Clinical trial results:
Exploratory multicentre prospective double blinded randomised controlled pilot study of the effect of intravenous iron supplementation (Monofer)in iron deficient but not anaemic patients with Chronic Kidney Disease stages 3b or worse on functional status and cardiac structure and function.

Summary

EudraCT number	2014-004133-16
Trial protocol	GB
Global end of trial date	21 May 2019

Results information

Result version number	v1 (current)
This version publication date	21 May 2022
First version publication date	21 May 2022
Summary attachment (see zip file)	doi: 10.1186/s12882-021-02308-y (12882_2021_Article_2308.pdf)

Trial information

Trial identification

Sponsor protocol code	R1766

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Hull University Teaching Hospitals NHS Trust
Sponsor organisation address	Castle Road, Cottingham, United Kingdom, HU16 5JQ
Public contact	Research and Development Office , Hull University Teaching Hospitals NHS Trust , +44 01482 461903, research.development@hey.nhs.uk
Scientific contact	Academic Renal Research Office , Hull University Teaching Hospitals NHS Trust , +44 01482 605260, sunil.bhandari@hey.nhs.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	21 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 May 2019
Global end of trial reached?	Yes
Global end of trial date	21 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether IV iron supplementation in iron deficient non-anaemic CKD patients improves physical and functional status assessed by the 6MWT and questionnaires (KDQoL and MLHF).

Protection of trial subjects:

Safety assessment will occur continuously throughout the trial. Medical history at baseline will be recorded. A Physical examination along with blood sampling for routine biochemistry paying particular attention to renal excretory function and electrolytes as in the attached Table. Participants will be contacted by phone by a study nurse after 1 week for a safety assessment and evidence of adverse events will be sought at each routine follow-up visit. The participant will be asked to contact their study nurse if they have any concerns about safety at any time in between routine follow-up visits for the trial.

Serious adverse events will be identified and documented on the CRF at routine visits, based on participant reports and primary or secondary care reports. In addition, episodes of infection requiring hospitalisation and other infection episodes will be documented. In addition, haemoglobin, ferritin, platelet levels, and other laboratory measurements detailed above will be monitored.

Background therapy:

Intravenous saline was used as placebo for this trial. No other treatment was used in the trial apart from the trial drug and placebo.

Evidence for comparator:

Trial evidence on the effectiveness and safety of Monofer® in CKD is sparse but expanding; this is reflected in current guidelines, which provide no specific didactic instructions for its administration in patients with CKD. Thus, the proposed trial logically follows on from initial studies, and proposes an exploratory randomized double blinded placebo controlled pilot trial (using dummy solution normal saline without the added drug) in patients with CKD stages G3b to 5 (pre-dialysis) to address this issue further and fill the gap in knowledge. Also within the trial are mechanistic studies which will add to and advance our scientific understanding of these data.

Actual start date of recruitment	02 March 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: 54

Worldwide total number of subjects	54
EEA total number of subjects	0

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)	54
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants will be recruited from at least 3 renal units in the UK. Currently, patients with CKD under the care of a nephrologist are reviewed every 3-4 months in a hospital outpatient clinic. Potential trial participants will be identified when presenting for their routine hospital clinic visits. This reflects the proposed research care.

Pre-assignment

Screening details:

Fifty–four patients aged 18 years or over with CKD (stage G3b to G5) will be enrolled. Each patient must meet all of the inclusion criteria, and none of the exclusion criteria, at entry to the trial. Patients who meet the entry criteria may be recruited by the investigator or any medically qualified member of the local trial team who has delegated.

Period 1

Period 1 title	Visit 1
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Test

Arm description:

Addition of IV Monofer® 1g. Patient will receive 100ml of normal saline 0.9% with addition of Iron Isomaltoside (Monofer®) 1000mg infused intravenously over 30 minutes as a single total dose infusion.

Arm type	Active comparator
Investigational medicinal product name	IV Monofer 1g
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Addition of IV Monofer® 1g. Patient will receive 100ml of normal saline 0.9% with addition of Iron Isomaltoside (Monofer®) 1000mg infused intravenously over 30 minutes as a single total dose infusion.

Arm title	Placebo

Arm description:

Placebo – IV inert solution (no iron therapy). Patient will receive placebo (100ml of normal saline 0.9% only) infused intravenously over 30 minutes as a single total dose infusion.

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

Dosage and administration details:

Patient will receive placebo (100ml of normal saline 0.9% only) infused intravenously over 30 minutes as a single total dose infusion.

Number of subjects in period 1	Test	Placebo
Started	26	28
Completed	26	28

Period 2	
Period 2 title	Visit 2
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms	
Are arms mutually exclusive?	Yes
Arm title	Test

Arm description: -

Arm type	Experimental
Investigational medicinal product name	IV Monofer 1g
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Addition of IV Monofer® 1g. Patient will receive 100ml of normal saline 0.9% with addition of Iron Isomaltoside (Monofer®) 1000mg infused intravenously over 30 minutes as a single total dose infusion.

Arm title	Placebo

Arm description: -

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

Dosage and administration details:

Patient will receive placebo (100ml of normal saline 0.9% only) infused intravenously over 30 minutes as a single total dose infusion.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Visit 1 is the screening visit performed at week -4 to -2 to ensure compliance with the eligibility criteria.

Number of subjects in period 2	Test	Placebo
Started	26	28
Completed	26	28

Period 3	
Period 3 title	Visit 3
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Test

Arm description:

Addition of IV Monofer® 1g. Patient will receive 100ml of normal saline 0.9% with addition of Iron Isomaltoside (Monofer®) 1000mg infused intravenously over 30 minutes as a single total dose infusion.

Arm type	Active comparator
Investigational medicinal product name	IV Monofer 1g
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Addition of IV Monofer® 1g. Patient will receive 100ml of normal saline 0.9% with addition of Iron Isomaltoside (Monofer®) 1000mg infused intravenously over 30 minutes as a single total dose infusion.

Arm title	Placebo

Arm description:

Placebo – IV inert solution (no iron therapy). Patient will receive placebo (100ml of normal saline 0.9% only) infused intravenously over 30 minutes as a single total dose infusion.

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

Dosage and administration details:

Patient will receive placebo (100ml of normal saline 0.9% only) infused intravenously over 30 minutes as a single total dose infusion.

Number of subjects in period 3	Test	Placebo
Started	26	28
Completed	26	28

Period 4	
Period 4 title	Visit 4
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Test

Arm description:

Addition of IV Monofer® 1g. Patient will receive 100ml of normal saline 0.9% with addition of Iron Isomaltoside (Monofer®) 1000mg infused intravenously over 30 minutes as a single total dose infusion.

Arm type	Active comparator
Investigational medicinal product name	IV Monofer 1g
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Addition of IV Monofer® 1g. Patient will receive 100ml of normal saline 0.9% with addition of Iron Isomaltoside (Monofer®) 1000mg infused intravenously over 30 minutes as a single total dose infusion.

Arm title	Placebo

Arm description:

Placebo – IV inert solution (no iron therapy). Patient will receive placebo (100ml of normal saline 0.9% only) infused intravenously over 30 minutes as a single total dose infusion.

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

Dosage and administration details:

Patient will receive placebo (100ml of normal saline 0.9% only) infused intravenously over 30 minutes as a single total dose infusion.

Number of subjects in period 4	Test	Placebo
Started	26	28
Completed	26	28

Period 5	
Period 5 title	Visit 5
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Test

Arm description:

Addition of IV Monofer® 1g. Patient will receive 100ml of normal saline 0.9% with addition of Iron Isomaltoside (Monofer®) 1000mg infused intravenously over 30 minutes as a single total dose infusion.

Arm type	Active comparator
Investigational medicinal product name	IV Monofer 1g
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Addition of IV Monofer® 1g. Patient will receive 100ml of normal saline 0.9% with addition of Iron Isomaltoside (Monofer®) 1000mg infused intravenously over 30 minutes as a single total dose infusion.

Arm title	Placebo

Arm description:

Placebo – IV inert solution (no iron therapy). Patient will receive placebo (100ml of normal saline 0.9% only) infused intravenously over 30 minutes as a single total dose infusion.

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

Dosage and administration details:

Patient will receive placebo (100ml of normal saline 0.9% only) infused intravenously over 30 minutes as a single total dose infusion.

Number of subjects in period 5	Test	Placebo
Started	26	28
Completed	26	28

Baseline characteristics

End points

End points reporting groups

Reporting group title	Test

Reporting group description:

Addition of IV Monofer® 1g. Patient will receive 100ml of normal saline 0.9% with addition of Iron Isomaltoside (Monofer®) 1000mg infused intravenously over 30 minutes as a single total dose infusion.

Reporting group title	Placebo

Reporting group description:

Placebo – IV inert solution (no iron therapy). Patient will receive placebo (100ml of normal saline 0.9% only) infused intravenously over 30 minutes as a single total dose infusion.

Reporting group title	Test

Reporting group description: -

Reporting group title	Placebo

Reporting group description: -

Reporting group title	Test

Reporting group description:

Addition of IV Monofer® 1g. Patient will receive 100ml of normal saline 0.9% with addition of Iron Isomaltoside (Monofer®) 1000mg infused intravenously over 30 minutes as a single total dose infusion.

Reporting group title	Placebo

Reporting group description:

Placebo – IV inert solution (no iron therapy). Patient will receive placebo (100ml of normal saline 0.9% only) infused intravenously over 30 minutes as a single total dose infusion.

Reporting group title	Test

Reporting group description:

Addition of IV Monofer® 1g. Patient will receive 100ml of normal saline 0.9% with addition of Iron Isomaltoside (Monofer®) 1000mg infused intravenously over 30 minutes as a single total dose infusion.

Reporting group title	Placebo

Reporting group description:

Placebo – IV inert solution (no iron therapy). Patient will receive placebo (100ml of normal saline 0.9% only) infused intravenously over 30 minutes as a single total dose infusion.

Reporting group title	Test

Reporting group description:

Addition of IV Monofer® 1g. Patient will receive 100ml of normal saline 0.9% with addition of Iron Isomaltoside (Monofer®) 1000mg infused intravenously over 30 minutes as a single total dose infusion.

Reporting group title	Placebo

Reporting group description:

Placebo – IV inert solution (no iron therapy). Patient will receive placebo (100ml of normal saline 0.9% only) infused intravenously over 30 minutes as a single total dose infusion.

Primary: 6MWT

End point title	6MWT

End point description:

Adjusting for baseline 6MWT, the 6MWT in the main study participants at 1 month and 3 months showed no statistically significant difference between FDI and placebo arms ($p = 0.736$ and 0.741 respectively). (Fig. 1).
Analysis of change in 6MWT showed that the mean (SD) change for FDI patients from baseline to 3 months was 6.0 (89.1) metres compared to 1.9 (111.2) metres for

the placebo arm patients (Suppl Table 1). During follow
up there was a greater than 25 m increase in 6MWT observed in 8/22 (36.4%) of patients at 1 month and 10/20
(50%) at 3 months in the FDI arm vs 8/25 (32% - 1
month) and 10/24 (41.7% - 3 months) patients in the
placebo arm, respectively (p = 0.753, p = 0.580).

End point type	Primary
End point timeframe:	
1month and 3 month	

End point values	Test	Placebo	Test	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22[1]	25[2]	20[3]	24[4]
Units: meters				
arithmetic mean (standard deviation)	3.5 (± 108.1)	5.0 (± 58.8)	6.0 (± 89.1)	1.9 (± 111.2)

Notes:

[1] - Some participant's could not perform the 6 minute walking test due to other health conditions.

[2] - Some participant's could not perform the 6 minute walking test due to other health conditions.

[3] - Some participant's could not perform the 6 minute walking test due to other health conditions.

[4] - Some participant's could not perform the 6 minute walking test due to other health conditions.

Statistical analyses

Statistical analysis title	Change from baseline to 1 month, 6MWT
Comparison groups	Test v Placebo
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	Chi-squared corrected
Parameter estimate	N/A
Point estimate	0
Confidence interval	
level	90 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Change from baseline to 1 month, 6MWT
Comparison groups	Test v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.895
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	0

Confidence interval	
level	90 %
sides	2-sided
lower limit	0
upper limit	0
Variability estimate	Standard deviation

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Safety assessment will occur continuously throughout the trial and at each follow-up.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.1
Reporting groups	
Reporting group title	Test (IV Iron)
Reporting group description: Arm of the trial under test.	
Reporting group title	Placebo
Reporting group description: Arm of the study under placebo.	

Serious adverse events	Test (IV Iron)	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)	0 / 28 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Test (IV Iron)	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 26 (34.62%)	9 / 28 (32.14%)	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 26 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Hypoglycaemia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	0	
Lung cancer			

subjects affected / exposed	0 / 26 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	0	
Gout			
subjects affected / exposed	1 / 26 (3.85%)	0 / 28 (0.00%)	
occurrences (all)	0	0	
Had IV fluid for elective CT scan			
subjects affected / exposed	0 / 26 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Poor blood pressure control			
subjects affected / exposed	2 / 26 (7.69%)	0 / 28 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
shortness of breath			
subjects affected / exposed	0 / 26 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	0	
Cough			
subjects affected / exposed	1 / 26 (3.85%)	0 / 28 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
per rectal bleeding			
subjects affected / exposed	0 / 26 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 26 (3.85%)	0 / 28 (0.00%)	
occurrences (all)	0	0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 26 (3.85%)	0 / 28 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 26 (3.85%)	0 / 28 (0.00%)	
occurrences (all)	0	0	
Lower respiratory tract infection			

subjects affected / exposed	0 / 26 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	0	
Influenza			
subjects affected / exposed	1 / 26 (3.85%)	0 / 28 (0.00%)	
occurrences (all)	0	0	
Chronic obstructive pulmonary disease	Additional description: Exacerbation.		
subjects affected / exposed	1 / 26 (3.85%)	0 / 28 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 January 2016	Protocol • Protocol page 18 – Condoms have been added to the list of acceptable contraceptives in the first exclusion criterion • Protocol page 18 – Added 'N.B. Women of childbearing potential using condoms only as a contraceptive method will require a pregnancy test at the baseline visit, prior to administration of Monofer® therapy' to first exclusion criterion • Protocol page 21 – Added 'Women of childbearing potential using condoms only as a contraceptive method will additionally require a pregnancy test at the baseline visit, prior to administration of Monofer® therapy.'
07 December 2016	Protocol • In the original CT application, Question A28 "Will any participants be recruited by publicity through posters, leaflets, adverts or websites?" was answered "No". This has now been changed to "Yes". The study may now be advertised on patient facing websites and newsletters. • The number of patients in, Control Group 2 – patients with Chronic Kidney Disease without iron deficiency and anaemia, has been reduced from 20 to 10. This reduction in size does not affect the primary outcome. The following non-substantial amendments were also made: • An extension to the end date of study from 01.04.16 to 01.07.18. • In the Safety Reporting section of the protocol we have added some clarification to the type of infection that requires recording in the Case Report Form.
27 March 2017	Protocol • This amendment only affects the Hull site. Page numbers amended: 14, 16, 20, 21, 22, 35 and 39. The number of patients in the parallel sub-study (Group 4) has been changed from 6 to 4.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported