Clinical trial results:
A multi-center, randomized, double-blind, placebo-controlled clinical trial of deferasirox in patients with myelodysplastic syndromes (low/int-1 risk) and transfusional iron overload (TELESTO)

Summary

EudraCT number	2009-012418-38
Trial protocol	IT FI DK GB BE GR NL BG
Global end of trial date	27 February 2018

Results information

Result version number	v1 (current)
This version publication date	13 March 2019
First version publication date	13 March 2019

Trial information

Trial identification

Sponsor protocol code	CICL670A2302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00940602
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, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma, AG, +41 613241111, novartis.email@novartis.com

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	27 February 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate deferasirox and placebo with regard to event-free survival (EFS) (a composite primary endpoint including death and non-fatal events related to cardiac and liver function and transformation to acute myeloid leukemia (AML)) in low and int-1 risk myelodysplastic syndromes (MDS) patients with transfusional iron overload (IO).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 March 2010
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	Australia: 2
Country: Number of subjects enrolled	Bulgaria: 7
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	China: 85
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	United Kingdom: 25
Country: Number of subjects enrolled	Greece: 9
Country: Number of subjects enrolled	Hong Kong: 3
Country: Number of subjects enrolled	Italy: 24
Country: Number of subjects enrolled	Malaysia: 4
Country: Number of subjects enrolled	Mexico: 16
Country: Number of subjects enrolled	New Zealand: 8
Country: Number of subjects enrolled	Russian Federation: 5
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Thailand: 8
Country: Number of subjects enrolled	United States: 12
Worldwide total number of subjects	225
EEA total number of subjects	68

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)	108
From 65 to 84 years	115
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

As of database lock (date 28-Apr-2018), a total of 225 patients were randomized, including 149 patients in deferasirox arm and 76 in the placebo arm.

Pre-assignment

Screening details:

The planned sample size of 210 patients randomized in a ratio of 2:1 in favor of deferasirox was based on the feasibility of enrolling the patients and consultations with the Health Authorities.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Deferasirox

Arm description:

10 mg/kg/day (once daily) for the first 2 weeks of treatment, followed by 20 mg/kg/day (once daily) from Week 2 to End of Treatment. After 3 months of treatment at 20 mg/kg/day, the dose was allowed to be adjusted by 5 or 10 mg/kg/day up to 40 mg/kg/day based on serum ferritin responses. When a target serum ferritin level was reached (usually between 500 and 1000 µg/L), the dose could be reduced by 50% to maintain the serum ferritin within the target range.

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

Dosage and administration details:

Deferasirox (ICL670) was dosed at the below schedule:
- 10 mg/kg/day (once daily) for first 2-weeks, followed by 20 mg/kg/day (once daily) (Week 2-End of treatment)
- After 3 months of treatment at the dose of 20 mg/kg/day the dose could be adjusted by 5 or 10 mg/kg/day up to 40 mg/kg/day based on serum ferritin response

Arm title	Placebo

Arm description:

10 mg/kg/day (once daily) for the first 2 weeks of treatment, followed by 20 mg/kg/day (once daily) from Week 2 to End of Treatment. After 3 months of treatment at 20 mg/kg/day, the dose was allowed to be adjusted by 5 or 10 mg/kg/day up to 40 mg/kg/day based on serum ferritin responses. When a target serum ferritin level was reached (usually between 500 and 1000 µg/L), the dose could be reduced by 50% to maintain the serum ferritin within the target range.

Arm type	Placebo
Investigational medicinal product name	Deferasirox Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Deferasirox Placebo was dosed at the below schedule:
- 10 mg/kg/day (once daily) for first 2-weeks, followed by 20 mg/kg/day (once daily) (Week 2-End of

treatment)
- After 3 months of treatment at the dose of 20 mg/kg/day the dose could be adjusted by 5 or 10 mg/kg/day up to 40 mg/kg/day based on serum ferritin response

Number of subjects in period 1	Deferasirox	Placebo
Started	149	76
Safety Analysis Set	148	76
Full Analysis Set	149	76
Treated	148	76
Untreated	1	0
Completed	0	0
Not completed	149	76
Adverse event, serious fatal	38	19
Physician decision	8	5
Patient withdrew consent	26	13
Disease progression	8	2
Protocol Deviation	1	-
Adverse event, non-fatal	7	2
Administrative problems	1	1
Pregnancy	1	-
Study terminated by sponsor	43	5
Patient/guardian decision	13	28
Lost to follow-up	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Deferasirox
Reporting group description:	
10 mg/kg/day (once daily) for the first 2 weeks of treatment, followed by 20 mg/kg/day (once daily) from Week 2 to End of Treatment. After 3 months of treatment at 20 mg/kg/day, the dose was allowed to be adjusted by 5 or 10 mg/kg/day up to 40 mg/kg/day based on serum ferritin responses. When a target serum ferritin level was reached (usually between 500 and 1000 µg/L), the dose could be reduced by 50% to maintain the serum ferritin within the target range.	
Reporting group title	Placebo
Reporting group description:	
10 mg/kg/day (once daily) for the first 2 weeks of treatment, followed by 20 mg/kg/day (once daily) from Week 2 to End of Treatment. After 3 months of treatment at 20 mg/kg/day, the dose was allowed to be adjusted by 5 or 10 mg/kg/day up to 40 mg/kg/day based on serum ferritin responses. When a target serum ferritin level was reached (usually between 500 and 1000 µg/L), the dose could be reduced by 50% to maintain the serum ferritin within the target range.	

Reporting group values	Deferasirox	Placebo	Total
Number of subjects	149	76	225
Age categorical Units: Subjects			
Adults (18-64 years)	71	37	108
From 65-84 years	76	39	115
From 85 years and over	2	0	2
Age Continuous Units: years			
arithmetic mean	61.2	60.7	
standard deviation	± 16.13	± 15.05	-
Sex: Female, Male Units: Subjects			
Female	56	32	88
Male	93	44	137
Race/Ethnicity, Customized Units: Subjects			
Hispanic/latino	14	5	19
Chinese	61	29	90
Mixed ethnicity	1	0	1
Other	73	42	115
MDS risk category			
International Prognostic Scoring System (IPSS}			
Units: Subjects			
Low (combined score 0)	41	21	62
Intermediate 1 (combined score 0.5 - 1.0)	108	55	163

End points

End points reporting groups

Reporting group title	Deferasirox

Reporting group description:

10 mg/kg/day (once daily) for the first 2 weeks of treatment, followed by 20 mg/kg/day (once daily) from Week 2 to End of Treatment. After 3 months of treatment at 20 mg/kg/day, the dose was allowed to be adjusted by 5 or 10 mg/kg/day up to 40 mg/kg/day based on serum ferritin responses. When a target serum ferritin level was reached (usually between 500 and 1000 µg/L), the dose could be reduced by 50% to maintain the serum ferritin within the target range.

Reporting group title	Placebo

Reporting group description:

10 mg/kg/day (once daily) for the first 2 weeks of treatment, followed by 20 mg/kg/day (once daily) from Week 2 to End of Treatment. After 3 months of treatment at 20 mg/kg/day, the dose was allowed to be adjusted by 5 or 10 mg/kg/day up to 40 mg/kg/day based on serum ferritin responses. When a target serum ferritin level was reached (usually between 500 and 1000 µg/L), the dose could be reduced by 50% to maintain the serum ferritin within the target range.

Primary: Event-free Survival

End point title	Event-free Survival

End point description:

Event-free survival was defined as the time from the date of randomization to the date of the first documented non-fatal event (worsening cardiac function, hospitalization for congestive heart failure, liver function impairment, liver cirrhosis, transformation to AML, as defined in the protocol), or death, whichever occurred first. Participants who did not experience a non-fatal event as of the time of data cut-off (end of study), as well as participants who did not experience a non-fatal event and stopped study participation before the data cut-off, were censored as specified in the protocol.

End point type	Primary

End point timeframe:

Time to event, Day 1 to end of study evaluation period (data cutoff 28th April, 2018)

End point values	Deferasirox	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	76		
Units: days				
median (confidence interval 95%)	1440 (1167 to 1559)	1091 (820 to 1348)		

Statistical analyses

Statistical analysis title	Estimation of treatment effect - EFS
Comparison groups	Deferasirox v Placebo

Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.015 [1]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.636
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.96

Notes:

[1] - Exploratory p-value is one tailed and is based on the stratified log-rank test.

Secondary: Percentage of participants with hematologic improvement (HI) in terms of erythroid response

End point title	Percentage of participants with hematologic improvement (HI) in terms of erythroid response

End point description:

HI in terms of erythroid responses was assessed based on International Working Group (IWG) criteria, with improvement defined as follows: • Hemoglobin increase of ≥ 1.5 g/dL OR • Reduction of ≥ 4 RBC transfusions/8 weeks in comparison to pre-treatment values and lasting at least 8 weeks. The last hemoglobin value measured prior to randomization was used as the pre-treatment value. The last available lab assessment date was used as the cut-off date for the analysis.

End point type	Secondary

End point timeframe:

Baseline (prior to or on the day of randomization [Day 1]) to end of study evaluation period (data cutoff 28th April, 2018)

End point values	Deferasirox	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	76		
Units: percentage of participants				
number (confidence interval 95%)	39.6 (31.4 to 47.6)	27.6 (16.9 to 38.3)		

Statistical analyses

Statistical analysis title	Descriptive statistics -Hematologic improvement
Comparison groups	Deferasirox v Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Wilson score test
Point estimate	12

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	25.7

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival was calculated as the date of death (irrespective of cause) minus date of randomization plus 1.

End point type	Secondary

End point timeframe:

Time to event, Day 1 to end of study evaluation period (data cutoff 28th April, 2018)

End point values	Deferasirox	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	76		
Units: days				
median (confidence interval 95%)	1907 (1440 to 9999)	1509 (1095 to 1804)		

Statistical analyses

Statistical analysis title	Estimation of treatment effect - OS
Comparison groups	Deferasirox v Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.832
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.28

Secondary: Percentage of participants with newly occurring hypothyroidism compared to baseline

End point title	Percentage of participants with newly occurring hypothyroidism

	compared to baseline

End point description:

As assessed by annual measurement of Thyroid Stimulating Hormone (TSH) and free T4. Hypothyroidism was defined as follows and is inclusive of: • Primary hypothyroidism: serum TSH >upper limit of normal (ULN) and free T4 <lower limit of normal (LLN); • Secondary hypothyroidism: serum TSH <ULN and free T4 <lower limit of normal; • Subclinical hypothyroidism: TSH >ULN and a free T4 within normal limits. The last available lab assessment date was used as the cut-off date for the analysis.

End point type	Secondary

End point timeframe:

Baseline (prior to or on the day of randomization [Day 1]) to end of study evaluation period (data cutoff 28th April, 2018)

End point values	Deferasirox	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	76		
Units: percentage of participants				
number (confidence interval 95%)	5.4 (1.4 to 9.3)	3.9 (0.0 to 9.0)		

Statistical analyses

Statistical analysis title	Descriptive statistics - Hypothyroidism
Comparison groups	Deferasirox v Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Wilson score test
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.3
upper limit	8.1

Secondary: Percentage of participants with worsening glucose metabolism compared to baseline

End point title	Percentage of participants with worsening glucose metabolism compared to baseline

End point description:

As assessed by an annual glucose tolerance test (OGTT). Worsening glucose metabolism was defined as an increase in glucose metabolism category (normal, impaired glucose metabolism, diabetes mellitus) based on the American Diabetes Association criteria (American Diabetes Association 2009) compared to the baseline result. The last available lab assessment date was used as the cut-off date for the analysis.

End point type	Secondary

End point timeframe:

Baseline (prior to or on the day of randomization [Day 1]) to end of study evaluation period (data cutoff 28th April, 2018)

End point values	Deferasirox	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	76		
Units: percentage of participants				
number (confidence interval 95%)	18.1 (11.6 to 24.6)	18.4 (9.0 to 27.8)		

Statistical analyses

Statistical analysis title	Descriptive statistics - worsening glucose
Comparison groups	Deferasirox v Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Wilson score test
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12
upper limit	11.4

Secondary: Time to disease progression

End point title	Time to disease progression

End point description:

Disease progression was defined as follows: - MDS progression: Transition into a higher MDS risk group based on IPSS scoring - Progression to AML: 20 percent or more blasts seen in the bone marrow collected by biopsy or aspirate. Disease progression was calculated as follows: Date of diagnosis of MDS progression or date of first diagnosis of AML, minus date of randomization plus 1. Participants who neither experienced MDS progression nor progression to AML were censored at the last contact date. Median estimation is not available as there is no data in any of the groups.

End point type	Secondary

End point timeframe:

Baseline (prior to or on the day of randomization [Day 1]) to end of study evaluation period (data cutoff 28th April, 2018)

End point values	Deferasirox	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	76		
Units: days				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)		

Statistical analyses

Statistical analysis title	Estimation of treatment effect - TTP
Comparison groups	Deferasirox v Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.184
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.725
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	1.46

Secondary: Time to first occurrence of serum ferritin level >2 times the baseline value at two consecutive assessments (at least two weeks apart)

End point title	Time to first occurrence of serum ferritin level >2 times the baseline value at two consecutive assessments (at least two weeks apart)

End point description:

Assessed by blood draw and calculated as follows: Date of first occurrence of serum ferritin >2 times the baseline value at two consecutive assessments (at least two weeks apart), minus date of randomization plus 1. Participants who did not experience such an increase were censored at the last date when serum ferritin was available.

End point type	Secondary

End point timeframe:

Baseline (prior to or on the day of randomization [Day 1]) to end of study evaluation period (data cutoff 28th April, 2018)

End point values	Deferasirox	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	76		
Units: days				
median (confidence interval 95%)	999 (999 to 999)	592 (397 to 877)		

Statistical analyses

Statistical analysis title	Estimation of treatment effect - Serum Ferritin
Comparison groups	Deferasirox v Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.195
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	0.36

Secondary: Time to at least a 10% increase from baseline in left ventricular end-diastolic internal (LVIDD) at two consecutive assessments at least two weeks apart

End point title	Time to at least a 10% increase from baseline in left ventricular end-diastolic internal (LVIDD) at two consecutive assessments at least two weeks apart

End point description:

Assessed by echocardiography and calculated as follows: Date of echocardiography assessment where a minimum of 10% increase of LVIDD first occurred, minus date of randomization plus 1. Participants who did not experience such an increase were censored at the last date when LVIDD was available.

End point type	Secondary

End point timeframe:

Time to event, Baseline (prior to or on the day of randomization [Day 1]) to end of study evaluation period (data cutoff 28th April, 2018)

End point values	Deferasirox	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	76		
Units: days				
median (confidence interval 95%)	999 (871 to 999)	999 (732 to 999)		

Statistical analyses

Statistical analysis title	Estimation of treatment effect - LVIDD
Comparison groups	Deferasirox v Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.303
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.871
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.46

Secondary: Time to at least a 10% increase from baseline in left ventricular internal systolic diameter (LVISD) at two consecutive assessments at least two weeks apart

End point title	Time to at least a 10% increase from baseline in left ventricular internal systolic diameter (LVISD) at two consecutive assessments at least two weeks apart

End point description:

Assessed by echocardiography and calculated as follows: Date of echocardiography assessment where a minimum of 10% increase of LVISD first occurred, minus date of randomization plus 1. Participants who did not experience such an increase were censored at the last date when LVISD was available.

End point type	Secondary

End point timeframe:

Time to event, Baseline (prior to or on the day of randomization [Day 1]) to end of study evaluation period (data cutoff 28th April, 2018)

End point values	Deferasirox	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	76		
Units: days				
median (confidence interval 95%)	1179.0 (532 to 9999)	999 (502 to 999)		

Statistical analyses

Statistical analysis title	Estimation of treatment effect - LVISD
Comparison groups	Deferasirox v Placebo

Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.389
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.072
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.75

Secondary: Total number of infections requiring intravenous antimicrobials

End point title	Total number of infections requiring intravenous antimicrobials

End point description:

The total number of infections were counted and summarized per treatment group. For this number, one participant can contribute more than one infection event. Infections were determined from the reported AEs with system organ class "Infections and infestations" and action taken "Concomitant medication taken." Antimicrobial therapy was determined from the reported concomitant medications for participants who had an infection AE. The route of administration needed to be specified as "intravenous (i.v.)". End of treatment period was defined as the treatment period plus 28 days.

End point type	Secondary

End point timeframe:

Day 1 to end of treatment period

End point values	Deferasirox	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	76		
Units: infections	253	111		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with major gastrointestinal bleeding

End point title	Percentage of participants with major gastrointestinal bleeding

End point description:

Major gastrointestinal bleeding was defined as an AE that could include one of the following MedDRA preferred terms: gastric hemorrhage, gastrointestinal hemorrhage, small intestinal hemorrhage, esophageal hemorrhage, large intestinal hemorrhage, rectal hemorrhage, melaena, duodenal ulcer hemorrhage, gastric ulcer hemorrhage, peptic ulcer hemorrhage, large intestinal ulcer hemorrhage, esophageal ulcer hemorrhage, and hematochezia. The end of treatment period was defined as the treatment period plus 28 days.

End point type	Secondary

End point timeframe:

Day 1 to end of treatment period (up to data cutoff 28th April, 2018)

End point values	Deferasirox	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	76		
Units: percentage of participants				
number (confidence interval 95%)	5.4 (1.4 to 9.4)	3.9 (0.0 to 9.0)		

Statistical analyses

Statistical analysis title	Descriptive statistics - gastroint. bleeding
Comparison groups	Deferasirox v Placebo
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Wilson score test
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.2
upper limit	8.1

Secondary: Percentage of participants with significant renal dysfunction

End point title	Percentage of participants with significant renal dysfunction

End point description:

Significant renal dysfunction was defined as a serum creatinine value ≥ 2 times upper limit of normal (ULN) at two consecutive assessments at least 7 days apart

End point type	Secondary

End point timeframe:

Day 1 to end of study evaluation period (data cutoff 28th April, 2018)

End point values	Deferasirox	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	76		
Units: percentage of participants				
number (confidence interval 95%)	0.7 (0.0 to 2.3)	0 (0.0 to 0.7)		

Statistical analyses

Statistical analysis title	Descriptive statistics - renal dysfunction
Comparison groups	Deferasirox v Placebo
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Wilson score test
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	3

Secondary: Percentage of participants with newly occurring moderate or severe neutropenia

End point title	Percentage of participants with newly occurring moderate or severe neutropenia

End point description:

Moderate or severe neutropenia was defined as neutrophil counts less than 1.0×10E9/L.

End point type	Secondary

End point timeframe:

Baseline (prior to or on the day of randomization [Day 1]) to end of study evaluation period (data cutoff 28th April, 2018)

End point values	Deferasirox	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	76		
Units: percentage of participants				
number (confidence interval 95%)	27.7 (20.2 to 35.5)	26.3 (15.8 to 36.9)		

Statistical analyses

Statistical analysis title	Descriptive statistics - neutropenia
Comparison groups	Deferasirox v Placebo

Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Wilson score test
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.9
upper limit	14.6

Secondary: Percentage of participants with newly occurring severe thrombocytopenia

End point title	Percentage of participants with newly occurring severe thrombocytopenia

End point description:

Severe thrombocytopenia was defined as platelets counts less than 50×10E9/L.

End point type	Secondary

End point timeframe:

Baseline (prior to or on the day of randomization [Day 1]) to end of study evaluation period (data cutoff 28th April, 2018)

End point values	Deferasirox	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	76		
Units: percentage of participants				
number (confidence interval 95%)	10.1 (4.9 to 15.3)	19.7 (10.1 to 29.3)		

Statistical analyses

Statistical analysis title	Descriptive statistics - thrombocytopenia
Comparison groups	Deferasirox v Placebo
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Wilson score test
Point estimate	-9.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.8
upper limit	1.6

Secondary: Time to study drug discontinuation due to an AE or laboratory abnormality

End point title	Time to study drug discontinuation due to an AE or laboratory abnormality

End point description:

As recorded on the Study Treatment Completion electronic Case Report Form (eCRF), date and reason given.Only participants for whom the reason for stopping study medication was entered as AE or laboratory abnormality were considered. This time to event endpoint was calculated as the date of study drug discontinuation due to an AE or laboratory abnormality minus date of randomization plus 1. Participants who did not discontinue study medication due to an AE or laboratory abnormality were censored at the date of study drug discontinuation.

End point type	Secondary

End point timeframe:

Day 1 to end of study evaluation period (data cutoff 28th April, 2018)

End point values	Deferasirox	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	76		
Units: days				
median (confidence interval 95%)	9999 (1486 to 9999)	1022 (904 to 9999)		

Statistical analyses

Statistical analysis title	Estimation of treatment effect time to disc.
Comparison groups	Deferasirox v Placebo
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.232
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.797
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	1.46

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from Day1 (study drug) up to 28 days post treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Deferasirox

Reporting group description:

10 mg/kg/day (once daily) for the first 2 weeks of treatment,
followed by 20 mg/kg/day (once daily) from Week 2 to End of Treatment. After 3 months of treatment at 20 mg/kg/day, the dose was allowed to be adjusted by 5 or 10 mg/kg/day up to 40 mg/kg/day based on serum ferritin responses. When a target serum ferritin level was reached (usually between 500 and 1000 µg/L), the dose could be reduced by 50% to maintain the serum ferritin within the target range.

Reporting group title	Placebo

Reporting group description:

10 mg/kg/day (once daily) for the first 2 weeks of treatment,
followed by 20 mg/kg/day (once daily) from Week 2 to End of Treatment. After 3 months of treatment at 20 mg/kg/day, the dose was allowed to be adjusted by 5 or 10 mg/kg/day up to 40 mg/kg/day based on serum ferritin responses. When a
target serum ferritin level was reached (usually between 500 and 1000 µg/L), the dose could be reduced by 50% to
maintain the serum ferritin within the target range.

Reporting group title	All Patients

Reporting group description:

Combined patients from the Deferasirox and Placebo arms.

Serious adverse events	Deferasirox	Placebo	All Patients
Total subjects affected by serious adverse events			
subjects affected / exposed	80 / 148 (54.05%)	38 / 76 (50.00%)	118 / 224 (52.68%)
number of deaths (all causes)	24	10	34
number of deaths resulting from adverse events	1	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute leukaemia			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myeloid leukaemia			
subjects affected / exposed	2 / 148 (1.35%)	2 / 76 (2.63%)	4 / 224 (1.79%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bladder neoplasm			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Light chain disease			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelodysplastic syndrome			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelofibrosis			
subjects affected / exposed	1 / 148 (0.68%)	1 / 76 (1.32%)	2 / 224 (0.89%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration			

site conditions			
Asthenia			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Face oedema			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	2 / 148 (1.35%)	0 / 76 (0.00%)	2 / 224 (0.89%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	2 / 2	0 / 0	2 / 2
Non-cardiac chest pain			
subjects affected / exposed	2 / 148 (1.35%)	0 / 76 (0.00%)	2 / 224 (0.89%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 148 (0.00%)	2 / 76 (2.63%)	2 / 224 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral swelling			

subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	14 / 148 (9.46%)	5 / 76 (6.58%)	19 / 224 (8.48%)
occurrences causally related to treatment / all	0 / 16	0 / 9	0 / 25
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypogammaglobulinaemia			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine haemorrhage			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine polyp			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			

subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	2 / 148 (1.35%)	0 / 76 (0.00%)	2 / 224 (0.89%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	3 / 148 (2.03%)	3 / 76 (3.95%)	6 / 224 (2.68%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	1 / 148 (0.68%)	2 / 76 (2.63%)	3 / 224 (1.34%)
occurrences causally related to treatment / all	1 / 1	0 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oropharyngeal pain			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 148 (0.68%)	1 / 76 (1.32%)	2 / 224 (0.89%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			

subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary fibrosis			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary mass			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	2 / 148 (1.35%)	0 / 76 (0.00%)	2 / 224 (0.89%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatine increased			

subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood pressure decreased			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Back injury			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Face injury			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			

subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue injury			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic rupture			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	1 / 148 (0.68%)	1 / 76 (1.32%)	2 / 224 (0.89%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			

subjects affected / exposed	1 / 148 (0.68%)	2 / 76 (2.63%)	3 / 224 (1.34%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	2 / 148 (1.35%)	0 / 76 (0.00%)	2 / 224 (0.89%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Cardiac failure			
subjects affected / exposed	3 / 148 (2.03%)	1 / 76 (1.32%)	4 / 224 (1.79%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 5
deaths causally related to treatment / all	2 / 2	0 / 0	2 / 2
Cardio-respiratory arrest			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Cardiomyopathy			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiopulmonary failure			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiovascular insufficiency			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Left ventricular failure			

subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular dysfunction			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus node dysfunction			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haematoma			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	2 / 148 (1.35%)	0 / 76 (0.00%)	2 / 224 (0.89%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Cognitive disorder			

subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coma			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Dizziness			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemianopia homonymous			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy peripheral			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 148 (0.68%)	2 / 76 (2.63%)	3 / 224 (1.34%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Abdominal lymphadenopathy			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			

subjects affected / exposed	11 / 148 (7.43%)	3 / 76 (3.95%)	14 / 224 (6.25%)
occurrences causally related to treatment / all	0 / 16	0 / 8	0 / 24
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone marrow failure			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytopenia			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	2 / 148 (1.35%)	3 / 76 (3.95%)	5 / 224 (2.23%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenitis			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 148 (0.68%)	1 / 76 (1.32%)	2 / 224 (0.89%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Normochromic normocytic anaemia			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic infarction			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic lesion			

subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenomegaly			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	5 / 148 (3.38%)	2 / 76 (2.63%)	7 / 224 (3.13%)
occurrences causally related to treatment / all	0 / 5	0 / 4	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Aural polyp			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal haemorrhage			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous floaters			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 148 (0.68%)	1 / 76 (1.32%)	2 / 224 (0.89%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Abdominal pain upper			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	3 / 148 (2.03%)	0 / 76 (0.00%)	3 / 224 (1.34%)
occurrences causally related to treatment / all	1 / 3	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Crohn's disease			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	5 / 148 (3.38%)	4 / 76 (5.26%)	9 / 224 (4.02%)
occurrences causally related to treatment / all	3 / 5	2 / 4	5 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 148 (0.68%)	1 / 76 (1.32%)	2 / 224 (0.89%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	4 / 148 (2.70%)	2 / 76 (2.63%)	6 / 224 (2.68%)
occurrences causally related to treatment / all	1 / 4	0 / 2	1 / 6
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Gastrointestinal perforation			

subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gingival bleeding			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gingival hypertrophy			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus hernia			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 148 (0.68%)	1 / 76 (1.32%)	2 / 224 (0.89%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal mass			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Intestinal obstruction			

subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mouth haemorrhage			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	3 / 148 (2.03%)	0 / 76 (0.00%)	3 / 224 (1.34%)
occurrences causally related to treatment / all	1 / 3	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 148 (0.68%)	2 / 76 (2.63%)	3 / 224 (1.34%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Vomiting			
subjects affected / exposed	5 / 148 (3.38%)	0 / 76 (0.00%)	5 / 224 (2.23%)
occurrences causally related to treatment / all	1 / 5	0 / 0	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	3 / 148 (2.03%)	0 / 76 (0.00%)	3 / 224 (1.34%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic function abnormal			

subjects affected / exposed	2 / 148 (1.35%)	0 / 76 (0.00%)	2 / 224 (0.89%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic lesion			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 148 (2.03%)	1 / 76 (1.32%)	4 / 224 (1.79%)
occurrences causally related to treatment / all	1 / 3	0 / 1	1 / 4
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Anuria			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	1 / 148 (0.68%)	2 / 76 (2.63%)	3 / 224 (1.34%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephropathy toxic			

subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 148 (0.68%)	1 / 76 (1.32%)	2 / 224 (0.89%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypogonadism			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 148 (1.35%)	0 / 76 (0.00%)	2 / 224 (0.89%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint swelling			
subjects affected / exposed	1 / 148 (0.68%)	1 / 76 (1.32%)	2 / 224 (0.89%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mobility decreased			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle atrophy			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal pain			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sjogren's syndrome			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovial cyst			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess soft tissue			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	1 / 148 (0.68%)	1 / 76 (1.32%)	2 / 224 (0.89%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal infection			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendiceal abscess			
subjects affected / exposed	2 / 148 (1.35%)	0 / 76 (0.00%)	2 / 224 (0.89%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

subjects affected / exposed	1 / 148 (0.68%)	2 / 76 (2.63%)	3 / 224 (1.34%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridial infection			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	1 / 148 (0.68%)	1 / 76 (1.32%)	2 / 224 (0.89%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Diarrhoea infectious			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile infection			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gingivitis			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin abscess			
subjects affected / exposed	2 / 148 (1.35%)	0 / 76 (0.00%)	2 / 224 (0.89%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver abscess			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	2 / 148 (1.35%)	2 / 76 (2.63%)	4 / 224 (1.79%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Lung infection			
subjects affected / exposed	9 / 148 (6.08%)	4 / 76 (5.26%)	13 / 224 (5.80%)
occurrences causally related to treatment / all	0 / 13	0 / 5	0 / 18
deaths causally related to treatment / all	1 / 1	2 / 2	3 / 3
Neutropenic sepsis			
subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orchitis			

subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 148 (2.03%)	3 / 76 (3.95%)	6 / 224 (2.68%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 6
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Respiratory tract infection			
subjects affected / exposed	2 / 148 (1.35%)	0 / 76 (0.00%)	2 / 224 (0.89%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scrub typhus			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	6 / 148 (4.05%)	2 / 76 (2.63%)	8 / 224 (3.57%)
occurrences causally related to treatment / all	0 / 6	0 / 2	0 / 8
deaths causally related to treatment / all	3 / 3	0 / 0	3 / 3
Septic shock			
subjects affected / exposed	2 / 148 (1.35%)	0 / 76 (0.00%)	2 / 224 (0.89%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Skin graft infection			

subjects affected / exposed	0 / 148 (0.00%)	1 / 76 (1.32%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	0 / 148 (0.00%)	2 / 76 (2.63%)	2 / 224 (0.89%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tongue fungal infection			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	4 / 148 (2.70%)	2 / 76 (2.63%)	6 / 224 (2.68%)
occurrences causally related to treatment / all	0 / 7	0 / 2	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 148 (0.00%)	3 / 76 (3.95%)	3 / 224 (1.34%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Dehydration			

subjects affected / exposed	1 / 148 (0.68%)	1 / 76 (1.32%)	2 / 224 (0.89%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 148 (0.68%)	1 / 76 (1.32%)	2 / 224 (0.89%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 148 (0.68%)	0 / 76 (0.00%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Deferasirox	Placebo	All Patients
Total subjects affected by non-serious adverse events			
subjects affected / exposed	135 / 148 (91.22%)	65 / 76 (85.53%)	200 / 224 (89.29%)
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	13 / 148 (8.78%)	8 / 76 (10.53%)	21 / 224 (9.38%)
occurrences (all)	15	15	30
Fatigue			
subjects affected / exposed	21 / 148 (14.19%)	12 / 76 (15.79%)	33 / 224 (14.73%)
occurrences (all)	21	13	34
Non-cardiac chest pain			
subjects affected / exposed	7 / 148 (4.73%)	6 / 76 (7.89%)	13 / 224 (5.80%)
occurrences (all)	9	6	15
Oedema peripheral			
subjects affected / exposed	22 / 148 (14.86%)	9 / 76 (11.84%)	31 / 224 (13.84%)
occurrences (all)	28	12	40

Pyrexia			
subjects affected / exposed	42 / 148 (28.38%)	13 / 76 (17.11%)	55 / 224 (24.55%)
occurrences (all)	84	20	104
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	30 / 148 (20.27%)	11 / 76 (14.47%)	41 / 224 (18.30%)
occurrences (all)	41	11	52
Dyspnoea			
subjects affected / exposed	10 / 148 (6.76%)	7 / 76 (9.21%)	17 / 224 (7.59%)
occurrences (all)	14	9	23
Epistaxis			
subjects affected / exposed	9 / 148 (6.08%)	5 / 76 (6.58%)	14 / 224 (6.25%)
occurrences (all)	14	5	19
Oropharyngeal pain			
subjects affected / exposed	10 / 148 (6.76%)	4 / 76 (5.26%)	14 / 224 (6.25%)
occurrences (all)	16	4	20
Productive cough			
subjects affected / exposed	9 / 148 (6.08%)	5 / 76 (6.58%)	14 / 224 (6.25%)
occurrences (all)	11	7	18
Psychiatric disorders			
Insomnia			
subjects affected / exposed	9 / 148 (6.08%)	3 / 76 (3.95%)	12 / 224 (5.36%)
occurrences (all)	9	4	13
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	14 / 148 (9.46%)	9 / 76 (11.84%)	23 / 224 (10.27%)
occurrences (all)	17	12	29
Blood bilirubin increased			
subjects affected / exposed	9 / 148 (6.08%)	2 / 76 (2.63%)	11 / 224 (4.91%)
occurrences (all)	20	3	23
Blood creatinine increased			
subjects affected / exposed	37 / 148 (25.00%)	1 / 76 (1.32%)	38 / 224 (16.96%)
occurrences (all)	68	2	70
Creatinine renal clearance decreased			
subjects affected / exposed	16 / 148 (10.81%)	3 / 76 (3.95%)	19 / 224 (8.48%)
occurrences (all)	19	3	22

Protein urine present			
subjects affected / exposed	8 / 148 (5.41%)	1 / 76 (1.32%)	9 / 224 (4.02%)
occurrences (all)	8	1	9
Weight decreased			
subjects affected / exposed	12 / 148 (8.11%)	6 / 76 (7.89%)	18 / 224 (8.04%)
occurrences (all)	14	7	21
Nervous system disorders			
Dizziness			
subjects affected / exposed	19 / 148 (12.84%)	6 / 76 (7.89%)	25 / 224 (11.16%)
occurrences (all)	22	10	32
Headache			
subjects affected / exposed	17 / 148 (11.49%)	13 / 76 (17.11%)	30 / 224 (13.39%)
occurrences (all)	20	21	41
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	14 / 148 (9.46%)	5 / 76 (6.58%)	19 / 224 (8.48%)
occurrences (all)	28	7	35
Thrombocytopenia			
subjects affected / exposed	9 / 148 (6.08%)	4 / 76 (5.26%)	13 / 224 (5.80%)
occurrences (all)	11	4	15
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	8 / 148 (5.41%)	4 / 76 (5.26%)	12 / 224 (5.36%)
occurrences (all)	10	6	16
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	9 / 148 (6.08%)	6 / 76 (7.89%)	15 / 224 (6.70%)
occurrences (all)	10	9	19
Abdominal distension			
subjects affected / exposed	11 / 148 (7.43%)	4 / 76 (5.26%)	15 / 224 (6.70%)
occurrences (all)	13	4	17
Abdominal pain			
subjects affected / exposed	13 / 148 (8.78%)	9 / 76 (11.84%)	22 / 224 (9.82%)
occurrences (all)	15	14	29
Abdominal pain upper			
subjects affected / exposed	12 / 148 (8.11%)	9 / 76 (11.84%)	21 / 224 (9.38%)
occurrences (all)	13	11	24

Constipation			
subjects affected / exposed	17 / 148 (11.49%)	12 / 76 (15.79%)	29 / 224 (12.95%)
occurrences (all)	20	18	38
Diarrhoea			
subjects affected / exposed	51 / 148 (34.46%)	17 / 76 (22.37%)	68 / 224 (30.36%)
occurrences (all)	88	30	118
Dyspepsia			
subjects affected / exposed	11 / 148 (7.43%)	6 / 76 (7.89%)	17 / 224 (7.59%)
occurrences (all)	12	6	18
Gingival bleeding			
subjects affected / exposed	5 / 148 (3.38%)	5 / 76 (6.58%)	10 / 224 (4.46%)
occurrences (all)	8	5	13
Mouth ulceration			
subjects affected / exposed	13 / 148 (8.78%)	1 / 76 (1.32%)	14 / 224 (6.25%)
occurrences (all)	19	1	20
Nausea			
subjects affected / exposed	23 / 148 (15.54%)	10 / 76 (13.16%)	33 / 224 (14.73%)
occurrences (all)	31	16	47
Vomiting			
subjects affected / exposed	12 / 148 (8.11%)	6 / 76 (7.89%)	18 / 224 (8.04%)
occurrences (all)	19	10	29
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	16 / 148 (10.81%)	8 / 76 (10.53%)	24 / 224 (10.71%)
occurrences (all)	18	8	26
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	12 / 148 (8.11%)	1 / 76 (1.32%)	13 / 224 (5.80%)
occurrences (all)	21	1	22
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 148 (5.41%)	8 / 76 (10.53%)	16 / 224 (7.14%)
occurrences (all)	9	10	19
Back pain			
subjects affected / exposed	15 / 148 (10.14%)	7 / 76 (9.21%)	22 / 224 (9.82%)
occurrences (all)	18	10	28

Bone pain			
subjects affected / exposed	1 / 148 (0.68%)	4 / 76 (5.26%)	5 / 224 (2.23%)
occurrences (all)	1	4	5
Muscle spasms			
subjects affected / exposed	3 / 148 (2.03%)	7 / 76 (9.21%)	10 / 224 (4.46%)
occurrences (all)	3	8	11
Musculoskeletal pain			
subjects affected / exposed	8 / 148 (5.41%)	3 / 76 (3.95%)	11 / 224 (4.91%)
occurrences (all)	9	3	12
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	2 / 148 (1.35%)	4 / 76 (5.26%)	6 / 224 (2.68%)
occurrences (all)	2	4	6
Influenza			
subjects affected / exposed	8 / 148 (5.41%)	6 / 76 (7.89%)	14 / 224 (6.25%)
occurrences (all)	9	12	21
Lower respiratory tract infection			
subjects affected / exposed	6 / 148 (4.05%)	4 / 76 (5.26%)	10 / 224 (4.46%)
occurrences (all)	8	4	12
Nasopharyngitis			
subjects affected / exposed	10 / 148 (6.76%)	4 / 76 (5.26%)	14 / 224 (6.25%)
occurrences (all)	14	4	18
Oral herpes			
subjects affected / exposed	5 / 148 (3.38%)	5 / 76 (6.58%)	10 / 224 (4.46%)
occurrences (all)	6	6	12
Upper respiratory tract infection			
subjects affected / exposed	34 / 148 (22.97%)	19 / 76 (25.00%)	53 / 224 (23.66%)
occurrences (all)	67	30	97
Urinary tract infection			
subjects affected / exposed	14 / 148 (9.46%)	8 / 76 (10.53%)	22 / 224 (9.82%)
occurrences (all)	21	13	34
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	18 / 148 (12.16%)	8 / 76 (10.53%)	26 / 224 (11.61%)
occurrences (all)	19	9	28
Hyperglycaemia			

subjects affected / exposed	11 / 148 (7.43%)	3 / 76 (3.95%)	14 / 224 (6.25%)
occurrences (all)	19	3	22
Hypokalaemia			
subjects affected / exposed	12 / 148 (8.11%)	3 / 76 (3.95%)	15 / 224 (6.70%)
occurrences (all)	16	3	19

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 June 2010	The inclusion/exclusion criteria were changed due to a greater than 90% pre-screen failure rate in patients for the study. The main purpose of the amendment was to: • Change the maximum serum ferritin level for inclusion from 2500 to 3500 mcg/L with a concurrent increase of the maximum number of transfused units of blood from 50 to 75 • Change the exclusion criteria of more than 3 years from diagnosis of MDS to more than 3 years from the time the patient became transfusion dependent • Clarify the need for baseline Brain Natriuretic Peptide assessment and for a baseline chest X-ray, as well as to allow for local laboratories could be used for weekly serum creatinine assessments that were required at the initiation of treatment and at the time of dose adjustments • Update the composite primary endpoint to include transformation to AML. Based upon recent data (Sanz et al 2008), iron overload could play a role in AML transformation in patients with MDS as patients with serum ferritin levels of ≥ 1000 ng/ml had a significantly higher rate of AML transformation than patients with serum ferritin levels of <1000 mg/ml. Given that progression to AML is an extremely significant medical event in terms of both morbidity and mortality, it was appropriate to include as part of the composite primary endpoint
06 January 2011	The inclusion/exclusion criteria were changed due to a greater than 90% pre-screen failure rate in patients for the study. The main purpose of the amendment was to: • Change the inclusion criteria to allow patients into the trial that had been previously iron chelated for no more than six months cumulatively (such as daily deferasirox (Exjade) or deferiprone or 5×/week deferoxamine) from only including those who were chelation naïve • Change the minimum number of transfused units of blood from 20 units to 15 units and patients entering the study could be transfused with at least 8 units of PRBC annually from 8 times annually • Serum creatinine entry criteria was changed from requiring serum creatinine >ULN at screening to serum creatinine >1.2 × ULN at screening • Clarify the exclusion criteria of prior diagnosis of liver cirrhosis defined as either an established diagnosis or diagnosis by liver biopsy or central ultrasound reading • Clarify that the exclusion criteria pertaining to left ventricular ejection fraction <50% by echocardiography was to be confirmed by the central reading facility used in this trial • Clarify the exclusion criteria, patients with a history of another malignancy within the past five years, with the exception of basal cell skin carcinoma or cervical carcinoma in situ, was expanded to include completely resected colonic polyps carcinoma in situ. • Screening visit period was revised to allow for a 35-day screening window

21 March 2012	The inclusion/exclusion criteria were modified to address the most common reasons for the 60% screen failure rate observed among patients that were screened for the study and were in alignment with the study steering committee discussions. This allowed MDS patients that were more commonly seen in the real-world setting as described by the Investigators to be enrolled, hence allowing more patients to participate in the study. The main purpose of the amendment was to: • Remove the upper limit of serum ferritin inclusion criterion so that patients qualify for inclusion if their serum ferritin was >1000 µg/L • Change the liver transaminases ALT/AST exclusion criterion from >2.5 × ULN at screening to ALT/AST >3.5 × ULN at screening • Change the exclusion criteria from total bilirubin >ULN at screening to total bilirubin >1.5 × ULN at screening • Change the exclusion criteria from serum creatinine >1.2 × ULN at screening to serum creatinine >1.5 × ULN at screening • Modify the component of the composite endpoint defining liver function impairment as reflected by ALT or AST changes in correspondence with the change in ALT/AST exclusion criterion from been >2 × the baseline value and >3 × ULN to >2 × the baseline value and >3.5 × ULN
01 August 2013	The main purpose of the amendment was to: • Change the study phase from phase III to phase II • Change the number of patients to be enrolled to at least 210 • Change the purpose of the study to evaluate clinical benefit instead of demonstrating superiority. The primary objective was changed from statistical comparison to descriptive evaluation of the effect of deferasirox and placebo with regard to event-free survival • Change overall survival from key secondary to secondary endpoint • To incorporate hematological function expressed in frequency/total amount of blood transfusions in the added endpoint of proportion of patients with hematologic improvement • Rename time to MDS progression and progression to AML to time to disease progression • Add the frequency and rate of infections requiring IV antimicrobials • Remove the interim analyses • Clarify that the duration of study was no longer events driven. The study was to be completed 3 years after the last patient was enrolled.
22 September 2014	At the time of writing this protocol amendment, 192 patients had been randomized in the study and 175 patients failed screening. The key points of the amendment are given below: • Excluded patients with moderate and severe hepatic impairment (Child-Pugh Class B and C). • Guidance on treating patients who develop moderate hepatic impairment (Child-Pugh Class B) during the trial and immediate discontinuation if severe hepatic impairment (Child-Pugh Class C) or Stevens-Johnson syndrome occurred • Guidance included on the use of contraception. • Guidance was added regarding treatment discontinuation of patients with creatinine clearance <40 mL/min or serum creatinine >2 time the age appropriate ULN, and caution in patients with creatinine clearance between 40 and less than 60 mL/min • Guidance on the concomitant administration of deferasirox with compounds metabolized through CYP3A4, CYP2C8, and CYP1A2; and the concomitant use of Uridine 5'-diphospho-glucuronosyltransferase inducers and bile acid sequestrants

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported