Clinical trial results:
Clinical trial phase I/II multicentric, open, randomized and controlled for the study of stem cells as therapy critical ischemia in low limbs in insulinized type 2 diabetic patients: study of the insulin

Summary

EudraCT number	2010-019774-33
Trial protocol	ES
Global end of trial date	30 April 2015

Results information

Result version number	v1 (current)
This version publication date	09 April 2021
First version publication date	09 April 2021
Summary attachment (see zip file)	Clinical Report (SINOPSIS Informe Clínico_.pdf)

Trial information

Trial identification

Sponsor protocol code	CeTMMoTa/ICPDI/2010

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Red Andaluza de Diseño y Traslación en Terapias Avanzadas (former Iniciativa Andaluza en Terapias Avanzadas) – Fundación Progreso y Salud
Sponsor organisation address	Avda. Américo Vespucio 15 · Edificio S-2 ·2ª Pta., Sevilla, Spain,
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Scientific contact	Rosario Carmen Mata Alcázar-Caballero, Red Andaluza de Diseño y Traslación en Terapias Avanzadas – Fundación Progreso y Salud, +34 955 048 366, terapias.avanzadas@juntadeandalucia.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 November 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 April 2015
Global end of trial reached?	Yes
Global end of trial date	30 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To study the effect of the infusion intrarterial of mononuclear cells of bony marrow, cells CD133 + and cells mesenquimales of adipose tissue, on the inflammatory citoquinas, the resistance to the insulin and the decrease of the needs of this one, beside to evaluate the safety, viability and efficiency of the intra-arterial injection of cells in diabetic patients type 2. The aims of the study gather in efficiency and safety.
- Safety: there will be evaluated the possible complications derived from the procedure in the first 24 hours after the administration of stem cells.
- Efficiency: quantification of the degree of neovascularizacion (angio/arteriogenesis and vasculogenesis) to 6 months of the administration

Protection of trial subjects:

The trial has been carried out in accordance with the recommendations for Clinical Trials and the evaluation of the product under investigation in humans, which appear in the Declaration of Helsinki, revised in successive world assemblies (WMA, 2008), and the current Spanish Legislation on Clinical Trials. In addition, the ICH-GPC standards have been followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 September 2011
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: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	9
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Type 2 diabetic, on insulin treatment for at least 3 previous months.
Severe grade atherosclerotic infrapopliteal vascular disease (patients with Rutherford-Becker category ≥4), mono or bilateral.
Impossibility of surgical or endovascular revascularization or failure of revascularization surgery.
Life expectancy> 2 year.

Pre-assignment

Screening details:

The predicted population was 48 clinically evaluable diabetic patients with critical chronic ischemia of at least one lower limb and no possibility of revascularization. Finally, it was not possible to reach the predicted "n", including 20 patients who were randomized to the 4 predicted groups.

Period 1

Period 1 title	Recruitment and follow-up
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A

Arm description:

Expanded autologous adipose tissue adult mesenchymal stem cells

Arm type	Experimental
Investigational medicinal product name	Expanded autologous adipose tissue adult mesenchymal stem cells
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

0.5x10E6 cells/kg

Arm title	Group B

Arm description:

CD133 + Unexpanded Autologous Bone Marrow Adult Mononuclear Stem Cells

Arm type	Experimental
Investigational medicinal product name	CD133 + Unexpanded Autologous Bone Marrow Adult Mononuclear Stem Cells
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

2-7 x10E6 CD133+ cells

Arm title	Group C

Arm description:

Unexpanded autologous bone marrow adult mononuclear stem cells

Arm type	Experimental

Investigational medicinal product name	Unexpanded autologous bone marrow adult mononuclear stem cells
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: 150-250 x 10E6 cells	
Arm title	Group D
Arm description: Conventional treatment	
Arm type	Standard of care
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Group A	Group B	Group C
Started	8	6	3
Completed	8	6	3

Number of subjects in period 1	Group D
Started	3
Completed	3

Period 2	
Period 2 title	Data analysis
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes
Arm title	Group A
Arm description: Expanded autologous adipose tissue adult mesenchymal stem cells	
Arm type	Experimental
Investigational medicinal product name	Expanded autologous adipose tissue adult mesenchymal stem cells
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: 0.5x10E6 cells/kg	

Arm title	Group B
Arm description: CD133 + Unexpanded Autologous Bone Marrow Adult Mononuclear Stem Cells	
Arm type	Experimental
Investigational medicinal product name	CD133 + Unexpanded Autologous Bone Marrow Adult Mononuclear Stem Cells
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: 2-7 x10E6 CD133+ cells	
Arm title	Group C
Arm description: Unexpanded autologous bone marrow adult mononuclear stem cells	
Arm type	Experimental
Investigational medicinal product name	Unexpanded autologous bone marrow adult mononuclear stem cells
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: 150-250 x 10E6 cells	
Arm title	Group D
Arm description: Conventional treatment	
Arm type	Standard of care
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	Group A	Group B	Group C
Started	8	6	3
Completed	8	6	3

Number of subjects in period 2	Group D
Started	3
Completed	3

Baseline characteristics

Reporting groups	
Reporting group title	Group A
Reporting group description:	
Expanded autologous adipose tissue adult mesenchymal stem cells	
Reporting group title	Group B
Reporting group description:	
CD133 + Unexpanded Autologous Bone Marrow Adult Mononuclear Stem Cells	
Reporting group title	Group C
Reporting group description:	
Unexpanded autologous bone marrow adult mononuclear stem cells	
Reporting group title	Group D
Reporting group description:	
Conventional treatment	

Reporting group values	Group A	Group B	Group C
Number of subjects	8	6	3
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
median	64.5	61.5	73
full range (min-max)	45 to 77	49 to 73	70 to 77
Gender categorical Units: Subjects			
Female	2	2	1
Male	6	4	2
Cardiovascular disease Units: Subjects			
Yes	8	6	3
No	0	0	0

Reporting group values	Group D	Total	
Number of subjects	3	20	
Age categorical Units: Subjects			
In utero		0	

Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
median	78		
full range (min-max)	63 to 79	-	
Gender categorical			
Units: Subjects			
Female	1	6	
Male	2	14	
Cardiovascular disease			
Units: Subjects			
Yes	3	20	
No	0	0	

End points

End points reporting groups

Reporting group title	Group A
Reporting group description: Expanded autologous adipose tissue adult mesenchymal stem cells	
Reporting group title	Group B
Reporting group description: CD133 + Unexpanded Autologous Bone Marrow Adult Mononuclear Stem Cells	
Reporting group title	Group C
Reporting group description: Unexpanded autologous bone marrow adult mononuclear stem cells	
Reporting group title	Group D
Reporting group description: Conventional treatment	
Reporting group title	Group A
Reporting group description: Expanded autologous adipose tissue adult mesenchymal stem cells	
Reporting group title	Group B
Reporting group description: CD133 + Unexpanded Autologous Bone Marrow Adult Mononuclear Stem Cells	
Reporting group title	Group C
Reporting group description: Unexpanded autologous bone marrow adult mononuclear stem cells	
Reporting group title	Group D
Reporting group description: Conventional treatment	

Primary: Degree of neovascularization (Total tube area)

End point title	Degree of neovascularization (Total tube area)[1][2]
End point description:	
End point type	Primary
End point timeframe: During the study	

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: No statistical analyses for this end point

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analyses for this end point

End point values	Group A	Group B	Group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	6	3	
Units: TTA				
arithmetic mean (full range (min-max))				
Infusion	9384.58 (8052.76 to 10716.40)	7626.42 (6412.81 to 8840.03)	10143.88 (9782.32 to 10505.43)	
6th month	8304.88 (7202.91 to 9406.85)	8557.63 (7616.74 to 9498.51)	10394.50 (9770.25 to 11018.76)	

Statistical analyses

No statistical analyses for this end point

Primary: Degree of neovascularization (branching points)

End point title	Degree of neovascularization (branching points)[3][4]

End point description:

End point type	Primary

End point timeframe:

During the study

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: No statistical analyses for this end point

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analyses for this end point

End point values	Group A	Group B	Group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	6	3	
Units: Branching points (BP)				
arithmetic mean (full range (min-max))				
Infusion	13.67 (8.62 to 18.71)	8.08 (4.00 to 12.16)	28.75 (26.00 to 31.50)	
6th month	10.50 (6.21 to 14.79)	14.13 (10.72 to 17.53)	14.75 (11.15 to 18.36)	

Statistical analyses

No statistical analyses for this end point

Primary: Degree of neovascularization (Segments)

End point title	Degree of neovascularization (Segments)[5][6]

End point description:

End point type	Primary

End point timeframe:

During the study

Notes:

[5] - 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: No statistical analyses for this end point

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analyses for this end point

End point values	Group A	Group B	Group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	6	3	
Units: Segments (S)				
arithmetic mean (full range (min-max))				
Infusion	238.00 (183.5 to 292.5)	176.67 (132.15 to 221.18)	375.88 (347.96 to 403.80)	
6th month	185.00 (144.73 to 225.28)	235.88 (191.80 to 279.95)	264.63 (230.12 to 299.14)	

Statistical analyses

No statistical analyses for this end point

Primary: Degree of neovascularization (Total tube length)

End point title	Degree of neovascularization (Total tube length)[7][8]

End point description:

End point type	Primary

End point timeframe:

During the study

Notes:

[7] - 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: No statistical analyses for this end point

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analyses for this end point

End point values	Group A	Group B	Group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	6	3	
Units: Total tube length (TTL)				
arithmetic mean (full range (min-max))				
Infusion	1953.40 (1586.74 to 2320.06)	2090.92 (1775.40 to 2406.44)	2602.69 (2492.12 to 2713.26)	

6th motnh	2248.28 (1966.72 to 2529.84)	2382.89 (2124.87 to 2640.90)	2914.51 (2744.72 to 3084.30)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the inclusion of the first patient to the last visit of the last patient.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	NA

Reporting groups

Reporting group title	All groups

Reporting group description: -

Serious adverse events	All groups		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 19 (42.11%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Post procedural complication	Additional description: Admission to ICU after torpid evolution after multinodular goiter surgery		
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Ischaemia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Stroke			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute coronary syndrome			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Progressive dyspnea			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Right foot abscess			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	All groups		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 19 (57.89%)		
Injury, poisoning and procedural complications			
Non-drug-eluting stent implantation in a vessel			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Cardiac disorders			

Hypotensive episodes			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Nervous system disorders			
Right sciatica			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Increased leukocytes, neutrophils, and ESR			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Refers moderate pain in lower limbs			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Pain in both legs and fatigue from being fasting			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Joint pain in the left ankle			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Heaviness in lower limbs			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Occasional pain in right lower limb			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Pain in lower limbs	Additional description: Pain in the 4th finger of lower left limb, edema, occasional cramps and stitches at rest		
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Infections and infestations			
Flu			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 August 2011	• Update on the procedure for obtaining bone marrow cells, both mononucleated and CD133: • Inclusion of a clinical test in the protocol. The use of Optical Coherence Tomography (OCT) is incorporated in 3 visits for better monitoring of the general condition of the patient.
01 April 2014	The difficulties of inclusion of patients and development of the trial led the promoter and research team to review the protocol and eliminate those tests from which the necessary information was not obtained to achieve the objectives of the trial. In addition, it was agreed to review the validity of the results of the tests (their expiration), to extend as much as possible the period allowed from their performance to the randomization of patients, thus avoiding deviations from the protocol. For all this, it was necessary to make a new amendment to the protocol This amendment represented a simplified version of the initial protocol, although it maintained the "n" of 48 patients initially expected.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Reported in the summary

Notes: