Imperial College London

What is the effect of intravenous iron supplementation on exercise capacity and quality of life in patients with IPAH and iron deficiency?

(Short title: Ferinject® for iron deficiency in IPAH patients)

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study according to the protocol and in compliance with Good Clinical Practice standards and other applicable regulatory requirements.

- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.

- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receive the appropriate information throughout the study.

Investigator Name:		
Investigator Address:		
Investigator Signature:		Date:

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GLOSSARY OF ABBREVIATIONS

6MWT	6 –minute walk test
AE	Adverse event
AR	Adverse reaction
BP	Blood pressure
bpm	Beats per minute
CAMPHOR	Cambridge Pulmonary Hypertension Outcome Review
CMR	Cardiac Magnetic Resonance
CPET	Cardiopulmonary exercise test
CRF	Case Report Form
FPFV	First patient first visit
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigation Medicinal Product
IPAH	Idiopathic pulmonary arterial hypertension
i.v.	Intravenous
LPLV	Last patient last visit
NT pro-BNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PAH	Pulmonary arterial hypertension
PAP	Pulmonary arterial pressure
PCWP	Pulmonary capillary wedge pressure
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance
RA	Regulatory Authority
REC	Research Ethics Committee
RHC	Right heart catheterisation
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SPM	Study Procedures Manual (study specific SOP binder)
sTfR	Soluble transferrin receptor
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Systemic vascular resistance
WHO	World Health Organisation

Study Summary

TITLE	What is the effect of intravenous iron supplementation on exercise capacity and quality of life in patients with idiopathic pulmonary arterial hypertension (IPAH) and iron deficiency?
PHASE	II
DESIGN	Multi-centre, double-blind, randomised, placebo-controlled, crossover study
OBJECTIVES	To assess the clinical value of using intravenous iron (ferric carboxymaltose) infusion (Ferinject®) in iron deficient patients with IPAH.
OUTCOME MEASURES	**Primary:** • Endurance time at the end of endurance bicycle cardiopulmonary exercise testing at 80% peak work rate determined from the incremental exercise test **Secondary:** • Incremental bicycle cardiopulmonary exercise testing - peak VO_2 (ml/min/kg), VO_2 at metabolic threshold, VE/VCO_2 slope, VO_2/WR slope and O_2 pulse. • VO_2 at the end of endurance bicycle cardiopulmonary exercise testing at 80% peak work rate determined from the incremental exercise test • Gas exchange at 3 minutes after the start of the work phase of an endurance exercise test at 80% peak work rate determined from the incremental exercise test • Iron indices – serum iron, transferrin saturations, ferritin, soluble transferrin receptor (sTfR), unsaturated iron binding capacity (UIBC), red cell distribution width (RDW) and erythropoietin (EPO) levels • 6 minute walk distance and Borg dyspnoea scale • NYHA WHO functional class • NT-pro-BNP • Quality of life (CAMPHOR questionnaire) and the self-reported Patient Global Assessment • Safety - the occurrence of adverse events • Cardiac MRI - right ventricular volumes, mass, ejection fraction, stroke volume and diastolic function (at sites where facility is available)
POPULATION	An estimated 60 patients will be enrolled.
STUDY CENTRES	5 centres in UK/EU.
STUDY DURATION	**FPFV:** Q4 2011 **LPLV:** Q4 2017
ELIGIBILITY	**Inclusion criteria** 1. Males or females aged between 16–75 years old 2. PAH which is idiopathic, heritable or associated with anorexigens. 3. Iron deficiency as defined by any one of the following criteria: sTfR levels > 28.1 nmol/l (where sTfR analysis is available) or one of the following: Ferritin < 37 ug/l; transferrin saturations < 16.4%; iron < 10.3 umol/l. 4. Documented diagnosis of PAH by right heart catheterisation performed at any time prior to Screening showing: resting mean pulmonary artery pressure >25mmHg, pulmonary capillary wedge pressure =/< 15 mm Hg and normal or reduced cardiac output; 5. 6 minute walking distance greater than 50m at entry; 6. Stable on an unchanged PAH therapeutic regime (any combination of endothelin receptor antagonist, phosphodiesterase inhibitor or prostacyclin

	analogue) for at least 1 month. 7. Able to provide written informed consent prior to any study-mandated procedures 8. Female subjects of child-bearing potential are eligible to participate if they agree to use one of the following contraception methods: • Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: o oral o intravaginal o transdermal • Progestogen-only hormonal contraception associated with inhibition of ovulation: o oral o injectable o implantable • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion • Vasectomised partner • Sexual abstinence **Exclusion criteria** 1. Unable to provide informed consent. 2. Clinically-significant renal disease (Creatinine clearance < 30 ml/min per 1.73 m^2 calculated from CKD-Epi http://www.qxmed.com/renal/Calculate-CKD-EPI-GFR.php) or liver disease (including serum transaminases > 3 times upper limit of normal). 3. Haemoglobin concentration <10 g/dl. 4. Patients will be excluded if any single parameter (iron, ferritin or transferrin saturation) exceeds 1x upper limit of normal (ULN) in the local lab reference range. 5. Patients with moderate to severe hypophosphatemia as defined as <0.65mmol/L 6. Known to have haemoglobinopathy e.g. sickle cell disease, thalassaemia. 7. Admission to hospital related to PAH or change in PAH therapy within 1 month prior to Screening. 8. Evidence of left ventricular disease or significant lung disease on high-resolution CT scanning or lung function as judged by the investigator 9. Acute or chronic infection or inflammation. 10. Significant uncontrolled asthma as judged by the investigator, eczema or atopic allergies. 11. Females who are lactating or pregnant. 12. Individuals known to have HIV, Hepatitis B or C or Creutzfeld-Jakob disease. 13. Known hypersensitivity to Ferinject® or any of its excipients and any other iron supplement preparation. 14. Evidence of disturbances in utilisation of iron. 15. Significant blood loss (e.g. GI bleed) within the last 3 months or history of menorrhagia.

	16. Unable to perform a Cardiopulmonary Exercise Test i.e. due to syncope or musculoskeletal factors. 17. Patients who have received an investigational medicinal product within 30 days of entering the baseline visit
TREATMENT	All the study participants will attend a screening visit, two treatment periods at Week 0 and Week 12, telephone visits at Week 2 and Week 14 and a follow up visit at Week 24 to evaluate the kinetics of iron re-depletion. Potential participants will be screened using data collected during their routine outpatient appointment at the Pulmonary Hypertension Service. Any unavailable or missing data will be collected at the baseline visit (week 0) once the patient has provided written informed consent. Eligible participants will be admitted to the research unit for up to 3 days in order to complete the Baseline (Week 0) assessments including a physical examination, medical history, ECG, bloods to assess routine haematology and clinical chemistry and measure biomarkers, 6-Minute Walk Test, CAMPHOR questionnaire and incremental and endurance cardiopulmonary exercise tests (CPET). As outlined in Figures 1, following completion of the Baseline assessments at Week 0 patients will be randomly allocated 1:1 to receive an infusion of either Ferinject® or saline. At Week 2, participants will attend a phone call from the research unit for a follow up visit. This will include any AE or medication and PGA questionnaire. At Week 12 all participants will be admitted to the research unit for up to 3 days to repeat the assessments done at Baseline (Week 0). Following completion of the Week 12 procedures, the patients will be switched to the other treatment arm (i.e. those who received Ferinject® at baseline will be administered a saline infusion, and vice versa). Thereafter participants will have a telephone follow up assessments at Weeks 14. The assessments at these visits are the same as for Week 2. Participants will have a final hospital follow up visit at Week 24 during which the assessments will be the same as those performed at baseline and Week 12. At selected centres participants will be given the option to undergo additional cardiac MRI (Weeks 0, 12 and 24). At the Sheffield site only, if participants agree, they will have two extra blood samples taken (50 ml extra in total) to assess neutrophil and peripheral blood mononuclear cell function and expression at Week 0 and 2 or Week 0 and 12 of study participation.

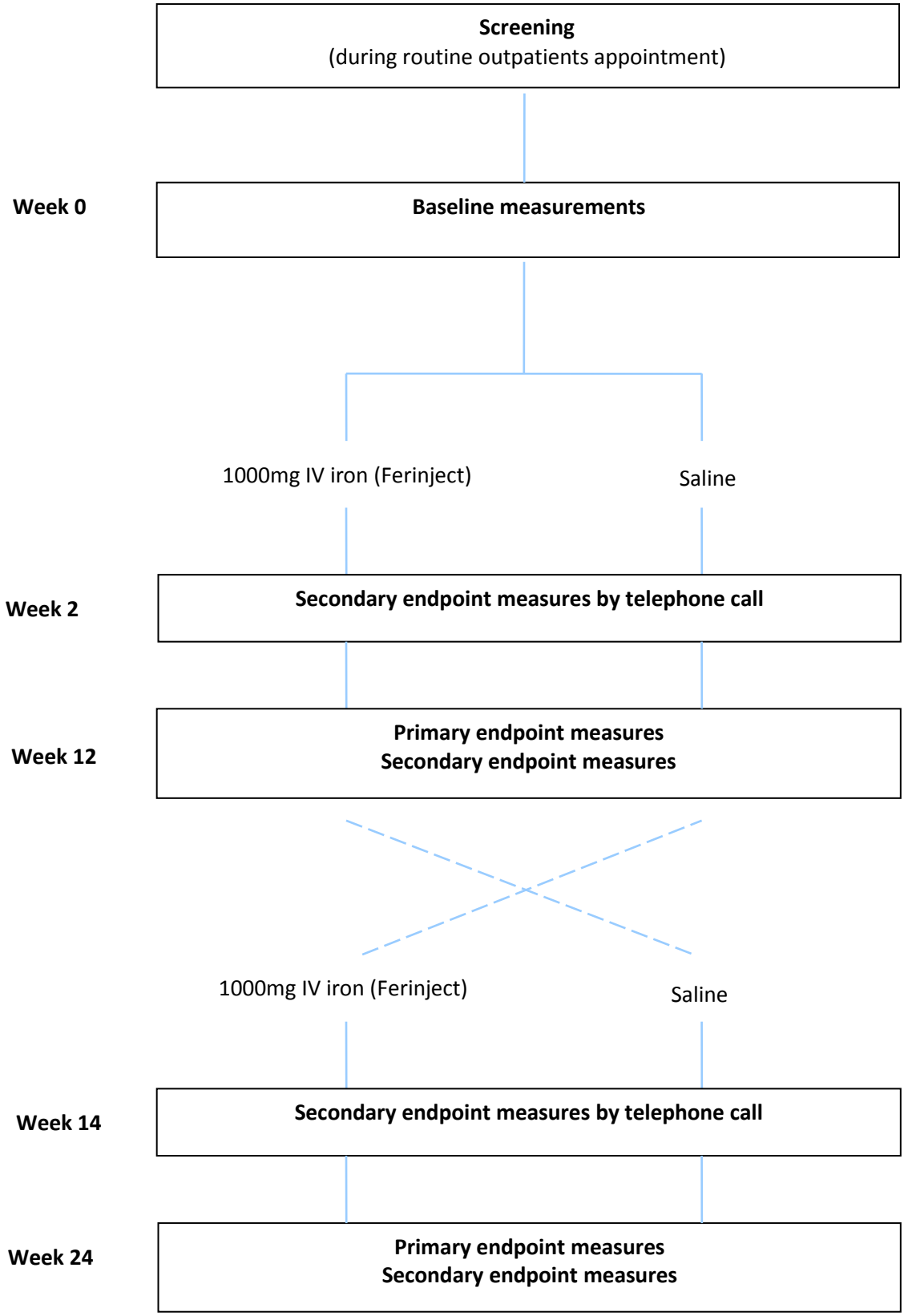

Figure 1 – Schematic overview of study to determine the effect of intravenous iron supplementation on cardiopulmonary haemodynamics and exercise capacity in iron deficient patients with IPAH.

1. BACKGROUND AND RATIONALE

Iron deficiency in the absence of anaemia is now well documented in patients with idiopathic pulmonary arterial hypertension, IPAH (1-3). Estimates suggest a prevalence of 43 to 60% and it is associated with poor survival (1). Oral iron replacement has been explored as a treatment by Ruiter et al (2011) with only limited response in 44% of patients, consistent with impaired absorption of oral iron from the gut from raised hepcidin levels (1), and the authors conclude that a trial of intravenous iron therapy is required. Ruiter et al (2015) have treated 15 patients with ferric carboxymaltose (Ferinject®) given as a single infusion and demonstrated restoration of serum iron levels (4). Viethen et al (2013) have treated 20 patients, again through a single infusion of 1000mg over 15min of ferric carboxymalose (Ferinject®), and successfully restored serum iron (5). The authors conclude "that parenteral iron supplementation with ferric carboxymaltose … is well tolerated in patients with PAH and iron deficiency". But as these studies were open-label, a double-blind proof-of-concept study is essential to help decide on the future use of intravenous ferric carboxymaltose (Ferinject®) in IPAH. This study will establish whether iron supplementation has clinical benefit. If there is no evidence of improvement, only a small patient population has been exposed and costs are kept to a minimum. If the data support a potentially useful therapeutic effect and suggest this drug is safe, the study will be used to power a Phase 3 study to address efficacy.

A 24-week double-blind, randomised, placebo-controlled, crossover study will investigate whether a single dose of 1g of Ferinject® improves exercise capacity and quality of life and is well-tolerated. This is a multicentre study. All patients will be followed for up to 24 weeks after dosing with Ferinject® to measure the kinetics of iron re-depletion.

Patients with IPAH and iron-deficiency, who have been stable on their current therapy for the preceding 1 month, will be treated with 1000 mg or 15 mg/kg (whichever is the smaller) Ferinject® in line with the Summary of Product Characteristics (SmPC) and clinical experience with the product. Soluble transferrin receptor (sTfR) is the best measure of iron deficiency in inflammatory diseases such as IPAH (>28.1 nmol/l). Where available, sTfR levels will be used as the screening tool to assess iron deficiency and inclusion in to the study. But as it is not routinely available at all participating centres, iron deficiency will also be defined by standard laboratory measures of ferritin < 37 ug/l, iron < 10.3 umol/l or transferrin saturations < 16.4%. Using these criteria, modelling of data from our previous work (1) show that 83% of patients will have raised sTfR levels> 28.1 nmol/l.

A formula exists to guide the amount of iron replacement required to render patients with anaemia iron-replete. This is based on the difference between current and target haemoglobin. In IPAH, this formula is likely to be inappropriate since the target haemoglobin is not known as patients may be hypoxaemic and thus require higher levels of haemoglobin. Indeed, many patients with iron deficiency have normal haemoglobin levels, but increased circulating EPO levels, implying an ongoing drive to increased red cell mass. Patients in the FERRIC-HF trial of iron supplementation in congestive heart failure were defined as having iron deficiency if ferritin was less than 100 ug/l or between 100 and 300 ug/l with transferrin saturations < 20% (6). By 4 and 16 weeks, 781 ± 94 and 1269 ± 297 mg iron sucrose had been given to the non-anaemic group (Hb > 12.5 g/dl) and 1051 ±219 and 1583 ± 366 mg had been given to the anaemic group. Iron sucrose can be given in doses up to 200mg, whereas Ferinject® can be given in doses up to 1000mg due their differing pharmacokinetics. We will give a single 1000mg (or 15 mg/kg) dose to answer whether this simple strategy is of benefit and well-tolerated. Experience from Viethen et al (2013) and Ruiter et al (2015) in a total of 35 patients indicate that this is well tolerated and does not lead to iron overload (4,5). Using full iron profiling we will be able to determine how long this dose maintains iron repletion.

Ferinject® has recently been used in a large phase III trial in heart failure (7). Adverse events were few in 304 patients assigned to receive Ferinject® and were not significantly different from the placebo group (n=105). Only 2 patients reported injection site pain and no allergic reactions were described.

2. STUDY OBJECTIVES

To assess the clinical value of using intravenous iron (Ferinject®) infusion in iron deficient patients with IPAH.

3. STUDY OUTCOME MEASURES

3.1. Primary outcome

Endurance time at the end of endurance bicycle cardiopulmonary exercise testing at 80% peak work rate determined from the incremental exercise test.

3.2. Secondary outcomes:

The secondary outcomes will be measured by capturing other data, particularly exercise parameters and NT-pro-BNP data.

A summary of the measurements that will be made is as follows:

- Incremental bicycle cardiopulmonary exercise testing – measurements will include peak VO_2 (ml/min/kg), VO_2 at metabolic threshold, VE/VCO_2 slope, VE/VCO_2 equivalents at metabolic threshold, VO_2/WR slope and O_2 pulse. Details are described in the Study Procedures Manual (SPM).
- VO2 at the end of endurance bicycle cardiopulmonary exercise testing at 80% peak work rate determined from the incremental exercise test
- Gas exchange at 3 minutes after the start of the work phase of an endurance exercise test at 80% peak work rate determined from the incremental exercise test
- Iron indices – serum iron, transferrin saturations, ferritin, soluble transferrin receptor, RDW, EPO, and UIBC
- 6 minute walk distance and Borg dyspnoea scale
- WHO functional class
- NT-proBNP
- Quality of life (CAMPHOR questionnaire) and the self-reported Patient Global Assessment
- Safety - the occurrence of adverse events
- Cardiac MRI - right ventricular volumes, mass, ejection fraction, stroke volume and diastolic function. Details are described in the SPM.

4. INVESTIGATIONAL PLAN

4.1. Overall study design and plan

This study is a Phase II, multicentre, double-blind, randomised, placebo-controlled, crossover study.

The study consists of a screening process, two treatment periods at Week 0 and Week 12 plus a follow up phase to evaluate the kinetics of iron re-depletion.

Potential participants will be screened using data collected during their routine outpatient appointment at the Pulmonary Hypertension Service or PH Clinic. Any unavailable or missing data will be collected at the screening visit (week 0) once the patient has provided written informed consent.

The study will involve hospital visits at Weeks 0, 12 and 24 while participants will be followed up by telephone on week 2 and 14.

Eligible participants will be admitted to the research unit for up to 3 days in order to complete the Baseline (Week 0) assessments including a physical examination, medical history, ECG, bloods to assess routine haematology and clinical chemistry and measure biomarkers, 6-Minute Walk Test, CAMPHOR questionnaire and incremental and endurance cardiopulmonary exercise tests (CPET).

As outlined in Figure 1, following completion of the Baseline assessments at Week 0 patients will be randomly allocated 1:1 to receive an infusion of either Ferinject® or saline.

At Week 2 participants will receive a telephone call from the research unit for follow up. This will include a general assessment of AEs, other medication and PGA questionnaire.

At Week 12 participants will be admitted to the research unit for up to 3 days to repeat the assessments done at Baseline (Week 0). Following completion of the Week 12 procedures, the patients will be switched to the other treatment arm (i.e. those who received Ferinject® at baseline will be administered a saline infusion, and vice versa).

Thereafter participants will have follow up assessments by telephone at Week 14 (which will be the same as week 2) and a final hospital visit at week 24 (which will be the same as the Weeks 0 and 12 visits)

At the sites where facility is available, participants will be given the option to undergo additional cardiac MRI (Weeks 0, 12 and 24).

At the Sheffield site only, if participants agree, at each of the week 0 and week 12 visits they will have two extra blood samples taken (50 ml extra in total) to assess neutrophil and peripheral blood mononuclear cell function and expression.

4.2. Discussion of study design

Patients will be randomised 1:1 to Ferinject® or saline, with a 6-minute walk test, cardiac MRI and incremental and endurance cardiopulmonary exercise tests to measure changes in cardiopulmonary performance. Patients will then receive the alternative treatment and 6-minute walk test and endurance and incremental cardiopulmonary exercise testing repeated after a further 12 weeks (Figures 1). This crossover design maximises the data available on exercise testing at 12 weeks post-iron for analysis.

4.3. Selection of Study Population

Patients participating in this study are adult males and females with symptomatic IPAH as defined by the eligibility criteria below.

4.3.1. Inclusion criteria:

Eligible patients must meet all of the following inclusion criteria:

1. Males or females aged between 16–75 years old.
2. PAH which is idiopathic, heritable or associated with anorexigens.
3. Iron deficiency as defined by any one of the following criteria: sTfR levels > 28.1 nmol/l (where sTfR analysis is available) or one of the following: ferritin <37 µg/l; transferrin saturations <16.4%; iron < 10.3 µmol/l.

4. Documented diagnosis of PAH by right heart catheterisation performed at any time prior to Screening showing: resting mean pulmonary artery pressure >25mmHg, pulmonary capillary wedge pressure =/< 15 mm Hg and normal or reduced cardiac output.
5. 6 minute walking distance greater than 50m at entry.
6. Stable on an unchanged PAH therapeutic regime (any combination of endothelin receptor antagonist, phosphodiesterase inhibitor or prostacyclin analogue) for at least 1 month.
7. Able to provide written informed consent prior to any study-mandated procedures.
8. Female subjects of child-bearing potential are eligible to participate if they agree to use one of the following contraception methods:
    - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
        - oral
        - intravaginal
        - transdermal
    - Progestogen-only hormonal contraception associated with inhibition of ovulation:
        - oral
        - injectable
        - implantable
    - intrauterine device (IUD)
    - intrauterine hormone-releasing system (IUS)
    - bilateral tubal occlusion
    - vasectomised partner
    - sexual abstinence

4.3.2. Exclusion criteria:

Patients will not be enrolled into the study if they meet any of the following criteria:

1. Unable to provide informed consent.
2. Clinically-significant renal disease (Creatinine clearance < 30 ml/min per 1.73 m^2 calculated from CKD-Epi http://www.qxmed.com/renal/Calculate-CKD-EPI-GFR.php) or liver disease (including serum transaminases > 3 times upper limit of normal).
3. Haemoglobin concentration <10 g/dl.
4. Patients will be excluded if any single parameter (iron, ferritin or transferrin saturation) exceeds 1x upper limit of normal (ULN) in the local lab reference range.
5. Patients with moderate to severe hypophosphatemia as defined as <0.65mmol/L
6. Known to have haemoglobinopathy e.g. sickle cell disease, thalassaemia.
7. Admission to hospital related to PAH or change in PAH therapy within 1 month prior to Screening.
8. Evidence of left ventricular disease or significant lung disease on high-resolution CT scanning or lung function as judged by the investigator.
9. Acute or chronic infection or inflammation.
10. Significant uncontrolled asthma as judged by the investigator, eczema or atopic allergies.
11. Females who are lactating or pregnant.
12. Individuals known to have HIV, Hepatitis B or C or Creutzfeld-Jakob disease.
13. Known hypersensitivity to Ferinject® or any of its excipients and any other iron preparations.
14. Evidence of disturbances in utilisation of iron.
15. Significant blood loss (e.g. GI bleed) within the last 3 months or history of menorrhagia.

16. Unable to perform a Cardiopulmonary Exercise Test i.e. due to syncope or musculoskeletal factors.
17. Patients who have received an investigational medicinal product within 30 days of entering the baseline visit.

4.3.3. Subject Completion

Subjects will be considered complete for the purpose of this study once they have completed all procedures at the end of Week 24.

The end of study is defined as the last visit of the last subject undergoing the trial.

4.3.4. Withdrawal of Subjects from Study

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator can withdraw subjects from the study for any of the following reasons:

- Occurrence of an unacceptable adverse event
- Subject request
- Subject is lost to follow up
- Administrative reasons
- Development of an intercurrent illness, condition, or procedural complication, which would interfere with the subject's continued participation
- Patient becomes pregnant

The investigator also reserves the right to withdraw subjects in the interest of subject safety and welfare.

4.3.5. Replacement policy

Patients who are prematurely discontinued from the study will not be replaced.

5. INVESTIGATIONAL PRODUCT(S)

Patients who are eligible to participate in the study will receive Ferinject® and normal saline (placebo).

5.1. Ferinject®

Ferinject® is currently licensed up to doses of 1000 mg as an intravenous infusion for the treatment of iron deficiency when oral preparations cannot be used or are ineffective.

5.1.1. Composition, packaging and storage

A dark brown, non-transparent, aqueous solution. Ferinject® is available as 50 mg iron/mL solution for injection/infusion.

Ferinject® will be supplied by Vifor Pharma, Glattbrugg, Switzerland as 2ml and 10 ml solutions in a vial (type I glass) with bromobutyl rubber stopper and aluminium cap. One mL of solution contains 50 mg of iron as ferric carboxymaltose.

The study drug should not be stored above 30°C; it should not be refrigerated or frozen.

5.2. IMP preparation and administration

5.2.1. IMP Preparation

The total dose of Ferinject® to be administered will be 1000mg or 15mg/kg, whichever is the smaller.

The study treatments will be prepared either by the hospital pharmacy or as per local SOP at individual site.

Ferinject® will be diluted up to 50ml in sterile 0.9% sodium chloride solution.

The same volume of saline will be given as for the active drug.

5.2.2. IMP Administration

Ferinject® will be administered by intravenous infusion and infused over 15 minutes. The patient will receive a single infusion of Ferinject® at either Week 0 or Week 12, depending on the treatment allocation.

5.3. Labelling

The study drug will be labelled in accordance with local regulatory requirements.

5.4. Study drug accountability

Accountability for the study drug at the study site is the responsibility of the Principal Investigator. The investigator will ensure that the study drug is used only in accordance with this protocol. Where allowed, the investigator may choose to assign some of the drug accountability tasks to a pharmacist or other appropriate individual.

Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each subject, and end-of-study destruction and disposal of the drug, will be maintained by each clinical site. These records will adequately document that the subjects were provided the doses as specified in the protocol and should reconcile all study drug received from Vifor Pharma, Switzerland.

5.5. Treatment assignment and blinding

5.5.1. Treatment assignment

Patients will be randomised on 1:1 ratio to each treatment arm. Randomisation will be performed at the Baseline (Week 0) visit using InForm™. Randomisation will be stratified by gender, with an appropriate fixed block size, in order to ensure equal allocation to Ferinject® and placebo. The computer-generated randomisation list will be prepared by a statistician independent of the study team and will be provided to Imperial College staff (who are not otherwise involved in the study) responsible for building the InForm™ system.

5.5.2. Blinding

This study will be conducted as a double-blind trial therefore the investigator, study staff, and patients will remain blinded to the patient's study treatment until the end of the study.

Ferinject® is a dark-brown solution. To ensure that the patient remains blinded to the treatment they are receiving, patients will be blindfolded for a short time during the infusion. Further details are described in the SPM.

Site personnel involved in the preparation and administration of the study drug will not be permitted to undertake any of the study assessments. In addition, an unblinded physician will be identified at each participating site and will be assigned to review iron profile results after patients have been dosed in order to prevent accidental unblinding of treatment allocation.

5.5.3. Emergency unblinding procedures

The identity of the study treatment may be revealed only if the patient experiences a medical emergency whose management would be improved by the knowledge of the treatment assignment. Emergency unblinding can be performed immediately by the study investigator by examination of the remaining solution in the syringe or infusion line.

5.6. Concomitant medications

5.6.1. Permitted concomitant medications

Approved endothelin receptor antagonists (ERAs), phosphodiesterase-5 (PDE-5) type inhibitors and/or prostacyclin analogues are permitted for the treatment of PAH. The dose must be stable for at least 1 month prior to entry into the study.

5.6.2. Prohibited concomitant medications

Patients are not permitted to take oral iron therapy whilst on the study.

6. VISIT AND ASSESSMENT SCHEDULE

For a tabulated summary of all visits and assessments described in the following section see Table 1.

It is recognised that the schedule of investigations may be difficult for patients with severe pulmonary hypertension. Therefore, it will be made clear to patients that they need not see through every investigation if they do not feel able to. Forgoing an investigation will not prevent patients from continuing the study.

6.1. Screening Visit

The Screening Visit should be performed no more than 28 days prior to the Baseline/Randomisation Visit.

Participants' eligibility with respect to IPAH status and Iron status will usually be determined using from routine outpatient clinical record. The following data will be recorded during the visit or obtained from the hospital records where possible.

- Obtain written informed consent
- Demographics
- Medical history
- Physical examination
- Concomitant medications

- Vital signs: Resting supine blood pressure (BP), pulse measurement, temperature, pulse oximetry, height and weight.
- Modified NYHA/WHO Functional Class
- 6MWT and Borg dyspnoea index
- Blood samples for routine haematology, blood chemistry (including iron parameters, sTfR (where available) and serum pregnancy test where clinically indicated (woman of childbearing potential only).

Any missing or unavailable data (e.g. 6MWT or pregnancy test) or data which are not collected during routine outpatient visit should be collected at this visit or at Visit 1 after written informed consent has been obtained and before confirmation of the patient's eligibility for the trial. Randomisation will only occur after confirmation of eligibility. Screening and Baseline/randomisation procedures can be recorded in a combined visit.

6.2. Baseline/Randomisation Visit (Week 0)

The patient will be admitted to the research unit for up to 3 days in order to undergo the following procedures:

- Physical examination
- Concomitant medications
- Document adverse events
- ECG
- Research blood sampling (NT pro-BNP, IL-6, hepcidin, sTfR and EPO). Neutrophil and peripheral blood mononuclear cell function and expression (Sheffield site only)
- Fasting glucose and insulin
- Incremental Cardiopulmonary Exercise Test
- Endurance Cardiopulmonary Exercise Test
- CAMPHOR questionnaire
- Cardiac MRI

Following completion of the above procedures, the patient will be randomised and receive an infusion of either the study drug (Ferinject®) or placebo (saline).

6.3. Week 2 (+/- 3 days) Telephone Follow up

Patients will undergo a telephone review at week 2 to check for AEs and concomitant medication. The PGA questionnaire will be completed over the phone.

6.4. Week 12 (+/- 3 days)

The patient will be admitted to the research unit for up to 3 days in order to undergo the following procedures:

- Physical examination
- Concomitant medications
- Document adverse events
- Vital signs: Resting supine blood pressure (BP), pulse measurement, temperature, pulse oximetry and weight
- ECG
- Modified NYHA/WHO Functional Class
- 6MWT and Borg dyspnoea index

- Blood samples for routine haematology, blood chemistry, (including iron indices), and serum pregnancy test (woman of childbearing potential only)
- Research blood sampling (NT pro-BNP, IL-6, hepcidin, sTfR and EPO; neutrophil and peripheral blood mononuclear cell function and expression (Sheffield site only)
- Fasting glucose and insulin (taken after an overnight stay and before dosing)
- Incremental Cardiopulmonary Exercise Test
- Endurance Cardiopulmonary Exercise Test
- Cardiac MRI (where the facility is available)
- CAMPHOR questionnaire
- Patient Global Assessment (PGA)

Following completion of the above procedures, the patient will be administered either the study drug (Ferinject®) or placebo (saline).

6.5. Week 14 (+/- 3 days) Telephone Follow up

Patients will undergo a telephone review as at week 2 to check for AEs and concomitant medication. The PGA questionnaire will be completed over the phone.

6.6. Week 24 (+/- 3 days)

The patient will attend the research unit in order to undergo the following procedures (these assessments can either be done as outpatient visits or on an inpatient basis involving an overnight stay at selected centres):

- Physical examination
- Concomitant medications
- Document adverse events
- Vital signs: Resting supine blood pressure (BP), pulse measurement, temperature, pulse oximetry and weight
- ECG
- Modified NYHA/WHO Functional Class
- 6MWT and Borg dyspnoea index
- Blood samples for routine haematology, blood chemistry, (including iron indices), and serum pregnancy test (woman of childbearing potential only)
- Research blood sampling (NT pro-BNP, IL-6, hepcidin, sTfR and EPO)
- Fasting glucose and insulin (taken after an overnight stay)
- Incremental Cardiopulmonary Exercise Test
- Endurance Cardiopulmonary Exercise Test
- Cardiac MRI (where the facility is available)
- CAMPHOR questionnaire
- Patient Global Assessment (PGA)

7. STUDY ASSESSMENTS

7.1. Physical Examination and Medical History

Physical examinations will be performed to ensure suitability according to the inclusion and exclusion criteria at screening and to document the health status at the time points specified in the Schedule of Events (Table 1). The physical examination comprises measurement of height and body weight and a routine medical examination.

A medical history will be recorded at screening or at Visit 1. The medical history will elicit information concerning existing medical conditions, major illnesses, and related surgical procedures. Any prescribed or over-the-counter medications that the subject received within the past 30 days should be recorded on the CRF. Medication prescribed for the treatment of PAH for the 8 weeks prior to enrolment should be recorded on the CRF. Subjects will be instructed to notify the study doctor before beginning new prescribed or over-the-counter medications.

7.2. Modified NYHA (WHO) Classification

Functional assessment of PAH will be made according to the modified New York Heart Association (NYHA) (WHO) classification system (World Symposium on Primary Pulmonary Hypertension, 1998, Evian, France, sponsored by the World Health Organization).

Class I: Patients with PAH without limitation of physical activity. Ordinary physical activity does not cause increased dyspnoea or fatigue, chest pain, or near syncope.

Class II: Patients with PAH resulting in slight limitation of physical activity. No discomfort at rest. Normal physical activity causes increased dyspnoea or fatigue, chest pain, or near syncope.

Class III: Patients with PAH resulting in marked limitation of physical activity. There is no discomfort at rest. Less than ordinary activity causes increased dyspnoea or fatigue, chest pain, or near syncope.

Class IV: Patients with PAH with inability to carry out any physical activity without discomfort. Indications of manifest right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by the least physical activity.

7.3. Vital signs

Systolic and diastolic systemic BP will be measured by means of either a standard manual or an automatic BP measuring device (cuff method). For each subject, the same method should be used during the entire study, and the type of device used should be recorded on the CRF. The same arm will be used for each measurement of BP, and BP will be measured after 5 minutes seated.

At each visit heart rate (HR) and oxygen saturation will be measured by pulse oximetry after the subject has been at rest for at least 5 minutes.

7.4. Endurance cardiopulmonary exercise test

Endurance exercise testing has been shown to be a much more sensitive indicator of change in exercise capacity in studies of rehabilitation in chronic lung disease, but remains an exploratory endpoint in pulmonary hypertension. Work rate will be set at 80% of the patient's peak work rate achieved on the baseline CPET and patients will be asked to exercise to a point where they are unable to continue. The same equipment and monitoring will be used as in the incremental test and end-test VO_2 will be used to gauge validity of the test, as it ought to be the same as the patient's maximal VO_2. Measurement of steady-state gas exchange will be made also at 3 minutes and peak. Details are described in the SPM.

7.5. Six minute walk distance

Distance walked during an unencouraged 6 minute walk test conducted according to American Thoracic Society (ATS) guidelines (8). This is a standard tool for the study of functional capacity in PAH patients and is primarily determined by cardiac output and hence right ventricular function. We are aware that a possible increase in haemoglobin might be a confounding factor, improving 6 minute walk not because of the increase in cardiac output but because of increased oxygen delivery.

This is the rationale behind assessing exercise haemodynamics. We will interpret the 6 minute walk in the context of the overall results. [The screening walk test may be done according to local protocol.]

7.6. Incremental cardiopulmonary exercise test

Exercise testing is increasingly used to evaluate the level of exercise intolerance in patients with lung and heart diseases (9). Patients will undergo cycle ergometry cardiopulmonary exercise testing (CPX) following a ramp protocol (Jaeger Masterscreen CPX) according to ATS guidelines (10). Using CPX, we can extract effort-independent data from exercise. Endpoints taken from CPX will include VO_2 at peak and anaerobic threshold, VE/VCO_2 slope, VE/VCO_2 equivalents at metabolic threshold, VO_2/WR slope and O_2 pulse. All data will be analysed centrally to ensure similar measurement techniques for CPET variables. Details are described in the SPM.

7.7. Cardiac Magnetic Resonance (CMR) Imaging

Cardiac Magnetic Resonance Imaging will be performed at selected centres at Weeks 0, 12 and 24 following a standardised clinical protocol. Patients who are unable to undergo MR scanning will be excluded from this part of the protocol. This may be for reasons such as a metal implant, cardiac arrhythmias or claustrophobia. Using balanced steady state free precession sequences, we will measure right ventricular mass and function. Velocity-encoded sequences will be used to measure the flows through R-sided heart cavities and assess the severity of tricuspid regurgitation. Analysis of the acquired images will be performed using dedicated software. Tracing of epicardial and endocardial borders of SA slices in end-diastole (image phase with the largest cavity area) and endocardial border in end-systole (smallest cavity area) allows calculation of right and left myocardial volume, end-diastolic and end-systolic volumes. From this stroke volume and ejection fraction can be derived. For mass calculation, the myocardial volume is multiplied by the specific density of myocardium (taken as 1.05 g/cm^3). Cardiac output is calculated from the images using the left ventricular stroke volume multiplied by heart rate and cardiac index is then derived by normalization to body surface area. Quantification of right ventricular diastolic function will be made by measuring R-R interval normalised isovolumetric relaxation time on the right two-chamber view, and early peak filling rate (E), atrium-induced peak filling rate (A) on the short-axis images.

A core lab will be established at Hammersmith Hospital to interpret the CMR scans from all sites by CMR trained personnel, blinded to the study timing. Further details are described in the SPM.

7.8. Laboratory measurements

Blood sampling will be performed at each visit to include: NT-pro-BNP as an indicator of cardiac workload; Iron status, as assessed by serum iron, UIBC or TIBC, transferrin saturation, sTfR, ferritin, and hepcidin levels; EPO levels and RDW to assess erythrogenesis. Inflammation status is known to affect hepcidin expression and will be determined by measuring CRP and IL-6 levels. Possible haemolysis will be assessed by measuring unconjugated bilirubin, LDH, haptoglobin and reticulocytes.

7.8.1. Type of laboratory

Central laboratories (see contact details on page 3) will be used to analyse the research bloods. All other routine clinical laboratory parameters (haematology, chemistry, coagulation panel, iron profile) will be analysed by local accredited hospital laboratories. Tests may vary slightly depending on the availability of local hospital assays and so some flexibility with regards to the specific tests will be tolerated e.g. folate or folic acid etc.

Routine clinical laboratory tests include the following:

Haematology	White blood cell count with differential, red blood cell count, platelet count, haemoglobin, hematocrit and reticulocytes, RDW
Standard chemistry	Albumin, Total bilirubin, Unconjugated bilirubin, Urea, Creatinine, Glucose, Total protein, CRP, Urate, Serum electrolytes (Calcium, Chloride, Sodium, Phosphate, Potassium) Bicarbonate, Aspartate aminotransferase (AST); alanine aminotransferase (ALT); γ-glutamyl transpeptidase (Gamma-GT); alkaline phosphatase (ALP); lactate dehydrogenase (LDH); creatine kinase (CK) Folic acid and Vitamin B12
Iron profile	Transferrin saturations, ferritin, iron, UIBC/TIBC
Serum pregnancy test	-hCG
Others	EPO

7.8.2. Research samples

Blood samples to measure circulating factors including sTfR, IL-6, Hepcidin, NT pro-BNP haptoglobin, and GDF-15 will be taken at Baseline and Weeks 12 and 24 for research purposes.

Detailed instructions for the preparation, labeling, storage and shipment of the samples can be found in the laboratory manual.

Two additional research blood samples (25ml each) will be collected by the Royal Hallamshire Hospital site only at Week 0 (baseline) and week 12. This is to enable the isolation and study of neutrophil and peripheral blood mononuclear cell function (apoptosis, respiratory burst, phagocytosis, chemotaxis, bacterial killing, integrin expression) and expression (mRNA and protein) in response to iron loading. Patients at this site will be given the option to opt out of these extra blood collections if they wish.

7.8.3. Volume of Blood Collection

The approximate blood volume collected from each individual during the study will be as follows:

Assessment	mL/Collection	Number of Collections	Total (mL)
Clinical chemistry	10	7	70.0
Haematology	3.0	7	21.0
Serum pregnancy test*	1.5	2	3.0
Research blood	15.0	6	90.0
	25.0**	2**	50.0**
	Total blood volume :		184.0mL 234.0mL**

* for women of childbearing potential

** 2 extra research blood collections (25ml each) will be performed at Weeks 0 and 12 of study participation to freshly isolate human neutrophils and peripheral blood mononuclear cells for functional and expression studies at the Royal Hallamshire Hospital, Sheffield. The total volume of extra blood collection by this site will be 50 ml. Patients at this site will be given the option to opt out of these extra blood collections if they wish.

7.9. Quality of Life

CAMPHOR is a disease-specific patient-reported outcome instrument which has been developed for patients with pulmonary hypertension (11). It is sensitive to small changes in health and quality of life in this patient group. It will be collected on Baseline, Week 12 and on Week 24.

7.10. Patient Global Assessment

The self-reported Patient Global Assessment will be used at Weeks 2, 12, 14 and 24 to assess patient-perceived response to the intervention.

8. PHARMACOVIGILANCE

8.1. Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. *An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.*

Adverse Reaction (AR): all untoward and unintended responses to an IMP related to any dose administered. *All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.*

Unexpected Adverse Reaction: an AR, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product*). When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected. Side effects documented in the SmPC which occur in a more severe form than anticipated are also considered to be unexpected.*

Serious Adverse Event (SAE) or **Serious Adverse Reaction (SAR):** any untoward medical occurrence or effect that at any dose:

- Results in death
- Is life-threatening
- Requires hospitalisation, or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Suspected Unexpected Serious Adverse Reaction (SUSAR): any suspected adverse reaction related to an IMP that is both unexpected and serious.

8.2. Assigning Causality

Each adverse event must be assessed by the investigator as to whether or not there is a reasonable possibility of a causal relationship to the study drug. The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions below. If any doubt about the causality exists the local investigator should inform the study coordination centre who will notify the Chief Investigator. Vifor Pharma and/or other clinicians may be asked to advise in some cases.

In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, REC/Regulatory Authority will be informed of both points of view.

8.2.1. Causality Description

Unrelated: There is no evidence of any causal relationship

Unlikely: There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).

Possible: There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).

Probable: There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

Definitely: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Not assessable: There is insufficient or incomplete evidence to make a clinical judgment of the causal relationship.

8.3. Assigning Severity

For each AE intensity should be defined according to the following criteria:

- **Mild***:* Awareness of sign or symptom, but easily tolerated.
- **Moderate***:* Discomfort enough to cause interference with normal daily activities.
- **Severe:** Inability to perform normal daily activities.
- **Life threatening or disabling:** Immediate risk of death from the reaction as it occurred.
- **Death:** The event resulted in death.

8.4. Adverse event reporting procedures

8.4.1. Screening period

All adverse events should be documented. SAEs occurring between signing the Informed Consent Form and study drug initiation are only required to be reported if they are considered by the investigator to be related to study-mandated procedures.

8.4.2. Treatment period

All adverse events should be documented. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the study coordination centre in the first instance.

8.4.2.1. Non serious AR/AEs

All such toxicities, whether expected or not, should be recorded in the Adverse Events section of the case report form.

8.4.2.2. Serious AR/AEs

All SAEs must be reported to the study coordination centre within 24 hours of the investigator being made aware of the event. The investigator should complete the SAE form and send it to the study coordination centre together with relevant treatment forms and anonymised copies of all relevant investigations. Follow up information about a previously reported SAE must be reported within 24 hours of receiving it.

However relapse and death due to pulmonary hypertension, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

8.5. Reporting to the Regulatory Authorities

The Sponsor has delegated the responsibility for notifying the Regulatory authority and REC of all SUSARs occurring during the study to the Chief Investigator. All SAEs and SUSARs must be reported in accordance with local regulatory guidelines:

*Life threatening SUSARs should be reported to the RA and REC n*o later than **7 days** after the CI has first knowledge of the minimum criteria for expedited reporting. Further relevant information should be given within a further 8 days.

*Non-fatal and non-life threatening SUSARs should be reported to the RA and REC n*o later than **15 days** after the CI has first knowledge of the minimum criteria for expedited reporting. Further relevant information should be given as soon as possible.

An annual safety report will be submitted on the anniversary of the Clinical Trial Application to the RA and REC.

8.6. Reporting to the Sponsor

All SAEs and SUSARs must be forwarded the Imperial College Joint Research Office within 24 hours of the Investigator learning of its occurrence.

8.7. Reporting to Vifor Pharma Drug Safety

All SAEs that are considered possibly, probably or definitely related to the study drug must be forwarded to Vifor Pharma Pharmacovigilance by fax or e-mail within 1 business day of learning of the event:

Fax: +41 68 851 86 59
safety@viforpharma.com

8.8. Follow up of adverse events

All adverse events that are still ongoing at the end of the study will be followed up until resolution.

9. DOCUMENTATION OF DATA

9.1. Data collection

The data collection tool for this study will be electronic case report forms (eCRFs). Case report forms (CRFs) will be completed for each subject and will contain study data which are verifiable to the source data (i.e., original recordings, laboratory reports, and subject records). In addition, all source data should be attributable (signed and dated).

Only the Investigator and authorized co-workers are entitled to make entries on the CRF. Concomitant medications may be entered as they appear in the participant's record or as per local standards (generic or trade names may be entered).

It is the responsibility of the Investigator to ensure that the CRFs are kept up-to-date so that they always contain the latest observations on the subjects enrolled.

Laboratory values outside the normal range will be commented upon by the Investigator. Other data than those requested by this protocol may be recorded as "additional data" in the comments section of the case report form; the clinical significance of any additional data should be described.

9.2. Data monitoring

The Sponsor is responsible for ensuring that the study is monitored appropriately in order to ensure compliance with GCP and local regulatory guidelines. The monitor will check the completeness of medical records, verify the accuracy of entries in the CRF, and ensure adherence to the protocol and compliance with local regulatory requirements.

10. STATISITICS AND DATA ANALYSIS

This is a proof-of-concept study, thus the sample size has been chosen with respect to safety (in terms of exposure to the drug and investigations) and feasibility (patient population) and with the aim of measuring effect size. We would expect that a sample size of 60 will be sufficient to detect clinically meaningful changes in cardiopulmonary exercise end-points, NT-pro-BNP and quality of life in the direction consistent with benefit.

The null hypothesis is that iron replacement has no effect on cardiopulmonary performance in patients with iron deficiency and IPAH, with a two-sided alternative that iron replacement changes cardiopulmonary performance in patients with iron deficiency and IPAH.

For the cardiopulmonary exercise tests, if a 12-weekly drop-out rate of 10% and standard deviation of 5 ml/min/kg for peak VO_2 we would have 80% power to detect a mean change of 1.94 ml/min/kg at a significance level of alpha=0.05 using a paired analysis (cf 2.2ml difference in FERRIC-HF with 35 patients). Other pre-specified secondary endpoints will be change in CPET at 2 weeks, change in cardiac output at 12 weeks, and change in 6 minute walk distance and circulating biochemical markers at 12 weeks. A full statistical analysis plan will be developed for each endpoint, using linear mixed models for analysis of the crossover data. Primary analysis will be intention-to-treat, with sensitivity analyses to explore the effect of dropout. Due to the exploratory nature of the study no multiplicity adjustment will be made to p-values for secondary analyses, though results will be interpreted with caution if the primary endpoint does not achieve significance.

It will only be possible to measure sTfR for every study participant after enrolment and thus a separate analysis will be performed to analyse the effect of Ferinject® in patients with sTfR > 28.1 nmol/l. Additionally, on recruitment of the 20^{th}, 40^{th} and 60^{th} patient, serum samples will be analysed to establish the number of patients enrolled with sTfR > 28.1 nmol/l and an additional number of patients will be recruited to achieve 60 enrolled iron-deficient patients.

Data from all centres will be pooled and analysed at Hammersmith. Due to the small sample sizes in each centre, the assessment of consistency of results amongst the centres will be made on an informal basis.

11. ADMINISTRATIVE AND LEGAL CONSIDERATIONS

11.1. General Legal Requirements

This trial will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031 and its amendments) or any legislation that supersedes these regulations and the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

11.2. Ethics Committee/RA approvals

Approval must be obtained from a Research Ethics Committee (REC) and the Regulatory Authority (RA) before starting the study and must be documented in a dated letter to the investigator clearly identifying the trial, the documents reviews, and the date of the approval.

A list of the Ethics Committee members must be provided. If any study staff were present, it must be clear that none of these persons voted.

Modifications made to the protocol after receipt of the REC/RA approval must also be submitted as amendments by the investigator to the REC/RA in accordance with local procedures and regulations.

11.3. Informed consent

It is the Investigator's responsibility to explain to each subject the study procedures, potential benefits and hazards of trial participation, the right to withdraw from the study at any time, and to obtain written informed consent prior to any study-specific procedures. The original copy of the signed and dated Informed Consent Form must be filed in the Investigator Site File. The subject, the subject's legally authorised representative, or both will be given a copy of the signed and dated Informed Consent Form. A copy will also be placed in the subject's medical hospital notes.

11.4. Patient confidentiality

The Investigators affirm and uphold the principle of the subject's right to protection against invasion of privacy. Personal health data will be kept confidential.

On CRFs or other documents, subjects will be identified by their initials and a subject number only. However, each Investigator will keep in his/her file a *Subject Identification List*. With respect to the processing of data, every subject has to agree with this in writing. This agreement should be documented together with the written informed consent for trial participation.

11.5. Protocol Amendments

Any changes in the protocol will require a formal amendment. Such amendments will be agreed upon and approved in writing by the Investigator. Amendments to the protocol will be submitted to the relevant authorities and the REC for approval prior to implementation.

Administrative changes which have no significant impact on the medical or scientific validity of the study will be documented in a statement. The REC will be notified of administrative changes, if applicable.

11.6. Premature Termination of the Trial

The Chief Investigator reserves the right to terminate the trial for well-documented reasons. Instructions will be provided in a separate document should it be determined that assessments beyond those defined by the protocol are required.

Further recruitment of subjects will not take place under the following conditions:

- Premature termination of the trial.
- Drug-related events, i.e. SUSARs, emerging adverse effects that are serious and the risk/benefit ratio is unacceptable.
- Procedure-related events, i.e., the recruitment rate is too low or the number of dropouts for administrative reasons is too high.

11.7. Sponsor

Imperial College Academic Health Science Centre will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

11.8. Indemnity

Imperial College holds Public Liability ("negligent harm") and Clinical Trial ("non-negligent harm") insurance policies which apply to this trial.

11.9. Record Retention

The PI must retain all study records by the applicable regulations in a secure and safe facility. The PI/institution must take measures to prevent accidental or premature destruction of essential documents, that is, documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, including paper copies of study records (e.g. subject charts) as well as any original source documents that are electronic as required by applicable regulatory requirements.

The PI/institution should retain subject identifiers for at least 15 years after the completion or discontinuation of the study. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, but not less than 15 years. These documents should be retained for a longer period, however, if required by the applicable

regulatory requirements. It is the responsibility of the PI to inform the institution as to when these documents no longer need to be retained.

If an Investigator moves, withdraws from an investigation, retires, requests to move records to another location or to assign these records to another party or (e.g. other Investigator) who will accept the responsibility, written notice of this transfer must be made to and agreed upon by each party.

11.10. Confidentiality

All information concerning this study and which was not previously published is considered confidential information and shall not be used except in the performance of this study.

11.11. Publications

Publication of the results of the study, whether in whole or in part, shall be within the responsibility of the Investigator(s).

11.12. Audits and Inspections

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor may conduct a quality assurance audit in accordance with their local internal procedures.

Audits and/or inspections may also be carried out by local authorities, or authorities to which information on this trial has been submitted. All documents pertinent to the trial must be made available for such inspection after an adequate announcement.

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Table 1. Visit and Assessment Schedule

Assessment	Screening[#] ≤ 28 days before week 0 visit	Week 0 Baseline/ randomisation Visit 1[§]	Week 2 (+/- 3 days) Telephone Visit 2	Week 12 (+/- 3 days) Visit 3	Week 14 (+/- 3 days) Telephone Visit 4	Week 24 (+/- 3 days) Visit 5
Written informed consent	X					
Medical history (incl. demographics)	X					
Physical examination	X	X		X		X
Concomitant medication	X	X	X	X	X	X
Modified NYHA (WHO) Functional Class	X		X	X	X	X
Vital signs	X	X		X		X
ECG		X		X		X
6MWT and Borg Dyspnoea Score	X			X		X
CAMPHOR Questionnaire		X		X		X
Patient Global Assessment (PGA)			X	X	X	X
Routine laboratory assessments (e.g. iron status)	X	X		X		X
Research blood sampling		X		X		X
Serum pregnancy testing (if applicable)	X			X		X
Incremental Cardiopulmonary Exercise Test		X		X		X
Endurance Cardiopulmonary Exercise Test		X		X		X
Administration of study drug or placebo		X		X		
Adverse events		X	X	X	X	X
*Cardiac MRI**		*X*		*X*		*X*

Visit 2 & 4 (Week 2 & 14) will be done by telephone call.

#; Iron status and IPAH status will be determined from routine clinical care records.

§; Screening procedures can be combined with Visit 1 wherever convenient for patient and where data from routine clinical visits are not available.

; Additional exploratory assessments, where research facility for MRI available for this protocol