Clinical trial results:
Effects of intravenous iron in COPD.

Summary

EudraCT number	2012-002952-17
Trial protocol	GB
Global end of trial date	05 July 2017

Results information

Result version number	v1 (current)
This version publication date	18 November 2018
First version publication date	18 November 2018
Summary attachment (see zip file)	Table of secondary outcomes (Table - Primary and secondary outcomes.pdf) Table of laboratory parameter outcomes (Table - Laboratory parameters.pdf) Table of adverse events (Table - Adverse events.pdf)

Trial information

Trial identification

Sponsor protocol code	COPDIron

Additional study identifiers

ISRCTN number	ISRCTN09143837
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford, CTRG
Sponsor organisation address	Joint Research Office, 1st floor, Boundary Brook House, Churchill Drive, Oxford, United Kingdom, OX3 7LQ
Public contact	Co-ordinating centre, Oxford Respiratory Trials Unit, 0044 01865225205, magda.laskawiec@ouh.nhs.uk
Scientific contact	Co-ordinating centre, Oxford Respiratory Trials Unit, 0044 01865225205, magda.laskawiec@ouh.nhs.uk

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 July 2017
Global end of trial reached?	Yes
Global end of trial date	05 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether intravenous administration of ferric carboxymaltose improves peripheral arterial oxygen saturation in patients with COPD at one week following an infusion of iron compared to saline control.

Protection of trial subjects:

The only intervention in this study was the administration of intra-venous ferric carboxymaltose, which had been shown to be safe and well tolerated. The most common side-effects are a headache (occurring in 3.3% of patients) and rash. All team members involved in administration of intravenous drugs were competent in the recognition and treatment of potential adverse reactions such as allergy or anaphylaxis. Appropriate emergency medications and cardiopulmonary resuscitation facilities were available.
All AEs, immediately after and up to 1 week after IMP administration were recorded in the study CRF. The following information relevant to the AE was recorded: description, date of onset and end date, severity, assessment of relatedness to study medication, other suspect drug or device and action taken. Follow-up information was provided as necessary.
It was up to the investigator's clinical judgment whether or not an AE was of sufficient severity (mild, moderate or severe) to require the participant's removal from treatment. A participant could have also voluntarily withdrawn from treatment due to what they perceived as an intolerable AE. In such a case, the participant would have undergone an end of study assessment and be given appropriate care under medical supervision until symptoms cease or the condition became stable.

Background therapy:

Patients continued to take their medication for the underlying disease and other comorbidities as instructed by their treating physicians.

Evidence for comparator:

Iron has been shown to be important in the regulation of pulmonary vascular responses to hypoxia, which is a crucial feature underlying the pathogenesis of COPD. As such, low iron levels were shown to increase pulmonary arterial pressure, which is associated with worse outcomes in COPD. On the other hand, administration of iron could attenuate this increase. It was therefore postulated, that administration of intravenous iron to patients with COPD, which is characterized by hypoxia and increased pulmonary arterial pressure, might be of benefit. Furthermore, patients with COPD were shown to be iron deficient significantly more often than healthy controls. iron deficient COPD patients were also more hypoxemic and showed more inflammation than iron-replete patients with COPD.

Actual start date of recruitment	29 October 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: 48

Worldwide total number of subjects	48
EEA total number of subjects	48

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	16
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited between March 2015 and July 2017 in Oxford, UK. Recruitment occurred Oxford Centre for Respiratory Medicine, hospital wards, the respiratory outpatient clinics, the Respiratory Research Registry (held at the Churchill Hospital), from primary care settings or via study posters in hospital, outpatient clinic & GP surgeries.

Pre-assignment

Screening details:

Screening included review of medical history. physical examination, blood test and lung function testing. Participants were instructed in daily measurement of oxygen saturation and peak expiratory flow at home. 71 participants attended a screening visit, of which 55 met eligibility criteria. 7 withdrew consent after screening.

Period 1

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

Blinding implementation details:

Team members undertaking patient assessments were blinded. Team members preparing and administering intravenous iron/saline were unblinded. Blinding of these research team members was not possible since the iron solution is brown and saline is colourless. The iron infusion had to be made up immediately prior to administration. Given the colour difference in the solutions, opaque covers were used for giving sets and cannulae to maintain blinding of the patient and other researchers.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo control

Arm description:

The control arm was given normal saline (placebo)

Arm type	Placebo
Investigational medicinal product name	Physiological saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

A solution of 0.9% weight per volume sodium chloride at physiological osmolality at around 300 mOsm/L was used. 250 ml of normal saline (0.9%) was infused, using the same schedule as for the iron infusion.

Arm title	Intravenous iron

Arm description:

This arm received intravenous ferric carboxymaltose, the experimental drug studied in this trial.

Arm type	Experimental
Investigational medicinal product name	Ferric carboxymaltose
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

The iron formulation used was ferric carboxymaltose (Ferinject®). This comprises a macromolecular

iron-hydroxide complex of polynuclear iron (III) hydroxide in a carbohydrate shell60. The complex is very stable, therefore does not release ionic iron under physiological conditions. The slow release of iron avoids the acute toxicity of many other iron compounds, but allowing large amounts of iron to be delivered. It has a half-life of 16 hours. The dose of ferric carboxymaltose is 15 mg/kg up to a maximum dose of 1000mg. The dose required is added to a bag of 250 ml normal saline, and infused over 15 minutes.

Number of subjects in period 1	Placebo control	Intravenous iron
Started	24	24
Completed	24	24

Period 2	
Period 2 title	Week 1 follow up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor
Blinding implementation details:	
No further intervention occurred. Blinding was maintained throughout the whole study period for the roles selected above.	

Arms	
Are arms mutually exclusive?	Yes
Arm title	Intravenous iron
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Placebo control
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	Intravenous iron	Placebo control
Started	24	24
Completed	24	24

Period 3	
Period 3 title	Week 8 follow up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

No further intervention occurred. Blinding was maintained throughout the whole study period for the roles selected above.

Arms	
Are arms mutually exclusive?	Yes
Arm title	Placebo control
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Intravenous iron
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 3	Placebo control	Intravenous iron
Started	24	24
Completed	24	24

Baseline characteristics

Reporting groups	
Reporting group title	Placebo control
Reporting group description:	
The control arm was given normal saline (placebo)	
Reporting group title	Intravenous iron
Reporting group description:	
This arm received intravenous ferric carboxymaltose, the experimental drug studied in this trial.	

Reporting group values	Placebo control	Intravenous iron	Total
Number of subjects	24	24	48
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			
Age at baseline visit.			
Units: years			
arithmetic mean	68	69.2	
standard deviation	± 7	± 8.4	-
Gender categorical			
Gender			
Units: Subjects			
Female	5	9	14
Male	19	15	34
Smoking status Units: Subjects			
Former smoker	16	18	34
Current smoker	7	6	13
Never smoked	1	0	1
GOLD stage			
GOLD stage at baseline			
Units: Subjects			
Mild (I)	0	0	0
Moderate (II)	10	9	19
Severe (III)	10	10	20
Very severe (IV)	4	5	9

BMI			
Bodz mass index			
Units: kg/m2			
arithmetic mean	25.4	25.7	
standard deviation	± 4.1	± 6.1	-
Pack years			
Number of pack years smoked			
Units: years			
median	39	43	
inter-quartile range (Q1-Q3)	28 to 67	31 to 67	-
Age of COPD onset			
Units: years			
arithmetic mean	58.2	57.2	
standard deviation	± 5.3	± 11.3	-
Age of smoking initiation			
Units: years			
arithmetic mean	14.6	14.8	
standard deviation	± 3.0	± 2.9	-
Age of smoking cessation			
Age of smoking cessation (if applicable)			
Units: years			
arithmetic mean	57.5	59.0	
standard deviation	± 8.7	± 6.5	-
Exacerbations in previous years			
Units: number of events			
median	2	1	
inter-quartile range (Q1-Q3)	1 to 3	0 to 3	-
FEV1 predicted			
Forced expiratory volume in 1 second as percentage of normal range			
Units: percent			
arithmetic mean	49.8	48.0	
standard deviation	± 16.9	± 17.6	-
FEV1/FVC			
FEV1 to FVC ratio			
Units: percent			
arithmetic mean	40.4	44.8	
standard deviation	± 10.2	± 9.0	-
Serum iron			
Units: micromole(s)/litre			
median	15.2	16.1	
inter-quartile range (Q1-Q3)	13.2 to 19.5	11.0 to 19.3	-
Serum ferritin			
Units: microgram(s)/litre			
median	69.6	84.3	
inter-quartile range (Q1-Q3)	38.5 to 151.9	65.1 to 110.6	-
Serum transferrin			
Units: gram(s)/litre			
arithmetic mean	2.53	2.53	
standard deviation	± 0.31	± 0.32	-
Transferrin saturation			
Units: percent			
median	26.5	28.0	

inter-quartile range (Q1-Q3)	23.0 to 38.3	21.3 to 37.0	-
Serum soluble transferrin receptor Units: nanomole(s)/litre			
arithmetic mean	17.1	16.2	
standard deviation	± 5.0	± 4.4	-
Plasma hepcidin Units: nanogram(s)/millilitre			
median	17.7	20.7	
inter-quartile range (Q1-Q3)	8.0 to 25.1	12.7 to 29.1	-

End points

End points reporting groups

Reporting group title	Placebo control
Reporting group description:	
The control arm was given normal saline (placebo)	
Reporting group title	Intravenous iron
Reporting group description:	
This arm received intravenous ferric carboxymaltose, the experimental drug studied in this trial.	
Reporting group title	Intravenous iron
Reporting group description: -	
Reporting group title	Placebo control
Reporting group description: -	
Reporting group title	Placebo control
Reporting group description: -	
Reporting group title	Intravenous iron
Reporting group description: -	

Primary: Peripheral oxygen saturation

End point title	Peripheral oxygen saturation
End point description:	
Change in peripheral arterial oxygen saturation at one week at rest using pulse oximetry	
End point type	Primary
End point timeframe:	
Assessed at week 1 follow up.	

End point values	Placebo control	Intravenous iron		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: percent				
arithmetic mean (standard error)	-0.39 (± 0.36)	0.39 (± 0.32)		

Attachments (see zip file)	Peripheral oxygen saturation (primary outcome)/Primary

Statistical analyses

Statistical analysis title	Primary outcome analysis
Statistical analysis description:	
The primary outcome (change in peripheral oxygen saturation from baseline to week 1 between groups) was analysed by two-tailed unpaired Student t-test.	
Comparison groups	Placebo control v Intravenous iron

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.116
Method	t-test, 2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs, immediately after and up to 1 week after IMP administration were recorded in the study CRF. All Serious Adverse Events were recorded for the entire study duration and reported within 24 hours of knowledge of the event to the sponsor.

Adverse event reporting additional description:

Adverse events were recorded on the week 1 follow up visit and recorded on dedicated CRFs. If necessary, follow up about adverse event solution was provided. Serious adverse events were recorded up until the end of the study (week 8 visit).

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Placebo control

Reporting group description:

The control arm was given normal saline (placebo)

Reporting group title	Intravenous iron

Reporting group description:

This arm received intravenous ferric carboxymaltose, the experimental drug studied in this trial.

Serious adverse events	Placebo control	Intravenous iron	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 24 (8.33%)	0 / 24 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Fall	Additional description: Fall requiring hospitalisation		
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Lung infection	Additional description: Lung infection requiring hospitalisation		
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo control	Intravenous iron	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 24 (70.83%)	22 / 24 (91.67%)	
Investigations			
Hypophosphatemia	Additional description: Hypophosphatemia was defined as phosphate levels <0.8 mmol/L. Numbers reported here are based on the retrospective analysis of stored serum samples from all participants.		
subjects affected / exposed	2 / 24 (8.33%)	22 / 24 (91.67%)	
occurrences (all)	2	22	
Other abnormal laboratory tests	Additional description: These included in order of frequency: elevated C-reactive protein, hypoalbuminemia, thrombocytosis, hypokalemia, anemia, hyperkalemia, elevated white cell and neutrophil counts		
subjects affected / exposed	7 / 24 (29.17%)	8 / 24 (33.33%)	
occurrences (all)	8	10	
Cardiac disorders			
Hypertension			
subjects affected / exposed	4 / 24 (16.67%)	5 / 24 (20.83%)	
occurrences (all)	4	5	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 24 (16.67%)	2 / 24 (8.33%)	
occurrences (all)	4	2	
General disorders and administration site conditions			
Haematoma			
subjects affected / exposed	2 / 24 (8.33%)	2 / 24 (8.33%)	
occurrences (all)	2	2	
Fever			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Dizziness			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Diarrhea			

subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	0 / 24 (0.00%)	3 / 24 (12.50%)	
occurrences (all)	0	3	
Upper respiratory infection			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Nasal congestion			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Lung infection			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 October 2012	Changes to the protocol exclusion criteria. Changes to the acceptable forms of effective contraception. Changes to withdrawal procedures of participants from study treatment due to pregnancy. Changes to safety profile of procedures section. Changes to the SAE reporting section. Additional information added to the Patient Information Sheet.
30 June 2013	Addition of tertiary objective: Enrich the detailed phenotyping of the COPD Cohort. Information to Withdrawal of Participants from Study Treatment section added. Due to the design of the database, data already entered onto it cannot be deleted, but will be excluded from analysis. Clarification regarding adverse event followup of patients following withdrawal from the trial. Addition of safety reporting procedure for unexpected adverse events which the PI deems are possibly related to the trial medication or trial procedures. Clarification that SAEs must be reported to the sponsor (CTRG) and not ORTU (Oxford Respiratory Trials Unit) within 24 hours of knowledge of the event. Explanation of why full dataset will be collected from screen failures at the screening visit. The patient information sheet has been altered to explain to the patient why the researcher's wish to complete the full set of screening assessments even if the patient is not eligible to take part in the study. The consent form now has an additional question (question 7) so that patients can give their consent for this. Minimisation to be carried out using the sofware program Sealed Envelope.
18 March 2014	New primary endpoint: oxygen status in response to intravenous iron. This has led to the following changes in the text of the protocol as detailed below: 2. Rationale 3. New endpoints 4. Inclusion exclusion criteria 5. Simplification of study visits 6. Revised sample size Corresponding changes have also been made in the patient information sheet and GP letter. The final change is that not all patients will already be carrying out daily diary cards as part of their participation in the COPD Cohort (this protocol was simplified), and therefore this test was described as if it is new to the patient. Patients had to be free of an exacerbation as documented on the daily diary card for at least four weeks prior to the baseline study.
25 July 2014	Change of CI from Dr Annabel Nickol to Dr Mona Bafadhel.

09 December 2014	Minor admin updates. Addition of blood tests and lung function testing at screening visit for patients who did not have a recent result in either of these tests. The study team felt that the patients should not be asked to keep a diary card beyond the end of the study as no provision of diary follow-up had been made and the study had ends at 8 weeks post baseline for each patient. Clarification of who will carry out the study assessments. The protocol and the Patient Information Sheet were updated to reflect this. Simplification for recording AEs and a time limit on when to stop recording AEs. The CI and the sponsor felt that this section of the protocol was not clear and needed clarification. Clarification of safety reporting to confirm which SAEs must be reported immediately and a time frame for the end of reporting. The CI and sponsor felt it was unnecessary to report all SAEs and that there needed to be a time limit on when to stop reporting SAEs. The Patient Information Sheet has been updated to inform patients that a blood test and spirometry may be performed at the screening visit if a recent test is not available. The Patient Information Sheet has been updated to inform patients that diary cards only need to be kept for the duration of the study and no longer. The Patient Information Sheet has been updated to inform patients that the Baseline visit is more likely going to take 4 hours rather than 3 hours.
14 January 2015	As requested by the MHRA in order to comply with UK Statutory Instrument 2004 No 1031 Part, the protocol was updated to clarify that all Serious Adverse Events, regardless of the causality, must be reported within 24 hours of knowledge of the event to the sponsor.
26 March 2015	This study stopped recruiting from the COPD cohort. Patients first to be identified in the Oxford Centre for Respiratory Medicine or in a Primary Care by a member of their clinical care team who asked them if they wished to be contacted about the study. The following additional tests were added which were originally carried out in the COPD Cohort: - Patient’s weight, height and neck circumference measurements - A 12 lead electrocardiogram (ECG) GP letter and Consent form removal of references to COPD cohort.
04 March 2016	To ensure the study recruitment target was met, the study staff were looking at a number of ways of encouraging recruitment including the use of recruitment posters and fliers for patients to take away. The study team to send out a study appointment letter for the remaining study visits once the patient has had their screening visit and to thank them for taking part in the study. Letter from patient's clinician or GP inviting patient to take part in the study and to accompany Patient Information Sheet. New document: PULSOX instruction sheet. Patient Information Sheet updated. Recruitment section of the protocol updated to reflect the additional sources where patients will be recruited from and how they will be recruited.

26 October 2016	Removal of a need to collect sputum samples and conduct an exacerbation visit post baseline in the event of infective exacerbation (removal of observation of change in sputum microbiology as a secondary outcome) (protocol and PIS updated). Introduction of a "Consent to Contact Form" to maximise recruitment opportunities. Addition of a new poster (to enable the poster to be displayed electronically).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported