Clinical trial results:
The Postoperative Iron in Cardiac Surgery (PICS-) trial: A randomised clinical trial comparing the efficacy of single-, high-dose intravenous iron and oral iron for the treatment of anaemia following cardiac surgery.

Summary

EudraCT number	2020-001389-12
Trial protocol	DK
Global end of trial date	26 June 2023

Results information

Result version number	v1 (current)
This version publication date	05 December 2024
First version publication date	05 December 2024

Trial information

Trial identification

Sponsor protocol code	PICS1.0

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04608539
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aarhus University Hospital
Sponsor organisation address	Palle Juul-Jensens Boulevard 99, Aarhus N, Denmark, 8200
Public contact	Department of Cardiothoracic and Vascular Surgery, Aarhus University Hospital, +45 30911059, michhinr@rm.dk
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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	01 July 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 June 2023
Global end of trial reached?	Yes
Global end of trial date	26 June 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effectiveness of single-, high-dose intravenous iron infusion versus oral iron supplementation for the treatment of anaemia following cardiac surgery.

Protection of trial subjects:

1. Baseline blood samples were taken in the operating room from preexisting arterial katheters, therefore not inflicting unnecessary pain on participants.
2. During the first 5 minutes of study drug infusion, infusion speed was reduced to half speed to monitor for potential infusion reactions. Participants were monitored during infusion with standard monitoring of postoperative cardiac surgery patients, i.e. ECG, invasive arterial blood pressure and pulsoxymetry.

Background therapy:

Participants underwent standard cardiac surgery and received perioperative care in accordance with institutional protocols. Routine interventions to optimize hemoglobin levels before surgery, such as intravenous iron therapy or treatment with erythropoiesis-stimulating agents (ESA), were not performed. Throughout the hospital stay, red blood cell transfusions were considered for hemoglobin levels below 7.5 g/dL, with discretion for higher levels in specific cases such as unstable or actively bleeding patients, or those experiencing symptoms of anemia. Following cardiac surgery, participants were transferred to the cardiac surgery ICU. In the absence of active bleeding or severe anemia, fluid therapy consisted of crystalloid solutions (e.g., Ringer's acetate) or colloid fluids (e.g., 5% or 20% albumin solution). Stable patients were discharged to the cardiothoracic ward on the first postoperative day.

Evidence for comparator:

Oral iron supplementation is the standard treatment for mild or moderate anemia following cardiac surgery (i.e. anemia not requiring blood transfusion). In our trial, oral iron supplementation with ferrous sulfate (Ferro Duretter®, ACO, Upplands Väsby, Sweden) was started on postoperative day 4, in line with our department’s standard practice.

Actual start date of recruitment	01 January 2021
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	Denmark: 110
Worldwide total number of subjects	110
EEA total number of subjects	110

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)	27
From 65 to 84 years	83
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were approached for participation by a cardiac surgeon or anesthesiologist during their preoperative visit, usually held on the last working day before their scheduled surgery.

Pre-assignment

Screening details:

We screened adult patients aged 18 years or older who were scheduled for non-emergent cardiac surgery with cardiopulmonary bypass. This included isolated coronary artery bypass grafting, valve surgery, or a combination of both.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The trial had a double-blind design until POD4 and changed to open-label format after initiation of oral iron could, as this caused black an tarry stools and could not be concealed.
The distinctive dark brown color of ferric derisomaltose made it easily distinguishable from the placebo. To maintain blinding, non-transparent bags, black infusion lines (B. Braun Medical, Melsungen, Germany), and aluminum foil sheaths covering the central venous line were used during the infusion.

Arms

Are arms mutually exclusive?	Yes
Arm title	IV iron (intervention)

Arm description:

Study participants in the IV iron group received a single, high-dose infusion of 20 mg/kg ferric derisomaltose on the morning of the first postoperative day.

Arm type	Experimental
Investigational medicinal product name	Ferric derisomaltose
Investigational medicinal product code	B03AC
Other name	MonoFer
Pharmaceutical forms	Solution for injection/infusion, Sterile concentrate
Routes of administration	Infusion , Intravenous use

Dosage and administration details:

20 mg/kg body weight via central venouse line, infused in 30 minutes

Arm title	Oral iron (control)

Arm description:

Participants in the oral iron group received treatment with oral ferrous sulfate 100 mg x 2 from postoperative day 4 until 4 weeks after randiomization

Arm type	Active comparator
Investigational medicinal product name	Ferrous sulfate
Investigational medicinal product code	B03AA07
Other name	Ferro Duretter
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg twice daily from postoperative day 4 until 4-week follow-up

Number of subjects in period 1	IV iron (intervention)	Oral iron (control)
Started	57	53
Completed	53	51
Not completed	4	2
Lost to follow-up	4	2

Baseline characteristics

Reporting groups	
Reporting group title	IV iron (intervention)
Reporting group description:	
Study participants in the IV iron group received a single, high-dose infusion of 20 mg/kg ferric derisomaltose on the morning of the first postoperative day.	
Reporting group title	Oral iron (control)
Reporting group description:	
Participants in the oral iron group received treatment with oral ferrous sulfate 100 mg x 2 from postoperative day 4 until 4 weeks after randiomization	

Reporting group values	IV iron (intervention)	Oral iron (control)	Total
Number of subjects	57	53	110
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
median	71	70	
full range (min-max)	42 to 84	28 to 77	-
Gender categorical			
Units: Subjects			
Female	20	17	37
Male	37	36	73
Risk profile: urgent surgery			
Proportion of participants undergoing urgent surgery			
Units: Subjects			
Urgent surgery	2	4	6
Elective surgery	55	49	104
Not recorded	0	0	0
Type of surgery			
The type of cardiac surgery participants underwent before randomization			
Units: Subjects			
CABG	20	17	37
Aortic valve only	22	17	39
Mitral valve only	6	9	15
Combined / other procedures	9	10	19
Preoperative anemia			
Preoperative anemia (according to the WHO definition: hemoglobin < 13 g/dl in men, < 12 g/dl in			

women)			
Units: Subjects			
Anemic (WHO definition)	10	9	19
Non-anemic (WHO definition)	47	44	91
Not recorded	0	0	0
Preoperative iron deficiency (ferritin <30 µg/l)			
Preoperative iron deficiency (defined as ferritin level <30 µg/l)			
Units: Subjects			
Ferritin <30 µg/l	13	9	22
Ferritin >= 30 µg/	44	44	88
Not recorded	0	0	0
Preoperative iron deficiency (ferritin <100 µg/l)			
Preoperative iron deficiency (defined as ferritin level <100 µg/l)			
Units: Subjects			
Ferritin <100 µg/l	31	34	65
Ferritin >=100 µg/l	26	19	45
Not recorded	0	0	0
Preoperative iron deficiency (TSAT <20%)			
Preoperative iron deficiency (defined as transferrin saturation <20%)			
Units: Subjects			
TSAT <20%	21	15	36
TSAT >= 20%	36	38	74
Not recorded	0	0	0
Risk profile: recent myocardial infarction (MI) Units: Subjects			
Recent MI	5	4	9
No recent MI	52	49	101
Not recorded	0	0	0
Risk profile: reduced LVEF			
Risk profile: reduced LVEF			
Units: Subjects			
Reduced LVEF	6	7	13
Normal LVEF	51	46	97
Not recorded	0	0	0
Risk profile: diabetes mellitus			
Risk profile: patients medically treated for diabetes mellitus			
Units: Subjects			
Diabetes	7	9	16
No diabetes	50	44	94
Not recorded	0	0	0
Risk profile: chronic lung disease			
Proportion of patients medically treated for chronic lung disease			
Units: Subjects			
Chronic lung disease	9	2	11
No chronic lung disease	48	51	99
Not recorded	0	0	0
Risk profile: chronic kidney disease			
Participants with estimated glomerular filtration rate ≤50 mL/min/1.73 m²			

Units: Subjects			
Chronic kidney disease	1	5	6
No chronic kidney disease	56	48	104
Not recorded	0	0	0
Risk profile: preoperative oral iron therapy Units: Subjects			
Preoperative oral iron	2	1	3
No preoperative oral iron	55	52	107
Not recorded	0	0	0
BMI			
Body Mass Index			
Units: kg/m2			
arithmetic mean	27.1	26.2	
standard deviation	± 4.0	± 3.6	-
EuroSCORE			
Perioperative mortality risk assesment via EuroSCORE calculation			
Units: percent			
arithmetic mean	2.0	1.5	
standard deviation	± 1.5	± 1.1	-
Preoperative hemoglobin			
Preoperative hemoglobin			
Units: gram(s)/decilitre			
arithmetic mean	13.3	13.5	
standard deviation	± 1.1	± 1.0	-
Preoperative reticulocytes			
Preoperative reticulocytes			
Units: 10^9/L			
arithmetic mean	71	70	
standard deviation	± 19	± 19	-
Preoperative ferritin level			
Preoperative ferritin level			
Units: mikrogram/litre			
median	82	72	
inter-quartile range (Q1-Q3)	34 to 158	38 to 162	-
Preoperative transferrin saturation			
Preoperative transferrin saturation			
Units: percent			
arithmetic mean	23	25	
standard deviation	± 10	± 11	-
Preoperative creatinine Units: micromole(s)/litre			
arithmetic mean	84	82	
standard deviation	± 18	± 23	-
Preoperative estimated glomerular filtration rate (eGFR)			
Preoperative estimated glomerular filtration rate (eGFR)			
Units: mL/min/1.73 m²)			
arithmetic mean	74	78	
standard deviation	± 12	± 15	-
Preoperative vitamin B12 level			
Preoperative vitamin B12 level			

Units: pikomol/l			
arithmetic mean	376	358	
standard deviation	± 148	± 148	-
Preoperative folate level			
Preoperative folate level			
Units: nmol/L			
arithmetic mean	32	32	
standard deviation	± 13	± 13	-

End points

End points reporting groups

Reporting group title	IV iron (intervention)
Reporting group description:	
Study participants in the IV iron group received a single, high-dose infusion of 20 mg/kg ferric derisomaltose on the morning of the first postoperative day.	
Reporting group title	Oral iron (control)
Reporting group description:	
Participants in the oral iron group received treatment with oral ferrous sulfate 100 mg x 2 from postoperative day 4 until 4 weeks after randiomization	

Primary: Treatment success (no anemia at 4 weeks, no postoperative blood transfusion)

End point title	Treatment success (no anemia at 4 weeks, no postoperative blood transfusion)
End point description:	
The proportion of participants who were a) no longer anemic and b) had not received allogeneic RBC transfusions after randomization. Anemia was defined according to World Health Organization (WHO) criteria as hemoglobin levels <13 g/dL in men and <12 g/dL in women.	
End point type	Primary
End point timeframe:	
Evaluated at a follow-up visit four weeks after randomization.	

End point values	IV iron (intervention)	Oral iron (control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	51		
Units: Percentage	15	8		

Statistical analyses

Statistical analysis title	Pearson's two-tailed chi-squared test
Comparison groups	IV iron (intervention) v Oral iron (control)
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.121
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.13

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.28

Secondary: Prevalence of anemia

End point title	Prevalence of anemia

End point description:

The proportion of participants with anemia at 4-weeks after randomization. Anemia was defined according to World Health Organization (WHO) criteria as hemoglobin levels <13 g/dL in men and <12 g/dL in women.

End point type	Secondary

End point timeframe:

Evaluated at a follow-up visit four weeks after randomization.

End point values	IV iron (intervention)	Oral iron (control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	51		
Units: Proportion of participants	35	42		

Statistical analyses

Statistical analysis title	Pearson's two-tailed chi-squared test
Comparison groups	IV iron (intervention) v Oral iron (control)
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.058
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	0

Secondary: Postoperative allogeneic red blood cells transfusion

End point title	Postoperative allogeneic red blood cells transfusion

End point description:

The proportion of participants receiving any allogeneic RBC transfusion in the period from randomization to the 4-week follow-up visit.

End point type	Secondary

End point timeframe:

Evaluated at a follow-up visit four weeks after randomization.

End point values	IV iron (intervention)	Oral iron (control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	51		
Units: RBC units	9	17		

Statistical analyses

Statistical analysis title	Pearson's two-tailed chi-squared test
Comparison groups	IV iron (intervention) v Oral iron (control)
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.054
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	0

Secondary: Mean change in haemoglobin (baseline / 4 weeks)

End point title	Mean change in haemoglobin (baseline / 4 weeks)

End point description:

The increase in hemoglobin level from the time of randomization until 4-week follow-up visit.

End point type	Secondary

End point timeframe:

Evaluated at a follow-up visit four weeks after randomization.

End point values	IV iron (intervention)	Oral iron (control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	51		
Units: g/dl				
arithmetic mean (confidence interval 95%)	2.3 (2.0 to 2.7)	1.8 (1.5 to 2.3)		

Statistical analyses

Statistical analysis title	Two-tailed t-test
Comparison groups	IV iron (intervention) v Oral iron (control)
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.053
Method	t-test, 2-sided
Parameter estimate	Median difference (final values)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1

Secondary: Mean hemoglobin level at 4 weeks

End point title	Mean hemoglobin level at 4 weeks
End point description:	
The difference in hemoglobin level between groups	
End point type	Secondary
End point timeframe:	
Evaluated at a follow-up visit four weeks after randomization.	

End point values	IV iron (intervention)	Oral iron (control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	51		
Units: g/dl				
arithmetic mean (standard deviation)	12.0 (± 1.1)	11.4 (± 1.3)		

Statistical analyses

Statistical analysis title	Two-tailed t-test
Comparison groups	IV iron (intervention) v Oral iron (control)
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	1.1

Secondary: Ferritin < 100 µg/l at 4 weeks	
End point title	Ferritin < 100 µg/l at 4 weeks
End point description:	
The proportion of participants with ferritin levels below 100 µg/l	
End point type	Secondary
End point timeframe:	
Measured at 4-weeks after randomization	

End point values	IV iron (intervention)	Oral iron (control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	51		
Units: Proportion of participants	0	13		

Statistical analyses

Statistical analysis title	Pearson's two-tailed chi-squared test
Comparison groups	IV iron (intervention) v Oral iron (control)
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-0.26

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	-0.14

Secondary: Transferrin saturation < 20% at 4 weeks

End point title	Transferrin saturation < 20% at 4 weeks
End point description:	
The proportion of participants with transferrin saturation below 20%	
End point type	Secondary
End point timeframe:	
Evaluated 4 weeks after randomization	

End point values	IV iron (intervention)	Oral iron (control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	51		
Units: Proportion of participants	25	37		

Statistical analyses

Statistical analysis title	Pearson's two-tailed chi-squared test
Comparison groups	Oral iron (control) v IV iron (intervention)
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.45
upper limit	-0.08

Secondary: Mean reticulocyte count at 4 weeks

End point title	Mean reticulocyte count at 4 weeks
End point description:	
Mean reticulocyte count 4 weeks after randomization	

End point type	Secondary
End point timeframe: 4 weeks after randomization	

End point values	IV iron (intervention)	Oral iron (control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	49		
Units: number/l				
number (not applicable)	52	49		

Statistical analyses

Statistical analysis title	two-tailed t-test
Statistical analysis description: two-tailed t-test	
Comparison groups	IV iron (intervention) v Oral iron (control)
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.917
Method	t-test, 2-sided
Parameter estimate	Median difference (final values)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.9
upper limit	13.2
Variability estimate	Standard error of the mean
Dispersion value	6.3

Secondary: Mean ferritin level at 4 weeks

End point title	Mean ferritin level at 4 weeks
End point description: Mean ferritin level at 4 weeks	
End point type	Secondary
End point timeframe: Measured at 4-weeks after randomization	

End point values	IV iron (intervention)	Oral iron (control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	50		
Units: µg/l				
arithmetic mean (standard deviation)	699 (± 596)	219 (± 180)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean transferrin saturation at 4 weeks

End point title	Mean transferrin saturation at 4 weeks
End point description: Mean transferrin saturation at 4 weeks	
End point type	Secondary
End point timeframe: Measured at a 4-week follow-up meeting	

End point values	IV iron (intervention)	Oral iron (control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	49		
Units: %				
arithmetic mean (standard deviation)	20.6 (± 7.4)	16.3 (± 8.6)		

Statistical analyses

Statistical analysis title	two-tailed t-test
Comparison groups	IV iron (intervention) v Oral iron (control)
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	7.5
Variability estimate	Standard error of the mean
Dispersion value	1.6

Secondary: 6-minute walk distance	
End point title	6-minute walk distance
End point description: 6-minute walk distance	
End point type	Secondary
End point timeframe: Measured at 4 weeks after randomization	

End point values	IV iron (intervention)	Oral iron (control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	41		
Units: m				
arithmetic mean (standard deviation)	400 (± 96)	423 (± 79)		

Statistical analyses

Statistical analysis title	two-tailed t-test
Comparison groups	IV iron (intervention) v Oral iron (control)
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.208
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-61
upper limit	14
Variability estimate	Standard error of the mean
Dispersion value	19

Secondary: New York Heart Association (NYHA) functional class I	
End point title	New York Heart Association (NYHA) functional class I

End point description:

The NYHA classification is a valid tool for assessing functional status in patients with heart failure [44]. A trained trial nurse describes the participant's functional status with one of four NYHA classes at follow-up:
I. No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea.

II. Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea.
III. Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnoea.
IV. Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.
The outcome of interest is the proportion of participants with a NYHA functional class of I.

End point type	Secondary
End point timeframe:	
At 4 week after randomization	

End point values	IV iron (intervention)	Oral iron (control)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	43		
Units: participants	23	14		

Statistical analyses

Statistical analysis title	Pearson chi2
Comparison groups	Oral iron (control) v IV iron (intervention)
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.136
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.35

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time of randomization on the morning of the first postoperative day until follow-up at 4 weeks after randomization

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.1

Reporting groups

Reporting group title	IV iron group

Reporting group description:

The participants who were randomized to treatment with 20 mg/kg ferric derisomaltose on postoperative day 1

Reporting group title	Oral iron group

Reporting group description: -

Serious adverse events	IV iron group	Oral iron group	
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 57 (64.91%)	33 / 53 (62.26%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Pulmonary embolism	Additional description: Pulmonary embolism		
subjects affected / exposed	1 / 57 (1.75%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	19 / 57 (33.33%)	16 / 53 (30.19%)	
occurrences causally related to treatment / all	0 / 19	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion	Additional description: Clinically relevant pericardial effusion		
subjects affected / exposed	6 / 57 (10.53%)	3 / 53 (5.66%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block	Additional description: AV-blok		

subjects affected / exposed	3 / 57 (5.26%)	3 / 53 (5.66%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Embolic stroke	Additional description: Embolic stroke		
subjects affected / exposed	4 / 57 (7.02%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage	Additional description: Gastrointestinal bleeding		
subjects affected / exposed	1 / 57 (1.75%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal ischaemia			
subjects affected / exposed	1 / 57 (1.75%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation	Additional description: Severe constipation		
subjects affected / exposed	0 / 57 (0.00%)	3 / 53 (5.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion	Additional description: Pleural effusion requiring pleurocentesis		
subjects affected / exposed	8 / 57 (14.04%)	9 / 53 (16.98%)	
occurrences causally related to treatment / all	0 / 8	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury	Additional description: Participants with acute kidney injury		
subjects affected / exposed	0 / 57 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Wound infection	Additional description: Wound infection		

subjects affected / exposed	3 / 57 (5.26%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	IV iron group	Oral iron group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 57 (8.77%)	2 / 53 (3.77%)	
Cardiac disorders			
Ventricular arrhythmia			
subjects affected / exposed	2 / 57 (3.51%)	0 / 53 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Nausea	Additional description: Nausea during study drug infusion		
subjects affected / exposed	1 / 57 (1.75%)	2 / 53 (3.77%)	
occurrences (all)	1	2	
Taste disorder	Additional description: Metal taste during study drug infusion		
subjects affected / exposed	1 / 57 (1.75%)	0 / 53 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Pruritus	Additional description: Itching during study drug infusion		
subjects affected / exposed	1 / 57 (1.75%)	0 / 53 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The main limitation of our study is that it was likely underpowered to demonstrate a significant difference in the primary outcome. The choice of a composite primary outcome may have contributed to this.

Notes: