

**Clinical trial results:****Mechanisms of Exercise Benefit with Intravenous Iron in Chronic Heart Failure: The Ferric Iron in Heart Failure (FERRIC HF) II Trial****Summary**

EudraCT number	2012-005592-13
Trial protocol	GB
Global end of trial date	20 December 2016

Results information

Result version number	v1 (current)
This version publication date	21 March 2019
First version publication date	21 March 2019
Summary attachment (see zip file)	FINAL STUDY REPORT (FERRIC HF II CLINICAL STUDY REPORT.pdf)

Trial information**Trial identification**

Sponsor protocol code	FERRICHFII
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	King's College London
Sponsor organisation address	The Strand, London, United Kingdom, WC2R 2LS
Public contact	Dr Darlington Okonko, King's College London, 0044 207848 5017, darlington.okonko@kcl.ac.uk
Scientific contact	Dr Darlington Okonko, King's College London, 0044 207848 5017, darlington.okonko@kcl.ac.uk
Sponsor organisation name	King's College Hospital
Sponsor organisation address	Denmark Hill, London, United Kingdom, SE59RS
Public contact	Dr Darlington Okonko, King's College NHS Foundation Trust, 0044 207848 5017, darlington.okonko@kcl.ac.uk
Scientific contact	Dr Darlington Okonko, King's College NHS Foundation Trust, 0044 207848 5017, darlington.okonko@kcl.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 December 2016
Global end of trial reached?	Yes
Global end of trial date	20 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of iv iron repletion on skeletal muscle oxidative capacity as quantified by PCr t1/2 and ADP t1/2 following gastrocnemius muscle exercise using 31-P MRS.

Protection of trial subjects:

Number and incidence of adverse events; changes in liver function tests and renal function tests; changes in vital parameters will be recorded throughout the study.

Background therapy:

Participants will be receiving optimal conventional therapy for at least 4 weeks prior to recruitment and without dose changes for at least 2 weeks.

Evidence for comparator:

not applicable

Actual start date of recruitment	07 January 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	16
From 65 to 84 years	23
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from one clinical site within the UK, between 2014 and 2016.

Pre-assignment

Screening details:

≥30 years of age, 50% anaemic and 50% non-anaemic participants with CHF.

The study consists of a screening (week -1 to -4) and baseline assessment period (week 0), followed by a baseline assessment and first treatment phase (day 0 of week 0),

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Blinding will be achieved by shielding the infusion arm from patients and using opaque iv giving sets

Arms

Are arms mutually exclusive?	Yes
Arm title	IV IRON

Arm description:

Stratified Randomisation (Anaemia defined as Hb<12 in females and <13 in males)

10 anaemic participants and 10 non anaemic participants will receive Monofer Infusion at week 0 (and week 1 if dose ≥ 20 mg iron/kg

Arm type	Experimental
Investigational medicinal product name	Monofer 100 mg/ml solution for injection/infusion
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

In patients randomised to total dose iv iron infusion, the repletion dose will be calculated by the following Ganzoni equation and rounded up to the nearest multiple of 100mg:
body weight (kg) × 2.4 × (15- patients haemoglobin [g/dl]) + 500 mg (for stores), administered at week 0 (and week 1 if dose ≥ 20 mg iron/kg

Arm title	PLACEBO
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Arm description:

Stratified Randomisation (Anaemia defined as Hb<12 in females and <13 in males)

10 anaemic participants and 10 non anaemic participants will receive Normal Saline Infusion at week 0 (and week 1 if dose ≥ 20 mg iron/kg

Arm type	Placebo
Investigational medicinal product name	0.9% Normal Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients randomised to the placebo group will have their total iron repletion dose calculated using the Ganzoni formula as detailed for the IRON group and their infusion duration worked out. These subjects will receive 100ml of sterile 0.9% sodium chloride over their respective infusion periods in a resuscitation area with blood pressure monitoring as above.

Number of subjects in period 1	IV IRON	PLACEBO
Started	21	19
Completed	21	19

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial
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Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	40	40	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	16	16	
From 65-84 years	23	23	
85 years and over	1	1	
Gender categorical			
Units: Subjects			
Female	11	11	
Male	29	29	

End points

End points reporting groups

Reporting group title	IV IRON
Reporting group description: Stratified Randomisation (Anaemia defined as Hb<12 in females and <13 in males) 10 anaemic participants and 10 non anaemic participants will receive Monofer Infusion at week 0 (and week 1 if dose \geq 20 mg iron/kg)	
Reporting group title	PLACEBO
Reporting group description: Stratified Randomisation (Anaemia defined as Hb<12 in females and <13 in males) 10 anaemic participants and 10 non anaemic participants will receive Normal Saline Infusion at week 0 (and week 1 if dose \geq 20 mg iron/kg)	

Primary: Change in skeletal muscle oxidative capacity

End point title	Change in skeletal muscle oxidative capacity ^[1]
End point description: Change in skeletal muscle oxidative capacity as assessed by PCr t1/2 from baseline to 2 weeks post last treatment	
End point type	Primary
End point timeframe: Until 2 weeks post last treatment/infusion	
Notes:	

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Please see attached charts and documents for results.

End point values	IV IRON	PLACEBO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	19		
Units: whole	21	19		

Attachments (see zip file)	Results Tables/FERRIC II.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoints

End point title	Secondary Endpoints
End point description: Change in skeletal muscle oxidative capacity as assessed by ADP t1/2 from baseline to 2 weeks post last treatment. Change in skeletal muscle oxidative capacity as reflected by mitochondrial oxygen consumption per mg of muscle tissue measured using a respirometer from baseline to 2 weeks post last treatment. Change in skeletal muscle ferritin, free iron content, and transferrin receptor levels from baseline to 2 weeks post last treatment.	

Change in skeletal muscle fibre type, immunohistochemistry, and aerobic enzyme mRNA and protein levels from baseline to 2 weeks post last treatment.

Change in distance walked in 6 minutes from baseline to 2 weeks post last treatment.

Change in cardiopulmonary exercise (CPEX) parameters (peak oxygen consumption and ventilation to carbon dioxide production ratio) from baseline to 2 weeks post last treatment.

Change in symptom status (NYHA class, Kansas City Cardiomyopathy questionnaire [KCCQ], visual analogue fatigue scale [VAFS]) from

End point type	Secondary
End point timeframe:	
From baseline to two weeks post treatment/infusion	

End point values	IV IRON	PLACEBO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	19		
Units: whole	21	19		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety

End point title	Safety
End point description:	
Number and incidence of adverse events; changes in liver function tests and renal function tests; changes in vital parameters.	
End point type	Secondary
End point timeframe:	
Baseline until completion of trial.	

End point values	IV IRON	PLACEBO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	19		
Units: whole	21	19		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Enrolment until trial completion.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

Reporting group title	IV IRON GROUP
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Reporting group description: -

Reporting group title	PLACEBO GROUP
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Reporting group description: -

Serious adverse events	IV IRON GROUP	PLACEBO GROUP	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 21 (4.76%)	0 / 19 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Acute myocardial Infarction & Respiratory Failure			
subjects affected / exposed	1 / 21 (4.76%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	IV IRON GROUP	PLACEBO GROUP	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 21 (9.52%)	1 / 19 (5.26%)	
General disorders and administration site conditions			
Rash at venepuncture site			
subjects affected / exposed	1 / 21 (4.76%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
coryzal symptoms			

subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 19 (5.26%) 1	
Musculoskeletal and connective tissue disorders Arthralgia during Infusion subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	0 / 19 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 September 2015	1)Change of folate in incluision 2) Change of exclusion critera (NSA study duration)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported