IRON-PH PROTOCOL SYNOPIS

Trial Title	A randomized, double-blind, placebo-controlled, multicentre trial, assessing the impact of ferric carboxymaltose on exercise capacity and functional status in pulmonary hypertension
Short title	IRON-PH
EudraCT number	2025-522936-14-00
Clinicaltrials.gov	TBD
Internal reference	Z-2025090
Trial Design	Double-blind, placebo-controlled, randomized trial testing the effect of ferric carboxymaltose on the change in 6 minute walking distance (6MWD) from baseline to 24 weeks in patients with pulmonary hypertension.
Trial Participants and setting	Main <u>inclusion criteria</u> (detailed definitions in the text): • ≥18 years of age • WHO functional class II – IV • Iron deficiency defined as TSAT <21% • Pulmonary hypertension (PH) defined by echocardiography and/or right heart catheterization (RHC) according to definition specific for group 1, group 2 and group 4 PH. Main <u>exclusion criteria</u> • Screening haemoglobin < 8 g/dl or >15 g/dl • Screening Ferritin > 700 ng/mL • Known hypersensitivity reaction to any component of FCM • Group 1 PH associated with veno-occlusive diseases. • Primary diagnosis of group 3 PH • Primary diagnosis of group 5 PH • Treatment with oral or other IV iron therapies at screening • Current or planned mechanical circulatory support or lung/heart transplantation. • Any planned surgery or procedure leading to expected significant blood loss (defined as more than 250 ml = equal to 125mg of iron).

	• Haemodialysis or peritoneal dialysis (current or planned within the next 24 weeks). • Inability to return for follow up visits within the necessary windows. • Concurrently in a study with another investigational product. • Uncorrected moderate to severe aortic stenosis (AVA <1.5cm² and mean gradient >20 mmHg) or severe valvular regurgitation (except tricuspid regurgitation) • Impression by the investigator that the patient cannot perform a 6MWT. • Active infection as judged by the investigator. • Pregnancy or desire to become pregnant during the study duration.
Intervention	Ferric carboxymaltose (masked to assure blinding) diluted in 100 ml of NaCl 0.9% administered intravenously over 15 minutes. The individualized dose administration will be determined according to summaries of product characteristics (SmPC) and administered at baseline (and at 4 weeks if applicable [e.g. total dose > 1 gram]).
Control	Masked placebo will consist of NaCl 0.9% 100 ml administered intravenously over 15 minutes, with dose frequency similar to the intervention arm to assure blinding.
Primary Endpoint	The change in 6 minute walking distance from baseline to the 24 week follow-up visit.
Secondary Endpoint(s)	• The change in EQ5D from baseline to the 24 week follow-up visit. • The change in Minnesota living with heart failure questionnaire from baseline to the 24 week follow-up visit. • The change in Fatigue Severity Scale from baseline to the 24 week follow-up visit. • The hazard ratio between allocated treatment arms in developing the composite clinical worsening event during the entire trial follow-up (from FPI to LPLV). • The incremental cost-effectiveness ratio of ferric carboxymaltose relative to the control arm. • The proportion of patients developing serious AE related to the study drug or AE leading to study drug discontinuation
Planned Sample Size	306 patients

Treatment duration	Maximum of 4 weeks. The intervention or control will be given at the day of randomization and during a 4 week visit when applicable (patients requiring a total dose of ferric carboxymaltose > 1gram).
Follow up duration	24 weeks
Duration of the trial (FPI-CSR)	3 years