The Efficacy and Safety of Intra-Arterial Administration of REX-001 to Treat Ischemic Ulcers in Subjects with Chronic Limb Threatening Ischaemia Rutherford Category 5 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 treat ischemic ulcers in subjects with CLTI Rutherford Category 5 and DM.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Vascular disorders NEC
Study type	Interventional

Summary

ID

NL-OMON55357

Source
ToetsingOnline

Brief title
REX-001-005 Rutherford Category 5

Condition

- Vascular disorders NEC

Synonym
peripheral artery disease; rest pain in legs and feet

Research involving
Human

Sponsors and support

Primary sponsor: Ixaka Limited
Source(s) of monetary or material Support: Ixaka Limited

Intervention

Keyword: Chronic Limb Threatening Ischaemia (CLTI), REX-001

Outcome measures

Primary outcome

Change in Rutherford classification from CLTI Category 5 to Category 4 or lower

12 months after administration of REX-001 or placebo. Success is defined as

complete healing of all ischemic ulcers 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 classification from CLI Category 5 to Category 3 or

lower.

• Change from Baseline to Visit 9 (12 months) in TcpO2

• Partial healing of ischemic ulcers ((>= 50% reduction in size as compared to

ulcer size at baseline).

• AFS.

Study description

Background summary

CLTI also referred to as limb threat, is an advanced stage of peripheral artery disease. It includes ischemic 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 ischemia.

CLTI 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 treat ischemic ulcers in subjects with CLTI Rutherford Category 5 and DM.

Study design

This trial is a pivotal, placebo-controlled, double-blind, parallel-group, adaptive trial conducted in subjects with CLTI Rutherford Category 5 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 matching 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-001or 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 × 109 WBCs (range: 5 × 108 to 1 × 109 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 × 108 - 1 × 109 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-u p 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
Ixaka Limited

Pont Street 45
London SW1X 0BD
GB
Scientific
Ixaka 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 CLTI Rutherford Category 5.
The blood circulation in these patients must be compromised at screening, can be defined as:
• Ankle systolic pressure < 70 mmHg, or
• Toe systolic pressure < 50 mmHg, or
• TcpO2 < 30 mmHg (lying down).
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.

*IMPORTANT: All three measurements must be performed and only one may be used to meet this criteria

Exclusion criteria

1. Advanced CLTI defined as presence of major tissue loss (i.e significant ulceration and/or gangrene) proximal to the metatarsal heads (CLTI 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. CLTI Rutherford Category 4.
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 ischemia 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:	Recruitment stopped
Start date (anticipated):	01-10-2019
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cells autologous

Ethics review

Approved WMO

Date:	09-01-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO 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)
Approved WMO Date:	16-12-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-07-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	20-09-2022
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	EUCTR2016-003980-21-NL
ClinicalTrials.gov	NCT03174522
CCMO	NL60060.000.16