



Clinical trial results:

Treatment of Osteoarthritis by intra-articular injection of mesenchymal stem cells from bone marrow and plasma rich in growth factors (PRGF).

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2011-006036-23 |
| Trial protocol | ES |
| Global end of trial date | 27 June 2018 |

Results information

| | |
|-----------------------------------|---|
| Result version number | v1 (current) |
| This version publication date | 19 September 2021 |
| First version publication date | 19 September 2021 |
| Summary attachment (see zip file) | SPANISH REPORT (INFORME FINAL-CMM-PRGF-ART.pdf) |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CMM-PRGF/ART |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02365142 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Clínica Universidad de Navarra |
| Sponsor organisation address | Avda. Pío XII, 36, Pamplona, Spain, 31008 |
| Public contact | UCICEC, Clínica Universidad de Navarra, 34 948 255 400 1144, ucicec@unav.es |
| Scientific contact | UCICEC, Clínica Universidad de Navarra, 34 948 255 400 1144, ucicec@unav.es |

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 | 20 January 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 27 June 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 27 June 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Compare the effectiveness of PRGF versus PRGF + CMM in patients with osteoarthritis of the knee refractory to treatment with hyaluronic acid.

Protection of trial subjects:

NA

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 07 October 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Spain: 60 |
| Worldwide total number of subjects | 60 |
| EEA total number of subjects | 60 |

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) | 48 |
| From 65 to 84 years | 12 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Patient recruitment will be carried out in each of the centres by the specialists in Orthopaedic Surgery and Traumatology or Rheumatology participating in the project. Once randomised, patients assigned to group 2 undergo a bone marrow extraction to create the autologous mesenchymal stem cell product for intrarticular infusion.

Pre-assignment

Screening details:

Patients between 18 and 80 years diagnosed by osteoarthritis of the knee according to the criteria of the ACR and refractory to previous treatment with hyaluronic acid. Joint pain greater than or equal to 2.5 points on the VAS scale, and with radiological classification greater than or equal to 2 on the Kellgren-Lawrence scale.

Period 1

| | |
|------------------------------|--|
| Period 1 title | Treatment and follow-up (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Grupo I |

Arm description:

This group receives 3 infiltrations of 8ml (one per week) of plasma rich in growth factors (PRGF).

| | |
|--|-------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | PRGF |
| Investigational medicinal product code | |
| Other name | Plasma rich in growth factors |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intraarticular use |

Dosage and administration details:

Three doses of 8ml of PRGF are administered intra-articularly, once a week.

| | |
|------------------|----------|
| Arm title | Group II |
|------------------|----------|

Arm description:

Patients are administered by three doses of plasma rich in growth factors (PRGF) and one dose of Mesenchymal Stem Cells (MSC). MSC injection is performed on the first day of treatment, followed by the first PRGF injection. The next two PRGF injections are performed at week 2 and week 3.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Autologous mesenchymal stem cells from bone marrow cultivated ex - vivo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intraarticular use |

Dosage and administration details:

A single dose of 100 million units is administered intra-articularly on the first day of treatment. PRGF shall be administered after the administration of the cells, using the same intrarticular route.

| Number of subjects in period 1 | Grupo I | Group II |
|---------------------------------------|---------|----------|
| Started | 30 | 30 |
| Completed | 26 | 24 |
| Not completed | 4 | 6 |
| Consent withdrawn by subject | - | 1 |
| Physician decision | - | 1 |
| do not like the assigned group | 2 | - |
| Lost to follow-up | 2 | 4 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | Treatment and follow-up |
|-----------------------|-------------------------|

Reporting group description: -

| Reporting group values | Treatment and follow-up | Total | |
|---------------------------------------|-------------------------|-------|--|
| Number of subjects | 60 | 60 | |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 48 | 48 | |
| From 65-84 years | 12 | 12 | |
| Gender categorical Units: Subjects | | | |
| Female | 20 | 20 | |
| Male | 40 | 40 | |

End points

End points reporting groups

| | |
|---|----------|
| Reporting group title | Grupo I |
| Reporting group description: | |
| This group receives 3 infiltrations of 8ml (one per week) of plasma rich in growth factors (PRGF). | |
| Reporting group title | Group II |
| Reporting group description: | |
| Patients are administered by three doses of plasma rich in growth factors (PRGF) and one dose of Mesenchymal Stem Cells (MSC). MSC injection is performed on the first day of treatment, followed by the first PRGF injection. The next two PRGF injections are performed at week 2 and week 3. | |

Primary: Improvement in the rates of clinical and functional assessment

| | |
|---|--|
| End point title | Improvement in the rates of clinical and functional assessment |
| End point description: | |
| Improvements in Clinical and Functional Assessment Indices will be evaluated to determine the effectiveness of treatments. The VAS, WOMAC, Lanesque, Euroqol 5D and mobility range scales are used. The most important clinical scales evaluated are the VAS and the WOMAC. On the VAS scale, the evolution of pain showed no statistically significant differences between the two groups. According to the results of the WOMAC scale, there is a clinical improvement in both groups, with a greater improvement in Group II (37.3%) than in Group I (23.4%), but there are no significant differences between the two groups either. There were no notable differences between the two groups in the Lanesque scale, Euroqol 5D and mobility range. | |
| End point type | Primary |
| End point timeframe: | |
| Evaluation at a week and in 1, 3 and 6 months. | |

| End point values | Grupo I | Group II | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 24 | | |
| Units: NA | | | | |
| arithmetic mean (standard deviation) | | | | |
| EVA Baseline | 5 (\pm 1.8) | 5.3 (\pm 1.9) | | |
| EVA 3 months | 3.8 (\pm 1.6) | 3.8 (\pm 2) | | |
| EVA 6 months | 3.5 (\pm 2) | 3.3 (\pm 2.2) | | |
| EVA 12 months | 4.5 (\pm 2.2) | 3.5 (\pm 2.5) | | |
| WOMAC Baseline | 31.9 (\pm 16.2) | 33.4 (\pm 18.7) | | |
| WOMAC 3 months | 21.7 (\pm 17.1) | 24.4 (\pm 17.4) | | |
| WOMAC 6 months | 23 (\pm 15) | 21.3 (\pm 16.6) | | |
| WOMAC 12 months | 22.3 (\pm 15.8) | 23.0 (\pm 16.6) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Sum of ranks Wilcoxon (U de Mann-Whitney). |
| Comparison groups | Grupo I v Group II |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 50 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Wilcoxon (Mann-Whitney) |

Primary: Radiographic Evaluation

| | |
|-----------------|-------------------------|
| End point title | Radiographic Evaluation |
|-----------------|-------------------------|

End point description:

Radiographic evaluation is performed to determine the effectiveness of the treatment. A knee X-ray is performed to classify the degree of osteoarthritis and an assessment of the joint interlining, before treatment and at 12 months. Analysis of the interline on radiography showed no clinical change. Magnetic resonance imaging is also performed following the WOMS protocol before treatment and at 12 months. MRI analysis showed no significant change during follow-up.

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

End point timeframe:

Before treatment and in 6 months.

| End point values | Grupo I | Group II | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 24 | | |
| Units: mm | | | | |
| arithmetic mean (standard deviation) | | | | |
| WORMS Baseline | 73.8 (± 30.9) | 74.4 (± 28) | | |
| WORMS 12 months | 77.4 (± 31.5) | 79.8 (± 29.1) | | |

Statistical analyses

| | |
|---|---------------------------|
| Statistical analysis title | Comparison between groups |
| Comparison groups | Grupo I v Group II |
| Number of subjects included in analysis | 50 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | ≤ 0.05 |
| Method | Wilcoxon (Mann-Whitney) |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs will be collected from the time the patient receives the first dose of the investigational drug until the end of the patient's follow-up. The maximum period for notification of suspected RAGI will be 15 days from the time the promoter become aware.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|----|
| Dictionary name | ND |
| Dictionary version | ND |

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | All the patients |
|-----------------------|------------------|

Reporting group description: -

| | | | |
|---|------------------|--|--|
| Serious adverse events | All the patients | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 60 (5.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | | | |
| Social circumstances | | | |
| disorientation | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Ovarian cystectomy and endometrial ablation | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| Non-serious adverse events | All the patients | | |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 12 / 60 (20.00%) | | |
| Vascular disorders | | | |
| Venous thrombosis superficial | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences (all) | 1 | | |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Cluster headache | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration site conditions | | | |
| Shoulder pain | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences (all) | 1 | | |
| Left knee pain | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences (all) | 1 | | |
| Pain at the point of extraction of bone marrow | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences (all) | 1 | | |
| Eye disorders | | | |
| Blepharoplasty | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences (all) | 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| cold | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences (all) | 1 | | |
| Skin and subcutaneous tissue disorders | | | |
| Removal of benign neck cyst | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences (all) | 1 | | |

| | | | |
|---|--|--|--|
| <p>Musculoskeletal and connective tissue disorders</p> <p>Ruptured extensor ligament of the 4th finger of the right hand</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>1 / 60 (1.67%)</p> <p>1</p> <p>Monoarthritis of the left knee</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>1 / 60 (1.67%)</p> <p>1</p> <p>Joint inflammation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>1 / 60 (1.67%)</p> <p>1</p> | | | |
| <p>Infections and infestations</p> <p>pharyngitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>1 / 60 (1.67%)</p> <p>1</p> <p>Flu</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>1 / 60 (1.67%)</p> <p>1</p> | | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|------------------------------|
| 06 June 2013 | New version of protocol (v5) |
| 05 September 2013 | New version of protocol (v6) |
| 20 December 2013 | New version of protocol (v7) |
| 03 July 2015 | New version of protocol (v8) |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported