## INFORMATION SHEET AND INFORMED CONSENT FORM FOR THE PATIENT

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|---|---|
| **Study Title** | A multicenter, randomized, dose-seeking, parallel group, double-blind, placebo-controlled clinical trial to evaluate safety and efficacy of intramuscular administration of adipose-derived allogeneic mesenchymal stromal cells in diabetic patients with critical lower limb ischemia without possibility of revascularization. |
| **Study Identification** | Code: NOMA (No More Amputations)<br>EudraCT number: 2018-002653-29 |
| **Sponsor** | Health Research Foundation Jimenez Diaz University Hospital<br>Avda. Reyes Católicos nº2, 28040 Madrid, Spain |
| **Principal Investigator** | (to fill in the centre) |
| **Centre** | (to fill in the centre) |

### Introduction

The following information refers to the study you have been invited to participate in. The study has been approved by an FJD Ethics Committee and by the Spanish Agency for Medicines and Health Products, in accordance with current legislation, Royal Decree 1090/2015 of December 4 and European Regulation 536/2014 of April 16, which regulates clinical trials with drugs.

This information will help you decide whether or not to participate in the study. Please read this sheet carefully before making your decision or request that it be read to you and properly explained. The professional in charge of the study will discuss the

following information with you, but it is important that you ask for explanations of anything that is not clear to you. Take your time to decide whether or not you want to participate in the study. If you decide not to participate, this decision will not affect your future medical care.

**Voluntary participation**

We invite you to participate in this study because you have been diagnosed with an obstruction (known as Peripheral Artery Disease) of the blood supply in your legs as a complication of your diabetes, which is serious and has not responded or it is not possible to improve with the usual techniques to unclog the arteries (such as surgery or other non-surgical bypass techniques). If you agree to participate in the clinical trial, we will ask you to sign this informed consent to state that you understand the study and that you wish to participate. Your decision to participate is completely voluntary and you may withdraw your consent at any time, without having to give a reason or without it altering your future treatment and your legal rights.

**The purpose of the study**

Current medical treatment for Peripheral Arterial Disease basically consist of controlling vascular risk factors (such as diabetes itself, smoking, cholesterol, hypertension) and avoiding the formation of new clots or thrombi that worsen the obstruction. However, once the obstruction of the arteries in the legs is significant, these measures are not enough, and surgical treatment is needed (opening the vessel with different techniques to remove the thrombus or even replace the vessel). Still, many of these patients have to undergo surgery again, without solving their problem or improving their quality of life. If a patient fails to respond to all of these treatments, the affected leg, toe, or foot may need to be amputated.

In recent years, drugs are being developed that are included in what is known as "cell therapy", which consists of the use of living cells for different purposes. In this study, the "drug" to be used is known as allogeneic mesenchymal cells derived from adipose tissue, and it has been seen in previous studies that it can induce the formation of blood vessels in the affected leg. The mesenchymal cell is a type of stem cell, that is, a cell that is potentially capable of generating another cell like it and of forming other types of cells. These cells are harvested from donor fat and frozen for use when needed. The main objective of this study is to evaluate if this treatment is safe and effective in forming new blood vessels, and if its effects improve the quality of life in patients like you.

**Study description**

This study consists of a Clinical Trial that plans to include 90 patients like you in various centers in Spain. It is a randomized study, which means that you will be randomly assigned to receive one of the three treatment arms described below:

- group 1 (placebo): a single dose of HypoThermosol®FRS will be administered. It looks the same as cell therapy and does not contain any pharmacologically active substances, so it is not expected to have any effect.
- group 2 (low dose): 1 million cells per kg of weight will be administered.
- group 3 (high dose): 2 million cells per kg of weight will be administered.

You have a 67% chance of receiving the treatment and a 33% chance of receiving the placebo. In this study, a “placebo” group is included because although the treatment is expected to improve the blood flow in your legs, it is necessary to be able to assess whether the improvement observed is due to the treatment or, for example, to the intervention in itself or the evolution of the disease itself. Furthermore, this is a “double-

blind" design study, which means that neither your treating physician nor you will know what treatment you are going to receive.

**Activities in the studio**

Once you have signed the informed consent, your doctor will carry out a medical history and a complete physical examination, a urine pregnancy test if you are a woman, a blood sample will be drawn, you will be asked to fill in quality scales of For life, you will have pictures of your leg ulcers if you have them, and you will have an imaging study called Magnetic Resonance Imaging (MRI) perfusion. In addition, you will be examined by the Anesthesia Service, which will assess the best measure to guarantee your comfort during the treatment administration procedure (sedation, spinal anesthesia or general anesthesia). During this visit, you will be able to consult with the specialist any questions in this regard and your authorization for the selected procedure will be requested.

If you meet the criteria to be part of the study, you will be assigned to one of the 3 treatment groups and will be scheduled for the next appointment, where you will be given the treatment. Administration is done in the operating room, intramuscularly, below the knee, at 25 points in the area where there is a lack of irrigation. On the same day of the intervention, if everything goes well, you will be discharged and you will go home.

Within 24 hours of the administration, you will have to return to the hospital for a review (with physical examination, questionnaires to assess your response to treatment, questions about whether you have had any adverse effects). Then you will be scheduled for three check-ups at three, six and twelve months after treatment. At these

reviews, you will have the exploration, analytics, and questionnaires repeated. The MRI will be repeated only 12 months after treatment.

Otherwise, you will continue with the treatment and follow-up at the discretion of the attending physician. Please consult with your study physician before taking any prescription or over-the-counter medications while in the study.

You should make sure that you tell your other doctors that you are currently participating in this study. These other doctors will contact your study doctor to discuss other treatments that may be necessary.

If you complete the study, your participation will last approximately 13 months. Once finished, you will continue your regular follow-up and treatment with your doctor. Once your participation in the study is over, we may need to review your medical history to collect data regarding your long-term evolution, over a period of approximately 5 years.

You should know that you can be excluded from the study if the sponsor or the study investigators consider it appropriate, either for safety reasons (your disease does not respond adequately, any adverse event that occurs due to the study medication, etc.) or because they consider that you are not complying with the established procedures. In either case, you will receive an adequate explanation of the reason for your withdrawal from the study.

By signing the attached consent form, you agree to comply with the study procedures that have been set forth to you.

**Benefits and risks derived from your participation in the study**

You may not get any direct benefit from participating in this clinical trial. By participating in this study, you will be contributing to scientific knowledge in this area in order to gain more information and make progress towards improving future treatments for the benefit of society. We hope that you or others will benefit well in the future. If during the course of this study any new information is obtained about the investigated treatment, your doctor will inform you about it so that you can learn more about your situation and can proceed to improve your treatment.

Adipose tissue derived allogeneic mesenchymal cell therapy is not currently marketed as a drug for the treatment of peripheral arterial disease. However, to date there have been more than 70 studies in which its safety has been demonstrated in patients with peripheral arterial disease, and approximately 25% of these studies have been carried out in patients with diabetes. No side effects attributable to the application of these cells have been described in any patient. Injecting the cells into the leg may cause pain, numbness, bruising, or infection at the injection site. Most of these effects are mild and most often resolve with minor treatment.

The possible long-term effects of this cell therapy, as novel, are unknown. Therefore, it is important that you notify your study doctor immediately of any unusual symptoms. The side effects could be a minor inconvenience or they could be serious, but the doctor in charge of your care will observe you closely to mitigate the consequences of them as much as possible, should they occur.

Also, during the study, different tests will be carried out. Some of them, such as blood tests, would be done in the same way even if he did not participate, and an attempt will

be made as far as possible to obtain the blood necessary for the study determinations, avoiding additional punctures.

Magnetic Resonance is an imaging test that does not use ionizing radiation, so you will not suffer direct radiation on your body. In order to perform it, you will lie on a table that is inserted into a cylindrical tube of a large diameter and the antennas that allow the images to be acquired will be placed on the torso. Before entering the MRI, a venous line will be channeled into the arm to introduce contrast. The contrast used is called gadolinium and it is very safe, less likely to have an allergic reaction than iodinated contrast agents. It will be used in the usual approved dose in conventional cardiac resonance studies, adjusted to your weight and age. The injection of the contrast is done with a pump that adjusts the injection quantity and speed very precisely. This is not painful, although your arm may feel cold, a metallic taste, or heat. These are normal reactions and do NOT indicate an allergic reaction. When using this contrast there is a possibility to develop a condition called systemic nephrogenic fibrosis (it consists of the hardening of different structures of the body, from the skin, joints to internal organs) that has been described in patients with severe alterations of function renal. Despite the fact that the risk in these patients is low (2-3%), patients with significant renal failure have been excluded from this study. With the dose and type of contrast used in this study, the risk is exceptional.

During the administration of the treatment, the anesthetist will decide the type of anesthesia to be administered, and will inform you appropriately about it through a specific informed consent that you will have to sign separately.

**Pregnancy Warnings**

Although it is a safe treatment, the effects of cell therapies on the fetus are currently unknown. If you are a woman of childbearing age, or a man with a partner of childbearing age, you are informed of the need to take contraceptive measures. In the event that you become pregnant while participating in the study, the pregnancy and the health of the newborn will be monitored after delivery. In the event that you are a male participant and your partner becomes pregnant, you must inform the doctor or partner to request specific consent for the collection of pregnancy and fetus data.

**Alternative treatments**

As previously mentioned, there is currently no curative treatment for peripheral arterial disease with critical ischemia of the legs. If you do not wish to participate or wish to discontinue your participation, you will continue to receive the treatment and follow-up that your doctor considers best for you. Check with your doctor for more information on this.

**Economic Aspects**

You will not receive financial compensation for being part of this study. Your participation will not entail any expense. This is a non-profit study, an initiative of a group of researchers, which has been funded by the Carlos III Health Institute. Neither the researchers nor the participating centers receive financial compensation for participating.

**Insurance**

Insurance has been contracted in accordance with the current legislation of Royal Decree 1090/2015. The policy was contracted with the QBE company, and the number of the same is (PENDING TO COMPLETE). In the event of impairment of your health or injuries related to participation in this clinical trial, you will be provided with compensation and compensation. For more information, do not hesitate to ask the study's principal investigator.

**Personal data protection**

The Sponsor undertakes that the treatment, communication and transfer of personal data of all participating subjects will comply with the provisions of Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights, complementary to regulation (EU) 2016/679 of the European Parliament and of the European Council of April 27, 2016 on data protection (RGPD).

In addition to the rights that you already know (access, modification, opposition and cancellation of data) you can now also limit the processing of data that are incorrect, request a copy or that the data that you have provided is transferred to a third party (portability) to the study. To exercise your rights, contact the study's principal investigator or the Center's Data Protection Officer (DPO) through the following email address: (DPO@fjd.es). We remind you that data cannot be deleted even if you stop participating in the trial to ensure the validity of the research and to comply with legal duties and drug authorization requirements. Likewise, you have the right to contact the Data Protection Agency if you are not satisfied. Both the Center and the Sponsor are respectively responsible for the processing of your data and undertake to comply with the data protection regulations in force. The data collected for the study will be

identified by a code, so that information that can identify you is not included, and only your study doctor / collaborators will be able to relate said data to you and to your medical history. Therefore, your identity will not be revealed to any other person except to the health authorities, when required or in cases of medical emergency. The FJD Ethics Committees, the representatives of the Health Authority in matters of inspection and the personnel authorized by the Sponsor, may only access to verify personal data, clinical study procedures and compliance with the rules of good clinical practice (always maintaining the confidentiality of the information).

The Researcher and the Sponsor are obliged to keep the data collected for the study for at least 25 years after its completion. Subsequently, your personal information will only be kept by the center for the care of your health. The information collected in the study by the sponsor may be used for other scientific research purposes if you have given your consent to do so and if this is permitted by law and applicable ethical requirements. These purposes refer to continuing research into efficacy and safety studies of treatment with this cell therapy.

If we transfer your encrypted data outside the EU to the entities of our group, to service providers or to scientific researchers who collaborate with us, the participant's data will be protected with safeguards such as contracts or other mechanisms by the protection authorities of data. If the participant wants to know more about it, they can contact the sponsor Data Protection Officer at the contact address indicated above.

**Other information and contact in case of doubts**

The description of this clinical trial will be available for consultation on the following public access research study registration websites https://www.clinicaltrialsregister.eu, http://www.ClinicalTrials.gov and in the Spanish Registry of Clinical Studies,

https://reec.aemps.es, as required by law. Information that can identify you will not be included in these records.

As a participant in this clinical trial, you have the responsibility to comply with the visits and activities of the study, and to report any adverse event that happens to you or changes in medication, noting that, except in an emergency, do not modify the medication that is taking or taking other medications or "herbal remedies" without first consulting with the study physician.

You have the right to ask all the questions you want and to know more about this study now or at any time during the study. To do this, you can contact the study investigator at your center:

Dr. (to be filled in by each center), on the phone (to be filled in by each center, include telephone service hours)

## INFORMED CONSENT FORM

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|---|---|
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| **Principal Investigator** | (to fill in the centre) |
| **Centre** | (to fill in the centre) |

I, …… (Name and surname of the participant)

□ I have read the information sheet given to me about the study.

□ I have been able to ask questions about the study.

□ I have received enough information about the study.

□ I have spoken with …… (Investigator's name).

□ I understand that my participation is voluntary.

□ I understand that I can withdraw from the study:

- Anytime.

- Without having to explain.
- Without this affecting my medical care.

□ I will receive a signed and dated copy of this informed consent document.

□ I freely give my consent to participate in the study.

□ I consent to my personal information being kept for other scientific research purposes.

□YES □NO

| Participant signature<br><br>(Name and signature) | Investigator signature |
|---|---|
| Date: ____/____/____ | Date: ____/____/____ |

## WITNESSES INFORMED CONSENT FORM

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| **Sponsor** | Health Research Foundation Jimenez Diaz University Hospital<br>Avda. Reyes Católicos nº2, 28040 Madrid, Spain |
| **Principal Investigator** | (to fill in the centre) |
| **Centre** | (to fill in the centre) |

I, …… .. (name and surname of the witness), as a witness, affirm that in my presence Ms / Mr …… has been informed …… (name and surname of the participant) and the information sheet given to them about the study has been read.

□ She/he has been able to ask questions about the study.

□ She/he has received enough information about the study.

□ She/he has have spoken with …… (name of researcher).

□ She/he understands that participation is voluntary.

□ She/he understands that can withdraw from the study:

- Anytime.
- Without having to explain.
- Without this affecting your medical care.

□ She/he will receive a signed and dated copy of this informed consent document.

□ She/he freely agrees to participate in the study.

□ She/he consents to his/her personal information being kept for other scientific research purposes.

□YES □NO

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|---|---|
| Witnesses signature<br><br>(Name and signature) | Investigator signature |
| Date: ____/____/____ | Date: ____/____/____ |