



## 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,                                                                                                                    |
| 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                       | 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 neovascularization (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  $\geq 4$ ), 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     |
| <b>Arm title</b>             | 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

|                  |         |
|------------------|---------|
| <b>Arm title</b> | 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

|                  |         |
|------------------|---------|
| <b>Arm title</b> | 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:<br>150-250 x 10E6 cells |                                                                |
| <b>Arm title</b>                                           | Group D                                                        |
| Arm description:<br>Conventional treatment                 |                                                                |
| Arm type                                                   | Standard of care                                               |
| No investigational medicinal product assigned in this arm  |                                                                |

| <b>Number of subjects in period 1</b> | Group A | Group B | Group C |
|---------------------------------------|---------|---------|---------|
| Started                               | 8       | 6       | 3       |
| Completed                             | 8       | 6       | 3       |

| <b>Number of subjects in period 1</b> | 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                                                             |
| <b>Arm title</b>                                                                    | Group A                                                         |
| Arm description:<br>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:<br>0.5x10E6 cells/kg                             |                                                                 |

|                                                                                            |                                                                        |
|--------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| <b>Arm title</b>                                                                           | Group B                                                                |
| Arm description:<br>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:<br>2-7 x10E6 CD133+ cells                               |                                                                        |
| <b>Arm title</b>                                                                           | Group C                                                                |
| Arm description:<br>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:<br>150-250 x 10E6 cells                                 |                                                                        |
| <b>Arm title</b>                                                                           | Group D                                                                |
| Arm description:<br>Conventional treatment                                                 |                                                                        |
| Arm type                                                                                   | Standard of care                                                       |
| No investigational medicinal product assigned in this arm                                  |                                                                        |

| <b>Number of subjects in period 2</b> | Group A | Group B | Group C |
|---------------------------------------|---------|---------|---------|
| Started                               | 8       | 6       | 3       |
| Completed                             | 8       | 6       | 3       |

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

| Reporting group values             | Group D | Total |  |
|------------------------------------|---------|-------|--|
| Number of subjects                 | 3       | 20    |  |
| Age categorical<br>Units: Subjects |         |       |  |
| In utero                           |         | 0     |  |

|                                                       |          |    |  |
|-------------------------------------------------------|----------|----|--|
| Preterm newborn infants<br>(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) <sup>[1][2]</sup> |
| 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<br>(8052.76 to 10716.40) | 7626.42<br>(6412.81 to 8840.03) | 10143.88<br>(9782.32 to 10505.43) |  |
| 6th month                              | 8304.88<br>(7202.91 to 9406.85)  | 8557.63<br>(7616.74 to 9498.51) | 10394.50<br>(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) <sup>[3][4]</sup> |
|-----------------|-------------------------------------------------------------------|

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) <sup>[5][6]</sup> |
|-----------------|-----------------------------------------------------------|

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) <sup>[7][8]</sup> |
|-----------------|--------------------------------------------------------------------|

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<br>(1966.72 to<br>2529.84) | 2382.89<br>(2124.87 to<br>2640.90) | 2914.51<br>(2744.72 to<br>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 %

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





## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date           | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 15 August 2011 | <ul style="list-style-type: none"><li>• Update on the procedure for obtaining bone marrow cells, both mononucleated and CD133:</li><li>• 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.</li></ul>                                                                                                                                                                                                                                                                                                                                                                                           |
| 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: