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PLX-PAD for critical limb ischaemia (with minor tissue loss) in patients unsuitable for revascularisation

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LAY SUMMARY

Critical Limb Ischaemia (CLI) is a cardiovascular condition resulting in the deterioration of blood vessels that supply the muscles in the limb. In CLI, blockages within the arteries restrict the flow of blood to affected limbs – typically the lower extremities. Pain in the feet, toes, and/or legs ensues and further complications may include ulcers and gangrenous non-healing wounds. Through surgery, blood circulation may be restored to the affected limb (revascularisation). However, in instances where this is not possible, amputation may be the only option to reduce pain and/or the risk of serious infection.

PLX-PAD is a type of cell therapy derived from the human placenta and works by stimulating the body's own regenerative mechanisms in healing damaged tissues. PLX-PAD responds to chemical distress signals from tissues that have been damaged by the restriction of blood flow, improving blood and oxygen supply, and promoting healing. PLX-PAD is administered by injection to the muscles of the limb(s). If approved, it may offer CLI patients who are unsuitable for surgical management a minimally invasive alternative to reduce instances of amputation and improve overall quality of life.

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TARGET GROUP

Critical limb ischaemia (with minor tissue loss) unsuitable for revascularisation

TECHNOLOGY

DESCRIPTION

PLacental eXpanded (PLX) cells are placenta-derived, mesenchymal-like adherent stromal cells that are designed to be administered to patients without the need for tissue or genetic matching. PLX-PAD is a form of cell therapy based on the PLX cell drug delivery platform that releases a combination of therapeutic proteins in response to a variety of local and systemic environmental signals. These cells release soluble biomolecules (such as cytokines, chemokines and growth factors), which act in a paracrine or endocrine manner to facilitate healing of damaged tissue by stimulating the body's own regenerative mechanisms. [1]

PLX-PAD responds to chemical distress signals from tissues that have been damaged by ischemia, muscle trauma, or inflammation by secreting a range of therapeutic proteins that trigger the body's own repair mechanisms. These secreted proteins drive the body to grow collateral blood vessels to bring oxygenated blood to ischemic tissue, heal damaged muscle, and dampen inflammation. PLX-PAD cells also modulate the immune system, which plays a central role in the body's response to injuries.[2]

PLX-PAD is in phase III development for the treatment of critical limb ischaemia (CLI) with minor tissue loss (Rutherford category 5) that is unsuitable for revascularisation.[3] In the ongoing phase III trial (NCT03006770), patients in the experimental arm receive PLX-PAD administered via 30 intramuscular injections (0.5 mL each) in the index leg. Each patient will be treated twice, with an interval of 8 weeks between treatments.[4]

PLX-PAD does not currently have a Marketing Authorisation in the EU for any indication. PLX-PAD is also in phase II clinical development in the EU and globally for intermittent claudication (IC) and musculoskeletal disorders including muscle injury.[1]

INNOVATION and/or ADVANTAGES

In view of the lack of suitable therapeutic options for the growing population of CLI patients, new approaches are warranted in order to reduce the number of amputations and their impact on quality of life and life expectancy. Minimally invasive via intermuscular injection, PLX-PAD cell therapy may provide an innovative regenerative treatment option for CLI patients that are unsuitable for revascularization.[5]

DEVELOPER

Pluristem Ltd.

AVAILABILITY, LAUNCH or MARKETING

PLX-PAD was granted Fast Track Designation for CLI by the US FDA in 2017.[1]

PATIENT GROUP

BACKGROUND

Critical limb ischaemia (CLI) is a severe manifestation of peripheral arterial disease (PAD), caused by progressive narrowing of one or more arteries in the lower extremities resulting in decreased blood flow and oxygen to the affected tissues and muscles. Risk factors for PAD and subsequent CLI include:[6]

- smoking
- diabetes
- high blood pressure
- raised cholesterol
- age

PAD is often not diagnosed or proactively treated until it becomes severe and obvious, significantly increasing the likelihood of a patient requiring a lower limb amputation. The most common initial symptom of PAD is leg pain while walking, known as intermittent claudication (IC). In most patients with IC the symptoms remain stable, but approximately 20% will deteriorate and develop CLI. Diabetes is a key risk factor for development of CLI as it is frequently associated with severe PAD, and diabetes sufferers are 20 times more likely to have a lower limb amputation.[6]

Symptoms of CLI include:[7]

- severe burning pain in legs and/or feet that continues at rest (ischaemic rest pain)
- pale, shiny, smooth and dry skin
- non-healing wounds and ulcers on feet and legs
- loss of muscle mass in legs

CLI is a complex condition, with significant variability in clinical practice ranging from either medical management or surgical management by revascularization or amputation.[8,9] For patients with CLI, both ulceration and amputation greatly reduces quality of life and are associated with high mortality. Patients who do not experience sufficient relief with paracetamol and/or opioids, or continue to experience pain after revascularisation or amputation, may be referred to a specialist pain management service.[10]

CLINICAL NEED and BURDEN OF DISEASE

In the United Kingdom 50-100 per 100,000 population cases of CLI are diagnosed each year, with anticipated increase due to aging population.[11] Within 1 year of onset, 25% of patients will have died, and 25% will have undergone major amputation.[12] Lower leg amputation is a high-risk procedure with a 30-day mortality of ±10% and less than 30% of surviving patients being ambulatory outdoors at 17 months of follow-up.[13] Diabetes UK have indicated that 20 diabetes-related amputations are performed in England every day with 7,370 diabetes-related amputations annually across the country.[6]

It is not possible to identify hospital admissions for patients with a primary diagnosis of CLI. However, in England in 2016/17 there were 3,298 hospital admission with primary procedure code (OPCS) X09 Amputation of leg, resulting in 112,215 Finished Consultant Episode bed days. 1,374 admissions were

coded with admission method of waiting list/planned/other (i.e. not emergency admissions), implying that these amputations were not following an immediate trauma.[14]

There are wide variations in amputation rates across the country, with differences in regional ethnicity and organisation of care a contributing factor.[15] The population likely to be eligible to receive PLX-PAD cell therapy could not be estimated from available published sources.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin (TA159). October 2008.
- NICE clinical guideline. Hypothermia: prevention and management in adults having surgery (CG65). December 2016.
- NICE clinical guideline. Peripheral arterial disease: diagnosis and management (CG147). August 2012.
- NICE quality standard. Diabetes in adults (QS6). August 2016.
- NICE quality standard. Peripheral artery disease (QS52). January 2014.
- NICE medical technologies guidance. The Debrisoft monofilament debridement pad for use in acute or chronic wounds (MTG17). March 2014.
- NICE medical technologies guidance. The MIST Therapy system for the promotion of wound healing (MTG5). July 2011.
- NICE guideline. Diabetic foot problems: prevention and management (NG19). January 2016.
- NICE guideline. Type 2 diabetes in adults: management (NG28). December 2015.
- NICE evidence summary. Critical limb ischaemia in peripheral vascular disease: intravenous iloprost (ESUOM24). December 2013.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. Service Specification: Specialized Vascular Services (Adult). 170004/S

OTHER GUIDANCE

- Recommended standards for reports dealing with lower extremity ischemia: revised version. *Journal of Vascular Surgery*, 1997[16]
- European Society for Vascular Surgery Guidelines Committee. Guidelines for Critical Limb Ischaemia and Diabetic Foot, 2011[17]

CURRENT TREATMENT OPTIONS

CLI treatments are predominantly limited to surgical interventions (revascularisation) that aim to bypass or remove arterial blockage. In CLI patients that are unsuitable for revascularisation, either as a result of calcified blood vessels or other underlying conditions, the alternative is limb amputation.[18] While other non-surgical treatment options have been studied including iloprost (an antiplatelet

drug), sympathectomy, and spinal cord stimulation, none merit sufficient evidence to support their routine use in the treatment of CLI patients.[19]

EFFICACY and SAFETY

Trial	NCT03006770; PLX-PAD in critical limb ischaemia; PLX-PAD vs placebo; phase III
Sponsor	Pluristem Ltd.
Status	Ongoing
Source of Information	Trial registry[4], company press release[20], Global Data[3]
Location	6 EU countries (incl UK), USA
Design	Randomised, placebo-controlled, parallel assignment, double-blind
Participants	n=246 (planned); aged ≥45 years; critical limb ischaemia (CLI); Fontaine class IV, CLI with minor tissue loss (Rutherford category 5), phase III subjects with Rutherford category 5 who are unsuitable candidates for revascularization
Schedule	Randomised to receive either placebo or PLX-PAD administered via 30 IM injections in the index leg (0.5 mL each); each subject treated twice, with an interval of 8 weeks between treatments
Follow-up	Twelve months for last patient, up to 3 years from enrolment
Primary Outcomes	• Amputation Free Survival (AFS) (up to 3 years from enrolment)
Secondary Outcomes	• Time to first occurrence of any of the events (in index leg) - major amputation, revascularization due to worsening of CLI, a new gangrene, all-cause mortality (up to 3 years from enrolment) • Time to major amputation of the index leg (up to 3 years from enrolment) • Complete wound healing in the index leg (up to 1 year from enrolment) • Change from baseline in ischemic pain as assessed by numerical rating scale (NRS) (up to 6 months from enrolment) • Time to adjudicated major amputation of the index leg or death (up to 3 years from enrolment)
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date estimated May 2020

ESTIMATED COST and IMPACT

COST

The cost of PLX-PAD is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☒ Other: *improved quality of life for patients/carers*

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☒ Other reduction in costs: *reduction in cost of amputations, treatment for non-healing wounds, and associated disabilities*

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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