Clinical trial results:
De-Iron: A phase 2 study of the efficacy and safety of Deferasirox administered at early iron loading in patients with transfusion-dependent Myelodysplastic Syndromes

Summary

EudraCT number	2011-004559-38
Trial protocol	GB
Global end of trial date	01 May 2017

Results information

Result version number	v1 (current)
This version publication date	16 May 2018
First version publication date	16 May 2018

Trial information

Trial identification

Sponsor protocol code	RG_12-101

Additional study identifiers

ISRCTN number	ISRCTN62162141
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Sponsors SAF number : ERN_11-0870

Notes:

Sponsors

Sponsor organisation name	University of Birmingham
Sponsor organisation address	CR UK Clinical Trials Unit, Birmingham, United Kingdom, B15 2TT
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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	26 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 December 2016
Global end of trial reached?	Yes
Global end of trial date	01 May 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary aim is to assess the activity of the oral iron chelator, deferasirox, given at early iron overload to patients with transfusion-dependent MDS. The secondary aim is to assess the safety and tolerability of deferasirox.

Protection of trial subjects:

The study protocol involves two additional visits to the hospital than would usually be required, both visits are for blood tests that are extra to what would be performed in standard clinical care. Some patients consent to take part in the Magnetic Resonance Imaging (MRI) scan part of the study, which involves two extra MRI scans. The risks of these extra tests are minimal, and it is possible that early intervention with iron chelating agents may prevent clinically overt or subclinical end organ damage. All patients will benefit from close monitoring during the trial period. As with all medications, treatment with deferasirox has potential side effects, for which all trial staff and patients are full informed. Close monitoring during the treatment period will allow prevention, detection and treatment of these side effects.

Background therapy:

The only treatment provided in the study is deferasirox, however participants are required to have clinical red blood cell transfusion requirements to enter the study. This is defined as transfusion of at least 2 units of red blood cells in the 8 week period preceding registration in the absence of active bleeding.

Evidence for comparator:

N/A

Actual start date of recruitment	19 June 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: 13
Worldwide total number of subjects	13
EEA total number of subjects	13

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)	1
From 65 to 84 years	11
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Trial open to recruitment: 25-Jan-2013, First patient registered: 19-Jun-2013, Last Patient Last Visit: 02-Jun-2016.

Pre-assignment

Screening details:

Full Blood Count, ALT/AST, Serum Creatinine, EGFR, CRP, Bilirubin and ALP
Serum Creatinine and EGFR
Serum Ferritin
CRP
Transfusion need assessment
Medical history
Bone marrow for IPSS categorisation
Hearing and ocular testing

Please refer to the protocol for eligibility criteria.

Period 1

Period 1 title	Phase I (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Arm title	Treatment

Arm description:

Deferasirox treatment

Arm type	Experimental
Investigational medicinal product name	Deferasirox
Investigational medicinal product code	
Other name	Exjade
Pharmaceutical forms	Soluble tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg/kg/day, rounded to the nearest multiple of 125mg. Taken on an empty stomach at least 30 min before food and preferably at the same time each day. The tablets are to be dispersed by stirring in a glass of water or orange/apple juice (100-200 mL) until a fine suspension is obtained. After the suspension has been swallowed, any residue must be re-suspended in a small volume of water and swallowed.

Number of subjects in period 1	Treatment
Started	13
Completed	6
Not completed	7
Disease progression	2
Adverse event, non-fatal	2

Toxicity-related treatment modification	1
Non-trial treatment	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups	
Reporting group title	Phase I (overall period)
Reporting group description:	
This group contains the full number of patients that took part in the trial.	

Reporting group values	Phase I (overall period)	Total	
Number of subjects	13	13	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	1	1	
From 65-84 years	11	11	
85 years and over	1	1	
Age continuous			
Units: years			
median	72		
full range (min-max)	61 to 86	-	
Gender categorical			
Units: Subjects			
Female	6	6	
Male	7	7	
Number of blood transfusions in 8 weeks prior to registration			
Units: Subjects			
One transfusion	0	0	
Two transfusions	5	5	
Three transfusions	4	4	
Four transfusions	3	3	
Five transfusions	1	1	
Serum Ferritin			
Units: µg/L			
median	753		
full range (min-max)	336 to 1336	-	
HbA1c			
Units: mmol/mol			
median	43.5		
full range (min-max)	25 to 53	-	
Thyroid stimulating hormone			
Units: mU/L			
median	2.3		

full range (min-max)	0.8 to 7.9	-	
T4 Units: pmol/L median full range (min-max)	 14.6 10.3 to 21.3	 -	
T3 Units: pmol/L median full range (min-max)	 4.5 3.6 to 5.0	 -	
FSH			
(females only)			
Units: IU/mL median full range (min-max)	 70.7 51.6 to 85.9	 -	
LH			
(females only)			
Units: IU/mL median full range (min-max)	 24.9 19.5 to 36.1	 -	
Cardiac relaxation time Units: ms median full range (min-max)	 28.0 16.2 to 36.0	 -	
Hepatic relaxation time Units: ms median full range (min-max)	 8.1 5.0 to 11.6	 -	
Testosterone			
(males only)			
Units: nmol/L median full range (min-max)	 10.6 3.2 to 16.4	 -	
Sex hormone binding globulin			
(males only)			
Units: nmol/L median full range (min-max)	 69 33 to 84	 -	
Cortisol Units: nmol/L median full range (min-max)	 337 30 to 558	 -	

End points

End points reporting groups

Reporting group title	Treatment
Reporting group description: Deferasirox treatment	
Subject analysis set title	Evaluable population set
Subject analysis set type	Safety analysis
Subject analysis set description: The evaluable population set includes all patients who have completed 12 months of treatment and have reached the month 11 assessment of serum ferritin level.	
Subject analysis set title	Full population set
Subject analysis set type	Full analysis
Subject analysis set description: The full population set includes all patients who have taken at least 1 dose of study drug.	

Primary: Assessment of Activity

End point title	Assessment of Activity[1]
End point description: To assess the activity of the oral iron chelator, deferasirox, given at early iron overload to patients with transfusion-dependent MDS.	
End point type	Primary
End point timeframe: Within 12 months of deferasirox therapy	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical analysis has been carried out on the primary outcome due to small sample size.

End point values	Evaluable population set	Full population set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	13		
Units: ug/L	3	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety and tolerability of deferasirox

End point title	Safety and tolerability of deferasirox
End point description: Safety and tolerability of deferasirox based on CTCAE criteria version 4.0	
End point type	Secondary
End point timeframe: Within 12 months of deferasirox therapy	

End point values	Full population set			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: Number of participants				
Grade 3/4 non-haematological events	2			
Non-haematological SUSARs	0			
Auditory events	0			
Ocular events	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean serum ferritin >1500µg/L

End point title	Mean serum ferritin >1500µg/L
End point description:	
Proportion of patients with mean serum ferritin >1500µg/L within 12 months	
End point type	Secondary
End point timeframe:	
Within 12 months of deferasirox therapy	

End point values	Full population set			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: ug/L				
Mean SF>1500	3			
Mean SF<=1500	10			

Statistical analyses

No statistical analyses for this end point

Secondary: Maintain serum ferritin <1500 µg/L

End point title	Maintain serum ferritin <1500 µg/L
End point description:	
Proportion of patients maintaining serum ferritin <1500 µg/L at 12 months	
End point type	Secondary
End point timeframe:	
Within 12 months of deferasirox therapy	

End point values	Full population set			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: ug/L				
SF maintained	8			
SF not maintained	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Haematological improvement

End point title	Haematological improvement

End point description:

Proportion of patients achieving hematologic improvement (per IWG2006 criteria), time to haematological improvement (per IWG2006 criteria) measured from entry into the trial to first haematological improvement and duration of haematological improvement (per IWG2006 criteria) from first documented improvement to progression/relapse.

End point type	Secondary

End point timeframe:

Within 12 months of deferasirox therapy

End point values	Full population set			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: Haematological improvement	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in Cardiac iron loading

End point title	Mean change in Cardiac iron loading

End point description:

Cardiac iron loading quantified by mean change in relaxation time between pre-treatment (baseline) and post-treatment (at 12 months or when SF >1500 µg/L) assessments measured by MRI R2* and T2*

End point type	Secondary

End point timeframe:

at 12 months of deferasirox therapy

End point values	Full population set			
Subject group type	Subject analysis set			
Number of subjects analysed	2			
Units: seconds				
arithmetic mean (standard deviation)	7.8 (± 12.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in hepatic iron loading

End point title	Mean change in hepatic iron loading

End point description:

Hepatic iron loading quantified by mean change in relaxation time between pre-treatment (baseline) and post-treatment (at 12 months or when SF >1500 µg/L) assessments measured by MRI R2* and T2*.

End point type	Secondary

End point timeframe:

at 12 months of deferasirox therapy

End point values	Full population set			
Subject group type	Subject analysis set			
Number of subjects analysed	2			
Units: seconds				
arithmetic mean (standard deviation)	-1.6 (± 0.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in endocrine function

End point title	Mean change in endocrine function

End point description:

Endocrine function defined as the mean change from baseline at 6 and 12 months in the following parameters: HbA1c (glycated haemoglobin), Thyroid function (as measured by TSH, free T4, and T3 if indicated), FSH and LH (women only), Testosterone and Sex hormone binding globulin (men only), Cortisol

End point type	Secondary

End point timeframe:

Within 12 months of deferasirox therapy

End point values	Full population set			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: Endocrine function				
arithmetic mean (standard deviation)				
Diabetes	-2.4 (± 3.5)			
Thyroid	0 (± 0.7)			
FSH	2.5 (± 3.3)			
LH	-0.5 (± 5.6)			
Cortisol 30	0 (± 0)			
Cortisol 60	0 (± 0)			
Testosterone	-2.9 (± 4.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in biochemical iron parameters

End point title	Mean change in biochemical iron parameters

End point description:

Mean change from baseline at 6 and 12 months in the following biochemical iron parameters: Transferrin saturation, Hepcidin, Non-transferrin bound iron, GDF15

End point type	Secondary

End point timeframe:

Within 12 months of deferasirox therapy

End point values	Full population set			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: Biochemical iron parameters				
arithmetic mean (standard deviation)				
Transferrin saturation 6 months	5.36 (± 23.41)			
Transferrin saturation 12 months	6.11 (± 30.52)			
Hepcidin 6 months	3.01 (± 25.7)			
Hepcidin 12 months	4.38 (± 33.78)			
Non-transferrin bound iron 6 months	0.26 (± 1.83)			
Non-transferrin bound iron 12 months	0.52 (± 1.51)			
GDF15 6 months	682.38 (± 5691.45)			
GDF15 12 months	1439.26 (± 5898.6)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Date of commencement of protocol-defined treatment(e.g. first date of taking deferasirox) until 30 days after the administration of the last trial treatment

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	All patients

Reporting group description: -

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 13 (30.77%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Surgical and medical procedures			
Incarcerated hernia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urinary tract infection	Additional description: Chronic kidney disease. Fever.		

subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 13 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cyst			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Basal cell carcinoma			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Surgical and medical procedures			
Incarcerated inguinal hernia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 13 (38.46%)		
occurrences (all)	6		
Fever			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Flu like symptoms			

subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Leg oedema			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Dyspnoea			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Sore throat			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Psychiatric disorders			
Confusion			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 13 (30.77%)		
occurrences (all)	6		

Alkaline Phosphatase increased				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	3			
Aspartate aminotransferase increased				
subjects affected / exposed	5 / 13 (38.46%)			
occurrences (all)	3			
Blood bilirubin increased				
subjects affected / exposed	3 / 13 (23.08%)			
occurrences (all)	4			
Cholesterol high				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Creatinine increased				
subjects affected / exposed	7 / 13 (53.85%)			
occurrences (all)	18			
Raised white cell count				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Raised platelets				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	3			
Haematocrit decreased				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Testosterone reduced				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Urea reduced				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
C-reactive protein increased				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Serum ferritin decreased				

subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Lymphocyte count decreased			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	11		
Neutrophil count decreased			
subjects affected / exposed	4 / 13 (30.77%)		
occurrences (all)	13		
Platelet count decreased			
subjects affected / exposed	4 / 13 (30.77%)		
occurrences (all)	27		
White blood cell count decreased			
subjects affected / exposed	4 / 13 (30.77%)		
occurrences (all)	11		
Injury, poisoning and procedural complications			
Bruising			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Cardiac disorders			
Mitral valve disease			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Palpitations			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Sinus bradycardia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 13 (30.77%)		
occurrences (all)	4		
Dysgeusia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Headache			

subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 2		
Lethargy subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Cold feet subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Numbness-calfs (hypoesthesia) subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Paresthesia subjects affected / exposed occurrences (all)	3 / 13 (23.08%) 3		
Peripheral motor neuropathy subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	7 / 13 (53.85%) 48		
Febrile neutropenia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Ear and labyrinth disorders Blocked ears subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Ear pain subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Vertigo subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Eye disorders			

Gritty eyes subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Puffiness around eyes subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Puffy eyes subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 2		
Abdominal pain subjects affected / exposed occurrences (all)	3 / 13 (23.08%) 4		
Bloating subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 2		
Constipation subjects affected / exposed occurrences (all)	4 / 13 (30.77%) 5		
Diarrhoea subjects affected / exposed occurrences (all)	3 / 13 (23.08%) 6		
Dry mouth subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Dyspepsia subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 3		
Faecal incontinence subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Gastroesophageal reflux disease			

subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Small bowel obstruction			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Loss of appetite			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Mucositis oral			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	5		
Rectal haemorrhage			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Stomach pain			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Pruritis			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Rash maculo-papular			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Night sweats			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		

Rash			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	5		
Chronic kidney disease			
subjects affected / exposed	4 / 13 (30.77%)		
occurrences (all)	7		
Haematuria			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Nocturia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Urea raised			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	2		
Urinary frequency			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Endocrine disorders			
Hypoparathyroidism			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Flank pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		

Cramp - legs/feet			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Shoulder pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Achey legs			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Pain - shoulders and back			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Cramps			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Infections and infestations			
Bronchial infection			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Device related infection			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Cold			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Cold sore - nose			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Unknown source			

subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Lung infection			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Rhinitis infective			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Skin infection			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Upper respiratory infection			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Hypercalcaemia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Hyperkalaemia			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	3		
Hypoalbuminaemia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Hypophosphataemia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		

Iron overload subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 August 2012	• Change in exclusion criteria from >40ml/min creatinine clearance to >60ml/min creatinine clearance
20 November 2012	• Addition of 2 secondary endpoints: (time to Haematological response and duration of response) • Reduction of Iron parameter sampling from 8 to 4 time points • Clarifications of dose modifications and discontinuation • Minor typing errors
28 December 2012	• The addition of four sites: - University Hospital Southampton NHS Foundation Trust - University Hospital of Leicester NHS Trust - East Cheshire NHS Trust - Sherwood Forest NHS Foundation Trust
25 April 2013	• The addition of two sites: The Royal Wolverhampton Hospitals NHS Trust Epsom and St Helier University Hospitals NHS Trust • Change of Trust name of Oxford Radcliff Hospitals NHS Trust to the Oxford University Hospitals NHS Trust.
17 May 2013	Addition of three sites: • Northampton General Hospital NHS Trust • North West London Hospitals NHS Trust • North Bristol NHS Trust
05 September 2013	• Change of Eligibility criteria - inclusion criteria updated to prevent patients entering the De-Iron study with platelets <30 x109/L and/or Neutrophils ≤0.5 x109/L • Addition of Trial Management staff and contact numbers • Clarification of MRI endpoint analysis • Correction of the schedule of events • Advice for missed doses and clarification of patient follow up and treatment discontinuation • Change to the IMP Label wording • Updates to Patient Information Sheet/Informed Consent Form - correction of the version of the Patient Information Sheet referenced in the Informed Consent Form, addition to clarify that patients may have to have a bone marrow biopsy, if they had not had one in the 6 months prior to entering the trial, and further information about the procedure
20 September 2013	• Addition of 1 site - East Sussex Healthcare NHS Trust
18 October 2013	• Addition of 1 site: - Royal Cornwall Hospitals NHS Trust
02 December 2013	• Update to the Reference Safety Information (RSI) to reflect new information provided in the SPC (aggravated anaemia added as a new expected side effect) • Update to the Patient Information Sheet/Informed Consent Form to reflect the above change
06 March 2014	• Modification of serum ferritin inclusion criteria to extend range from <1000µg/l to <1200µg/l • Minor typing errors • Changes to trials office contact details

21 March 2014	• Addition of 1 site - Shrewsbury and Telford Hospitals NHS Trust
28 May 2014	• Reordering of secondary endpoints • Changes to the definition of transfusion dependence - patients now able to start screening as soon as they start transfusions, rather than waiting 12 weeks before starting screening • Update to the schedule of assessments for clarity • Rewording of dose escalation for clarity • Updates and rewording of dose modification regarding Steven Johnsons Syndrome and pancreatitis • Update to the Patient Information Sheet to include Steven Johnsons Syndrome as a potential adverse event of unknown frequency and has added pancreatitis as a potential complication of gallstones that can develop from Deferasirox treatment
22 September 2014	Update to the Reference Safety Information (RSI) to include Stevens-Johnson Syndrome and Pancreatitis added as new expected side effects of unknown frequency
21 October 2014	• Addition of 1 site: - Taunton & Somerset NHS Foundation Trust
11 May 2015	• Change of Principal Investigator at St James' Hospital, Leeds
15 July 2015	• Addition of 1 site: - South Tees Hospitals NHS Foundation Trust
02 September 2015	• An extension of the recruitment period due to poor recruitment • A reduction in the recruitment target due to poor recruitment • Changes in the statistical considerations due to the updated recruitment target • An update of the eligibility criteria to include patients receiving erythropoietin • Changes in exclusion criteria to reduce use of prior investigational agents from 6 to 4 weeks, and clarification of active infection to ≥ grade 3 according to CTCAE v4 • Clarification of outcome measures to ensure appropriate statistical analysis • Clarifications to the trial assessments schedule to remove some inconsistencies observed by sites • Clarifications to the dose escalation section to include CRP <3 x ULN and EGFR ≥60 ml/min and change of serum ferritin tfrom 1500µg//L to 1350µg//L • Update to the dose modification section to include changes in the Deferasirox SPC • Clarifications to the discontinuation and follow-up procedures • Changes to adverse event reporting to exclude reporting of abnormal laboratory findings unless the abnormal laboratory finding results in early discontinuation, requires drug modification or interruption, requires therapeutic intervention or is of significant clinical importance • Inclusion of travel expenses to patients • Update to the Patient Information Sheet/Informed Consent Form to include updated information on dose modifications, travel expenses, Deferasirox information and side effects and to include the update that samples are not sent to Kings College, London. • Update to the GP letter to reflect updates to trial objectives, prescription of medication affecting hepatic and/or renal function or known to trigger skin reactions and care of patients who develop diarrhoea or vomiting. • Updates to the patient diary
29 October 2015	• Change of Principal Investigator at Royal Cornwall Hospitals NHS Trust

19 September 2016	• Update to the Reference Safety Information (RSI) to reflect new information provided in the SPC in the reporting year: - minor changes to the wording of the summary of the safety profile including the description of reduced creatinine cases in patients with beta thalassemia and iron overload - small changes to the terminology in the list of adverse reactions - Toxic Epidermal Necrolysis (TEN) has been added as a "not known" frequency side effect under Skin and subcutaneous tissue disorders - Acute pancreatitis has been added as a "not known" frequency side effect within gastrointestinal disorders - An additional paragraph added concerning creatinine clearance cases as identified in a retrospective meta-analysis
21 March 2017	• Change of Principal Investigator at Conquest Hospital, East Sussex

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.

Due to poor recruitment, the initial recruitment target of 54 was reduced and a total of 13 patients were recruited into the trial.

Notes: