Junta de Andalucía
Consejería de Salud y Consumo
Fundación Progreso y Salud

red andaluza
de diseño y traslación de
terapias avanzadas

CLINICAL TRIAL SYNOPSIS

CMMo-ICC-2009

Multi-Center, Open and Randomized Phase II Clinical Trial on the Therapeutic Use of Intra-Arterial Infusion of Autologous Bone Marrow Mononuclear Cells in Non-Diabetic Patients with Chronic Critical Nonrevascularizable Ischemia of the Lowe Limbs

Sponsor: Fundación Progreso y Salud M.P.- Red Andaluza de Diseño y Traslación de Terapias Avanzadas

Version 15 December 2022

Name of Sponsor/Company: Fundación Progreso y Salud M.P.- Red Andaluza de Diseño y Traslación de Terapias Avanzadas
Name of finished product: BM-MNC
Name of active ingredient: Autologous bone marrow mononuclear cells
Title: Multi-Center, Open and Randomized Phase II Clinical Trial on the Therapeutic Use of Intra-Arterial Infusion of Autologous Bone Marrow Mononuclear Cells in Non-Diabetic Patients with Chronic Critical Nonrevascularizable Ischemia of the Lowe Limbs
Protocol code: CMMo/ICC/2009
EudraCT No.: 2009-013636-20
Investigators: *A complete list of investigators is provided in the Appendix of this CSR.*
Investigational sites: This study was conducted at five investigational sites in Spain that randomized patients: • Reina Sofía University Hospital, 14004 Cordova • Virgen del Rocío University Hospital, 41013 Seville • Morales Meseguer General University Hospital, 30008 Murcia • San Cecilio University Hospital, 18012 Granada • Ciudad Sanitaria Virgen de la Arrixaca, 30008 Murcia
Study period: First patient enrolled: 01 July 2009 Last patient completed: 29 Sep 2011 — **Phase of development:** Phase II
Objectives: The main objective was to evaluate the safety and feasibility of autologous bone marrow mononuclear cell self-transplantation, administered intra-arterially in non-diabetic patients with chronic critical lower limb ischemia without the possibility of revascularization or other therapeutic alternatives.

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Methodology: This study was stopped prematurely due to lack of financial support. This was an early phase, prospective, multicentre, open-label, randomized, parallel-group trial using three dose levels of autologous bone marrow mononuclear cells and standard of care treatment as comparator. The study population consisted of non-diabetic patients with critical chronic ischemia of at least one lower limb and without possibilities of revascularization. Eligible patients were randomly assigned in a 1:1:1:1 ratio to one of the three experimental groups receiving either $1x10^8$ BM-MNCs, $5x10^8$ BM-MNCs, or $1x10^9$ BM-MNCs, or to the control group receiving standard of care treatment only. Randomization of patients was stratified by their functional stage group (Rutherford-Becker grade II-III) at the screening visit to achieve homogeneous distribution of grade II and grade III patients among treatment groups. At baseline visit, bone marrow was extracted from the patient's iliac crest from which the BM-MNCs were isolated at a local laboratory. According to his/her treatment group, the respective number of BM-MNCs was injected into the popliteal artery of the patient's more severely affected limb. Patients of the control group received standard of care treatment throughout the study, they did not undergo bone marrow extraction at the baseline visit. Patients were followed-up for 12 months with visits at 1 day, 1 month, 3 months, 6 months, 9 months, and 12 months after the baseline visit.

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Number of patients: Planned Overall, 37 subjects were randomized: • Group 1: Control group: 9 patients • Group 2: Treatment group $1x10^8$ BM-MNCs: 6 patients • Group 3: Treatment group $5x10^8$ BM-MNCs: 14 patients • Group 4: Treatment group $1x10^9$ BM-MNCs: 8 patients
Diagnosis and main criteria for inclusion: Main inclusion criteria • Patients of both sexes ranging from ≥ 18 to ≤ 80 years. • Non-diabetic • Severe grade atherosclerotic infrapopliteal vascular disease (Rutherford-Becker class II-III), of at least one lower limb. Critical foot ischemia was defined as a persistent/recurrent pain requiring analgesia and/or non-healing ulcers persisting for more than 4 weeks, with no evidence of improvement with conventional therapies and/or walking test between 1-6 minutes in two ergometries separated by at least 2 weeks and/or a <0.8 resting ankle brachial index. • Impossibility of surgical or endovascular revascularization according to TASC recommendations. • Life expectancy > 2 years. • No major amputation was foreseen in the limb to be treated in the next 12 months after inclusion. • Normal biochemical parameters, defined by: ○ White blood cells ≥ 3000 / µl ○ Neutrophils ≥ 1500 / µl

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○ Platelets ≥ 100000 / µl ○ AST / ALT ≤ 2.5 Laboratory Reference Range Value ○ Creatinine ≤ 2.5 mg/dl <u>Main exclusion criteria</u> • History of neoplasia or haematological disease (myeloproliferative disease, myelodysplastic syndrome or leukaemia) • Patients with uncontrolled hypertension (defined as blood pressure > 180/110 on more than one occasion). • Severe cardiac insufficiency (NYHA IV). • Patients with malignant ventricular arrhythmias or unstable angina. • Diagnosis of deep vein thrombosis in the previous 3 months. • Active infection or wet gangrene on the day of BM-MNCs infusion. • Concomitant therapy including hyperbaric oxygen, vasoactive substances, anti-angiogenesis agents or cyclooxygenase-2 inhibitors. • Body mass index > 40 kg/m^2. • Proliferative retinopathy. • Concomitant disease reducing life expectancy to less than one year. • HIV infection, Hepatitis B or Hepatitis C. • Heart failure or ejection fraction < 30%. • Stroke or myocardial infarction in the last 3 months. • Anaemia (Haemoglobin < 10 mg/dl).
Test product, dose and mode of administration, batch number: Autologous BM-MNCs were individually prepared for each patient by aspiration of bone marrow from the iliac crest and isolation of mononuclear cells by density gradient centrifugation, without modification or addition of any product that impaired their

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biological functionality. The final product was injected into the popliteal artery of the patient's more severely affected leg. Depending on the group a patient was randomized into, the patients were to receive the following cell counts: • $1x10^8$ BM-MNCs • $5x10^8$ BM-MNCs • $1x10^9$ BM-MNCs Batch numbers: Not applicable.
Duration of treatment: The investigational product was administered once at the baseline visit. The patients were followed-up over a period of 12 months.
Reference therapy, dose and mode of administration, batch number: The control group received standard treatment as established in the Trans-Atlantic Inter-Society Consensus (TASC) II Therapeutic Guidelines (Inter-Society Consensus for the Management of Peripheral Arterial Disease TASC II. Eur J Vasc Endovasc Surg Vol 33, Supplement 1, 2007) throughout the study.
Criteria for evaluation: The trial was not powered to show statistically significant differences between active treatment and standard of care but examined the development at different time-points over a 12-month period post-administration of BM-MNC of the following efficacy variables: Efficacy variables • Rutherford grade at baseline, 1 month, 3 months, 6 months, 9 months and 12 months • Number and size of ulcers at baseline, 1 month, 3 months, 6 months, 9 months and 12 months • Transcutaneous Oxygen Pressure ($TcPO_2$) at baseline, 1 month, 3 months, 6 months, 9 months and 12 months

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- Amputations at baseline, 1 month, 3 months, 6 months, 9 months and 12 months
- Ankle-brachial index (ABI) at baseline, 1 month, 3 months, 6 months, 9 months and 12 months
- Calf perimeter at baseline, 1 month, 3 months, 6 months, 9 months and 12 months
- Deaths at baseline, 1 month, 3 months, 6 months, 9 months and 12 months

Safety variables

- Number and percentage of patients with at least one following events:
  - Treatment Emerging Adverse Events (TEAEs)
  - Severe TEAEs
  - Serious TEAEs
  - TEAEs related to study treatment

The total number of events is presented according to treatment groups.

- Number and percentage of patients with at least one adverse event were presented by System Organ Class (SOC) and Preferred Term (PT) and according to treatment groups. Analyses are presented for:
- TEAEs
- Serious TEAEs

Statistical methods:

Populations

Efficacy analyses except for assessments of ulcers were done on the Intention to Treat (ITT) population that consisted of all randomized subjects. The safety population (SAF) included

all subjects of the control group and subjects where bone marrow collection was performed. Subjects were analysed according to the treatment they actually received.

Demographic and baseline data

Descriptive analysis was made for all demographic variables and baseline characteristics. Qualitative variables were tabulated as absolute and relative frequencies. Quantitative variables were tabulated as mean and standard deviation (SD), median, 1st and 3rd quartiles, minimum and maximum.

Efficacy evaluation

Quantitative variables were described using number of filled and missing data, mean (if relevant), standard deviation, median, 1st and 3rd quartiles, minimum and maximum. Qualitative variables were described using number of filled and missing data and, for each modality, the frequency and percentage. The time course of quantitative outcomes was estimated through Mixed Model Repeat Measures (MMRM). The model included treatment, visit, baseline value, treatment by visit interaction as fixed effects and patient as a random effect. The contrast between pooled doses and control at M12 was the main contrast of interest. If significant, further contrast M9 (then M6 then M3) was provided (according to a hierarchical procedure) in order to explore the time response of the effect. AR1 covariance matrix was used to model the within-patient error and the Kenward-Roger approximation was used to estimate the degrees of freedom. Comparison between groups for binary outcomes was estimated through a logistic regression adjusted on baseline value if relevant. To account for the magnitude of the change of Rutherford grade and ulcer size over the 12-month course of the study, i.e., factoring in the different impacts of a change from Grade III

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to I versus a change from Grade III to II, the response to treatment in the combined Active treatment group compared to the Control group (and if significant, also between the Control group and the three individual Active treatment groups) with a van Elteren Test using Rutherford grade at baseline as a stratification factor. Moreover, for exploratory purposes, a Cox proportional hazard model adjusted on the baseline Rutherford grade was used to demonstrate amputation-free-survival (AFS) up to Month 12. Finally, a stepwise regression model was utilized to identify potential covariates impacting response to treatment at month-12.

Missing data was imputed with the "best plausible outcome", as determined at the data review by an independent adjudication committee, in the most conservative manner where amputations and deaths were considered failures.

Safety analyses

The number and percentages of TEAEs, severe TEAEs, serious TEAEs and treatment-related TEAEs were calculated by treatment arm as were the numbers and percentages of patients experiencing at least one TEAE by category (overall, serious, severe, treatment-related). Numbers and percentages of TEAEs as well as numbers and percentages of patients experiencing TEAEs were calculated by SOC and PT (MedDRA version 12.1). Likewise, numbers and percentages of serious TEAEs as well as numbers and percentages of patients experiencing serious TEAEs were calculated by SOC and PT.

Summary

Efficacy results

30% in treated subject of Response in CLI Rutherford grade (decrease of grade from baseline) at 12 months versus 17% in control (NS). Note that 21 (57%) data are missing at month 12.

No major amputations occurred.

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Safety results • 27 overall TEAEs (2 from control and 25 from treatment) for 15 patients (1 control 14 treated subject) • 6 SAEs (0 from control): 1 Acute Myocardial Infarction, 1 Cardiac Arrest, 1 Infected Skin Ulcer, 1 Localized Infection • 1 SAEs related to study treatment in Experimental group 3 (Infected skin ulcer) • 5 AEs leading to death in treated subject
Conclusions: Large effects between active treatment and standard of care on the main efficacy parameters (change in Rutherford grade and ulcer healing) were demonstrated and no unexpected safety issues emerged during the study. Although limitations of this study include small size and lack of blinding and placebo treatment, the totality of data indicates that autologous cell therapy as performed in this study provides valuable clinical outcomes for patients with chronic limb-threatening ischemia (CLTI).
Date of final report: 16 December 2021

Signature of Trial Sponsor

Approved: Rosario Mata Alcázar-Caballero
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Signed: Gonzalo Balbontin Casillas
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