Clinical trial results:
An open label study to determine the efficacy of ferric carboxymaltose in preoperative colorectal cancer related anaemia, and to develop biomarkers to predict response to this treatment strategy

Summary

EudraCT number	2011-002185-21
Trial protocol	GB
Global end of trial date	08 August 2016

Results information

Result version number	v1 (current)
This version publication date	15 September 2016
First version publication date	15 September 2016
Summary attachment (see zip file)	End of study report (11GS005_End of Study Report_signed.pdf)

Trial information

Trial identification

Sponsor protocol code	11GS005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	REC reference number: 11/EM/0237

Notes:

Sponsors

Sponsor organisation name	Nottingham University Hospitals
Sponsor organisation address	Derby Road, Nottingham, United Kingdom, NG7 2UH
Public contact	Rachelle Ward, Nottingham University Hospitals, +44 115 924 9924 x70258, Rachelle.Ward@nuh.nhs.uk
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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	08 August 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 August 2016
Global end of trial reached?	Yes
Global end of trial date	08 August 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The principal research question is can we reduce the need for peri-operative allogeneic blood transfusion in the treatment group (intravenous ferric carboxymaltose) compared to the control group (oral ferrous sulphate)?

Protection of trial subjects:

We have conducted this study in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996, Good Clinical Practices (GCP) and Nottingham University Hospitals NHS Trust (NUH) Research and Innovation (R&I) Procedures.

The protocol, informed consent form, participant information sheet and any proposed advertising material was submitted to the Research Ethics Committee (REC), regulatory authorities (MHRA in the UK), and host institution(s) for written approval. We obtained approval from the above parties for the study.

In this trial, both the intervention and control group received iron in order to treat the anaemia pre-operatively. Therefore, there was no non-treatment of the participants.

There were clear guidelines that the clinicians should adhere to when considering transfusion for the participants in this trial. However, the guidelines could be overruled in any situation where the clinician feels that the clinical situation requires a different management from that detailed in the guidelines.

This study did not involve any vulnerable participants and all participants had to be able to give valid, informed consent to be enrolled in this trial.

Background therapy:

All subjects for this study are undergoing colorectal surgery to remove histologically colorectal adenocarcinoma. They were all received standard anaethesia, surgical bowel resection and post-operative care.

Evidence for comparator:

Oral iron supplementation and allogeneic blood transfusion are the current standard practice of treatment for pre-operative anaemia. Pre-operative oral iron supplementation has been proven to be effective in the treatment of anaemia and for reducing the need for blood transfusion in colorectal surgery. It is cheap, widely available and easily administered.

However, oral iron is associated with a number of gastrointestinal side-effects such as abdominal pain, constipation, diarrhoea and dyspepsia. Non-compliance as a result of these side-effects is a problem. Oral iron supplementation may also be insufficient to compensate for ongoing blood losses due to poor intestinal absorption.

Parenteral iron was first introduced in the early 20th century in the form of intramuscular and subcutaneous injections. However, these early formulations caused severe toxic reactions leading to their disuse. Towards the latter half of the 20th century, high molecular weight iron dextran was introduced for both intravenous and intramuscular use. However, the use of high molecular weight iron dextran has been phased out and replaced with low molecular weight iron dextran and other newer formulations of intravenous iron such as iron sucrose, ferric gluconate, ferumoxytol, ferric carboxymaltose and iron isomaltoside. This was due to reports of anaphylactic-type reactions with the use of high molecular weight iron dextran due to the instability of the molecule as well as the formation of anti-dextran antibodies.

Iron sucrose, a safer formulation not associated with anaphylactic-type reactions, had to be given in small maximum dosages of 200 mg for each infusion, thus requiring several small dose infusions to achieve the calculated iron deficit. Newer agents such as ferric carboxymaltose and iron isomaltoside have since been developed which allow total dose infusion and have much higher maximum approved doses and have not been associated with anaphylactic-type reactions.

Actual start date of recruitment	16 May 2012
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: 116
Worldwide total number of subjects	116
EEA total number of subjects	116

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)	21
From 65 to 84 years	83
85 years and over	12

Subject disposition

Recruitment

Recruitment details:

Recruitment of patients who are awaiting surgery and have pre-operative anaemia as defined by a haemoglobin 1g/dL below the World Health Organisation threshold for normal haemoglobin (12g/dL for males and 11g/dL for females) would take place after the cancer diagnosis of histologically confirmed colorectal adenocarcinoma.

Pre-assignment

Screening details:

Patients were screened against the following inclusion criteria: able to consent, adult age >18 years, histologically proven colorectal adenocarcinoma, anaemic (male Hb <12 g/dL, female <11 g/dL), fit for surgery, date of surgery > 14 days from intervention.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Are arms mutually exclusive?	Yes
Arm title	IV iron

Arm description:

Intravenous ferric carboxymaltose

Arm type	Experimental
Investigational medicinal product name	Ferric carboxymaltose
Investigational medicinal product code	
Other name	Ferinject
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

As per SmPC

Arm title	Oral iron

Arm description:

Oral ferrous sulphate

Arm type	Active comparator
Investigational medicinal product name	Ferrous sulphate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

200mg twice a day by mouth

Number of subjects in period 1	IV iron	Oral iron
Started	55	61
Completed	55	61

Period 2	
Period 2 title	Pre-operative
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms	
Are arms mutually exclusive?	Yes
Arm title	IV iron

Arm description:

Intravenous ferric carboxymaltose

Arm type	Experimental
Investigational medicinal product name	Ferric carboxymaltose
Investigational medicinal product code	
Other name	Ferinject
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

As per SmPC

Arm title	Oral iron

Arm description:

Oral ferrous sulphate

Arm type	Active comparator
Investigational medicinal product name	Ferrous sulphate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

200mg twice a day by mouth

Number of subjects in period 2	IV iron	Oral iron
Started	55	61
Completed	53	57
Not completed	2	4
Adverse event, serious fatal	1	-
Adverse event, non-fatal	-	1
Operation cancelled	1	3

Period 3

Period 3 title	Post-operative
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:
N/A

Arms

Are arms mutually exclusive?	Yes
Arm title	IV iron

Arm description:
Intravenous ferric carboxymaltose

Arm type	Experimental
Investigational medicinal product name	Ferric carboxymaltose
Investigational medicinal product code	
Other name	Ferinject
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use

Dosage and administration details:
As per SmPC

Arm title	Oral iron

Arm description:
Oral ferrous sulphate

Arm type	Active comparator
Investigational medicinal product name	Ferric carboxymaltose
Investigational medicinal product code	
Other name	Ferinject
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use

Dosage and administration details:
As per SmPC

Investigational medicinal product name	Ferrous sulphate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
200mg twice a day by mouth

Number of subjects in period 3	IV iron	Oral iron
Started	53	57
Completed	53	57

Baseline characteristics

Reporting groups	
Reporting group title	IV iron
Reporting group description: Intravenous ferric carboxymaltose	
Reporting group title	Oral iron
Reporting group description: Oral ferrous sulphate	

Reporting group values	IV iron	Oral iron	Total
Number of subjects	55	61	116
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	9	12	21
From 65-84 years	41	42	83
85 years and over	5	7	12
Age continuous Units: years			
arithmetic mean	73.8	74.7	
inter-quartile range (Q1-Q3)	67.4 to 78.6	67.9 to 80.8	-
Gender categorical Units: Subjects			
Female	20	24	44
Male	35	37	72
Inclusion Hb Units: g/dL			
arithmetic mean	9.59	9.91	
standard deviation	± 1.44	± 0.82	-

End points

End points reporting groups	
Reporting group title	IV iron
Reporting group description: Intravenous ferric carboxymaltose	
Reporting group title	Oral iron
Reporting group description: Oral ferrous sulphate	
Reporting group title	IV iron
Reporting group description: Intravenous ferric carboxymaltose	
Reporting group title	Oral iron
Reporting group description: Oral ferrous sulphate	
Reporting group title	IV iron
Reporting group description: Intravenous ferric carboxymaltose	
Reporting group title	Oral iron
Reporting group description: Oral ferrous sulphate	

Primary: Mean volume of blood transfused DOS	
End point title	Mean volume of blood transfused DOS
End point description:	
End point type	Primary
End point timeframe: Until end of day of surgery	

End point values	IV iron	Oral iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	57		
Units: Units				
arithmetic mean (standard deviation)	0.226 (± 0.72)	0.351 (± 1.3)		

Statistical analyses	
Statistical analysis title	Students-T test
Comparison groups	Oral iron v IV iron

Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.524 [1]
Method	t-test, 2-sided

Notes:
[1] - NS

Primary: Mean volume of blood transfused Day 7

End point title	Mean volume of blood transfused Day 7

End point description:

End point type	Primary

End point timeframe:
Until end of post-op day 7

End point values	IV iron	Oral iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[2]	57		
Units: unit(s)				
arithmetic mean (standard deviation)	0.157 (± 0.505)	0.597 (± 1.376)		

Notes:
[2] - Two patients excluded with severe intra-operative blood loss

Statistical analyses

Statistical analysis title	Students-T test
Comparison groups	IV iron v Oral iron
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.027 [3]
Method	t-test, 2-sided

Notes:
[3] - Significant

Primary: Mean volume of blood transfused Day 14

End point title	Mean volume of blood transfused Day 14

End point description:

End point type	Primary

End point timeframe:
Until end of post-op day 14

End point values	IV iron	Oral iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[4]	57		
Units: unit(s)				
arithmetic mean (standard deviation)	0.275 (± 0.964)	0.597 (± 1.376)		

Notes:

[4] - Two patients excluded with severe intra-operative blood loss

Statistical analyses

Statistical analysis title	Students-T test
Comparison groups	Oral iron v IV iron
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.158
Method	t-test, 2-sided

Primary: Mean volume of blood transfused Day 28

End point title	Mean volume of blood transfused Day 28

End point description:

End point type	Primary

End point timeframe:

Until end of post-op day 28

End point values	IV iron	Oral iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[5]	57		
Units: unit(s)				
arithmetic mean (standard deviation)	0.294 (± 0.964)	0.632 (± 1.41)		

Notes:

[5] - Two patients excluded with severe intra-operative blood loss

Statistical analyses

Statistical analysis title	Students-T test
Comparison groups	IV iron v Oral iron

Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.146
Method	t-test, 2-sided

Primary: Mean volume of blood transfused OPD

End point title	Mean volume of blood transfused OPD

End point description:

End point type	Primary

End point timeframe:

Until out patients appointment

End point values	IV iron	Oral iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[6]	57		
Units: unit(s)				
arithmetic mean (standard deviation)	0.412 (± 1.316)	0.632 (± 1.41)		

Notes:

[6] - Two patients excluded with severe intra-operative blood loss

Statistical analyses

Statistical analysis title	Students-T test
Comparison groups	IV iron v Oral iron
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.404
Method	t-test, 2-sided

Primary: Number of patients transfused DOS

End point title	Number of patients transfused DOS

End point description:

End point type	Primary

End point timeframe:

Until end of day of surgery

End point values	IV iron	Oral iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	57		
Units: Patients	7	6		

Statistical analyses

Statistical analysis title	Chi squared test
Comparison groups	IV iron v Oral iron
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.876
Method	Chi-squared

Primary: Number of patients transfused day 7

End point title	Number of patients transfused day 7

End point description:

End point type	Primary

End point timeframe:

Until end of day 7

End point values	IV iron	Oral iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[7]	57		
Units: Patients	5	14		

Notes:

[7] - Two patients excluded with severe intra-operative blood loss

Statistical analyses

Statistical analysis title	Chi squared test
Comparison groups	Oral iron v IV iron

Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.044 [8]
Method	Chi-squared

Notes:
[8] - Significant

Primary: Number of patients transfused day 14

End point title	Number of patients transfused day 14

End point description:

End point type	Primary

End point timeframe:
Until end of post op day 14

End point values	IV iron	Oral iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[9]	57		
Units: Patients	6	14		

Notes:
[9] - Two patients excluded with severe intra-operative blood loss

Statistical analyses

Statistical analysis title	Chi squared test
Comparison groups	IV iron v Oral iron
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.087
Method	Chi-squared

Primary: Number of patients transfused day 28

End point title	Number of patients transfused day 28

End point description:

End point type	Primary

End point timeframe:
Until post op day 28

End point values	IV iron	Oral iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[10]	57		
Units: Patients	7	14		

Notes:

[10] - Two patients excluded with severe intra-operative blood loss

Statistical analyses

Statistical analysis title	Chi squared test
Comparison groups	IV iron v Oral iron
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.155
Method	Chi-squared

Primary: Number of patients transfused OPD

End point title	Number of patients transfused OPD

End point description:

End point type	Primary

End point timeframe:

Until out patients appointment

End point values	IV iron	Oral iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[11]	57		
Units: Patients	8	14		

Notes:

[11] - Two patients excluded with severe intra-operative blood loss

Statistical analyses

Statistical analysis title	Chi squared test
Comparison groups	IV iron v Oral iron
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.253
Method	Chi-squared

Secondary: Haemoglobin

End point title	Haemoglobin

End point description:

End point type	Secondary

End point timeframe:

Day of surgery

End point values	IV iron	Oral iron	IV iron	Oral iron
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	55	61	53	57
Units: g/dL				
arithmetic mean (inter-quartile range (Q1-Q3))	10.2 (9.8 to 10.5)	10.42 (10.1 to 10.7)	11.9 (11.5 to 12.3)	11 (10.6 to 11.4)

Statistical analyses

Statistical analysis title	Students-T test

Statistical analysis description:

Comparison haemoglobin at baseline

Comparison groups	IV iron v Oral iron
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.24
Method	t-test, 2-sided

Statistical analysis title	Students-T test

Statistical analysis description:

Comparison haemoglobin pre-operatively

Comparison groups	Oral iron v IV iron
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.01
Method	t-test, 2-sided

Secondary: Ferritin

End point title	Ferritin

End point description:

End point type	Secondary
End point timeframe: Recruitment to day of surgery	

End point values	IV iron	Oral iron	IV iron	Oral iron
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	55	61	53	57
Units: microgram(s)/litre				
median (inter-quartile range (Q1-Q3))	21 (8 to 46)	26 (15 to 50)	558 (329.8 to 1085.3)	27.5 (17 to 51.5)

Statistical analyses

Statistical analysis title	Students-T test
Comparison groups	IV iron v Oral iron
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.224
Method	t-test, 2-sided

Statistical analysis title	Students-T test
Comparison groups	IV iron v Oral iron
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	t-test, 2-sided

Secondary: Transferrin saturations

End point title	Transferrin saturations
End point description:	

End point type	Secondary
End point timeframe: Recruitment to day of surgery	

End point values	IV iron	Oral iron	IV iron	Oral iron
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	55	61	53	57
Units: percent				
median (inter-quartile range (Q1-Q3))	7 (5 to 15)	8 (6 to 20)	19 (16 to 29)	9 (5 to 14)

Statistical analyses

Statistical analysis title	Students-T test
Comparison groups	Oral iron v IV iron
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.038
Method	t-test, 2-sided

Statistical analysis title	Students-T test
Comparison groups	IV iron v Oral iron
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	t-test, 2-sided

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

The Nottingham University Hospitals Trust undertook an immediate review of reported SAEs for the study. All SAEs were to be reported to R&I within one working day of discovery or notification of the event.

Adverse event reporting additional description:

AEs considered related to the study medication as judged by a medically qualified investigator or the sponsor were followed until resolution or the event was considered stable. All related AEs that resulted in a participant's withdrawal from the studywere followed up until a satisfactory resolution occurred.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14

Reporting groups

Reporting group title	IV iron

Reporting group description:

Intravenous ferric carboxymaltose

Reporting group title	Oral iron

Reporting group description:

Oral ferrous sulphate

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: See end of study report (summary attachment)

Serious adverse events	IV iron	Oral iron	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 55 (18.18%)	11 / 61 (18.03%)	
number of deaths (all causes)	2	3	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour progression			
subjects affected / exposed	1 / 55 (1.82%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anastomotic leak			
subjects affected / exposed	1 / 55 (1.82%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocutaneous fistula			

subjects affected / exposed	1 / 55 (1.82%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aneurysm			
subjects affected / exposed	1 / 55 (1.82%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 55 (1.82%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 55 (1.82%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 55 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perforation	Additional description: Bowel perforation		
subjects affected / exposed	0 / 55 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ileus			
subjects affected / exposed	0 / 55 (0.00%)	3 / 61 (4.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction	Additional description: Bowel obstruction		
subjects affected / exposed	0 / 55 (0.00%)	1 / 61 (1.64%)	
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			
Pneumonia			
subjects affected / exposed	1 / 55 (1.82%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 55 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin and subcutaneous tissue disorders			
Rash	Additional description: Rash and swelling		
subjects affected / exposed	1 / 55 (1.82%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	0 / 55 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	1 / 55 (1.82%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Wound infection			
subjects affected / exposed	1 / 55 (1.82%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection	Additional description: Surgical infection		
subjects affected / exposed	0 / 55 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	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	Oral iron	
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 55 (0.00%)	0 / 61 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 March 2012	(a) Value specified for definition of anaemia (b) Electrocardiogram assessment will not be performed. (c) Patients will be followed up at 6-12 weeks to coincide with routine clinical follow-up. (d) Addition of second quality of life questionnaire which will be retested at final review (e) IBC, IL-1 and IL-6 will no longer be measured (f) All females will have a pregnancy test (g) Hepcidin/erythropoietin level to be retested as part of planned blood tests at final review.
09 October 2012	-Addition of a new site (Derby) -Additional QoL Questionnaire (FACT-An)
13 March 2013	a) Addition of new site: St James University Hospitals Leeds b) Addition of new site: University Hospitals of Leicester NHS Trust c) Addition of new site: Yeovil District Hospital NHS Foundation Trust d) Addition of new site: University Hospitals Bristol Foundation NHS Trust e) Page 17 – Clarification that tumour specimen will only be collected at Nottingham site f) Page 25 -Clarification of pregnancy testing – only to be performed in females under 55 years of age or currently menstruating
01 November 2013	(a) Page 22 Age limit re-submitted for MHRA review. This was reviewed by ethics committee in amendment 4 but was erroneously not submitted to MHRA at that point. (b) Page 23 - Clarification that patients with confirmed liver and lung metastases will be excluded. (c) Page 29 - Patients who are lost to follow up or who fail to undergo surgery will still have data to review in line with an intention to treat basis. (d) Page 37 - Clarification of composition of the Trial Management Group
12 August 2014	New PI added to investigators
06 May 2015	(a) Correct version control of addition of PI as an investigator. (b) Page 16 - Addition of P selectin test

Notes:

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.

See end of study report (summary attachment)

Notes: