



Clinical trial results:

Ensayo clínico multicéntrico fase I/II aleatorizado y controlado, para la evaluación de seguridad y factibilidad de la terapia con dos dosis distintas de células madre mesenquimales procedentes de tejido adiposo en pacientes con la enfermedad injerto contra huésped crónica extensa.

Summary

EudraCT number	2008-004014-27
Trial protocol	ES
Global end of trial date	10 June 2014

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 (EICH CSR Versión 06Feb2018_final.pdf)

Trial information

Trial identification

Sponsor protocol code	CMM/EICH/2008
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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,
Public 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
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
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Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 February 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 June 2014
Global end of trial reached?	Yes
Global end of trial date	10 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To analyze the safety and feasibility of the infusion of two doses of expanded allogeneic mesenchymal stem cells (MSCs) "in vitro" in the treatment of patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) who have developed extensive chronic graft-versus-host disease (GVHD).

Protection of trial subjects:

The trial was carried out in accordance with the recommendations for Clinical Trials and product evaluation in the research phase that appear in the Declaration of Helsinki, revised in successive world assemblies (WMA, 2004), and the Spanish Legislation on Clinicals Trials who were applying at the time of the study (RD 223/2004). ICH-GCP standards (CPMP/ICH/135/95) were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2010
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: 19
Worldwide total number of subjects	19
EEA total number of subjects	19

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)	19
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

- a) They have never received chronic GVHD therapy.
- b) They have extensive chronic de novo GVHD (never had acute GVHD) or quiescent (they had acute GVHD that was resolved).

Pre-assignment

Screening details:

In this study, 20 patients were planned in the protocol, 19 were considered for selection and 17 were finally randomized. The 2 non-randomized patients were selection failures: one of the patients because they did not develop chronic GVHD and the other because they did not sign the informed consent.

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:

1x10E6/Kg de CMM

Arm type	Experimental
Investigational medicinal product name	1x10E6/Kg de CMM
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

1x10E6/Kg de CMM

Arm title	Group B
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Arm description:

3x10E6/Kg de CMM

Arm type	Experimental
Investigational medicinal product name	3x10E6/Kg de CMM
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

3x10E6/Kg de CMM

Number of subjects in period 1 ^[1]	Group A	Group B
Started	9	6
Completed	9	6

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The study sample was 20 patients. A total of 19 patients were selected, of which 17 patients were randomized: 2 to the control group, 9 to group A and 6 to group B. The analysis of the collected data was carried out of all the patients assigned to group A, and 5 patients from group B, since one patient could not be treated as there was no availability or possibility of a central line.

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:

1x10E6/Kg de CMM

Arm type	Experimental
Investigational medicinal product name	1x10E6/Kg de CMM
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

1x10E6/Kg de CMM

Arm title	Group B
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Arm description:

3x10E6/Kg de CMM

Arm type	Experimental
Investigational medicinal product name	3x10E6/Kg de CMM
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

3x10E6/Kg de CMM

Number of subjects in period 2	Group A	Group B
Started	9	6
Completed	9	6

Baseline characteristics

Reporting groups

Reporting group title	Group A
Reporting group description: 1x10E6/Kg de CMM	
Reporting group title	Group B
Reporting group description: 3x10E6/Kg de CMM	

Reporting group values	Group A	Group B	Total
Number of subjects	9	6	15
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	9	6	15
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
median	54	44.00	
standard deviation	± 10.85	± 7.92	-
Gender categorical Units: Subjects			
Female	6	2	8
Male	3	4	7
Wiegth Units: Kg			
median	69	79.95	
standard deviation	± 12.93	± 22.84	-
Temperature Units: °C			
median	36.40	36.25	
standard deviation	± 0.87	± 0.28	-
PAS Units: mmHg			
median	120	111	
standard deviation	± 14.97	± 16.79	-
PAD Units: mmHg			
median	71	67	
standard deviation	± 11.63	± 12.97	-

End points

End points reporting groups

Reporting group title	Group A
Reporting group description: 1x10E6/Kg de CMM	
Reporting group title	Group B
Reporting group description: 3x10E6/Kg de CMM	
Reporting group title	Group A
Reporting group description: 1x10E6/Kg de CMM	
Reporting group title	Group B
Reporting group description: 3x10E6/Kg de CMM	

Primary: % SC

End point title	% SC ^[1]
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: The information regarding the statistical analysis is included in the attached clinical report.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	5		
Units: % SC				
median (standard deviation)	47.75 (± 39.04)	52 (± 2.83)		

Statistical analyses

No statistical analyses for this end point

Primary: Test Schirmer (OD)

End point title	Test Schirmer (OD) ^[2]
End point description:	
End point type	Primary
End point timeframe: During the study	

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: The information regarding the statistical analysis is included in the attached clinical report.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	5		
Units: Test Schirmer (OD)				
median (standard deviation)	7.33 ($\pm$ 6.66)	12.50 ($\pm$ 12.37)		

Statistical analyses

No statistical analyses for this end point

Primary: Test Schirmer (OI)

End point title	Test Schirmer (OI) ^[3]
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End point description:

End point type	Primary
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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: The information regarding the statistical analysis is included in the attached clinical report.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	6		
Units: Test Schirmer (OI)				
arithmetic mean (standard deviation)	7.33 ($\pm$ 6.43)	14.25 ($\pm$ 8.30)		

Statistical analyses

No statistical analyses for this end point

Primary: Leukocytes

End point title	Leukocytes ^[4]
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End point description:

End point type	Primary
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End point timeframe:

During the study

Notes:

[4] - 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: The information regarding the statistical analysis is included in the attached clinical report.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	5		
Units: x10 ⁹ /l				
arithmetic mean (standard deviation)	6.13 (± 1.93)	5.35 (± 1.53)		

Statistical analyses

No statistical analyses for this end point

Primary: Eosinophils

End point title	Eosinophils ^[5]
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End point description:

End point type	Primary
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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: The information regarding the statistical analysis is included in the attached clinical report.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	5		
Units: x10E9/l				
arithmetic mean (standard deviation)	0.56 (± 0.71)	0.63 (± 0.45)		

Statistical analyses

No statistical analyses for this end point

Primary: ECOG

End point title	ECOG ^[6]
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End point description:

End point type	Primary
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End point timeframe:

During the study

Notes:

[6] - 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: The information regarding the statistical analysis is included in the attached clinical report.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	6		
Units: Units				
ECOG 0	2	1		
ECOG 1	3	5		
ECOG 2	4	0		
ECOG 3	0	0		
ECOG 4	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

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

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	NA
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Reporting groups

Reporting group title	All groups
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Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Both AE and SAE are collected and classified by SOC and PT in the attached clinical report.

Serious adverse events	All groups		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Itching in the face and lower limbs up to the knee. Feeling of poise and dizziness	Additional description: Itching in the face and lower limbs up to the knee. Feeling of poise and dizziness		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Thrombosis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Clostridium difficile infection			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Flu A			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cytomegalovirus infection reactivation			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rotavirus infection			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperglucagonaemia			
subjects affected / exposed	1 / 10 (10.00%)		
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	0 / 10 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 December 2008	Extension of the recruitment period. Recruitment was slower than initially estimated, due to the pathology itself and the difficulty in recruiting patients who meet all the selection criteria. Initially, an inclusion period of 12 to 24 months was estimated, but since the desired sample size was not reached, it was decided to extend the recruitment period to 36 months.
06 April 2010	Control branch removal. The recruitment rate was much lower than expected, despite having used various strategies to activate it. In order to speed up the completion of the clinical trial and to be able to analyze the primary safety and feasibility objective of allogeneic mesenchymal stem cell (MSC) infusion, it was decided to eliminate the control branch, since it was a phase I-II trial the existence of a control group is not necessary.
25 October 2010	Modification of donor selection. The difficulty in the availability of adipose tissue from living donors, together with the start-up of the Biobank of the Andalusian Public System, led to the inclusion as a source of adipose tissue to multi-organ donors, through the consent granted by relatives for the use of Research samples, extracted in any case secondary to extraction for transplantation.
22 March 2011	Update of the test diagram. To clarify the instructions regarding the biological study, extraction and delivery of the sample, which must be carried out to the patient at the baseline visits, week 7, week 20, 42nd week and 56th week, the following text was entered in Appendix F Study follow-up: "Se extraerá una muestra de sangre venosa, de 5cc como mínimo, de forma aséptica por punción venosa en tubo con anticoagulante EDTA (tubo de hemograma) y otra de 5cc en tubo con activador del coágulo para suero (tubo de bioquímica). La muestra de sangre se debe conservar a 4 °C hasta su procesamiento. Se enviará la muestra de sangre el mismo día de la extracción (antes de las 10h. del día siguiente) al departamento de Hematología del Hospital U. Virgen de las Nieves."
14 October 2011	Clarifications to the protocol and to the HIP, after the inclusion of Hospital Meseguer in the trial.
31 January 2012	Modification No. 6 refers to the information sheet for the patient and informed consent.
03 July 2012	Protocol amendment

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/28662983>