Clinical trial results:
A randomised double-blind controlled phase III study to compare the efficacy and safety of intravenous ferric carboxymaltose with placebo in patients with anaemia undergoing major open abdominal surgery

Summary

EudraCT number	2012-002786-35
Trial protocol	GB
Global end of trial date	10 May 2019

Results information

Result version number	v1 (current)
This version publication date	09 October 2020
First version publication date	09 October 2020

Trial information

Trial identification

Sponsor protocol code	12/0246

Additional study identifiers

ISRCTN number	ISRCTN67322816
ClinicalTrials.gov id (NCT number)	NCT01692418
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Gower Street, London, United Kingdom, WC1E 6BT
Public contact	Toby Richards, University of Western Australia, toby.richards@uwa.edu.au
Scientific contact	Toby Richards, University of Western Australia, toby.richards@uwa.edu.au

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	28 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 May 2019
Global end of trial reached?	Yes
Global end of trial date	10 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine if a single dose of intravenous iron given to patients with anaemia prior to major open abdominal surgery, reduces the need for peri-operative blood transfusion (the peri-operative period is defined as from randomisation to the trial until 30 days following operation)

Protection of trial subjects:

This trial was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. All subjects provided written informed consent before undergoing any trial related procedures. The trial was reviewed and approved by a Research Ethics Committee (REC) and the Medicines & Healthcare products Regulatory Agency (MHRA).

Administration of the IMP was given in a hospital setting with appropriate resuscitation facility and staff available in the event of an emergency. Patients were administered the study medication by the unblinded person. Patients were closely monitored for signs of hypersensitivity during and for at least 30 minutes following the administration of the treatment.

Background therapy:

N/A

Evidence for comparator: -

Actual start date of recruitment	01 September 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 487
Worldwide total number of subjects	487
EEA total number of subjects	487

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)	234
From 65 to 84 years	248
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

The trial was conducted in 46 sites in England and Wales. 487 subjects were randomised, the first on 06/01/2014 and the last on 28/09/2018.

Pre-assignment

Screening details:

Patients with a planned major abdominal surgery were screened for the trial. During screening conformance with inclusion/exclusion criteria was assessed.

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	Investigator, Subject

Blinding implementation details:

Blinding will be obtained by shielding the patients from seeing preparation of the study drug and having unblinded study personnel not involved in any study assessments (efficacy or safety) responsible for preparing and administering the study treatment. This will be achieved by preparing and administering the study drug behind a screen or curtain. The drug will then be shielded from vision (light protection bags) and administered through black tubing.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ferinject (ferric carboxymaltose)

Arm description:

1000 mg of ferric carboxymaltose will be administered as an i.v. infusion (100ml normal saline) over a minimum of 15 minutes using a black infusion kit

Arm type	Experimental
Investigational medicinal product name	Ferinject (ferric carboxymaltose)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

One off dose of 1000 mg of ferric carboxymaltose will be administered as an i.v. infusion (100ml normal saline) over a minimum of 15 minutes using a black infusion kit

Arm title	Placebo

Arm description:

Normal saline will be administered as an i.v. infusion (100ml normal saline) over a minimum of 15 minutes using a black infusion kit

Arm type	Placebo
Investigational medicinal product name	Normal saline (0.9% weight/volume (w/v) NaCl)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

One off dose of normal saline will be administered as an i.v. infusion (100ml normal saline) over a minimum of 15 minutes using a black infusion kit

Number of subjects in period 1	Ferinject (ferric carboxymaltose)	Placebo
Started	244	243
Completed	226	226
Not completed	18	17
Consent withdrawn by subject	4	4
Patient died	12	10
Lost to follow-up	2	3

Baseline characteristics

Reporting groups	
Reporting group title	Ferinject (ferric carboxymaltose)
Reporting group description:	
1000 mg of ferric carboxymaltose will be administered as an i.v. infusion (100ml normal saline) over a minimum of 15 minutes using a black infusion kit	
Reporting group title	Placebo
Reporting group description:	
Normal saline will be administered as an i.v. infusion (100ml normal saline) over a minimum of 15 minutes using a black infusion kit	

Reporting group values	Ferinject (ferric carboxymaltose)	Placebo	Total
Number of subjects	244	243	487
Age categorical Units: Subjects			
Adults (18-64 years)	111	123	234
From 65-84 years	131	117	248
85 years and over	2	3	5
Age continuous Units: years			
median	66	65	
inter-quartile range (Q1-Q3)	57 to 72	50 to 72	-
Gender categorical Units: Subjects			
Female	125	142	267
Male	119	101	220
Ethnicity Units: Subjects			
Caucasian	211	217	428
Afro-caribbean	14	19	33
Asian	18	6	24
Other	1	1	2
American Society Anesthesiologists (ASA) grade Units: Subjects			
Grade I	30	31	61
Grade II	147	141	288
Grade III	56	65	121
Grade IV	1	1	2
Missing	10	5	15
Smoking history Units: Subjects			
Never	113	116	229
Ex	108	107	215
Current	22	19	41
Missing	1	1	2
Iron tablets			
Is the patient taking iron tablets?			

Units: Subjects			
Yes	46	49	95
No	197	194	391
Missing	1	0	1
Medical history - Myocardial infarction Units: Subjects			
Yes	12	20	32
No	232	223	455
Medical history - Angina/chest pain Units: Subjects			
Yes	15	16	31
No	229	227	456
Medical history - Heart failure Units: Subjects			
Yes	9	3	12
No	235	240	475
Medical history - Hypertension Units: Subjects			
Yes	89	93	182
No	155	150	305
Medical history - Breathlessness Units: Subjects			
Yes	25	28	53
No	219	215	434
Medical history - Liver disease Units: Subjects			
Yes	14	8	22
No	230	235	465
Medical history - Kidney/urinary problems Units: Subjects			
Yes	39	37	76
No	205	206	411
Medical history - Bleeding tendencies Units: Subjects			
Yes	11	7	18
No	233	236	469
Medical history - Iron deficiency Units: Subjects			
Yes	70	69	139
No	174	174	348
Medical history - COPD/bronchitis/asthma Units: Subjects			
Yes	27	37	64
No	217	206	423
Medical history - Acid reflux/stomach ulcer Units: Subjects			
Yes	54	54	108
No	190	189	379
Medical history - Hiatus hernia			

Units: Subjects			
Yes	17	23	40
No	227	220	447
Medical history - Coeliac disease Units: Subjects			
Yes	0	2	2
No	244	241	485
Medical history - Inflammatory bowel disease Units: Subjects			
Yes	13	13	26
No	231	230	461
Medical history - CVA/TIA Units: Subjects			
Yes	4	13	17
No	240	230	470
Medical history - Rheumatoid arthritis Units: Subjects			
Yes	10	12	22
No	233	231	464
Missing	1	0	1
Medical history - Diabetes Units: Subjects			
Yes	37	38	75
No	207	205	412
Pre-op chemotherapy			
Is the patient having preop chemotherapy?			
Units: Subjects			
Yes	50	59	109
No	194	184	378
Pre-op radiotherapy			
Is the patient having preop radiotherapy?			
Units: Subjects			
Yes	7	6	13
No	237	237	474
Current medication that affects bleeding - Warfarin Units: Subjects			
Yes	7	4	11
No	237	239	476
Current medication that affects bleeding - Aspirin Units: Subjects			
Yes	23	28	51
No	221	215	436
Current medication that affects bleeding - Clopidogrel Units: Subjects			
Yes	3	5	8
No	241	238	479
Current medication that affects bleeding - Other Units: Subjects			

Yes	22	25	47
No	222	218	440

End points

End points reporting groups

Reporting group title	Ferinject (ferric carboxymaltose)
Reporting group description:	
1000 mg of ferric carboxymaltose will be administered as an i.v. infusion (100ml normal saline) over a minimum of 15 minutes using a black infusion kit	
Reporting group title	Placebo
Reporting group description:	
Normal saline will be administered as an i.v. infusion (100ml normal saline) over a minimum of 15 minutes using a black infusion kit	

Primary: Blood transfusion or death at 30 days

End point title	Blood transfusion or death at 30 days
End point description:	

End point type	Primary
End point timeframe:	
From randomisation to 30 days post-operation	

End point values	Ferinject (ferric carboxymaltose)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	237	237		
Units: None				
Yes	69	67		
No	168	170		

Statistical analyses

Statistical analysis title	Blood transfusion or death
Statistical analysis description:	
The number and percentage of patients with the composite endpoint of blood transfusion or death will be reported by treatment group. A risk ratio (treatment versus placebo) and 95% confidence interval will be calculated using binomial regression (binary outcome with a log link). A p-value will be calculated using a likelihood ratio test.	
Comparison groups	Ferinject (ferric carboxymaltose) v Placebo
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.84
Method	Binomial regression with a log link
Parameter estimate	Risk ratio (RR)
Point estimate	1.03

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.37

Primary: Transfusions episodes at 30 days

End point title	Transfusions episodes at 30 days

End point description:

End point type	Primary

End point timeframe:

From randomisation to 30 days post-operation

End point values	Ferinject (ferric carboxymaltose)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	237	237		
Units: None				
0 transfusions	169	170		
1 transfusion	49	37		
2 transfusions	9	22		
3 transfusions	5	5		
4 transfusions	3	1		
5 transfusions	1	1		
6 transfusions	1	1		

Statistical analyses

Statistical analysis title	Transfusions episodes

Statistical analysis description:

A rate ratio and 95% confidence interval were calculated using a negative binomial regression model and a likelihood ratio test p-value reported. As some patients died before the end of the time period, the length of each patient’s period of observation was included as an exposure in the model.

Comparison groups	Ferinject (ferric carboxymaltose) v Placebo
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.93
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	0.98

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.43

Secondary: Total number of units of blood or blood products transfused at 30 days (excluding large transfusions)

End point title	Total number of units of blood or blood products transfused at 30 days (excluding large transfusions)

End point description:

End point type	Secondary

End point timeframe:

From randomisation to 30 days post-operation

End point values	Ferinject (ferric carboxymaltose)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	237	237		
Units: None				
0 units	171	173		
1 unit	21	14		
2 units	31	28		
3 units	7	12		
4 units	1	6		
5 units	3	2		
6+ units	3	2		

Statistical analyses

Statistical analysis title	Total units of blood or blood products transfused

Statistical analysis description:

A rate ratio (treatment versus placebo) and 95% confidence interval were calculated using a negative binomial regression model. A p-value was calculated using a likelihood ratio test.

Comparison groups	Ferinject (ferric carboxymaltose) v Placebo
Number of subjects included in analysis	474
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.92
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	0.98

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.47

Secondary: Total number of units of blood or blood products transfused at 6 months (excluding large transfusions)

End point title	Total number of units of blood or blood products transfused at 6 months (excluding large transfusions)

End point description:

End point type	Secondary

End point timeframe:

From randomisation to 6 months post-operation

End point values	Ferinject (ferric carboxymaltose)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	220	224		
Units: None				
0 units	148	151		
1 unit	21	13		
2 units	32	31		
3 units	10	15		
4 units	2	7		
5 units	2	2		
6+ units	5	5		

Statistical analyses

Statistical analysis title	Total units of blood or blood products transfused

Statistical analysis description:

A rate ratio (treatment versus placebo) and 95% confidence interval were calculated using a negative binomial regression model. A p-value was calculated using a likelihood ratio test.

Comparison groups	Ferinject (ferric carboxymaltose) v Placebo
Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.56
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	0.89

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.32

Secondary: Days alive and out of hospital at 30 days

End point title	Days alive and out of hospital at 30 days

End point description:

End point type	Secondary

End point timeframe:

From the index operation to 30 days post-operation

End point values	Ferinject (ferric carboxymaltose)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	232	226		
Units: days				
arithmetic mean (standard deviation)	19.7 (± 7.0)	19.8 (± 7.5)		

Statistical analyses

Statistical analysis title	Days alive and out of hospital (DAOH)

Statistical analysis description:

This end point was analysed using linear regression as described by Ariti et al (see reference below).

CA. Ariti, JGF. Cleland, SJ. Pocock et al. Days alive and out of hospital and the patient journey in patients with heart failure: Insights from the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program, American Heart Journal, Volume 162, Issue 5, 2011, Pages 900-906

Comparison groups	Ferinject (ferric carboxymaltose) v Placebo
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.84
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	1.2

Secondary: Post-operative complications up to discharge

End point title	Post-operative complications up to discharge

End point description:

Post-operative complications during the inpatient period were classified using the Clavien-Dindo (CD) system. For each patient, the most severe post-operative complication was identified and used for analysis.

End point type	Secondary

End point timeframe:

From the index operation to discharge

End point values	Ferinject (ferric carboxymaltose)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	233	227		
Units: None				
None	138	139		
Grade I	28	24		
Grade II	45	40		
Grade III	14	17		
Grade IV	8	5		
Grade V	0	2		

Statistical analyses

Statistical analysis title	Post-operative complications

Statistical analysis description:

The number and percentage of patients with any moderate or severe (Clavien-Dindo Grade III or above) are reported by treatment group. A risk ratio (treatment versus placebo) and 95% confidence interval were calculated using binomial regression (binary outcome with a log link). A p-value was calculated using a likelihood ratio test.

Comparison groups	Ferinject (ferric carboxymaltose) v Placebo
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.69
Method	Binomial regression with a log link
Parameter estimate	Risk ratio (RR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.55

Secondary: EQ-5D-5L utility score at 6 months

End point title	EQ-5D-5L utility score at 6 months

End point description:

End point type	Secondary

End point timeframe:

From randomisation to 6 months post-operation

End point values	Ferinject (ferric carboxymaltose)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	173		
Units: None				
arithmetic mean (standard deviation)	0.82 (± 0.22)	0.82 (± 0.21)		

Statistical analyses

Statistical analysis title	EQ-5D-5L

Statistical analysis description:

Differences in mean (treatment versus placebo) levels of the total score were calculated using analysis of covariance (ANCOVA) techniques with the baseline score included in the model.

Comparison groups	Ferinject (ferric carboxymaltose) v Placebo
Number of subjects included in analysis	350
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.05

Secondary: MFI total score at 6 months

End point title	MFI total score at 6 months

End point description:

End point type	Secondary

End point timeframe:

From randomisation to 6 months post-operation

End point values	Ferinject (ferric carboxymaltose)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	171		
Units: None				
arithmetic mean (standard deviation)	48.8 (± 18.9)	47.4 (± 19.1)		

Statistical analyses

Statistical analysis title	MFI

Statistical analysis description:

Differences in mean (treatment versus placebo) levels of the total score were calculated using analysis of covariance (ANCOVA) techniques with the baseline score included in the model.

Comparison groups	Ferinject (ferric carboxymaltose) v Placebo
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.94
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	3.2

Secondary: SQOM total score at 6 months

End point title	SQOM total score at 6 months

End point description:

End point type	Secondary

End point timeframe:

From randomisation to 6 months post-operation

End point values	Ferinject (ferric carboxymaltose)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	172		
Units: None				
arithmetic mean (standard deviation)	1.35 (± 1.70)	1.26 (± 1.83)		

Statistical analyses

Statistical analysis title	SQOM
Statistical analysis description:	
Differences in mean (treatment versus placebo) levels of the total score were calculated using analysis of covariance (ANCOVA) techniques with the baseline score included in the model.	
Comparison groups	Ferinject (ferric carboxymaltose) v Placebo
Number of subjects included in analysis	350
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.69
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.46

Secondary: Readmission to hospital at 8 weeks

End point title	Readmission to hospital at 8 weeks
End point description:	
This end point excludes planned readmissions.	
End point type	Secondary
End point timeframe:	
From discharge from the index operation to 8 weeks post-operation	

End point values	Ferinject (ferric carboxymaltose)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	234	234		
Units: None				
0 readmissions	203	183		
1+ readmissions	31	51		

Statistical analyses

Statistical analysis title	Readmission to hospital
Statistical analysis description:	
A risk ratio (treatment versus placebo) and 95% confidence interval were calculated using binomial regression (binary outcome with a log link). A p-value was calculated using a likelihood ratio test.	
Comparison groups	Ferinject (ferric carboxymaltose) v Placebo
Number of subjects included in analysis	468
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	Binomial regression with a log link
Parameter estimate	Risk ratio (RR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.91

Secondary: Readmission to hospital at 6 months

End point title	Readmission to hospital at 6 months
End point description:	
This end point excludes planned readmissions.	
End point type	Secondary
End point timeframe:	
From discharge from the index operation to 6 months post-operation	

End point values	Ferinject (ferric carboxymaltose)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227	223		
Units: None				
0 readmissions	169	150		
1+ readmissions	58	73		

Statistical analyses

Statistical analysis title	Readmission to hospital

Statistical analysis description:

A risk ratio (treatment versus placebo) and 95% confidence interval were calculated using binomial regression (binary outcome with a log link). A p-value was calculated using a likelihood ratio test.

Comparison groups	Ferinject (ferric carboxymaltose) v Placebo
Number of subjects included in analysis	450
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.09
Method	Binomial regression with a log link
Parameter estimate	Risk ratio (RR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1.04

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Any adverse events which occur within 30 days of the trial treatment will be recorded in the CRF

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Ferinject (ferric carboxymaltose)

Reporting group description:

1000 mg of ferric carboxymaltose will be administered as an i.v. infusion (100ml normal saline) over a minimum of 15 minutes using a black infusion kit

Reporting group title	Placebo

Reporting group description:

Normal saline will be administered as an i.v. infusion (100ml normal saline) over a minimum of 15 minutes using a black infusion kit

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: The threshold for reporting non-serious adverse events is set at 5%. There were no non-serious adverse events which exceeded that threshold.

Serious adverse events	Ferinject (ferric carboxymaltose)	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 240 (9.17%)	24 / 241 (9.96%)	
number of deaths (all causes)	12	10	
number of deaths resulting from adverse events	0	1	
Investigations			
Inflammatory marker increased			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anastomotic leak			
subjects affected / exposed	1 / 240 (0.42%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chemical peritonitis			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fall			
subjects affected / exposed	1 / 240 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stoma complication			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iatrogenic injury			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal excoriation			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 240 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative ileus			
subjects affected / exposed	5 / 240 (2.08%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound complication			
subjects affected / exposed	1 / 240 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention postoperative			
subjects affected / exposed	1 / 240 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Deep vein thrombosis			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Post procedural drainage			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal replacement therapy			
subjects affected / exposed	1 / 240 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Parkinson's disease			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Transient ischaemic attack			
subjects affected / exposed	1 / 240 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 240 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation			

subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 240 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 240 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 240 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			

subjects affected / exposed	1 / 240 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 240 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal fluid collection			
subjects affected / exposed	1 / 240 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 240 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Jaundice cholestatic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pleural effusion			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 240 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 240 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 240 (0.00%)	2 / 241 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethritis noninfective			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal sepsis			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 240 (0.42%)	0 / 241 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia			
subjects affected / exposed	1 / 240 (0.42%)	4 / 241 (1.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 240 (0.00%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 240 (0.42%)	1 / 241 (0.41%)	
occurrences causally related to treatment / all	0 / 1	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	Ferinject (ferric carboxymaltose)	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 240 (0.00%)	0 / 241 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 October 2012	Changes were requested by the MHRA: - Protocol section 8.6 now clarifies that the IMP administration will be done in an in-patient setting with appropriate resuscitation facilities & staff available - Protocol section 8.6 now clearly documents that the study treatment must stop immediately in the event of intolerance or allergic reaction during administration. Section 8.11 also clarifies this - Protocol section 2.0 flowchart time point for follow-up now clarifies that it is post operation - Protocol section 11.4 now states that SAEs will be reported to LSHTM CTU within 24 hours of their knowledge - Protocol section 8.4 now clarifies that the treating clinical physician will have the final decision to unblind, & that the reason & rational will be discussed with the PREVENTT office at UCL
23 May 2013	Summary of the main changes: - Physical Examination removed as this data will not be collected or needed and ECG monitoring removed from post baseline assessments as ECG monitoring not required by safety profile of IMP and some sites do not routinely perform this - Clarification to co-primary endpoint relating to risk of blood transfusion or death, and have added that deaths will be adjusted for in the analysis. - POMS: this data also needs to be collected at day 5, due to patients being discharged much sooner nowadays - Health Economics: these sections revised following review and update from the trial Health Economist - TSC & DSMC: membership of both these committees has been added, now they have been approved by the HTA - AE section: revised to reflect the LSHTM CTU AE processes (because the sponsor has delegated this responsibility to the LSHTM CTU) - Restarting treatment: following on from review by the TSC it was agreed that the treatment could be restarted under certain conditions

14 January 2014	Summary of main changes: - Changes made in light of updated advice from the MHRA on IV iron: a) added two new exclusion criteria (patients with severe asthma or severe allergy, patients unfit for elective surgery), and b) added the new information that patients should be monitored for at least 30 minutes following treatment - Updated the side effects to reflect changes in the latest version of the SmPC - Changes made to the preoperative visit: this additional visit to hospital has been removed and the preoperative QoL forms will now be completed at home, and the central bloods done on admission to hospital (sites had difficulties fitting in this extra visit) - Changes to the timelines from treatment to surgery: the lower limit of this timeline shortened from 14 to 10 days, as sites found this restrictive when trying to recruit and it also meant cancer patients were excluded (agreed by the TSC that 10 days was sufficient time for the IV iron to take effect) - Further clarified documentation for drug returns and drug destruction to ensure blinding is not compromised by blinded staff at site and the wording relating to destruction of remaining drug has been removed - Included the system which will be used to document the post-operative complications (Clavien) - Included UE tests as a requirement rather than if available in follow-up visits as this is needed to calculate eGFR - Further clarification to haemoglobin measurements, immunosuppressive therapy in exclusion criteria, timing of screening pregnancy test, vital signs assessment, DSUR and APR anniversary dates and non exclusion of those on oral iron supplements' - Clarified IMP administration masking with iodine so that it allows flexibility of other methods in the event of those patients who are allergic to iodine - Added additional details so sites can call patients prior to consenting (as requested by site R&Ds)
10 April 2015	Summary of main changes: - Changed inclusion criteria to increase the upper limit of haemoglobin for men, to match the WHO definition of anaemia, and to help aid recruitment - Amended the definition of major surgery, so sites can now include patients having surgery which doesn't include the removal of an organ - Changed the exclusion criteria so that is it clear that only untreated B12/folate deficiency would make a patient ineligible - Added in how severe asthma/allergy is defined in the exclusion criteria - Increased the number of sites from 20 to 35, to help aid recruitment - Removed brand names of masking IV bags and giving sets to allow flexibility across sites - Included 200ml vials of Ferinject to allow flexibility in use of hospital stocks across sites - SAE form can be submitted via online AE database - Data monitoring changed to reflect new Monitoring SOP requirements - Administrative changes to update TSC members and observers
05 September 2016	Summary of main changes: - Changed exclusion criteria for Liver Function Tests (LFTs) to reflect local hospital practise and pathways - Changed exclusion criteria so that patients who have had a previous blood transfusion within the previous 12 weeks can still be included in the trial - Changed assessment of LFTs at baseline to clarify this is only done if clinically indicated according to local hospital practice and pathways - Updated the risk/benefits section of the protocol to reflect the change to the exclusion criteria for patients who have not had their LFTs checked - Increased the number of sites from 35 to 40 to help with recruitment - Update to reflect the approval by the funder of an additional 2 years of recruitment - Updated summary of product characteristics

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported