# 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 |

**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 |

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 chronicle 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 |

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 Aand 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 |

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:<br>1x10E6/Kg de CMM | |
| Reporting group title | Group B |
| Reporting group description:<br>3x10E6/Kg de CMM | |

| Reporting group values | Group A | Group B | Total |
|---|---|---|---|
| Number of subjects | 9 | 6 | 15 |
| Age categorical<br>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<br>Units: years | | | |
| median | 54 | 44.00 | |
| standard deviation | ± 10.85 | ± 7.92 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 6 | 2 | 8 |
| Male | 3 | 4 | 7 |
| Wieght<br>Units: Kg | | | |
| median | 69 | 79.95 | |
| standard deviation | ± 12.93 | ± 22.84 | - |
| Temperature<br>Units: ºC | | | |
| median | 36.40 | 36.25 | |
| standard deviation | ± 0.87 | ± 0.28 | - |
| PAS<br>Units: mmHg | | | |
| median | 120 | 111 | |
| standard deviation | ± 14.97 | ± 16.79 | - |
| PAD<br>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 (± 6.66) | 12.50 (± 12.37) | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Test Schirmer (OI)

| End point title | Test Schirmer (OI)[3] |
|---|---|

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: 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 (± 6.43) | 14.25 (± 8.30) | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Leukocytes

| End point title | Leukocytes[4] |
|---|---|

End point description:

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

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: x109/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] |
|---|---|

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: 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] |
|---|---|

End point description:

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

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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | NA |

### Reporting groups

| | |
|---|---|
| Reporting group title | All groups |

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.<br>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.<br>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.<br>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.<br>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,<br>42nd week and 56th week, the following text was entered in Appendix F Study follow-up:<br>"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.<br>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