Clinical trial results:
A study of Magnetic Resonance Imaging Assessment of Cardiac and Liver Iron Load in patients with Haemoglobinopathies, Myelodysplastic Syndromes (MDS) or other anaemias treated with Exjade®(deferasirox). The MILE Study

Summary

EudraCT number	2016-000246-62
Trial protocol	Outside EU/EEA
Global end of trial date	08 September 2011

Results information

Result version number	v1 (current)
This version publication date	04 January 2017
First version publication date	04 January 2017

Trial information

Trial identification

Sponsor protocol code	CICL670AAU01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00673608
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH 4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,

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 September 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 September 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate the change in cardiac iron load and cardiac ejection fraction by Magnetic Resonance Imaging (MRI) after 53 weeks of deferasirox treatment in the following:
1. Transfused subjects with haemoglobinopathies (thalassaemia-major (Th-maj) and Sickle Cell Disease (SCD)) and a serum ferritin of > 500 microgram (µg)/liter (L).
2. Myelodysplastic Syndromes (MDS) and other rare anaemias (e.g. Myeloproliferative Disease (MPD), Diamond-blackfan anaemia [DBA]) subjects who demonstrate evidence of transfusional iron overload by a serum ferritin of > 1,000 µg/L.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 November 2007
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	Australia: 53
Worldwide total number of subjects	53
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)	5
Adults (18-64 years)	41

From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 1 center in Australia.

Pre-assignment

Screening details:

A total of 53 subjects were enrolled and 43 completed the study.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

The study was open label study, hence no blinding was performed

Arms

Are arms mutually exclusive?	Yes
Arm title	Th-maj and SCD: Deferasirox

Arm description:

Subjects with haemoglobinopathy like Th-maj or SCD who required regular blood cell transfusions were administered with once daily (o.d.) on an empty stomach at least 30 minutes before food, preferably at the same time each day. Dose was up to 40 milligram (mg)/kilogram (kg)/day.

Arm type	Experimental
Investigational medicinal product name	Deferasirox
Investigational medicinal product code	ICL670
Other name	Exjade
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were orally administered with deferasirox o.d. on an empty stomach at least 30 minutes before food, preferably at the same time each day. Dose was up to 40 mg/kg/day. Deferasirox was supplied as 125 mg, 250 mg and 500 mg tablets which were dispersed by stirring in water, orange or apple juice (tablets were dispersed in about 20 mL of water before dilution with the juice) until a fine suspension was obtained. After the suspension was swallowed, any residue was re-suspended in a small volume of water or juice and swallowed.

Arm title	MDS/anaemia: Deferasirox

Arm description:

Subjects having other inherited or acquired anaemia like MDS, MPD, DBA and other rare anaemias who required regular blood cell transfusions were administered with deferasirox o.d. on an empty stomach at least 30 minutes before food, preferably at the same time each day. Dose was up to 40 mg/kg/day.

Arm type	Experimental
Investigational medicinal product name	Deferasirox
Investigational medicinal product code	ICL670
Other name	Exjade
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were orally administered with deferasirox o.d. on an empty stomach at least 30 minutes before food, preferably at the same time each day. Dose was up to 40 mg/kg/day. Deferasirox was supplied as 125 mg, 250 mg and 500 mg tablets which were dispersed by stirring in water, orange or apple juice (tablets were dispersed in about 20 mL of water before dilution with the juice) until a fine suspension was obtained. After the suspension was swallowed, any residue was re-suspended in a small volume of

water or juice and swallowed.

Arm title	Bone marrow transplantation (BMT): Deferasirox

Arm description:

Subjects who had a post BMT who required regular blood cell transfusions were administered with deferasirox o.d. on an empty stomach at least 30 minutes before food, preferably at the same time each day. Dose was up to 40 mg/kg/day.

Arm type	Experimental
Investigational medicinal product name	Deferasirox
Investigational medicinal product code	ICL670
Other name	Exjade
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were orally administered with deferasirox o.d. on an empty stomach at least 30 minutes before food, preferably at the same time each day. Dose was up to 40 mg/kg/day. Deferasirox was supplied as 125 mg, 250 mg and 500 mg tablets which were dispersed by stirring in water, orange or apple juice (tablets were dispersed in about 20 mL of water before dilution with the juice) until a fine suspension was obtained. After the suspension was swallowed, any residue was re-suspended in a small volume of water or juice and swallowed.

Arm title	DBA: Deferasirox

Arm description:

Subjects having other inherited or acquired anaemia (MDS, MPD, DBA and other rare anaemias) who required regular blood cell transfusions were administered with deferasirox o.d. on an empty stomach at least 30 minutes before food, preferably at the same time each day. Dose was up to 40 mg/kg/day.

Arm type	Experimental
Investigational medicinal product name	Deferasirox
Investigational medicinal product code	ICL670
Other name	Exjade
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were orally administered with deferasirox o.d. on an empty stomach at least 30 minutes before food, preferably at the same time each day. Dose was up to 40 mg/kg/day. Deferasirox was supplied as 125 mg, 250 mg and 500 mg tablets which were dispersed by stirring in water, orange or apple juice (tablets were dispersed in about 20 mL of water before dilution with the juice) until a fine suspension was obtained. After the suspension was swallowed, any residue was re-suspended in a small volume of water or juice and swallowed.

Number of subjects in period 1	Th-maj and SCD: Deferasirox	MDS/anaemia: Deferasirox	Bone marrow transplantation (BMT): Deferasirox
Started	42	9	1
Completed	37	5	1
Not completed	5	4	0
Administrative reasons	2	-	-
Adverse event(s)	1	3	-
Lack of efficacy	1	-	-

Protocol deviation	1	1	-

Number of subjects in period 1	DBA: Deferasirox
Started	1
Completed	0
Not completed	1
Administrative reasons	-
Adverse event(s)	-
Lack of efficacy	-
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Th-maj and SCD: Deferasirox
Reporting group description:	
Subjects with haemoglobinopathy like Th-maj or SCD who required regular blood cell transfusions were administered with once daily (o.d.) on an empty stomach at least 30 minutes before food, preferably at the same time each day. Dose was up to 40 milligram (mg)/kilogram (kg)/day.	
Reporting group title	MDS/anaemia: Deferasirox
Reporting group description:	
Subjects having other inherited or acquired anaemia like MDS, MPD, DBA and other rare anaemias who required regular blood cell transfusions were administered with deferasirox o.d. on an empty stomach at least 30 minutes before food, preferably at the same time each day. Dose was up to 40 mg/kg/day.	
Reporting group title	Bone marrow transplantation (BMT): Deferasirox
Reporting group description:	
Subjects who had a post BMT who required regular blood cell transfusions were administered with deferasirox o.d. on an empty stomach at least 30 minutes before food, preferably at the same time each day. Dose was up to 40 mg/kg/day.	
Reporting group title	DBA: Deferasirox
Reporting group description:	
Subjects having other inherited or acquired anaemia (MDS, MPD, DBA and other rare anaemias) who required regular blood cell transfusions were administered with deferasirox o.d. on an empty stomach at least 30 minutes before food, preferably at the same time each day. Dose was up to 40 mg/kg/day.	

Reporting group values	Th-maj and SCD: Deferasirox	MDS/anaemia: Deferasirox	Bone marrow transplantation (BMT): Deferasirox
Number of subjects	42	9	1
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 29.6 ± 11.74	 68 ± 8.54	 55 ± 0
Gender categorical Units: Subjects			
Female	26	5	1
Male	16	4	0

Reporting group values	DBA: Deferasirox	Total	
Number of subjects	1	53	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 16 ± 0	 -	
Gender categorical Units: Subjects			
Female	0	32	

Male	1	21	

End points

End points reporting groups

Reporting group title	Th-maj and SCD: Deferasirox

Reporting group description:

Subjects with haemoglobinopathy like Th-maj or SCD who required regular blood cell transfusions were administered with once daily (o.d.) on an empty stomach at least 30 minutes before food, preferably at the same time each day. Dose was up to 40 milligram (mg)/kilogram (kg)/day.

Reporting group title	MDS/anaemia: Deferasirox

Reporting group description:

Subjects having other inherited or acquired anaemia like MDS, MPD, DBA and other rare anaemias who required regular blood cell transfusions were administered with deferasirox o.d. on an empty stomach at least 30 minutes before food, preferably at the same time each day. Dose was up to 40 mg/kg/day.

Reporting group title	Bone marrow transplantation (BMT): Deferasirox

Reporting group description:

Subjects who had a post BMT who required regular blood cell transfusions were administered with deferasirox o.d. on an empty stomach at least 30 minutes before food, preferably at the same time each day. Dose was up to 40 mg/kg/day.

Reporting group title	DBA: Deferasirox

Reporting group description:

Subjects having other inherited or acquired anaemia (MDS, MPD, DBA and other rare anaemias) who required regular blood cell transfusions were administered with deferasirox o.d. on an empty stomach at least 30 minutes before food, preferably at the same time each day. Dose was up to 40 mg/kg/day.

Subject analysis set title	Full analysis set population
Subject analysis set type	Full analysis

Subject analysis set description:

Full analysis set population was defined as all subjects in the safety population (all subjects who received at least one dose of study drug) with a cardiac iron sensitive relaxation time (T2*) at baseline and one post-baseline efficacy assessment (cardiac iron load, liver iron concentration, serum ferritin, cardiac function assessment or blood magnetic susceptibility (BMS) assessment)).

Primary: Change from baseline in cardiac iron load fraction of deferasirox treatment from baseline to 53 weeks

End point title	Change from baseline in cardiac iron load fraction of deferasirox treatment from baseline to 53 weeks[1][2]

End point description:

Cardiac iron load was evaluated as log ratio of cardiac T2* at 53 weeks to baseline, ln(T2*53 /T2*0). The T2* relaxometry MRI method was used to evaluate cardiac iron load. A positive change from baseline indicated decrease in iron load. The analysis was performed in FAS population. The missing values were not imputed.

End point type	Primary

End point timeframe:

From baseline to Week 53

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: Least squares estimates for change in cardiac iron load from baseline to end of study was determined and has been reported relative change.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to evaluate for the specified arm only.

End point values	Th-maj and SCD: Deferasirox	MDS/anaemia: Deferasirox	Full analysis set population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	42	8	52	
Units: Relative change in cardiac iron load				
number (confidence interval 95%)	1.1 (1.03 to 1.17)	1.12 (0.95 to 1.31)	1.1 (1.04 to 1.16)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from baseline in Left ventricular ejection fraction (LVEF) values, left ventricular end-systolic (LVES) and end-diastolic (LVED) volume; left ventricular mass (LVM) from baseline values after 53 weeks of deferasirox treatment

End point title	Absolute change from baseline in Left ventricular ejection fraction (LVEF) values, left ventricular end-systolic (LVES) and end-diastolic (LVED) volume; left ventricular mass (LVM) from baseline values after 53 weeks of deferasirox treatment[3]

End point description:

LVEF was defined as the fraction of the end-diastolic volume that was ejected out of left ventricle with each contraction. LVES volume was defined as the volume of blood in a left ventricle at the end of contraction. LVED volume was defined as the volume of blood in a left ventricle immediately before a contraction. LVM increase was a measure of increase in wall thickness, an increase in cavity size, or both. Global cardiac functions: LVEF; LVES and LVED volume; and LVM were assessed by MRI. The absolute change from baseline was calculated as the value at week 53 minus the value at baseline. A negative change from baseline in LVEF indicates improvement in cardiac function while for other parameters a positive change from baseline indicates improvement in cardiac function. The analysis was performed in FAS population. The missing values were not imputed.

End point type	Secondary

End point timeframe:

From baseline to Week 53

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to evaluate for the specified arm only.

End point values	Th-maj and SCD: Deferasirox	MDS/anaemia: Deferasirox	Full analysis set population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	42	9	52	
Units: Absolute change in cardiac function				
number (confidence interval 95%)				
Left Ventricular Ejection Fraction	-1.4 (-2.83 to 0.02)	0.11 (-3.91 to 4.13)	-1.23 (-2.56 to 0.1)	
Left Ventricular End Systolic Volume	3.02 (0.26 to 5.77)	4.54 (-3.33 to 12.41)	3.19 (0.62 to 5.75)	
Left Ventricular End Diastolic Volume	2.99 (-1.62 to 7.6)	14.11 (0.93 to 27.3)	4.22 (-0.16 to 8.61)	
Left Ventricular Mass	4.37 (1.92 to 6.82)	-3.09 (-9.88 to 3.69)	3.53 (1.15 to 5.91)	

Statistical analyses

No statistical analyses for this end point

Secondary: Changes from baseline in serum ferritin from baseline values to 53 weeks

End point title	Changes from baseline in serum ferritin from baseline values to 53 weeks[4]

End point description:

Serum ferritin level in the blood directly relate to the amount of iron stored in the body. Serum ferritin levels are indicators for symptoms of anemia. A negative change from baseline indicated increase in iron load. The analysis was performed in FAS population. The missing values were not imputed.

End point type	Secondary

End point timeframe:

From baseline to Week 53

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to evaluate for the specified arm only.

End point values	Th-maj and SCD: Deferasirox	MDS/anaemia: Deferasirox	Full analysis set population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	42	9	53	
Units: microgram(µg)/ Litre (L)				
number (confidence interval 95%)	-2.56 (-8.88 to 3.77)	-24.97 (-41.47 to -8.48)	-5.84 (-11.56 to 0.61)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in liver iron concentration (LIC) by MRI of the Proton Transverse Relaxation Rate (R2-MRI) from baseline values to 53 weeks

End point title	Change from baseline in liver iron concentration (LIC) by MRI of the Proton Transverse Relaxation Rate (R2-MRI) from baseline values to 53 weeks[5]

End point description:

Measurements of liver iron concentration (LIC) was an important predictors of iron burden, measured using relaxation rate [R2 = 1/relaxation time (T2)] magnetic resonance imaging (R2-MRI) technique at baseline and Week 52. R2-MRI scans using a specific sequence and raw image data were analysed centrally to determine the subject's LIC value. The analysis was performed in FAS population. The missing values were not imputed.

End point type	Secondary

End point timeframe:

From baseline to Week 53

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to evaluate for the specified arm only.

End point values	Th-maj and SCD: Deferasirox	MDS/anaemia: Deferasirox	Full analysis set population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	42	9	52	
Units: Relative change in LIC				
number (confidence interval 95%)	-1.89 (-3.91 to 0.13)	-3.88 (-10.72 to 2.96)	-2.18 (-4.06 to -0.31)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Adverse Events (AEs), Serious Adverse Events (SAEs), AE leading to discontinuation and who died

End point title	Number of subjects with Adverse Events (AEs), Serious Adverse Events (SAEs), AE leading to discontinuation and who died

End point description:

AEs are defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during study, having been absent at baseline, or, if present at baseline, appears to worsen. Serious adverse events are any untoward medical occurrences that result in death, are life threatening, require (or prolong) hospitalization, cause persistent or significant disability/incapacity, result in congenital anomalies or birth defects, or are other conditions which in judgment of investigators represent significant hazards. The analysis was performed on safety set population.

End point type	Secondary

End point timeframe:

From Day 1 to Week 53

End point values	Th-maj and SCD: Deferasirox	MDS/anaemia: Deferasirox	Bone marrow transplantation (BMT): Deferasirox	DBA: Deferasirox
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	9	1	1
Units: Subjects				
AEs	37	9	1	0
Deaths	0	0	0	0
SAEs	5	4	0	0
AEs leading to study drug discontinuation	1	2	0	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events are monitored from date of First Subject First Visit (FSFV) until Last Subject Last Visit (LSLV). All other adverse events are monitored from First Subject First Treatment until LSLV.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Th-maj and SCD: Deferasirox

Reporting group description:

Subjects with haemoglobinopathy like Th-maj or SCD who required regular blood cell transfusions were administered with o.d on an empty stomach at least 30 minutes before food, preferably at the same time each day. Dose was up to 40 mg/kg/day.

Reporting group title	MDS/anaemia: Deferasirox

Reporting group description:

Subjects having other inherited or acquired anaemia like MDS, MPD, DBA and other rare anaemias who required regular blood cell transfusions were administered with deferasirox o.d. on an empty stomach at least 30 minutes before food, preferably at the same time each day. Dose was up to 40 mg/kg/day.

Reporting group title	Bone marrow transplantation (BMT): Deferasirox:

Reporting group description:

Subjects who had a post BMT who required regular blood cell transfusions were administered with deferasirox o.d. on an empty stomach at least 30 minutes before food, preferably at the same time each day. Dose was up to 40 mg/kg/day.

Reporting group title	DBA: Deferasirox

Reporting group description:

Subjects having other inherited or acquired anaemia (MDS, MPD, DBA and other rare anaemias) who required regular blood cell transfusions were administered with deferasirox o.d. on an empty stomach at least 30 minutes before food, preferably at the same time each day. Dose was up to 40 mg/kg/day.

Serious adverse events	Th-maj and SCD: Deferasirox	MDS/anaemia: Deferasirox	Bone marrow transplantation (BMT): Deferasirox:
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 42 (9.52%)	3 / 9 (33.33%)	0 / 1 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
WRIST FRACTURE			
subjects affected / exposed	1 / 42 (2.38%)	0 / 9 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			

SICKLE CELL ANAEMIA WITH CRISIS			
subjects affected / exposed	1 / 42 (2.38%)	0 / 9 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
CHEST PAIN			
subjects affected / exposed	1 / 42 (2.38%)	0 / 9 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYREXIA			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RECTAL HAEMORRHAGE			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
MANIA			
subjects affected / exposed	1 / 42 (2.38%)	0 / 9 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
RENAL COLIC			

subjects affected / exposed	1 / 42 (2.38%)	0 / 9 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
BONE PAIN			
subjects affected / exposed	1 / 42 (2.38%)	0 / 9 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MUSCULOSKELETAL PAIN			
subjects affected / exposed	1 / 42 (2.38%)	0 / 9 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
LOBAR PNEUMONIA			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUTROPENIC SEPSIS			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	DBA: Deferasirox		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
WRIST FRACTURE			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
SICKLE CELL ANAEMIA WITH CRISIS			

subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
CHEST PAIN			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PYREXIA			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
RECTAL HAEMORRHAGE			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
VOMITING			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
MANIA			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
RENAL COLIC			

subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
BONE PAIN			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
MUSCULOSKELETAL PAIN			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
LOBAR PNEUMONIA			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
NEUTROPENIC SEPSIS			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Th-maj and SCD: Deferasirox	MDS/anaemia: Deferasirox	Bone marrow transplantation (BMT): Deferasirox:
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 42 (88.10%)	9 / 9 (100.00%)	1 / 1 (100.00%)
Investigations			
BLOOD CREATININE INCREASED			
subjects affected / exposed	8 / 42 (19.05%)	2 / 9 (22.22%)	1 / 1 (100.00%)
occurrences (all)	8	2	1
ALANINE AMINOTRANSFERASE INCREASED			

subjects affected / exposed	6 / 42 (14.29%)	2 / 9 (22.22%)	0 / 1 (0.00%)
occurrences (all)	6	2	0
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
SERUM FERRITIN INCREASED			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Basophil count increased			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
EOSINOPHIL COUNT INCREASED			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
INTERNATIONAL NORMALISED RATIO INCREASED			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
PALLOR			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
HEADACHE			
subjects affected / exposed	3 / 42 (7.14%)	2 / 9 (22.22%)	0 / 1 (0.00%)
occurrences (all)	3	2	0
LETHARGY			

subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
DIZZINESS			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	0 / 42 (0.00%)	2 / 9 (22.22%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
FATIGUE			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
CHILLS			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
OEDEMA PERIPHERAL			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	0 / 42 (0.00%)	0 / 9 (0.00%)	1 / 1 (100.00%)
occurrences (all)	0	0	1
LYMPHADENOPATHY			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
NEUTROPENIA			
subjects affected / exposed	0 / 42 (0.00%)	0 / 9 (0.00%)	1 / 1 (100.00%)
occurrences (all)	0	0	1
Eye disorders			
DRY EYE			
subjects affected / exposed	0 / 42 (0.00%)	0 / 9 (0.00%)	1 / 1 (100.00%)
occurrences (all)	0	0	1
EYE HAEMORRHAGE			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			

DIARRHOEA			
subjects affected / exposed	10 / 42 (23.81%)	5 / 9 (55.56%)	0 / 1 (0.00%)
occurrences (all)	10	5	0
NAUSEA			
subjects affected / exposed	7 / 42 (16.67%)	4 / 9 (44.44%)	0 / 1 (0.00%)
occurrences (all)	7	4	0
ABDOMINAL PAIN			
subjects affected / exposed	4 / 42 (9.52%)	4 / 9 (44.44%)	0 / 1 (0.00%)
occurrences (all)	4	4	0
ABDOMINAL PAIN UPPER			
subjects affected / exposed	6 / 42 (14.29%)	0 / 9 (0.00%)	0 / 1 (0.00%)
occurrences (all)	6	0	0
CONSTIPATION			
subjects affected / exposed	4 / 42 (9.52%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	4	1	0
VOMITING			
subjects affected / exposed	3 / 42 (7.14%)	2 / 9 (22.22%)	0 / 1 (0.00%)
occurrences (all)	3	2	0
ABDOMINAL DISTENSION			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
BOWEL MOVEMENT IRREGULARITY			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
DRY MOUTH			
subjects affected / exposed	0 / 42 (0.00%)	0 / 9 (0.00%)	1 / 1 (100.00%)
occurrences (all)	0	0	1
MOUTH HAEMORRHAGE			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
RECTAL HAEMORRHAGE			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			

DYSPNOEA			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
COUGH			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
EPISTAXIS			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
RALES			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
RASH			
subjects affected / exposed	3 / 42 (7.14%)	2 / 9 (22.22%)	0 / 1 (0.00%)
occurrences (all)	3	2	0
ECCHYMOSIS			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
PETECHIAE			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	7 / 42 (16.67%)	0 / 9 (0.00%)	0 / 1 (0.00%)
occurrences (all)	7	0	0
ARTHRALGIA			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
JOINT SWELLING			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	13 / 42 (30.95%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	13	1	0

URINARY TRACT INFECTION			
subjects affected / exposed	4 / 42 (9.52%)	2 / 9 (22.22%)	0 / 1 (0.00%)
occurrences (all)	4	2	0
NASOPHARYNGITIS			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
VIRAL INFECTION			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
LOBAR PNEUMONIA			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
LOCALISED INFECTION			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
NEUTROPENIC SEPSIS			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
DEHYDRATION			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
GOUT			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
HYPOKALAEMIA			
subjects affected / exposed	0 / 42 (0.00%)	1 / 9 (11.11%)	0 / 1 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	DBA: Deferasirox		

Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 1 (0.00%)		
Investigations			
BLOOD CREATININE INCREASED subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
ALANINE AMINOTRANSFERASE INCREASED subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
ASPARTATE AMINOTRANSFERASE INCREASED subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
BLOOD ALKALINE PHOSPHATASE INCREASED subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
BLOOD BILIRUBIN INCREASED subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
SERUM FERRITIN INCREASED subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Basophil count increased subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
EOSINOPHIL COUNT INCREASED subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
INTERNATIONAL NORMALISED RATIO INCREASED subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Vascular disorders			
DEEP VEIN THROMBOSIS subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
PALLOR			

subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Nervous system disorders HEADACHE subjects affected / exposed occurrences (all) LETHARGY subjects affected / exposed occurrences (all) DIZZINESS subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		
General disorders and administration site conditions PYREXIA subjects affected / exposed occurrences (all) FATIGUE subjects affected / exposed occurrences (all) CHILLS subjects affected / exposed occurrences (all) OEDEMA PERIPHERAL subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		
Blood and lymphatic system disorders ANAEMIA subjects affected / exposed occurrences (all) LYMPHADENOPATHY subjects affected / exposed occurrences (all) NEUTROPENIA subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		
Eye disorders			

DRY EYE			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
EYE HAEMORRHAGE			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
NAUSEA			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
ABDOMINAL PAIN			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
CONSTIPATION			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
VOMITING			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
ABDOMINAL DISTENSION			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
BOWEL MOVEMENT IRREGULARITY			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
DRY MOUTH			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
MOUTH HAEMORRHAGE			

subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
RECTAL HAEMORRHAGE			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
COUGH			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
EPISTAXIS			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
RALES			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
RASH			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
ECCHYMOSIS			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
PETECHIAE			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
ARTHRALGIA			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
JOINT SWELLING			

subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Infections and infestations			
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
NASOPHARYNGITIS			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
VIRAL INFECTION			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
LOBAR PNEUMONIA			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
LOCALISED INFECTION			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
NEUTROPENIC SEPSIS			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
DEHYDRATION			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
GOUT			

subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
HYPOKALAEMIA			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 October 2010	The amendment updated: the title of study; inclusion and exclusion criteria; subject population; starting dose of study drug; dose adjustments; cardiac assessments; restricted concomitant therapies; study visit window; subject numbers and statistical analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported