Protocol and rationale for the Study of Angiogenic cell therapy for Progressive Pulmonary Hypertension: Intervention with Repeat dosing of eNOS-enhanced EPCs (SAPPHIRE)

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Rationale: Pulmonary Arterial Hypertension (PAH) is a progressive and incurable disease. PAH is associated with perturbations in endothelial function, in particular decreased nitric oxide (NO) bioavailability, and profound loss of lung microvasculature. SAPPHIRE is a phase II clinical trial to establish the efficacy and safety of angiogenic therapy to restore the microvasculature with repeat dosing of autologous Endothelial Progenitor Cells (EPCs) transfected with human endothelial nitric oxide synthase (eNOS) in patients with refractory PAH (NCT03001414).
Objective: To determine whether a course of four doses of eNOS gene-enhanced autologous EPCs, delivered monthly, is effective in improving exercise tolerance in participants with severe PAH who are also receiving PAH-targeted treatments.
Study Design: We designed a 3-arm randomized trial to address the patients' desire to receive therapy while evaluating the efficacy of repeated and continuous doses. A total of 45 participants will be enrolled in this multi-centre, phase II, randomized, double-blind, placebo-controlled trial to receive 4-monthly IV injections of eNOS-enhanced EPCs (20M) or saline as follows: group 1 will receive saline in the first 6-month course and then cross over to cell therapy; group 2 will receive cells followed by saline; and group 3 will receive two courses of cells for a total 8 treatments (160M cells). Up to 8 centres across Canada will participate. The primary endpoint is the difference in six-minute walk distance (6MWD) at 6 months between participants receiving a course of 4 monthly doses of eNOS-EPCs compared to placebo. Blinding will continue beyond 6 months in order to address a number of secondary endpoints, including 6MWD, pulmonary vascular resistance and right ventricular function, over the entire 12-month period of the study, which will provide additional insights into the safety and efficacy of this treatment. Enrolment began in Sept 2017 and 4 clinical sites have been initiated to date.

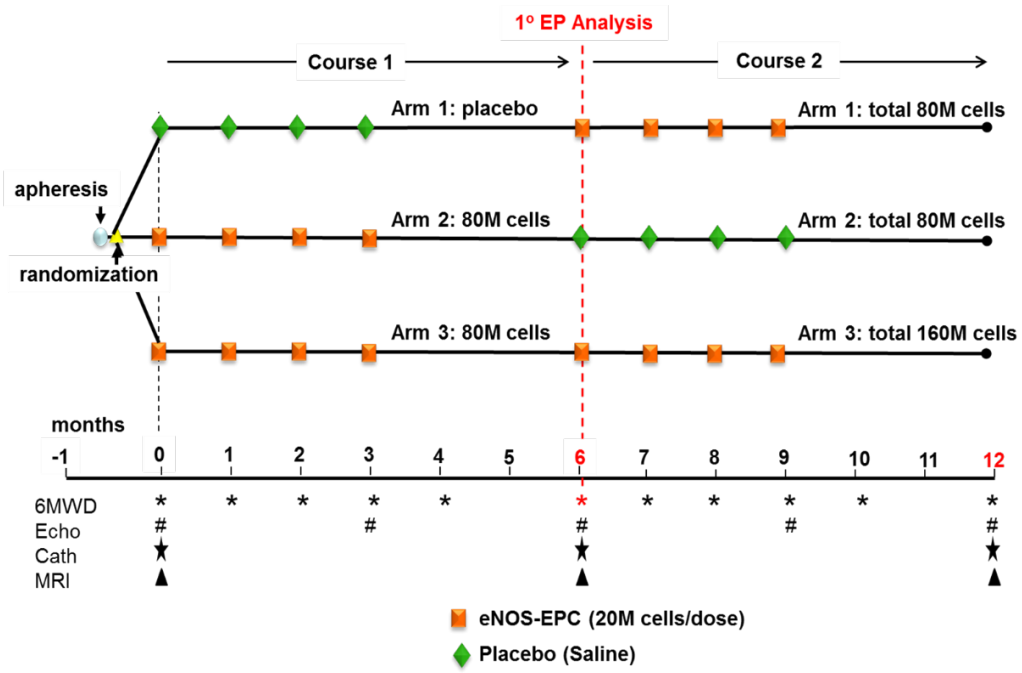

Figure 1: The SAPPHIRE study design