Clinical trial results:
Instant MSC Product accompanying Autologous Chondron Transplantation (IMPACT) for focal articular cartilage lesions of the knee; feasibility and safety

Summary

EudraCT number	2012-001570-29
Trial protocol	NL
Global end of trial date	10 February 2016

Results information

Result version number	v1 (current)
This version publication date	19 March 2020
First version publication date	19 March 2020

Trial information

Trial identification

Sponsor protocol code	NL4014200012

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02037204
WHO universal trial number (UTN)	-
Other trial identifiers	CCMO File nr: NL40142.000.12, METC protocol nr: 12-452

Notes:

Sponsors

Sponsor organisation name	UMC Utrecht
Sponsor organisation address	Heidelberglaan 100, Utrecht, Netherlands, 3584 CX
Public contact	Department of Orthopaedics, University Medical Centre Utrecht, +31 887556971, d.saris@umcutrecht.nl
Scientific contact	Department of Orthopaedics, University Medical Centre Utrecht, +31 887556971, d.saris@umcutrecht.nl

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	25 January 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to examine clinical safety and feasibility of the IMPACT therapy.

Protection of trial subjects:

This study was conducted according to the principle of the Declaration of Helsinki (Tokyo, 2004) and in accordance with the Medical Research Involving Human Subjects Act (WMO). An Independan data monitoring committee was involved.
As this is a phase I/II monocenter study in relatively healthy patients, an independent safety officer was appointed to monitor the safety in terms of AE occurrence for the first six patients prior to starting the study. This safety officer was an independent physician with knowledge in the field. This safety officer looked into all clinical patient data, including operation and clinical reports. An independent knowledgeable investigator about the disease indication also looked at the data in terms of data quality, main outcomes and statistical analysis. Both investigators report on the first six patients within two months after inclusion of the sixth patient. The study proceeded after the conclusion of both investigators that it was safe to continue. The independent safety officer and investigator continued to monitor the study with reports at twelve months and at final follow-up (18 months).

Background therapy:

All patients received a mini-arthrotomy with macroscopic inspection of the knee joint. All patients received treatments that are part of the standard surgery protocol.

Evidence for comparator:

Articular cartilage defects in the knee have poor intrinsic healing capacity and may lead to functional disability and osteoarthritis. Cartilage cell therapy using autologous chondrocyte implantation has been established as the first advanced treatment therapy medicinal product. Although this technique has achieved good mid-term results, it is a costly and extensive two-stage procedure which is limited by the number of chondrocytes obtained by biopsy and the dedifferentiation resulting from the expansion phase. Therefore, there is a need for improvement. A new cartilage repair technique should aim at decreasing surgical trauma, lowering complexity, improving logistics and cost-effectiveness while retaining or improving clinical outcome. Direct contact between mesenchymal stromal cells (MSCs) and dedifferentiated articular chondrocytes in vitro showed improvement of the chondrogenic phenotype of dedifferentiated articular chondrocytes. In addition, preserving the pericellular matrix of chondrocytes improves cartilage formation. These chondrons (chondrocytes with their pericellular matrix), which we can obtain using a rapid digestion protocol in 40 minutes, have shown improved cartilage formation when combined with allogeneic MSCs. These cells can be mixed with a widely used, commercially available, fibrin cell carrier (Beriplast®) and applied to the cartilage lesion within one surgical procedure, using a minimally invasive and eventually arthroscopic technique. This will reduce patient morbidity and improve patient care through immediate transplantation of a potent cell-based cartilage product.

Actual start date of recruitment	03 September 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Regulatory reason, Scientific research
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 35
Worldwide total number of subjects	35
EEA total number of subjects	35

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)	35
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited at the outpatient clinic of the department of Orthopaedics of the UMC Utrecht from 10-04-2013 up untill 6-8-2014.

Pre-assignment

Screening details:

- Provides written informed consent, is able to understand the content of the study, understands the requirements for follow-up visits and is willing to provide the required information at follow-up visits.
- Symptomatic isolated articular cartilage lesion on the femoral condyle or trochlea.
- Age >18 and <45 years old

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	IMPACT - Baseline

Arm description: -

Arm type	Experimental
Investigational medicinal product name	INSTANT MSC PRODUCT ACCOMPANYING AUTOLOGOUS CHONDRON TRANSPLANTATION (IMPACT)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Intracartilaginous use

Dosage and administration details:

The surgical procedure started with a mini-arthrotomy, followed by inspection of the articular surfaces of the knee with identification and macroscopic scoring of the isolated articular cartilage lesion. Following this, the defect was debrided to create a stable surgical base and borders. This debrided tissue was transported to the CellTherapyFacility. The cartilage was cut into small pieces and the rapid digestion protocol (RDP) was performed. In parallel with the RDP the cryopreserved allogeneic MSCs were thawed and counted for later combination with the isolated chondrons. Once the cells were added together, they mixed with the fibrinogen component of Beriplast®. When the product was finished it was transported back to the operation theatre and the surgeon applied the Beriplast® loaded with the chondrons and MSCs to the cartilage defect.

Number of subjects in period 1	IMPACT - Baseline
Started	35
Completed	35

Period 2

Period 2 title	Safety analysis day 1
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	IMPACT - Safety analysis day 1

Arm description:

During one surgical procedure and using a minimally invasive technique autologous chondrons (chondrocytes with their pericellular matrix) and allogeneic MSCs are mixed with a fibrin cell carrier (Beriplast®) and applied to the cartilage lesion in the knee.

Arm type	Experimental
Investigational medicinal product name	INSTANT MSC PRODUCT ACCOMPANYING AUTOLOGOUS CHONDRON TRANSPLANTATION (IMPACT)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Intracartilaginous use

Dosage and administration details:

The surgical procedure started with a mini-arthrotomy, followed by inspection of the articular surfaces of the knee with identification and macroscopic scoring of the isolated articular cartilage lesion. Following this, the defect was debrided to create a stable surgical base and borders. This debrided tissue was transported to the CellTherapyFacility. The cartilage was cut into small pieces and the rapid digestion protocol (RDP) was performed. In parallel with the RDP the cryopreserved allogeneic MSCs were thawed and counted for later combination with the isolated chondrons. Once the cells were added together, they mixed with the fibrinogen component of Beriplast®. When the product was finished it was transported back to the operation theatre and the surgeon applied the Beriplast® loaded with the chondrons and MSCs to the cartilage defect.

Number of subjects in period 2	IMPACT - Safety analysis day 1
Started	35
Completed	35

Period 3

Period 3 title	Safety analysis week 1
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	IMPACT - Safety analysis week 1

Arm description:

During one surgical procedure and using a minimally invasive technique autologous chondrons (chondrocytes with their pericellular matrix) and allogeneic MSCs are mixed with a fibrin cell carrier (Beriplast®) and applied to the cartilage lesion in the knee.

Arm type	Experimental
Investigational medicinal product name	INSTANT MSC PRODUCT ACCOMPANYING AUTOLOGOUS CHONDRON TRANSPLANTATION (IMPACT)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Intracartilaginous use

Dosage and administration details:

The surgical procedure started with a mini-arthrotomy, followed by inspection of the articular surfaces of the knee with identification and macroscopic scoring of the isolated articular cartilage lesion. Following this, the defect was debrided to create a stable surgical base and borders. This debrided tissue was transported to the CellTherapyFacility. The cartilage was cut into small pieces and the rapid digestion protocol (RDP) was performed. In parallel with the RDP the cryopreserved allogeneic MSCs were thawed and counted for later combination with the isolated chondrons. Once the cells were added together, they mixed with the fibrinogen component of Beriplast®. When the product was finished it was transported back to the operation theatre and the surgeon applied the Beriplast® loaded with the chondrons and MSCs to the cartilage defect.

Number of subjects in period 3	IMPACT - Safety analysis week 1
Started	35
Completed	35

Period 4

Period 4 title	Safety analysis week 2
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	IMPACT - Safety analysis week 2

Arm description:

During one surgical procedure and using a minimally invasive technique autologous chondrons (chondrocytes with their pericellular matrix) and allogeneic MSCs are mixed with a fibrin cell carrier (Beriplast®) and applied to the cartilage lesion in the knee.

Arm type	Experimental
Investigational medicinal product name	INSTANT MSC PRODUCT ACCOMPANYING AUTOLOGOUS CHONDRON TRANSPLANTATION (IMPACT)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Intracartilaginous use

Dosage and administration details:

The surgical procedure started with a mini-arthrotomy, followed by inspection of the articular surfaces of the knee with identification and macroscopic scoring of the isolated articular cartilage lesion. Following this, the defect was debrided to create a stable surgical base and borders. This debrided tissue was transported to the CellTherapyFacility. The cartilage was cut into small pieces and the rapid digestion protocol (RDP) was performed. In parallel with the RDP the cryopreserved allogeneic MSCs were thawed and counted for later combination with the isolated chondrons. Once the cells were added together, they mixed with the fibrinogen component of Beriplast®. When the product was finished it was transported back to the operation theatre and the surgeon applied the Beriplast® loaded with the chondrons and MSCs to the cartilage defect.

Number of subjects in period 4	IMPACT - Safety analysis week 2
Started	35
Completed	35

Period 5

Period 5 title	Safety analysis week 4
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	IMPACT - Safety analysis week 4

Arm description:

During one surgical procedure and using a minimally invasive technique autologous chondrons (chondrocytes with their pericellular matrix) and allogeneic MSCs are mixed with a fibrin cell carrier (Beriplast®) and applied to the cartilage lesion in the knee.

Arm type	Experimental
Investigational medicinal product name	INSTANT MSC PRODUCT ACCOMPANYING AUTOLOGOUS CHONDRON TRANSPLANTATION (IMPACT)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Intracartilaginous use

Dosage and administration details:

The surgical procedure started with a mini-arthrotomy, followed by inspection of the articular surfaces of the knee with identification and macroscopic scoring of the isolated articular cartilage lesion. Following this, the defect was debrided to create a stable surgical base and borders. This debrided tissue was transported to the CellTherapyFacility. The cartilage was cut into small pieces and the rapid digestion protocol (RDP) was performed. In parallel with the RDP the cryopreserved allogeneic MSCs were thawed and counted for later combination with the isolated chondrons. Once the cells were added together, they mixed with the fibrinogen component of Beriplast®. When the product was finished it was transported back to the operation theatre and the surgeon applied the Beriplast® loaded with the chondrons and MSCs to the cartilage defect.

Number of subjects in period 5	IMPACT - Safety analysis week 4
Started	35
Completed	35

Period 6

Period 6 title	Safety analysis week 6
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	IMPACT - Safety analysis week 6

Arm description:

During one surgical procedure and using a minimally invasive technique autologous chondrons (chondrocytes with their pericellular matrix) and allogeneic MSCs are mixed with a fibrin cell carrier (Beriplast®) and applied to the cartilage lesion in the knee.

Arm type	Experimental
Investigational medicinal product name	INSTANT MSC PRODUCT ACCOMPANYING AUTOLOGOUS CHONDRON TRANSPLANTATION (IMPACT)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Intracartilaginous use

Dosage and administration details:

The surgical procedure started with a mini-arthrotomy, followed by inspection of the articular surfaces of the knee with identification and macroscopic scoring of the isolated articular cartilage lesion. Following this, the defect was debrided to create a stable surgical base and borders. This debrided tissue was transported to the CellTherapyFacility. The cartilage was cut into small pieces and the rapid digestion protocol (RDP) was performed. In parallel with the RDP the cryopreserved allogeneic MSCs were thawed and counted for later combination with the isolated chondrons. Once the cells were added together, they mixed with the fibrinogen component of Beriplast®. When the product was finished it was transported back to the operation theatre and the surgeon applied the Beriplast® loaded with the chondrons and MSCs to the cartilage defect.

Number of subjects in period 6	IMPACT - Safety analysis week 6
Started	35
Completed	35

Period 7	
Period 7 title	3 months
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	IMPACT - 3 months

Arm description: -

Arm type	Experimental
Investigational medicinal product name	INSTANT MSC PRODUCT ACCOMPANYING AUTOLOGOUS CHONDRON TRANSPLANTATION (IMPACT)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Intracartilaginous use

Dosage and administration details:

The surgical procedure started with a mini-arthrotomy, followed by inspection of the articular surfaces of the knee with identification and macroscopic scoring of the isolated articular cartilage lesion. Following this, the defect was debrided to create a stable surgical base and borders. This debrided tissue was transported to the CellTherapyFacility. The cartilage was cut into small pieces and the rapid digestion protocol (RDP) was performed. In parallel with the RDP the cryopreserved allogeneic MSCs were thawed and counted for later combination with the isolated chondrons. Once the cells were added together, they mixed with the fibrinogen component of Beriplast®. When the product was finished it was transported back to the operation theatre and the surgeon applied the Beriplast® loaded with the chondrons and MSCs to the cartilage defect.

Number of subjects in period 7	IMPACT - 3 months
Started	35
Completed	35

Period 8	
Period 8 title	6 months
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	IMPACT - 6 months
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	INSTANT MSC PRODUCT ACCOMPANYING AUTOLOGOUS CHONDRON TRANSPLANTATION (IMPACT)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Intracartilaginous use

Dosage and administration details:

The surgical procedure started with a mini-arthrotomy, followed by inspection of the articular surfaces of the knee with identification and macroscopic scoring of the isolated articular cartilage lesion. Following this, the defect was debrided to create a stable surgical base and borders. This debrided tissue was transported to the CellTherapyFacility. The cartilage was cut into small pieces and the rapid digestion protocol (RDP) was performed. In parallel with the RDP the cryopreserved allogeneic MSCs were thawed and counted for later combination with the isolated chondrons. Once the cells were added together, they mixed with the fibrinogen component of Beriplast®. When the product was finished it was transported back to the operation theatre and the surgeon applied the Beriplast® loaded with the chondrons and MSCs to the cartilage defect.

Number of subjects in period 8	IMPACT - 6 months
Started	35
Completed	35

Period 9

Period 9 title	12 months
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	IMPACT - 12 months
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	INSTANT MSC PRODUCT ACCOMPANYING AUTOLOGOUS CHONDRON TRANSPLANTATION (IMPACT)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Intracartilaginous use

Dosage and administration details:

The surgical procedure started with a mini-arthrotomy, followed by inspection of the articular surfaces of the knee with identification and macroscopic scoring of the isolated articular cartilage lesion. Following this, the defect was debrided to create a stable surgical base and borders. This debrided tissue was transported to the CellTherapyFacility. The cartilage was cut into small pieces and the rapid digestion protocol (RDP) was performed. In parallel with the RDP the cryopreserved allogeneic MSCs were thawed

and counted for later combination with the isolated chondrons. Once the cells were added together, they mixed with the fibrinogen component of Beriplast®. When the product was finished it was transported back to the operation theatre and the surgeon applied the Beriplast® loaded with the chondrons and MSCs to the cartilage defect.

Number of subjects in period 9	IMPACT - 12 months
Started	35
Completed	35

Period 10	
Period 10 title	18 months
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	IMPACT - 18 months
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	INSTANT MSC PRODUCT ACCOMPANYING AUTOLOGOUS CHONDRON TRANSPLANTATION (IMPACT)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Intracartilaginous use

Dosage and administration details:

The surgical procedure started with a mini-arthrotomy, followed by inspection of the articular surfaces of the knee with identification and macroscopic scoring of the isolated articular cartilage lesion. Following this, the defect was debrided to create a stable surgical base and borders. This debrided tissue was transported to the CellTherapyFacility. The cartilage was cut into small pieces and the rapid digestion protocol (RDP) was performed. In parallel with the RDP the cryopreserved allogeneic MSCs were thawed and counted for later combination with the isolated chondrons. Once the cells were added together, they mixed with the fibrinogen component of Beriplast®. When the product was finished it was transported back to the operation theatre and the surgeon applied the Beriplast® loaded with the chondrons and MSCs to the cartilage defect.

Number of subjects in period 10	IMPACT - 18 months
Started	35
Completed	35

Period 11	
Period 11 title	12 months - second look
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	IMPACT - second look

Arm description: -

Arm type	Experimental
Investigational medicinal product name	INSTANT MSC PRODUCT ACCOMPANYING AUTOLOGOUS CHONDRON TRANSPLANTATION (IMPACT)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Intracartilaginous use

Dosage and administration details:

The surgical procedure started with a mini-arthrotomy, followed by inspection of the articular surfaces of the knee with identification and macroscopic scoring of the isolated articular cartilage lesion. Following this, the defect was debrided to create a stable surgical base and borders. This debrided tissue was transported to the CellTherapyFacility. The cartilage was cut into small pieces and the rapid digestion protocol (RDP) was performed. In parallel with the RDP the cryopreserved allogeneic MSCs were thawed and counted for later combination with the isolated chondrons. Once the cells were added together, they mixed with the fibrinogen component of Beriplast®. When the product was finished it was transported back to the operation theatre and the surgeon applied the Beriplast® loaded with the chondrons and MSCs to the cartilage defect.

Number of subjects in period 11	IMPACT - second look
Started	35
Completed	33
Not completed	2
No consent was provided for this part	2

Period 12	
Period 12 title	12 months - biopsy
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	IMPACT - biopsy
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	INSTANT MSC PRODUCT ACCOMPANYING AUTOLOGOUS CHONDRON TRANSPLANTATION (IMPACT)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Intracartilaginous use

Dosage and administration details:

The surgical procedure started with a mini-arthrotomy, followed by inspection of the articular surfaces of the knee with identification and macroscopic scoring of the isolated articular cartilage lesion. Following this, the defect was debrided to create a stable surgical base and borders. This debrided tissue was transported to the CellTherapyFacility. The cartilage was cut into small pieces and the rapid digestion protocol (RDP) was performed. In parallel with the RDP the cryopreserved allogeneic MSCs were thawed and counted for later combination with the isolated chondrons. Once the cells were added together, they mixed with the fibrinogen component of Beriplast®. When the product was finished it was transported back to the operation theatre and the surgeon applied the Beriplast® loaded with the chondrons and MSCs to the cartilage defect.

Number of subjects in period 12	IMPACT - biopsy
Started	33
Completed	32
Not completed	1
Lack of efficacy	1

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	35	35	
Age categorical Units: Subjects			
Age continuous			
Inclusion between 18 and 45 years old.			
Units: years			
arithmetic mean	30		
standard deviation	± 8	-	
Gender categorical Units: Subjects			
Female	11	11	
Male	24	24	
Location cartilage defect			
Location of the cartilage defect in the knee.			
Units: Subjects			
Medial femoral condyle	17	17	
Lateral femoral condyle	12	12	
Trochlea	6	6	
Previous surgeries			
Previous surgeries performed in same knee			
Units: Subjects			
Menisectomy	6	6	
Debridement	4	4	
Bone marrow stimulation by microfracture	10	10	
No previous surgeries	15	15	
Cellular mixture			
Autologous chondrons and allogeneic MSCs were combined in a 10:90 ratio (standard yield) or 20:80 ratio (high yield), depending on the amount of chondrons isolated.			
Units: Subjects			
10:90 cellular mixture	17	17	
20:80 cellular mixture	18	18	

End points

End points reporting groups

Reporting group title	IMPACT - Baseline
Reporting group description: -	
Reporting group title	IMPACT - Safety analysis day 1
Reporting group description:	
During one surgical procedure and using a minimally invasive technique autologous chondrons (chondrocytes with their pericellular matrix) and allogeneic MSCs are mixed with a fibrin cell carrier (Beriplast®) and applied to the cartilage lesion in the knee.	
Reporting group title	IMPACT - Safety analysis week 1
Reporting group description:	
During one surgical procedure and using a minimally invasive technique autologous chondrons (chondrocytes with their pericellular matrix) and allogeneic MSCs are mixed with a fibrin cell carrier (Beriplast®) and applied to the cartilage lesion in the knee.	
Reporting group title	IMPACT - Safety analysis week 2
Reporting group description:	
During one surgical procedure and using a minimally invasive technique autologous chondrons (chondrocytes with their pericellular matrix) and allogeneic MSCs are mixed with a fibrin cell carrier (Beriplast®) and applied to the cartilage lesion in the knee.	
Reporting group title	IMPACT - Safety analysis week 4
Reporting group description:	
During one surgical procedure and using a minimally invasive technique autologous chondrons (chondrocytes with their pericellular matrix) and allogeneic MSCs are mixed with a fibrin cell carrier (Beriplast®) and applied to the cartilage lesion in the knee.	
Reporting group title	IMPACT - Safety analysis week 6
Reporting group description:	
During one surgical procedure and using a minimally invasive technique autologous chondrons (chondrocytes with their pericellular matrix) and allogeneic MSCs are mixed with a fibrin cell carrier (Beriplast®) and applied to the cartilage lesion in the knee.	
Reporting group title	IMPACT - 3 months
Reporting group description: -	
Reporting group title	IMPACT - 6 months
Reporting group description: -	
Reporting group title	IMPACT - 12 months
Reporting group description: -	
Reporting group title	IMPACT - 18 months
Reporting group description: -	
Reporting group title	IMPACT - second look
Reporting group description: -	
Reporting group title	IMPACT - biopsy
Reporting group description: -	

Primary: Change in C-reactive protein between day 1 to week 6

End point title	Change in C-reactive protein between day 1 to week 6[1]
End point description:	
All patients were monitored for inflammation and signs of a foreign body response by an independent physician (rheumatologist) using blood analysis including serum C-reactive protein.	
End point type	Primary
End point timeframe:	
At day 1, week 1, week 2, week 4 and week 6.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: A clinical immune/rheumatologist independent of the design and surgical treatment team performed the clinical monitoring. No signs of a foreign body response were identified by the independent rheumatologist. Levels were monitored and supposed to remain low after typical post-surgical procedure responses.

End point values	IMPACT - Safety analysis day 1	IMPACT - Safety analysis week 1	IMPACT - Safety analysis week 2	IMPACT - Safety analysis week 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	35	35	35
Units: milligram(s)/litre				
arithmetic mean (full range (min-max))				
C-reactive protein count	20.3 (1.6 to 103)	6.5 (0.8 to 59)	5.1 (0.5 to 32)	2.8 (0.5 to 12)

End point values	IMPACT - Safety analysis week 6			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: milligram(s)/litre				
arithmetic mean (full range (min-max))				
C-reactive protein count	3 (0.5 to 21)			

Statistical analyses

No statistical analyses for this end point

Primary: Change in erythrocyte sedimentation rate between day 1 to week 6

End point title	Change in erythrocyte sedimentation rate between day 1 to week 6[2]

End point description:

All patients were monitored for inflammation and signs of a foreign body response by an independent physician (rheumatologist) using blood analysis including

End point type	Primary

End point timeframe:

At day 1, week 1, week 2, week 4 and week 6.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: A clinical immune/rheumatologist independent of the design and surgical treatment team performed the clinical monitoring. No signs of a foreign body response were identified by the independent rheumatologist. Levels were monitored and supposed to remain low after typical post-surgical procedure responses.

End point values	IMPACT - Safety analysis day 1	IMPACT - Safety analysis week 1	IMPACT - Safety analysis week 2	IMPACT - Safety analysis week 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	35	35	35
Units: millimole(s)/hour				
arithmetic mean (full range (min-max))				
Erythrocyte sedimentation rate count	7 (2 to 28)	8.4 (1 to 34)	6.2 (2 to 18)	5.0 (1 to 19)

End point values	IMPACT - Safety analysis week 6			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: millimole(s)/hour				
arithmetic mean (full range (min-max))				
Erythrocyte sedimentation rate count	5.1 (1 to 18)			

Statistical analyses

No statistical analyses for this end point

Primary: Change in numeric rating scale for pain between day 1 to week 6

End point title	Change in numeric rating scale for pain between day 1 to week 6

End point description:

End point type	Primary

End point timeframe:

Preop, day 1, week 1, week 2, week 4, week 6

End point values	IMPACT - Baseline	IMPACT - Safety analysis day 1	IMPACT - Safety analysis week 1	IMPACT - Safety analysis week 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	35	35	35
Units: points	46	33	18	14

End point values	IMPACT - Safety analysis week 4	IMPACT - Safety analysis week 6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: points	10	8		

Statistical analyses

Statistical analysis title	NRS test
Comparison groups	IMPACT - Baseline v IMPACT - Safety analysis week 6 v IMPACT - Safety analysis week 4 v IMPACT - Safety analysis week 2 v IMPACT - Safety analysis day 1 v IMPACT - Safety analysis week 1
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.0001
Method	t-test, 2-sided

Primary: Change in leukocyte count between day 1 to week 6

End point title	Change in leukocyte count between day 1 to week 6[3]

End point description:

End point type	Primary

End point timeframe:

Day 1, week 1, week 2, week 4, week 6

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: A clinical immune/rheumatologist independent of the design and surgical treatment team performed the clinical monitoring. No signs of a foreign body response were identified by the independent rheumatologist. Levels were monitored and supposed to remain low after typical post-surgical procedure responses.

End point values	IMPACT - Safety analysis day 1	IMPACT - Safety analysis week 1	IMPACT - Safety analysis week 2	IMPACT - Safety analysis week 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	35	35	35
Units: 1000/µL	8	8	8	7

End point values	IMPACT - Safety analysis week 6			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: 1000/µL	7			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in VAS pain score from baseline to 18 months postop

End point title	Change in VAS pain score from baseline to 18 months postop

End point description:

End point type	Secondary

End point timeframe:

Baseline, 3 months, 6 months, 12 months and 18 months

End point values	IMPACT - Baseline	IMPACT - 3 months	IMPACT - 6 months	IMPACT - 12 months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	35	35	35
Units: point scale				
arithmetic mean (standard deviation)	45.3 (± 24.2)	12.9 (± 9)	15.3 (± 8.9)	13.3 (± 10.2)

End point values	IMPACT - 18 months			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: point scale				
arithmetic mean (standard deviation)	9.7 (± 15.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in KOOS from baseline to 18 months postop

End point title	Change in KOOS from baseline to 18 months postop

End point description:

End point type	Secondary

End point timeframe:

Baseline, 3 months, 6 months, 12 months and 18 months

End point values	IMPACT - Baseline	IMPACT - 3 months	IMPACT - 6 months	IMPACT - 12 months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	35	35	35
Units: Point scale				
arithmetic mean (standard deviation)	57.9 (± 16.1)	76.6 (± 11.1)	79.9 (± 12.9)	83.5 (± 10.6)

End point values	IMPACT - 18 months			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Point scale				
arithmetic mean (standard deviation)	85.4 (± 13.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Grade score at second look arthroscopy

End point title	Grade score at second look arthroscopy

End point description:

End point type	Secondary

End point timeframe:

At 12 months

End point values	IMPACT - second look			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: macroscopic ICRS score				
Grade 1	22			
Grade 2	11			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in KOOS from baseline to 3 and 18 months	
End point title	Mean change in KOOS from baseline to 3 and 18 months

End point description:

End point type	Secondary

End point timeframe:

Questionnaire at 3 and 18 months.

End point values	IMPACT - Baseline	IMPACT - 3 months	IMPACT - 18 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	35	35	35	
Units: point scale				
arithmetic mean (standard deviation)	57.9 (± 16.1)	85.4 (± 13.3)	79.9 (± 12.9)	

Statistical analyses

Statistical analysis title	Repeated-measures analysis of variance

Statistical analysis description:

Predefined statistical analyses were performed with SPSS version 21.0 (IBM, Chicago, IL). A repeated-measures analysis of variance was used to test for differences in clinical outcome between baseline and 3, 6 and 18 months after surgery.

Comparison groups	IMPACT - Baseline v IMPACT - 3 months v IMPACT - 18 months
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	equivalence[4]
P-value	< 0.0001
Method	ANOVA

Notes:

[4] - To test for differences in clinical outcome.

Secondary: Mean change in VAS pain from baseline to 18 months	
End point title	Mean change in VAS pain from baseline to 18 months

End point description:

End point type	Secondary

End point timeframe:

Questionnaire 18 months after surgery

End point values	IMPACT - Baseline	IMPACT - 18 months		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: Point scale				
number (not applicable)	45.4	15.3		

Statistical analyses

Statistical analysis title	Repeated-measures analysis of variance
Comparison groups	IMPACT - Baseline v IMPACT - 18 months
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 1E-7
Method	ANOVA

Secondary: STR analysis

End point title	STR analysis

End point description:

Detection of DNA of the allogeneic MSCs within the detection limit of the assay (1 in 100,000 cells).

End point type	Secondary

End point timeframe:

At 12 months with the second look arthroscopy

End point values	IMPACT - biopsy			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: cells				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
General adverse events were monitored througout the study.	
Adverse event reporting additional description:	
A data safety monitoring board (DSMB) was assembled.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups	
Reporting group title	Overall trial
Reporting group description: -	

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 35 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 35 (62.86%)		
Cardiac disorders			
Hypertension			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Nervous system disorders			
Vasovagal episode	Additional description: Vasovagal episode in the morning (light headed, sweaty, nausea, temporary black cloud like spots in eye sight)		
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Headache	Additional description: After surgery		
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Nausea	Additional description: Nausea after surgery		

subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	4		
Pain	Additional description: Pain of the knee		
subjects affected / exposed	12 / 35 (34.29%)		
occurrences (all)	15		
Immune system disorders			
Elevated erythrocyte sedimentation rate	Additional description: After surgery		
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	3		
C-reactive protein increased	Additional description: Elevated C-reactive protein level		
subjects affected / exposed	4 / 35 (11.43%)		
occurrences (all)	4		
Leukocytosis			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Pruritus	Additional description: Facial pruritus after surgery		
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Renal and urinary disorders			
Urinary retention	Additional description: After surgery		
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Increase in pain and instability			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Crepitations	Additional description: Crepitations of the knee		
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	3		
Swelling	Additional description: Swelling of the knee		
subjects affected / exposed	5 / 35 (14.29%)		
occurrences (all)	7		
Swelling and pain	Additional description: Swelling and pain of toes		
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		

Lesion in trochlea	Additional description: Lesion in trochlea detected during arthroscopy at 12 months		
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Meniscus tear	Additional description: Meniscus tear detected during arthroscopy at 12 months		
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 April 2013	Removal of KOOS <55 points from inclusion criteria and change in the MRI protocol.
22 November 2013	Change in the IMPD concerning the correction in dosage of cells.
06 May 2014	Lowering the frequency of follow-up moments at the first period after surgery.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28600828

http://www.ncbi.nlm.nih.gov/pubmed/27507787

http://www.ncbi.nlm.nih.gov/pubmed/27401932