

The Efficacy and Safety of Intra-Arterial Administration of REX-001 to treat ischaemic rest pain in Subjects with Critical Limb Ischaemia Rutherford Category 4 and Diabetes Mellitus: A Pivotal, Placebo Controlled, Double-Blind, Parallel-Group, Adaptive Trial

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To confirm the efficacy and safety of a single intra-arterial administration of REX-001 to relieve ischaemic rest pain in subjects with critical limb ischaemia (CLI) Rutherford Category 4 and diabetes mellitus (DM).

| | |
|------------------------------|------------------------|
| Ethical review | Approved WMO |
| Status | Will not start |
| Health condition type | Vascular disorders NEC |
| Study type | Interventional |

Summary

ID

NL-OMON47803

Source

ToetsingOnline

Brief title

REX-001-004 Rutherford Category 4

Condition

- Vascular disorders NEC

Synonym

peripheral artery disease; rest pain in legs and feet

Research involving

Human

Sponsors and support

Primary sponsor: Rexgenero Limited

Source(s) of monetary or material Support: Rexgenero Limited

Intervention

Keyword: critical limb ischaemia (CLI), REX-001

Outcome measures

Primary outcome

Primary Efficacy Endpoint:

Change in Rutherford classification from CLI Category 4 to Category 3 or lower

12 months after administration of REX-001 or placebo. Success is defined as complete relief of ischaemic rest pain with the absence of the development of ischaemic lesions on the index leg.

Secondary outcome

The following secondary endpoints at 12 months after administration of REX-001 or placebo are defined:

- Change in Rutherford score (Categories 0-6).
- Presence of ischaemic ulcers (yes/no).
- Amputation free survival (AFS).

Study description

Background summary

CLI also referred to as limb threat, is an advanced stage of peripheral artery disease. It includes ischaemic rest pain, arterial insufficiency, ulcers and

gangrene. The latter two conditions are jointly referred to as tissue loss, reflecting the development of surface damage to the limb tissue due to the most severe stage of ischaemia.

CLI was conceived to identify patients at high-risk for major amputation, but the increasing prevalence of diabetes mellitus has led to a broader conception of limb threat that includes the risk of amputation associated with severely infected and non-healing wounds

The primary objective of the trial is to show that treatment with REX-001 is superior to treatment with placebo by the change in Rutherford classification 12 months after administration.

Study objective

To confirm the efficacy and safety of a single intra-arterial administration of REX-001 to relief ischaemic rest pain in subjects with critical limb ischaemia (CLI) Rutherford Category 4 and diabetes mellitus (DM).

Study design

This trial is a pivotal, placebo-controlled, double-blind, parallel-group, adaptive trial conducted in subjects with CLI Rutherford Category 4 and DM. Minimization will be used to assign eligible subjects in a 2:1 ratio to receive a single intra-arterial administration of REX-001 or placebo into the index limb.

Trial subjects will be assessed at the screening visit, the BM collection visit, the baseline visit and at months 1, 2, 3, 6, 9, 12, 18, and 24 after administration of REX-001 or placebo. The primary endpoint for this trial will be assessed at 12 months.

Intervention

REX-001 is an autologous cell suspension for infusion, administered through an intra-arterial catheter. The subject will receive one batch of REX-001 at a target dose of 1×10^9 WBCs (range: 5×10^8 to 1×10^9 autologous WBCs) in a volume of 20 mL.

For the control group, placebo will be prepared. Placebo will be matched for colour and volume and its composition is tested to confirm absence of detectable levels of WBCs.

Target limb arteries are selectively cannulated through a transfemoral approach with an over the-wire catheter balloon that is positioned in the target artery of the index leg (in general the popliteal artery). At this point, the balloon

will be inflated to block blood flow and REX-001 or placebo will be slowly infused. After administration, the balloon will be deflated and antegrade blood flow restored.

All subjects will undergo a bone marrow (BM) collection (Visit 2). Under general or local anesthesia and sedation approximately 250 mL BM is harvested from the iliac crest. All trial subjects will be administered REX-001 or placebo unless the yield of the BM collection is insufficient (e.g it is not possible to manufacture REX-001 at the required dose, between 5×10^8 - 1×10^9 WBCs, or the final product does not meet the release specifications). In these situations, subjects will be discontinued from the trial. If REX-001 cannot be manufactured at the required dose, the Sponsor will discuss with the Investigator whether the subject can be treated with the lower dose, but outside of the trial.

The subjects assigned to the placebo group may be offered the possibility to receive REX-001 after the 12 month follow-up visit has been completed for all subjects, and if this approach is approved by the national Competent Authorities. If, at that time, the index leg can no longer be treated, the treating physician can propose to treat the contralateral leg. For these subjects, REX-001 will be frozen and stored at an external facility in Spain or in Germany, depending on where the product was manufactured.

Study burden and risks

During patient participation various examinations and tests will be done. Many of these tests (associated with burden and risks) are performed to monitor patient health and well-being and evaluate REX-001 safety and Efficacy

Physical examination: Some examinations/tests can make the patient uncomfortable.

Vital signs, blood pressure, heart rates are measured.

Blood Draws: patients will have blood drawn at multiple times during the study. There may be some pain or bruising at the site where patients are pricked.

Pregnancy: In the event that patients become(s) pregnant during the study, the sponsor will be informed about pregnancy and outcome delivery and health of the new born. It is not known if REX-001 causes any damage to unborn children. Therefore, female patients participating in the study must not be pregnant or be breastfeeding. It is important for patient to understand that contraception must be used while participating in this study.

Questionnaire: some questions may feel too personal or make the patient uncomfortable.

General risks associated with participation. There is a very small chance of

allergic reactions. These types of reactions can start shortly after taking the medication and may appear in the form of itching and redness or difficulty breathing and may be severe in some cases.

Angiography: patients will be exposed to a small amount of radiation to visualize the arteries in their leg.

6-minute walking test will be performed to assess how far the subject can walk and at what time he start to feel pain in legs.

The measurement of oxygen levels of the tissue below the skin on subjects legs as well the number and size of subject ulcers can make the patient uncomfortable.

Bone marrow collection will be performed in the hospital and requires hospitalization overnight.

Contacts

Public

Rexgenero Limited

Pont Street 45
London SW1X 0BD
GB

Scientific

Rexgenero Limited

Pont Street 45
London SW1X 0BD
GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

1. Aged ≥ 18 to ≤ 85 years.
2. Diagnosis of Type I or II DM, established more than one year ago.
3. Glycosylated hemoglobin (HbA1c) $< 9\%$.
4. Subjects with poor or no (surgical or endovascular) revascularization option, classified as CLI Rutherford Category 4.

The blood circulation in these subjects must be compromised at screening defined as:

- Ankle systolic pressure < 50 mm Hg, or
- Toe systolic pressure < 30 mm Hg, or
- Transcutaneous oxygen pressure (tcpO₂) < 30 mm Hg, and
- Flat or barely pulsatile ankle or metatarsal pulse volume recording (PVR)

The subject should have rest pain without tissue loss, and the rest pain must be persistent and require analgesics for at least two weeks for the subject to be eligible. Subjects with non-compressible vessels must qualify on toe pressure or tcpO₂.

Poor or no revascularization option means that, in the opinion of the Investigator, revascularization using surgical or endovascular methods is not feasible due to unsuitable anatomy of existing vessels, existing comorbidity and/or previously failed surgical or endovascular revascularization.

Exclusion criteria

1. Advanced CLI defined as presence of major tissue loss (i.e. as significant ulceration and/or gangrene) proximal to the metatarsal heads (CLI Rutherford Category 6). Significant ulceration/gangrene means any ulceration that extends beyond the subcutaneous tissue layer, or any gangrene or tissue necrosis proximal to the metatarsal heads.
2. CLI Rutherford Category 5.
3. Uncontrolled or untreated proliferative retinopathy.
4. Failed surgical or endovascular revascularization on the index leg within 10 days prior to screening.
5. Subjects in whom arterial insufficiency in the lower extremity is the result of acute limb ischaemia or an immunological or inflammatory or non-atherosclerotic disorder (e.g., thromboangiitis obliterans (Buerger's Disease), or systemic sclerosis (both limited and diffuse forms)).
6. Clinical evidence of invasive infection on index leg defined as major tissue loss at the mid-foot or heel involving tendon and/or bone, and/or when according to the Investigator intravenous antibiotics are required to treat the infection.
7. At screening, the presence of only neuropathic ulcers on the index leg.
8. Amputation at or above the talus on the index leg.
9. Planned major amputation within the first month after randomization.

10. Subjects who may not be healthy enough to successfully complete all protocol requirements including BM collection, or who are not expected to survive more than 12 months, or in whom results may be particularly difficult to assess, as assessed by the Investigator.

Study design

Design

| | |
|---------------------|-------------------------------|
| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

Recruitment

| | |
|---------------------|----------------|
| NL | |
| Recruitment status: | Will not start |
| Enrollment: | 6 |
| Type: | Anticipated |

Medical products/devices used

| | |
|---------------|--------------------------|
| Product type: | Medicine |
| Generic name: | Somatic cells autologous |

Ethics review

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| Approved WMO | |
| Date: | 09-01-2017 |
| Application type: | First submission |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO | |

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| Date: | 09-05-2018 |
| Application type: | First submission |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO | |
| Date: | 24-09-2018 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO | |
| Date: | 11-12-2018 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO | |
| Date: | 07-03-2019 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO | |
| Date: | 13-05-2019 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

| Register | ID |
|----------|------------------------|
| EudraCT | EUCTR2016-000240-34-NL |
| CCMO | NL57337.000.16 |