# Clinical trial results:
# An Extension Protocol for Participants of Genzyme-Sponsored Prospective, Randomized, Open-Label, Parallel-Group, Multicenter Study of Matrix-Induced Autologous Chondrocyte Implantation (MACI® implant) for the Treatment of Symptomatic Articular Cartilage Defects of the Femoral Condyle Including the Trochlea

## Summary

| | |
|---|---|
| EudraCT number | 2009-016970-33 |
| Trial protocol | NL CZ GB SE PL |
| Global end of trial date | 18 March 2015 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 04 October 2019 |
| First version publication date | 04 October 2019 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | MACI00809 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01251588 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Vericel Corporation |
| Sponsor organisation address | 64 Sidney Street, Cambridge, United States, 02139 |
| Public contact | Jon Hopper, Vericel Corporation, 01 (617) 588 5702, jhopper@vcel.com |
| Scientific contact | Jon Hopper, Vericel Corporation, 01 (617) 588 5702, jhopper@vcel.com |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 08 June 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 18 March 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 March 2015 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The objective of this study is to examine the 5-year efficacy and safety of Matrix-Induced Autologous Chondrocyte Implantation (MACI® Implant), compared with arthroscopic microfracture, in patients who received study treatment in Genzyme-sponsored study MACI00206 for treatment of symptomatic articular cartilage defects of the femoral condyle, including the trochlea.

Protection of trial subjects:

This is the extension study with no planned intervention. Patients are followed up for long term safety and efficacy, and provided all necessary medical care.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 02 December 2010 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Netherlands: 58 |
| Country: Number of subjects enrolled | Norway: 6 |
| Country: Number of subjects enrolled | Poland: 25 |
| Country: Number of subjects enrolled | Sweden: 2 |
| Country: Number of subjects enrolled | United Kingdom: 6 |
| Country: Number of subjects enrolled | Czech Republic: 16 |
| Country: Number of subjects enrolled | France: 15 |
| Worldwide total number of subjects | 128 |
| EEA total number of subjects | 128 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |

| | |
|---|---|
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 128 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

All patients who were treated in the parent study (MACI00206) are offered the opportunity to participate in this extension study.

### Pre-assignment

Screening details:

128 out of 144 patients who were treated in the parent study (MACI00206) consented to participate in this extension study.

### Period 1

| | |
|---|---|
| Period 1 title | Baseline |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | MACI |

Arm description:

autologous cultured chondrocytes on porcine collagen membrane implant received in previous MACI00206 study

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | MACI |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Implant |
| Routes of administration | Route of administration not applicable |

Dosage and administration details:

autologous cultured chondrocytes on porcine collagen membrane: Implantation, received in the parent study (MACI00206)

| | |
|---|---|
| **Arm title** | Microfracture |

Arm description:

Arthroscopic Microfracture treatment received in the previous MACI00206 study

| | |
|---|---|
| Arm type | No intervention |

No investigational medicinal product assigned in this arm

| **Number of subjects in period 1** | MACI | Microfracture |
|---|---|---|
| Started | 65 | 63 |
| Completed | 65 | 63 |

| **Period 2** | |
|---|---|
| Period 2 title | Overall |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

| **Arms** | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | MACI |

Arm description:

autologous cultured chondrocytes on porcine collagen membrane: Implantation

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | MACI |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Implant |
| Routes of administration | Route of administration not applicable |

Dosage and administration details:

Autologous cultured chondrocytes on porcine collagen membrane, received study treatment (MACI) in the parent study (MACI00206).

| | |
|---|---|
| **Arm title** | Microfracture |

Arm description:

Microfracture: Arthroscopic Microfracture received in the parent study (MACI00206)

| | |
|---|---|
| Arm type | No intervention |

No investigational medicinal product assigned in this arm

| **Number of subjects in period 2** | MACI | Microfracture |
|---|---|---|
| Started | 65 | 63 |
| Completed | 65 | 59 |
| Not completed | 0 | 4 |
| Lost to follow-up | - | 4 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | MACI |
| Reporting group description: | |
| autologous cultured chondrocytes on porcine collagen membrane implant received in previous MACI00206 study | |
| Reporting group title | Microfracture |
| Reporting group description: | |
| Arthroscopic Microfracture treatment received in the previous MACI00206 study | |

| Reporting group values | MACI | Microfracture | Total |
|---|---|---|---|
| Number of subjects | 65 | 63 | 128 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 65 | 63 | 128 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Age at the date of informed consent | | | |
| Units: years | | | |
| arithmetic mean | 34.4 | 32.7 | |
| standard deviation | ± 8.94 | ± 8.80 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 25 | 21 | 46 |
| Male | 40 | 42 | 82 |

| Subject analysis sets | |
|---|---|
| Subject analysis set title | Safety Analysis Set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| Safety Analysis | |

| Reporting group values | Safety Analysis Set | | |
|---|---|---|---|
| Number of subjects | 128 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |

| | | | |
|---|---|---|---|
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 0 | | |
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 128 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Age continuous | | | |
| Age at the date of informed consent | | | |
| Units: years | | | |
| arithmetic mean | 33.6 | | |
| standard deviation | ± 8.88 | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 46 | | |
| Male | 82 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | MACI |
| Reporting group description: | |
| autologous cultured chondrocytes on porcine collagen membrane implant received in previous MACI00206 study | |
| Reporting group title | Microfracture |
| Reporting group description: | |
| Arthroscopic Microfracture treatment received in the previous MACI00206 study | |
| Reporting group title | MACI |
| Reporting group description: | |
| autologous cultured chondrocytes on porcine collagen membrane: Implantation | |
| Reporting group title | Microfracture |
| Reporting group description: | |
| Microfracture: Arthroscopic Microfracture received in the parent study (MACI00206) | |
| Subject analysis set title | Safety Analysis Set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| Safety Analysis | |

### Primary: Change From MACI00206 Baseline for the Participant's Knee Injury and Osteoarthritis Outcome (KOOS) Pain Scores

| | |
|---|---|
| End point title | Change From MACI00206 Baseline for the Participant's Knee Injury and Osteoarthritis Outcome (KOOS) Pain Scores |
| End point description: | |
| The KOOS is a validated knee-specific instrument developed to assess the patients' opinion of their knee and associated problems. KOOS consists of 5 subscales: Pain, Function in sports and recreational activities, other Symptoms, Function in activities of daily living (ADL), and knee related Quality of life (QOL). 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). Subscales are not combined to calculate a total score.<br>Change From MACI00206 Baseline for the Participant's Knee Injury and Osteoarthritis Outcome (KOOS) Pain and Function (Sports and Recreational Activities) Scores are pre-specified co-primary end points | |
| End point type | Primary |
| End point timeframe: | |
| MACI00206 Baseline to Week 156 | |

| End point values | MACI | Microfracture | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65 | 57 | | |
| Units: Change of Pain Scores | | | | |
| arithmetic mean (full range (min-max)) | 42.14 (-36.1 to 83.3) | 35.77 (-2.8 to 83.3) | | |

## Statistical analyses

| Statistical analysis title | MANCOVA |
|---|---|

Statistical analysis description:

At Week 156 (3 years, co-primary endpoint), the improvement in the MACI group compared with microfracture was analyzed using the MANCOVA model.

| | |
|---|---|
| Comparison groups | MACI v Microfracture |
| Number of subjects included in analysis | 122 |
| Analysis specification | Pre-specified |
| Analysis type | other[1] |
| Parameter estimate | LS Means |
| Point estimate | 6.77 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.79 |
| upper limit | 16.33 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.84 |

Notes:

[1] - Descriptive analysis

## Primary: Change From MACI00206 Baseline for the Participant's Knee Injury and Osteoarthritis Outcome (KOOS) Function (Sports and Recreational Activities) Scores.

| End point title | Change From MACI00206 Baseline for the Participant's Knee Injury and Osteoarthritis Outcome (KOOS) Function (Sports and Recreational Activities) Scores. |
|---|---|

End point description:

The KOOS is a validated knee-specific instrument developed to assess the patients' opinion of their knee and associated problems. KOOS consists of 5 subscales: Pain, Function in sports and recreational activities, other Symptoms, Function in activities of daily living (ADL), and knee related Quality of life (QOL). 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). Subscales are not combined to calculate a total score.
Change From MACI00206 Baseline for the Participant's Knee Injury and Osteoarthritis Outcome (KOOS) Pain and Function (Sports and Recreational Activities) Scores are pre-specified co-primary end points

| End point type | Primary |
|---|---|

End point timeframe:

MACI00206 Baseline to Week 156

| End point values | MACI | Microfracture | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65 | 57 | | |
| Units: Change in function scores | | | | |
| arithmetic mean (full range (min-max)) | 45.63 (-20.0 to 95.0) | 36.95 (-23.8 to 100) | | |

## Statistical analyses

| Statistical analysis title | MANCOVA |
|---|---|
| Comparison groups | Microfracture v MACI |
| Number of subjects included in analysis | 122 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | LS Mean |
| Point estimate | 10.45 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.23 |
| upper limit | 24.13 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 5.49 |

## Secondary: Change From MACI00206 Baseline for the Participant's Knee Injury and Osteoarthritis Outcome (KOOS) Pain Scores

| End point title | Change From MACI00206 Baseline for the Participant's Knee Injury and Osteoarthritis Outcome (KOOS) Pain Scores |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

From MACI00206 Baseline to Week 260

| End point values | MACI | Microfracture | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65 | 59 | | |
| Units: Change in pain scores | | | | |
| arithmetic mean (full range (min-max)) | 45.17 (0 to 83.3) | 38.42 (-11.1 to 88.9) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From MACI00206 Baseline for the Participant's Knee Injury and Osteoarthritis Outcome (KOOS) Function (Sports and Recreational Activities) Scores.

| End point title | Change From MACI00206 Baseline for the Participant's Knee Injury and Osteoarthritis Outcome (KOOS) Function (Sports and Recreational Activities) Scores. |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

From MACI00206 Baseline to Week 260

| End point values | MACI | Microfracture | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 64 | 59 | | |
| Units: Change in function scores | | | | |
| arithmetic mean (full range (min-max)) | 47.17 (-10.0 to 95.0) | 37.56 (-20.0 to 100) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Magnetic Resonance Imaging (MRI) Assessments of Degree of Defect Fill

| End point title | Magnetic Resonance Imaging (MRI) Assessments of Degree of Defect Fill |
|---|---|

End point description:

MRI was assessed by the independent blinded evaluators by means of consensus. The number of participants with a degree of defect fill of >50% is reported.

| End point type | Secondary |
|---|---|

End point timeframe:

Week 260

| End point values | MACI | Microfracture | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65 | 55 | | |
| Units: Patient | 44 | 39 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of Patients Who Achieve at Least a 10-point Improvement From MACI00206 Baseline in KOOS Pain and Function (Sports and Recreational Activities) Scores

| End point title | Proportion of Patients Who Achieve at Least a 10-point Improvement From MACI00206 Baseline in KOOS Pain and Function (Sports and Recreational Activities) Scores |
|---|---|

End point description:

A responder is defined as a participant with at least a 10-point improvement in both the KOOS Pain and Function (Sports and Recreational activities) scores from MACI00206 Baseline scores.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Up to week 260

| **End point values** | MACI | Microfracture | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65 | 63 | | |
| Units: Patient | 51 | 46 | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: The Proportion of Patients in Each Treatment Group Assessed as Treatment Failures

| | |
|---|---|
| End point title | The Proportion of Patients in Each Treatment Group Assessed as Treatment Failures |

End point description:

Patients were considered as a treatment failure if all of the following 5 criteria were met:

Patient's global assessment of their knee joint compared to Baseline was the same or worse
Physician's global assessment of the patient's knee joint compared to Baseline was the same, worse, or significantly worse.
Percent improvement from Baseline in KOOS Pain score was less than 10%.
Physician diagnostic evaluation of failure excluded etiologies (eg, meniscal tear) other than failed treatment of the index lesion.
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 ACI.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Years 2 through 5 post treatment (MACI or microfracture)

| **End point values** | MACI | Microfracture | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65 | 63 | | |
| Units: Patient | 1 | 1 | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From MACI00206 Baseline in the Remaining 3 Subscales (Activities of Daily Living) of KOOS

| End point title | Change From MACI00206 Baseline in the Remaining 3 Subscales (Activities of Daily Living) of KOOS |
|---|---|

End point description:

The KOOS is a validated knee-specific instrument developed to assess the patients' opinion of their knee and associated problems. KOOS consists of 5 subscales: Pain, Function in sports and recreational activities, other Symptoms, Function in activities of daily living (ADL), and knee related Quality of life (QOL). 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). Subscales are not combined to calculate a total score.

| End point type | Secondary |
|---|---|

End point timeframe:

From MACI00206 Baseline to Week 260

| **End point values** | MACI | Microfracture | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65 | 59 | | |
| Units: Change in Activities of Daily Living Sco | | | | |
| arithmetic mean (full range (min-max)) | 42.82 (-8.8 to 82.4) | 35.86 (-20.6 to 89.7) | | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Change From MACI00206 Baseline in the Remaining 3 Subscales (Quality of Life) of KOOS**

| End point title | Change From MACI00206 Baseline in the Remaining 3 Subscales (Quality of Life) of KOOS |
|---|---|

End point description:

The KOOS is a validated knee-specific instrument developed to assess the patients' opinion of their knee and associated problems. KOOS consists of 5 subscales: Pain, Function in sports and recreational activities, other Symptoms, Function in activities of daily living (ADL), and knee related Quality of life (QOL). 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). Subscales are not combined to calculate a total score.

| End point type | Secondary |
|---|---|

End point timeframe:

From MACI00206 Baseline to Week 260

| End point values | MACI | Microfracture | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65 | 59 | | |
| Units: Change in QoL Score | | | | |
| arithmetic mean (full range (min-max)) | 39.9 (-18.8 to 93.8) | 34.53 (-37.5 to 100) | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From MACI00206 Baseline in the Remaining 3 Subscales (Other Symptoms) of KOOS

| End point title | Change From MACI00206 Baseline in the Remaining 3 Subscales (Other Symptoms) of KOOS |
|---|---|

End point description:

The KOOS is a validated knee-specific instrument developed to assess the patients' opinion of their knee and associated problems. KOOS consists of 5 subscales: Pain, Function in sports and recreational activities, other Symptoms, Function in activities of daily living (ADL), and knee related Quality of life (QOL). 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). Subscales are not combined to calculate a total score.

| End point type | Secondary |
|---|---|

End point timeframe:

From MACI00206 Baseline to Week 260

| End point values | MACI | Microfracture | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65 | 57 | | |
| Units: Change in Other Symptoms Score | | | | |
| arithmetic mean (full range (min-max)) | 32.53 (-7.1 to 78.6) | 28.45 (-14.3 to 89.3) | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From MACI00206 Baseline in the Patient's Evaluation of Overall Knee Condition Using the International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form

| End point title | Change From MACI00206 Baseline in the Patient's Evaluation of Overall Knee Condition Using the International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form |
|---|---|

End point description:

The IKDC Subjective Knee Evaluation Form is a validated knee-specific measure of symptoms, function,

and sports activity that is appropriate for patients with a wide variety of knee problems. The form consists of 18 items covering the domains of symptoms, functioning during activities of daily living and sports, and current function of the knee.

The IKDC Subjective Knee Evaluation Form is scored by summing the scores for the individual items and then transforming the score to a scale that ranges from 0 to 100. The transformed score is interpreted as a measure of function such that higher scores represent higher levels of function and lower levels of symptoms. A score of 100 is interpreted to mean no limitation with activities of daily living or sports activities and the absence of symptoms.

| End point type | Secondary |
|---|---|

End point timeframe:

From MACI00206 Baseline to Week 260

| **End point values** | MACI | Microfracture | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 64 | 59 | | |
| Units: Change in IKDC Score | | | | |
| arithmetic mean (full range (min-max)) | 35.48 (-11.5 to 80.5) | 31.58 (-21.8 to 85.1) | | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Change From MACI00206 Baseline in the Patient's Evaluation of Overall Knee Condition Using the Modified Cincinnati Knee Rating System**

| End point title | Change From MACI00206 Baseline in the Patient's Evaluation of Overall Knee Condition Using the Modified Cincinnati Knee Rating System |
|---|---|

End point description:

The Modified Cincinnati Knee Rating System is a self-assessment of the intensity of sports participation, functional limitations, and the ability to participate in different types of sports. The Modified Cincinnati Knee Rating System overall knee condition score ranges from 1 (poor) to 10 (excellent).

| End point type | Secondary |
|---|---|

End point timeframe:

From MACI00206 Baseline to Week 260

| **End point values** | MACI | Microfracture | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65 | 59 | | |
| Units: Change in MCKR score | | | | |
| arithmetic mean (full range (min-max)) | 3.55 (-1.0 to 8.0) | 2.71 (-3.0 to 8.0) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From MACI00206 Baseline in the 12-Item Short-Form Health Survey (SF-12) Physical Scores

| End point title | Change From MACI00206 Baseline in the 12-Item Short-Form Health Survey (SF-12) Physical Scores |
|---|---|

End point description:

The SF-12 is a subset of the 36-Item Short–Form Health Survey (SF-36) and includes 8 subscales (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health) that are used to calculate the physical (PCS) and mental (MCS) summary component scores.

MCS and PCS are summarized as Z-scores using standard SF-12 scoring and a US population means. The Z-score indicates how many standard deviations a score is from the population mean. Higher values reflect better health. Changes from Baseline are reported.

| End point type | Secondary |
|---|---|

End point timeframe:

From MACI00206 Baseline to Week 260

| **End point values** | MACI | Microfracture | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65 | 55 | | |
| Units: Change in SF-12 physical score | | | | |
| arithmetic mean (full range (min-max)) | 1.52 (-1.6 to 4.0) | 1.28 (-1.3 to 3.8) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From MACI00206 Baseline in the European Quality of Life 5 Dimensions (EQ-5D) Visual Analog Scale (VAS) Score

| End point title | Change From MACI00206 Baseline in the European Quality of Life 5 Dimensions (EQ-5D) Visual Analog Scale (VAS) Score |
|---|---|

End point description:

The EQ-5D is a standardized instrument for use as a measure of health outcome (see the EuroQOL Website for details: www.euroqol.org). Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. The EQ Visual Analogue Scale (VAS) was used to record the respondents' self-rated health status on a vertical graduated (0-100) VAS where 0 is 'the worst health you can imagine' and 100 is 'the best health you can imagine'.

| End point type | Secondary |
|---|---|

End point timeframe:

From MACI00206 Baseline to Week 260

| End point values | MACI | Microfracture | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65 | 58 | | |
| Units: Change in VAS scale | | | | |
| arithmetic mean (full range (min-max)) | 20.14 (-15.0 to 68.0) | 17.1 (-40.0 to 85.0) | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From MACI00206 Baseline in the 12-Item Short-Form Health Survey (SF-12) Mental Component Scores

| End point title | Change From MACI00206 Baseline in the 12-Item Short-Form Health Survey (SF-12) Mental Component Scores |
|---|---|

End point description:

The SF-12 is a subset of the 36-Item Short–Form Health Survey (SF-36) and includes 8 subscales (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health) that are used to calculate the physical (PCS) and mental (MCS) summary component scores.

MCS and PCS are summarized as Z-scores using standard SF-12 scoring and a US population means. The Z-score indicates how many standard deviations a score is from the population mean. Higher values reflect better health. Changes from Baseline are reported.

| End point type | Secondary |
|---|---|

End point timeframe:

From MACI00206 Baseline to Week 260

| End point values | MACI | Microfracture | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65 | 55 | | |
| Units: Change in SF-12 Mental score | | | | |
| arithmetic mean (full range (min-max)) | 0.38 (-2.2 to 3.3) | 0.52 (-2.0 to 3.9) | | |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| Years 2 through 5 post treatment (MACI or microfracture) | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 18.0 |

| Reporting groups | |
|---|---|
| Reporting group title | MACI |
| Reporting group description: | |
| Patients treated with MACI in the parent study (MACI00206) and consented to participate in the MACI00809 study | |
| Reporting group title | Microfracture |
| Reporting group description: | |
| Treatment received in the parent study (MACI00206) and consented to participate in the MACI00809 study | |

| Serious adverse events | MACI | Microfracture | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 16 / 65 (24.62%) | 17 / 63 (26.98%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Salivary gland neoplasm | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Cartilage Injury | | | |
| subjects affected / exposed | 2 / 65 (3.08%) | 7 / 63 (11.11%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Graft delamination | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meniscus Injury | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 65 (1.54%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural pain | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tendon rupture | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transplant failure | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Contusion | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Head injury | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatic injury | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal fracture | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Varicose vein | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 65 (1.54%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Retained placenta or membranes | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Treatment Failure | | | |
| subjects affected / exposed | 3 / 65 (4.62%) | 5 / 63 (7.94%) | |
| occurrences causally related to treatment / all | 3 / 3 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Impaired healing | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | 2 / 63 (3.17%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Otosclerosis | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric stenosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 65 (1.54%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Endometriosis | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 3 / 65 (4.62%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | 5 / 63 (7.94%) | |
| occurrences causally related to treatment / all | 1 / 1 | 4 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthropathy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 65 (1.54%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ligament laxity | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone disorder | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chondropathy | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemarthrosis | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint effusion | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint lock | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 2 / 63 (3.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint swelling | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Loose body in joint | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 63 (1.59%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | 0 / 63 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| **Non-serious adverse events** | MACI | Microfracture | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 49 / 65 (75.38%) | 46 / 63 (73.02%) | |
| Injury, poisoning and procedural complications | | | |
| Procedural Pain | | | |
| subjects affected / exposed | 2 / 65 (3.08%) | 5 / 63 (7.94%) | |
| occurrences (all) | 4 | 5 | |
| Ligament sprain | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | 5 / 63 (7.94%) | |
| occurrences (all) | 1 | 6 | |
| Cartilage Injury | | | |
| subjects affected / exposed | 3 / 65 (4.62%) | 5 / 63 (7.94%) | |
| occurrences (all) | 3 | 5 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 11 / 65 (16.92%) | 13 / 63 (20.63%) | |
| occurrences (all) | 25 | 28 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 29 / 65 (44.62%) | 32 / 63 (50.79%) | |
| occurrences (all) | 62 | 61 | |
| Tendonitis | | | |
| subjects affected / exposed | 4 / 65 (6.15%) | 1 / 63 (1.59%) | |
| occurrences (all) | 4 | 1 | |
| Back Pain | | | |
| subjects affected / exposed | 3 / 65 (4.62%) | 4 / 63 (6.35%) | |
| occurrences (all) | 5 | 5 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 2 / 65 (3.08%) | 5 / 63 (7.94%) | |
| occurrences (all) | 2 | 6 | |
| Joint Effusion | | | |
| subjects affected / exposed | 2 / 65 (3.08%) | 5 / 63 (7.94%) | |
| occurrences (all) | 2 | 5 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 7 / 65 (10.77%) | 2 / 63 (3.17%) | |
| occurrences (all) | 20 | 3 | |
| Influenza | | | |
| subjects affected / exposed | 4 / 65 (6.15%) | 5 / 63 (7.94%) | |
| occurrences (all) | 6 | 5 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported