SYNOPSIS

NAME OF COMPANY	SUMMARY TABLE	FOR NATIONAL AUTHORITY USE ONLY:
Genzyme Europe BV Gooimeer 10 1411 DD Naarden The Netherlands **NAME OF FINISHED PRODUCT** MACI® **NAME OF ACTIVE INGREDIENT** Matrix applied characterised autologous cultured chondrocytes	Referring to Part …… of the Dossier: Volume: Page: Reference:	

TITLE OF STUDY:

A prospective, randomized, open-label, parallel-group, multicenter study to demonstrate the superiority of matrix-induced autologous chondrocyte implantation (MACI® implant) versus arthroscopic microfracture for the treatment of symptomatic articular cartilage defects of the femoral condyle including the trochlea

INVESTIGATORS:

[redacted]

STUDY SITES:

Patients were enrolled at 16 study sites located 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); 1 study site in Poland, 1 in Sweden, and 2 in the United Kingdom were closed because no patients were enrolled.

PUBLICATION (REFERENCE): Not applicable for this report.

STUDIED PERIOD:	PHASE OF DEVELOPMENT:
Date First Patient Consented: 21 May 2008 **Date of Last Patient Out:** 20 March 2012	Phase 3

OBJECTIVES:

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.

METHODOLOGY:

This was a prospective, randomised, open-label, parallel-group, multicentre study designed to demonstrate the superiority 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. The planned patient population consisted of male and female patients aged 18 to 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 $\geq$3.0 cm^2, irrespective of location).

After meeting screening criteria at the initial visit, all patients had an index arthroscopy within approximately 8 weeks to further assess study eligibility. All patients also underwent a Baseline magnetic resonance imaging (MRI) scan prior to the arthroscopy. Study sites were allowed 1 opportunity to re-screen each patient who failed to meet eligibility criteria at the Screening visit or index arthroscopy. If patients failed the re-screen, they were no longer considered for entry into the study.

During the index arthroscopy, patients were further evaluated against entry criteria. Cartilage lesion size was measured prior to any cartilage repair procedure and randomisation. Patients had to have at least 1 lesion with a size of $\geq$3.0 cm^2 on the MFC, LFC, and/or trochlea. All patients who met the eligibility criteria and were considered suitable for treatment in the study by the surgeon had a cartilage biopsy taken prior to randomisation to

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study treatment. Eligible patients were then randomised during the index arthroscopy procedure to receive either MACI or microfracture treatment.

All biopsied tissue was sent to a Genzyme manufacturing facility where the sample was processed to isolate the autologous chondrocytes. Cells from patients randomised to the MACI group were used in the preparation of the MACI implant.

Patients randomised to treatment with MACI returned within approximately 4 to 8 weeks of the index arthroscopy to undergo the chondrocyte implantation procedure via arthrotomy. Patients randomised to microfracture underwent the procedure during the index arthroscopy. Patients followed a recommended post-operative rehabilitation programme and compliance with the rehabilitation schedule and achievement of rehabilitation goals was monitored.

Patients treated with microfracture were assessed post-arthroscopy at Weeks 6 and 12 for safety only and at Weeks 24, 36, 52, 78, and 104 for safety and efficacy. Patients treated with MACI were assessed post-arthrotomy (i.e., following implantation) at Weeks 6 and 12 for safety only and at Weeks 24, 36, 52, 78, and 104 for safety and efficacy. At Week 104 the structural repair of both the microfracture and the MACI treatments were assessed arthroscopically. For the purpose of histological evaluation of the structural repair a cartilage biopsy was harvested from the core of the index lesion. The estimated maximum duration of a patient's involvement in the study from randomisation was 104 weeks for patients treated with microfracture and 112 weeks for patients treated with MACI (i.e., up to an additional 8 weeks for the MACI group due to the time between index arthroscopy and implantation).

From Week 24 post-surgery onwards, any patient 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 was considered a treatment failure. Per Protocol Amendment 2, patients who were considered treatment failures by the Investigator and the Independent Treatment Failure Evaluation Committee were allowed to receive appropriate alternative treatment, at the discretion of the Investigator, which could have been MACI. Additionally, patients who did not meet the specific treatment failure criteria as defined in the protocol but required re-treatment in the opinion of both the Investigator and the Independent Treatment Failure Evaluation Committee, may also have received re-treatment which could have been MACI (such cases were not to be included in the pre-specified Statistical Analysis Plan (SAP) analyses of treatment failure rates and time to treatment failure). Patients who required re-treatment were withdrawn from the study following the surgical re-treatment.

NUMBER OF PATIENTS (PLANNED AND ANALYSED):

Planned: 144 patients (72 in the MACI group and 72 in the microfracture group).

Screened: 189 patients.

Randomised: 144 patients (72 in the MACI group and 72 in the microfracture group).

Full Analysis set: 144 patients (72 in the MACI group and 72 in the microfracture group).

MAIN CRITERIA FOR INCLUSION/EXCLUSION:

Inclusion Criteria:

Inclusion Criteria at Screening Visit:

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

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required information at the scheduled evaluations

2. Symptomatic focal cartilage defects as defined by Knee Injury and Osteoarthritis Outcome Score (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 HIV-1, HIV-2, hepatitis B, hepatitis C, and syphilis

Inclusion Criteria During Index Arthroscopy:

Patients had to meet the following criteria during the index arthroscopy in order to be randomised to study treatment:

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

Exclusion Criteria:

Exclusion Criteria at Screening Visit:

Patients who met any of the following criteria at the Screening visit were not eligible for the study:

1. Any surgery on the knee joint within 6 months prior to Screening (not including diagnostic arthroscopy)
2. Symptomatic musculoskeletal conditions in the lower limbs that could impede measurement of efficacy for the target knee joint
3. In the target knee joint, patient required or had a history of a total meniscectomy or meniscal allograft, or had a bucket handle tear or displaced tear that required a meniscectomy removing >50% of the meniscus
4. Malalignment requiring an osteotomy to correct tibial-femoral or patella-femoral alignment. Retinaculum releases were allowed if indicated to correct patella maltracking
5. History of osteoarthritis (Kellgren-Lawrence Grade 3 or 4) in the target knee joint as diagnosed by clinically appropriate X-rays obtained at the Screening visit or within the previous 12 weeks
6. Concomitant inflammatory disease or other condition that affects the joints (e.g., rheumatoid arthritis, metabolic bone disease, psoriasis, gout, symptomatic chondrocalcinosis)
7. History of septic arthritis in the target knee joint within 1 year prior to Screening

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8. Current malignancy or treatment for malignancy within the past 5 years, except non-melanoma skin cancer
9. Known history of anaphylaxis to gentamicin or any of the products used in the preparation and implantation of MACI implant
10. Patients who, in the opinion of the Investigator, had significant medical or psychosocial problems that warranted exclusion. Examples of significant problems included but were not limited to:
    - Any condition that had potential for negatively impacting intra- or post-operative course, for example,
      - conditions that could severely impair wound healing (e.g., peripheral vascular disease [PVD])
      - conditions that limited compliance with rehabilitation programme (e.g., unstable or poorly controlled angina)
      - active infection, including unexplained fever (temperature >38.1°C) or antibiotic therapy within 1 week prior to Screening
    - Any condition that had potential for significantly limiting patient's ability to assess post-operative knee function, for example,
      - PVD with symptomatic claudication
    - Any condition, psychiatric or otherwise, that would preclude informed consent, consistent follow-up, or compliance with any aspect of the study
    - Current abuse of drugs or alcohol or, in the opinion of the Investigator, high risk for poor compliance
11. Previous investigational drug or device use within 3 months prior to Screening
12. Females who were pregnant or lactating at the time of Screening (patients must agree to not become pregnant between the Screening visit and the surgical treatment visit [i.e., arthroscopy for those randomised to treatment with microfracture, and arthrotomy for those randomised to MACI implant treatment])
13. Ongoing litigation for compensation for musculoskeletal injuries or disorders

Exclusion Criteria During Index Arthroscopy:

Patients who met the following criterion during the index arthroscopy were not eligible for randomisation to study treatment:

1. Modified Outerbridge Grade III or IV defect(s) located on the patella or tibia

DOSE/ROUTE/REGIMEN (TEST ARTICLE):

MACI consisted of autologous cultured chondrocytes seeded onto a CE marked purified resorbable porcine-derived collagen type I/III membrane (ACI-Maix™, Matricel GmbH, Germany). The final MACI product started as a 20 cm^2 (5 x 4 cm) 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.

REFERENCE TREATMENT:

Arthroscopic microfracture of the cartilage defect(s).

DURATION OF TREATMENT:

A cartilage biopsy was taken at the index arthroscopy, prior to randomisation to study treatment, for the 144 patients that were found to meet the eligibility criteria and were considered suitable for treatment in the study

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by the surgeon. Patients randomised to microfracture underwent the procedure during the index arthroscopy. Patients randomised to treatment with MACI returned within approximately 4 to 8 weeks of the index arthroscopy to undergo the chondrocyte implantation procedure via arthrotomy. The planned duration of post-treatment follow-up within MACI00206 was 2 years.

CRITERIA FOR EVALUATION:

Efficacy:

Co-primary efficacy variable:

- Change 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):

- 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 since the parameters were scored as ordinal data)

  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 (i.e., other Symptoms, Knee-Related Quality of Life [QOL], Activities of Daily Living [ADL])

Tertiary efficacy variables

- Change from Baseline at Weeks 24, 36, 52, and 78 in all 5 subscales of the KOOS instrument (i.e., Pain, other Symptoms, QOL, ADL, Function [SRA])
- Response rate based on KOOS Pain and Function (SRA) scores: the proportion of patients who responded to treatment at Weeks 24, 36, 52, and 78

NAME OF COMPANY Genzyme Europe BV Gooimeer 10 1411 DD Naarden The Netherlands **NAME OF FINISHED PRODUCT** MACI® **NAME OF ACTIVE INGREDIENT** Matrix applied characterised autologous cultured chondrocytes	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

- Treatment failure rate: the proportion of patients in each treatment group assessed as treatment failures at Weeks 24, 36, 52, and 78 (Note: this analysis was planned but not completed as the low number of treatment failures made this not evaluable)
- Average time to treatment failure: the time to treatment failure was based on the date that the surgeon decided that surgical re-treatment of the original index lesion was required relative to the date of the original study surgery (i.e., arthroscopy for microfracture and arthrotomy for MACI implant). Treatment failure was only determined in relation to the original treated defect(s) (Note: this analysis was planned but not completed as the low number of treatment failures made this not evaluable)
- Change from Baseline at Weeks 52 and 104 in the patient's evaluation of overall knee condition using the Modified Cincinnati Knee Rating System
- Change from Baseline at Weeks 52 and 104 in the patient's evaluation of overall knee condition using the International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form
- Change from Baseline at Weeks 52 and 104 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 Baseline at Weeks 52 and 104 in the European Quality of Life (EuroQOL) 5 dimensions (EQ-5D) health state
- Macroscopic ICRS "Cartilage Repair Assessment" score during arthroscopy at Week 104 in patients undergoing arthroscopy for harvesting of biopsy of the index lesion

Safety:

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

Exploratory:

In evaluating MRI as an appropriate tool for assessing structural repair, MRI was compared with the co-primary variables and histology.

STATISTICAL METHODS:

Power and Sample Size:

The sample size calculation was based on the bivariate co-primary efficacy parameters of change from Baseline to Week 104 in KOOS Pain score and Function (SRA). The test was performed at α=0.05. The power was chosen to be 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 to be randomised and treated, resulting in 72 patients per treatment group (144 patients in total).

Analysis Sets:

Three analysis populations were defined for this study:

NAME OF COMPANY Genzyme Europe BV Gooimeer 10 1411 DD Naarden The Netherlands **NAME OF FINISHED PRODUCT** MACI® **NAME OF ACTIVE INGREDIENT** Matrix applied characterised autologous cultured chondrocytes	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

The Full Analysis set, consisting of all randomised patients who received study treatment (i.e., microfracture during the index arthroscopy or MACI implant during arthrotomy). The Full Analysis set was used to analyse efficacy.

The Per Protocol (PP) set, defined as those patients in the Full Analysis set 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 Safety set, consisting of all randomised patients who underwent arthroscopy at Visit 2. The Safety set was used for analysis of safety variables.

Efficacy:

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

Safety:

The number (%) of patients with treatment-emergent AEs and treatment-related AEs was presented for each treatment group by Medical Dictionary for Regulatory Activities System Organ Class and Preferred Term.
The incidence rate of treatment-emergent SAEs was also presented for each treatment group.
The incidence rate of treatment-emergent AEs was compared between treatment groups overall and in 2 time periods following surgery: the early post-operative period (up to and including 12 weeks after study treatment) and late post-operative period (more than 12 weeks after study treatment). Any SAEs reported between the Screening visit and prior to the index arthroscopy were listed. For patients in the MACI group, AEs starting after biopsy but before implantation were listed. Additional listings of AEs leading to discontinuation were generated. The number (%) of patients with SSPs was presented by treatment group. The frequency of SSP 0, ≥1 (the number of different dates at which surgical repair occurred, not the number at a specified date) was analysed using a logistic regression model with treatment, age, gender, and total surface area of all lesions as covariates in the model.

Exploratory:

The relationship between MRI and the co-primary variables at Weeks 52 and 104 was explored by means of canonical correlation analyses and visually with the aid of scatterplots. The relationship between MRI and histology at Week 104 was similarly investigated.

As a *post hoc* exploration, the association of change from Baseline in KOOS Pain and KOOS Function (SRA) at Week 104 by ICRS II Overall Assessment was graphically presented with scatterplots.

RESULTS:

Disposition and Demography:

Of the 72 patients randomised to MACI, 70 completed the study and 2 discontinued prematurely (1 due to an AE and 1 wished to withdraw). Of the 72 patients randomised to microfracture, 67 completed the study and 5 discontinued prematurely (1 due to an AE, 1 wished to withdraw, and 3 due to lack of efficacy).

Overall, patient's age, sex, race, weight, height, and body mass index (BMI) were similar across the treatment groups. The majority of patients were male and the median age was in the middle 30s. The mean BMI was 26 for both treatment groups. All patients were White and none were Hispanic or Latino.

For both treatment groups, acute trauma was the most common underlying aetiology of the index lesion; chronic

NAME OF COMPANY Genzyme Europe BV Gooimeer 10 1411 DD Naarden The Netherlands **NAME OF FINISHED PRODUCT** MACI® **NAME OF ACTIVE INGREDIENT** Matrix applied characterised autologous cultured chondrocytes	**SUMMARY TABLE** Referring to Part …… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

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; the index lesion was most frequently located in the MFC. Prior to treatment, the median size of the index lesion and the median total defect size surface area were the same for both groups (4.0 cm^2 and 4.5 cm^2, respectively). The duration in years since onset of symptoms was longer in the MACI group.

The proportion of patients with at least 1 prior orthopaedic 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 that for patients in the microfracture group. The type and frequency of concurrent surgical procedures and use of concomitant medications was comparable for both groups.

Efficacy:

From Baseline to Week 104, an improvement in Pain and Function (SRA) ratings were reported for patients in both treatment groups, however, the mean improvement in both Pain and Function (SRA) was significantly greater (p=0.001) for patients treated with MACI compared to those treated with microfracture. The additional improvement of MACI over microfracture in change from Baseline at Week 104 was >10 points for both Pain and Function (SRA).

The percentage of patients who responded to treatment at Week 104 (had at least a 10-point improvement in both Pain and Function [SRA] from Baseline) was significantly greater (p=0.016) for patients in the MACI group (87.50%) compared to the microfracture group (68.06%).

Improvements from Baseline to Week 104 for all 3 KOOS subscales were significantly greater for patients in the MACI group compared to the microfracture group. Across all 3 subscales, the change from Baseline to Week 104 was >25 points for both treatment groups, however the changes in ADL (p<0.001), QOL (p=0.029), and Other Symptoms (p<0.001) were superior for patients treated with MACI.

Additional support for improved clinical efficacy with MACI treatment was evident in other patient-reported outcome (PRO) measures included in the study. Improvement on the Modified Cincinnati Knee Rating System and the SF-12 physical health score from Baseline to Weeks 52 and 104 was significantly greater for patients in the MACI group. For the IKDC Subjective Knee Evaluation, there was a significant difference between the treatment groups in favour of the MACI group for change from Baseline at Week 52 and a trend towards a significantly greater mean improvement at Week 104. Comparable improvement was seen for both treatment groups on the EQ-5D and SF-12 mental component score.

The mean ICRS II Overall Assessment score at Week 104 was comparable for the MACI and microfracture groups and there was no significant difference between the treatment groups.

There was no significant difference between the treatment groups in MRI Degree of Defect Fill at Week 52 or Week 104. Improvement in defect fill was evident for patients in both treatment groups.

The Macroscopic ICRS Cartilage Repair scores were comparable for patients treated with MACI or microfracture.

Safety:

The proportion of patients with at least 1 treatment-emergent AE was 76.4% in the MACI group and 83.3% in the microfracture group. In both treatment groups, most treatment-emergent AEs were of moderate or mild intensity.

The incidence of treatment-emergent AEs considered related to study treatment was comparable between the 2 treatment groups (25 patients [34.7%] in the MACI group and 28 patients [38.9%] in the microfracture group). The most common related event was arthralgia (19 patients [26.4%] in the MACI group and 23 patients [31.9%] in

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the microfracture group).

One patient (1.4%) in each treatment group discontinued the study prematurely due to treatment-emergent AEs.

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. No deaths occurred in this study.

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. Haemarthrosis 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).

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).

Exploratory:

At both Week 52 and Week 104, there were no significant associations found between the MRI and KOOS data.

At Week 104, there were no significant associations found between the MRI and microscopic ICRS II histology data.

Based on *post hoc* exploration, at Week 104 a lack of association between the pain and function outcomes and the overall histology assessment score was observed, regardless of treatment group.

CONCLUSIONS:

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