



Clinical trial results:

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

Summary

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|--------------------------|------------------|
| 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 Independent 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.

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|---|--|
| 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 until 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 CHONDROGEN 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 CHONDROTON 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 CHONDROTON 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 CHONDROTON 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 CHONDROCYTE 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 CHONDROTRANSPANTATION (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 CHONDROTRANSPANTATION (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 CHONDROTRANSPANTATION (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 CHONDROTRANSPANTATION (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 CHONDROCYTE 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 CHONDROTRANSPANTATION (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 CHONDROGEN 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 | | | |
| Meniscectomy | 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/ μ L | 8 | 8 | 8 | 7 |

| End point values | IMPACT - Safety analysis week 6 | | | |
|-----------------------------|---------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 35 | | | |
| Units: 1000/ μ L | 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 throughout 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>