Clinical trial results:
A pilot trial of intravenous iron for the treatment of iron deficiency in adult patients with cystic fibrosis

Summary

EudraCT number	2018-002366-39
Trial protocol	GB
Global end of trial date	30 September 2021

Results information

Result version number	v1 (current)
This version publication date	23 April 2023
First version publication date	23 April 2023

Trial information

Trial identification

Sponsor protocol code	12800

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03632525
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford / Clinical Trials and Research Governance
Sponsor organisation address	Joint Research Office, Boundary Brook House, Churchill Drive, Headington, Oxford, United Kingdom, OX3 7LE
Public contact	CTRG, University of Oxford / Clinical Trials and Research Governance, 00 000000, ctrg@admin.ox.ac.uk
Scientific contact	CTRG, University of Oxford / Clinical Trials and Research Governance, 00 000000, ctrg@admin.ox.ac.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	Interim
Date of interim/final analysis	02 May 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 March 2020
Global end of trial reached?	Yes
Global end of trial date	30 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the early safety profile of IV iron in adults with CF by comparing the incidence of new infective events during the 4 weeks before and after IV iron

Protection of trial subjects:

The trial interventions were all standard clinical interventions to which the participants could be exposed in routine clinical practice, and all were delivered with the same safeguards/safety measures that would have been used in routine clinical practice. Trial-specific data and samples were handled /managed according to standard GCP and clinical trial regulations.

Background therapy:

Participants continued on their standard background therapy for cystic fibrosis, including antibiotics and mucolytic therapy. The details of this therapy varied between participants, and was not influenced by participation in the clinical trial.

Evidence for comparator:

This was an interventional cohort study in which all participants received the main study intervention (intravenous iron, as ferric carboxymaltose). The primary comparison was between the incidence of new infective events in the four weeks before and the four weeks after the study intervention.

Actual start date of recruitment	11 March 2019
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: 20
Worldwide total number of subjects	20
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	20
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were all recruited in a single centre (Oxford) in the UK, during the period 11/03/2019 to 12/12/2019.

Pre-assignment

Screening details:

Participants with iron deficiency were identified by the clinical team, and screened for eligibility based on the inclusion/exclusion criteria.

Pre-assignment period milestones

Number of subjects started	20
Number of subjects completed	20

Period 1

Period 1 title	Pre iron
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

No blinding or allocation method - all participants received the study intervention (intravenous ferric carboxymaltose) in an open label design.

Arms

Arm title	All participants (pre iron)

Arm description:

Participants were studied as a single group in this intervention cohort study, in which the primary comparison is bring made between the pre- and post-iron periods for the cohort.

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

Dosage and administration details:

The dose of ferric carboxymaltose (Ferinject) used was 20 mg/kg, up to a maximum dose of 1000 mg for patients with a haemoglobin concentration less than 14 g/dL or a maximum of 500 mg for patients with a haemoglobin concentration more than or equal to 14 g/dL. The appropriate dose was given in 250 ml of normal (0.9%) saline over 15 minutes.

Number of subjects in period 1	All participants (pre iron)
Started	20
Visit 1 (baseline, 4 weeks pre iron)	20
Visit 2 (day of iron administration)	20

Completed	20

Period 2

Period 2 title	Post iron
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

No blinding or allocation method - all participants received the study intervention (intravenous ferric carboxymaltose) in an open label design

Arms

Arm title	All participants (post iron)

Arm description:

Participants were studied as a single group in this intervention cohort study, in which the primary comparison is bring made between the pre- and post-iron periods for the cohort.

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

Dosage and administration details:

The dose of ferric carboxymaltose (Ferinject) used was 20 mg/kg, up to a maximum dose of 1000 mg for patients with a haemoglobin concentration less than 14 g/dL or a maximum of 500 mg for patients with a haemoglobin concentration more than or equal to 14 g/dL. The appropriate dose was given in 250 ml of normal (0.9%) saline over 15 minutes.

Number of subjects in period 2	All participants (post iron)
Started	20
Visit 3 (4 weeks post iron)	20
Visit 4 (12 weeks post iron)	20
Completed	20

Baseline characteristics

Reporting groups

Reporting group title	Pre iron

Reporting group description: -

Reporting group values	Pre iron	Total	
Number of subjects	20	20	
Age categorical Units: Subjects			
Adults (18-64 years)	20	20	
Age continuous			
Age of participants at recruitment			
Units: years arithmetic mean standard deviation	 30.1 ± 10.2	 -	
Gender categorical Units: Subjects			
Female Male	10 10	10 10	
Chronic Pseudomonas colonisation			
Number of patients known to have chronic Pseudomonas colonisation.			
Units: Subjects			
Pseudomonas colonisation No Pseudomonas colonisation	10 10	10 10	
Body mass index Units: kg/m2 arithmetic mean standard deviation	 22.7 ± 4.4	 -	
Forced expiratory volume in 1 second (FEV1) Units: % predicted value arithmetic mean standard deviation	 63 ± 22.2	 -	
Ferritin Units: microgram(s)/litre arithmetic mean standard deviation	 11.9 ± 10.1	 -	
Haemoglobin			
Blood haemoglobin concentration			
Units: gram(s)/litre arithmetic mean standard deviation	 124 ± 21	 -	

Subject analysis sets

Subject analysis set title	All participants
Subject analysis set type	Full analysis

Subject analysis set description:
All participants

Reporting group values	All participants		
Number of subjects	20		
Age categorical Units: Subjects			
Adults (18-64 years)	20		
Age continuous			
Age of participants at recruitment			
Units: years arithmetic mean standard deviation	 30.1 ± 10.2		
Gender categorical Units: Subjects			
Female Male	10 10		
Chronic Pseudomonas colonisation			
Number of patients known to have chronic Pseudomonas colonisation.			
Units: Subjects			
Pseudomonas colonisation No Pseudomonas colonisation	10 10		
Body mass index Units: kg/m2 arithmetic mean standard deviation	 22.7 ± 4.4		
Forced expiratory volume in 1 second (FEV1) Units: % predicted value arithmetic mean standard deviation	 63 ± 22.2		
Ferritin Units: microgram(s)/litre arithmetic mean standard deviation	 11.9 ± 10.1		
Haemoglobin			
Blood haemoglobin concentration			
Units: gram(s)/litre arithmetic mean standard deviation	 124 ± 21		

End points

End points reporting groups

Reporting group title	All participants (pre iron)

Reporting group description:

Participants were studied as a single group in this intervention cohort study, in which the primary comparison is bring made between the pre- and post-iron periods for the cohort.

Reporting group title	All participants (post iron)

Reporting group description:

Participants were studied as a single group in this intervention cohort study, in which the primary comparison is bring made between the pre- and post-iron periods for the cohort.

Subject analysis set title	All participants
Subject analysis set type	Full analysis

Subject analysis set description:

All participants

Primary: New infective events (4 weeks)

End point title	New infective events (4 weeks)

End point description:

The primary outcome is a comparison of the incidence of new infective events in the 4-week period before iron infusion (i.e. between the baseline visit and visit 2) and the 4-week period after iron infusion (i.e. between visits 2 and 3). A deterioration of infective status was defined as ANY one of the following:

- New microbiological isolate in sputum (i.e. an organism not cultured during the prior 12 months)
- Clinical infection requiring intravenous antibiotics (as judged by the clinical team)
- Admission to hospital for infection-related reason (as judged by clinical team)
- More than 10% fall in FEV1, not otherwise explained (as judged by clinical team)

End point type	Primary

End point timeframe:

Comparison of infective events in four weeks prior to IV ferric carboxymaltose and four weeks following

End point values	All participants (pre iron)	All participants (post iron)	All participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	20[1]	20[2]	20	
Units: % experiencing infective event				
number (not applicable)	20	20	20	

Notes:

[1] - Cohort study: the 20 patients in the pre-iron group are the same as those in the post-iron group.

[2] - Cohort study: the 20 patients in the pre-iron group are the same as those in the post-iron group.

Attachments (see zip file)	Baseline characteristics and primary outcome /Tables 1-2

Statistical analyses

Statistical analysis title	Incidence of infective events (primary outcome)

Statistical analysis description:

Comparison on incidence of infective events in four weeks prior to iron, compared with four weeks after iron administration, using McNemar's test.

Comparison groups	All participants (pre iron) v All participants (post iron)

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	> 0.9 [4]
Method	Mcnemar

Notes:

[3] - This is an interventional cohort study in which the primary comparison is between the four week period before iron administration and the four week period after iron administration. All 20 participants (i.e. the whole study cohort) are included in the analysis. The automatically populated data above wrongly suggests that 40 participants are included because the pre- and post-iron groups (which are in fact the same participants) have been added together.

[4] - No evidence for any difference in the incidence of infective events in the four week period before iron compared with the four week period after iron administration.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of baseline visit to end of final study visit

Adverse event reporting additional description:

All adverse events included, whether before or after iron. Note that the protocol includes a list of symptoms/clinical events that occur commonly in patients with cystic fibrosis. These symptoms/events were recorded as adverse events only if new or worse than usual for the patients (or if felt to be directly attributable to iron administration).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	All participants

Reporting group description:

This is an interventional cohort study, so there is a single reporting group. All 20 participants received a single dose of ferric carboxymaltose. Adverse events occuring both before and after the iron administration are included.

Serious adverse events	All participants		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 20 (35.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
Distal intestinal obstruction syndrome	Additional description: Distal intestinal obstruction syndrome (DIOS) requiring admission.		
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Haemoptysis	Additional description: Haemoptysis requiring admission		
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Respiratory tract infection	Additional description: Infective exacerbation of cystic fibrosis, requiring admission to hospital. This study is investigating whether iron may indirectly contribute to infective episodes (see primary outcome), but none was felt to be directly attributable to iron.		

subjects affected / exposed	6 / 20 (30.00%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	All participants		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 20 (100.00%)		
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Headache	Additional description: Headache, new or worse than normal for participant.		
subjects affected / exposed	6 / 20 (30.00%)		
occurrences (all)	6		
General disorders and administration site conditions			
Fatigue	Additional description: Fatigue, new or worse than usual for participant, and not felt to be attributable to infective exacerbation.		
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	5		
Flu-like symptoms	Additional description: Flu-like symptoms, not felt to be attributable to infective exacerbation (or other infection).		
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Myalgia	Additional description: Myalgia, new or worse than normal for participant, and not felt to be attributable to infective exacerbation.		
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Fever	Additional description: Fever, not felt to be attributable to infection.		
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Ear infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Gastrointestinal disorders			

Gastrointestinal upset	Additional description: Diarrhoea/gastrointestinal upset, new or worse than normal for participant.		
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Sore throat			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Respiratory tract infection	Additional description: Infective exacerbation not requiring admission (including those for which intravenous antibiotics were given at home).		
subjects affected / exposed	12 / 20 (60.00%)		
occurrences (all)	15		
Haemoptysis	Additional description: Haemoptysis not requiring admission, and not felt to be attributable to infective exacerbation.		
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	6		
Cough	Additional description: Cough, new or worse than normal for participant, and not felt to be attributable to infective exacerbation.		
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Chest tightness	Additional description: Chest tightness or wheeze, new or worse than normal for participant, and not felt to be attributable to infective exacerbation.		
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Chest pain	Additional description: Chest or rib pain, new or worse than normal for participant, and not felt to be attributable to infective exacerbation.		
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Dyspnoea	Additional description: Dyspnoea, new or worse than normal for participant, and not felt to be attributable to infective exacerbation.		
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Sputum increased	Additional description: Increased sputum production, worse than normal for participant, and not felt to be attributable to infective exacerbation.		
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Hepatobiliary disorders			
High ALP	Additional description: Elevated alkaline phosphatase, not normal for patient.		
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Tongue blistering			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Muscle cramps	Additional description: Muscle cramps, new or worse than normal for participant.		
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Infections and infestations			
Sputum culture positive	Additional description: Isolation of new organism in sputum culture (i.e. not identified in previous 12 months). Long term/recurrent isolates were not regarded as an adverse event, as this is normal finding in this patient group.		
subjects affected / exposed	7 / 20 (35.00%)		
occurrences (all)	10		
High CRP	Additional description: High c-reactive protein (CRP), not normal for participant, and not felt to be attributable to infective exacerbation.		
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hyperglycaemia	Additional description: Hyperglycaemia, worse than normal for participant, and not felt to be attributable to infective exacerbation.		
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 November 2019	The primary purpose of this substantial amendment was to update the list of foreseeable events, and clarify the procedure for recording/collections of these events. The amendment also included some changes to the wording of several other sections, including around safety monitoring and assessment of adverse events, to reflect changes to the standard wording used by the Sponsor for clinical studies.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
27 March 2020	Following the final study visit, the analysis and laboratory work associated with the study was paused due to the global COVID-19 pandemic.	-

Notes:

Limitations and caveats

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

The results of the primary outcome have been posted, along with baseline characteristics and adverse events. The analysis of secondary outcomes will be completed and published in due course.

Notes: