

## CRITICAL LIMB ISCHEMIA

### DISEASE BURDEN AND CLINICAL NEED

Critical Limb Ischemia (CLI) is an advanced stage of the peripheral artery disease (PAD) spectrum characterized by chronic ischemic rest pain, ulcers, or gangrene and associated with high amputation and mortality rates and poor quality of life. CLI is an eminent condition in the general population with a strong social impact.

The prevalence of CLI in the population aged 60-90 years is about 1% (range 0.5-1.2%) with a male to female ratio of about 3:1. In total 5-10% of patients with asymptomatic peripheral arterial obstructive disease (PAD) or claudication will progress to CLI within 5 years from the first diagnosis.

Despite improvements in medical care and revascularization, patients with CLI continue having a high risk of major amputation (below the knee or higher) and death from cardiovascular complications. In addition to symptomatic therapy, the main line of treatment for CLI is surgical or endovascular revascularization. However, up to 40% of patients are eligible for such interventions, due to excessive operative risk or unfavorable vascular involvement.

Patients suffering from CLI, who are unsuitable for revascularization, face severely limited treatment options. Indeed, apart from statins and anti-platelet drugs (to control cardiovascular risk factors), painkillers for pain relief and local wound care, there is no effective treatment option other than limb amputation. Based on a Cochrane meta-analysis, despite some positive results regarding rest pain relief, ulcer healing and decreased amputation rate, there is no conclusive evidence on the long-term effectiveness and safety of different prostanoids in patients with CLI.

In conclusion, in those CLI patients unsuitable for revascularization, there is a crucial need for new medical therapies in order to substantially reduce the number of amputations, to relieve the impact on patients' quality of life and increase life expectancy.

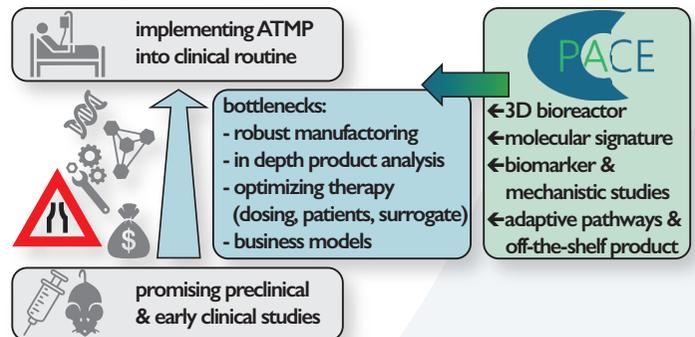
## PACE FOCUS

PACE aims for advancing the clinical application of the "off-the-shelf" allogeneic placenta-derived stromal cell product (PLX-PAD) for critical limb ischemia (CLI) - by performing a clinical phase III trial integrated with mechanism-based research.

The specific objectives of PACE are:

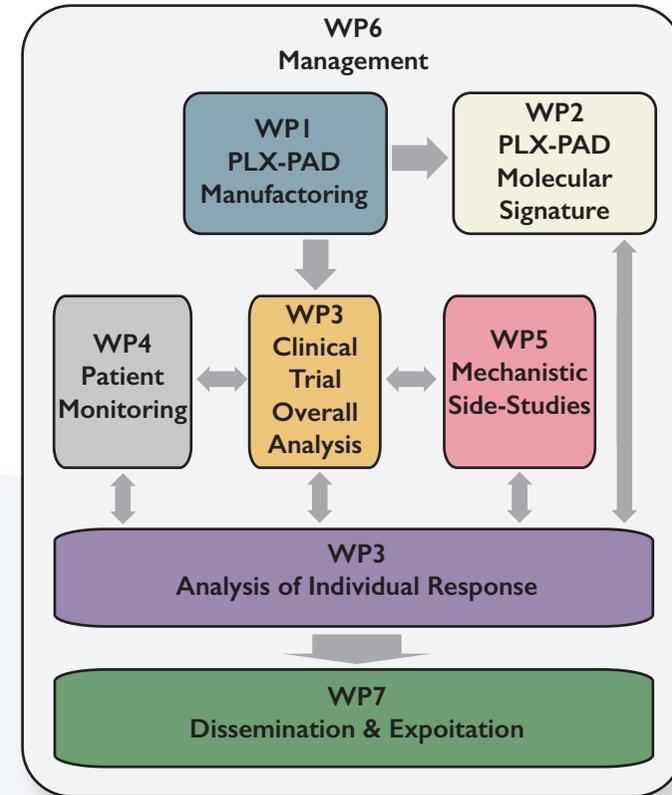
- To evaluate the efficacy and safety of local intramuscular (IM) injections of PLX-PAD in CLI patients with minor tissue loss who are unsuitable for revascularization.
- To confirm the robustness of the manufacturing process of PLacenta-eXpanded stromal cells optimized to support regeneration in CLI by in-depth characterization of the PLX-PAD product batches.
- To present a model for the clinical development of PLX-PAD using the new "Adaptive pathways" approach defined by the European Medicines Agency (EMA).
- To look beyond the traditional clinical trial endpoints of safety and efficacy by actively investigating the mechanisms of action of PLX-PAD therapy, exploring biomarkers in order to understand response/non-response in particular patients and to reveal the impact of the major risk factor, type2 diabetes (T2D), on the response to therapy.
- To disseminate project results thereby advancing the clinical use of Advanced Therapy Medicinal Products (ATMP) for diseases with high, unmet medical need by performing a high quality clinical trial with emerging therapeutics integrated with mechanism-based research.

**PACE targets key bottlenecks** on the road towards integrating cell therapy into routine medical care



## PACE DESIGN

The specific objectives of PACE will be achieved in seven work packages (WP).



## PACE ALLIANCE

The PACE consortium is coordinated by the Charité Berlin and it brings together seven partners from four countries with excellent expertise in the fields of cell therapy and CLI studies.

PACE partners, from industrial and academic background, are world-leading experts in biotechnological clinical grade (GMP) cell manufacturing, preclinical and clinical cell therapy, and biomarker analyses with well-recognized expertise in designing and performing clinical trials, including those with ATMPs, integrated with scientific studies. The PACE Consortium has access to a clinically well-characterized patient cohort and to biological material from those patients. Experts in clinical research and patient care of both peripheral arterial diseases and diabetes guide the study.

## PARTICIPANTS



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A multicenter phase III study using HLA-unmatched allogeneic placenta-derived stromal cells (PLX-PAD) for the treatment of severe critical limb ischemia accompanied by mechanistic studies

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