 3 Independent Treatment Failure Evaluation Committee Members.

The applicant also provided Form FDA 3454 of 52 investigators involved in the (b) (4) [REDACTED].

The CBER Bioresearch Monitoring team inspected three sites and did not find any issues requiring regulatory action.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

Please refer to the Chemistry, Manufacturing, and Controls (CMC) Review for a complete and detailed review of BLA Application.

4.2 Assay Validation

Please see CMC/Device reviewers' memo for details.

4.3 Nonclinical Pharmacology/Toxicology

Please refer to the Nonclinical Pharmacology/Toxicology) Review for details.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The mechanism of action of MACI is based on expanded autologous chondrocytes to generate a repair tissue that fills the defect and restores joint function in subjects with knee OA. Because MACI is an autologous cell product, administration of MACI is not subject to conventional chemical analyses and therefore, standard absorption, distribution, metabolism, and excretion and PK testing techniques and profiles are not applicable.

4.4.2 Human Pharmacodynamics (PD)

N/A

4.4.3 Human Pharmacokinetics (PK)

N/A

4.5 Statistical

The statistical reviewer verified that the primary study endpoint analyses cited by the applicant were supported by the submitted data.

Please refer to the Statistical Review Memo for a complete discussion of the review and analyses.

4.6 Pharmacovigilance

Regarding safety information from the European Post-marketing Surveillance, 196 AEs in 6,032 patients receiving MACI were reported in non-study MACI cases in the post-marketing safety database as of 31 August 2015. Adverse events reported in $\geq 5\%$ of non-study MACI cases were graft complication, treatment failure, tendonitis, graft delamination, and arthralgia. Approximately 8.7% of events involved failure of treatment (preferred terms: 12/196 treatment failure cases and 5/196 transplant failure cases).

In the SUMMIT protocol, the age range of enrolled subjects was 18-55 years. Use of MACI during pregnancy or lactation is not recommended at this time because reproductive toxicology studies have not been done. Evaluation of the safety and

efficacy of MACI in pediatric patients (ages 10-17) is planned. Children less than 10 years of age are not expected to receive MACI treatment; a waiver has been requested (and agreed upon) for that patient population.

The clinical review team and the reviewers from the Office of Biostatistics and Epidemiology have agreed with the applicant's plan for voluntary training of orthopedic surgeons at the sites where MACI will be implanted post-approval. The team does not recommend any Risk Evaluation and Mitigation Strategies (REMS). The only postmarketing required study will be that related to the PREA requirement and described in detail elsewhere in this review.

Please refer to the Pharmacovigilance Review Memo for details.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

In order to support this BLA submission, the applicant provides clinical data from the SUMMIT study and the SUMMIT Extension study (long-term follow-up program for SUMMIT study). (b) (4)

SUMMIT (MACI00206) Study

SUMMIT (MACI00206) was a 2-year prospective, Phase 3, multicenter, randomized, open-label, parallel-group clinical trial designed to evaluate efficacy and safety of MACI compared with arthroscopic microfracture in the treatment of subjects (N = 144, 72 subjects in each treatment group), ages 18 to 55 years, with at least 1 symptomatic Outerbridge Grade III or IV focal cartilage defect of the medial femoral condyle, lateral femoral condyle, and/or the trochlea (defect size ≥ 3.0 cm², irrespective of location). Failure of a prior cartilage surgery (MACI) was not eligible for this study entry.

The Full Analysis set (FAS) is the data set for the primary analysis of effectiveness; the FAS consists of all randomized subjects who received study treatment (i.e., microfracture during the index arthroscopy or MACI implant during arthrotomy).

The Per Protocol (PP) set is used for sensitivity analyses of the same efficacy variables as for the FAS. The PP set is defined as those subjects in the FAS without any significant protocol deviations that could possibly influence the efficacy analyses.

The Safety set consists of all randomized subjects who underwent arthroscopy at Visit 2. The Safety set was used for analysis of safety variables.

SUMMIT Extension (MACI00809) Study

The SUMMIT Extension (MACI00809) was a 3-year, open-label, multicenter, elective enrollment study for subjects who were randomized and treated in SUMMIT, providing efficacy data regarding maintenance of effect within each treatment group over a total of 5 years. Safety and efficacy assessments were performed at scheduled visits 3, 4, and 5

years following treatment in SUMMIT (i.e., at Weeks 156, 208, and 260 post-arthrotomy for subjects treated with MACI implant or microfracture). 128 subjects (65 in the MACI group and 63 in the microfracture group) were enrolled in this study

Sixteen subjects randomized into the SUMMIT study (7 in the MACI group and 9 in the microfracture group) were not enrolled in the SUMMIT extension study. Eight of these subjects (5 in MACI and 3 in the microfracture group) had been studied at two investigation sites, both of which declined participation due to financial/corporate reasons likely unrelated to study outcomes. The other 8 subjects did not participate for other reasons described in this review. Thus 128 subjects enrolled in the SUMMIT Extension study from the SUMMIT study. The percent of missing data was only 11% in a three-year extension study. The applicant stated that, due to the elective participation in this extension study, efficacy evaluations were focused on the maintenance of the effect within each treatment group using change in KOOS Pain and Function scores as the primary evaluation. There was no study hypothesis and no statistical testing of results.

Three analysis populations were defined for this extension study:

Modified Full Analysis Set

The modified Full Analysis Set (mFAS) consists of all subjects who were included in the FAS defined in the SUMMIT study and provided informed consent for enrollment in the SUMMIT Extension study. A total of 128 subjects (65 MACI-treated subjects and 63 microfracture-treated subjects) comprise this analysis set.

The Per Protocol (PP) set: defined as those subjects in the FAS without any significant evaluable criteria/ violation that could possibly influence the efficacy analyses. This PP set was used for sensitivity analyses of primary and secondary efficacy variables.

Non-Modified Full Analysis Set

The non-modified Full Analysis Set (non-mFAS) consists of all subjects included in the FAS, defined in the SUMMIT study, who did not provide informed consent for enrollment in the SUMMIT Extension study. A total of 16 subjects randomized in SUMMIT (7 in the MACI group and 9 in the microfracture group) and not enrolled in the extension study comprise this analysis set.

Modified Safety Set

The modified Safety (mSafety) Set consists of the 128 subjects who were in the Safety Set defined in the SUMMIT study and provided informed consent for enrollment in the SUMMIT Extension study; the mSafety and mFAS are comprised of the same set of subjects.

Consistent with the original trial design, the population in the SUMMIT Extension study consisted of the same subjects as in the SUMMIT study. Therefore, the reviewers consider the SUMMIT Extension study as a part of a planned long-term follow-up of the SUMMIT study, rather than an independent pivotal clinical study in this BLA submission.

(b) (4)

(b) (4) [Redacted text block]

(b) (4) [Redacted text block]

(b) (4) [Redacted text block]

(b) (4) [Redacted text block]
The establishment of effectiveness was based on the SUMMIT trial alone,

with some information regarding long-term durability of effect derived from the SUMMIT Extension Study.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

- Pre-BLA submissions;
- Original BLA 125603 eCTD submission;
- (b) (4)

5.3 Table of Studies/Clinical Trials

Study Identifier	Study Design	Dosage Regimen; Route of Administration	Number of Subjects	Patient Population	Primary endpoint	Met Primary Endpoint
SUMMIT Study (MACI00206)	Efficacy and Safety Randomized, Controlled, open-label, multi-center, 2-year study	Each MACI implant contains approximately 500,000 to 1,000,000 autologous cells per cm ² . The amount of MACI administered is dependent upon the size of the cartilage defect. Multiple implants may be used. The implant is trimmed by the surgeon to the size and shape of the defect, to ensure the damaged area is completely covered. Multiple defects may be treated. The implant is performed using sterile surgical techniques and requires both the preparation of the defect bed and the application of fibrin sealant to the base and rim of the defect in order to secure the implant.	144 enrolled 144 (FAS/ITT) 72 in MACI group 72 in Microfracture group	Males and females, ages 18 to 55 years, with at least 1 symptomatic Outerbridge Grade III or IV focal cartilage defect of the medial femoral condyle, lateral femoral condyle, and/or the trochlea (defect size ≥3.0 cm ² , irrespective of location).	KOOS pain and KOOS function (SRA)	Yes
SUMMIT Extension Study (MACI00809)	3-year, open-label, multicenter, elective enrollment study for subjects who were randomized and treated in SUMMIT	None	Planned: 144 subjects Actual: 128 subjects enrolled 65 in MACI group 63 in Microfracture group	The same as SUMMIT study: a subset of 89% of the original SUMMIT population.	Not prespecified. No study hypothesis presented. Objective was to measure overall safety as well as effectiveness	N/A

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

N/A

5.4.2 External Consults/Collaborations

Patient Representative

Please see the “Summary of Consultation to Dr. Phillip Posner (Patient Representative, SGE)” in Appendix 1 for details.

FDA Pediatric Research Committee (PeRC)

On 04-07-2015, the applicant submitted a pre-BLA meeting package to obtain FDA feedback on the MACI BLA filing plan. In accordance with the requirements of the Food and Drug Administration Safety and Innovation Act (FDASIA), FDA suggested that the sponsor submit an initial Pediatric Study Plan (iPSP) 210 calendar days prior to submission of a Biologic License Application (BLA) for MACI. As agreed, Vericel submitted the initial pediatric study plan (iPSP) as a pre-IND submission for FDA review on 05-22-2015.

In the iPSP, the applicant requested: 1) A partial waiver for patients under 12 years of age on the grounds that the MACI does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group; 2) A partial waiver for patients ages 12 to 18 with open growth plates, on the grounds that the necessary studies will be difficult to conduct due to the rare incidence of disease in patients presenting with open growth plate in this age group.

Summary of PeRC meeting on 08-05-2015: The PeRC did not agree with the plan for full waiver for the proposed indication and instead offered a recommendation for a partial waiver in patients less than 10 years of age and a deferral of studies in patients 10 through 17 years of age.

On 11-17-2015, the applicant submitted an agreed PSP, proposing a brief pediatric study plan to evaluate safety and efficacy of MACI in patients aged 10 to 17 years with symptomatic chondral or osteochondral defects in the knee due to (b) (4) acute trauma. FDA agreed to the proposed PSP and asked that the agreed PSP be submitted with the marketing application or a reference to the agreed PSP be made in the BLA submission.

Center for Devices and Radiological Health (CDRH)

Please see the “Summary of Consultation to Dr. Neil Barkin (Orthopedic Surgeon, CDRH)” in Appendix 2 for details.

Advertising and Promotional Labeling Branch (APLB), Division of Case Management (DCM)

A formal complete consult memo from Dr. Oluchi Elekwachi (Regulatory Review Officer, APLB/DCM) was received on 02-01-2016. The conclusion was that the proprietary name (MACI) is acceptable. Please see Dr. Oluchi Elekwachi's review for details.

5.5 Literature reviewed (if applicable)

Please refer to the list of references in Appendix of this document.

6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1

SUMMIT Study

6.1.1 Objectives (Primary, Secondary, etc.)

The primary objective of this study was to test the hypothesis that the effectiveness of MACI will be superior to that of arthroscopic microfracture in reducing joint pain and improving joint function in the above population of patients with symptomatic articular cartilage defects of the femoral condyle, including the trochlea. The SUMMIT trial was also designed to evaluate the safety of MACI, compared to that of arthroscopic microfracture.

6.1.2 Design Overview

The SUMMIT (MACI00206) study was a two-year prospective, Phase 3, multicenter, randomized, open-label, parallel-group clinical trial designed to demonstrate superior efficacy of MACI to reduce pain and improve function compared with arthroscopic microfracture in the treatment of subjects (N = 144, 72 subjects in each treatment group), ages 18 to 55 years, with at least one symptomatic Outerbridge Grade III or IV focal cartilage defect of the medial femoral condyle (MFC), lateral femoral condyle (LFC), and/or the trochlea. Failure of a prior cartilage surgery was not required for study entry. The co-primary endpoints were changes from baseline in KOOS pain and KOOS function (SRA) of MACI compared to microfracture treatment.

Microfracture, a marrow stimulation technique, is a common first-line treatment for cartilage defects of the knee in the US.¹⁴ Due to the differences in surgical techniques between MACI (two surgical procedures) and microfracture treatment (one surgical procedure), subjects and Investigators could not be blinded; the study design was by necessity open-label.

Reviewer's comment:

The design of the SUMMIT Study was in accordance with current FDA policy as outlined in the FDA Guidance on trials for knee cartilage repair. The SUMMIT Study employed a randomized, concurrent-control design, comparing MACI to microfracture. The choice of microfracture as comparator is in accordance with the Guidance, as well as with EU policy. In particular, the choice of endpoints and scales to measure these endpoints (KOOS pain and KOOS function), as well as the independent assessment of pain and function is in keeping with FDA policy, as is the use of a superiority hypothesis for treatment-group comparison of both clinical outcomes (pain and function) at Week 104. (The design mandates a statistical "win" ($p < 0.05$) on each outcome for overall success.)

The weakness of the design (as described in Section 2) is its (necessarily) open-label nature and use of subjective clinical outcomes in subjects who are aware of their treatment assignment. Unfortunately, there are no "hard" outcomes, such as MRI or histology data, that have been validated as surrogates or even as biomarkers for clinical response. Such is the state of the art in this field at the time of this review.

The SUMMIT Study was conducted at 16 sites across seven countries in the EU (Netherlands, France, Czech Republic, Norway, Poland, Sweden, and United Kingdom).

14 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(10):2053-63.

According to the applicant, the study was performed in accordance with GCP as defined by the ICH, the principles defined in the Declaration of Helsinki and its amendments, and all applicable national and international laws. The SUMMIT Study was registered on clinicaltrials.gov under identification number NCT00719576.

Reviewer's comment:

The fact that the study was multi-center offers the ability to assess consistency of outcomes, which is important in establishing cogency and robustness of outcomes. This is especially important here, given that SUMMIT is the only RCT submitted in support of a BLA.

A description of method of subject recruitment and criteria for selection of investigative study sites appears below. It is important to understand as much as possible about these issues, in order to make some determination regarding the degree to which the SUMMIT population may be representative of the US target population.

Knee cartilage lesion size was measured during arthroscopy, prior to any cartilage repair procedure and randomization. Subjects had to have at least one lesion with a size of ≥ 3.0 cm² on the MFC, LFC, and/or trochlea. All subjects who met the eligibility criteria and were considered suitable for treatment in the study by the surgeon had a cartilage biopsy taken during the arthroscopy but prior to randomization to study treatment. Eligible subjects were randomized during the index arthroscopy procedure to receive either MACI or microfracture through an Interactive Voice Response System (IVRS). Subjects randomized to treatment with MACI returned within approximately four to eight weeks of the index arthroscopy to undergo the chondrocyte implantation procedure via arthrotomy. Subjects randomized to microfracture underwent the procedure during the index arthroscopy. All subjects followed a recommended postoperative rehabilitation program (see below).

All biopsied tissue that was harvested (for the purpose of manufacturing) during the index arthroscopy was sent to a Genzyme manufacturing facility (Cambridge, MA) where the sample was processed to isolate the autologous chondrocytes. Cells from subjects randomized to the MACI group were used in the preparation of the MACI product. Cells isolated from all subjects, regardless of treatment group, were (b) (4) so that an autologous chondrocyte sample would be available for a future MACI treatment should it be required.

Subjects randomized to MACI received a one-time implant of autologous chondrocytes seeded onto a resorbable Type I/III (ACI-Maix) collagen membrane, at a density of 500,000 to 1,000,000 cells per cm². The membrane was trimmed by the surgeon to the size and shape of the defect being treated.

The subjects treated with microfracture were assessed post-arthroscopy at Weeks 6 and 12 for safety only and at Weeks 24, 36, 52, 78, and 104 for safety and efficacy. The subjects treated with MACI were assessed post-arthrotomy (i.e., following implantation) at Weeks 6 and 12 for safety only and at Weeks 24, 36, 52, 78, and 104 for safety and efficacy. At Week 104, the structural repair of both the subjects with microfracture and MACI treatments was assessed arthroscopically, following the study protocol. For the purpose of histological evaluation of the structural repair, a cartilage biopsy was harvested from the core of the index lesion during the arthroscopy at Week 104.

The estimated maximum duration of a subject's involvement in the study from randomization was 104 weeks for subjects treated with microfracture and 112 weeks for patients in the MACI group (i.e., up to an additional 8 weeks for the MACI group due to the time between index arthroscopy and implant). All subjects followed a recommended postoperative rehabilitation program. Details were provided in the Rehabilitation Guidelines; the rehabilitation program was the same for subjects in both treatment groups.

Reviewer comments:

By design, all subjects underwent cartilage biopsy procedures prior to randomization. As a consequence, the MACI treatment outcomes are compared to those of microfracture plus a biopsy. It is not clear whether the knee cartilage biopsy itself could have an effect (positive vs. negative) on pain/function outcomes and/or other safety measurements for the treatment groups. This issue was addressed by our CDRH consultant and found to be of minor clinical significance (see descriptions of consultations above).

6.1.3 Population

Eligibility criteria: Subjects, aged 18 to 55 years, with at least one symptomatic Outerbridge Grade III or IV focal cartilage defect of the medial femoral condyle (MFC), lateral femoral condyle (LFC), and/or the trochlea were enrolled in this study. Failure of a prior cartilage surgery was not required for study entry. A total of 189 subjects were screened. Forty-five of the 189 subjects did not meet study entry criteria, and 144 subjects were randomized (72 subjects in MACI group and 72 subjects in microfracture treatment group). Reasons for failure to meet entry criteria are presented below, along with a complete description of subject disposition from screening to end of study.

Reviewer comments:

Regarding study population: the SUMMIT Study was conducted at 16 sites across seven countries in the EU (Netherlands, France, Czech Republic, Norway, Poland, Sweden, and United Kingdom). The applicant provided justification that the study population is comparable to the target patient population in the US. The applicant's justification was based on similarity between the demographics of the MACI SUMMIT and Carticel populations. However, 87% of subjects in the STAR study were Caucasian, and the demographics of the broad US population differ from those of the STAR population as well.

Inclusion Criteria:

1. ≥ 18 and ≤ 55 years of age
2. Modified Outerbridge Grade III or IV focal cartilage defect(s) located on femoral condyles, including trochlea
3. Symptomatic focal cartilage defects as defined by KOOS pain score < 55
4. Cartilage lesions with ≥ 1 defect size ≥ 3.0 cm² on femoral condyles and/or trochlea (including osteochondritis dissecans lesions not requiring bone graft)
5. Stable knee; ligament repair and reconstruction procedures were allowed

6. Intact meniscus or partial meniscus ($\geq 50\%$ of functional meniscus remaining).
7. Consenting to screening for infectious diseases, and requirement to attend follow up visits and a rehabilitation program.

Inclusion Criteria during the Index Arthroscopy

1. Modified Outerbridge Grade III or IV focal cartilage defect(s) located on the femoral condyles, including the trochlea that allowed treatment with the same surgical procedure as determined at randomization. Note: concurrent Outerbridge Grade I or II defects were acceptable on the patella or tibia if they remained untreated (or were treated with debridement only) at the time of arthroscopy and/or arthrotomy (Modified Outerbridge grades are defined in Table 3).
2. Cartilage lesions determined by arthroscopy prior to randomization and treatment with at least 1 defect size $\geq 3.0 \text{ cm}^2$ on the femoral condyles and/or the trochlea (including osteochondritis dissecans lesions that did not require a bone graft).
3. Stable knee (i.e., anterior and posterior cruciate ligaments should be free of laxity as well as stable and intact). Ligament repair or reconstruction procedures were allowed prior to or concurrent with arthroscopy and/or arthrotomy.
4. Intact meniscus or partial meniscus ($\geq 50\%$ of functional meniscus remaining). Meniscal repair or resection might be performed either staged or concurrent with the cartilage repair procedure provided that the surgeon was able to confirm that $\geq 50\%$ of functional meniscus would remain after the corrective meniscal treatment.

Table 3. Modified Outerbridge Grades (Noyes, 1989 Am J Sports Med)

Grade I	Softening and swelling of the cartilage
Grade II	Fragmentation and fissuring in an area $\leq 1.27 \text{ cm}$ (\leq half an inch) in diameter
Grade III	Fragmentation and fissuring in an area $> 1.27 \text{ cm}$ ($>$ half an inch) in diameter
Grade IV	Erosion of cartilage to the bone

Exclusion Criteria

1. Modified Outerbridge Grade III or IV defect(s) located on patella or tibia
2. Requiring or history of total meniscectomy or meniscal allograft in target knee joint or had a bucket handle tear or displaced tear that required a meniscectomy removing $> 50\%$ of the meniscus
3. Known history of anaphylaxis to gentamicin or any other products used in preparation and implantation of MACI implant
4. History of osteoarthritis (Kellgren-Lawrence Grade 3 or 4) in target knee joint as diagnosed by clinically appropriate X-rays obtained at the Screening visit or within the previous 12 weeks (Kellgren-Lawrence Grades are defined in Table 4)
5. Pregnancy or lactation
6. Any surgery in knee joint within 6 months prior to Screening
7. Symptomatic musculoskeletal conditions in lower limb that could impede efficacy assessment in target knee joint

8. Malalignment requiring osteotomy to correct tibial-femoral or patellofemoral alignment (retinaculum releases were allowed if indicated to correct patella tracking)
9. Concomitant inflammatory disease or other condition affecting joints
10. History of septic arthritis in target knee joint within 1 year of Screening
11. Known history of anaphylaxis to gentamicin or any of the products used in the preparation and implantation of MACI implant
12. Current malignancy or treatment for malignancy within past 5 years (except nonmelanoma skin cancer)
13. Significant medical or psychosocial problems that warranted exclusion (examples listed in the protocol)
14. Prior investigational drug or device use within 3 months prior to Screening

Table 4. Kellgren-Lawrence Grading Scale

Grade 0 (None)	Normal
Grade 1 (Doubtful)	Doubtful narrowing of joint space and possible osteophytic lipping
Grade 2 (Minimal)	Definite osteophytes, possible narrowing of joint space
Grade 3 (Moderate)	Moderate multiple osteophytes, definite narrowing of joints space, some sclerosis and possible deformity of bone contour
Grade 4 (Severe)	Large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone contour

6.1.4 Study Treatments or Agents Mandated by the Protocol

MACI

MACI consists of autologous cultured chondrocytes seeded onto a purified resorbable collagen Type I/III membrane (ACI-Maix™, Matricel GmbH, Germany). The final MACI product started as a (b) (4) Type I/III collagen membrane seeded with autologous cultured chondrocytes at a density of 500,000 to 1 million cells per cm². The amount of MACI administered per patient was dependent upon the size (surface in cm²) of the cartilage defect. The implant was trimmed by the treating surgeon to the size and shape of the defect, to ensure the damaged area was completely covered. As discussed in Section 2, the MACI implant is placed cell-side down into the defect and secured in place using fibrin sealant.

The ACI-Maix membrane was supplied to the manufacturing site (Genzyme Biosurgery [now Vericel Corporation], Cambridge, MA, USA), where it was seeded with autologous cultured chondrocytes. The final MACI product was prepared by the manufacturing site and transported to the surgical study site by courier. The preparation of the final MACI product for administration occurred as close as possible to the time of actual treatment.

Microfracture

Microfracture, a marrow stimulation technique, is a common first-line treatment for cartilage defects of the knee in the US¹⁴. Microfracture is intended to stimulate the marrow to provide “an enriched environment for tissue regeneration” (Mithoefer).

The result of microfracture is the development of fibrocartilage at the site of the procedure. This type of cartilage is less durable, less resilient and less able to withstand shock and shearing forces, compared to native articular hyaline cartilage. Moreover, clinical improvement after microfracture is not consistently observed: about 25% of patients with microfracture treatment reported no or minimal relief in pain and symptoms within the first 12-24 months of treatment and clinical improvement can wane after 24 months.

6.1.5 Directions for Use

Initial biopsy for both treatment groups

During the initial index arthroscopy, all biopsies were obtained by surgical removal of approximately 200 mg of articular cartilage harvested from a non-weight-bearing, healthy area of the femoral condyle. The cartilage biopsies were collected in accordance with standard medical practice utilizing appropriate aseptic techniques.

MACI

Preparation and administration of the final MACI product has been described above.

Microfracture

Microfracture begins with debridement of the cartilage defect down to the subchondral bone, and then an awl is used to pierce the subchondral bone at regular intervals. The prepared lesion provides a pool that helps hold the marrow clot.

Rehabilitation Program

All subjects followed a recommended postoperative rehabilitation program, which was the same for both treatment groups. All subjects were monitored for compliance with the rehabilitation schedule and achievement of rehabilitation goals. The rehabilitation program was divided into four phases based on the postoperative healing process.

1. Early Protection Phase (Weeks 0-6) – focus was on protection of the repair tissue and restoration of joint homeostasis involving in restrictions in weight-bearing and range of motion.
2. Transition Phase (Weeks 6-12) – focus was on restoring full range of motion and beginning to work on muscle strength.
3. Remodeling Phase (Weeks 12-26) – focus was on improving muscle strength and endurance and reintroducing activities.
4. Maturation Phase (Weeks 26-52) – focus was on returning the patient to full unrestricted activity.

The subject was to meet all the specific criteria as detailed in the protocol guidelines to progress from one phase to the next phase.

Alternative treatment or re-treatment

As per Protocol Amendment 2, subjects who were considered treatment failures or those who were considered to require re-treatment in the opinion of both the Investigator and the Independent Treatment Failure Evaluation Committee were allowed to receive appropriate alternative treatment (which could have been MACI), at the discretion of the Investigator, and were withdrawn from the study following the surgical re-treatment.

Justifiable reasons for removing a patient from the study included, but were not limited to, the following:

- The subject was uncooperative, including failure to attend study visits
- The Investigator believed it was in the best interest of the subject
- The subject experienced an intolerable adverse event (AE)/serious adverse event (SAE)

The Investigator had to document the primary reason for withdrawal in the eCRF. Subjects who were withdrawn from the study were not replaced.

Use of concomitant medications was not prohibited, but was discouraged, particularly in the 4 weeks prior to each study visit where the KOOS questionnaire was to be recorded. Two weeks prior to each visit, the study site contacted subjects to remind them to record medication use. All medication use through the study was recorded by subjects, reviewed with the investigators and the recorded use transferred to the eCRF.

Reviewer Comment: The practice of withdrawing a subject from a study without follow-up evaluation is not acceptable. As it turned out, 7 subjects (2 MACI and 5 microfracture) withdrew due to an adverse event (2), withdrawal of consent (2), and “lack of efficacy” (3). (Fig 1)

6.1.6 Sites and Centers

Study sites and subject enrollment information are provided in Table 5, below.

Table 5. SUMMIT Study: Site and Subject Enrollment Information

Site number	Country	Number of Subjects Screened	Number of Subjects Randomized	Number of Subjects discontinued
01	The Czech Republic	11	8	0
02	The Czech Republic	12	7	0
03	The Czech Republic	12	9	0
04	France	3	1	1
05	France	14	11	2
06	France	5	2	1
11	The Netherlands	56	40	2
12	The Netherlands	12	11	0
14	Norway	8	6	0
15	Poland	20	18	1
17	Poland	3	2	0
18	Poland	8	8	0
19	Sweden	4	2	0
21	The United Kingdom	13	8	0
23	The Netherlands	11	7	0
29	France	5	4	0

Reviewer comments: Sites 5, 11 and 15 were inspected. The BIMO report recommended No Action Indicated for any of the sites, indicating data integrity at those sites.

6.1.7 Surveillance/Monitoring

All subjects were randomly assigned to the MACI implant or microfracture treatment groups during the index arthroscopy using an Interactive Voice Response System (IVRS). Subjects were allocated to treatment according to a computer-generated randomization schedule provided by Genzyme. Upon enrollment all subjects were assigned a 5-digit patient screen number as follows: 1) A 2-digit center number

(predetermined by the Sponsor); 2) Followed by a 3-digit screening number. This number is sequentially based and corresponds to when the patient enrolled in the study (e.g., 001, 002, etc.). The computer-generated randomization codes were kept by the applicant. Randomization proceeded in blocks of 4 subjects, for subjects who met all eligibility criteria. Of 189 subjects screened, 45 did not meet entry criteria and were not randomized (screen failures, mostly due to arthroscopic findings). Nine of these were subsequently rescreened and found to be eligible, and therefore randomized.

The applicant conducted audits of the study sites and provided certificates of these audits in the BLA submission.

There was no Data Monitoring Committee for this study and no interim analyses were conducted.

Due to the nature of MACI and microfracture treatment, no measures of treatment compliance were required for these study treatments. Subject compliance with the rehabilitation schedule (e.g., attendance and adherence to advice) and the achievement of rehabilitation goals (e.g., weight-bearing status and range-of-motion status) were monitored.

Table 6 shows the schedule of assessments in the SUMMIT study for subjects randomized to microfracture.

Table 6. Schedule of assessments in the SUMMIT Study for subjects randomized to microfracture

	Visit 1	Visit 2	Visit 3 ^a	Visit 4 ^b	Visit 5 ^b	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10 ^c
Arthroscopic microfracture patients	Screen	Arthroscopy within approx 8 wks after Visit 1	N/A	Week 6 ± 2 wks	Week 12 ± 2 wks	Week 24 ± 4 wks	Week 36 ± 4 wks	Week 52 ± 4 wks	Week 78 ± 4 wks	Week 104 ± 4 wks
Informed consent	X									
Eligibility criteria	X	X								
Urine pregnancy test ^d	X									
Radiograph	X ^e									
Demography data	X									
Medical/surgical history (incl knee joint)	X									
Enrollment		X								
Cartilage biopsy		X ^f								
Blood sample for lab tests ^g		X								
Randomization during arthroscopy		X								
Microfracture		X								
MRI	X							X		X
Adverse events	X ^h	X		X	X	X	X	X	X	X
Query for SSPs				X	X	X	X	X	X	X
Concomitant medication ⁱ	X	X		X	X	X	X	X	X	X
Compliance with rehab program				X	X	X	X	X		
Brief physical and knee exam	X				X	X	X	X		X
KOOS	X					X	X	X	X	X
Patient/physician global assessment						X	X	X	X	X
Modified Cincinnati Knee Rating	X							X		X
IKDC	X							X		X
EQ-5D	X							X		X
SF-12 Health Survey	X							X		X
Macroscopic ICRS Cartilage Repair Assessment										X ^j
Core biopsy for histological evaluation										X ^j

^a Visit 3 not applicable for patients randomized to treatment with microfracture. First post-treatment assessment will be at Week 6 (± 2 weeks) after arthroscopy.

^b Assessment only for safety and compliance with rehabilitation program at Weeks 6 and 12.

^c Patients who discontinue participation after receiving study treatment (including treatment failures) will be asked to complete the assessments scheduled for the Week 104 visit.

^d Women of childbearing potential only. Enrolled patients will be asked to avoid becoming pregnant between Screening and Arthroscopy visits.

^e Screening radiograph may be performed up to 12 weeks before Screening visit.

^f Cartilage biopsy during index arthroscopy taken for all patients before randomization to study treatment.

^g Testing for HIV-1, HIV-2, hepatitis B, hepatitis C, and syphilis in patients who have cartilage biopsy.

^h Only SAEs reported between signing of informed consent at Screening visit and index arthroscopy.

ⁱ Concomitant medications taken for any AE will be recorded at each visit. In addition, the use of concomitant pain medications taken during the 4 weeks prior to each visit at which the KOOS questionnaire is performed will also be recorded.

^j It is planned to continue arthroscopic assessment and cartilage biopsy harvesting at the Week 104 visit until 50 evaluable samples have been obtained from each treatment group; patients having their Week 104 visit thereafter will not undergo arthroscopy and biopsy harvesting.

Source: Table 9.1 under Protocol and Amendments in the BLA submission (page 42 / 217) Definitions of all abbreviations are in the Glossary, except that EQ-5D = European Quality of Life 5 Dimensions.

Table 7 shows the schedule of assessments in the SUMMIT study for subjects randomized to MACI.

Table 7. Schedule of assessments in the SUMMIT Study for subjects randomized to MACI

MACI implant patients	Visit 1	Visit 2	Visit 3	Visit 4 ^a	Visit 5 ^a	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10 ^b
	Screen	Arthroscopy within approx 8 wks after Visit 1	Implantation approx 4-8 wks after Visit 2	Week 6 ± 2 wks	Week 12 ± 2 wks	Week 24 ± 4 wks	Week 36 ± 4 wks	Week 52 ± 4 wks	Week 78 ± 4 wks	Week 104 ± 4 wks
Informed consent	X									
Eligibility criteria	X	X								
Urine pregnancy test ^c	X									
Radiograph	X ^d									
Demography data	X									
Medical/surgical history (incl knee joint)	X									
Enrollment		X								
Cartilage biopsy		X ^e								
Blood sample for lab tests ^f		X								
Randomization during arthroscopy		X								
Implantation procedure			X							
MRI	X							X		X
Adverse events	X ^g	X	X	X	X	X	X	X	X	X
Query for SSPs				X	X	X	X	X	X	X
Concomitant medication ^h	X	X	X	X	X	X	X	X	X	X
Compliance with rehab program				X	X	X	X	X		
Brief physical and knee exam	X				X	X		X		X
KOOS	X					X	X	X	X	X
Patient/physician global assessment						X	X	X	X	X
Modified Cincinnati Knee Rating	X							X		X
IKDC	X							X		X
EQ5D	X							X		X
SF-12 Health Survey	X							X		X
Macroscopic ICRS Cartilage Repair Assessment										X ⁱ
Core biopsy for histological evaluation										X ⁱ

^a Assessment only for safety and compliance with rehabilitation program at Weeks 6 and 12.
^b Patients who discontinue participation after receiving study treatment (including treatment failures) will be asked to complete the assessments scheduled for the Week 104 visit.
^c Women of childbearing potential only. Enrolled patients will be asked to avoid becoming pregnant between Screening and Implantation visits.
^d Screening radiograph may be performed up to 12 weeks before Screening visit.
^e Cartilage biopsy during index arthroscopy taken for all patients before randomization to study treatment.
^f Testing for HIV-1, HIV-2, hepatitis B, hepatitis C, and syphilis.
^g Only SAEs reported between signing of informed consent at Screening visit and index arthroscopy.
^h Concomitant medications taken for any AE will be recorded at each visit. In addition, the use of concomitant pain medications taken during the 4 weeks prior to each visit at which the KOOS questionnaire is performed will also be recorded.
ⁱ It is planned to continue arthroscopic assessment and cartilage biopsy harvesting at the Week 104 visit until 50 evaluable samples have been obtained from each treatment group; patients having their Week 104 visit thereafter will not undergo arthroscopy and biopsy harvesting.

Source: Table 9.2 under Protocol and Amendments in the BLA submission (page 44 / 217).) Definitions of all abbreviations are in the Glossary, except that EQ-5D = European Quality of Life 5 Dimensions.

6.1.8 Endpoints and Criteria for Study Success

Co-primary efficacy endpoints

The co-primary efficacy outcomes were changes in KOOS pain and KOOS function (Sports and Recreational Activities) or SRA scores from baseline to Week 104.

The KOOS scoring system, which was used for the primary effectiveness analysis, is a validated knee-specific instrument developed to assess the subjects' opinion of their knee and associated problems (15). The KOOS included the following 5 separately scored subscales which in total addressed 42 items:

- Pain (9 items)
- Function (SRA) (5 items)
- Function in Activities of Daily Living (ADL; 17 items)

15 Roos, EM, Lohmander LS The Knee Injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. Health Qual Life Outcomes 1:64, 2003.

- Knee-Related Quality of Life (QOL; 4 items)
- Other Symptoms (e.g., swelling, restricted range of motion [7 items])

A 5-point Likert scale was used to record the response to each item ranging from 0 (no problems) to 4 (extreme problems). Within each subscale, items were added up and normalized to a value between 0 (extreme problems) and 100 (no problems).

Although SUMMIT was by necessity an open-label study, the KOOS subject-completed questionnaire, which formed the basis of determining the co-primary endpoints, was, according to the applicant, designed and administered in a fashion intended to minimize bias, in line with FDA guidance on PROs (FDA, 2009; *Guidance for Industry; Patient-Reported Outcome Measures*). The co-primary endpoints were chosen because of their clinical importance to this patient population, especially given the relatively broad age range: relief of pain and increase in ability to perform sports and recreational activities as well as improvement in the level of activities of daily life.

Secondary Efficacy Analysis

Ranked by the sponsor “in order of importance,” the secondary efficacy outcome variables were:

1. Histological evaluation of structural repair of evaluable biopsies harvested from the core of the index lesion during arthroscopy at Week 104.

For the purpose of histological evaluation, a cartilage biopsy was harvested from the core of the index lesion at week 104. The cartilage biopsy was to be a full-thickness sample with a diameter of 2 to 3 mm harvested using a standardized procedure from the index cartilage defect. The biopsy was sent to a central laboratory for processing.

During the arthroscopy at the week 104 (i.e., final) study visit for harvesting of a biopsy sample of the index lesion, a macroscopic ICRS “Cartilage Repair Assessment” of the index lesion was performed prior to taking the biopsy sample. The ICRS “Cartilage Repair Assessment” used the following three criteria:

1. Degree of defect repair (from “0% repair of defect depth” to “level with surrounding cartilage”)
2. Integration to border zone (from “no contact to ¼ of graft integrated with surrounding cartilage” to “complete integration with surrounding cartilage”)
3. Macroscopic appearance of the repair (from “total degeneration of grafted area” to “intact smooth surface”)

Each assessment parameter had five possible outcomes. Each of these parameters was given a score from 0 (worst outcome) to 4 (best outcome). The individual scores were combined to give an overall repair assessment rating (from “severely abnormal” to “normal”). See the ICRS Website for details:

http://www.cartilage.org/files/contentmanagement/ICRS_evaluation.pdf

The histological evaluation of biopsies was performed by independent central reviewers. Scoring of the cartilage repair biopsies was completed using the ICRS II histology scoring system (Mainil-Varlet, 2010, Am J Sports Med) by two independent pathologists blinded to treatment assignment. This scoring system includes 14 parameters related to

chondrocyte phenotype, tissue structure, and other factors, each scored on a scale from 0 to 100 representing poor to good quality cartilage. The histological evaluation also included special assessment of the presence and distribution of aggrecan, type I and II collagen, and elastin; this assessment was performed by a third independent pathologist blinded to treatment assignment.

2. MRI assessments of structural repair parameters at Baseline and at Weeks 52 and 104.

All MRI scans were read by two independent central reviewers blinded to both the subject's assigned study treatment and the order in which the MRI scans were obtained. Image evaluations included degree of defect fill based on the thickness of repair tissue relative to that of the surrounding tissue, degree of integration of the repair tissue, and signal intensity of the repair tissue relative to that of adjacent native cartilage. The degree of defect fill was regarded as the most important MRI assessment variable addressing the related MRI efficacy endpoint. Additional assessments included the presence of graft and bone hypertrophy and subchondral edema. As part of the exploratory assessment of using the Whole-Organ MRI Scoring (WORMS) score as a means of assessing the overall joint status in this study population, all WORMS attributes were scored. Comparisons of MRI imaging outcomes between MACI and microfracture at screening, and at the Week 52 and Week 104 study visits were scheduled using following parameters:

- Degree of defect fill based on the thickness of repair tissue
- Degree of integration of the repair tissue with adjacent native cartilage
- Signal intensity of the repair tissue relative to adjacent native cartilage
- Change from Baseline at Weeks 52 and 104 in the above repair parameters

3. Response rate based on pre-specified changes in KOOS Pain and Function (SRA) scores: the proportion of patients who responded to treatment at Week 104.

A responder is defined as a subject with at least a 10-point improvement in both the KOOS Pain and Function (SRA) scores from baseline.

4. Treatment failure rate: the proportion of subjects in each treatment group assessed as treatment failures at Week 104 (Note: this analysis was planned but not completed as the low number of treatment failures made this not evaluable).

Subjects were considered as a treatment failure at any time point from Week 24 post-surgery onwards if all of the following criteria were met:

1. Subject's global assessment of their knee joint compared to Baseline was the same (i.e., no improvement), worse (i.e., deterioration), or significantly worse (i.e., significant deterioration)
2. Physician's global assessment of the subject's knee joint compared to Baseline was the same, worse, or significantly worse
3. Percent improvement from Baseline in KOOS Pain score was less than 10%
4. Physician diagnostic evaluation of failure, to include history, physical therapy status, physical examination, and either an MRI and/or a diagnostic arthroscopy, excluded etiologies (e.g., meniscal tear) other than failed treatment of the index lesion

5. The physician decided that surgical re-treatment of the index lesion(s) was required that involved either extensive debridement for lesion expansion, violation of the subchondral bone, or ACL. Note: In general, minor surgical treatment of repair tissue in the index lesion(s) (e.g., shaving or trimming of hypertrophic repair tissue) would be considered as AEs but not as treatment failures, and would be an accepted part of the surgical “maintenance” and modification of the primary repair procedure.

The time to treatment failure was also assessed and was based on the date that the surgeon decided that surgical re-treatment of the original index lesion was required relative to the date of the original study surgery (i.e., arthroscopy for microfracture and arthrotomy for MACI).

Treatment failure was determined only in relation to the original treated defect(s) and was based on the date the surgeon decided that surgical re-treatment was required. Subjects who were considered treatment failures were allowed, at the discretion of the investigator, to receive appropriate alternative treatment, which could have been MACI. Subjects who were considered to require re-treatment were withdrawn from the study following the surgical re-treatment.

5. Change from Baseline at Week 104 in the remaining three subscales of the KOOS instrument (i.e., Other Symptoms, QOL, and ADL)

Reviewer’s Comments:

The first two endpoints are appropriate for this investigation and have the potential to support the primary outcome, both clinically and in terms of “hard” scientific outcomes, including MRI imaging and histological analysis. The responder analysis conveys important clinical information indicating the proportion of subjects with improvement in both pain and function. The sponsor’s ordering of the secondary endpoints was done without consultation from FDA. Because of the (appropriate) closed-testing approach to statistical analysis, it would have been more prudent to place the responder (composite endpoint) analysis first: Achieving success on the co-primary outcomes would suggest, but not ensure, success in the responder analysis. MRI and histology analyses, while providing “hard” scientific data, had never been explored formally prior to conducting the SUMMIT trial, and their placement as the first and secondary endpoints was “risky.” As it turned out (see below), failure on the first endpoints precluded formal statistical testing of the composite.

Tertiary efficacy variables

The sponsor lists 9 tertiary endpoints. These are considered as exploratory and will not be discussed in this review.

Safety Endpoints

All AEs were collected after the signing of the Informed Consent Form. They were categorized according to severity, attribution of causality and outcome (e.g., recovered, recovered with sequelae, not yet recovered, etc.). All AEs were categorized according to Version 14.1 of the Medical Dictionary for Regulatory Activities (MedDRA). The definition of AEs and SAEs met the FDA regulatory definition of such terms. In addition, the applicant collected AEs of special interest, as follows:

- Potential perioperative complications in relation to arthroscopy/arthrotomy:
 - Hemarthrosis, hematomas at surgical site, intra-articular adhesions, arthrofibrosis, localized surgical site inflammation, localized surgical site infection, thromboembolic events
- Potential complications related to MACI:
 - Symptomatic graft hypertrophy, graft delamination (complete or partial, possibly leading to loose bodies in the joint or graft failure)

The applicant also collected information regarding subsequent surgical procedures (SSPs). SSPs were defined as any surgical procedure including arthroscopy, arthrotomy, or manipulation under anesthesia) performed on the target knee joint during the study. Multiple interventions might be performed at the time of the SSP, but not all SSPs were considered as an indication of treatment failure.

Intervention via arthroscopy was considered an SSP, and clinically significant findings were also classified as “important medical events” thus meeting the criteria for an SAE, irrespective of whether the procedure was performed on an outpatient basis. Therefore, significant clinical findings were categorized as “serious” AEs.

The arthroscopy assessment planned for Week 104 was not considered an SSP for SAE reporting and analysis purposes and was not recorded as an SSP, unless during the arthroscopy there was an unexpected event or finding (other than the planned biopsy) that met the SAE criteria.

All SSPs were recorded in the eCRF.

Reviewer comment:

SSPs were important as they could confound the primary efficacy results. Thus, it is relevant that the applicant collected these data, so that primary efficacy results would be interpretable.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Study Hypothesis

Study hypotheses were tested 2-sided (or equivalent) with a significance level of 5%, unless stated otherwise. Data were presented by visit and treatment group, and reported in listings and/or tables and/or figures. The default summary statistics for continuous variables were the number of patients (n), mean, standard deviation (SD), median, minimum (Min), and maximum (Max). Categorical variables were summarized with the number of patients and proportion of occurrence (n, %).

Power and sample size

The sample size calculation was based on the bivariate co-primary efficacy parameters of change from Baseline to Week 104 in KOOS Pain score and Function (SRA). The test was performed at $\alpha = 0.05$ for each co-primary. The power was chosen to be 85%. The calculation assumed an improvement difference between groups at Week 104 of 12 points in KOOS Pain and 12 points in Function (SRA), standard deviations (SDs) of 20

for KOOS Pain and 30 for KOOS Function (SRA). Power calculations were also based on a correlation coefficient of 0.56 between the change from Baseline at Week 104 between KOOS Pain and Function (SRA). Sixty-two subjects per treatment group (124 totals) would be needed to have 85% power. In order to account for possible early discontinuations from the study, an additional 20 subjects were to be randomized and treated, yielding 72 subjects per treatment group.

Analysis sets

-The Full Analysis set (FAS), consisting of all randomized subjects who received study treatment (i.e., microfracture during the index arthroscopy or MACI implant during arthroscopy). The FAS was used to analyze efficacy.

-The Per Protocol (PP) set, defined as those subjects in the FAS without any significant evaluable criteria violation that could possibly influence the efficacy analyses. This PP set was used for sensitivity analyses of primary and secondary efficacy variables.

-The Safety set, consisting of all randomized patients who underwent arthroscopy at Visit 2. The Safety set was used for analysis of safety variables.

Reviewer comments:

Generally, the primary efficacy analysis should be performed on an ITT population consisting of all randomized subjects. The use of the FAS as an ITT population may be acceptable if there were no randomized subjects for whom the MACI product could not be produced, or randomized subjects who failed to receive microfracture. As it turned out, the FAS was identical to the ITT population.

Efficacy Analyses

The co-primary efficacy parameter, change from Baseline to Week 104 in KOOS Pain and Function (SRA) scores, was analyzed with a multivariate analysis of variance (MANOVA) model. The analysis was conducted at the significance level of $\alpha = 0.05$.

Secondary endpoints: See reviewer comments about ordering and analysis of secondary endpoints above. The closed testing approach to analysis of secondary endpoints precluded testing of subsequent endpoints following failure of an endpoint to meet statistical significance.

Missing Data Handling

For continuous variables, missing values were imputed using the LOCF technique. For questionnaire data, two types of missing data were recognized: individual questions from a questionnaire and, where applicable, missing/incalculable entire subscale scores. Missing/incalculable subscale scores were handled according to LOCF. Specifically to the co-primary parameter and in order to preserve correlation, LOCF was employed if either or both of the subscales were unavailable.

Reverser Comments:

The applicant's choice of methodology for handling missing data was not worked out with FDA in advance. LOCF represents a single imputation method for handling missing data, and this approach is not generally acceptable (see, for example, Prevention and Treatment of Missing Data in Clinical Trials, a National Academies Press monograph). LOCF is not validly based on a missing-at-random (MAR) assumption. LOCF methodology may be anti-conservative or conservative, depending on the "real" course (trajectory) of the outcomes. In the present case, use of LOCF could even be conservative for one study arm (e.g., MACI) and anti-conservative for the other. Depending on the degree of missing data, other imputation methods (MI) are required. The sponsor added other statistical models.

The multiple imputation (MI) scheme employed two stages, the first of which used a Markov-chain-Monte-Carlo (MCMC) method to produce monotone missingness, and the second used a predicted mean matching method (REGPMM).

Safety Analyses

The number (%) of subjects with treatment-emergent AEs and treatment-related AEs was presented for each treatment group by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT). The incidence rates of treatment-emergent SAEs were also presented for each treatment group. The incidence rates of TEAEs were compared between treatment groups overall and in two time periods following surgery: the early postoperative period (up to and including 12 weeks after study treatment) and late postoperative period (more than 12 weeks after study treatment). Any SAEs reported between the screening visit and prior to the index arthroscopy were listed. For patients in the MACI group, AEs starting after biopsy but before implantation were listed. Additional listings of AEs leading to discontinuation were generated. The number (%) of subjects with SSPs was presented by treatment group. The frequency of SSP 0, ≥ 1 (the number of different dates at which surgical repair occurred, not the number at a specified date) was analyzed using a logistic regression model with treatment, age, gender, and total surface area of all lesions as covariates.

6.1.10 Study Population and Disposition

All 144 randomized subjects received study treatment: 72 subjects with MACI and 72 subjects with microfracture. All 144 randomized subjects had a biopsy completed during the arthroscopy at Visit 2. The 72 subjects randomized to microfracture treatment underwent the procedure during Visit 2. The 72 subjects randomized to MACI treatment underwent the implantation procedure during Visit 3.

Demographic characteristics are shown in Table 1-1. Since the study was conducted entirely outside the US, the applicant compared the demographic summary data (and baseline disease characteristics from the SUMMIT population to the study populations of the STAR study and the RBS, which were conducted in the US. Although the age, sex and BMI distributions were very similar, SUMMIT enrolled 100 % of White subjects, and minorities were also underrepresented in the US studies.

6.1.10.1 Populations Enrolled/Analyzed

Source of study subjects and selection of study sites:

According to the applicant, Genzyme chose the investigational sites for the SUMMIT study based on the sites' clinical experience with autologous chondrocyte implantation and microfracture as well as data indicating an adequate number of available patients that could meet the study entrance criteria. This information is documented in the MACI00206 Trial Master File (TMF). No site-management organizations were used for investigator selection. Although not EMA-approved, MACI was commercially available in several countries in the EU at the time this study was conducted; the Genzyme orthobiologics business unit provided names of potential investigators for site evaluation assessment. In addition to the surgical expertise of the investigator, all sites were required to have the appropriate clinical staff, tissue procurement license, an MRI (minimum 1.5T), and on-site patient rehabilitation capability.

Patient Recruitment

In general, patients were recruited from a site's current patient pool, walk-ins, and referrals. Advertising for patients was not used. At the highest enrolling site (Dr Saris at site 11, University Medical Center of Utrecht, a government-based academic hospital in the Netherlands), approximately 80% of patients came from more than 50 km away as the site is considered a secondary or tertiary hospital. The site also had referrals, local patients and did not use advertising.

The Clinical Project Management Plan and other internal sponsor documents filed in the MACI00206 TMF describe a variety of patient-recruitment initiatives that were used to aid recruitment efforts:

1. Genzyme facilitated physician-to-physician MACI00206 referral letters for investigators to send to physicians at neighboring hospitals to ask for referral of potential patients. According to the applicant, there is no documentation regarding the extent of use of the physician-to-physician referral letters or the extent of referrals.
2. In France, MACI00206 information leaflets were distributed to orthopedic surgeons at neighboring hospitals. There is no documentation regarding the number of successful contacts.
3. A medical records search criterion was provided for investigators to search their list of current patients. According to the applicant there is no documentation was not located regarding extent of use of the Genzyme-provided search criteria.

The above initiatives started in July 2009 and resulted in an increased rate of enrollment starting in September 2009. Although it is not known how each of these initiatives contributed to the up-tick in enrollment rate, it appears that the study sites were able to recruit patients beyond those considered ongoing patients or office walk-ins.

According to the applicant, these approaches to recruitment mirror those in the US, in that there are orthopedic surgeons who specialize in cartilage repair and are often referred patients from outside their practice.

Reviewer Comment:

The recruitment process appears to be reasonable and probably not unusual for trials requiring subspecialty-level investigator and site expertise. The process was certainly

not inconsistent with the notion that the trial population was representative of the overall target population, at least in the countries in which the trial was conducted. The only question, one for which an answer was not provided or documented, is how the experimental (MACI) option was presented to the subject, relative to description of the expected performance of microfracture. This is of potential importance in an open-label trial with outcomes dependent on subject-reporting, because any suggestion of presumed advantage of MACI over microfracture could introduce bias. Examination of the informed consent document (by the reviewers) yielded no indication of bias in written presentation of expectations.

A total of 189 patients were screened. Forty-five of the 189 patients did not meet study entry criteria, and 144 subjects were randomized (72 subjects in MACI group and 72 subjects in microfracture group). All subjects randomized were included in the Full Analysis Set (FAS). As proposed in the study plan, the sponsor emphasized that the FAS is the same as the intent-to-treat (ITT) population. Overall number of subjects in each of the defined analysis sets is listed in Table 8.

Table 8. Datasets analyzed

	Total
All Patients Screened Set, n	189
All Patients Randomized Set, n (%)	144/189 (76.2)
Safety Set, n (%)	144/144 (100.0)
Full Analysis Set - MI, n (%)	144/144 (100.0)
Full Analysis Set – LOCF, n (%)	144/144 (100.0)
Per Protocol Set - MI, n (%)	127 ^a /144 (88.19)
Per Protocol Set - LOCF, n (%)	126 ^{a, b} /144 (87.54)

LOCF = last observation carried forward; MI = multiple imputation.

^a Includes 6 patients with data excluded at specific visits for concomitant pain medication use (2 patients at Week 52, 3 patients at Week 78, and 1 patient at Week 104)

^b Patient 21004 had only partial data for KOOS pain and function scoring at baseline; therefore, was excluded from the LOCF sensitivity analysis of the ITT (FAS) population.

Source: Final Analysis Sets Report in Appendix 16.2.3 and Listing 16.1.1.3

Full Analysis Set

The FAS [for both the multiple imputation (MI) and last observation carried forward (LOCF) approaches] included 144 subjects and was the primary population used for the analysis of efficacy. No subjects were excluded from the FAS. All subjects randomized were included in the FAS.

Per Protocol Analysis Set

Per protocol (PP) set was used for sensitivity analysis of primary and secondary efficacy endpoints. The PP set for the MI approach included 127 subjects (121 subjects with full data and 6 subjects with data excluded at specific visits for concomitant pain medication use), and the PP set for the LOCF approach included 126 subjects (120 subjects with

full data and 6 subjects with data excluded at specific visits for concomitant pain medication use).

Of the 24 subjects with full or partial data not included in the PP set, all had protocol deviations assessed by medical review as significant (see Table 6-1-7) for protocol deviations). As described in Appendix 16.2.3, Analysis Sets Report and Listing 16.1.1.3 in this BLA submission, for the PP analysis using LOCF, 18 (11 MACI and 7 microfracture) of the 24 patients had full data excluded; for MI analysis 17 (11 MACI and 6 microfracture) had full data excluded. Six subjects were included in the PP set but had partial data excluded by visit (2 patients at Week 52, 3 at Week 73, and 1 at Week 10).

Reviewer Comment:

The sponsor's approach to defining the PP set is appropriate. Analysis of the results in the PP set confirmed the primary analysis and will not be discussed in this review.

Safety Data Set

The Safety set consisted of all subjects in the all subjects Randomized set (the FAS set) who had undergone an arthroscopy at Visit 2. This was the population used for analysis of safety variables.

6.1.10.1.1 Demographics

The demographic characteristics (gender, race, and ethnicity) appear to be evenly balanced between the MACI and microfracture treatment arms. The study population was about 60% male in both treatment arms. The enrolled population was 100% Caucasian, relatively young, with mean age about 35 years and maximum age 54 years.

Baseline disease severity: 23 subjects in the MACI group and 28 subjects in the microfracture group had one prior cartilage surgery of the target knee. Aside from musculoskeletal problems, the study population was relatively healthy. Only 5% had "metabolic/endocrine/nutritional" disorders.

Reviewer Comments:

The fact that only 5% had metabolic/endocrine/nutritional disorders implies that the proportion of diabetics must have been no greater than about 4%. This is lower than the expected proportion of diabetics in a random sample of the US population (which would be about 8-9% in this age range). Thus the trial population would differ substantially from a randomly selected US population in several demographic and baseline characteristics. Since most subjects had been physically active (from recreation to elite sports) and the mean and median BMI were around 26, this would explain a lower incidence of "metabolic / nutritional disorders" compared to the average US population, and would be closer to an equivalent segment of the US population.

Perhaps of greatest importance in this regard, there is no information regarding the safety and effectiveness of MACI in patients over 55 years of age.

The demographic characteristics of age, sex, race and ethnicity were presented in Table 1.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

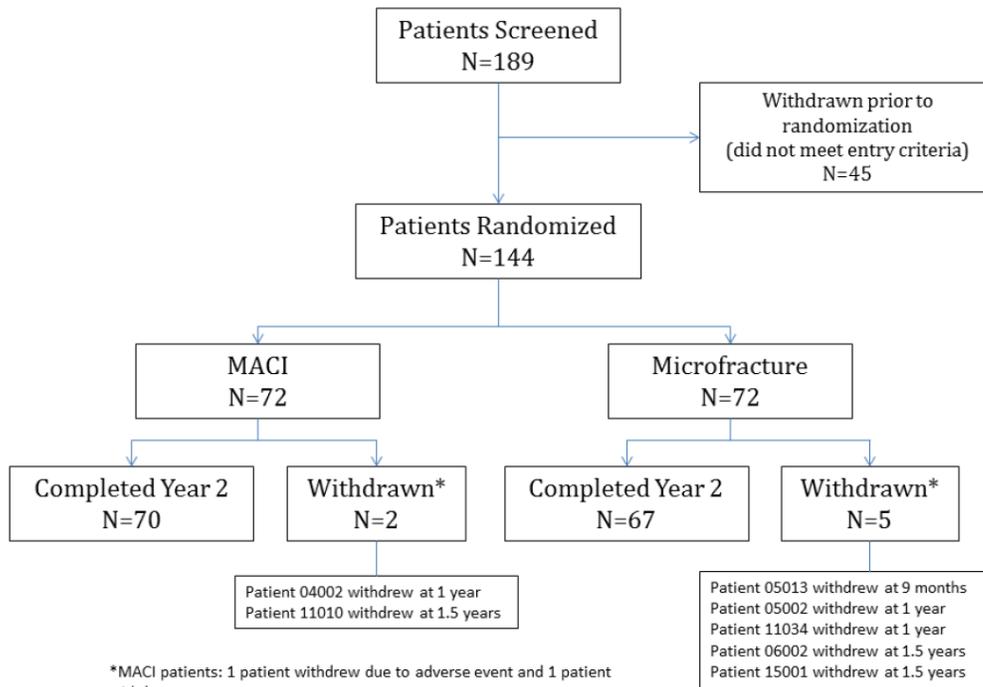
Most subjects were young, and two thirds were male. The majority of these subjects engaged in at least recreational activity. The etiology of the cartilage defect was acute trauma in 46% of subjects randomized to MACI and 63% of subjects randomized to microfracture. Only 8 (11%) of MACI-randomized subjects had a cartilage defect due to osteochondritis dissecans, while 12 subjects (17%) in the microfracture group had cartilage defects due to osteochondritis dissecans. Subject compliance with rehabilitation at Visit 4 (Week 6), Visit 5 (Week 12), Visit 6 (Week 24), Visit 7 (Week 36), and Visit 8 (Week 52) is summarized for the FAS in Table 6-1-19.

6.1.10.1.3 Subject Disposition

Figure 1 shows the disposition of subjects in the SUMMIT Study. Most screen failures were due to arthroscopic findings that did not meet specific inclusion criteria, although some subjects had higher KOOS pain or function scores than allowed for entry.

Of the 144 subjects randomized only 7 did not complete their participation in the SUMMIT Study.

Figure 1. Subject Disposition in the SUMMIT Study



*MACI patients: 1 patient withdrew due to adverse event and 1 patient withdrew consent.

*Microfracture patients: 1 patient withdrew due to adverse event, 1 patient withdrew consent, and 3 patients withdrew due to lack of efficacy.

Source: Figure 3 of the Integrated Summary of Efficacy, page 42 / 300.

6.1.11 Efficacy Analyses

This review focuses on analysis of the primary and secondary endpoints, as well as on analysis of subgroups (lesion size, lesion location, etiology, prior surgical history, and gender; additional subgroup analyses of primary endpoint by age and BMI were requested by the review team and reviewed).

6.1.11.1 Analyses of Primary Endpoint(s)

Methods

Primary Analysis

The co-primary efficacy endpoints were change from Baseline to Week 104 for the subjects' KOOS Pain and KOOS Function (SRA) scores, which were analyzed with a multivariate analysis of variance (MANOVA) model. The analysis population was the Full Analysis Set (FAS, the same as the Intent-to-Treat, or ITT).

The initial MANOVA model included treatment, study site, Baseline KOOS Pain score, Baseline KOOS Function (SRA) score, age, total defect size, occurrence of previous surgery, duration of symptoms, and index lesion location. The contribution of the individual covariates was tested at a significance level of 5% and was included in the final reduced model only if found to be significant in the initial model. This produced a Wilks' λ test statistic for which the corresponding p-value was calculated. Last observation carried forward (LOCF) was used for imputation of missing data.

Reviewer Comment: See previous comments regarding adequacy of LOCF as a single imputation method.

Sensitivity Analyses

With the multiple imputation (MIO method for handling missing data, the MANOVA models included treatment, baseline KOOS Pain score, and baseline KOOS Function (SRA) score. Resulting point estimates and sample covariance matrices were combined to produce a Wald test statistic with corresponding p-value.

Only 7/144 subjects (2 [2.8%] MACI and 5 [6.9%] microfracture) withdrew prior to week 104. Overall subject dropout rate was <5%.

Results

Primary Analysis

An overview of the efficacy results for the co-primary endpoint of KOOS pain and function is shown in Table 9. At week 104 (2 years), the improvement in the MACI group compared with microfracture was analyzed ($p = 0.001$) based on MANOVA using LOCF for missing data.

Table 9. Co-Primary Efficacy Endpoints - KOOS Pain and Function (SRA) Scores

		MACI N = 72		Microfracture N = 72	
		Pain	Function (SRA)	Pain	Function (SRA)
Baseline	n; Mean (SD)	72; 37.00 (13.52)	72; 14.86 (14.68)	71; 35.45 (12.09)	71; 12.57 (16.67)
Week 104	n; Mean (SD)	72; 82.45 (16.18)	72; 60.90 (27.84)	70; 70.85 (24.22)	70; 48.71 (30.33)
Change From Baseline to Week 104	n; Mean (SD)	72; 45.45 (21.08)	72; 46.04 (28.35)	69; 35.23 (23.91)	69; 35.83 (31.63)
LS Means (Week 104)		44.13	46.05	32.37	34.64
Difference * [MACI – Microfracture]		11.76	11.41		
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 at Week 104 based on multivariate analysis of variance that included treatment, center, baseline KOOS Pain, and baseline KOOS Function (SRA) as covariates.

Source: Table 2 in Section 14 of the proposed labeling text.

The MANOVA model-adjusted LS means of the differences between treatment groups were 11.8 for KOOS Pain scores, and 11.4 for KOOS Function (SRA) scores. These results met statistical significance.

Reviewer Comments:

In terms of the clinical meaningfulness of the results, independent authors have examined the thresholds for a “minimal detectable change” in KOOS scores. Roos¹⁵ suggested the threshold of “10” as the minimal important change. Engelhart validated the KOOS and its subscales in a population undergoing articular cartilage repair, and using distribution-based methods, based on FDA recommendations in the PRO Guidance, also stated that a minimal change of approximately 10 in the KOOS scores is clinically meaningful in the detection of improvement or deterioration¹⁶.

Thus, mean microfracture-subtracted mean changes in the MACI-group for both pain and function scores exceed the threshold of minimal change that is clinically detectable.

Sensitivity Analyses

The sponsor also examined the effect of MACI in the Per Protocol (PP) population, with LOCF imputation. The results were essentially the same as for the FAS population and will not be discussed here.

Effect of MACI in the Full Analysis Set (FAS) population, with MI for missing data

A sensitivity analysis using a second method of imputation (multiple imputation) for missing values was also statistically significant (p = 0.004).

16 Engelhart L, Nelson, L, Lewis S, et al. Validation of the Knee Injury and Osteoarthritis Outcome Score Subscales for Patients With Articular Cartilage Lesions of the Knee. Am J Sports Med, 40:2264, 2012.

Similar statistically significant results were obtained by the applicant in the analyses of the PP population set, when using MI for handling missing data (data not shown in this review).

The applicant also conducted an exploratory, time-weighted analysis of the treatment effect of MACI, compared to microfracture, at 24 weeks, 36 weeks, 52 weeks, and 78 weeks, in addition to the landmark timepoint of 104 weeks. At each timepoint, the differences in KOOS pain and function reached nominal statistical significance (no correction for multiple comparisons), using both LOCF and MI methods for imputation of missing data in either the FAS or the PP populations.

Comment: Since KOOS pain and function were not assessed earlier than 24 weeks, it is not possible to ascertain the onset of this treatment effect.

6.1.11.2 Analyses of Secondary Endpoints

As noted above, the sponsor (Genzyme) listed the secondary endpoints in the following order “of importance.” This was done without input from FDA. The sponsor did not define “importance.” The pre-specified analysis of secondary endpoints employed a closed hierarchical testing procedure.

- 1) Histological evaluation of structural repair of evaluable biopsies harvested from the core of the index lesion during arthroscopy at Week 104.
- 2) MRI assessments of structural repair parameters at baseline and at weeks 52 and 104.
- 3) Response rate based on KOOS Pain and Function (SRA) scores: the proportion of patients who responded to treatment at week 104.
- 4) Treatment failure rate: the proportion of patients in each treatment group assessed as treatment failures at week 104 (Note: this analysis was not completed as the low number of treatment failures made this not evaluable)
- 5) Change from Baseline at week 104 in the remaining 3 subscales of the KOOS instrument (i.e., other Symptoms, Knee-Related Quality of Life [QOL], Activities of Daily Living [ADL])

Histological evaluation of structural repair

Of the 144 randomized subjects, 116 underwent a second-look arthroscopy and biopsy at Week 104. There were no differences between the groups in nonparticipation in second-look arthroscopy and biopsy as the 116 patients included 60 MACI group subjects and 56 microfracture group subjects.

The mean ICRS II Overall Assessment score was comparable for the MACI and microfracture groups and there was no difference ($p = 0.717$) between the treatment groups (Table 12).

Table 10. Histology – Microscopic ICRS II Overall Assessment at Week 104: Full Analysis Set

	MACI N = 72	Microfracture N = 72
All Patients With Histology Follow-up Data	n = 60	n = 56
Mean (SD)	64.3 (22.34)	64.5 (22.78)
Median	75.0	70.8
Min, Max	0, 95	7, 97
LS Means	63.82	62.31
Difference (LS Means)	1.52	
p-Values		
Treatment	0.717	
Centre	0.108	

ICRS = International Cartilage Repair Society; LS = least squares; Max = maximum; Min = minimum; SD = standard deviation.

Overall Assessment refers to the overall quality of the repair tissue on a scale from 0 (fibrous tissue) to 100 (articular cartilage).

Source: original BLA 125603-000, MACI0206 final clinical study report, Page 98/946

Reviewer comments:

Nearly 81% of the 144 subjects were included in this analysis, with approximately the same numbers of subjects in each treatment group. It is unclear how this subset was chosen by the sponsor, but 81% provided data and the overall scores of ICRS II at Week 104 did not differ between the MACI and microfracture treatment groups and, in fact were essentially identical.

Imaging Evaluation of Structural Repair

Of the 144 randomized subjects, 134 (69 in MACI group and 65 in microfracture group) had MRI evaluation at Week 52 and 139 (70 in MACI group and 69 in microfracture group) had MRI at Week 104. There were no differences ($p = 0.717$) between the treatment groups, in terms of MRI assessments, at Week 52 ($p=0.744$) and Week 104 ($p=0.920$) (Table 11).

Table 11. MRI degree of defect fill: Full Analysis Set

n (%)	MACI N = 72	Microfracture N = 72	p-Value ^a
Visit 8 (Week 52)			
76 to 100%	35 (48.6)	40 (55.6)	0.744
51 to 75%	20 (27.8)	11 (15.3)	
26 to 50%	7 (9.7)	5 (6.9)	
0 to 25%	7 (9.7)	9 (12.5)	
Measure of agreement	Weighted kappa 95% CI	0.604 0.459, 0.748	
Visit 10 (Week 104)			
76 to 100%	35 (48.6)	41 (56.9)	0.920
51 to 75%	23 (31.9)	12 (16.7)	
26 to 50%	4 (5.6)	7 (9.7)	
0 to 25%	8 (11.1)	9 (12.5)	
Missing (not done)	2 (2.8)	3 (4.2)	
Measure of agreement	Weighted kappa 95% CI	0.571 0.421, 0.722	

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; MRI = magnetic resonance imaging.

p-Value: calculated for MRI degree of defect fill intervals, using a CMH χ^2 Test: Row Means Score Differ ($\alpha = 0.05$) to compare between treatment groups.

Note: MRI as assessed by the independent blinded evaluators by means of consensus.

Degree of Defect Fill is a measure of the completeness of defect repair produced by the graft.

Source: original BLA 125603-000, MACI0206 final clinical study report, Page 99/946

Reviewer Comments:

134 subjects (69 in MACI group and 65 in microfracture group) had MRI evaluation at Week 52 and 139 (70 in MACI group and 69 in microfracture group) had MRI at Week 104. It is notable that there was improvement in defect fill from baseline at both the 52-week and 104-week time points in both treatment groups. Also, there were very little missing data. The defects were filled to more than 50% for the majority of subjects and the proportion of patients with >75% defect fill was comparable between subjects treated with MACI or microfracture. There was no difference between the treatment groups in MRI Degree of Defect Fill at Week 52 or Week 104. The results of the FAS analysis were confirmed by analysis of the PP set (data not shown in this review). Although the outcomes of this secondary endpoint analysis do not support the primary clinical endpoint, the results are still of potential scientific value, especially considering that nearly identical MRI fill-data were found in two treatment groups with small but statistically significantly different clinical outcomes. Perhaps these MRI data are consistent with the fact that both groups had substantial improvement in pain and function. The sponsor conducted an exploratory analysis to see whether, within each treatment group, there is a correlation between degree of fill and KOOS score. This additional study is presented in the section on exploratory analyses. Again, we believe that this MRI information, which is difficult to obtain other than in the context of a well-conducted clinical trial, is important scientifically and should be conveyed to the public.

Analyses of Responder Rate Based on KOOS Pain and KOOS SRA

An overview of the KOOS Pain and Function (SRA) response rate results in the Full Analysis Set population is presented in Table 12. The percentage of subjects who responded to treatment at Week 104 (had at least a 10-point improvement from baseline in both KOOS pain and KOOS SRA) was numerically greater (nominal p-value = 0.016) for subjects in the MACI group compared to the microfracture group.

Table 12. KOOS Response Rate: Full Analysis Set

n (%)	MACI N = 72	Microfracture N = 72	p-Value ^a
Visit 10 (Week 104) Stratified by center			
Responded	63 (87.50)	49 (68.06)	0.016
Not Responded	9 (12.50)	20 (27.78)	
Missing	0	3 (4.17)	
Visit 10 (Week 104) Unstratified			
Responded	62 (86.11)	48 (66.67)	0.011
Not Responded	7 (9.72)	18 (25.00)	
Missing	3 (4.17)	6 (8.33)	

CMH = Cochran-Mantel-Haenszel; KOOS = Knee Injury and Osteoarthritis Outcome Score.
p-Value: calculated for response categories 'Responded' and 'Not responded' using a CMH χ^2 Test ($\alpha = 0.05$) to compare between treatment groups.

KOOS Response Rate: a patient is regarded as a responder for KOOS if a 10-point improvement in both KOOS Pain and Function (SRA) scores was achieved with respect to Baseline. Otherwise, the patient is regarded as a nonresponder.

Source: original BLA 125603-000, MACI0206 final clinical study report, Page 100/946

Results from an analysis in the per protocol population were similar and also reached nominal statistical significance.

Reviewer comments:

The responder analysis shows that the response rates of KOOS pain and KOOS SRA, using a 10-point cutoff, are statistically significantly greater in the MACI group compared to microfracture. The comparison was also statistically significant using the FA set, the PP set (not shown in this review) and in an un-stratified analysis at Week 104. These outcomes support the co-primary endpoint, but the between-group differences in response rates were relatively small (depending on the analysis, 63 subjects in the MACI group (87.5%) vs 49 (68%) in the microfracture group, about 14 more subjects. The general pattern of greater responders in MACI appears in most, but not all treatment centers, but again, the absolute numbers are small.

As noted above, the closed-testing procedure precludes applying formal statistical analysis of this secondary endpoint, since the prior (two) secondary endpoints failed to show statistically significant treatment-group differences. Accordingly, the p-values presented here cannot be used to describe the outcomes. These responder outcomes, if used at all, should be considered exploratory.

The applicant included these results regarding responder rates under the Clinical Studies section of the product label, submitted with the BLA. The clinical review team

*has discussed the issue: on the one hand, this analysis of proportion of responders discloses the proportion of subjects who had clinically meaningful (at least 10-point change from baseline) changes in **both** pain and function, and this information could be useful to health care providers and patients deciding on the type of cartilage repair therapy they choose. As noted above, and based mainly on validation analyses of Roos et al, a 10-point change is clinically meaningful for both pain and function domains. On the other hand, this secondary endpoint was tested for statistical significance after failure of the other two hierarchically “more important” endpoints. As a consequence, we cannot rely on a test of statistical significance that does not provide a prospective adjustment for multiple comparisons and could lead to a higher type 1 error than that prespecified. Because these results are meaningful to physicians and patients, it may be appropriate to permit a description of these outcomes in the product label, but without p-values.*

Analysis of Treatment Failure Rate at Week 104

As the applicant stated in the BLA, the planned analyses concerning treatment failure rates and treatment group differences were not possible due to the small number of per protocol treatment failure cases. The criteria for meeting the definition of treatment failure have been presented earlier in this review.

Five subjects (4 in microfracture group and 1 in MACI group) were referred to the Independent Treatment Failure Evaluation Committee. Of these 5, 2 subjects (both in the microfracture group) were considered to be treatment failures by the Committee, and three subjects were not considered treatment failures. All 3 did not meet the criterion for KOOS Pain score being less than 10% improved from baseline.

Analysis of Changes from Baseline at Week 104 in Other KOOS Score Subscales

From Baseline to Week 104, improvement in the Activities of Daily Living (ADL), Quality of Life (QOL), and Other Symptoms in the FAS population was reported for subjects in both treatment groups; the improvements for all 3 KOOS subscales were significantly greater for subjects in the MACI group compared to the microfracture group.

Across all 3 subscales, the change from Baseline to Week 104 was >25 points within both treatment groups. The between-group difference in LS mean changes in ADL (12, $p < 0.001$), QOL (9, $p = 0.029$), and Other Symptoms (12, $p < 0.001$) were favorable to treatment with MACI.

6.1.11.3 Subpopulation Analyses

Primary Endpoint

To assess the treatment effect of pre-specified subgroups: lesion size, lesion location, etiology, prior surgical history, and sex (referred to as gender by the applicant), the applicant performed analyses by subgroup within the FAS. Statistical testing was not performed within treatment by subgroup or between treatment groups by subgroup due to the smaller numbers of subjects. Changes of KOOS scores from baseline to week 104 were numerically greater in the MACI group compared with the microfracture group for all subgroups, with the exception of subjects with no prior surgery on the target knee, subjects with no prior cartilage repair on the target knee and KOOS function in female subjects, where results between MACI and microfracture were similar.

Results of analysis of three of the pre-specified subgroups for the primary endpoint (KOOS pain and function) are shown below in Table 13.

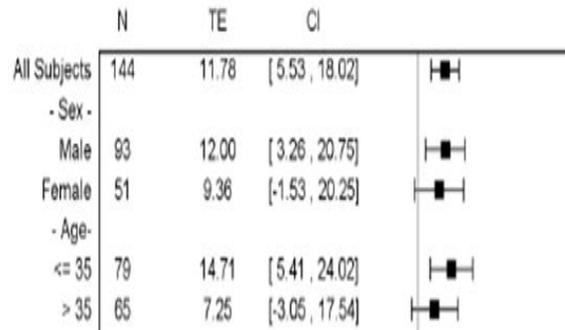
Table 13. Summary of KOOS Pain and Function for Prespecified Subgroups

	MACI		Microfracture	
	Pain	Function (SRA)	Pain	Function (SRA)
Gender: Male; mean (SD)				
	N = 45	N = 45	N = 47	N = 47
Baseline	37.35 (13.26)	15.56 (13.54)	35.93 (12.43)	14.95 (18.55)
Week 104	82.96 (16.95)	66.78 (26.09)	70.17 (25.21)	50.21 (30.37)
Δ to Week 104	45.62 (19.45)	51.22 (28.07)	34.40 (24.41)	35.27 (30.68)
Gender: Female; mean (SD)				
	N = 27	N = 27	N = 22	N = 22
Baseline	36.42 (14.17)	13.70 (16.62)	34.49 (11.61)	7.92 (11.12)
Week 104	81.58 (15.06)	51.11 (28.36)	72.35 (22.38)	45.45 (30.70)
Δ to Week 104	45.16 (23.94)	37.41 (27.15)	36.99 (23.26)	37.05 (34.28)
Index Lesion >5 cm²; mean (SD)				
	N = 21	N = 21	N = 21	N = 21
Baseline	35.32 (12.46)	12.14 (14.10)	31.75 (13.19)	10.89 (21.12)
Week 104	85.71 (10.51)	62.86 (29.01)	75.13 (26.17)	54.05 (30.97)
Δ to Week 104	50.40 (17.51)	50.71 (28.56)	43.39 (28.63)	43.15 (36.87)
Etiology: Osteochondritis dissecan; mean (SD)				
	N = 8	N = 8	N = 12	N = 12
Baseline	32.29 (12.15)	15.00 (16.69)	32.18 (14.29)	11.15 (16.98)
Week 104	87.50 (13.11)	68.13 (26.04)	76.39 (23.50)	60.83 (31.39)
Δ to Week 104	55.21 (21.23)	53.13 (27.77)	44.21 (20.50)	46.69 (31.48)
Etiology: No Osteochondritis dissecan; mean (SD)				
	N = 64	N = 64	N = 57	N = 57
Baseline	37.59 (13.65)	14.84 (14.56)	36.11 (11.63)	12.86 (16.74)
Week 104	81.81 (16.50)	60.00 (28.12)	69.71 (24.40)	46.21 (29.77)
Δ to Week 104	44.23 (20.91)	45.16 (28.51)	33.33 (24.31)	32.92 (31.15)

Source: Table 31 of Study MACI00206 – Study Report Body, pages 117 – 120 / 946.

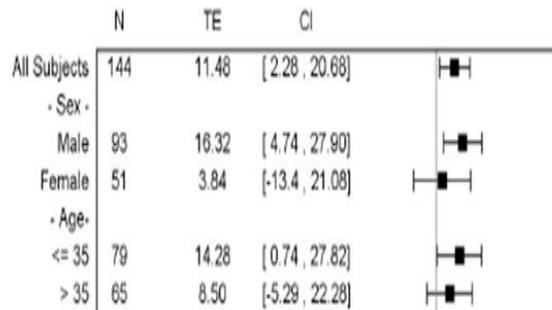
The sponsor also provided figures showing outcomes by age, using a binary cut-off of 35 years. These data, together with outcomes by sex, are shown below (Sponsor's Figures 14 and 15)

Figure 14: KOOS Pain Treatment Effect (95% CI) at Year 2 (Month 24) Subgroup Analyses: SUMMIT



TE = Treatment Effect

Figure 15: KOOS Function (Sports and Recreational Activities) Treatment Effect (95% CI) at Year 2 (Month 24) Subgroup Analyses: SUMMIT



Reviewer Comments:

The data demonstrate consistency of primary outcomes across age and gender, in that the point estimates all lie to the right of the vertical (0) demarcation. However, for females and for all subjects >35, the lower boundary of the 95% CI included 0 for both pain and function.

Regarding subgroup analyses by lesion size and etiology: Analysis by lesions larger than 5 cm² is important because of the prevalent notion that microfracture is more effective in smaller lesions. Lesion size did not appear to influence the effect of MACI versus microfracture in the SUMMIT study. According to the sponsor's data, results for subjects with index lesions >5 cm² were similar to those for subjects with smaller lesions.

Analysis by etiology is important because of the indication sought by the applicant --- namely, full thickness cartilage defects (b) (4)

(b) (4)

During the review, the applicant was requested to provide further information regarding treatment effect (primary endpoints) by age quartile, as well as treatment effect by body mass index (BMI). The applicant provided the following two tables. Data for treatment effect by age quartile are shown in the following table.

Table 1: Summary of KOOS Pain and Function by Age Subgroup

	MACI		Microfracture	
	Pain	Function (SRA)	Pain	Function (SRA)
Full Analysis Set LOCF; mean (SD)				
	N = 72	N = 72	N = 72	N = 72
Baseline	37.00 (13.52)	14.86 (14.68)	35.45 (12.09)	12.57 (16.67)
Week 104	82.45 (16.18)	60.90 (27.84)	70.85 (24.22)	48.71 (30.33)
Δ to Week 104	45.45 (21.08)	46.04 (28.35)	35.23 (23.91)	35.83 (31.63)
Age 18 to 26 years; mean (SD)				
	N = 14	N = 14	N = 18	N = 18
Baseline	35.71 (12.98)	13.57 (12.62)	38.24 (11.77)	16.18 (13.05)
Week 104	90.48 (9.23)	68.57 (25.90)	76.16 (25.45)	60.83 (31.82)
Δ to Week 104	54.76 (17.31)	55.00 (26.09)	38.73 (25.60)	45.29 (35.55)
Age 27 to 35 years; mean (SD)				
	N = 24	N = 24	N = 23	N = 23
Baseline	39.58 (11.39)	15.83 (15.08)	36.71 (12.28)	13.21 (14.85)
Week 104	83.68 (13.98)	62.71 (31.07)	67.03 (26.02)	42.17 (28.64)
Δ to Week 104	44.10 (17.90)	46.88 (30.10)	30.31 (25.28)	28.97 (29.91)
Age 36 to 44 years; mean (SD)				
	N = 24	N = 24	N = 25	N = 25
Baseline	34.61 (14.33)	13.13 (14.58)	34.78 (11.95)	11.75 (21.45)
Week 104	79.51 (19.76)	56.04 (24.85)	72.80 (19.69)	49.38 (28.37)
Δ to Week 104	44.91 (23.95)	42.92 (25.58)	37.96 (18.78)	37.34 (30.24)
Age 45 to 54 years; mean (SD)				
	N = 10	N = 10	N = 6	N = 6
Baseline	38.33 (17.46)	18.50 (17.80)	25.46 (10.00)	3.33 (4.08)
Week 104	75.28 (16.11)	57.50 (30.39)	60.00 (32.07)	32.00 (34.21)
Δ to Week 104	36.94 (23.83)	39.00 (34.06)	32.78 (36.24)	28.00 (32.13)

Reviewer Comments:

Positive changes from baseline in both pain and function at Week 104 were seen in all 16 “cells.” A positive treatment effect was seen for all treatment-group comparisons (MACI vs microfracture) --- that is, for both pain and function for all four age quartiles. The treatment-effect sizes (ranging from a low of 4 to a high of 16) were highest in the two youngest age groups, with the youngest group demonstrating the highest improvement scores for both pain and function in both MACI and microfracture subjects. The most consistent (monotonic) age-related decline was in baseline-subtracted function in the MACI group. The 10 subjects in the oldest MACI quartile showed the lowest baseline-subtracted improvements in both pain and function.

Overall, although the numbers are small, particularly in the oldest quartile, the data suggest a decline in robustness of outcomes in the oldest group.

The applicant provided data on primary effectiveness outcomes according to BMI in the following table.

Table 2: Summary of KOOS Pain and Function by BMI Subgroup

	MACI		Microfracture	
	Pain	Function (SRA)	Pain	Function (SRA)
Full Analysis Set LOCF; mean (SD)				
	N = 72	N = 72	N = 72	N = 72
Baseline	37.00 (13.52)	14.86 (14.68)	35.45 (12.09)	12.57 (16.67)
Week 104	82.45 (16.18)	60.90 (27.84)	70.85 (24.22)	48.71 (30.33)
Δ to Week 104	45.45 (21.08)	46.04 (28.35)	35.23 (23.91)	35.83 (31.63)
BMI <25 kg/m²; mean (SD)				
	N = 29	N = 28	N = 28	N = 28
Baseline	38.70 (12.53)	13.79 (13.93)	38.99 (10.54)	14.11 (11.55)
Week 104	79.89 (20.46)	59.83 (29.05)	68.25 (25.82)	49.11 (33.45)
Δ to Week 104	41.19 (24.14)	46.03 (31.46)	29.27 (24.20)	35.00 (34.80)
BMI ≥25 kg/m²; mean (SD)				
	N = 42	N = 42	N = 40	N = 40
Baseline	35.65 (14.28)	15.24 (15.30)	33.89 (12.27)	11.81 (19.93)
Week 104	84.26 (12.61)	62.02 (27.52)	74.97 (21.03)	50.13 (28.14)
Δ to Week 104	48.61 (18.61)	46.79 (26.29)	40.95 (22.46)	38.01 (29.55)

Reviewer Comments:

The data show consistency of results according to BMI. Heavier subjects in both treatment groups showed greater increases in pain scores, compared to Improvements in function scores, which tended to remain stable across BMI groups. However, the

treatment-effect size for both pain and function was smaller in the heavier group, compared to that in the subjects with BMI < 25kg/m²

Analysis by site: Table 14 shows results by clinical site.

Table 14. Summary of KOOS Pain and Function by Site

	MACI		Microfracture	
	Pain	Function (SRA)	Pain	Function (SRA)
Full Analysis Set LOCF; mean (SD)				
	N = 72	N = 72	N = 72	N = 72
Baseline	37.00 (13.52)	14.86 (14.68)	35.45 (12.09)	12.57 (16.67)
Week 104	82.45 (16.18)	60.90 (27.84)	70.85 (24.22)	48.71 (30.33)
Δ to Week 104	45.45 (21.08)	46.04 (28.35)	35.23 (23.91)	35.83 (31.63)
Site 01	N = 4	N = 4	N = 4	N = 4
Baseline	50.00 (3.93)	30.00 (17.32)	45.14 (6.16)	23.75 (24.96)
Week 104	76.39 (15.13)	63.75 (17.50)	76.39 (8.02)	46.25 (18.87)
Δ to Week 104	26.39 (12.53)	33.75 (20.56)	31.25 (6.16)	22.50 (15.55)
Site 02	N = 4	N = 4	N = 3	N = 3
Baseline	36.11 (23.02)	7.50 (15.00)	38.89 (0)	8.33 (10.41)
Week 104	90.28 (13.13)	67.50 (34.28)	80.56 (11.11)	53.33 (16.07)
Δ to Week 104	54.17 (20.60)	60.00 (27.39)	41.67 (11.11)	45.00 (26.46)
Site 03	N = 5	N = 5	N = 4	N = 4
Baseline	38.89 (14.96)	23.00 (18.91)	37.50 (8.64)	15.00 (7.07)
Week 104	76.11 (21.39)	49.00 (36.81)	61.81 (23.39)	35.00 (30.28)
Δ to Week 104	37.22 (10.87)	26.00 (26.32)	24.31 (27.72)	20.00 (35.36)
Site 05	N = 5	N = 5	N = 5	N = 5
Baseline	25.00 (5.20)	3.00 (2.74)	18.52 (7.17)	0.83 (2.04)
Week 104	86.11 (10.58)	67.00 (27.75)	56.11 (39.79)	33.00 (41.02)
Δ to Week 104	61.11 (14.57)	64.00 (25.35)	37.22 (35.61)	32.00 (42.07)
Site 11	N = 20	N = 20	N = 20	N = 20
Baseline	38.08 (13.22)	11.50 (14.15)	35.97 (14.18)	8.75 (10.50)
Week 104	81.67 (13.77)	55.75 (32.90)	75.00 (23.78)	53.00 (30.84)
Δ to Week 104	43.61 (20.03)	44.25 (31.43)	39.03 (22.23)	44.25 (30.19)
Site 12	N = 5	N = 5	N = 6	N = 6
Baseline	38.89 (13.18)	11.00 (8.94)	36.57 (8.68)	21.46 (36.06)
Week 104	77.78 (14.83)	60.00 (22.36)	68.98 (25.48)	37.50 (21.39)
Δ to Week 104	38.89 (21.70)	49.00 (25.84)	32.41 (19.62)	16.04 (27.05)

	MACI		Microfracture	
	Pain	Function (SRA)	Pain	Function (SRA)
Site 14	N = 3	N = 3	N = 3	N = 3
Baseline	32.41 (16.74)	20.00 (26.46)	41.67 (7.35)	11.67 (16.07)
Week 104	66.67 (22.22)	48.33 (29.30)	40.74 (8.49)	8.33 (10.41)
Δ to Week 104	34.26 (38.92)	28.33 (36.17)	-0.93 (15.80)	-3.33 (5.77)
Site 15	N = 9	N = 9	N = 8	N = 8
Baseline	43.83 (7.05)	26.67 (9.01)	41.05 (11.09)	18.33 (18.87)
Week 104	89.20 (9.15)	61.11 (23.82)	81.94 (11.97)	66.88 (26.45)
Δ to Week 104	45.37 (11.11)	34.44 (17.93)	39.93 (15.85)	46.88 (32.62)
Site 18	N = 4	N = 4	N = 4	N = 4
Baseline	25.00 (5.56)	10.00 (7.07)	24.31 (4.17)	6.25 (7.50)
Week 104	90.28 (8.64)	73.75 (18.87)	96.53 (2.66)	83.75 (11.09)
Δ to Week 104	65.28 (11.68)	63.75 (24.96)	72.22 (6.00)	77.50 (17.08)
Site 21	N = 4	N = 4	N = 3	N = 3
Baseline	33.33 (15.21)	10.00 (12.25)	34.26 (6.42)	25.00 (8.66)
Week 104	70.14 (32.19)	61.25 (33.01)	48.96 (12.80)	55.00 (33.17)
Δ to Week 104	36.81 (25.19)	51.25 (34.25)	10.19 (12.83)	31.67 (32.53)
Site 23	N = 3	N = 3	N = 4	N = 4
Baseline	26.85 (16.97)	5.00 (5.00)	30.56 (8.78)	2.50 (2.89)
Week 104	88.89 (2.78)	53.33 (23.63)	59.72 (34.88)	27.50 (20.62)
Δ to Week 104	62.04 (18.07)	48.33 (18.93)	29.17 (26.30)	25.00 (20.41)

Three sites were not included in the table: data not available for Site 29; Sites 17 and 19 had only 1 patient.

Note: 'N's in the table reflect the number of patients used to calculate change from baseline.

Source: Table 30 in the application, pages 115-116.

Reviewer Comments:

Since surgeon's skill and training can influence the outcomes, it is particularly important to look at differences according to sites. For this application, the sites with the greatest number of enrolled subjects had effects consistent with the overall FAS population. Smaller sites had effects much larger or smaller than the overall population: for example, in Site 14 (n = 3 per group) the effect was amplified due to worsening scores in subjects with microfracture and was minimized in Site 18 (n=4 per group), where the effect in MACI-treated subjects was smaller than that seen in the microfracture group, even though both groups had large improvements.

Secondary Endpoints

To assess the impact of pre-specified subgroups (lesion size, lesion location, etiology, prior surgical history, and gender) on efficacy, analyses were performed by subgroup within the FAS. Statistical testing was not performed within treatment by subgroup or between treatment groups by subgroup due to the smaller numbers of subjects. The

outcomes of these subgroup analyses of secondary endpoints are not directly pertinent to this BLA review and will not be presented here.

6.1.11.4 Dropouts and/or Discontinuations

Seven subjects (4.8%) withdrew from the study after randomization but prior to study completion. Of these 7 subjects (2 [2.8%] MACI and 5 [6.9%] microfracture), 6 completed evaluations for ≥ 1 year, and 1 completed evaluations for 9 months. Of the 7 subjects, 2 subjects withdrew due to adverse events (1 subject in MACI group and 1 subject in microfracture group), 2 subjects withdrew consent (1 subject in MACI group and 1 subject in microfracture group), and 3 subjects withdrew due to lack of efficacy (3 subjects in microfracture group).

6.1.11.5 Exploratory and Post Hoc Analyses

Exploratory analyses were conducted to evaluate MRI as an appropriate tool for assessing structural repair. The MRI results for Degree of Defect Fill, Graft Integration, and Signal Intensity were compared with the 5 KOOS subscales and 14 ICRS II histology parameters. In addition, post hoc exploration was performed to evaluate the association of change from Baseline in KOOS Pain and KOOS SRA at Week 104 by ICRS II Overall Assessment.

Comparison of MRI measurements and KOOS Scores (Pain and SRA)

There were no associations found between the MRI and KOOS data at Week 52 ($p=0.342$) and Week 104 ($p=0.508$). The test of overall multivariate multiple regression was not statistically significant ($P= 0.508$).

Reviewer comments:

There were no associations between the MRI outcomes and KOOS data at Week 52 and Week 104. These results, as well as the (negative) outcomes for MRI as secondary endpoints, while negative and not directly pertinent to a review decision, are of potential scientific value to investigators and sponsors in this field and should be disseminated by the applicant, although this is not a regulatory requirement.

Comparison of MRI measurements and Histology Assessments

At week 104, there were no associations found between the MRI and microscopic ICRS II histology data. The canonical correlation between MRI and histology was estimated at 0.469, and was not statistically significant ($p = 0.779$). The univariate correlations were weak and ranged from -0.103 to 0.104.

Reviewer comments:

There were no associations between the MRI and ICRS II histology data at Week 104. Again, these results, although negative, are of potential scientific value to investigators and sponsors.

Comparison of KOOS Scores (pain and SRA) and Histology Assessments

As a post hoc exploration, there was a lack of association between the KOOS pain and KOOS SRA and the overall histology assessment score ($p=0.145$).

Reviewer comments:

There were no associations between KOOS scores (pain and SRA) and ICRS II histology data at Week 104. Again, these outcomes are of potential scientific value to investigators in the field of cartilage repair.

6.1.12 Safety Analyses

6.1.12.1 Methods

The SUMMIT study evaluated the single treatment of cartilage lesion(s) at the index knee in 144 patients treated with MACI (72 subjects) or microfracture (72 subjects). The proposed safety study endpoints in this study are listed below:

- Rate of treatment-emergent adverse events (TEAEs)
- Rate of treatment-emergent serious adverse events (SAEs)
- Rate of subsequent surgical procedures (SSPs)
- Physical examination and knee examination findings

6.1.12.2 Overview of Adverse Events

A brief summary of all reported AEs is presented in Table 15 by category. No subjects died in the study.

All Adverse Events

The following is an overview of TEAEs reported in >5% of subjects in either treatment group, regardless of severity and relationship to study treatment. Treatment-emergent AEs were most frequently reported within the system organ class (SOC) of musculoskeletal and connective tissue disorders for both treatment groups (48 subjects [66.7%] in the MACI group and 52 subjects [72.2%] in the microfracture group).

By preferred term (PT), the most common (>10% of subjects in any treatment group) TEAEs were nasopharyngitis (13.9% in the MACI group versus 9.7% in the microfracture group), cartilage injury (4.2% MACI versus 12.5% microfracture), arthralgia (51.4% versus 63.9%), back pain (11.1% versus 9.7%), and headache (18.1% versus 29.2%). Three events occurred with $\geq 5\%$ difference in frequency between treatment groups: cartilage injury, based on the investigator's clinical judgment (4.2% in MACI group vs. 12.5% in microfracture group), arthralgia (51.4% in MACI group vs. 63.9% in microfracture group), and headache (18.1% in MACI group vs. 29.2% in microfracture group), (Table 15).

Table 15. Treatment-Emergent Adverse Events per System Organ Class and Preferred Term Reported in >5% of Subjects in Any Treatment Group – Safety Set

n (%)	MACI N = 72	Microfracture N = 72
Any TEAE	55 (76.4)	60 (83.3)
Gastrointestinal Disorders	6 (8.3)	7(9.7)
Abdominal pain	0 (0.0)	5 (6.9)
General Disorders and Administration Site Conditions	10 (13.9)	10 (13.9)
Pyrexia	4 (5.6)	2 (2.8)
Treatment failure	1 (1.4)	4 (5.6)
Infections and Infestations	23 (31.9)	17 (23.6)
Influenza	4 (5.6)	5 (6.9)
Nasopharyngitis	10 (13.9)	7 (9.7)
Injury, Poisoning and Procedural Complications	19 (26.4)	20 (27.8)
Cartilage injury	3 (4.2)	9 (12.5)
Procedural pain	3 (4.2)	4 (5.6)
Musculoskeletal and Connective Tissue Disorders	48 (66.7)	52 (72.2)
Arthralgia	37 (51.4)	46 (63.9)
Back pain	8 (11.1)	7 (9.7)
Joint effusion	5 (6.9)	4 (5.6)
Joint swelling	7 (9.7)	4 (5.6)
Ligament sprain	2 (2.8)	
Nervous System Disorders	16 (22.2)	24 (33.3)
Headache	13 (18.1)	21 (29.2)
Respiratory, Thoracic and Mediastinal Disorders	5 (6.9)	5 (6.9)

MedDRA = Medical Dictionary for Regulatory Activities, TEAE = treatment-emergent adverse event.

System Organ Class and Preferred Term are ordered alphabetically. AEs were coded using MedDRA Version 14.1.

TEAE: defined as an AE with a start date beyond or equal to that of study treatment at Day 1.

If a patient experienced more than 1 AE with the same Preferred Term or Primary System Organ Class, each subject was counted at most once within each Preferred Term or Primary System Organ Class.

A cut-off point of 5% was applied to the incidence of Preferred Terms.

Source: original BLA 125603-000, MACI0206 final clinical study report, Page 131/946, Page 807/946 and Page 815/946

During the early part of the trial, the treatment of the MACI group differed from that of the microfracture group, due to the nature of the two treatments. Thirteen subjects (18.1%) in the MACI group had at least 1 AE during the time between arthroscopy and MACI implantation. Among these 13 subjects, arthralgia (4 subjects, 5.6%) and hemarthrosis (2 subjects, 2.8%) were the only AEs reported in more than 1 subject (Table 16).

Table 16. Incidence of AEs between Arthroscopy and MACI Implantation All Subjects Randomized (To MACI Only)

Primary SOC PT	Statistic	MACI (N=72)
Number of Patients With at Least One AE	n (%)	13 (18.1)
Immune System Disorders	n (%)	1 (1.4)
Drug Hypersensitivity	n (%)	1 (1.4)
Infections And Infestations	n (%)	3 (4.2)
Gastroenteritis	n (%)	1 (1.4)
Influenza	n (%)	1 (1.4)
Postoperative Wound Infection	n (%)	1 (1.4)
Injury, Poisoning And Procedural Complications	n (%)	1 (1.4)
Post Procedural Complication	n (%)	1 (1.4)
Investigations	n (%)	1 (1.4)
Hiv Test Positive	n (%)	1 (1.4)
Musculoskeletal And Connective Tissue Disorders	n (%)	6 (8.3)
Arthralgia	n (%)	4 (5.6)
Haemarthrosis	n (%)	2 (2.8)
Joint Effusion	n (%)	1 (1.4)
Joint Range Of Motion Decreased	n (%)	1 (1.4)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	n (%)	1 (1.4)
Prostate Cancer	n (%)	1 (1.4)

Source: original BLA 125603-000, MACI0206 final clinical study report, Page 852/946

AEs by severity

In both treatment groups, the majority of TEAEs were of mild or moderate intensity. 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 severe TEAE reported in >5% of subjects in any treatment group was arthralgia (2 subjects [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 subject [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).

Reviewer comments:

The overall incidence of TEAEs and severe AEs was lower in the MACI group relative to the microfracture group for all categories with the exception of discontinuations from study due to TEAEs (1 subject in each treatment group discontinued due to AEs).

6.1.12.3 Deaths

No deaths occurred in the study.

6.1.12.4 Nonfatal Serious Adverse Events

An overview of treatment-emergent SAEs, regardless of severity and relationship to study treatment, is provided in Table 17.

Table 17. Treatment-Emergent SAEs per System Organ Class and Preferred Term – Safety Set

n (%)	MACI N = 72	Microfracture N = 72
Any TESAE	11 (15.3)	19 (26.4)
Cardiac Disorders	1 (1.4)	0 (0.0)
Arrhythmia	1 (1.4)	0 (0.0)
Gastrointestinal Disorders	0 (0.0)	1 (1.4)
Abdominal pain	0 (0.0)	1 (1.4)
General Disorders and Administration Site Conditions	2 (2.8)	4 (5.6)
Impaired healing	1 (1.4) ^a	1 (1.4) ^a
Treatment failure	1 (1.4) ^a	4 (5.6) ^a
Infections and Infestations	1 (1.4)	1 (1.4)
Pneumonia	1 (1.4)	0 (0.0)
Postoperative wound infection	0 (0.0)	1 (1.4)
Wound infection staphylococcal	0 (0.0)	1 (1.4)
Injury, Poisoning and Procedural Complications	5 (6.9)	7 (9.7)
Cartilage injury	2 (2.8)	6 (8.3)
Graft delamination	1 (1.4) ^a	0 (0.0)
Head injury	0 (0.0)	1 (1.4)
Meniscus lesion	2 (2.8)	0 (0.0)
Transplant failure	1 (1.4) ^a	0 (0.0)
Traumatic fracture	0 (0.0)	1 (1.4)
n (%)	MACI N = 72	Microfracture N = 72
Musculoskeletal and Connective Tissue Disorders	1 (1.4)	7 (9.7)
Arthralgia	0 (0.0)	3 (4.2) ^a
Arthritis	0 (0.0)	1 (1.4)
Joint lock	0 (0.0)	1 (1.4) ^a
Knee deformity	1 (1.4)	0 (0.0)
Loose body in joint	0 (0.0)	1 (1.4)
Osteochondrosis	0 (0.0)	1 (1.4)
Pain in extremity	0 (0.0)	1 (1.4)
Patellofemoral pain syndrome	0 (0.0)	1 (1.4)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	1 (1.4)	0 (0.0)
Prostate cancer	1 (1.4)	0 (0.0)
Nervous System Disorders	0 (0.0)	1 (1.4)
Multiple sclerosis	0 (0.0)	1 (1.4)
Pregnancy, Puerperium and Perinatal Conditions	1 (1.4)	1 (1.4)
Abortion spontaneous	1 (1.4)	1 (1.4)
Renal and Urinary Disorders	1 (1.4)	0 (0.0)
Urinary retention	1 (1.4)	0 (0.0)
Respiratory, Thoracic and Mediastinal Disorders	1 (1.4)	1 (1.4)
Pulmonary embolism	1 (1.4)	1 (1.4) ^a
Vascular Disorders	1 (1.4)	0 (0.0)
Thrombosis	1 (1.4)	0 (0.0)

AEs were coded using MedDRA Version 14.1. Treatment-emergent: defined as an SAE with a start date beyond or equal to that of study treatment at Day 1. Data is based on Table 38 of the full clinical study report, page 134-135.

Reviewer Comments:

Treatment-emergent SAEs were reported more frequently in the microfracture group (26.4%) than in the MACI group (15.3%). Treatment-emergent SAEs reported in more than 1 subject within any treatment group were treatment failure (1 subject [1.4%] in the MACI group and 4 subjects [5.6%] in the microfracture group), cartilage injury (2 subjects [2.8%] in the MACI group and 6 subjects [8.3%] in the microfracture group), meniscus lesion (2 subjects [2.8%] in the MACI group and no subjects in the microfracture group), and arthralgia (no subjects in the MACI group and 3 subjects [4.2%] in the microfracture group). Based upon the information from the Case Report Forms, 10 subjects (03007, 05002, 05013, 06002, 15001, 15008, 18005, 21010, 23006 and 23011) in the microfracture group were hospitalized compared to 4 subjects (11010, 18007, 23005 and 23009) in MACI group. The difference in incidence rates was mainly due to more serious cases of treatment failure, cartilage injury, and arthralgia in the microfracture group compared with the MACI group.

6.1.12.5 Adverse Events of Special Interest (AESI)

Adverse Dropouts

One subject (1.4%) in each treatment group prematurely discontinued the study due to TEAEs (Original BLA 125603-000, MACI0206 final clinical study report, Page 877-878/946).

In the MACI group, Subject 11010 was reported to have impaired healing, arthralgia, and headache. The subject was discontinued from the study on Study Day 619 due to event of impaired healing of the target knee; the event was considered by the Investigator to be moderate in intensity and possibly related to study treatment. The Investigator considered the impaired healing as remote/unlikely related to overall surgery.

In the microfracture group, Subject 06002 was reported with head injury and traumatic fracture due to a car accident; both events were considered by the Investigator to be severe in intensity and not related to study treatment or to overall surgery. The patient was discontinued from the study on Study Day 724.

Adverse Events related to the surgical procedure

The safety evaluation included protocol-defined AEs of special interest: those related to potential perioperative complications in relation to the arthroscopy or arthrotomy (such as hemarthrosis, hematomas, arthrofibrosis, local surgical site infection) and those potentially related to the MACI product (specifically: symptomatic graft hypertrophy, graft delamination leading to loose bodies in the joint, or graft failure). Table 20 lists these AEs of special interest by treatment group.

Table 18. Adverse Events of Interest per System Organ Class and Preferred Term: Safety Set

n (%)	MACI N = 72	Microfracture N = 72
Any AE of Interest	7 (9.7)	3 (4.2)
Infections and Infestations	1 (1.4)	0 (0.0)
Postoperative wound infection	1 (1.4)	0 (0.0)
Injury, Poisoning and Procedural Complications	1 (1.4)	0 (0.0)
Graft Delamination	1 (1.4)	0 (0.0)
Musculoskeletal and Connective Tissue Disorders	3 (4.2)	2 (2.8)
Arthritis	0 (0.0)	1 (1.4)
Arthrofibrosis	1 (1.4)	0 (0.0)
Hemarthrosis	2 (2.8)	1 (1.4)
Respiratory, Thoracic and Mediastinal Disorders	1 (1.4)	1 (1.4)
Pulmonary embolism	1 (1.4)	1 (1.4)
Vascular Disorders	2 (2.8)	0 (0.0)
Deep vein thrombosis	1 (1.4)	0 (0.0)
Thrombosis	1 (1.4)	0 (0.0)

Data is based on Table 39 of the MACI00206 full clinical study report, Page 136/ 946.

Reviewer Comment:

Actually, there were 8 AEs of special interest in the MACI group. Hemarthrosis was the only AE of interest reported in more than 1 subject in any treatment group (2 subjects [2.8%] in the MACI group and 1 subject [1.4%] in the microfracture group).

Subsequent surgical procedures

Subsequent surgical procedures (SSPs) were defined as any surgical procedure performed on the target knee joint in the study, the methods of which might include arthroscopy, arthrotomy, or manipulation under anesthesia. Multiple interventions might be performed at the time of the SSP, but not all SSPs were considered as an indication of treatment failure. For example, a minor trimming of hypertrophic repair tissue was not considered treatment failure, per protocol, while extensive debridement for lesion expansion, or violation of the subchondral bone was a re-treatment (SSP) defined as treatment failure per protocol. All SSPs were recorded as AEs, and any clinically significant findings were considered important medical events and, therefore, SAEs.

An overview of the number of subjects with SSPs is provided in Table 19.

Table 19. Overview of Subsequent Surgical Procedures – Safety Set

n (%)	MACI N = 72	Microfracture N = 72
Any SSP	6 (8.3)	7 (9.7)
1 SSP	6 (8.3)	5 (6.9)
2 SSPs	0	2 (2.8)

Data is based on Table 40 of the full clinical study report, Page 137/946.

Reviewer Comment:

The proportion of subjects with at least 1 SSP was comparable for the 2 treatment groups (8.3% in the MACI group and 9.7% in the microfracture group).

Pregnancies

Subject 29004 in the MACI group and subject 11024 in the microfracture group were reported to have spontaneous abortions (Source: original BLA 125603-000, maci0206 16.2.7 Adverse Event Listing, Page 15/221). These events were classified as serious.

Subject 23002 in the microfracture treatment group was reported with a non-serious event of gestational hypertension that was considered by the Investigator as mild and not related to study treatment or to overall surgery; the subject was treated with medication and the outcome was described as recovered.

Reviewer comments:

Spontaneous abortion (which occurred in one subject in MACI and one in microfracture) can occur in this young patient population. The microfracture-treated subject aborted two years after treatment. The MACI-treated subject aborted six months after treatment. It is impossible to conclude that these abortion events were due to microfracture treatment or MACI implantation.

Concurrent Surgical Procedures (CSPs) at Baseline and Week 104

For subjects in the MACI group, CSPs include those occurring during either the Visit 2 (Arthroscopy and cartilage biopsy) or the Visit 3 surgeries (MACI implantation) or at the Week 104 (i.e., final) visit core biopsy, while for subjects in the microfracture group, CSPs include those occurring during the Visit 2 surgery (arthroscopy, cartilage biopsy, and microfracture treatment) or at the Week 104 (i.e., final) visit core biopsy.

Concurrent surgical procedures were limited to procedures permitted during the index Arthroscopy --- such as, debridement, ligament repair or reconstruction, and meniscal repair. An overview is listed in Table 6-1-45 of CSPs reported in subjects in the FAS for whom a biopsy was done during the Visit 2 or 3 surgery or during the Week 104 (i.e., final) visit core biopsy.

During the cartilage biopsy/implantation, CSPs were performed in approximately one-third of subjects in both treatment groups, while during the core biopsy at Week 104, CSPs were performed in approximately one-fourth of subjects in both treatment groups.

For both treatment groups, loose body removal was the most frequently performed CSP during the cartilage biopsy/implantation and the core biopsy at Week 104, followed by synovectomy or synovial plica excision.

6.1.12.6 Clinical Test Results

Clinical laboratory tests were not assessed during the study. Other clinical and imaging / histologic assessments were study endpoints and their results are described under the efficacy results in this review document.

6.1.12.7 Dropouts and/or Discontinuations

Seven subjects (2 [2.8%] MACI and 5 [6.9%] microfracture) withdrew prior to completion of the study (Week 104); 6 completed evaluations for ≥ 1 year, and 1 completed evaluations for 9 months. Of the 7 subjects, 2 subjects withdrew due to adverse events (1 MACI and 1 microfracture), 2 withdrew consent (1 MACI and 1 microfracture), and 3 subjects withdrew due to lack of efficacy (all 3 in the microfracture group).

6.1.13 Study Summary and Conclusions

SUMMIT was a randomized, active-controlled (microfracture), multicenter study conducted in 16 sites in 7 European countries. The study was adequately designed and powered to ascertain the efficacy of MACI, with regard to the co-primary endpoints, KOOS pain and SRA (function). Although not conducted under an IND, or following FDA review, the study was conducted according to FDA guidance. Each treatment group had 72 subjects (1:1 randomization) and they were followed for 2 years after the initial procedure(s).

The primary analysis was conducted with MANOVA comparing the change from baseline to Week 104 in both groups in the ITT population. Missing data were to be imputed using LOCF for the primary analysis (MI for sensitivity analysis).

Of those 144 subjects enrolled, only seven dropped out during the 2-year study period. The randomized groups were generally well balanced for demographic and important baseline characteristics. Mean pain and function scores improved substantially in both groups (LS Means for MACI change from baseline was 44 for pain and 46 for function. In the microfracture group, the LS means scores improved 32 for pain and 37 for function. The between-group treatment difference in change from baseline was 12 for pain and 11 for function, which met statistical significance for both co-primary endpoints. The threshold improvement of 10 points for each of the KOOS subscores is generally considered a clinically meaningful effect by several authors, including the creator of the KOOS instrument and those who validated it. By this criterion, both treatments provided substantial mean improvement in pain and function to subjects, with MACI being superior to microfracture. Although these results show success of the investigational treatment, it is important to repeat that these are based on a single trial (without replication of findings), and based on a patient-reported outcome instrument in an open-label trial. Of the seven dropout subjects, 3 were due to subject-perceived lack of efficacy and all 3 had been randomized to microfracture. Of the 5 subjects referred to the Independent Treatment Failure Evaluation Committee, only two were considered treatment failures and both subjects had been treated with microfracture. All sensitivity analyses confirmed the superiority of MACI over microfracture.

Genzyme, the sponsor of the SUMMIT study, had listed secondary endpoints in order of hierarchical importance, as follows:

1. histology assessment of the structural repair from a harvested biopsy in the index lesion at Week 104
2. MRI assessment of the surgical repair at Week 104
3. Responder rate based on both pain and function scores meeting the threshold of at least 10 points
4. Treatment failure rate
5. Change from baseline in the 3 remaining subscales of KOOS (other symptoms, activities of daily living and quality of life).

Of these secondary endpoints, the clinical review team would have liked to see an effect on histology and / or MRI, which could serve to strengthen the findings based on a PRO in an open-label trial. Unfortunately, the results for these first two secondary endpoints were not statistically significant between the groups, although they both show improvements from baseline. Because of the hierarchical order of testing, statistical inference for the responder rate cannot be assessed, due to the potential inflation of the type 1 error. Responder rate would have been an informative endpoint, as it indicates the proportion of subjects who have achieved benefits in both pain and function in each of the groups. The results here also favored MACI, but again statistical testing could not be conducted.

Given the invasive nature of both treatments, the safety assessments did not reveal any surprises: most AEs were related to the surgical procedures themselves, regardless of the specific treatment. There were no deaths and no clinically significant findings of cartilage hypertrophy or migration in the MACI group. The profile of SAEs was not unexpected for the procedures: most reported events were associated with the surgery or the surgical site. For the few systemic SAEs, there were no imbalances between the groups. Uncommon events, such as thrombosis and pulmonary embolism in one subject in the MACI group (none in microfracture), are not unexpected for the type of surgery and subsequent immobilization.

6.2 Trial #2

SUMMIT Extension Study

The applicant considered SUMMIT Extension a second trial, but the FDA clinical review team considers this as a 3-year extension of the SUMMIT Study --- that is, SUMMIT Extension cannot be considered as an independent clinical trial. According to the protocol for SUMMIT Extension, all subjects randomized in SUMMIT who completed that study would be eligible to participate in the extension study. Thus, SUMMIT Extension was a 3-year, open label, multicenter, non-randomized but controlled (microfracture) long-term follow up, to provide overall 5-year data on efficacy and safety of MACI, compared to microfracture.

6.2.1 Objectives

The objective of this study was to examine the 5-year efficacy and safety of MACI implant, compared with arthroscopic microfracture, in subjects who received study treatment in the SUMMIT study.

Reviewer Comments:

As described below, there was no formal hypothesis or statistical analysis plan for comparing outcomes of MACI with those of microfracture. More accurately stated, the objective of the study was to determine the long-term outcomes for both treatment groups.

6.2.2 Design Overview

This was an open-label, multicenter extension to the SUMMIT Study. All subjects who completed their participation through the 2-year study period of SUMMIT were eligible to participate in the extension study. Subjects had until the end of the visit window for the last visit of this extension study (i.e., Week 260 + 6 weeks) to consent to enter this extension study. Efficacy and safety assessments were performed at scheduled Visits 3, 4, and 5 years following treatment in SUMMIT study. Subjects who were withdrawn from the SUMMIT study prior to their scheduled Week 104 visit and enrolled into the SUMMIT Extension study were allowed to have their remaining scheduled assessment(s) (from the SUMMIT study) within the extension study, in addition to the assessments mentioned for Weeks 156, 208, and 260. Data for any visits for which the visit window had passed were not collected and were considered missing data.

Any subject requiring surgical re-treatment of the treated defect(s) and meeting other specific criteria relating to changes in the condition of the treated knee joint were considered a treatment failure and may have received alternative treatment, which may have included MACI implant. Additionally, subjects who did not meet the specific treatment failure criteria as defined in the study protocol but required re-treatment in the opinion of both the Investigator and the Independent Treatment Failure Evaluation Committee, may also have received re-treatment which may have included MACI implant. Subjects determined to be treatment failures (per the Independent Treatment Failure Evaluation Committee or Investigator) and/or required surgical re-treatment was not withdrawn from this extension study.

6.2.3 Population

As stated above, subjects were eligible if they participated in the SUMMIT Study and provided written informed consent to participate in the extension study.

6.2.4 Study Treatments or Agents Mandated by the Protocol

No study treatment was administered during this extension study. Subjects who required re-treatment may have received a re-treatment. Subjects who were considered treatment failures were allowed to receive appropriate alternative treatment, at the discretion of the Investigator; the alternative treatment could have been MACI. If the investigator recommended MACI as the alternative treatment, the MACI product was provided as an investigational product.

6.2.5 Directions for Use

See above under the corresponding section of the review of Trial # 1 (the SUMMIT Study).

6.2.6 Sites and Centers

The SUMMIT study was conducted at 16 sites across 7 countries in the European Union (Netherlands, France, Czech Republic, Norway, Poland, Sweden, and United Kingdom). Sixteen subjects randomized in the SUMMIT study (7 MACI and 9 microfracture) were not enrolled in the extension study. Two study sites (8 subjects, 5 in MACI and 3 in microfracture) from the SUMMIT study did not participate in the SUMMIT Extension study. The reasons for non-participation at these sites were financial / corporate and had no obvious relation to study outcomes, although this could not be determined with certainty. In addition to those 8 subjects from these 2 sites, an additional 8 subjects withdrew for other reasons. Table 20 lists the SUMMIT Study participants who did not enroll in SUMMIT Extension study and the reasons for not participating in the extension study.

Table 20. Subjects randomized in SUMMIT and not enrolled in the SUMMIT Extension

Reason not Enrolled	SUMMIT Study (MACI00206) Patient Identification Number	
	MACI (N = 7)	Microfracture (N = 9)
Study site did not participate in SUMMIT Extension	02002, 02005, 02011, 02012, 04002	02001, 02007, 02009
Patient could not be reached	17001, 21007	21004
Patient unwilling to participate	--	03002, 15001, 15016
Patient not asked to enroll per Investigator decision	--	05013, 29003

Source: Original BLA 125603, Summary of SUMMIT Extension study report, Page 50/529

Reviewer Comment: The reasons the 3 microfracture subjects were unwilling to participate, as well as the reasons the 2 microfracture subjects were not asked to enroll per Investigator decision, were not provided in the submission.

6.2.7 Surveillance/Monitoring

The schedule of events, which identifies the assessments performed during this study and their timing, is shown in Table 21 for subjects who completed their scheduled Week 104 visit within the SUMMIT study. Subjects withdrawn from the SUMMIT study prior to their scheduled Week 104 visit and enrolled into the Extension study had their remaining scheduled assessment from the SUMMIT study within the Extension study in addition to the assessments mentioned for Weeks 156, 208 and 260.

At each applicable study visit, all questionnaires to be completed by the subject had to be administered before the subject was seen by the physician. In addition to the physical examination and questionnaires, the subjects also underwent MRIs of the knee in their yearly visits.

Table 21. Schedule of Assessments in the SUMMIT Extension Study

	Screen ^a	Baseline ^b	Weeks 156, 208, and 260 Visits ^c ± 6 Weeks
Informed consent/Enrollment	X		
Eligibility criteria	X		
Adverse events			X
Query for SSPs			X
Concomitant medication ^d			X
Demography data		X	
Medical/surgical history		X	
Brief physical and knee exam		X	X ^e
KOOS ^f		X	X
Patient/physician global assessment ^f		X	X
Modified Cincinnati Knee Rating		X	X
IKDC		X	X
EQ-5D		X	X
SF-12		X	X
MRI		X	X ^{g,h}

EQ-5D = European Quality of Life 5 Dimensions; IKDC = International Knee Documentation Committee; KOOS = Knee Injury and Osteoarthritis Outcome Score; MRI = magnetic resonance imaging; SF-12 = 12-Item Short-Form Health Survey; SSP = subsequent surgical procedure.

^a Patients had until the end of the visit window for the last visit of this extension study (Week 260 + 6 weeks) to consent to this extension study.

^b Note: The baseline (Visit 1) assessments from SUMMIT served as the baseline assessments for this extension study. There was no baseline Visit in this extension study.

^c Weeks are relative to day of operative procedure in the SUMMIT study (ie, arthroscopy for microfracture and arthrotomy for MACI implant).

^d Concomitant medications taken for any AE were recorded at each visit. The use of concomitant pain medications, taken during the 4 weeks prior to each visit in this extension study, was recorded. The patient recorded the medications taken prior to the visit on a medication list provided to the patient. The study site contacted the patient by telephone approximately 4 weeks (± 1 week) before the visit to remind the patient to record the relevant information on the medication list. If an unscheduled visit was needed for treatment failure assessment, during the visit the patient provided the medication list to the Investigator, who worked together with the patient to complete any missing information.

^e Including assessment of body weight.

^f If an unscheduled visit was needed for treatment failure assessment, the questionnaire was completed at the visit for treatment failure evaluation.

^g At Weeks 156 and 260.

^h Patients in the SUMMIT Extension study who completed their Week 156 visit prior to implementation of Protocol Amendment 2 (ie, no MRI scan was completed at the visit) were allowed to complete the missed MRI scan up to Week 182 for a missed Week 156 MRI scan.

Source: Table 5 of the Study MACI00809 Study Report, page 31/529.

The day of the operative procedure in the SUMMIT study is the day of arthroscopy for subjects treated with microfracture and the day of implantation (arthrotomy) for subjects in the MACI group. Subjects were followed up to approximately 260 weeks (i.e., Year 5 ± 6 weeks) after their SUMMIT study treatment.

6.2.8 Endpoints and Criteria for Study Success

The co-primary efficacy endpoints were changes in KOOS Pain and Function (SRA) from baseline in the SUMMIT Study to Week 156 (3 years) in the Extension Study for the all subjects who started in SUMMIT and remained in the Extension Study. (This population is termed modified FAS, or mFAS.) The LS Means were estimated through the same MANCOVA model as used in the SUMMIT Study, but only for the purpose of displaying the summary data, not for inferential comparisons between the groups. Therefore, there were no pre-defined criteria for success in the Extension Study.

As such, p-values for treatment group comparisons were not presented and the evaluation of results was to be descriptive in nature. The interpretation focused on the longitudinal aspect of the results --- that is, evaluating the maintenance of any effect seen in this specific population throughout the Extension Study, compared to the 2-year results from the SUMMIT Study.

Secondary endpoints were:

- Change from SUMMIT baseline to Weeks 24, 36, 52, 78, 104, 208, and 260 for the subject's KOOS Pain and Function (SRA) scores
- Magnetic resonance imaging (MRI) assessments of structural repair parameters at Weeks 52, 104, 156, and 260 including:
 - Degree of defect fill based on the thickness of repair tissue; defect fill is regarded as the principle MRI indicator of response to treatment
 - Degree of integration of the repair tissue with adjacent native cartilage
 - Signal intensity of the repair tissue relative to adjacent native cartilage
- Response rate based on KOOS Pain and Function (SRA) scores: the proportion of subjects who responded to treatment at Weeks 24, 36, 52, 78, 104, 156, 208, and 260. A responder was defined as a subject with at least a 10-point improvement in both the KOOS Pain and Function (SRA) scores from SUMMIT Baseline (Roos, 2003, Health Qual Life Outcomes).
- Treatment failure rate: the proportion of patients in each treatment group assessed as treatment failures at Weeks 24, 36, 52, 78, 104, 156, 208, and 260.
- Average time to treatment failure: the time to treatment failure will be based on the date that the physician decides that surgical re-treatment of the original index lesion is required relative to the date of the original study surgery (i.e., arthroscopy for microfracture and arthrotomy for MACI implant). Treatment failure is only determined in relation to the original treated defect(s).
- Change from SUMMIT baseline at Weeks 24, 36, 52, 78, 104, 156, 208, and 260 in the remaining 3 subscales of the KOOS instrument (i.e., Other Symptoms, Quality of Life [QOL], Activities of Daily Living [ADL])
- Change from SUMMIT baseline at Weeks 52, 104, 156, 208, and 260 in the subject's evaluation of overall knee condition using the Modified Cincinnati Knee Rating System

- Change from SUMMIT baseline at Weeks 52, 104, 156, 208, and 260 in the subject's evaluation of overall knee condition using the International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form
- Change from SUMMIT baseline at Weeks 52, 104, 156, 208, and 260 in the 12-Item Short-Form Health Survey (SF-12) Acute Version 2.0 for the 8 subscales (physical functioning, role-physical, bodily pain, general health, vitality, social function, role-emotional, mental health), and the physical and mental summary components
- Change from SUMMIT baseline at Weeks 52, 104, 156, 208, and 260 in the European
- Quality of Life (EuroQOL) 5 dimensions (EQ-5D) health state.

Safety endpoints were:

- Rate of treatment-emergent adverse events (TEAEs)
- Rate of treatment-emergent serious adverse events (SAEs)
- Rate of subsequent surgical procedures (SSPs)
- Physical examination and knee examination findings

6.2.9 Statistical Considerations & Statistical Analysis Plan

The former study sponsor (Genzyme) amended the SAP in April 2013 and changed the primary population for the analysis of efficacy data from the mFAS1 (all randomized who did not have re-treatment during the study period) to the FAS. The rationale for this change was that the mFAS1 was not a true intent-to-treat (ITT) population. In addition, the multiple imputation method was added as the primary method for missing data imputation for the analyses of continuous primary and secondary variables with the objective of conducting analyses for the FAS across the SUMMIT and SUMMIT Extension studies.

However, prior to database lock, Vericel disregarded the April 2013 SAP revision due to the nonparticipation of 2 study sites in the SUMMIT Extension study; the SAP was amended in April 2015 by Vericel to revise the subject population analyzed and to further characterize the subgroup of subjects who did not enroll in the extension study. In the revised SAP, the population set for analyses was defined as all subjects randomized in the SUMMIT Study who provided informed consent to participate in the Extension Study, and the analyses were to be conducted on observed data only, without imputation for missing data. Additionally, based on Vericel Corporation's meeting with the FDA on 07 May 2015, the SAP was amended on 14 May 2015 to include exploratory subgroup analyses of the co-primary endpoints.

Reviewer Comments:

The applicant changed the SAP because 16 subjects did not participate (7 in MACI group and 9 in microfracture group) and the applicant thought that their non-participation

resulted in an inherent selection bias that would substantially limit and confound the inferential value of statistical comparisons between the 2 groups at the extension study 3-, 4-, and 5-year endpoints. This conclusion is unwarranted. The reason for non-participation was a financial/corporate decision made by their study sites, a decision that in all likelihood had nothing to do with the trial outcomes. This leaves only 8 out of 144 subjects (5.5%) with data that may not have been missing at random. At any rate, it is not evident how a participation rate of 89% of the original population indicates a biased sample, if outcomes are dependent on mean values. On the other hand, if rare and serious adverse events of concern were to occur in this small excluded subset, then this could present a problem in the long-term safety evaluation. At any rate, the review team does not believe that the non-participation of these 16 subjects should have precluded formal hypothesis-testing for differences between means.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

See section 6.1 for details.

6.2.10.1.1 Demographics

See section 6.1 for details.

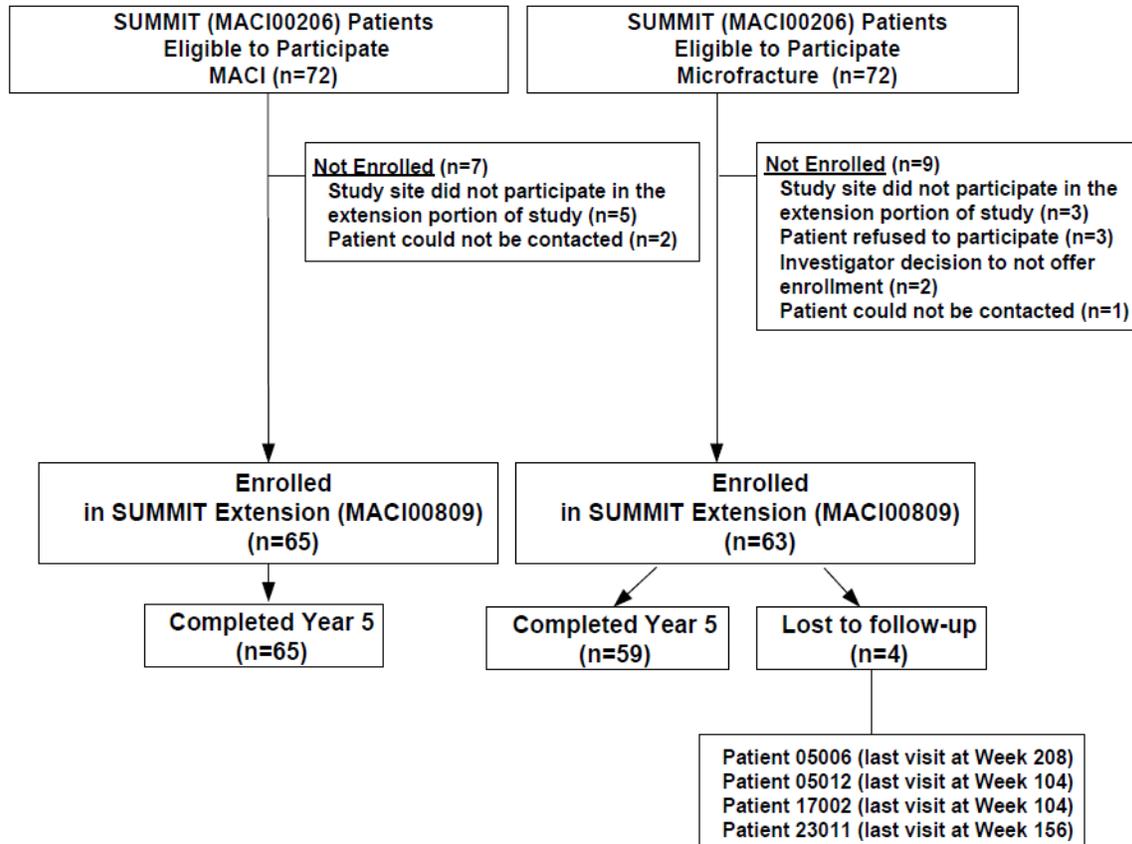
6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

See section 6.1 for details.

6.2.10.1.3 Subject Disposition

The subject disposition is depicted in Figure 2.

Figure 2. Subject disposition in the Extension Study



Source: Figure 2 of the Study MACI00809 Study Report, page 49 / 529.

Reviewer comments:

The overall retention rate of 89% of the original SUMMIT population is remarkably good for a five-year study, as is the retention rate of 97% of the Extension population.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

The changes in KOOS Pain and Function (SRA) scores for both treatment groups at 2years (end of the SUMMIT Study) and at 5 years (end of the Extension Study) based on the modified FAS (n= 128), which excluded 16 subjects either withdrawn from SUMMIT or whose sites decided not to participate in the Extension. The results are based on observed data, but the LS Means were estimated based on a MANCOVA model with treatment as fixed effects and baseline KOOS Pain and Function (SRA) as covariates.

Table 22. Scores of KOOS Pain and Function changes in SUMMIT and Extension in the modified Full Analysis Set

		MACI (N = 65)		Microfracture (N = 63)	
SUMMIT Study Visits		Pain	Function (SRA)	Pain	Function (SRA)
Baseline ^a	n	65	65	63	63
	Mean (SD)	37.05 (13.10)	15.38 (14.82)	35.19 (12.31)	11.88 (16.15)
Visit 10 (Week 104) ^b	n	63	63	60	60
	Mean (SD)	82.19 (15.79)	60.48 (26.54)	71.76 (23.89)	48.92 (30.64)
Change from Baseline to Week 104	n	63	63	60	60
	Mean (SD)	45.02 (19.95)	44.60 (26.84)	36.30 (24.47)	37.19 (31.68)
Estimated Difference from Microfracture ^c	LS Mean (SE)	10.00 (3.66)	9.82 (5.11)		
SUMMIT Extension Study Visits		Pain	Function (SRA)	Pain	Function (SRA)
Visit 11 (Week 156)	n	65	65	57	57
	Mean (SD)	79.19 (20.06)	61.02 (29.17)	72.32 (22.27)	50.00 (31.69)
Change from Baseline to Week 156	n	65	65	57	57
	Mean (SD)	42.14 (22.60)	45.63 (30.40)	35.77 (23.44)	36.95 (33.75)
Estimated Difference from Microfracture ^c	LS Mean (SE)	6.77 (3.84)	10.45 (5.49)		
Visit 12 (Week 208)	n	63	62	59	59
	Mean (SD)	80.42 (19.21)	61.35 (31.07)	73.07 (23.71)	50.17 (30.72)
Change from Baseline to Week 208	n	63	62	59	59
	Mean (SD)	43.39 (22.63)	45.87 (33.23)	36.96 (24.66)	38.07 (33.24)
Estimated Difference from Microfracture ^c	LS Mean (SE)	7.05 (3.95)	10.68 (5.66)		
Visit 13 (Week 260)	n	65	64	59	59
	Mean (SD)	82.22 (20.13)	61.93 (30.92)	74.81 (21.68)	50.25 (32.33)
Change from Baseline to Week 260	n	65	64	59	59
	Mean (SD)	45.17 (21.65)	47.17 (32.15)	38.42 (23.60)	37.56 (33.65)
Estimated Difference from Microfracture ^c	LS Mean (SE)	7.28 (3.77)	11.14 (5.66)		

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

^a Baseline = SUMMIT Study baseline value(s) for the modified Full Analysis Set.

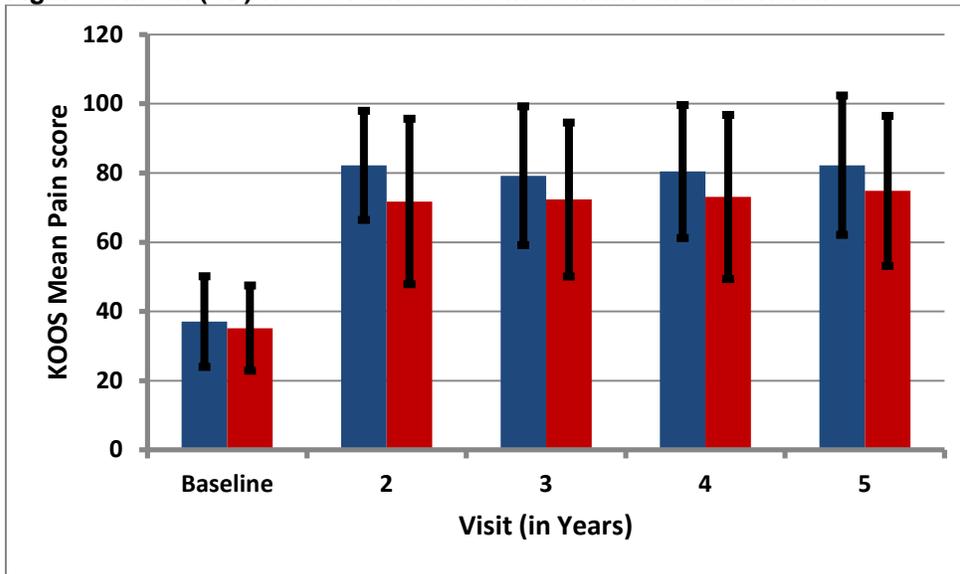
^b Week 104 = Final visit (Visit 10) values in SUMMIT Study for the modified Full Analysis Set.

^c Parameter estimates and covariance matrices from Multivariate Analysis of Covariance conducted with treatment as fixed effects and Baseline KOOS Pain and Function (SRA) as covariates.

Source: Based on Table 14 of the Study Report page 59.

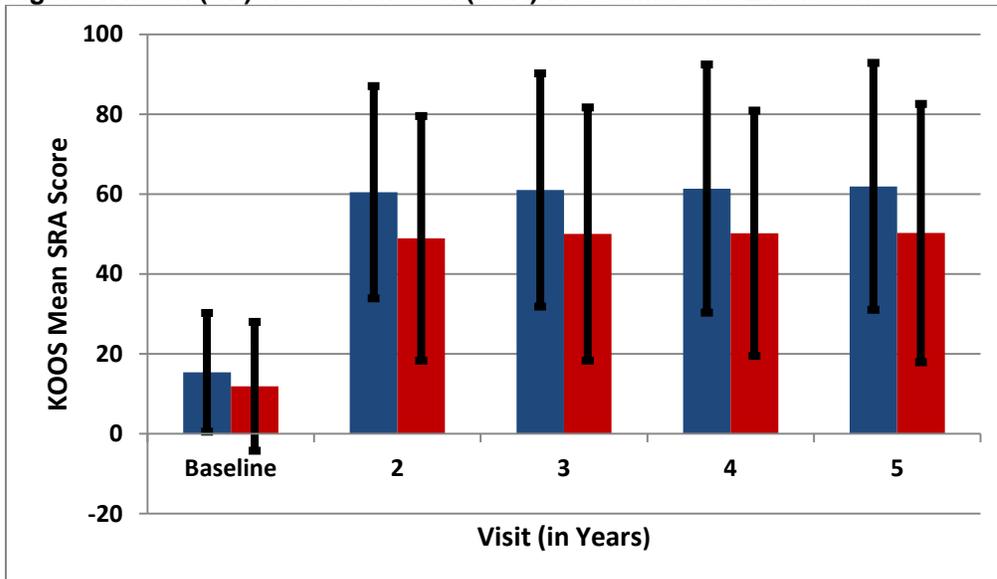
The same data describing mean scores for each treatment group can be more easily visualized in Figure 3 for changes in KOOS Pain over time and in Figure 4 for changes in KOOS Function over time, based on observed data only, without imputation.

Figure 3. Mean (SD) KOOS Pain Scores in SUMMIT and Extension



Blue bars: MACI Red bars: Microfracture

Figure 4. Mean (SD) KOOS Function (SRA) in SUMMIT and Extension



Blue bars: MACI Red bars: Microfracture

The applicant also plotted the mean between-group differences in KOOS pain (Figure 5) and function (SRA) (Figure 6) scores with the 95% confidence intervals in the mFAS population.

Figure 5. KOOS Co-Primary Efficacy – Pain – modified Full Analysis Set

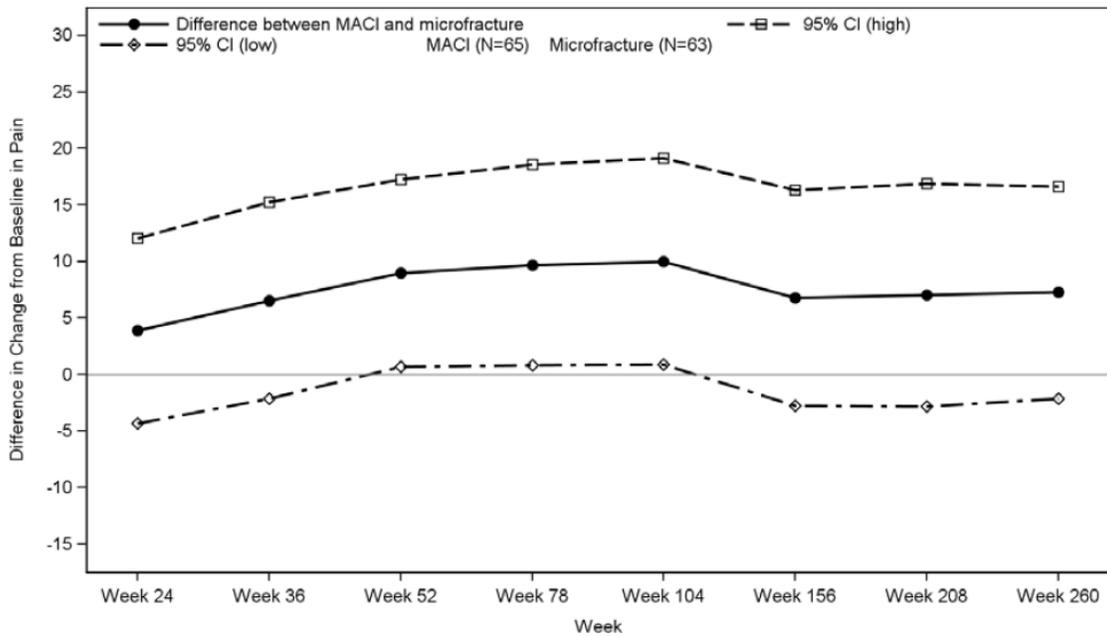
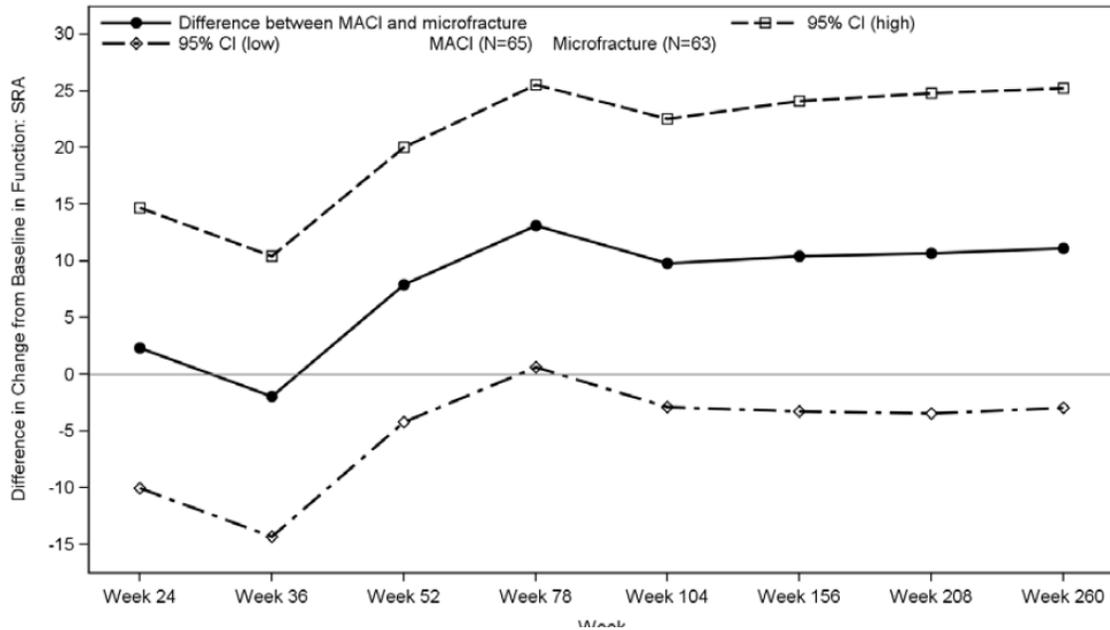


Figure 6. KOOS Co-Primary Efficacy – Function (SRA) – modified Full Analysis Set



Reviewer Comments:

As noted above, formal between-group comparisons, as well as analyses of differences from baseline within groups over time) had not been planned. The data in Figures 3 and 4 and Table 24 show that the mean effects of either treatment at 2 years remained fairly stable over an additional 3 years. Regarding maintenance of treatment effect size over time (Fig 6), exclusion of the 16 subjects from these analyses resulted in slightly wider confidence intervals, which cross the neutral “zero” line after Week 104 for KOOS Pain and remain slightly below the neutral “zero” line for KOOS Function, suggesting that the treatment-effect size may not be as robustly maintained over time. Nonetheless, the

scores for pain and function show stability in maintenance in improvements over baseline in both treatment groups, and the review team believes that this information is important for patients and physicians alike, and should be included in the product label. Presentation of this information in the label should include Figs 3-6 for scientific accuracy.

At the late-cycle meeting, this issue was discussed with Vericel. The applicant expressed concern about showing results that were derived from a subset of subjects, not subject to prespecified statistical analyses. In particular, the applicant pointed out that the responses to MACI and microfracture interventions in the 128 subjects who were included in the analyses of MACI Extension were different from the responses recorded for the 16 subjects who completed SUMMIT but were not enrolled in the Extension Study. Table 23 shows these mean changes in the three analyses populations (FAS, mFAS and non-mFAS). (Non-mFAS includes those 16 subjects who did not participate in the Extension study.) Figure 7 shows the differences in responses in the mFAS against the non-mFAS.

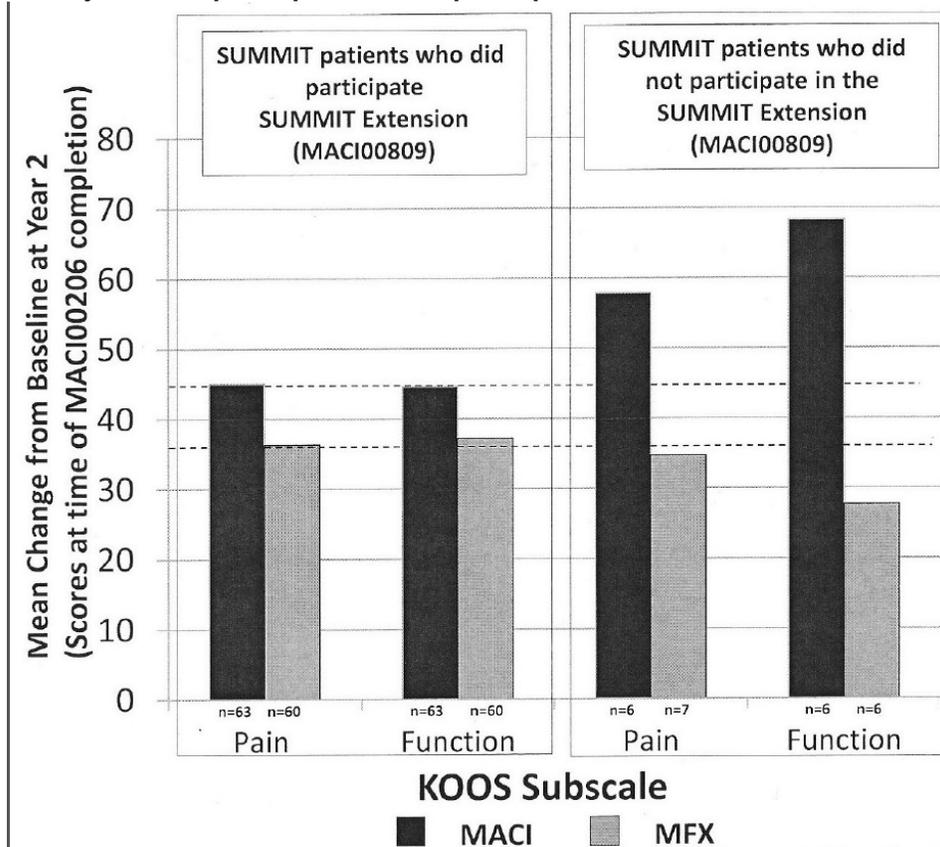
Table 23. KOOS Pain and Function Scores – Full Analysis Set, modified Full Analysis Set, and non-modified Full Analysis Set

	FAS (All Patients Randomized in SUMMIT)		mFAS (All Patients Enrolled in SUMMIT Extension)		non-mFAS (All Patients Not Enrolled in SUMMIT Extension)	
	MACI (N = 72)	Microfracture (N = 72)	MACI (N = 65)	Microfracture (N = 63)	MACI (N = 7)	Microfracture (N = 9)
Baseline KOOS Pain Score^a						
n	72	71	65	63	7	9
Mean (SD)	37.00 (13.52)	35.45 (12.09)	37.05 (13.10)	35.19 (12.31)	36.51 (18.25)	35.19 (12.19)
Median	38.89	36.11	38.89	36.11	33.33	38.89
Min, Max	8.3, 69.4	5.6, 52.8	8.3, 52.8	5.6, 52.8	19.4, 69.4	16.7, 52.8
Week 104 KOOS Pain Score^b						
n	72	70	63	60	6	7
Mean (SD)	82.45 (16.18)	70.85 (24.22)	82.19 (15.79)	71.76 (23.89)	91.67 (10.54)	72.82 (13.65)
Median	86.11	75.00	83.33	77.78	94.44	75.00
Min, Max	22.2, 100.0	11.1, 100.0	22.2, 100.0	11.1, 100.0	72.2, 100.0	50.0, 91.7
KOOS Pain Score Change from Baseline to Week 104						
n	72	69	63	60	6	7
Mean (SD)	45.45 (21.08)	35.23 (23.91)	45.02 (19.95)	36.30 (24.47)	57.87 (16.98)	34.72 (12.90)
Median	44.44	36.11	44.44	37.50	59.72	33.33
Min, Max	-11.1, 80.6	-13.9, 83.3	-5.6, 80.6	-13.9, 83.3	30.6, 80.6	16.7, 52.8
Baseline KOOS Function Score^a						
n	72	71	65	63	7	8
Mean (SD)	14.86 (14.68)	12.57 (16.67)	15.38 (14.82)	11.88 (16.15)	10.00 (13.23)	17.97 (20.81)
Median	10.00	5.00	10.00	5.00	0.00	10.00
Min, Max	0.0, 55.0	0.0, 93.8	0.0, 55.0	0.0, 93.8	0.0, 30.0	0.0, 55.0

	FAS (All Patients Randomized in SUMMIT)		mFAS (All Patients Enrolled in SUMMIT Extension)		non-mFAS (All Patients Not Enrolled in SUMMIT Extension)	
	MACI (N = 72)	Microfracture (N = 72)	MACI (N = 65)	Microfracture (N = 63)	MACI (N = 7)	Microfracture (N = 9)
Week 104 KOOS Function Score^b						
n	72	70	63	60	6	7
Mean (SD)	60.90 (27.84)	48.71 (30.33)	60.48 (26.54)	48.92 (30.64)	75.83 (29.90)	50.71 (19.24)
Median	65.00	50.00	65.00	50.00	87.50	60.00
Min, Max	0.0, 100.0	0.0, 100.0	0.0, 100.0	0.0, 100.0	25.0, 100.0	15.0, 65.0
KOOS Function Score Change from Baseline to Week 104						
n	72	69	63	60	6	6
Mean (SD)	46.04 (28.35)	35.83 (31.63)	44.60 (26.84)	37.19 (31.68)	68.33 (26.58)	27.71 (26.15)
Median	50.00	30.00	45.00	35.00	70.00	18.13
Min, Max	-5.0, 100.0	-28.8, 100.0	-5.0, 100.0	-28.8, 100.0	25.0, 100.0	0.0, 65.0

Source: Table 13 of the Study MACI00809 Study Report – page 56 / 529.

Figure 7. Mean changes in KOOS pain and function scores at 2 years of the SUMMIT Study in subjects who participated or not participated in the SUMMIT Extension



Source: Vericel presentation at the Late Cycle meeting

Reviewer Comments: The MACI subset (N=7) of this small group of excluded subjects appeared to have responded better (at two years) in both pain and function scores, compared to responses in the overall group of MACI subjects who did participate. A slight trend in the opposite direction is seen in the subset of microfracture subjects (N=9), but only for function. The small numbers of subjects make these comparisons

unconvincing, and at any rate it is not easy to see how exclusion of these 16 subjects could have biased the outcomes of the Extension study.

6.2.11.2 Analyses of Secondary Endpoints

MRI Findings

Of the 128 subjects enrolled in this Extension study, 120 underwent MRI evaluation at Week 260. At Week 260, improvement since study treatment in defect fill was evident for subjects in both treatment groups. Defects were filled >50% for the majority of subjects, and the proportion of subjects with >75% defect fill was similar in both treatment groups at Week 260 (MACI: 49.3%, microfracture: 54.5%). There were 10 more subjects in the MACI group than in microfracture group with MRI evaluation at Week 260.

KOOS Scores in Pain and Function (SRA): Responder Rate

Table 24 shows the rate of responders (those subjects with increment in score of more than 10 points from baseline, in both KOOS pain and KOOS Function) in each treatment group, in the modified FAS population.

Table 24. KOOS Response Rate: modified Full Analysis Set

n (%)	MACI N = 65	Microfracture N = 63
SUMMIT Study Visit		
Visit 10 (Week 104)^a		
Responded	56 (86.2)	43 (68.3)
Not Responded	7 (10.8)	17 (27.0)
Missing	2 (3.1)	3 (4.8)
SUMMIT Extension Study Visits		
Visit 11 (Week 156)		
Responded	54 (83.1)	38 (60.3)
Not Responded	11 (16.9)	19 (30.2)
Missing	0	6 (9.5)
Visit 12 (Week 208)		
Responded	49 (75.4)	40 (63.5)
Not Responded	13 (20.0)	19 (30.2)
Missing	3 (4.6)	4 (6.4)
Visit 13 (Week 260)		
Responded	51 (78.5)	46 (73.0)
Not Responded	13 (20.0)	13 (20.6)
Missing	1 (1.5)	4 (6.4)

Source: Table 16 in the MACI 00809 Study Report, page 83 / 529.

Reviewer Comments:

The proportion of responders in MACI declined slightly over the course of the 3 years of the Extension study. The proportion of responders showed a slight increase in the microfracture group by Week 260. In keeping with the results of the changes in scores over this period (above), the between-group difference in response rates diminished

from 18% at Week 104 to 5% at Week 260. Missing data rates were higher in the microfracture group than in MACI, and a small number of subjects responding in either direction at either time point could have changed the outcomes of the statistical analysis. In other words, the between-group statistical significance seen at Week 104 may well have vanished by Week 260. The review team recommends that this analysis not appear in the label because the data may be confusing to patients.

Treatment Failure Rate

The planned analyses of treatment failure rates and treatment-group differences were not possible due to the small number of per-protocol treatment failure cases. Defined treatment failure criteria in this study are the same as described for the SUMMIT study. In the SUMMIT Extension, 6 subjects (4 microfracture and 2 MACI) were referred to the Independent Treatment Failure Evaluation Committee. Two of the 6 subjects referred were considered to be per-protocol treatment failures by the Committee (1 MACI subject and 1 microfracture subject).

ADL, QoL and Other Symptoms subscales of KOOS

Improvement in scores of ADL, QOL, and Other Symptoms was comparable numerically for subjects in the 2 treatment groups from Baseline to Years 3, 4 and 5. The improvements for all 3 KOOS subscales were comparable numerically for subjects in the MACI group compared to the microfracture group at all follow-up visits.

6.2.11.3 Subpopulation Analyses

The applicant did not analyze effects of MACI with regard to the demographic characteristics.

6.2.11.4 Dropouts and/or Discontinuations

Of the 128 subjects enrolled in the Extension Study, 4 subjects (all in microfracture) dropped out.

6.2.11.5 Exploratory and Post Hoc Analyses

Not applicable.

6.2.12 Safety Analyses

6.2.12.1 Methods

The modified Safety Set (mSafety) consisted of the 128 subjects who were in the Safety Set defined in the SUMMIT study and provided informed consent for enrollment in the SUMMIT Extension study; the mSafety and mFAS are comprised of the same set of subjects. Safety results in this section are based upon modified Safety Set throughout the extension study (Year 3 to Year 5).

The SUMMIT Extension study evaluated 65 subjects treated with MACI and 63 subjects treated with microfracture in the SUMMIT Study. The mean +/- SD (2.7 ± 0.4 years) and

median (2.9 years) duration of participation in the MACI group were comparable to the microfracture group (mean \pm SD of 2.5 \pm 0.7 years and 2.7 years, respectively).

The proposed safety study endpoints in this study are listed below:

- Rate of treatment-emergent adverse events (TEAEs)
- Rate of treatment-emergent serious adverse events (SAEs)
- Rate of subsequent surgical procedures (SSPs)
- Physical examination and knee examination findings

6.2.12.2 Overview of Adverse Events

Table 25 shows the summary of treatment-emergent AEs (TEAEs) in both treatment groups during the SUMMIT Extension.

Table 25. Summary of Adverse events in the SUMMIT Extension Study – modified Safety Set

Number of Patients	MACI N = 65 n (%)	Microfracture N = 63 n (%)
At Least 1 TEAE (All years)	49 (75.4)	47 (74.6)
Year 3 ^a	32 (51.6)	24 (40.0)
Year 4 ^b	22 (33.8)	26 (41.9)
Year 5 ^b	14 (21.5)	25 (40.3)
At Least 1 Related TEAE	15 (23.1)	14 (22.2)
At Least 1 Severe TEAE	6 (9.2)	6 (9.5)
At Least 1 TESAE	16 (24.6)	17 (27.0)
Any Death	0	0
Discontinued Study Due to TEAE	0	0

Source: Table 24 of the Study MACI00809 Study Report, page 80 / 529.

Reviewer comments:

Over the 3 years, the proportion of subjects with at least 1 TEAE was 75.4% in the MACI group and 74.6% in the microfracture group. The overall frequency of subjects with TEAEs and SAEs was comparable numerically in both groups for all categories. No subjects in either treatment group discontinued the extension study prematurely due to a TEAE, and no subject died in the study.

Table 26 shows TEAEs that occurred in more than 5% of subjects in either treatment group, by system organ class and preferred term.

Table 26. Treatment-Emergent Adverse Events per System Organ Class and Preferred Term Reported in >5% of Patients in Any Treatment Group – modified Safety Set

System Organ Class Preferred Term	MACI N = 65 n (%)	Microfracture N = 63 n(%)
Any TEAE	49 (75.4)	47 (74.6)
Musculoskeletal and Connective Tissue Disorders	39 (60.0)	37 (58.7)
Arthralgia	30 (46.2)	32 (50.8)
Tendonitis	4 (6.2)	1 (1.6)
Back pain	3 (4.6)	4 (6.3)
Osteoarthritis	3 (4.6)	5 (7.9)
Joint effusion	2 (3.1)	5 (7.9)
Injury, Poisoning and Procedural Complications	15 (23.1)	25 (39.7)
Cartilage injury	4 (6.2)	10 (15.9)
Procedural pain	2 (3.1)	5 (7.9)
Ligament sprain	1 (1.5)	5 (7.9)
Infections and Infestations	14 (21.5)	11 (17.5)
Nasopharyngitis	7 (10.8)	2 (3.2)
Influenza	4 (6.2)	5 (7.9)
Nervous System Disorders	13 (20.0)	15 (23.8)
Headache	11 (16.9)	13 (20.6)
General Disorders and Administration Site Conditions	10 (15.4)	7 (11.1)
Treatment failure ^a	3 (4.6)	5 (7.9)

Source: Table 25 of the Study MACI00809 Study Report, page 82 / 529.

Only 3 types of events occurred with $\geq 5\%$ difference in frequency between treatment groups; cartilage injury and ligament sprain were lower in the MACI group relative to microfracture and nasopharyngitis was lower in the microfracture group relative to MACI.

Intensity: In both treatment groups the majority of AEs in subjects experiencing TEAEs were of mild or moderate intensity. The only severe TEAEs reported in more than 1 subject in any treatment group were arthralgia (1.5% MACI, 4.8% microfracture) and osteoarthritis (3.1% MACI, 0 microfracture).

TEAEs of moderate intensity reported in >5% of subjects in any treatment group were arthralgia (15.4% MACI vs. 22.2% microfracture), treatment failure reported as an AE (3.1% MACI vs. 6.3% microfracture), cartilage injury (1.5% MACI vs. 11.1% microfracture), and headache (0 MACI vs. 7.9% microfracture). All AEs of treatment failure met the protocol-specified definition of treatment failure and were adjudicated as treatment failures by the Independent Treatment Failure Evaluation Committee.

6.2.12.3 Deaths

No deaths occurred in the study.

6.2.12.4 Nonfatal Serious Adverse Events

Please refer to Table 27 for a list of all SAEs in the SUMMIT Extension Study. All SAEs were coded using MedDRA Version 18.0.

Table 27. Treatment-emergent SAEs per System Organ Class and Preferred Term in the modified Safety Set

System Organ Class Preferred Term	MACI N = 65 n (%)	Microfracture N = 63 n (%)
Any TESAE	16 (24.6)	17 (27.0)
Injury, Poisoning and Procedural Complications	7 (10.8)	11 (17.5)
Cartilage injury	2 (3.1)	7 (11.1)
Graft delamination	1 (1.5)	0 (0.0)
Meniscus injury	1 (1.5)	0 (0.0)
Procedural pain	1 (1.5)	1 (1.6)
Tendon rupture	1 (1.5)	0 (0.0)
Transplant failure	1 (1.5)	0 (0.0)
Contusion	0 (0.0)	1 (1.6)
Head injury	0 (0.0)	1 (1.6)
Pancreatic injury	0 (0.0)	1 (1.6)
Spinal fracture	0 (0.0)	1 (1.6)
Musculoskeletal and Connective Tissue Disorders	6 (9.2)	7 (11.1)
Osteoarthritis	3 (4.6)	0 (0.0)
Arthralgia	1 (1.5)	5 (7.9)
Arthropathy	1 (1.5)	1 (1.6)
Ligament laxity	1 (1.5)	0 (0.0)
Musculoskeletal pain	1 (1.5)	0 (0.0)
Bone disorder	0 (0.0)	1 (1.6)
Chondropathy	0 (0.0)	1 (1.6)
Haemarthrosis	0 (0.0)	1 (1.6)
Joint effusion	0 (0.0)	1 (1.6)
Joint lock	0 (0.0)	2 (3.2)
Joint swelling	0 (0.0)	1 (1.6)
Loose body in joint	0 (0.0)	1 (1.6)
System Organ Class Preferred Term	MACI N = 65 n (%)	Microfracture N = 63 n (%)
General Disorders and Administration Site Conditions	4 (6.2)	6 (9.5)
Treatment failure	3 (4.6)	5 (7.9)
Impaired healing	1 (1.5)	2 (3.2)
Ear and Labyrinth Disorders	1 (1.5)	0 (0.0)
Otosclerosis	1 (1.5)	0 (0.0)
Gastrointestinal Disorders	1 (1.5)	2 (3.2)
Gastric haemorrhage	1 (1.5)	0 (0.0)
Gastric stenosis	1 (1.5)	0 (0.0)
Gastrointestinal disorder	0 (0.0)	1 (1.6)
Inguinal hernia	0 (0.0)	1 (1.6)
Infections and Infestations	1 (1.5)	0 (0.0)
Erysipelas	1 (1.5)	0 (0.0)
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)	1 (1.5)	0 (0.0)
Salivary gland neoplasm	1 (1.5)	0 (0.0)
Respiratory, Thoracic and Mediastinal Disorders	1 (1.5)	0 (0.0)
Oropharyngeal pain	1 (1.5)	0 (0.0)
Vascular Disorders	1 (1.5)	0 (0.0)
Varicose vein	1 (1.5)	0 (0.0)
Cardiac Disorders	0 (0.0)	1 (1.6)
Cardiac arrest	0 (0.0)	1 (1.6)
Pregnancy, Puerperium and Perinatal Conditions	0 (0.0)	1 (1.6)
Retained placenta or membranes	0 (0.0)	1 (1.6)
Reproductive System and Breast Disorders	0 (0.0)	1 (1.6)
Endometriosis	0 (0.0)	1 (1.6)

Source: Table 28 of the MACI 00809 Study Report, pages 86 – 87 / 529.

Treatment-emergent SAEs were reported at a similar rate in the MACI and microfracture groups (24.6% MACI, 27.0% microfracture). Only 4 SAEs were reported in more than 2 subjects. One event occurred more frequently in the MACI group vs microfracture (osteoarthritis 4.6% vs 0, respectively). The other 3 SAEs occurred less frequently in MACI relative to microfracture (treatment failure 4.6% vs 7.9%; cartilage injury 3.1% vs 11.1%; arthralgia 1.5% vs 7.9%).

6.2.12.5 Adverse Events of Special Interest (AESI)

There were no TEAEs leading to premature study discontinuation during the SUMMIT Extension Study.

Three MACI-treated subjects experienced AEs of interest in the SUMMIT Extension Study. Two of the subjects experienced events (arthrofibrosis, treatment failure) that were ongoing from the SUMMIT Study. One subject in the MACI group experienced graft delamination during the Extension Study. The MACI graft delamination was reported to have occurred on Study Day 1224. In the Investigator's opinion, the direct cause of the damage was an episode of knee overload in the course of mountain trekking. The Investigator indicated that the event of graft delamination was moderate in intensity and definitely related to the study treatment, while not related to the overall surgery. It was reported that the subject recovered from the event of graft delamination without complications after MACI re-treatment on Study Day 1725.

Reviewer Comments: The delamination occurred more than 3 years after the surgery. However, the determination of relatedness to surgery, as judged by the investigator, cannot be considered to be entirely objective.

The proportion of subjects with at least 1 subsequent surgical procedure (SSP) during the 3-year extension study was comparable for the two treatment groups (10.8% in the MACI group and 9.5% in the microfracture group). Seven MACI-treated subjects and 6 microfracture-treated subjects underwent 12 and 8 SSPs, respectively, during the Extension Study.

6.2.12.6 Clinical Test Results

Clinical laboratory tests were not part of the safety assessments in this study.

6.2.12.7 Dropouts and/or Discontinuations

There were no dropouts due to adverse dropouts reported in the Extension Study. Four subjects in the microfracture group discontinued their participation, and the reason stated was "Lost to Follow-up".

6.2.13 Study Summary and Conclusions

Reviewer comments and conclusions:

The SUMMIT Extension (MACI00809) was a 3-year, open-label, multicenter, voluntary enrollment study for subjects who were randomized and treated in SUMMIT, providing efficacy data regarding maintenance of effect within each treatment group over a total of 5 years. Safety and efficacy assessments were performed at scheduled visits at 3, 4, and 5 years following treatment in SUMMIT (i.e., at Weeks 156, 208, and 260 post-arthrotomy for subjects treated with MACI implant or at Weeks 156, 208, and 260 post-arthroscopy for subjects treated with microfracture).

Two study sites from the SUMMIT study (with 8 subjects, 5 in MACI and 3 in microfracture) did not participate in the SUMMIT Extension study for reasons that were apparently unrelated to trial outcomes (the study sites declined to participate due to financial/corporate reasons). Another 8 subjects from the SUMMIT Study withdrew prior to enrollment in the Extension Study for other reasons described above. Of the 128 subjects enrolled in the SUMMIT Extension study from the SUMMIT study, 65 were in the original MACI group and 63 in the microfracture group. Thus the sample comprised 89% of the original SUMMIT trial population. Further analysis of the 16 non-participating subjects, in terms of pain and function scores at Week 104 (end of SUMMIT) disclosed no overt substantial differences from those who elected to enroll. Four additional subjects dropped out of the Extension study; thus the overall retention rate was 97% for the Extension study and 86% for the entire 5-year evaluation (SUMMIT plus Extension). The overall missing data rate at 5 years was only 13%. Efficacy evaluations were focused on the **maintenance** of the 2-year effect within each treatment group using the same KOOS Pain and Function scores as in SUMMIT for the primary evaluation.

There was no sample size calculation for this SUMMIT Extension Study and no statistical hypothesis.

Treatment-group comparisons were not conducted, as discussed above. The study interpretation was focused on the longitudinal aspect of the results --- that is, evaluating the maintenance of any effect seen in this specific population (128 subjects in the modified Full Analysis Set or mFAS) throughout the extension study.

Over the three years of the study (Years 3-5), the levels of improvement in KOOS Pain and Function (SRA) remained fairly stable in both treatment groups. This appeared to hold for each of the three years of the study. Over the 3 years, the treatment-group differences in both pain and function scores diminished.

The review team believes that the outcomes of the Extension study convey important clinical information to patients and physicians and should be included in the product label.

Secondary efficacy endpoints were comparable for both treatment groups in the SUMMIT Extension Study, with the exception of diminished treatment-related differences in proportion of responders. Please see a description of the results above.

Our overall conclusion is that the pain and function scores remained fairly stable in both the MACI and microfracture groups over the 3 years, but that the treatment-group differences, which achieved statistical significance at the end of SUMMIT, diminished and most likely would not have retained statistical significance had there been a hypothesis.

The safety analysis was unremarkable, with rates and types of TEAEs as expected for knee cartilage defect and other surgical interventions to treat the condition.

Postmarketing Studies with MACI Outside the US

In addition to this trial and its extension, Genzyme has collected safety information from 6,032 patients treated with MACI outside the US, as of 6/27/2015, according to the Genzyme Periodic Benefit-Risk Evaluation Report of August 2015 (Table 28).

Table 28. Summary of Characteristics of Adverse Events from Non-study MACI Cases in the MACI Postmarketing Safety Database

Characteristic	Total Events N = 196 n (%)
Seriousness	
Serious	110 (56.1)
Nonserious	86 (43.9)
Sex	
Male	89 (45.4)
Female	49 (25.0)
Unknown	58 (29.6)
Age (years)	
≤17	--
18-30	27 (13.8) with 20 male, 3 female ^a
31-40	29 (14.8) with 16 male, 13 female
41-51	35 (17.9) with 13 male, 21 female ^a
52-58	16 (8.2) with 16 male, 0 female
>58	--
Unknown	90 (45.9) with 25 male, 12 female ^a
Source	
Spontaneous	93 (47.4)
Literature	99 (50.5)
Solicited	4 (2.0)
Case Outcome	
Death	2 (1.0)
Recovered/recovering	25 (12.8)
Recovered with sequelae	1 (0.5)
Not recovered	22 (11.2)
Unknown	146 (74.5)

Source: Table 43 of the Integrated Summary of Safety, page 94 / 1839.

Adverse events reported in ≥5% of non-study MACI cases through 31 August 2015 were graft complication, treatment failure, tendonitis, graft delamination, and arthralgia. With the exception of graft complication, these AEs were also observed in the MACI trial.

Adverse event profiles appear to be similar between males and females. AEs exhibiting at least a 2-fold difference between males and females were:

- Males > females: tendonitis and treatment failure
- Females > males: synovitis, therapeutic product ineffective, joint effusion, joint swelling, and fall

Treatment failure and related events (PTs: treatment failure, graft delamination, graft complication, surgical procedure repeated, therapeutic product ineffective, and transplant failure) seemed to be slightly more frequent in male patients, whereas AEs regarding the joint (PTs: joint swelling, arthritis, joint effusion, bone marrow edema, synovitis, arthralgia, arthritis infective, arthritis bacterial, and arthropathy) seem to occur more frequently in female patients. In nearly 30% of AEs, the patient's sex was not reported. The most frequent AEs for which no sex information was provided include graft complication (36.1%), transplant failure and pain (6.9% each), and deep vein thrombosis (5.2%); all other events occurred in ≤ 2 (3.4%) patients.

Two non-study cases reporting death as an event outcome were identified in the MACI post-marketing safety database. In these 2 cases, the causes of death were pulmonary embolism in a 36-year-old patient and accident in a 58-year-old patient; both were male. The death due to pulmonary embolism occurred approximately 5 weeks after the patient received a MACI implant; no further details are available for this case.

Reviewer comments:

It is important to note that, in general, patients undergoing surgery are at increased risk of venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism. A recent study in 12,595 patients showed a low risk for VTE after knee arthroscopy, with an incidence of 0.34% (95% CI, 0.25% to 0.46%). Three subjects (4.1%) in the MACI group in SUMMIT had VTE; all 3 subjects recovered.

A comprehensive search of AEs from non-study cases in the MACI postmarketing safety database from 5/24/2005 through 8/31/2015 identified a total of 196 events. Overall, reported AEs, including cell-related events, correspond with the safety profile of MACI in the SUMMIT trial. The majority of AEs were joint-related.

Reviewer Comments:

The methodology of detection and selection for reporting of these 196 AEs has not been addressed. (Usually, safety events are underreported in such analyses.) Therefore, the clinical reviewers consider that safety information from this limited number of subjects with AEs in non-study MACI cases in the MACI post-marketing safety database is insufficient to draw any firm conclusions.

(b) (4)



(b) (4)

7. Integrated Overview of Efficacy

7.1 Indication #1

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

Reviewer Comments:

(b) (4)

7.1.1 Methods of Integration

Since the application contains only one adequate and well-controlled trial (and its extension), there is no integration or pooling of results in this review.

7.1.2 Demographics and Baseline Characteristics

Please see Section 6 for details.

7.1.3 Subject Disposition

Please see Section 6 for details.

7.1.4 Analysis of Primary Endpoint(s)

Please see Section 6 for details.

7.1.5 Analysis of Secondary Endpoint(s)

Please see Section 6 for details.

7.1.6 Other Endpoints

Please see Section 6 for details.

7.1.7 Subpopulations

Please see Section 6 for details.

7.1.8 Persistence of Efficacy

Please see Section 6 for details.

7.1.9 Product-Product Interactions

Not applicable.

7.1.10 Additional Efficacy Issues/Analyses

Please see Section 6 for details.

7.1.11 Efficacy Conclusions

Please see Section 6 for details.

8. Integrated Overview of Safety

8.1 Safety Assessment Methods

In the integrated safety summary, the applicant presented adverse events (AEs) from MACI studies. Adverse events for SUMMIT and the Extension are summarized as following:

-SUMMIT (MACI00206): events that occurred during the 2-year, Phase 3 pivotal study for the full Safety Set.

-SUMMIT Extension (MACI00809): events that occurred during the 3 years of the Extension for all subjects enrolled (modified Safety Set) in the Extension study.

-Combined SUMMIT + Extension (MACI00206/MACI00809): events that occurred across 5 years for the full Safety Set adjusted for patient-years of exposure (PYE).

The post-marketing experience with MACI outside the US was submitted in the application and summarized in this review, in Section 6.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Please see Section 6 for details.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Please see Section 6 for details.

8.2.3 Categorization of Adverse Events

Please see Section 6 for details.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Not applicable.

8.4 Safety Results

8.4.1 Deaths

Please see Section 6 for details. No deaths were reported in the SUMMIT or SUMMIT Extension Studies.

8.4.2 Nonfatal Serious Adverse Events

Please see Section 6 for details.

8.4.3 Study Dropouts/Discontinuations

Please see Section 6 for details.

8.4.4 Common Adverse Events

Please see Section 6 for details.

8.4.5 Clinical Test Results

Please see Section 6 for details.

8.4.6 Systemic Adverse Events

Please see Section 6 for details.

8.4.7 Local Reactogenicity

Please see Section 6 for details.

8.4.8 Adverse Events of Special Interest

Please see Section 6 for details.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

Not applicable to MACI.

8.5.2 Time Dependency for Adverse Events

Not applicable to MACI.

8.5.3 Product-Demographic Interactions

Not applicable to MACI.

8.5.4 Product-Disease Interactions

Not applicable to MACI.

8.5.5 Product-Product Interactions

Not applicable to MACI.

8.5.6 Human Carcinogenicity

There is no evidence of carcinogenicity based on animal or human studies with MACI, (b) (4)

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable to MACI.

8.5.8 Immunogenicity (Safety)

Not applicable to MACI.

8.5.9 Person-to-Person Transmission, Shedding

Not applicable to MACI.

8.6 Safety Conclusions

Please see Section 6 for details.

9. Additional Clinical Issues

9.1 Special Populations

Children and the elderly were not included in the SUMMIT Study. Therefore any effects related to the efficacy or safety of MACI in these age categories are unknown. The SUMMIT Study was conducted among White subjects only; therefore any effects in different races or ethnic groups are also unknown.

9.1.1 Human Reproduction and Pregnancy Data

The SUMMIT Study specifically excluded pregnant women. One subject in the MACI group and one subject in the microfracture group were reported to have spontaneous abortions. In addition, one subject in the microfracture group was reported with a non-serious event of gestational hypertension. With the low rate of these events, it is difficult to conclude about risks related to use of MACI during pregnancy.

The product label recommends that women of childbearing potential are advised to use effective birth control methods while on MACI treatment.

9.1.2 Use During Lactation

Based upon the clinical and pre-clinical information provided in the BLA, evidence of the presence of MACI in human milk, the effects of MACI on the breastfed child, or the effects of MACI on milk production are unknown.

9.1.3 Pediatric Use and Pediatric Research Equity Act (PREA) Considerations

In the pediatric population, chondral defects more often consist of local osteochondritic lesions and isolated traumatic injuries, as opposed to the diffuse degenerative patterns seen in many adult patients.¹⁷ The most common chondral-defect etiologies in children and adolescents are either trauma with sheared osteochondral fragments or underlying osteochondritis dissecans (OCD). Adolescent knee injury prevalence ranges between 10-25%.¹⁸ Cartilage damage is most often the result of Osteochondritis Dissecans (OCD¹⁹, 31%²⁰-61%), acute trauma (14%²¹-30%), and avascular necrosis (16%).

Prior to the submission of the BLA, the applicant submitted an initial Pediatric Study Plan (iPSP) requesting a complete waiver of the requirement to study their product in

17 ICRS pediatric chapter, "Chondral Injury and Disease in the Pediatric Population"

http://www.cartilage.org/files/File/Cartilag%20Restoration-pediatric_27%20May10 (1).pdf

18 Martin JA, Brown T, Heiner A, Buckwalter JA. Post-traumatic osteoarthritis: the role of accelerated chondrocyte senescence. *Biorheology* 2004;41(3-4):479-91.

19 Schmal, H. Pestka, J.M., Slazman, G "Autologous Chondrocyte Implantation in Children and Adolescents" *Knee Surge Sports Traumatol Arthrosc* (2013) 21: 671-677.

20 Salzman, Sah, Schmal "Microfracture for treatment of knee cartilage defects in children and adolescents" *Pediatric Reports* 2012 vol 4 e21 p 82.

21 Murphy, RT, Pennock AT, Bugbee WD. "Osteochondral Allograft TRansplanation of the knee in the Pediatric and Adolescent Population" *Am J Sports Med* 2014 2014 Mar; 42(3) 635-640

children. The review team and the PeRC did not agree to the request and recommended that the applicant propose a waiver for children younger than 10 years of age and a deferral of studies in children ages 10 – 17 years with symptomatic chondral or osteochondral defects in the knee due to (b) (4) acute trauma.

The applicant resubmitted the PSP and this plan was agreed upon by the review division. And the PeRCAt the time of this review, the agreed PSP has not been presented to PeRC, but if the plan is approved by PeRC, the deferred study in those subjects age 10 – 17 years would become a PREA-related post-marketing required study if the BLA is approved.

9.1.4 Immunocompromised Patients

In this BLA, there are no available data from studies conducted in an immunocompromised patient population.

9.1.5 Geriatric Use

In the SUMMIT study and its extension study, subjects' median age was 34 to 35 years old. Maximum age was 54 years in both treatment groups. As indicated, the age range for proposed target patient population in the SUMMIT study is between ≥ 18 and ≤ 55 years old. There are no available data or studies of MACI used in the geriatric patient population.

Reviewer Comments:

That MACI is less effective in elderly individuals is biologically plausible, given the autologous nature of the cells and the possible differences in responses in older people. Our review of outcomes by age within the SUMMIT (18-54 years of age) population suggested some decline in efficacy in older subjects. Accordingly, a caveat about lack of information in individuals over 55 years of age should be included in the product label in addition to the statement that there are no data in patients >65 years old.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Not applicable.

10. Conclusions

Efficacy in the SUMMIT Study

In this 2-year randomized controlled trial, the improvement in KOOS Pain and KOOS Function (SRA) score changes as the co-primary endpoints was statistically significantly greater ($p=0.001$) in the MACI group compared with improvements in these outcomes in the microfracture group. Thus, the co-primary effectiveness endpoint was met. The treatment-effect size (slightly greater than 11 points on both pain and function scales) is considered clinically meaningful, according to the authors who validated the KOOS instrument and other authors in the orthopedic community. The review team concurs with this opinion.

As a secondary endpoint, the applicant performed a responder analysis (defined as at least a 10-point improvement in both pain and function scores). The percentage of subjects who responded to treatment at week 104 from Baseline was statistically

significantly greater ($p = 0.016$) for subjects in the MACI group (87.50%) compared to the microfracture group (68.06%). However, this endpoint was ranked third by the applicant in a closed hierarchical testing scheme in which the first two endpoints failed; therefore, the results should be considered as exploratory. However, information regarding the proportion of subjects who experienced clinically meaningful improvements in both pain and function is important to patients and physicians and should be conveyed in the product label, although without p-values.

The applicant also analyzed changes in histology (mean ICRS II Overall Assessment Histology Score Week 104) and MRI (degree of defect fill, Weeks 52 and 104). There were essentially no differences between treatment groups in either of these evaluations. As these were the first and second-ranked secondary endpoints (this rank-ordering was done without consultation with FDA), further formal statistical testing of secondary endpoints was precluded, and all subsequent outcomes are regarded as exploratory (see above description of responder analysis).

Safety in the SUMMIT Study

Regarding the safety evaluation, the proportion of subjects with at least 1 TEAE was 76.4% in the MACI group and 83.3% in the microfracture group. Of the most common TEAEs (>10% in either treatment group), those occurring with greater frequency in MACI were back pain (11.1% in the MACI group versus 9.7% in the microfracture group), nasopharyngitis (13.9% in the MACI group versus 9.7% in the microfracture group); most common TEAEs occurring with greater frequency in the microfracture group were cartilage injury (4.2% in the MACI group versus 12.5% in the microfracture group), arthralgia (51.4% in the MACI group versus 63.9% in the microfracture group), and headache (18.1% in the MACI group versus 29.2% in the microfracture group).

Treatment-emergent SAEs were reported more in the microfracture group (26.4%) than in the MACI group (15.3%). The difference in incidence rates was mainly due 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 SSP was comparable for the 2 treatment groups (8.3% in the MACI group and 9.7% in the microfracture group).

No deaths occurred in this study.

All TEAEs and TESAAs were expected. Incidence rates of TEAEs and TESAAs in both study groups were comparable; if anything, the rates of TESAAs was higher in the microfracture group, compared to rates in the MACI group. There are no additional outstanding safety concerns identified in the safety database of SUMMIT study.

Efficacy in the SUMMIT Extension Study

The SUMMIT Extension Study was well-designed to assess durability of outcomes of pain and function. Eighty-nine percent of the SUMMIT study population entered the Extension study, and the retention rate was 97% over the 3 years of the study. Mean KOOS pain and function scores achieved by the 2-year completion of the SUMMIT Study remained essentially stable for the remaining three years in both MACI and microfracture groups. The study provides important information regarding treatment

durability and the reviewers strongly recommend that outcomes of the Extension study be presented in product labeling.

The results of other, secondary, outcomes are considered exploratory and have been described extensively in Section 6.

Safety in the SUMMIT Extension Study

Over the 3 years, the proportion of subjects with at least 1 TEAE was 75.4% in the MACI group and 74.6% in the microfracture group. The overall frequency of subjects with TEAEs and SAEs was comparable numerically in both groups for all categories. No subjects in either treatment group discontinued the extension study prematurely due to a TEAE, and no patients died in the study.

Treatment-emergent AEs were most frequently reported within the SOC of “musculoskeletal and connective tissue disorders” in both treatment groups (60.0% in the MACI group and 58.7% in the microfracture group). Based upon nature of study population, this profile is expected.

There are no outstanding safety concerns identified in the safety review of the SUMMIT Study or its extension.

For additional details, please refer to the review in Section 6.

11. Risk-Benefit Considerations and Recommendations

11.1 Risk-Benefit Considerations

Please refer to the consideration as listed in Table 29.

Table 29. Benefit-Risk Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> • Knee cartilage defect of the knee affects approximately 900,000 Americans annually, resulting in more than 200,000 surgical procedures. • Patients with moderate to severe cartilage defects complain of knee joint pain and impairment of knee joint function. • The current surgical procedures for knee cartilage repair are Microfracture, Drilling, Abrasion Arthroplasty, Autologous Chondrocyte Implantation (ACI), Osteochondral Autograft Transplantation and Osteochondral Allograft Transplantation. Microfracture is the most common first-line treatment for cartilage defects of the knee in both the US and EU. • Limitations associated with microfracture treatment include differences in filling of the chondral lesion, persistent subchondral bone exposure in some subpopulations; poor fill grade; increased treatment failures over time; and limited use in larger lesion sizes or in patients with multiple lesions. • Carticel is the only ACI therapy approved in the US to repair cartilage defects. • There is scant information from adequate and well-controlled clinical trials to provide the basis for meaningful comparisons among treatment options. 	<ul style="list-style-type: none"> • Knee cartilage defects are common in the US. • Several surgical treatments for patients with moderate to severe cartilage defects are available. ACI is also available (Carticel). • There have been few randomized clinical trials that have resulted in meaningful comparisons among treatment options. • Microfracture is the most common surgical treatment modality, but a treatment effect size for microfracture (compared to any standard of care) is not known due to lack of adequate and well-controlled studies. • No known medical or surgical approach is 100% effective in most patients with symptomatic knee cartilage injury, and there is need for improvement in therapeutic options.
Unmet Medical Need	<ul style="list-style-type: none"> • There is need for improvement in therapeutic options for knee cartilage injury, which can cause chronic pain and loss of function. • Carticel is the only ACI therapy approved in the US to repair cartilage defects. Carticel is administered with a periosteal flap with potential graft cartilage overgrowth and an increased need for subsequent reparative surgical procedures. • Clinical benefits of Carticel have not been conclusively demonstrated in randomized clinical trials. • It is generally accepted that Carticel does not provide long-term symptomatic improvement in all patients and there is an unmet need in injuries or defects of the knee cartilage. 	<ul style="list-style-type: none"> • There is an unmet medical need in knee cartilage defects resulting in symptoms of pain and reduced function. Although there are different surgical strategies, including ACI, many patients remain symptomatic, or symptoms return within one to two years of the intervention.
Clinical Benefit	<ul style="list-style-type: none"> • The effectiveness of MACI was demonstrated in a single adequate and well-controlled randomized clinical trial (the SUMMIT Study). In this 2-year trial, MACI demonstrated superiority to microfracture in improvement in knee joint pain and function. The improvement in changes from baseline of subjects' KOOS Pain and KOOS Function (SRA) scores (co-primary endpoints) in the MACI group compared with microfracture was statistically significant at Week 104 ($p = 0.001$). The mean improvements in both pain and function (over 10 points in each scale) are considered to be clinically meaningful. • In a three-year extension study, the mean KOOS pain and function scores remained essentially stable for the additional three years in both treatment groups. • There is no safety or effectiveness data for MACI in patients over 55 years of age. • Given that all subjects enrolled and treated in SUMMIT study and SUMMIT Extension study were white, the safety and effectiveness outcomes of the SUMMIT study and SUMMIT Extension Study may not be strictly applicable to the broad US population. • Effectiveness was demonstrated in a single trial with a (necessarily) open-label design and patient-reported outcomes. There are no independent data, either clinical or laboratory-based, to support this outcome. Performing another trial, if feasible, would not necessarily solve this conundrum, since the same inherent design problems would remain. 	<ul style="list-style-type: none"> • Clinical effectiveness of MACI has been demonstrated in a single adequate and well-controlled trial. The co-primary efficacy endpoint was met in the 2-year SUMMIT study. MACI was clinically superior to microfracture in this study. • Treatment-related differences of 11 points in improvement in both pain and function are likely to convey meaningful clinical benefit to patients, in terms of how they feel and function. • Durability of the effect on pain and function was demonstrated for an additional three years in the SUMMIT Extension Study. • The applicability of SUMMIT outcomes to a broader US population has not been established.

<p>Risk</p>	<ul style="list-style-type: none"> • All TEAEs and TSEAEs occurring in both treatment groups in the SUMMIT Study and its 3-year extension are expected in this population of patients. Incident rates of TEAEs and TSEAEs in both study groups were comparable. There are no additional outstanding safety concerns identified in the safety database of the SUMMIT study. • The safety of MACI in children, in geriatric patients and in pregnant or lactating women is unknown. 	<ul style="list-style-type: none"> • There are no outstanding safety issues, based on results of the SUMMIT Trial and its extension study. • The safety of MACI in children, geriatric patients, pregnant or lactating women is unknown. • The safety data from the SUMMIT Study, derived from a population that was 100% white, may not be strictly applicable to the broad US population.
<p>Risk Management</p>	<ul style="list-style-type: none"> • Adequate surgical training to implant the MACI graft is important, to obtain efficacy and safety similar to that seen in the SUMMIT Study. • In addition to the surgical procedure, a well-designed and defined rehabilitation program is equally important. • A study in children age 10 – 17 years will add important data on the effects of MACI in this age group. • Standard pharmacovigilance is necessary to continue to assess the benefit-risk of MACI post-approval. 	<ul style="list-style-type: none"> • Adequate surgical training and post-surgical rehabilitation are important, but should be considered under the practice of medicine, and not as REMS. • PREA-PMR will provide pediatric safety and efficacy data. • Standard pharmacovigilance will add more information on the safety and efficacy of MACI in the US population.

11.2 Risk-Benefit Summary and Assessment

Please refer to the specific Benefit-Risk considerations listed in the table above. Based on safety and efficacy outcomes of the SUMMIT trial and its extension study, the overall clinical benefit of MACI exceed that of microfracture, a standard practice whose benefit was measured in the SUMMIT head-to-head comparison. (A treatment-effect size for microfracture compared to no surgical procedure has not been established.)

The safety profile of MACI is at least as favorable as that of microfracture, based again on data in this BLA, The disadvantage of MACI is that its administration requires a two-stage procedure, and, while not a favorable factor, apparently carries little or no increased overall risk, according to the BLA data. Therefore, MACI has a superior overall benefit-risk profile, compared to microfracture.

11.3 Discussion of Regulatory Options

The applicant submitted clinical data from only one randomized phase 3 clinical trial (SUMMIT Study) with its extension study. This issue has been discussed elsewhere in this review, and we have concluded that results from a single adequate and well-controlled study would be acceptable depending on trial design, conduct, and consistency and robustness of outcomes. We believe that the SUMMIT trial meets these criteria.

While MACI has not been studied in older children and adolescents, the application contains sufficient information regarding the benefits and risks of the product in adults to warrant approval. Pediatric studies can be deferred, and conducted as a PREA-related post-marketing requirement.

11.4 Recommendations on Regulatory Actions

The clinical reviewers recommend approval of MACI for the indication stated in the proposed label, with the exception of the (b) (4) in adults.

Since the benefit demonstrated is clinically meaningful (not a surrogate or intermediate clinical endpoint), and based on an acceptable safety profile, this recommendation is for full approval.

There are no outstanding safety issues that warrant imposing REMS.

The only PMR would be a PREA-related PMR for a pediatric deferred study in children 10 to 17 years of age.

11.5 Labeling Review and Recommendations

The clinical reviewer identified the following labeling issues, under internal discussion at the time of the writing of this review document:

1. (b) (4)

(b) (4)

2. Vericel proposed a voluntary training program for orthopedic surgeons willing to prescribe and administer MACI to their patients. The team is discussing how this would be conveyed in the label, if at all.
3. The clinical team strongly recommends including information from the SUMMIT extension study in the label.
4. The clinical team recommends including the responder analysis in the label, with data presented without p-values.
5. The clinical team is discussing how to notify the health care provider about the need and the details of the rehabilitation program that should follow implantation of MACI.

11.6 Recommendations on Post-marketing Actions

The only required study would be a PREA-related PMR, as follows: a prospective, randomized, controlled study to evaluate safety and efficacy of MACI in subjects aged 10 to 17 years, who are with knee cartilage defects due to (b) (4) acute trauma.

Appendix 1: Summary of Consultation with Dr. Phillip Posner (Patient Representative, SGE)

On 04-21-2016, OCTGT sent a request for a patient representative (PR) to the Office of Health and Constituent Affairs (OHCA). On 05-25-2016, we discussed issues related to the clinical review of MACI with the FDA- screened PR, Dr. Phillip Posner who is as Special Government Employee (SGE) involved in evaluation of cardiovascular drugs.

Dr. Posner had knee cartilage problems before the current minimal invasive techniques. In the 60's and 70's he had repeated sports injuries and finally a tear of his left medial meniscus. Following several years of heat, hydro-, and physical therapy and cortisone injections following fluid drainage, his left knee began to have episodes of "locking." At that point surgery was recommended and he underwent an open meniscectomy of his left medial meniscus (1976). Since then he has had periodic bouts of pain due to small leftover floating chips. Since the pain is transient and the chips are quite small and move about, he has chosen to forgo further surgery.

We asked Dr. Posner the following questions:

1. Vericel reports results from only one phase 3 randomized controlled study. The SUMMIT trial was conducted in seven European countries. Do you think that the study population (100% Caucasian and aged 18-55) enrolled in SUMMIT is comparable to the target patient population in the US, in terms of demographic characteristics (age distribution, sex and race and ethnicity)?

Dr. Posner's response: he believed that the company did not include patients aged >55 years. He stated that in the US there are many older patients who suffer from knee problems. Dr. Posner believes that the company should conduct an additional study including patients aged 55-75 in the US. Otherwise, this European study cannot represent American patient population. Additionally, Dr. Posner thought that we can't predict how chondrocytes from older patients will grow or how the patients will respond. Also the KOOS scale needs to be changed to accommodate the older group.

2. In the MACI treatment, all patients will undergo arthroscopy with a cartilage biopsy procedure for MACI manufacture processing prior to a second surgical procedure for implantation of MACI. Microfracture can be accomplished as a single procedure under arthroscopy. As a patient, do you think a cartilage biopsy procedure is acceptable for knee cartilage repair?

Dr. Posner stated that he would take the option of knee cartilage biopsy for MACI manufacture processing if he were young. At his current age, he would not opt for arthroscopy with a cartilage biopsy procedure for MACI. Based upon his life experiences, he would select the minimally invasive procedure, such as microfracture, rather than MACI implantation.

When questioned further about the use of the KOOS rating scales in the setting of an open-label trial, he thought that the open-label nature with potential bias will not be important over time --- that is, by two years, or in the extension study of another three years.

3. In the SUMMIT trial, the primary efficacy endpoints are the changes in KOOS Pain and KOOS Function (Sports and Recreational Activities - SRA) Scores compared to the same measurements in the microfracture group (control group) from baseline to Week 104. KOOS scores are patient-reported outcomes (PRO) to evaluate patient's joint pain and function. Based upon your knowledge, do you think that the use of this PRO (e.g., KOOS scores) is adequate to assess meaningful changes in patients with this condition?

Dr. Posner's response: he thought that the PRO is adequate for evaluation of the outcomes of a knee joint post-surgical procedure. However, he stressed that evaluation of function is very important, and that the pain evaluation could be variable due to each individual's condition and tolerance for pain. Dr. Posner prefers a functional assessment rather than a PRO, The American Physical Therapy Society has developed a number of approaches to this.

4. In the SUMMIT trial, both treatment groups (MACI and microfracture) showed substantial improvements in both KOOS pain (82.5 ± 16.2 in MACI group vs. 70.8 ± 24.2 in microfracture group) and KOOS SRA (60.9 ± 27.8 in MACI group vs. 48.7 ± 30.3 in microfracture group) over baseline. However, the improvements in pain (45.5 ± 21.1 in MACI group vs. 35.2 ± 31.6 in microfracture group) and function (46.0 ± 28.3 in MACI group vs. 35.8 ± 31.6 in microfracture group) were statistically significantly greater in MACI, compared to microfracture. Based on your experience and knowledge, do you think that this level of improvement over microfracture is clinically meaningful? In other words, how would you interpret these mean differences in terms of activities of daily life as well as pain?

Dr. Posner's response: he acknowledged the statistical superiority of MACI over microfracture but pointed out that the standard deviations were large, with some overlap between the groups. He thought that the group differences probably conveyed some clinical meaning, but would have preferred to be able to express clinical meaning in more concrete and specific terms, for example, time and distance walking, ability to play tennis, ability to climb stairs.

5. Generally, a rehabilitation program is very important to patients receiving knee orthopedic procedures. For this product, do you think rehabilitation program post MACI implantation should be considered as a requirement, either as part of the labeling instructions to physicians who provide this treatment, or as a separate requirement to be imposed on the manufacturer to monitor adherence and report back to FDA?

Dr. Posner's response: he stated that, based on his own experience, a rehabilitation program to strengthen quadriceps after knee surgical procedure will have great benefit in terms of recovery from surgery. For MACI implantation, which involves two procedures, he highly recommends that a rehabilitation program be added as part of the labeled instructions to physicians who provide this treatment. Also, it will be helpful to the patient to get medical insurance coverage if the label includes a recommendation for a rehabilitation program.

Reviewer Comments: Regarding consultant's response in Item 6, above, we have noted in this review that the demographics of the broad US population (race, ethnicity) differ from the demographics of subjects enrolled in the SUMMIT trial. Regarding Item 7, a

change of 10 points in KOOS score has been noted to be of clinical meaning according to a publication by Roos et al, cited and discussed in this BLA review.

Appendix 2: Summary of Consultation to Dr. Neil, Barkin (Orthopedic Surgeon, CDRH)

On 03-02-2016, the clinical review team sent a consult request to Dr. Neil J. Barkin, an orthopedic surgeon, who is orthopedic surgeon in CDRH. He provided the following comments regarding MACI product development:

1. The biopsy procedure is designed to obtain cells to be cultured and concentrated for the definitive stage of the procedure, the implantation of the cell soaked collagen sponge. Since this was performed prior to randomization, the control microfracture subjects underwent this procedure as well. The trivial size of the created chondral defect compared to the chondral lesion being treated and the peripheral non-weight bearing location of the defect compared to the usual weight-bearing location of the lesion make the biopsy defect of negligible clinical significance.

2. 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. He estimated that this I would estimate this could be readily achieved in a half to a full day session utilizing cadaver and simulated joint models.

3. Regarding post-marketing risk evaluation and mitigation, long-term follow-up with KOOS evaluations and physical examinations would be most effective. Weight-bearing x-rays should also be obtained looking for joint space narrowing suggestive of the progression towards osteoarthritis. Evaluation for the potential adverse event of cartilage hypertrophy and/or arthrofibrosis would likewise be performed. The primary extended endpoint of all cartilage repair procedures is appraisal of progression or prevention of osteoarthritis, a condition that evolves generally over decades and justifies prolonged follow-up of at least 5-10 years.

4. (b) (4)



(b) (4)

5. Multiple studies comparing the three available most common cartilage repair techniques, i.e. microfracture, osteoarticular transplantation (OATS), and autologous chondrocyte implantation (ACI), have been performed. A study performed at the Hospital for Special Surgery, reported at the AAOS annual meeting in February 2012, reported a 40% return to sports after microfracture vs. 90% return to sports after OATS procedure. An activity level score (Marx) demonstrated improved scores in the OATS group from the microfracture group at 2, 3, and 5 years post-surgery.

An extensive report presented in *Arthroscopy* 2010 Jun; 26(6):841-52 by Harris et al. entitled Treatment of chondral defects in the athlete's knee compared the results of microfracture, OATS, and ACI. Eight clinical outcome measures were utilized to assess improvement in 658 subjects identified in 11 literature studies. Microfracture results deteriorated with time while ACI and OATS provided more durable improvement. Overall return to sports was 66% with OATS which also provided the most rapid return; ACI demonstrated the slowest return. Factors related to improved post-surgical performance included a defect size less than 2 cm², preoperative symptoms for fewer than 18 months, no prior surgical treatment, younger patient age, and higher preinjury and postsurgical level of sport participation. As lesion size increased, microfracture success decreased.

The use of microfracture as the control procedure likely ensures that insures the MACI comparison will be superior. This effect is further exaggerated by the required lesion size being > 3.0 cm². Use of OATS as a control might have been more realistic in comparing an established procedure with a better clinical result than microfracture to the subject procedure. (The Our orthopedic consultant agreed, however, that microfracture is the most prevalent procedure for knee cartilage repair in the US, and therefore it is an appropriate comparator for the SUMMIT Study).

6. The criteria for inclusion/exclusion in the SUMMIT study appear to closely match the demographics of the target U.S. population as demonstrated in the earlier Carticel studies with exceptions primarily on lesion size and depth. These differences, which are relatively minor, are unlikely to be of clinical significance.

7. Minimal perceptible clinical improvement with the KOOS scale has been determined by the developer of the PRO to be 8-10 points. Consequently, it does appear the KOOS response identified is clinically meaningful. I have no specific suggestions on how utilizing sub-sections of the KOOS score could enhance clinical evaluation of sub-groups within the cohort populations. The KOOS score is a generalized PRO designed to incorporate pain and function scores. It includes five components: pain, function in activities of daily living, function in sports and recreation, other symptoms, and quality of life. As such, it appears to be a reasonable tool for measuring overall function post-surgery and comparing to pre-surgical status.

Reviewer Comments: Regarding consultant's response in Item 6, above, we have noted in this review that the demographics of the broad US population (race, ethnicity) differ from the demographics of subjects enrolled in the SUMMIT trial. Regarding Item 7, a change of 10 points in KOOS score has been noted to be of clinical meaning according to a publication by Roos et al, cited and discussed in this BLA review.

