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Priority Review	No
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Review Completion Date / Stamped Date	
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Applicant	Vericel Corporation
Established Name	Autologous Cultured Chondrocytes Seeded on a Porcine Collagen Membrane (MACI)
(Proposed) Trade Name	MACI® implant
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	(b) (4) type I/III collagen membrane seeded with autologous cultured chondrocytes at a density of 500,000 to 1 million cells per cm^2.
Dosage Form(s) and Route(s) of Administration	Autologous cultured chondrocytes seeded onto a CE marked purified resorbable porcine-derived collagen type I/III membrane (ACI-Maix™, Matricel GmbH, Germany)
Dosing Regimen	MACI implant
Indication(s) and Intended Population(s)	Repair of symptomatic cartilage defects of the knee ((b) (4)) in adults

Table of Contents

1. Executive Summary 7

2. Clinical and Regulatory Background 7

2.1 Disease or Health-Related Condition(s) Studied 8
2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s) 8
2.4 Previous Human Experience with the Product (Including Foreign Experience) 9
2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission 9
2.6 Other Relevant Background Information 9

3. Submission Quality and Good Clinical Practices 10

3.1 Submission Quality and Completeness 10
3.2 Compliance With Good Clinical Practices And Data Integrity 10

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines 10

4.1 Chemistry, Manufacturing, and Controls 10
4.2 Assay Validation 10
4.3 Nonclinical Pharmacology/Toxicology 10
4.4 Clinical Pharmacology 10
4.5 Clinical 10
4.6 Pharmacovigilance 10

5. Sources of Clinical Data and Other Information Considered in the Review 10

5.1 Review Strategy 10
5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review 11
5.3 Table of Studies/Clinical Trials 11
5.4 Consultations 12
5.4.1 Advisory Committee Meeting (if applicable) 12
5.4.2 External Consults/Collaborations (if applicable) 12
5.5 Literature Reviewed (if applicable) 13

6. Discussion of Individual Studies/Clinical Trials 13

6.1 Study MACI00206 (SUMMIT) 13
6.1.1 Objective 13
6.1.2 Design Overview 13
6.1.3 Population 13
6.1.4 Study Treatments or Agents Mandated by the Protocol 13
6.1.6 Sites and Centers 14
6.1.7 Surveillance/Monitoring 15
6.1.8 Endpoints and Criteria for Study Success 15
6.1.9 Statistical Considerations & Statistical Analysis Plan 16
6.1.10 Study Population and Disposition 17
6.1.11 Efficacy Analyses 19
6.1.12 Safety Analyses 25
6.2 Study MACI00809 (SUMMIT Extension) 29
6.2.1 Objective 29
6.2.2 Design Overview 29
6.2.3 Population 29
6.2.4 Study Treatments or Agents Mandated by the Protocol 29
6.2.6 Sites and Centers 30
6.2.7 Surveillance/Monitoring 30
6.2.8 Endpoints and Criteria for Study Success 30
6.2.9 Statistical Considerations & Statistical Analysis Plan 31

6.2.10 Study Population and Disposition 31
6.2.11 Efficacy Analyses 33
6.2.12 Safety Analyses 36

10. CONCLUSIONS 37

10.1 Statistical Issues and Collective Evidence 37
10.2 Conclusions and Recommendations 38

Glossary/ Abbreviation

Abbreviation	Definition
α	level of significance
ACI	autologous chondrocyte implantation
ACL	anterior cruciate ligament
ADL	Activities of Daily Living
AE	adverse event
ANOVA	analysis of variance
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CSP	concurrent surgical procedure
CSR	clinical study report
eCRF	electronic Case Report Form
EMA	European Medicines Agency
EQ-5D	European Quality of Life (EuroQOL) 5 dimensions questionnaire
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICRS	International Cartilage Repair Society
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
IKDC	International Knee Documentation Committee
IND	Investigational New Drug
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KOOS	Knee Injury and Osteoarthritis Outcome Score

LCL	lateral collateral ligament
LFC	lateral femoral condyle
MACI	matrix applied characterized autologous cultured chondrocytes
MANOVA	multivariate analysis of variance
Max	maximum
MCL	medial collateral ligament
MedDRA	Medical Dictionary for Regulatory Activities
MCMC	Markov-chain-Monte-Carlo
MFC	medial femoral condyle
MI	multiple imputation
Min	minimum
MRI	magnetic resonance imaging
OCD	osteochondritis dissecans
PCL	posterior cruciate ligament
PP	Per Protocol
PRO	patient-reported outcome
PT	Preferred Term
PVD	peripheral vascular disease
QA	quality assurance
QOL	Knee-Related Quality of Life
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SF-12	12-Item Short-Form Health Survey
SF-36	36-Item Short-Form Health Survey
SOC	System Organ Class
SRA	Sports and Recreational Activities
SSP	subsequent surgical procedure
TEAE	treatment-emergent adverse event
US	United States
VAS	Visual Analogue Scale

WHO	World Health Organization
WORMS	Whole-Organ MRI Scoring

1. EXECUTIVE SUMMARY

A prospective, randomized, open-label, parallel-group and multicenter phase III study (MACI00206, also called SUMMIT) was conducted to demonstrate the superiority of matrix-induced autologous chondrocyte implantation (MACI implant) versus arthroscopic microfracture for the treatment of symptomatic articular cartilage defects of the femoral condyle including the trochlea. This is the largest randomized and controlled study of MACI compared to microfracture conducted to date. The study appears to be adequately designed with pre-specified statistical analysis plan (SAP). The primary efficacy analysis focused on co-primary endpoints, KOOS Pain and KOOS Function (SRA), to demonstrate MACI's treatment effect at 104 weeks post initial procedure, for which the study was completed successfully based on pre-specified statistical analysis method of multivariate analysis of variance (MANOVA). Statistical tests on the pain and function endpoints separately also showed statistically significant superiority of MACI over arthroscopic microfracture with p-values <0.05.

The study also listed 5 secondary endpoints to be compared between treatments in a pre-specified hierarchical order. However, the testing of the first secondary endpoint, microscopic ICRS II Overall Assessment at Week 104, was not statistically significant at level of 0.05. Therefore, statistical testing of the remaining secondary endpoints was not warranted. One of the secondary endpoints, the response rate based on KOOS Pain and Function (SRA) scores (had at least a 10-point improvement from baseline in both pain and function, at week 104), the third in the rank order of importance according to the study protocol, showed a p-value <0.05 (i.e., p=0.016 based on the pre-specified statistical testing procedure). However, when interpreted through the SAP pre-specified closed testing procedure to account for multiple hypotheses testing, a statistically significant difference between groups cannot be concluded. If one were to disregard the rank order, and apply the Bonferroni p-value adjustment, the difference in response rate, 87.5% vs 68%, still would not reach a statistical significance. Moreover, a limitation facing a single phase 3 study BLA is that there is not a second study with similar endpoints that can help the interpretation of statistical results of these secondary endpoints.

The SUMMIT Extension study, a 3-year extension part of SUMMIT trial for long-term safety follow-up and efficacy maintenance, faced several issues which make it difficult to draw statistical inferences on study results. However, based on the summarization of data that came out of the extension study, even though the measures for the treatment difference between groups appear to be smaller compared to those in SUMMIT primary study, the trend favoring MACI treatment continued in the extension study.

2. CLINICAL AND REGULATORY BACKGROUND

Chondral and osteochondral defects of the knee occur along a spectrum of disease and severity. At one end of the spectrum are small, acute lesions that are often diagnosed incidentally at the time of knee arthroscopy and are not necessarily initially symptomatic. At the other end are larger, more chronic lesions that are often symptomatic and may contribute to joint malalignment. These lesions can cause disabling symptoms such as pain, dysfunction, catching, locking, and swelling. Focal chondral lesions left untreated may progress to debilitating joint pain, dysfunction, and osteoarthritis.

Several approaches exist to manage symptomatic chondral and osteochondral defects in the knee including nonsurgical and non-reparative approaches (e.g., debridement and knee joint lavage), reparative procedures (marrow stimulation techniques including microfracture), and restorative procedures such as mosaicplasty and ACI. Autologous chondrocyte implantation (ACI) was first described in 1994.

Carticel, first approved by the United States (US) Food and Drug Administration (FDA) in 1997 (BL 103661), is an ACI therapy that is administered surgically with direct injection of expanded autologous chondrocytes into the cartilage defect and secured using a harvested autologous periosteal flap. FDA approved labeling supplements to include safety and efficacy data from the STAR (the Study of the Treatment of Articular Repair, CART012-99) (FDA STN: BL 103661/5155) and RBS (the Registry Based Study, CART013-99) (FDA STN: BL 103661/5082). Despite the efficacy of Carticel to repair cartilage, application with a periosteal flap may lead to the development of graft overgrowth and arthrofibrosis which may require additional surgery. To limit these complications, current clinical practice in the US is to apply the autologous cells supplied as Carticel to available marketed Type I/III collagen membranes for implantation. However, application of the cells and the type of membranes used are not standardized to ensure the safe and effective use of characterized autologous cultured chondrocytes for the treatment of cartilage defects of the knee. MACI, which is the subject of this BLA, was developed to address the unmet medical need for a safe and effective ACI that eliminates the need for a periosteal flap thereby improving clinical management of patients, and ensure consistency of the product.

MACI is a combination product where the characterized autologous cultured chondrocytes (cell component) are seeded onto a resorbable Type I/III collagen membrane, ACI-Maix™ (device component), to allow for delivery of the cell product to the chondral (b) (4) defect. MACI improves upon the delivery of the active cellular component by removing the need for the harvest, placement, and suture of a periosteal flap to retain the suspension of chondrocytes in the cartilage defect. At implantation, the MACI matrix implant is trimmed to the size and shape of the cartilage defect, implanted cell-side down into the defect, and secured in place using fibrin sealant. As a result, the reduction from a two-step to one-step procedure results in shorter operative time with MACI compared to Carticel, and should reduce postoperative symptoms such as pain, swelling, and graft overgrowth that would necessitate additional surgery.

2.1 Disease or Health-Related Condition(s) Studied

The disease or condition investigated in this BLA is symptomatic, full-thickness cartilage defects (single or multiple defects) of the knee with or without bone involvement (b) (4) in adults.

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

Several approaches to managing symptomatic cartilage defects in the knee exist, ranging from nonsurgical approaches and non-reparative, nonrestorative procedures (e.g., debridement and knee

joint lavage) that aim to relieve pain and improve mobility, to reparative procedures (i.e., marrow stimulation techniques such as abrasion arthroplasty, drilling, and microfracture) that aim to bring about bleeding from the subchondral bone leading to repair tissue formation, to restorative procedures (e.g., mosaicplasty, and autologous chondrocyte implantation [ACI]) that aim to re-establish the articular surface.

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

Previously published studies of MACI treatment for cartilage repair in the knee with 2- to 5-year follow-up in approximately 120 patients have shown some evidence of structural repair. In terms of clinical parameters such as pain and function, results from the studies showed clinical improvement over time, including at 2 and 5 years postoperatively. Three of the studies included the KOOS instrument for measurements; subjects' KOOS subscale scores, (ie, other Symptoms, Knee-Related Quality of Life [QOL], Activities of Daily Living [ADL],) consistently improved over time from baseline through to 2 and 5 years following treatment. A number of additional studies, with a range of study designs and patient follow-up to 9 years, have reported results that reinforce a positive benefit-risk profile for MACI treatment in the repair of cartilage defects.

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

FDA Guidance *"Guidance for Industry—Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products"* describes situations in which a single adequate and well-controlled study may be adequate to support evidence of effectiveness for approval. The MACI clinical development program consists of a single clinical study, the SUMMIT study (and its extension).

SUMMIT trial was conducted in Europe. The sponsor (formerly Genzyme and now Vericel) did not file an IND with FDA. Consequently SUMMIT trial was not conducted under an IND. The present study evaluates the safety and efficacy of MACI® (matrix applied characterized autologous cultured chondrocytes) in the treatment of full-thickness articular cartilage defects compared with microfracture, an arthroscopic standard-of-care procedure. This is the largest randomized and controlled study of MACI compared to microfracture conducted to date. The study was designed in accordance with current FDA guidelines (FDA, 2011), European Medicines Agency (EMA) guidelines, and guidelines of International Cartilage Repair Society (ICRS).

Though the sponsor did not file an IND with FDA, two Pre-BLA meetings were held with FDA on October 10, 2013 and May 7, 2015 in addition to numerous CMC/Product meetings.

2.6 Other Relevant Background Information

N/A

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices And Data Integrity

This study was conducted in accordance with Good Clinical Practice (GCP) as defined by the International Conference on Harmonization (ICH), the principles defined in the Declaration of Helsinki and its amendments, and all applicable national and international laws. The study was registered on clinicaltrials.gov under identification number NCT00719576.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

None

4.2 Assay Validation

None

4.3 Nonclinical Pharmacology/Toxicology

None

4.4 Clinical Pharmacology

None

4.5 Clinical

None

4.6 Pharmacovigilance

None

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This statistical review will focus on the single phase 3 study MACI00206 (SUMMIT): a prospective, randomized, open-label, parallel-group and multicenter study designed to evaluate safety and efficacy

of MACI versus arthroscopic microfracture in the treatment of articular cartilage defects of the medial femoral condyle (MFC), lateral femoral condyle (LFC), and/or trochlea.

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

- The original submission STN125603/0.0 Clinical Study Report (CSR) and tabulation data.
- Protocol and Protocol Amendments
- SAP and its amendment

5.3 Table of Studies/Clinical Trials

Table 1 lists clinical studies included in this BLA submission. MACI00206 (SUMMIT) study was a prospectively designed phase 3 study which is the focus of this review. MACI00809 (SUMMIT Extension) was the extension part of SUMMIT trial for long-term safety follow-up and efficacy maintenance.

Table 1: Listing of Clinical Studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
MACI									
Phase 3	MACI00206 (SUMMIT)	5.3.5.1	To demonstrate superior efficacy and evaluate the safety of MACI compared with arthroscopic microfracture in the treatment of patients (aged 18 to 55 years) with symptomatic articular cartilage defects of the femoral condyle, including the	Phase 3, randomized, open-label; controlled (microfracture) - 2-year duration. Conducted in the EU.	Single treatment: MACI implantation via arthrotomy or microfracture via arthroscopy	144 (72 MACI, 72 microfracture)	Patients with symptomatic articular cartilage defects of the femoral condyle including the trochlea	Single treatment	Complete; Clinical Study Report
Extension	MACI00809 (SUMMIT Extension)	5.3.5.1	To examine the 5-year efficacy and safety of MACI implant, compared with arthroscopic microfracture, in patients who received study treatment in the SUMMIT study	Extension; efficacy and safety follow-up and maintenance of effect for MACI00206 – 3-year duration.	No treatment	128 (65 MACI, 63 microfracture)	Patients with symptomatic articular cartilage defects of the femoral condyle including the trochlea	No treatment	Complete; Clinical Study Report

5.4 Consultations

None

5.4.1 Advisory Committee Meeting (if applicable)

N/A

5.4.2 External Consults/Collaborations (if applicable)

None

5.5 Literature Reviewed (if applicable)

None

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study MACI00206 (SUMMIT)

Study MACI00206 is the only clinical study conducted for this submission. This was a prospective, randomized, open-label, parallel-group and multicenter study to demonstrate the superiority of matrix-induced autologous chondrocyte implantation (MACI® implant) versus arthroscopic microfracture for the treatment of symptomatic articular cartilage defects of the femoral condyle including the trochlea.

6.1.1 Objective

The objective of the study was to demonstrate superior efficacy and evaluate the safety of MACI compared with arthroscopic microfracture in the treatment of patients (aged 18 to 55 years) with symptomatic articular cartilage defects of the femoral condyle, including the trochlea.

6.1.2 Design Overview

This was a prospective, randomized, open-label, parallel-group and multicenter study designed to demonstrate the superiority of MACI versus arthroscopic microfracture with respect to KOOS pain and KOOS function in the treatment of articular cartilage defects of the medial femoral condyle (MFC), lateral femoral condyle (LFC), and/or trochlea. Following patient consent, patients were evaluated against the screening criteria. The planned patient population consisted of male and female patients between the ages of 18 and 55 years (inclusive), with at least 1 symptomatic Outerbridge Grade III or IV focal cartilage defect on the MFC, LFC, and/or trochlea (defect size equal to or greater than 3.0 cm^2 irrespective of location). Patients with osteochondritis dissecans were also eligible for inclusion providing a bone graft was not required. Patients with osteoarthritis in the target knee joint (Kellgren-Lawrence Grade 3 or 4) were excluded.

6.1.3 Population

Patients had to meet the following criteria at the Screening visit to be eligible for the study:

1. Provided written informed consent, and was able to read and understand the language and content of the study material, understand the requirements for follow-up visits and rehabilitation, and was willing to provide required information at the scheduled evaluations
2. Symptomatic focal cartilage defects as defined by KOOS Pain score <55
3. Aged ≥18 and ≤55 years
4. Agreed to provide a blood sample at the time of cartilage biopsy during the index arthroscopy for testing of human immunodeficiency virus type 1 (HIV-1), HIV-2, hepatitis B, hepatitis C, and syphilis

6.1.4 Study Treatments or Agents Mandated by the Protocol

MACI consisted of autologous cultured chondrocytes seeded onto a CE-marked purified resorbable porcine-derived collagen type (b) (4) 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 cm^2. At implantation, the membrane was trimmed to the correct size and shape of the cartilage defect, and implanted cell-side down into the debrided base of the defect; the implant was secured in place using fibrin sealant in a thin layer on the base.

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.

A summary of the main materials used in the biopsy shipping, processing, expansion, and final MACI product preparation and shipping are provided in Table 2.

The preparation of the final MACI product for administration occurred as close as possible to the time of actual treatment. The MACI product remained in the closed shipping box until required. Per protocol, further required details on storage conditions were provided to all study sites.

Table 2: Materials Used in the Manufacture of MACI

Item	Function
(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
Purified porcine-derived collagen type I/III membrane (ACI-Maix membrane)	Carrier of autologous cultured chondrocytes
(b) (4)	(b) (4)
Foetal Bovine Serum ((b) (4))	Growth medium component
Gentamicin ((b) (4))	Growth medium component

(b) (4)

6.1.6 Sites and Centers

Participating investigators were selected based on suitability as assessed during pre-study evaluation visits performed by the Sponsor. A total of 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) enrolled patients to participate in this study.

6.1.7 Surveillance/Monitoring

A representative of the Sponsor or designee visited the investigators periodically for the purpose of monitoring the progress of this study in accordance with GCP regulations. Source document verification was performed for all data elements. During these routine monitoring visits, all data pertaining to a patient's participation in the study must have been made available to the monitor.

No interim analyses were performed for this study. No Data Monitoring Committee was used for this study.

6.1.8 Endpoints and Criteria for Study Success

Co-primary efficacy variables:

Changes from Baseline to Week 104 for the patient's KOOS Pain and Function (Sports and Recreational Activities [SRA]) scores

Secondary efficacy variables (ranked in order of importance in the protocol):

- Histological evaluation of structural repair of evaluable biopsies harvested from the core of the index lesion during arthroscopy at Week 104. Evaluation of histological data was performed by independent central review blinded to the patient's treatment. An appropriate histological evaluation score was used to assess the structural repair. The microscopic International Cartilage Repair Society (ICRS) II variable "Overall Assessment" was to be regarded as the most important histological assessment variable addressing the related histology efficacy endpoint
- MRI assessments of structural repair parameters at baseline and at Weeks 52 and 104 including:

  - 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 (Note: this analysis was planned but not completed.)

  Evaluation of MRI data was performed by independent central review blinded to the patient's treatment. Appropriate MRI sequences were used to image cartilage repair tissue to allow assessment of parameters. The variable "degree of defect fill" was to be regarded as the most important MRI assessment variable addressing the related MRI efficacy endpoint

- Response rate based on KOOS Pain and Function (SRA) scores: the proportion of patients who responded to treatment at Week 104. A responder was defined as a patient with at least a 10-point improvement in both the KOOS Pain and Function (SRA) scores from Baseline
- Treatment failure rate: the proportion of patients 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)

- Change from Baseline at Week 104 in the remaining 3 subscales of the KOOS instrument (ie, other Symptoms, Knee-Related Quality of Life [QOL], Activities of Daily Living [ADL])

6.1.9 Statistical Considerations & Statistical Analysis Plan

The co-primary efficacy parameters, changes from Baseline to Week 104 in KOOS Pain and Function (SRA) scores, were analyzed with a MANOVA model. The analysis evaluates the co-primary efficacy endpoints simultaneously and was conducted at the significance level of $\alpha = 0.05$ (two-sided).

With the LOCF method for handling missing data, 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 only included in the final reduced model if found to be significant in the initial model.

> **Comment:** Ordinarily LOCF imputation is discouraged. However, in the SUMMIT study, there were a few missing data (less than 5% in total) at the primary analysis time point 104 weeks. To support the primary efficacy analysis, the SAP specified multiple imputation for missing data and per-protocol analysis as supportive analyses.

Per the SAP, the secondary efficacy variables were ranked in order of importance and a sequential closed testing procedure was used (see previous section for the sequential testing order of the secondary efficacy variables).

Summary statistics of the histological scores at Week 104 will be presented. Differences between the treatment groups will be analyzed by MANOVA for quantitative variables and the Cochran-Mantel-Haenszel $\chi 2$ test for ordinal variables.

Summary statistics of the MRI assessments at Baseline and at Weeks 52 and 104 will be presented. The post-treatment proportion of defect fill will be compared between treatment groups using the Cochran-Mantel-Haenszel $\chi 2$ test at week 104.

A responder was defined as a patient with at least a 10-point improvement in both the KOOS Pain and Function (SRA) scores from Baseline. The number (%) of patients who responded at Week 104 will be given by treatment group. The difference in responder rates between the MACI and microfracture groups will be tested using the Cochran-Mantel-Haenszel $\chi 2$ test.

Summary statistics of the values and the changes from Baseline to Week 104 in the remaining 3 subscales of the KOOS instrument (ie, Other Symptoms, Quality of Life [QOL], and Activities of Daily Living [ADL]) will be presented. Change from Baseline in KOOS subscale scores will be analyzed by analysis of variance (ANOVA) using a last observation carried forward (LOCF) method for handling missing data supported by an analysis using multiple imputation (MI) method for missing data.

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) score. The calculation was performed at $\alpha = 0.05$ and a power of 85%. Assuming 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), as well as a correlation coefficient between the change from Baseline at Week 104 between KOOS Pain and Function (SRA) of 0.56, 62 patients per treatment group (124 patients in total) would be needed to have 85% power. In order to account for possible early discontinuations from the study, an additional 20 patients (15%) were planned, resulting in 72 patients per treatment group (144 patients in total).

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The Full Analysis set (FAS), consisting of all randomized patients who received study treatment (ie, microfracture during the index arthroscopy or MACI implant during arthrotomy). The FAS was used to analyze efficacy in the primary analysis of the primary endpoints.

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

The study planned to enroll 144 subjects. In total, 189 patients were screened and 144 patients were randomized and treated (72 in the MACI group and 72 in the microfracture group). Therefore, 144 subjects were included in the FAS set.

> **Comment:** All patients randomized were included in the FAS, and the FAS is the same as the intent-to-treat (ITT) population for this study.

6.1.10.1.1 Demographics

Overall, patients' age, sex, race, and body mass index (BMI) were similar in both treatment groups. The majority of patients were male and the median age was 34 to 35 (range: 16-54) years old. The mean BMI was approximately 26 for both treatment groups. All patients were white (100%), and none were Hispanic or Latino.

All patients in the study had an index lesion in 1 target knee. For both treatment groups, acute trauma was the most common underlying etiology of the index lesion (45.8% in the MACI and 62.5% in the microfracture groups). Chronic degenerative defects were twice as common in the MACI group (25.0%) compared to the microfracture group (12.5%). Defects due to osteochondritis dissecans were present in 11.1% of patients in the MACI group and 16.7% of patients in the microfracture group. The duration since the onset of symptoms was longer in the MACI group compared to the microfracture group (median 1142 days [3.1 years] versus 736 days [2.0 years], respectively).

As per the inclusion criteria, all patients in the study had a Modified Outerbridge Grade III or Grade IV index lesion: 21 (29.2%) and 15 (20.8%) patients, respectively, in the MACI group and the microfracture group had Grade III index lesion; while 51 (70.8%) and 57 (79.2%) patients in the respective group had Grade IV index lesion.

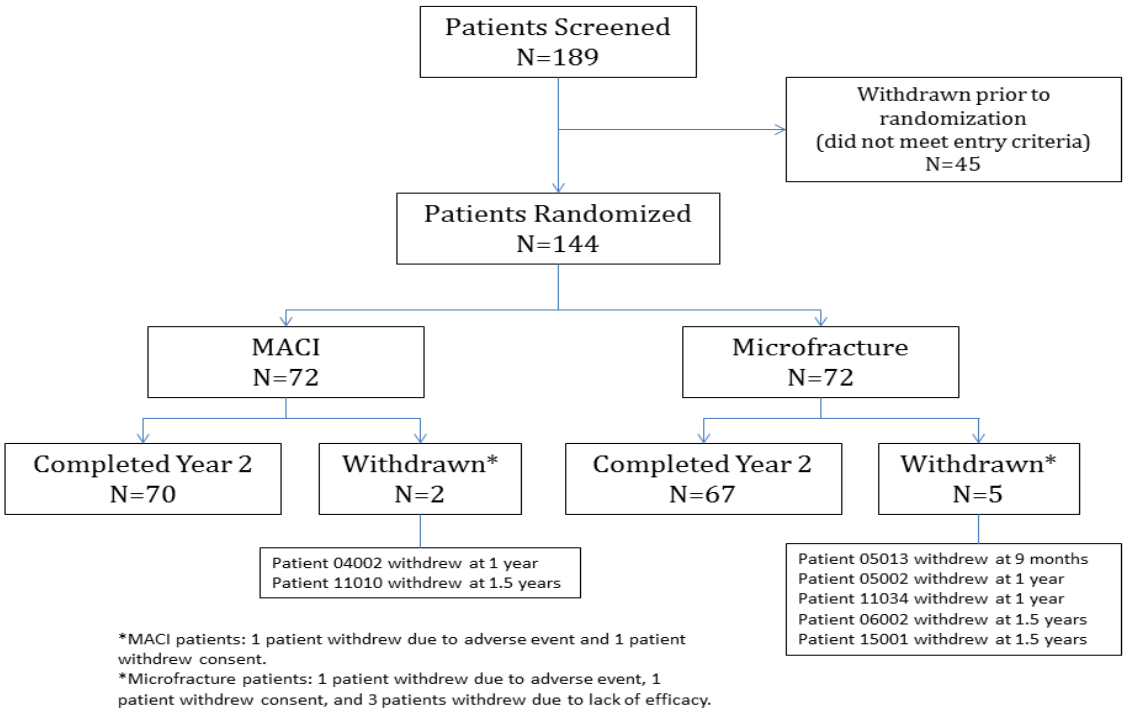
Overall, the target defects were similar between the 2 treatment groups at Baseline. For both treatment groups, the index lesion was most frequently located in the medial femoral condyle (75.0% MACI and 73.6% microfracture), next most frequently in the lateral femoral condyle (18.1% and 20.8%, respectively), followed by the trochlea (6.9% and 5.6%, respectively). Per protocol, no index lesions were located at the patella or tibia. Prior to treatment, the median size of the index lesion and the median total defect size surface area were similar for both treatment groups (4.0 cm^2 and 4.5 cm^2, respectively). The majority of patients in both treatment groups had an index lesion that was completely contained (69.4% in MACI and 63.9% in microfracture). Prior orthopedic knee surgeries had been performed on the index knee for 40.3% of MACI and 43.1% of microfracture patients. The level of sports activity with physical strain on the knee prior to the onset of symptoms was higher for patients in the microfracture group as compared to the MACI group. Sports activity was rated as highly competitive in 17 patients (23.6%) in the MACI group and 27 patients (37.5%) in the microfracture group.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

For both treatment groups, acute trauma was the most common underlying etiology of the index lesion; chronic degenerative defects were twice as common in the MACI group. The level of sports activity with physical strain on the knee prior to the onset of symptoms was higher in patients in the microfracture group. Overall the target defects were similar between the 2 treatment groups at Baseline as described in Section 6.1.10.1.1. The duration in years since onset of symptoms was longer in the MACI group. The proportion of patients with at least 1 prior orthopedic knee surgery (target or non-target knee) was comparable for the 2 treatment groups, however the median days since the last surgery for patients in the MACI group was more than twice the number for patients in the microfracture group.

6.1.10.1.3 Subject disposition

Subject disposition is depicted in the following diagram.



Comment: As shown in the diagram above, only 7 patients were withdrawn from the study, well after treatment started. Greater than 97% and 93% of the randomized patients in MACI and microfracture group, respectively, completed the two-year follow-up for the primary efficacy analysis.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

As shown in Table 3 below, at Week 104 (2 years), the improvement in the MACI group compared with microfracture was statistically significant ($p = 0.001$) based on MANOVA using last observation carried forward (LOCF) for missing data. The partial correlation for the primary analysis was 0.746 indicating a high strength of dependence of the co-primary endpoints.

Table 3: Co-Primary Efficacy Parameters - LOCF: Full Analysis Set

		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)
Visit 10 (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)
Final Model (Reduced)					
LS Means		44.13	46.05	32.37	34.64
Difference (LS Means)		11.76	11.41		
Partial Correlation (p-value)		0.746 (<0.001)			
p-Values					
Treatment		0.001			
Center		0.002			
Baseline KOOS Pain		<0.001			
Baseline KOOS Function (SRA)		<0.001			
Sample Covariance Matrix					
Pain		10.067	11.009		
Function (SRA)		11.009	21.612		

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

Comment: The partial correlation coefficient of +0.746 indicates there is consistency between the treatment effects on the co-primary endpoints pain and function.

Comment: A sensitivity analysis using a (per FDA's request in the SAP) multiple imputation (MI) for missing values also showed a statistically significant result based on MANOVA (p = 0.004). A sensitivity analysis using the PP set also confirmed the findings of primary analysis using LOCF and MI for missing data. It's not surprising that sensitivity analyses support the primary efficacy analysis because there were a few missing data (<5% in total) in this study.

Comment: The primary analysis MANOVA showed a p-value of 0.001 that the two treatment groups are different with respect to the joint assessment of the co-primary endpoints. However, such analysis did not provide degree of difference between groups with respect to each individual co-primary endpoints. However, confidence intervals for covariate adjusted mean difference in KOOS pain and KOOS function can be derived using the results listed in Table 3. For KOOS pain, the adjusted group difference was 11.76 with confidence interval: (9.43, 14.086); and for KOOS function, the difference in adjusted mean change was 11.41 with a confidence interval: (9.08, 13.74). These analyses can help the interpretation of the results from the primary efficacy analysis MANOVA.

6.1.11.2 Analyses of Secondary Endpoints

Histological Evaluation of Structural Repair:

Of the 144 randomized patients, 116 underwent a second-look arthroscopy and biopsy at Week 104. There were no apparent differences between the groups in the proportion of nonparticipants in

second-look arthroscopy and biopsy as the 116 patients included 60 MACI group patients and 56 microfracture group patients.

An overview of the results for the ICRS II Overall Assessment score at Week 104 is presented in Table 4. The mean ICRS II Overall Assessment score was comparable for the MACI and microfracture groups and there was no significant difference (p = 0.717) between the treatment groups.

Table 4: 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)

Imaging Evaluation of Structural Repair:

Of the 144 randomized patients, 134 (69 MACI and 65 microfracture) had MRI evaluation at Week 52 and 139 (70 MACI and 69 microfracture) had MRI at Week 104.

An overview of the results for MRI Degree of Defect Fill is presented in Table 5. Inferential analyses were not completed for MRI parameters other than Degree of Defect Fill. At Week 104, improvement since study treatment in defect fill was evident for patients in both treatment groups; the defects were filled to more than 50% for the majority of patients and the proportion of patients with >75% defect fill was comparable between patients treated with MACI or microfracture. Results at Week 52 were comparable to those at Week 104. There was no significant difference between the treatment groups in MRI Degree of Defect Fill at Week 52 (p=0.744) or Week 104 (p=0.920).

Table 5: MRI Degree of Defect Fill: Full Analysis Set

n (%)	MACI N = 72	Microfracture N = 72	p-Value
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)	
Missing (not done)	3 (4.2)	7 (9.7)	
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)	

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

Response Rate Based on KOOS Pain and Function Scores

An overview of the KOOS Pain and Function (SRA) response rate results using LOCF and MI for missing data is presented in Table 6. A majority of patients in both treatment groups responded to treatment. The percentage of patients who responded to treatment at Week 104 (had at least a 10-point improvement from Baseline in both Pain and Function [SRA]) was greater in the MACI group compared to those in the microfracture group ($p \leq 0.016$).

Table 6: KOOS Response Rate: Full Analysis Set with LOCF and MI for Missing Data

n (%)	MACI N = 72	Microfracture N = 72	p-Value
Visit 10 (Week 104) (LOCF)			
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) (MI)			
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

Comment: The SAP specifies a closed testing procedure for testing the secondary endpoints: For evaluation of the secondary endpoints, a sequential approach following an order of importance of the endpoints was followed to control the alpha level to 0.05. Significant results are regarded as valid until the first nonsignificant secondary endpoint is encountered. On the top of this order of importance is the Histological Evaluation of Structural Repair which did not meet a statistical significance following the primary efficacy analysis. Therefore, statistical testing of the remaining secondary endpoints is not warranted. Thus, the corresponding p-values for KOOS response rate should be interpreted with caution and not to be interpreted as showing a statistically significant difference between treatment groups.

Additionally, if one were to disregard the rank ordering of the secondary endpoints and apply the Bonferroni adjustment procedure post-hoc (dividing α=0.05 by 5 which is 0.01, for the five secondary endpoints), the p-values for the KOOS response rate from the Table 6 above would still not satisfy the significance threshold as $p > 0.01$.

6.1.11.3 Subpopulation Analyses

Pre-specified subgroups for efficacy assessment were lesion size, lesion location, etiology, prior surgical history, and sex. However, no statistical testing was performed within treatment by subgroup or between treatments by subgroup due to the small numbers of patients for the subgroups, i.e., the study was not designed with sufficient power to test differences between treatments within subgroups.

In terms of age, sex and ethnicity subgroups, it is first noted that all patients in SUMMIT trial were Caucasian white (100%), and none were Hispanic or Latino. The majority of patients were male and the median age was 34 to 35 years old. Age distribution was comparable between treatment groups. Patient age was not pre-specified for subgroup analysis (age range for patients enrolled in the SUMMIT Study was 18-54). It was included in the initial full model MANOVA analyses of efficacy

and was found not to be a significant factor that affects the outcomes of the co-primary efficacy endpoints. No numerical summarization of treatment effect based on age was provided.

Sex was pre-specified for subgroup summarization with the knowledge that sample size was not adequate to provide sufficient power to test for differences. Based on the results shown in the Table 7 below, there is no significant difference in the co-primary endpoints between treatments based on sex. The efficacy trend for the co-primary endpoints consistently shows that MACI is numerically better than microfracture for males and females.

Table 7: Summary of KOOS Pain and Function for Sex, Full Analysis Set

	MACI		**Microfracture**	
	Pain	**Function**	**Pain**	**Function**
Male; mean (SD)	**N = 45**	**N = 45**	**N = 48**	**N = 48**
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)
Female; mean (SD)	**N = 27**	**N = 27**	**N = 24**	**N = 24**
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)

6.1.11.4 Dropouts and/or Discontinuations

As mentioned in the section for patient disposition, there were only a few patient dropouts or discontinuations from this study. The statistical analysis of the efficacy data used LOCF and multiple imputation (per the agency requested) to impute the missing data. The few missing data did not impact the statistical significance testing results. The primary efficacy analyses based on LOCF and MI for missing data are similar. Additionally, a per-protocol analysis was also included and did not show inconsistent conclusions.

6.1.11.5 Treatment by study site interaction

The interaction of treatment and study site was assessed and found to be not statistically significant. Overwhelmingly majority of the sites have results favor MACI numerically. The results of KOOS pain and function scores by site are shown in Table A.1 in the Appendix. The improvement in the KOOS pain and function (SRA) scores was greater in the MACI group compared with microfracture at a majority (13/16) of the sites. Microfracture was associated with a greater improvement in KOOS pain scores at 3 sites: Site 1 (Czech Republic) and Sites 17 and 18 (both in Poland), and a greater improvement in KOOS function scores at 2 sites: Sites 15 and 18 (both in Poland).

6.1.12 Safety Analyses

6.1.12.1 Methods

A brief summary of all reported AEs is presented in Table 8 by category. The overall incidence of treatment-emergent adverse events (TEAEs) and SAEs 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 patient in each treatment group discontinued due to AEs). No patients died in the study.

Table 8: Summary of Adverse Events – Safety Set

n (%)	MACI N = 72	Microfracture N = 72
At Least 1 TEAE	55 (76.4)	60 (83.3)
At Least 1 Related TEAE	25 (34.7)	28 (38.9)
At Least 1 Severe TEAE	7 (9.7)	10 (13.9)
At Least 1 TESAE	11 (15.3)	19 (26.4)
Any Death	0	0
Discontinued Study Due to TEAE	1 (1.4)	1 (1.4)

TESAE = (treatment-emergent)(serious) adverse event; CRF = case report form
Treatment-emergent: defined as an AE with a start date beyond or equal to that of study treatment at Day 1 TEAEs leading to study discontinuation: obtained using the 'Primary reason for discontinuation' in the Completion/Discontinuation' CRF panel and the 'Other action taken' in the 'Adverse Event' CRF panel
Related: relationship to study treatment reported by the Investigator as Definite', 'Probable', 'Possible', or missing Severe: severity reported as 'Severe' or missing

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

6.1.12.3 Deaths

No patients died in this study.

6.1.12.4 Nonfatal Serious Adverse Events

Nonfatal treatment-emergent SAEs, regardless of severity and relationship to study treatments are provided in Table 9.

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.

Treatment-emergent SAEs reported in more than 1 patient within any treatment group were treatment failure (1 patient [1.4%] in the MACI group and 4 patients [5.6%] in the microfracture group), cartilage injury (2 patients [2.8%] in the MACI group and 6 patients [8.3%] in the microfracture group), meniscus lesion (2 patients [2.8%] in the MACI group and no patients in the microfracture group), and arthralgia (no patients in the MACI group and 3 patients [4.2%] in the microfracture group).

Table 9: Treatment-Emergent Serious Adverse Events 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)

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)

MedDRA = Medical Dictionary for Regulatory Activities, (TE)(S)AE = (treatment-emergent)(serious)adverse event.
SAE considered at least possibly related to study treatment by the Investigator.
System Organ Class and Preferred Term are ordered alphabetically. 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.

6.1.12.5 Adverse Events of Special Interest (AESI)

Adverse events of interest, based on previous clinical experience with MACI, include potential perioperative complications related to arthroscopy or arthrotomy and potential complications related to MACI. A summary of all AEs of interest is provided in Table 10.

The proportion of patients with at least 1 AE of interest was 9.7% in the MACI group and 4.2% in the microfracture group. Hemarthrosis was the only AE of interest reported in more than 1 patient in any treatment group (2 patients [2.8%] in the MACI group and 1 patient [1.4%] in the microfracture group).

Table 10: Adverse Events of Interest per System Organ Class and Preferred Term

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)

AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities
System Organ Class and Preferred Term are ordered alphabetically AEs were coded using MedDRA Version 14 1 AEs of Interest: include potential perioperative complications related to arthroscopy/arthrotomy and potential
complications related to MACI implant
If a patient experienced more than 1 AE of interest with the same Preferred Term or Primary System Organ Class, each patient was counted at most once within each Preferred Term or Primary System Organ Class

Subsequent Surgical Procedures (SSPs)

An overview of the number of patients with SSPs is provided in Table 11.

The proportion of patients 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). The difference between the 2 treatment groups was not significant (logistic regression analysis, p = 0.427).

Table 11: Overview of Subsequent Surgical Procedures

n (%)	MAC 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)

SSP = subsequent surgical procedure

6.1.12.6 Clinical Test Results

None

6.1.12.7 Dropouts and/or Discontinuations

None

6.2 Study MACI00809 (SUMMIT Extension)

Study MACI00809 is an extension study for participants of Genzyme-sponsored prospective, randomized, open-label, parallel-group and multicenter study (SUMMIT, MACI00206) of matrix-induced autologous chondrocyte implantation (MACI implant) for the treatment of symptomatic articular cartilage defects of the femoral condyle including the trochlea. Efficacy and safety assessments were performed at scheduled visits 3, 4, and 5 years following treatment in SUMMIT (i.e., at Weeks 156, 208, and 260).

Patients 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.

6.2.1 Objective

The objective of the extension study was to examine the 5-year efficacy and safety of MACI implant, compared with arthroscopic microfracture, in patients who received study treatment in the SUMMIT study for treatment of symptomatic articular cartilage defects of the femoral condyle, including the trochlea.

6.2.2 Design Overview

Follow-up to 2 years post-study treatment was completed as part of the SUMMIT study. Follow-up from 3 to 5 years post-study treatment in SUMMIT was completed in this extension study.

6.2.3 Population

All 144 patients who received study treatment in the SUMMIT study were eligible for enrollment into this extension study. Due to two non-participating centers, the extension enrolled: 128 patients (65 in the MACI group and 63 in the microfracture group). Patients 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.

6.2.4 Study Treatments or Agents Mandated by the Protocol

See section 6.1.4 above. Any patients 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 were asked to attend an unscheduled visit for treatment failure evaluation. Patients who were treatment failures may have received appropriate alternative treatment, at the discretion of the Investigator, which may have included MACI implant. Patients who did not meet the specific treatment failure criteria as defined in the protocol but required retreatment in the opinion of both the Investigator and the Treatment Failure Evaluation Committee, may have also

received re-treatment which may include MACI implant. All patients requiring re-treatment with MACI implant received MACI as investigational product provided for rescue treatment. Patients who were determined to be treatment failures were not withdrawn from this extension study.

6.2.6 Sites and Centers

A total of 14 out of 16 sites from the SUMMIT study participated in this extension study. Patients were enrolled at these 14 study sites across 7 countries in Europe (2 in the Czech Republic, 3 in France, 3 in the Netherlands, 1 in Norway, 3 in Poland, 1 in Sweden, and 1 in the United Kingdom).

6.2.7 Surveillance/Monitoring

As continued from the SUMMIT study, a representative of the Sponsor or designee visited the investigators periodically for the purpose of monitoring the progress of this study in accordance with GCP regulations. Source document verification was performed for all data elements. During these routine monitoring visits, all data pertaining to a patient's participation in the study must have been made available to the monitor.

6.2.8 Endpoints and Criteria for Study Success

Co-primary efficacy variables:
Changes from Baseline to Week 156 for the patient's Knee Injury and Osteoarthritis Outcome Score (KOOS) Pain and Function (Sports and Recreational Activities [SRA]) scores

Secondary efficacy variables (ranked in the order of importance according to the protocol) included the following. Note that earlier time points were included in the extension as the analyses would be performed based on available data points instead of FAS as in SUMMIT trial.

- Changes from SUMMIT baseline to Weeks 24, 36, 52, 78, 104, 208, and 260 for the patient'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 patients who responded to treatment at Weeks 24, 36, 52, 78, 104, 156, 208, and 260. A responder was defined as a patient with at least a 10-point improvement in both the KOOS Pain and Function (SRA) scores from SUMMIT Baseline.
- 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 (ie, 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 (ie, 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 patient'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 patient'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

6.2.9 Statistical Considerations & Statistical Analysis Plan

There were no sample size calculations for this extension study. Sample size in this extension study was based on elective participation of patients who received study treatment in SUMMIT.

For the primary analysis, the co-primary efficacy variables in this study were defined as the changes from SUMMIT Baseline to Week 156 in KOOS Pain and Function (SRA) scores. The same statistical methods used in the SUMMIT study were planned for extension study except time points and the analysis set are different. In the end, because two study sites chose not to continue into the extension study, only descriptive statistics were used to summarize the study data.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

The modified Full Analysis Set (mFAS) consisted of all patients included in the FAS defined in the SUMMIT study and provided informed consent for enrollment in the SUMMIT Extension study.

Non-Modified Full Analysis Set

The non-modified Full Analysis Set (non-mFAS) consisted of all patients 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 patients 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 consisted of the 128 patients 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 patients.

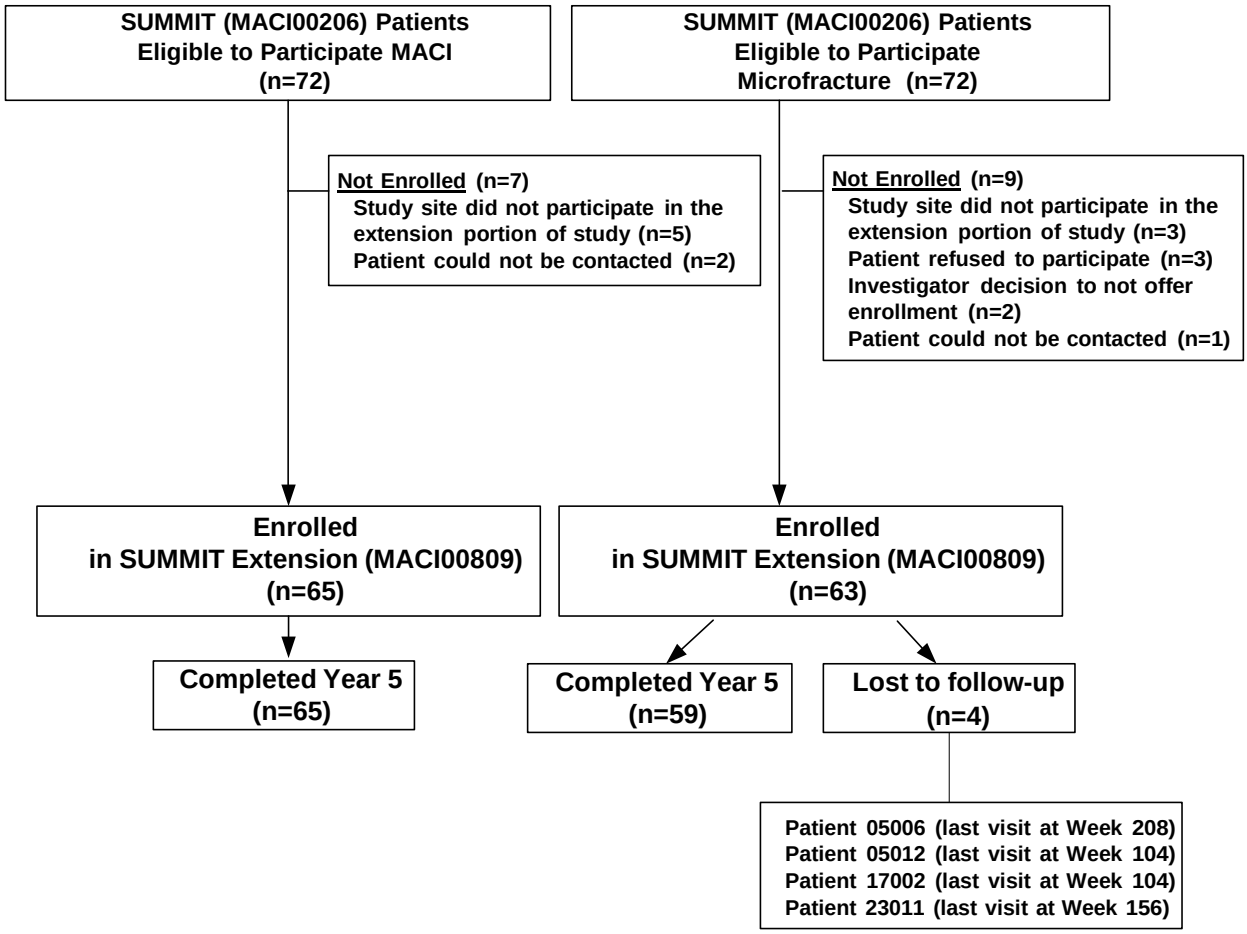
6.2.10.1.1 Demographics

Two sites from MACI00206 (a total of 16 subjects) elected not to participate in the extension study, which clearly resulted in loss of follow-up data in patients at those sites. In addition, the self-selection of study centers to enter a long-term follow-up study (as opposed to random assignment) may also introduce selection bias. Consequently, the value of inferential testing that compares the MACI and microfracture treatment groups in the extension study may be limited.

6.2.10.1.3 Subject disposition

The disposition of all patients enrolled in this 3-year extension study is illustrated in the following Figure. Of the 144 patients randomized in the SUMMIT study, 128 were enrolled in the SUMMIT Extension (MACI00809) study: 65 patients (90.3%) from the MACI group and 63 patients (87.5%) from the microfracture group.

Four patients in the microfracture group enrolled in the SUMMIT Extension were lost to follow-up and did not complete the study. Of the 4 patients in the microfracture group who discontinued early, 2 patients were lost to follow-up prior to the 3-year (Week 156) study visit and 2 patients had ≥3 years of data.



6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

An overview of the efficacy results for the co-primary endpoints of KOOS Pain and Function (SRA) is shown in Table 12. At Week 156 (3 years), the improvement in the MACI group compared with microfracture was greater based on the MANOVA model. Graphical displays of the longitudinal results for the difference in the co-primary endpoints of KOOS Pain and Function (SRA) in patients treated with MACI as compared to patients treated with microfracture are provided in Figure 1 (KOOS Pain) and Figure 2 (KOOS Function) below. At Week 156 (3 years), Week 208 (4 years), and Week 260 (5 years), the change from baseline value was greater in the MACI group compared with microfracture and was consistent with the change from baseline to Week 104 (2 years) for the mFAS (although the magnitude was smaller in the Extension study for the pain scores) (Table 12).

Table 12: KOOS Pain and Function Scores: modified Full Analysis Set - SUMMIT Extension **(MACI00809)**

		MACI (N = 65)		Microfracture (N = 63)	
SUMMIT Study Visits		**Pain**	**Function (SRA)**	**Pain**	**Function (SRA)**
Baseline[a]	n Mean (SD)	65 37.05 (13.10)	65 15.38 (14.82)	63 35.19 (12.31)	63 11.88 (16.15)
Visit 10 (Week 104)[b]	n Mean (SD)	63 82.19 (15.79)	63 60.48 (26.54)	60 71.76 (23.89)	60 48.92 (30.64)
Change from Baseline to Week 104	n Mean (SD)	63 45.02 (19.95)	63 44.60 (26.84)	60 36.30 (24.47)	60 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 Mean (SD)	65 79.19 (20.06)	65 61.02 (29.17)	57 72.32 (22.27)	57 50.00 (31.69)
Change from Baseline to Week 156	n Mean (SD)	65 42.14 (22.60)	65 45.63 (30.40)	57 35.77 (23.44)	57 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 Mean (SD)	63 80.42 (19.21)	62 61.35 (31.07)	59 73.07 (23.71)	59 50.17 (30.72)
Change from Baseline to Week 208	n Mean (SD)	63 43.39 (22.63)	62 45.87 (33.23)	59 36.96 (24.66)	59 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 Mean (SD)	65 82.22 (20.13)	64 61.93 (30.92)	59 74.81 (21.68)	59 50.25 (32.33)
Change from Baseline to Week 260	n Mean (SD)	65 45.17 (21.65)	64 47.17 (32.15)	59 38.42 (23.60)	59 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.

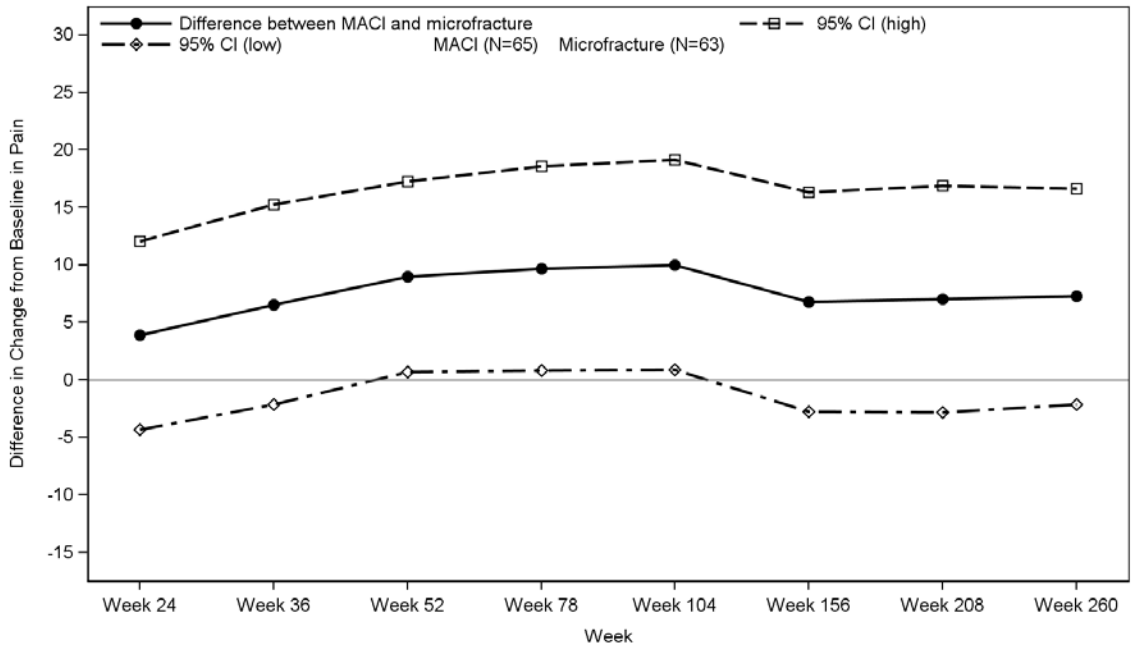
Though not shown in the memo, the baseline pain and function scores were comparable for the non-mFAS patients (from the two centers electing not participating in the extension study). Their mean changes from baseline at Week 104 in KOOS pain and KOOS function scores were more pronounced

than the mFAS patients in the extension study. The mean change for MACI patients in the non-mFAS (n = 7) (compared to MACI patients in the mFAS) was >10 points for Pain and >20 points for Function (SRA).

To examine the long-term efficacy of MACI, one can compare efficacy results in Table 12 with summary Table 3 in section 6.1.11.1 for the co-primary efficacy endpoints of the SUMMIT study based on full analysis set. The differences between treatment groups in mean change from baseline are smaller with 10.0 and 9.82 (pain and function, mFAS) in Table 12 compared to 11.76 and 11.41 (pain and function, FAS) in Table 3.

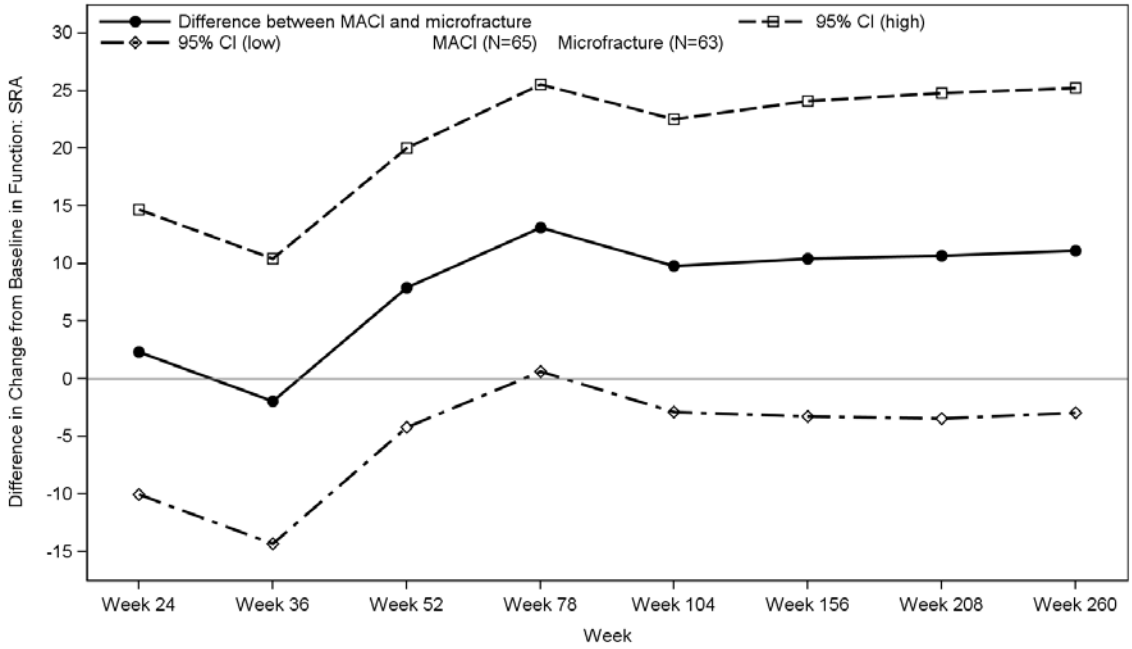
Whether results in Table 12 permit statistical inferences, it could be debatable. Because of potential violation of randomization and potential bias caused by the elective non-participation of the two centers described above, it would be difficult to interpret study results derived from inferential statistical tests, if they were performed, from this reviewer's perspective. However, the available data presented in Figures 1 and 2 below show that the differences in mean changes from baseline for the co-primary endpoints were numerically larger for MACI treated patients than for Microfracture treated patients during the extension study period.

Figure 1: KOOS Co-Primary Efficacy – Pain – modified Full Analysis Set



Note: Figure represents longitudinal results with simultaneous 95% confidence intervals for the difference in the co-primary endpoint of Pain in patients treated with MACI as compared to patients treated with microfracture

Figure 2: KOOS Co-Primary Efficacy – Function (SRA) – modified Full Analysis Set



Note: Figure represents longitudinal results with simultaneous 95% confidence intervals for the difference in the co-primary endpoint of Function (SRA) in patients treated with MACI as compared to patients treated with microfracture

6.2.11.2 Analyses of Secondary Endpoints

Because of non-participation of two centers in the extension study, there were no inferential statistical tests performed on the secondary endpoints.

6.2.11.4 Dropouts and/or Discontinuations

The analysis of efficacy data in the SUMMIT Extension study was based on the mFAS, which consisted of all patients who were included in the FAS defined in the SUMMIT study and provided informed consent for enrollment in the SUMMIT Extension study. All analyses were conducted based on the observed data (ie, no imputation of missing data was performed).

6.2.12 Safety Analyses

Treatment-emergent SAEs were reported at a similar rate in the MACI and microfracture groups (24.6% MACI, 27.0% microfracture). Within the 3 years of the extension study, no TESAEs had incidence >5% in the MACI treatment group whereas 3 TESAEs (cartilage injury, treatment failure, and arthralgia) had incidence >5% in the microfracture group.

Only 4 SAEs were reported in more than 2 patients. 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%).

6.2.12.3 Deaths

No patients died in this study.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The primary source of evidence to support the BLA is a Phase III, randomized, open-label and multicenter study, named SUMMIT. The study enrolled and randomized (1:1) 144 patients to MACI and Mircrofrature treatment groups. Per the SAP, The primary efficacy analysis method was MANOVA on co-primary endpoints, KOOS Pain and KOOS function, with LOCF imputation for missing data. Ordinarily LOCF imputation is discouraged. However, in the SUMMIT study, there were a few missing data (less than 5% in total) at the primary analysis time point 104 weeks. To support the primary efficacy analysis, the SAP specified multiple imputation for missing data and per-protocol analysis as supportive analyses. These analyses showed that there was superior MACI treatment effect compared to microfracture in KOOS Pain and KOOS Function related to sports activities as co-primary endpoints. Further analysis by this reviewer showed that MACI was also superior to microfracture with respect to each co-primary endpoints, Pain and Function. There was no significant treatment by center or treatment by patient subgroup interactions.

The SUMMIT study protocol also stipulated several important secondary endpoints to be statistically analyzed. These secondary endpoints were rank-ordered by importance and a sequential closed testing procedure was used to control the type I error rate. The rank-ordered secondary endpoints are 1) Histological evaluation of structural repair, 2) MRI assessments of structural repair, 3) Response rate based on KOOS Pain and Function (SRA) scores, 4) Treatment failure rate, and 5) Change from Baseline at Week 104 in the remaining 3 subscales of the KOOS instrument. When tested for a statistical significance, the only endpoint in this rank-ordered list that resulted in p-value ≤ 0.05 was the response rate. However, this does not lead to any assertion of it being statistically significant in treatment difference because the first two endpoints did not reach statistical significance ($p>0.70$). Therefore, by pre-specified statistical analysis approach, none of the secondary endpoints reached statistical significance. Further, it is an easy exercise to examine whether a Bonferroni multiple testing procedures would reveal any statistical significance on the secondary endpoints regardless of the order of importance. However, by doing so, none of the secondary endpoints could cross the significance threshold.

The SUMMIT Extension study faced the issue of potentially selective non-participation of two study centers. This potentially could result in a biased or/and non-random sample. Therefore, the SUMMIT Extension study clearly suffers from being a well-designed and controlled study which makes it difficult to draw statistical inferences. However, based on the summarization of data from the extension study, even though the measures for the treatment difference appear to be smaller

compared to the primary analysis in the SUMMIT study, the differences are still in favor of MACI treatment numerically.

10.2 Conclusions and Recommendations

A prospective, randomized, open-label, parallel-group and multicenter phase III study (MACI00206) was conducted to demonstrate the superiority of matrix-induced autologous chondrocyte implantation (MACI implant) versus arthroscopic microfracture for the treatment of symptomatic articular cartilage defects of the femoral condyle including the trochlea. The study appears to be adequately designed with pre-specified statistical analysis plan. The primary efficacy analysis focused on co-primary endpoints, KOOS Pain and KOOS Function (SRA), to demonstrate MACI's treatment effect at 104 weeks post initial procedure, for which the study was completed successfully based on pre-specified statistical analysis method of MANOVA. The estimated correlation coefficient between the pain and function measures was 0.746 ($p < 0.001$) indicating a high strength of dependence of the co-primary endpoints. So, not surprisingly, statistical tests on the pain and function endpoints separately showed significant superiority of MACI over arthroscopic microfracture with p-values <0.05.

The study also listed 5 secondary endpoints to be compared between treatments in a pre-specified hierarchical order. However, the testing of the first secondary endpoint, microscopic ICRS II Overall Assessment at Week 104, was not statistically significantly at the level of 0.05. Therefore, testing of the remaining secondary endpoints was not warranted. One of the secondary endpoints, the response rate based on KOOS Pain and Function (SRA) scores (had at least a 10-point improvement from baseline in both pain and function, at week 104), the third in rank order of importance according to the study protocol, showed a p-value <0.05 (i.e., $p=0.016$ based on CMH test with LOCF for missing data). However, when interpreted through the SAP pre-specified closed testing procedure to account for multiple hypotheses testing, a statistical significance between groups in response rate cannot be concluded. If one were to disregard the rank order, and apply the Bonferroni p-value adjustment, the difference in response rate, 87.5% vs 68% still would not reach a statistical significance. Moreover, a limitation facing a single phase 3 study BLA is that there is not a second study with similar endpoints that can help the interpretation of the secondary endpoint results.

For long term safety and efficacy of MACI, there are issues in SUMMIT Extension study which make it difficult to draw statistical inferences on study results. However, based on the summarization of data that came out of the extension study, even though the measures for the treatment difference appear to be smaller compared to the primary analysis in the SUMMIT study, the differences favored MACI numerically.

Appendix

Table A.1: Summary Table of KOOS Pain and Function by Site (SUMMIT)

	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 Wk 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 Wk 104	26.39 (12.53)	33.75 (28.22)	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 Wk 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 Wk 104	37.22 (10.87)	26.00 (26.32)	24.31 (27.72)	20.00 (35.36)
Site 04	**N=1**	**N=1**	**N=0**	**N=0**
Baseline	52.78 (.)	25.00 (.)	-	-
Week 104	41.67 (.)	30.00 (.)	-	-
Δ to Wk 104	-11.11 (.)	5.00 (.)	-	-
Site 05	**N=5**	**N=5**	**N=6**	**N=6**
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 Wk 104	61.11 (14.57)	64.00 (25.35)	37.22 (35.61)	32.00 (42.07)
Site 06	**N=1**	**N=1**	**N=1**	**N=1**
Baseline	22.22 (.)	0.00 (.)	47.22 (.)	20.00 (.)
Week 104	97.22 (.)	90.00 (.)	100.00 (.)	100.00 (.)
Δ to Wk 104	75.00 (.)	90.00 (.)	52.78 (.)	80.00 (.)

Table A.1: Summary Table of KOOS Pain and Function by Site (SUMMIT)

	MACI		Microfracture	
	Pain	**Function (SRA)**	**Pain**	**Function (SRA)**
Site 11	**N=20**	**N=20**	**N=20**	**N=20**
Baseline	38.06 (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 Wk 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 Wk 104	38.89 (21.70)	49.00 (25.84)	32.41 (19.62)	16.04 (27.05)
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 Wk 104	34.26 (38.92)	28.33 (36.17)	-0.93 (15.80)	-3.33 (5.77)
Site 15	**N=9**	**N=9**	**N=9**	**N=9**
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 Wk 104	45.37 (11.11)	34.44 (17.93)	39.93 (15.85)	46.88 (32.62)
Site 17	**N=1**	**N=1**	**N=1**	**N=1**
Baseline	33.33 (.)	15.00 (.)	19.44 (.)	0.00 (.)
Week 104	97.22 (.)	85.00 (.)	86.11 (.)	35.00 (.)
Δ to Wk 104	63.89 (.)	70.00 (.)	66.67 (.)	35.00 (.)
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 Wk 104	65.28 (11.68)	63.75 (24.96)	72.22 (6.00)	77.50 (17.08)
Site 19	**N=1**	**N=1**	**N=1**	**N=1**
Baseline	52.78 (.)	40.00 (.)	36.11 (.)	5.00 (.)
Week 104	94.44 (.)	80.00 (.)	44.44 (.)	15.00 (.)
Δ to Wk 104	41.67 (.)	40.00 (.)	8.33 (.)	10.00 (.)

Table A.1: Summary Table of KOOS Pain and Function by Site (SUMMIT)

	MACI		Microfracture	
	Pain	**Function (SRA)**	**Pain**	**Function (SRA)**
Site 21	**N=4**	**N=4**	**N=4**	**N=4**
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 Wk 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 Wk 104	62.04 (18.07)	48.33 (18.93)	29.17 (26.30)	25.00 (20.41)
Site 29	**N=2**	**N=2**	**N=2**	**N=2**
Baseline	38.89 (19.64)	15.00 (14.14)	50.00 (3.93)	34.38 (13.26)
Week 104	97.22 (3.93)	92.50 (10.61)	70.83 (5.89)	50.00 (21.21)
Δ to Wk 104	58.33 (23.57)	77.50 (24.75)	20.83 (1.96)	15.63 (7.65)

Note: SD not available where only one subject is in a treatment group.