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 f 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 he 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 Mesenquimal 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
Physician decision	-	1
Consent withdrawn by subject	-	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 Mesenquimal 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 (± 1.8)	5.3 (± 1.9)		
EVA 3 months	3.8 (± 1.6)	3.8 (± 2)		
EVA 6 months	3.5 (± 2)	3.3 (± 2.2)		
EVA 12 months	4.5 (± 2.2)	3.5 (± 2.5)		
WOMAC Baseline	31.9 (± 16.2)	33.4 (± 18.7)		
WOMAC 3 months	21.7 (± 17.1)	24.4 (± 17.4)		
WOMAC 6 months	23 (± 15)	21.3 (± 16.6)		
WOMAC 12 months	22.3 (± 15.8)	23.0 (± 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 WORMS 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		

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

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 occurrences (all)	1 / 60 (1.67%) 1		
Haemorrhoids subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Nervous system disorders Cluster headache subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
General disorders and administration site conditions Shoulder pain subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Left knee pain subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Pain at the point of extraction of bone marrow subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Eye disorders Blepharoplasty subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Respiratory, thoracic and mediastinal disorders cold subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Skin and subcutaneous tissue disorders Removal of benign neck cyst subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		

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

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