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, DoubleBlind, Parallel-Group, Adaptive Trial Investigational product REX-001 (autologous bone marrow-derived mononuclear cell enriched white blood cells)

Abbreviated Clinical Study Statement

Document	Abbreviated Clinical Study Statement
Sponsor	Ixaka Limited 45 Pont Street, London SW1X 0BD, United Kingdom
Document version	1.0
Document date	10 May 2023

GCP Statement: this clinical trial was conducted in full compliance with local, national and European Good Clinical Practice regulations

This clinical study statment is an abbreviated clinical study report to fulfill obligations of Article 37, Section 4, of Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

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1 - CLINICAL TRIAL IDENTIFICATION

This clinical study report is an abbreviated clinical study report to fulfill obligations of Article 37, Section 4, of Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.

1.1 - STUDY TITLE

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, DoubleBlind, Parallel-Group, Adaptive Trial Investigational product REX-001 (autologous bone marrow-derived mononuclear cell enriched white blood cells

1.2 - PROTOCOL CODE

REX-001-004

1.3 - EUDRACT NUMBER

2016-000240-34

1.4 - GCP STATUS

This clinical trial was conducted in full compliance with local, national and European Good Clinical Practice regulations. The study included internal audits, no major GCP breaches were found at any point in the study. The study was never inspected for GCP by any competent authority.

1.5 - SPONSOR AND COLLABORATORS

Sponsor:
Ixaka Limited (formerly Rexgenero Limited)
45 Pont Street,
London SW1X 0BD,
United Kingdom

Contract research organization:

Syneos Health
3201 Beechleaf Court
Suite 600
Raleigh, NC 27604-1547
United States

1.6 - INVESTIGATIONAL MEDICINAL PRODUCT

Autologous bone marrow-derived white blood cells (BM-WBCs) i.e., 1×10^9 WBCs isolated from the bone marrow, or placebo, in a 2:1 ratio, were administered to consenting subject one time at baseline, patients were then followed for 1 year for safety and efficacy evaluation. Additionally, patients were monitored for an additional 12 months for safety assessment. As the product was a biological product with minimal manipulation and autologous, there were no treatment associated adverse events of any kind during the entire duration of the study.

1.7 - TRIAL OBJECTIVES AND ENDPOINTS

The trial objective was to confirm the efficacy and safety of a single intra-arterial administration of REX-001 to treat ischaemic ulcers in subjects with CLTI Rutherford Category 4 and diabetes.

Study endpoints included the following, measured periodically, the primary endpoint was measured at month 12:

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 Endpoints

Primary Efficacy Endpoint

Change in Rutherford classification from CLI Category 4 to Category 3 or lower 12 months after administration of REX-001 or the placebo product (hereafter referred to as the 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 Endpoints

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

1.8 - TRIAL POPULATION

1.8.1 - Inclusion criteria

To be eligible for this trial subjects must satisfy all the following criteria:

1. Aged ≥ 18 to ≤ 85 years.
2. Diagnosis of Type I or II DM, established more than one year ago.
3. Glycosylated haemoglobin (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
- T_cpO_2 < 30 mm Hg, and
- Flat or barely pulsatile ankle or metatarsal 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 or calcified vessels must qualify on toe pressure or t_cpO_2.

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

5. In the opinion of the Investigator, the subject is controlled on medical therapy indicated for CLI (unless there is a documented contraindication or intolerance) and pain management is optimized.

6. Women of childbearing potential must have a negative pregnancy test at screening. A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. Men and women who are sexually active shall use effective contraceptive methods for the duration of their participation in this study if the partner of the male participant, or if the female participant is of childbearing potential. Examples of effective contraceptive methods are:

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal),
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable),
- Intrauterine device (IUD),
- Intrauterine hormone-releasing system (IUS),
- Bilateral tubal occlusion,
- Vasectomised partner, or
- Sexual abstinence.

The use of any contraceptive method should be continued for at least the time the subject participates in the trial,and should be continued thereafter as long as indicated by the Investigator.

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1.8.2 - Exclusion criteria

Subjects meeting any of the following criteria must not be enrolled in the trial:

1. Advanced CLI defined as presence of major tissue loss, i.e., significant ulceration/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 intravenous antibiotics are required to treat the infection according to the Investigator.
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. On the index leg, use of concomitant wound treatments not currently approved for ischaemic wound-healing within 30 days prior to screening or plans to initiate new treatments (not considered standard of care) to the index leg during the trial.
11. Blood clotting disorder not caused by medication (e.g., thrombophilia).

12. Severe hypertension according to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (stage 2 hypertension: Systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg).[16]
13. A platelet count < 50,000/μL.
14. International normalized ratio (INR) > 1.5. For patients on anticoagulant medication an INR > 1.5 is allowed, provided that the Investigator and the haematologist consider the patient eligible to collect BM.
15. Evidence of moderate to severe hepatocellular dysfunction according to the Investigator.
16. Positive test for human immunodeficiency virus 1 (HIV 1), HIV 2, hepatitis B virus (HBV), hepatitis C virus (HCV) or Treponema pallidum.
17. 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. For example:
    a. Concurrent severe congestive heart failure (New York Heart Association Classes III and IV).
    b. Life-threatening ventricular arrhythmias, unstable angina (characterized by increasingly frequent episodes with modest exertion or at rest, worsening severity, and prolonged duration), and/or myocardial infarction within four weeks before screening.
    c. Coronary artery bypass grafting or percutaneous coronary intervention within one month before screening.
    d. A renal and/or carotid revascularization procedure within one month of screening.
    e. Transient ischaemic attack within three months prior to screening.
    f. Deep vein thrombosis within three months prior to screening.
    g. Subjects with immunocompromised conditions, organ transplant recipients and/or subjects in need of immunosuppressive therapy.
    h. Neurological dementia (i.e., Alzheimer's Disease).
18. Subjects who participate in another clinical interventional trial.
19. Subjects who have been treated with experimental medication within 30 days of screening.
20. Subjects who were treated with other cell therapies for CLI within the last 12 months preceding the screening visit.

2 - SUBJECT DISPOSITION

The following is the disposition of subjects in the trial:

COUNTRY	Patients Screened	Screen Failures	Patients scheduled for BM collection	Patients Randomized	Patients Treated	Patients Ongoing	Patients Discontinued BEFORE treatment	Patients Discontinued AFTER treatment	Patients Completed Study
SPAIN									
POLAND	1	1		0					
AUSTRIA									
CZECH REP.	1	0		1			1		
HUNGARY	1	1		0					
NETHERLANDS									
PORTUGAL									
TOTAL	3	2	0	1	0	0	1		0

2.1 - SAFETY OUTCOMES

As the product was a biological product with minimal manipulation and autologous, there were no treatment associated adverse events of any kind during the entire duration of the study. There were no Suspected Unexpected Serious Adverse Reactions (SUSARs) reported in this trial.

3 - ADDITIONAL INFORMATION

3.1 - GLOBAL SUBSTANTIAL MODIFICATIONS

No global substantial modifications were required.

3.2 - GLOBAL INTERRUPTIONS AND RE-STARTS

The study was never interrupted until the Early Termination.

3.3 - LIMITATIONS

No limitations or implications to declare.

3.4 - ACCURACY OF SUBMITTED INFORMATION

The Sponsor of the conducted clinical trial confirms that the information provided in this abbreviated clinical study statement is accurate and directly from the clinical and pharmacovigilance databases.

4 - STUDY STATEMENT

This is a brief statement to state that after an internal assessment, due to enrolment issues for study REX-001-004, the Sponsor decided to discontinue enrolment and close the study. It is very important to note that this action is not based on any emerging safety concerns and is not for reasons affecting the benefit-risk balance.

Section 2 of this document illustrates the number of patients screened, screen-failed and randomised. No patients were treated with the REX-001 product. The REX-004 study started as a single study in 2016 designed as 2 sub-studies (trial 1: patients with Rutherford Category 4; trial 2: patients with Rutherford Category 5) having two EudraCT numbers and was than split in two studies (EudraCT: 2016-000240-34 REX-001-004 and EudraCT: 2016-003980-21 REX-001-005) in 2018. Both protocols were identical except for one inclusion and one exclusion criteria and all sites were initiated at the same time for both studies therefore most of the documentation included reference to both studies.

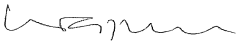
5 - SIGNATURE PAGE

Study title:	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, DoubleBlind, Parallel-Group, Adaptive Trial Investigational product REX-001 (autologous bone marrow-derived mononuclear cell enriched white blood cells
Investigational drug:	Autologous bone marrow mononuclear cells (BM-MNCs)
Protocol Code:	REX-001-004
EudraCT No.:	2016-000240-34

The undersigned has read this abbreviated clinical study report and hereby confirms that, to the best of his knowledge, it accurately describes the conduct and the results of the study.

Print First & Last Name: _____**Gilbert Wagener MD, PhD**_____

Affiliation:____**Chief Medical Officer of Ixaka (formerly Rexgenero Limited)**_____



Signature & Date: 19 June 2023