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 (if applicable)	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 inclusion criteria (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 exclusion criteria • 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 <1.5cm^2 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(s)	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

TRIAL FLOW CHART

Figure 1: Trial flow chart.

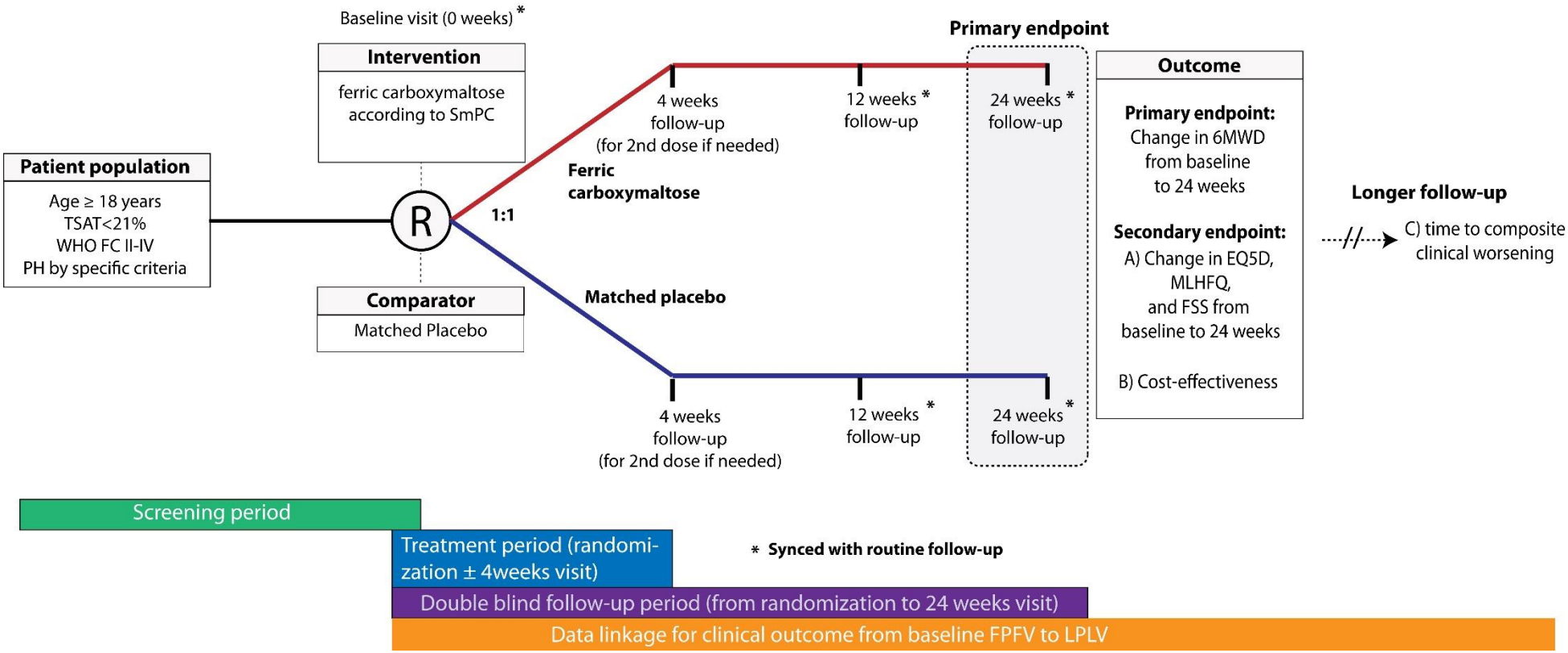

Table 1: Inclusion and exclusion criteria of the IRON-PH trial

Inclusion criteria	Exclusion criteria
• ≥18 years of age • WHO functional class II – IV • Iron deficiency defined as TSAT <21% (no more than ≥3 months old at randomization). • PH defined by echocardiography and/or right heart catheterization (RHC) according to the following WHO groups: - **Group 1 PH**: • Patients with a diagnosis of idiopathic PAH, hereditary PAH, drug induced PAH or PAH and associated with CTD or CHD (historical RHC available) on stable and optimized doses of PAH targeted therapies for at least 4 weeks before randomization. • Echocardiographic evidence of a high or intermediate probability for PH as per 2022 ESC PH guidelines.[19] - **Group 2 PH** and baseline LVEF > 50% on imaging modality within last 6 months before randomization and on stable doses of loop diuretics and HFpEF therapies[a] for 4 weeks. Group 2 PH can be included based on echocardiography or *RHC: • Echocardiography (<6mo before randomization): - Presence of LVH or LA-enlargement - E/e' >15 (at rest or exercise) - TRVmax >2.8 m/s (at rest) or mPAP/CO>3 mHg/L/min (exercise) or echocardiographic evidence of high or intermediate probability for PH as per 2022 ESC PH guidelines. [19] • *RHC (<6mo before randomization) - mPAP > 20 mmHg - PCWP > 15 mmHg at rest or PCWP/CO-slope > 2mmHg/L/min or exercise PCWP>25mmHg, or PCWP 13-15 mmHg with elevation ≥18mmHg after 500 cc Fluid Challenge - **Group 4 PH**: • Inoperable CTEPH • persistent/recurrent CTEPH (> 1 year after endarterectomy or > 6 months after balloon pulmonary angioplasty) ineligible for balloon pulmonary angioplasty. • Echocardiographic evidence of a high or intermediate probability for PH as per 2022 ESC PH guidelines.[19]	• Screening haemoglobin < 8 g/dl or >15 g/dl • 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 investigator that patient cannot perform a 6MWT • Active infection as judged by the investigator. • Pregnancy or desire to become pregnant during the study duration.

**** While patients can be enrolled exclusively on echocardiography it is highly recommended to perform a RHC in patients in group 2 PH at baseline, as this is also a class I recommendation in the ESC PH guidelines.*** ***Abbreviations****: AVA=aortic valve area, FCM= ferric carboxymaltose PH= pulmonary hypertension, mPAP= mean pulmonary artery pressure, PAH= pulmonary arterial hypertension, CHD= congenital heart disease, CTD= connective tissue disease, LVEF= left ventricular ejection fraction, CTEPH= chronic trombo-embolic PH, WHO FC= World Health Organization functional class. A: HFpEF therapies include mineralocorticoid receptor antagonists, sodium glucose linked*

transporter inhibitors and GLP1-receptor agonists. B= severe mitral regurgitation defined as Effective Regurgitant Orifice Area (EROA): ≥ 0.40 cm²), visual severe pulmonary regurgitation grade 4 by 4 and severe aortic regurgitation as EROA: ≥ 0.30cm².

Table 2: Study visit and data collection overview.

Procedure	Randomization visit (**Baseline**)	Week 4 Dosing 2 (if needed) (**W4**)	Week 12 (**W12**)	Week 24 **(W24)**	Long-term follow-up (**LT**)
Window	T0[1]	28 days post T0 ± 7d	84 days post T0 ± 7d	168 days post T0 ± 14d	Trial LPLV (+up to 2 months)
Demographics					
Inclusion/exclusion criteria	X (routine)				
Demography	X (routine)				
Medical history	X (routine)				
Disease history	X (routine)				
Concomitant medication	X (routine)		X (routine)	X (routine)	
Informed consent	X				
Study intervention information					
Dosing FCM/placebo	X	X			
Compliance/accountability	X	X			
Physical data					
Vital signs	X (routine)	X	X (routine)	X (routine)	
Height and weight	X (routine)				
12 lead ECG	X (routine)		X (routine)	X (routine)	
Study efficacy data					
6MWT	X		X	X	
WHO FC assessment	X (routine)		X (routine)	X (routine)	
EQ5D	X		X	X	
MLHFQ	X		X	X	
FSS	X		X	X	
Study safety data					
Adverse events related to intervention	X	X	X	X	
Serious adverse events	X	X	X	X	

Procedure	Randomization visit (**Baseline**)	Week 4 Dosing 2 (if needed) (**W4**)	Week 12 (**W12**)	Week 24 **(W24)**	Long-term follow-up (**LT**)
Window	T0[1]	28 days post T0 ± 7d	84 days post T0 ± 7d	168 days post T0 ± 14d	Trial LPLV (+up to 2 months)
Laboratory data					
Hematology[2]	X (routine)		X (blinded)	X (blinded)	
Iron levels[2]	X (routine)		X (blinded)	X (blinded)	
Chemistry	X (routine)		X (routine)	X (routine)	
Liver Function Test	X (routine)		X (routine)	X (routine)	
Phosphate	X (routine)		X (routine)	X (routine)	
Pregnancy test[3]	X (routine)	X (routine)			
Data collection related to composite clinical worsening event (vital status, heart or lung transplant and urgent admission requiring intravenous diuretics)					X (through data linking)

***Abbreviations**: 6MWT= 6 minute walking test, WHO FC= world health organization functional class, MLHFQ= Minnesota Living with Heart Failure Questionnaire, FSS = Fatigue Severity Scale, WOCBP = Women Of Childbearing Potential.* ***Explanation:** Grey boxes indicate routinely collected data during an in person visit. Green boxes indicate additional collection data (study specific) part of IRON-PH trial during an in person visit. Orange indicates data collected using data linkage not requiring an in person visit. [1] All routine assessments and data that are requested at the Randomization visit may be performed or collected within 3 months prior to this visit, except for vital signs which should be performed on the day of study medication administration. All study specific assessments are to be done on the day of study medication administration, except informed consent collection which may be performed within 3 months prior to study medication administration. See section 8.7.1 for more information. [2] All sample that are being collected in the light of this study are considered standard of care. However , during week 12 and 24 the results of the haematology and iron level test are to be blinded. Therefore these tests are considered study specific. [3] A pregnancy test should be performed in WOCBP who are not on effective contraceptive measures as per standard of care.*