The Efficacy and Safety of Intra-Arterial Administration of REX-001 to Treat Ischaemic Ulcers in Subjects with Critical Limb Ischaemia Rutherford Category 5 and Diabetes Mellitus: A Pivotal, Placebo-Controlled, Double-Blind, Parallel-Group, Adaptive Trial

Abbreviated Clinical Study Report

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

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

Table of Contents

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 Ulcers in Subjects with Critical Limb Ischaemia Rutherford Category 5 and Diabetes Mellitus: A Pivotal, Placebo-Controlled, Double-Blind, Parallel-Group, Adaptive Trial

1.2 - PROTOCOL CODE

REX-001-005

1.3 - EUDRACT NUMBER

2016-003980-21

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 - TRIAL DESIGN AND STAGE

This was a phase 3 randomized double-blind placebo controlled parallel group interventional clinical trial including patients with chronic limb threatening ischemia (CLTI). This study was stopped by the independent data safety monitoring committee (DSMB) prematurely at its predetermined interim analysis at 50% of information due to futility in September of 2022. Informed consent was obtained from all subjects before any trial procedure was conducted, patient could have withdrawn from the study at any time without the need to provide any justification. Patients were administered with the investigational product or placebo one time at baseline and then followed for 1-year, periodic visits every ~3 months were conducted for safety and efficacy assessment, and the primary endpoint was measured at month 12. All patients were followed up to month 24 for additional follow-up. The study had two interim analyses, at 30% (i.e., when 30% of the patient reached the primary endpoint at month 12), and one at 50%. The 30% interim analysis evaluated safety and futility. The study was continued after the 30% analysis as there were no safety risks and it was not found to be futile. At 50% the study was stopped, not due to a safety concern, but due to futility.

The sample size was calculated based on the efficacy results from the Phase II trial conducted with REX-001 in 60 subjects with CLTI and diabetes. Based on the data from the group of subjects with CLTI Rutherford Category 5, it is estimated that the proportion of subjects with complete healing of all ischemic ulcers on the index leg will be 20% in the placebo group versus 55% in the group treated with REX-001. In the trial an allocation ratio of 2:1 in favor of REX-001 was used. With these assumptions the sample size required was 64 subjects. An overage of 20% is added to the sample size to account for dropouts, thus the total sample size required was 78 subjects (approximately 52 subjects allocated to the treatment group and 26 subjects to the placebo group).

1.6 - SPONSOR AND COLLABORATORS

Sponsor:
Ixaka 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

1.7 - 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.

1.8 - 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 5 and diabetes.

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

Primary Efficacy Endpoint

Change in Rutherford classification from CLI Category 5 to Category 4 or lower 12 months after administration of REX-001 or the placebo product (hereafter referred to as Placebo). Success is defined as complete healing of all ischaemic ulcers on the index leg.

Secondary Endpoints

- Change in Rutherford classification from CLI Category 5 to Category 3 or lower.
- Change from Baseline to Visit 9 (12 months) in TcpO2 (transcutaneous oxygen pressure).
- Partial healing of ischaemic ulcers (≥ 50% reduction in size as compared to ulcer size at baseline).
- Amputation Free Survival.

The following additional efficacy endpoints at different time points after administration of REX-001 or Placebo are defined:

- Change in Rutherford classification at three, six, nine, 18 and 24 months.
- Presence of ischaemic ulcers at three, six, nine, 18, and 24 months.
- Partial healing of ischaemic ulcers at three, six, nine, 18 and 24 months.

- Presence of ischaemic rest pain at three,six, nine, 12, 18, and 24 months.
- Six-Minute Walking Test (to assess claudication time and distance) at three, six, nine, 12, 18 and 24 months. The Six-Minute walking test will only be performed if subjects are able to walk.
- Ankle pressure, toe pressure, ABI, and TBI at three, six, nine, 12, 18, and 24 months.
- T_cpO_2 at one, two, three, six, nine, 18, and 24 months.
- Vasculogenesis/arteriogenesis confirmed by angiography at 12 months.
- Disease-specific QoL as assessed by the Vascular Quality of Life Questionnaire (VascuQol) at three, six, nine, 12, 18 and 24 months.
- Health-related QoL using the EuroQoL five dimensions questionnaire (EQ-5D-5L) at three, six, nine, 12, 18 and 24 months.
- Incidence of minor amputations.
- AFS at 24 months.
- Cardiovascular morbidity including cardiovascular death, non-fatal myocardial infarction and non-fatal stroke (adjudicated by the IAC, recommended as per the CHMP note for guidance).
- Change in Wound, Ischemia and foot Infection (WIfI) risk score at three, six, nine, 12, 18 and 24 months.
- Frequency, extent and type of wound care at three, six, nine, 12, 18 and 24 months.
- Proportion of patients receiving a successful administration of REX-001 or Placebo after BM collection.

1.9 - TRIAL POPULATION

1.9.1 - 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 5.
   The blood circulation in these subjects must be compromised at screening, defined as:
   - Ankle systolic pressure < 70 mmHg, or
   - Toe systolic pressure < 50 mmHg, or
   - T_cpO_2 < 30 mmHg (lying down).

   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 for example the 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.

1.9.2 - 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 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 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 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 bone marrow collection	Patients Randomized	Patients Treated	Patients Ongoing	Patients Discontinued BEFORE treatment	Patients Discontinued AFTER treatment	Patients Completed Study	Product out of specification
SPAIN	53	17		36	28	11	8	5	12	8
POLAND	1	1		0	0	0			0	
AUSTRIA	1	0		1	1	0		1	0	
CZECH REP	4	0		4	4	0			4	
HUNGARY	4	2		2	2	1			1	
NETHERLANDS	3	1		2	2	1		1	0	
GERMANY										
UK										
PORTUGAL	2	1		1	1	0		1	0	
LATVIA	15	6		8	5	3	3	2	0	3
LITHUANIA	2	0		2	2	0		1	1	
GEORGIA	10	4		6	4	3	2	1	0	2
TOTALS	**95**	**32**	**0**	**62**	**49**	**19**	**13**	**12**	**18**	**13**

3 - BASELINE CHARACTERISTICS

The listing of all patients (screened, and randomized), their age and sex is provided below:

Subject	AGE	SEX
AUT-04-201	68	Male
CZE-01-103	69	Female
CZE-01-201	63	Male
CZE-01-202	52	Male
CZE-01-203	66	Male
CZE-01-204	57	Male
ESP-01-201	58	Male
ESP-01-202	67	Male
ESP-01-203	55	Male
ESP-01-204	85	Male
ESP-01-205	51	Male
ESP-01-206	58	Male
ESP-01-207	58	Male
ESP-01-208	51	Male
ESP-01-209	79	Male
ESP-01-210	59	Male
ESP-01-211	70	Male
ESP-01-212	77	Male
ESP-01-213	73	Male
ESP-01-214	80	Male
ESP-01-215	64	Male
ESP-01-216	64	Male
ESP-01-217	74	Male
ESP-01-218	67	Male
ESP-01-219	67	Male
ESP-03-201	69	Male
ESP-03-202	69	Male
ESP-03-203	68	Male
ESP-03-204	77	Male
ESP-03-205	73	Male
ESP-03-206	60	Male
ESP-03-207	68	Male
ESP-03-208	84	Male
ESP-03-209	65	Female
ESP-03-210	63	Female
ESP-03-211	60	Male
ESP-06-201	78	Male
ESP-06-202	71	Male
ESP-06-203	71	Male

Subject	AGE	SEX
ESP-06-204	73	Male
ESP-06-205	73	Male
ESP-06-206	81	Male
ESP-06-207	82	Male
ESP-07-201	71	Female
ESP-07-202	79	Male
ESP-08-201	80	Male
ESP-09-201	76	Male
ESP-09-202	65	Male
ESP-10-201	73	Male
ESP-10-202	84	Male
ESP-10-203	84	Male
ESP-11-201	62	Male
GEO-02-201	49	Male
GEO-02-202	71	Male
GEO-02-203	71	Female
GEO-03-201	55	Female
GEO-03-202	71	Male
GEO-03-203	60	Male
HUN-01-101	72	Female
HUN-01-201	68	Male
HUN-03-201	53	Female
HUN-03-202	63	Male
LTU-01-201	75	Female
LTU-01-202	72	Male
LVA-01-201	71	Female
LVA-01-202	60	Male
LVA-01-203	59	Male
LVA-01-204	76	Female
LVA-01-205	77	Male
LVA-01-206	65	Male
LVA-01-207	48	Male
LVA-02-201	67	Female
LVA-02-202	62	Male
LVA-02-203	71	Male
LVA-02-204	56	Male
LVA-02-206	65	Male
NLD-01-201	74	Female
NLD-03-201	74	Male
NLD-03-202	57	Male
POL-01-101	77	Male
POL-01-202	59	Male

Subject	AGE	SEX
PRT-04-201	69	Female
PRT-04-202	80	Female

3.1 - EFFICACY OUTCOMES

Endpoints were not analyzed statistically as the study was stopped prematurely. The following table provides the outcomes of the 50% interim analysis in a descriptive manner.

Subject	Treatment or placebo	RF category	Reason of failure	Clinical impression	Is there a clinical response (i.e., is the effect likely due to REX-001)?
AUT-04-201	Placebo	FAILURE	Major Amputation	N/A	No
CZE-01-201	Placebo	CAT5	Baseline ulcer: 30x30mm	N/A	No
CZE-01-202	Placebo	CAT3	Baseline ulcer: 14x21mm	ulcer very superficial, likely healed by good wound care	No
ESP-01-208	Placebo	CAT1	Baseline ulcer:8x8mm	ulcer very superficial, likely healed by good wound care	No
ESP-01-214	Placebo	CAT5	Baseline ulcer: 9x10 mm		No
ESP-01-216	Placebo	FAILURE	Died before Month 12	Cause of death = Covid-19	No
ESP-03-208	Placebo	FAILURE	Missed Visit		No
ESP-06-202	Placebo	FAILURE	Major Amputation	Gangrene at Screening; Randomized 2018-01-22, amputation on 2018-03-03	No
ESP-06-205	Placebo	CAT5	4 ulcers at basline, largest 50x24 mm	baseline ulcers were bad, most healed except 1, which puts the patient at RF 5	No
ESP-07-201	Placebo	CAT3	N/A	patient was only a responder because toe which had ulcers was amputated. Gangrene at Screening	No
GEO-02-202	Placebo	CAT5	N/A	2 baseline ulcers 20x20 and 17x16 mm	No
CZE-01-203	REX-001	CAT5	Baseline ulcer: 5x5 mm	original ulcer healed but another small one appeared	No
CZE-01-204	REX-001	CAT5	Baseline ulcer: 50x5 mm	ulcer huge at baseline and nearly healed at month 12	Yes (wound healed 99%, but did not fit FDA “full closure” definition)
ESP-01-207	REX-001	CAT2	Baseline ulcer: 20x15 mm	patient had all toes amputated before joining study, ulcer was on the foot and remarkably healed on month 12	Yes (no anomalies to describe response other than REX001 effect)
ESP-01-210	REX-001	CAT2	Baseline ulcer: 17x5 mm	patient had deep ulcer on side of foot which healed remarkably end of month 12	Yes (no anomalies to describe response other than REX001 effect)
ESP-01-212	REX-001	CAT1	Baseline ulcer: 45x52 mm	patient had a very large disfiguring ulcer at base of foot at baseline, completely healed at month 12	Yes (no anomalies to describe response other than REX001 effect)
ESP-01-218	REX-001	CAT5	Baseline ulcer:20x20 mm	all toes were amputated during study, patient didn’t have enough time to heal by month 12. Gangrene at Screening	No
ESP-03-202	REX-001	CAT5	Baseline ulcer: 15x15 mm, 20x20 mm	all ulcers healed, the initial ulcer was a gangrene which was amputated later in the study, it didn’t have a chance to heal by month 12. Gangrene at Screening	No

Subject	Treatment or placebo	RF category	Reason of failure	Clinical impression	Is there a clinical response (i.e., is the effect likely due to REX-001)?
ESP-03-203	REX-001	CAT5	Baseline ulcer:70x80 mm	patient very old (84 years old), at baseline all toes already amputated, no chance of healing from the beginning.	No
ESP-03-204	REX-001	FAILURE	Major Amputation	Gangrene at Administration; Randomized on 2018-11-19, amputation occurred on 2019-01-17	No
ESP-03-205	REX-001	FAILURE	Major Amputation	Randomized on 2019-02-11, amputation occurred on 2019-06-17	No
ESP-03-206	REX-001	CAT0	Baseline ulcer:8x8 mm	1 small superficial ulcer, otherwise foot normal. Healing could have been due to wound care and not REX001	No
ESP-03-207	REX-001	CAT2	Baseline ulcer: 15x10 mm 3x2 mm	A big ulcer was on middle toe, amputated later, and small ulcer healed. Gangrene at Screening	No
ESP-03-210	REX-001	FAILURE	Major Amputation	Extensive gangrene at Screening; Randomized on 2021-05-19, amputation occurred on 2021-07-28	No
ESP-06-206	REX-001	CAT5	Baseline ulcer: 15x10, 5x5, 3x4 mm	ulcer got much worse at month 12 but it was near gangrene at baseline, very rapid progression, by month 1 already very severe and not salvageable	No
HUN-03-201	REX-001	FAILURE	Major Amputation	Randomized on 2020-02-25, amputation occurred on 2020-11-09	No
LTU-01-201	REX-001	CAT3	Baseline ulcer: 3x3mm	very tiny ulcer on heel, healed likely due to wound care and not REX001	No
LTU-01-202	REX-001	FAILURE	Missed Visit	wound completely healed at month 9 (see image below)	Yes (ulcer completely healed at M9, assuming it stays healed at M12)
LVA-02-201	REX-001	FAILURE	Died before Month 12	Cause of death = Acute purulent pyelonephritis	No
LVA-02-202	REX-001	FAILURE	Died before Month 12	Cause of death = Cardiac death	No
NLD-03-201	REX-001	FAILURE	Died before Month 12	Cause of death = Sepsis and respiratory failure	No
PRT-04-201	REX-001	FAILURE	Major Amputation	Randomized on 2019-02-27, amputation occurred on 2019-04-01	No

Abbreviation: CAT = Category; RF = Rutherford; N/A = not applicable or no comments

Interpretation of efficacy: the RF category column described the success or failure of reaching the primary endpoint. Those less than 5 are a success. The last column shows the clinical interpretation despite a failed or successful reaching of the primary endpoint. As noted in the table, the efficacy of REX-001 cannot be ruled out with this study. i.e., the study likely was determined to be futile due to a design issue, as opposed to a failed product.

3.2 - 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) in the trial.

The following is the listing of all serious safety events.

Patient ID	Gender	Preferred Term	Event Start Date	Event Stop Date	Outcome of Event	Grade CTC/Severity	Reported Causality	Determined Causality
ESP-06-202	Male	Cardiac failure	25-JAN-2018	29-JAN-2018	Recovered	Mild	Unrelated	Unrelated
AUT-04-201	Male	Vascular graft occlusion	14-MAR-2018	14-MAR-2018	Recovered	Moderate	Unrelated	Unrelated
Unknown	Male	Peripheral arterial occlusive disease	03-MAR-2018	10-MAR-2018	Recovered w Sequelae	Severe	Unrelated	Unrelated
ESP-06-202	Male	Cardiac failure	14-MAR-2018	19-MAR-2018	Recovered	Severe	Unrelated	Unrelated
ESP-06-202	Male	Anaemia postoperative	10-MAR-2018	14-MAR-2018	Recovered	Severe	Unrelated	Unrelated
ESP-06-202	Male	Confusional state	15-MAR-2018	16-MAR-2018	Recovered	Moderate	Unrelated	Unrelated
AUT-04-201	Male	Peripheral arterial occlusive disease	18-APR-2018	19-APR-2018	Recovered w Sequelae	Severe	Possible	Unrelated
HUN-01-201	Male	Peripheral ischaemia	17-JAN-2019	30-JAN-2019	Recovered w Sequelae	Severe	Unrelated	Unrelated
ESP-03-204	Male	Rectal haemorrhage	26-JAN-2019	01-FEB-2019	Recovered	Moderate	Unrelated	Unrelated
ESP-03-204	Male	Peripheral ischaemia	17-JAN-2019	01-FEB-2019	Recovered w Sequelae	Severe	Unrelated	Unrelated

Patient ID	Gender	Preferred Term	Event Start Date	Event Stop Date	Outcome of Event	Grade CTC/Severity	Reported Causality	Determined Causality
PRT-04-201	Female	Necrosis ischaemic	15-APR-2019	12-MAY-2019	Recovered	Moderate	Unrelated	Unrelated
ESP-03-205	Male	Peripheral ischaemia	02-MAY-2019	16-MAY-2019	Recovered w Sequelae	Severe	Unrelated	Unrelated
ESP-10-201	Male	Acute kidney injury	21-MAY-2019	31-MAY-2019	Recovered	Severe	Unrelated	Unrelated
ESP-03-205	Male	Localised infection	17-JUN-2019	17-JUN-2019	Recovered w Sequelae	Severe	Unrelated	Unrelated
ESP-07-201	Female	Localised infection	05-OCT-2019	22-OCT-2019	Recovered	Moderate	Unrelated	Unrelated
CZE-01-201	Male	Peripheral ischaemia	22-OCT-2019	27-OCT-2019	Recovered	Moderate	Unrelated	Unrelated
ESP-01-207	Male	Acute coronary syndrome	16-DEC-2019	18-DEC-2019	Recovered	Severe	Unrelated	Unrelated
ESP-06-202	Male	Bronchospasm	08-JAN-2020	16-JAN-2020	Recovered	Moderate	Unrelated	Unrelated
ESP-06-202	Male	Cardiac failure	08-JAN-2020	16-JAN-2020	Recovered	Moderate	Unrelated	Unrelated
ESP-06-202	Male	Influenza	09-JAN-2020	16-JAN-2020	Recovered	Severe	Unrelated	Unrelated
ESP-01-207	Male	Vascular stent thrombosis	22-JAN-2020	23-JAN-2020	Recovered	Severe	Unrelated	Unrelated
ESP-01-207	Male	Cardiac failure	14-APR-2020	15-APR-2020	Recovered	Moderate	Unrelated	Unrelated
ESP-07-201	Female	Pain in extremity	30-JUL-2020	08-AUG-2020	Recovered	Severe	Unrelated	Unrelated
LVA-02-201	Female	Pyelonephritis acute	04-SEP-2020	06-SEP-2020	Death	Severe	Unrelated	Unrelated
LVA-02-201	Female	Vascular encephalopathy	01-AUG-2020		Not yet recovered	Severe	Unrelated	Unrelated

Patient ID	Gender	Preferred Term	Event Start Date	Event Stop Date	Outcome of Event	Grade CTC/Severity	Reported Causality	Determined Causality
LVA-02-201	Female	Peripheral ischaemia	20-AUG-2020	28-AUG-2020	Recovered w Sequelae	Severe	Unrelated	Unrelated
ESP-01-207	Male	Vascular stent stenosis	30-AUG-2020	01-SEP-2020	Recovered	Severe	Unrelated	Unrelated
ESP-03-208	Male	Anaemia	22-SEP-2020		Not yet recovered	Severe	Unrelated	Unrelated
ESP-03-208	Male	Hip fracture	21-SEP-2020	28-OCT-2020	Recovered w Sequelae	Severe	Unrelated	Unrelated
ESP-03-208	Male	COVID-19	11-SEP-2020	28-OCT-2020	Recovered	Moderate	Unrelated	Unrelated
ESP-03-203	Male	Death	17-NOV-2020	30-NOV-2020	Death	Severe	Unrelated	Unrelated
ESP-03-203	Male	Lung neoplasm malignant	17-NOV-2020		Not yet recovered	Severe	Unrelated	Unrelated
HUN-03-201	Female	Gangrene	09-NOV-2020	25-NOV-2020	Recovered w Sequelae	Severe	Unrelated	Unrelated
ESP-06-206	Male	Cellulitis	25-NOV-2020	08-MAR-2021	Recovered	Moderate	Unrelated	Unrelated
ESP-01-214	Male	Hip fracture	23-JAN-2021	30-JAN-2021	Recovered	Mild	Unrelated	Unrelated
ESP-07-201	Female	Peripheral ischaemia	03-FEB-2021	04-FEB-2021	Recovered	Moderate	Unrelated	Unrelated
ESP-06-206	Male	Peripheral ischaemia	08-MAR-2021	12-APR-2021	Recovered	Moderate	Unrelated	Unrelated
ESP-07-201	Female	Peripheral ischaemia	12-MAR-2021	19-MAR-2021	Recovered w Sequelae	Moderate	Unrelated	Unrelated
ESP-01-216	Male	COVID-19	08-MAR-2021	01-APR-2021	Death	Severe	Unrelated	Unrelated
ESP-01-216	Male	Pneumonia	14-MAR-2021	01-APR-2021	Death	Severe	Unrelated	Unrelated
ESP-03-208	Male	Urinary tract infection	07-MAY-2021	07-MAY-2021	Recovered w Sequelae	Moderate	Unrelated	Unrelated
ESP-03-208	Male	Physical disability	07-MAY-2021		Unknown	Severe	Unrelated	Unrelated

Patient ID	Gender	Preferred Term	Event Start Date	Event Stop Date	Outcome of Event	Grade CTC/Severity	Reported Causality	Determined Causality
ESP-07-201	Female	Postoperative wound infection	28-MAY-2021	11-JUN-2021	Recovered w Sequelae	Moderate	Unrelated	Unrelated
ESP-07-201	Female	Postoperative wound infection	21-MAY-2021	11-JUN-2021	Recovered w Sequelae	Moderate	Unrelated	Unrelated
LVA-02-202	Male	Cardiac death	17-JUN-2021	17-JUN-2021	Death	Severe	Unrelated	Unrelated
ESP-03-208	Male	Multiple organ dysfunction syndrome	07-JUN-2021	07-JUN-2021	Death	Severe	Unrelated	Unrelated
NLD-03-201	Male	Localised infection	18-AUG-2021	27-AUG-2021	Recovered w Sequelae	Severe	Unrelated	Unrelated
ESP-03-210	Female	Peripheral ischaemia	28-JUL-2021	02-AUG-2021	Recovered w Sequelae	Severe	Unrelated	Unrelated
GEO-03-201	Female	Diabetic gangrene	24-AUG-2021	26-AUG-2021	Recovered	Severe	Unrelated	Unrelated
CZE-01-201	Male	Peripheral ischaemia	12-FEB-2021	26-FEB-2021	Recovered	Moderate	Unrelated	Unrelated
ESP-01-214	Male	Gastrointestinal injury	03-OCT-2021	07-OCT-2021	Recovered	Moderate	Unrelated	Unrelated
GEO-03-201	Female	Diabetic gangrene	24-SEP-2021	30-SEP-2021	Recovered	Severe	Unrelated	Unrelated
ESP-06-205	Male	Peripheral ischaemia	23-AUG-2021	25-AUG-2021	Recovered	Moderate	Unrelated	Unrelated
GEO-02-203	Female	COVID-19 pneumonia	21-OCT-2021	05-NOV-2021	Death	Severe	Unrelated	Unrelated
NLD-03-201	Male	Sepsis	24-NOV-2021	25-NOV-2021	Death	Severe	Unrelated	Unrelated
NLD-03-201	Male	Respiratory failure	24-NOV-2021	25-NOV-2021	Death	Severe	Unrelated	Unrelated
LTU-01-202	Male	COVID-19 pneumonia	07-NOV-2021	15-NOV-2021	Recovered	Severe	Unrelated	Unrelated

Patient ID	Gender	Preferred Term	Event Start Date	Event Stop Date	Outcome of Event	Grade CTC/Severity	Reported Causality	Determined Causality
LTU-01-202	Male	Gangrene	07-NOV-2021	MAR-2022	Not yet recovered	Severe	Unrelated	Unrelated
LTU-01-202	Male	Cellulitis	07-NOV-2021	19-NOV-2021	Recovered w Sequelae	Severe	Unlikely	Unrelated
ESP-01-214	Male	Localised infection	20-JAN-2022	06-FEB-2022	Death	Severe	Unrelated	Unrelated
ESP-06-206	Male	Skin ulcer	08-NOV-2021	15-NOV-2021	Recovered w Sequelae	Severe	Unrelated	Unrelated
ESP-06-206	Male	Peripheral ischaemia	25-FEB-2022	02-MAR-2022	Recovered	Severe	Unrelated	Unrelated
ESP-03-210	Female	Peripheral ischaemia	12-APR-2022	14-APR-2022	Recovered w Sequelae	Severe	Unrelated	Unrelated
ESP-03-211	Male	Peripheral ischaemia	05-MAY-2022	08-MAY-2022	Recovered w Sequelae	Severe	Unrelated	Unrelated
LTU-01-202	Male	Gangrene	11-MAY-2022		Not yet recovered	Severe	Unrelated	Unrelated
NLD-03-202	Male	Skin ulcer	16-JUN-2022	21-JUN-2022	Recovered w Sequelae	Moderate	Unrelated	Unrelated
ESP-11-203	Male	Gangrene	21-JUL-2022	23-NOV-2022	Recovered w Sequelae	Severe	Unrelated	Unrelated
ESP-11-203	Male	Sepsis	20-SEP-2022	23-SEP-2022	Recovered	Severe	Unrelated	Unrelated
ESP-01-218	Male	Localised infection	29-JUL-2022	07-AUG-2022	Recovered w Sequelae	Severe	Unrelated	Unrelated
ESP-11-202	Male	Skin ulcer	02-AUG-2022	12-SEP-2022	Recovered w Sequelae	Severe	Unrelated	Unrelated
NLD-03-202	Male	Pain	30-AUG-2022	05-SEP-2022	Recovered w Sequelae	Severe	Unrelated	Unrelated
NLD-03-202	Male	Peripheral artery occlusion	30-AUG-2022	05-SEP-2022	Recovered w Sequelae	Severe	Unrelated	Unrelated
ESP-01-222	Male	Angina unstable	18-NOV-2022	30-NOV-2022	Recovered	Moderate	Unrelated	Unrelated

4 - ADDITIONAL INFORMATION

4.1 - GLOBAL SUBSTANTIAL MODIFICATIONS

No global substantial modifications were required.

4.2 - GLOBAL INTERRUPTIONS AND RE-STARTS

The study was never interrupted until the 50% interim analysis as described above.

4.3 - LIMITATIONS

No limitations or implications to declare.

4.4 - ACCURACY OF SUBMITTED INFORMATION

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

5 - CONTENT OF THE SUMMARY OF THE RESULTS OF THE CLINICAL TRIAL FOR LAYPERSONS

The information provided is an abbreviated report from a clinical study called "The Efficacy and Safety of Intra-Arterial Administration of REX-001 to Treat Ischaemic Ulcers in Subjects with Critical Limb Ischaemia Rutherford Category 5 and Diabetes Mellitus: A Pivotal, Placebo-Controlled, Double-Blind, Parallel-Group, Adaptive Trial." The study was conducted in accordance with Good Clinical Practice regulations and was a Phase 3 randomized, double-blind, placebo-controlled clinical trial that included patients with chronic limb threatening ischemia (CLTI) and diabetes.

The sample size was calculated based on the efficacy results from a Phase II trial conducted with REX-001 in 60 subjects with CLTI and diabetes. The study had two interim analyses, at 30% and 50%, and the primary endpoint was measured at month 12. The endpoints included the change in Rutherford classification from CLI Category 5 to Category 4 or lower 12 months after administration of REX-001 or placebo, change in Rutherford classification from CLI Category 5 to Category 3 or lower, change from baseline to visit 9 in TcpO2 (transcutaneous oxygen pressure), partial healing of ischemic ulcers (≥ 50% reduction in size as compared to ulcer size at baseline), and amputation-free survival. Patients were administered with the investigational product or placebo one time at baseline, and then followed for 1-year with periodic visits every ~3 months for safety and efficacy assessment. Additionally, patients were monitored for an additional 12 months for safety assessment. Autologous bone marrow-derived white blood cells (BM-WBCs) isolated from the bone marrow, or placebo, in a 2:1 ratio, were administered to consenting subject one time at baseline. 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.

The study was conducted with informed consent from all subjects before any trial procedure was conducted, and patients could have withdrawn from the study at any time without providing any justification. The primary objective of the study was 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 diabetes.

The study was stopped prematurely by the independent data safety monitoring committee (DSMB) at its predetermined interim analysis at 50% of information due to futility in September of 2022.

6 - SIGNATURE PAGE

Study title:	The Efficacy and Safety of Intra-Arterial Administration of REX-001 to Treat Ischaemic Ulcers in Subjects with Critical Limb Ischaemia Rutherford Category 5 and Diabetes Mellitus: A Pivotal, Placebo-Controlled, Double-Blind, Parallel-Group, Adaptive Trial
Investigational drug:	Autologous bone marrow mononuclear cells (BM-MNCs)
Protocol Code:	REX-001-005
EudraCT No.:	2016-003980-21

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**_____

Signature & Date: 19 June 2023