



Clinical trial results:

A multi-center, open-label, non-comparative, phase II trial on efficacy and safety of ICL670 given for 1 year with dose adjustments based on serum ferritin in patients with chronic anemia and transfusional hemosiderosis

A one-year extension to a multi-center, open-label, non-comparative, phase II trial on efficacy and safety of ICL670 given for 1 year with dose adjustments based on serum ferritin in patients with chronic anemia and transfusional hemosiderosis

Summary

EudraCT number	2006-003337-32
Trial protocol	ES
Global end of trial date	02 February 2012

Results information

Result version number	v1 (current)
This version publication date	22 July 2016
First version publication date	22 July 2016

Trial information

Trial identification

Sponsor protocol code	CICL670A2204
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00631163
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 February 2012
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	02 February 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the efficacy of deferasirox, based on liver iron concentration (LIC) decrease over one year in paediatric and adult subjects with chronic anemias and transfusional hemosiderosis other than β -thalassemia or sickle cell disease.

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. Rescue medication was not allowed during the course of the study. The investigator provided follow-up medical care for all subjects who were prematurely withdrawn from the study, or referred them for appropriate ongoing care.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 October 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	Spain: 4
Country: Number of subjects enrolled	Japan: 53
Country: Number of subjects enrolled	Poland: 20
Country: Number of subjects enrolled	Singapore: 3
Country: Number of subjects enrolled	Turkey: 22
Worldwide total number of subjects	102
EEA total number of subjects	24

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)	16
Adolescents (12-17 years)	8
Adults (18-64 years)	41
From 65 to 84 years	36
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 31 centres in 5 countries.

Pre-assignment

Screening details:

A total of 144 subjects were screened, of which only 102 subjects enrolled in the study. Remaining 42 subjects were considered as screen failures.

Period 1

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

Blinding implementation details:

This was an open-label study, hence no blinding was implemented.

Arms

Arm title	Deferasirox (Core Study)
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Arm description:

The recommended initial daily dose of deferasirox was 20 mg/kg based on the patient's body weight. An initial daily dose of 30 mg/kg was considered for patients receiving > 14 mL/kg/month of blood transfusions (defined as approximately more than 4 units (200 mL/unit) of packed red blood cells/month for adults) and the objective was reduction of iron overload. Alternatively, an initial daily dose of 10 mg/kg was considered for patients receiving < 7 mL/kg/month of blood transfusions (defined as approximately less than 2 units (200 mL/unit) of packed red blood cells/month for adults) and the objective was maintenance of iron level.

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 20 mg/kg was administered once daily. The dose of deferasirox was adjusted to either 10 mg/kg or 30 mg/kg based on the volumes of blood transfusions being administered in a month.

Number of subjects in period 1	Deferasirox (Core Study)
Started	102
Completed	68
Not completed	34
Consent withdrawn by subject	8
Adverse event, non-fatal	12
Death	6
Subject's condition no longer required study drug	1
Administrative problems	6

Lost to follow-up	1
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Period 2

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

Blinding implementation details:

The study was open-label, hence no blinding was implemented.

Arms

Arm title	Deferasirox (Extension study)
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Arm description:

The recommended initial daily dose of deferasirox was 20 mg/kg based on the patient's body weight. An initial daily dose of 30 mg/kg was considered for patients receiving > 14 mL/kg/month of blood transfusions (defined as approximately more than 4 units (200 mL/unit) of packed red blood cells/month for adults) and the objective was reduction of iron overload. Alternatively, an initial daily dose of 10 mg/kg was considered for patients receiving < 7 mL/kg/month of blood transfusions (defined as approximately less than 2 units (200 mL/unit) of packed red blood cells/month for adults) and the objective was maintenance of iron level.

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 20 mg/kg was administered once daily. The dose of deferasirox was adjusted to either 10 mg/kg or 30 mg/kg based on the volumes of blood transfusions being administered in a month.

Number of subjects in period 2^[1]	Deferasirox (Extension study)
Started	57
Completed	52
Not completed	5
Consent withdrawn by subject	2
Adverse event, non-fatal	1
Abnormal laboratory values	1
Protocol deviation	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Of 68 subjects who completed the preceding period, only 57 subjects opted to enroll in extension study.

Baseline characteristics

Reporting groups

Reporting group title	Deferasirox (Core Study)
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Reporting group description:

The recommended initial daily dose of deferasirox was 20 mg/kg based on the patient's body weight. An initial daily dose of 30 mg/kg was considered for patients receiving > 14 mL/kg/month of blood transfusions (defined as approximately more than 4 units (200 mL/unit) of packed red blood cells/month for adults) and the objective was reduction of iron overload. Alternatively, an initial daily dose of 10 mg/kg was considered for patients receiving < 7 mL/kg/month of blood transfusions (defined as approximately less than 2 units (200 mL/unit) of packed red blood cells/month for adults) and the objective was maintenance of iron level.

Reporting group values	Deferasirox (Core Study)	Total	
Number of subjects	102	102	
Age categorical			
Units: Subjects			
2 years to < 6years	11	11	
6 years to <12 years	5	5	
12 years to <18 years	8	8	
18 years to < 65 years	41	41	
>= 65 years	37	37	
Age continuous			
Units: years			
arithmetic mean	47.8		
standard deviation	± 25.9	-	
Gender categorical			
Units: Subjects			
Female	49	49	
Male	53	53	

End points

End points reporting groups

Reporting group title	Deferasirox (Core Study)
Reporting group description: The recommended initial daily dose of deferasirox was 20 mg/kg based on the patient's body weight. An initial daily dose of 30 mg/kg was considered for patients receiving > 14 mL/kg/month of blood transfusions (defined as approximately more than 4 units (200 mL/unit) of packed red blood cells/month for adults) and the objective was reduction of iron overload. Alternatively, an initial daily dose of 10 mg/kg was considered for patients receiving < 7 mL/kg/month of blood transfusions (defined as approximately less than 2 units (200 mL/unit) of packed red blood cells/month for adults) and the objective was maintenance of iron level.	
Reporting group title	Deferasirox (Extension study)
Reporting group description: The recommended initial daily dose of deferasirox was 20 mg/kg based on the patient's body weight. An initial daily dose of 30 mg/kg was considered for patients receiving > 14 mL/kg/month of blood transfusions (defined as approximately more than 4 units (200 mL/unit) of packed red blood cells/month for adults) and the objective was reduction of iron overload. Alternatively, an initial daily dose of 10 mg/kg was considered for patients receiving < 7 mL/kg/month of blood transfusions (defined as approximately less than 2 units (200 mL/unit) of packed red blood cells/month for adults) and the objective was maintenance of iron level.	
Subject analysis set title	All randomised subjects
Subject analysis set type	Full analysis
Subject analysis set description: The recommended initial daily dose of deferasirox was 20 mg/kg based on the patient's body weight. An initial daily dose of 30 mg/kg was considered for patients receiving > 14 mL/kg/month of blood transfusions (defined as approximately more than 4 units (200 mL/unit) of packed red blood cells/month for adults) and the objective was reduction of iron overload. Alternatively, an initial daily dose of 10 mg/kg was considered for patients receiving < 7 mL/kg/month of blood transfusions (defined as approximately less than 2 units (200 mL/unit) of packed red blood cells/month for adults) and the objective was maintenance of iron level.	
Subject analysis set title	Japanese subjects
Subject analysis set type	Sub-group analysis
Subject analysis set description: All subjects who were enrolled in Japan and received deferasirox as per the study protocol.	

Primary: Absolute change from baseline in liver iron concentration (LIC) to Year 1

End point title	Absolute change from baseline in liver iron concentration (LIC) to Year 1 ^[1]
End point description: LIC, a predictor of iron burden, was measured using relaxation rate magnetic resonance imaging (R2-MRI) technique. Relaxation rate was determined as $R2 = 1/\text{relaxation time (T2)}$. The baseline value of LIC of subjects was categorized as < 7, ≥ 7 to < 15, and ≥ 15 milligram of iron/tissue dry weight (mg Fe/g dw). A negative change from baseline favored study treatment in reducing LIC. The analysis was performed in per-protocol population in core study (PP1 Set), comprising of all enrolled subjects who had LIC assessments at baseline and Year 1.	
End point type	Primary
End point timeframe: Baseline, Year 1 (End of core study)	
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: only summary results available, no comparative statistics available	

End point values	Deferasirox (Core Study)			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: mg Fe/g dw				
arithmetic mean (standard deviation)	-10.9 (± 11.86)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from baseline in liver iron concentration (LIC) to end of Year 2

End point title	Absolute change from baseline in liver iron concentration (LIC) to end of Year 2
End point description:	
LIC, a predictor of iron burden, was measured using R2-MRI technique. Relaxation rate was determined as $R2 = 1/T2$. The baseline value of LIC of subjects was categorized as < 7 , ≥ 7 to < 15 , and ≥ 15 mg Fe/g dw. A negative change from baseline favoured study treatment in reducing LIC. The analysis was performed in per-protocol population in core study (PP2 Set), comprising of all enrolled subjects who had LIC assessments at baseline and at end of the extension phase.	
End point type	Secondary
End point timeframe:	
Baseline to End of Year 2 (End of extension study)	

End point values	Deferasirox (Extension study)			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: mg Fe/g dw				
arithmetic mean (standard deviation)	-13.5 (± 14.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from baseline in LIC in Japanese subgroup

End point title	Absolute change from baseline in LIC in Japanese subgroup
End point description:	
LIC, a predictor of iron burden, was measured using R2-MRI technique. Relaxation rate was determined as $R2 = 1/T2$. The baseline value of LIC was < 7 , ≥ 7 to < 15 , and ≥ 15 mg Fe/g dw. A negative change from baseline favoured study treatment in reducing LIC. The analysis was performed in PP1 set in Japanese subgroup defined as all subjects who were enrolled in Japan for core study (Year 1) and PP2 set in Japanese subgroup for extension study (Year 2). Here, 'n' signifies the subjects assessed for LIC in Japanese subgroup for each group, respectively.	
End point type	Secondary

End point timeframe:

Baseline, End of Year 1 (End of core study), End of Year 2 (End of extension study)

End point values	Japanese subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: mg Fe/g dw				
arithmetic mean (standard deviation)				
Year 1 (n= 31)	-13.9 (± 10.21)			
Year 2 (n= 26)	-18.4 (± 12.48)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from baseline in serum ferritin levels to Year 2

End point title	Absolute change from baseline in serum ferritin levels to Year 2
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End point description:

Serum ferritin was a marker for the monitoring of chelation therapy. Ferritin protein stores iron and provides overall iron levels, higher ferritin in blood showed more iron content. The analysis was performed in PP2 Set population and Japanese subgroup. Here, "Number of subjects analysed" signifies the subjects assessed for serum ferritin during the study for each arm, respectively.

End point type	Secondary
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End point timeframe:

Baseline up to Year 2 (End of extension study)

End point values	All randomised subjects	Japanese subjects		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98	51		
Units: nanogram(s)/millilitre				
arithmetic mean (standard deviation)	-677.9 (± 4462.11)	-892.8 (± 5724.89)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute serum ferritin levels over 2 years

End point title	Absolute serum ferritin levels over 2 years
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End point description:

Serum ferritin was a marker for the monitoring of chelation therapy. Ferritin protein stores iron and provides overall iron levels, higher ferritin in blood showed more iron content. The analysis was performed in PP1 set population for core study (Year 1) and PP2 set population for extension study (Year 2) and Japanese subgroup. Here, "Number of subjects analysed" signifies the subjects assessed for serum ferritin during the study for each arm, respectively.

End point type	Secondary
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End point timeframe:

Baseline, Year 1 (End of core study), Year 2 (End of extension study)

End point values	All randomised subjects	Japanese subjects		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	31		
Units: nanogram(s)/millilitre				
arithmetic mean (standard deviation)				
Year 1	2653.3 (\pm 5281.3)	2903.5 (\pm 3376)		
Year 2	2092.4 (\pm 2287.11)	2114.8 (\pm 2391.31)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total body iron elimination rate (TBIE), Iron intake, Iron excretion/iron intake and chelation efficiency after 2 years

End point title	Total body iron elimination rate (TBIE), Iron intake, Iron excretion/iron intake and chelation efficiency after 2 years
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End point description:

Total body iron excretion (TBIE) was used to investigate the chelation efficacy of deferasirox therapy. TBIE rate was estimated based on the iron influx as determined by the amount of red cells transfused and the change in total body iron (TBI) stores. The analysis was performed in PP2 set population and Japanese subgroup. Here, "Number of subjects analysed" signifies the subjects assessed for TBIE in the study arm. Total body iron elimination rate (TBIE), Iron intake, Iron excretion/iron intake and chelation efficiency

End point type	Secondary
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End point timeframe:

Baseline, Year 2 (End of extension study)

End point values	Deferasirox (Extension study)	Japanese subjects		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	41	26		
Units: ratio				
arithmetic mean (standard deviation)				
TBIE	0.46 (\pm 0.252)	0.54 (\pm 0.215)		

Iron intake	0.27 (\pm 0.15)	0.27 (\pm 0.16)		
Iron excretion/iron intake	2 (\pm 1.368)	2.44 (\pm 1.417)		
Chelation efficiency	0.4 (\pm 0.221)	0.5 (\pm 0.177)		

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation of LIC and serum ferritin at core and extension study

End point title	Correlation of LIC and serum ferritin at core and extension study
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End point description:

LIC, a predictor of iron burden, was measured using R2-MRI technique. Relaxation rate was determined as $R2 = 1/T2$. The baseline value of LIC was < 7 , ≥ 7 to < 15 , and ≥ 15 mg Fe/g dw. Serum ferritin was a marker for the monitoring of chelation therapy. Ferritin protein stores iron and provides overall iron levels, higher ferritin in blood showed more iron content. The correlation between absolute change in LIC and absolute change in serum ferritin was determined. The analysis was performed in PP1 set for core study (Year 1) and PP2 set for extension study (Year 2). Here, "Number of subjects analysed" signifies the subjects assessed for LIC and serum ferritin during the study for each arm, respectively.

End point type	Secondary
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End point timeframe:

Baseline, Year 1 (End of core study), Year 2 (End of extension study)

End point values	Deferasirox (Core Study)	Deferasirox (Extension study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	40		
Units: Correlation coefficient				
number (not applicable)	0.291	0.325		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with adverse events (AEs), serious adverse events (SAEs), adverse event of special interest (AESI), discontinuation and interruption

End point title	Number of subjects with adverse events (AEs), serious adverse events (SAEs), adverse event of special interest (AESI), discontinuation and interruption
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End point description:

Adverse events (AEs) were defined as any unfavourable 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 (SAEs) were defined as any untoward medical occurrences that result in death, are life threatening, require hospitalisation, cause persistent or significant disability/incapacity, result in congenital anomalies or birth defects, or are other conditions which in judgement of investigators represent significant hazards. Death was defined as a fatal event leading to permanent cessation of all vital functions of the body. The analysis was performed in the safety set (SAF) population, defined as subjects who received

at least one dose of study drug, which was defined as at least one administration record with a valid date and an actual total daily dose administrated above zero, and Japanese sub-group.

End point type	Secondary
End point timeframe:	
Baseline up to Year 2 (End of extension study)	

End point values	All randomised subjects	Japanese subjects		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	102	53		
Units: Subjects				
AEs	97	53		
SAEs	46	25		
Death	5	4		
Mild AEs	17	5		
Moderate AEs	39	25		
Severe AEs	41	23		
AEs suspected to study drug	65	43		
SAEs suspected to study drug	10	6		
AEs leading to discontinuation of study drug	14	7		
AEs leading to dose adjustment/interruption	67	42		
AESI	62	39		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with clinically significant ophthalmological abnormalities

End point title	Number of subjects with clinically significant ophthalmological abnormalities
End point description:	
Clinically significant changes in left eye and right eye were assessed by the investigator based on methods like visual acuity, slit lamp examination, tonometry and fundus oculi. The analysis was performed in the SAF population and Japanese subgroup. These patients comprise 2 year completer groups	
End point type	Secondary
End point timeframe:	
2 years (End of extension study)	

End point values	All randomised subjects	Japanese subjects		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50 ^[2]	28 ^[3]		
Units: Subjects				
Normal	25	12		
Abnormal Clin Insignificant	15	12		
Abnormal Clin Significant	10	4		
Not Available	0	0		
Total	50	28		

Notes:

[2] - number of patients at end of trial- completer group

[3] - Number of japanese patients at end of trial with ocular measurements- 2 year completers

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.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.1
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Reporting groups

Reporting group title	myelodysplastic syndrome
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Reporting group description:

myelodysplastic syndrome

Reporting group title	Other
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Reporting group description:

very rare diseases (e.g. Diamond Blackfan anemia, myelofibrosis, specific enzyme deficiency).

Reporting group title	aplastic anemia
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Reporting group description:

aplastic anemia,

Serious adverse events	myelodysplastic syndrome	Other	aplastic anemia
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 42 (52.38%)	10 / 31 (32.26%)	14 / 29 (48.28%)
number of deaths (all causes)	1	1	3
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ABDOMINAL NEOPLASM			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ACUTE MYELOID LEUKAEMIA			
subjects affected / exposed	0 / 42 (0.00%)	1 / 31 (3.23%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BLADDER NEOPLASM			

subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYELODYSPLASTIC SYNDROME			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYELOFIBROSIS			
subjects affected / exposed	0 / 42 (0.00%)	1 / 31 (3.23%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RECTAL CANCER			
subjects affected / exposed	0 / 42 (0.00%)	0 / 31 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
CHEST DISCOMFORT			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DISUSE SYNDROME			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FATIGUE			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (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 PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
GENERALISED OEDEMA			

subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (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
MALAISE			
subjects affected / exposed	0 / 42 (0.00%)	1 / 31 (3.23%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MULTI-ORGAN FAILURE			
subjects affected / exposed	2 / 42 (4.76%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYREXIA			
subjects affected / exposed	6 / 42 (14.29%)	1 / 31 (3.23%)	2 / 29 (6.90%)
occurrences causally related to treatment / all	3 / 8	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
HYPERSENSITIVITY			
subjects affected / exposed	0 / 42 (0.00%)	0 / 31 (0.00%)	2 / 29 (6.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
ADENOIDAL HYPERTROPHY			
subjects affected / exposed	0 / 42 (0.00%)	1 / 31 (3.23%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOXIA			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
NEUROSIS			
subjects affected / exposed	0 / 42 (0.00%)	1 / 31 (3.23%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Investigations			
BODY HEIGHT BELOW NORMAL			
subjects affected / exposed	0 / 42 (0.00%)	1 / 31 (3.23%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed	0 / 42 (0.00%)	0 / 31 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
CONTUSION			
subjects affected / exposed	0 / 42 (0.00%)	0 / 31 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUMBAR VERTEBRAL FRACTURE			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TOOTH FRACTURE			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRAUMATIC HAEMORRHAGE			
subjects affected / exposed	0 / 42 (0.00%)	0 / 31 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
TRAUMATIC INTRACRANIAL HAEMORRHAGE			
subjects affected / exposed	0 / 42 (0.00%)	0 / 31 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ATRIAL FIBRILLATION			

subjects affected / exposed	2 / 42 (4.76%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIAL FLUTTER			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC FAILURE			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERICARDITIS			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
CEREBELLAR HAEMORRHAGE			
subjects affected / exposed	0 / 42 (0.00%)	0 / 31 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
CEREBRAL HAEMORRHAGE			
subjects affected / exposed	0 / 42 (0.00%)	0 / 31 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBRAL INFARCTION			
subjects affected / exposed	0 / 42 (0.00%)	0 / 31 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIZZINESS			

subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (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
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 42 (2.38%)	1 / 31 (3.23%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
APLASTIC ANAEMIA			
subjects affected / exposed	0 / 42 (0.00%)	0 / 31 (0.00%)	3 / 29 (10.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DISSEMINATED INTRAVASCULAR COAGULATION			
subjects affected / exposed	2 / 42 (4.76%)	0 / 31 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
FEBRILE NEUTROPENIA			
subjects affected / exposed	0 / 42 (0.00%)	1 / 31 (3.23%)	2 / 29 (6.90%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
CATARACT			
subjects affected / exposed	0 / 42 (0.00%)	1 / 31 (3.23%)	0 / 29 (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
RETINAL HAEMORRHAGE			
subjects affected / exposed	0 / 42 (0.00%)	1 / 31 (3.23%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ASCITES			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

DIARRHOEA			
subjects affected / exposed	0 / 42 (0.00%)	1 / 31 (3.23%)	0 / 29 (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
ENTEROCOLITIS			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 42 (0.00%)	0 / 31 (0.00%)	2 / 29 (6.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL ULCER			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIODONTAL DISEASE			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIODONTITIS			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RADICULAR CYST			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			
subjects affected / exposed	0 / 42 (0.00%)	1 / 31 (3.23%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

CHOLECYSTITIS			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATIC FUNCTION ABNORMAL			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (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
Skin and subcutaneous tissue disorders			
HAEMORRHAGE SUBCUTANEOUS			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (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
PANNICULITIS			
subjects affected / exposed	0 / 42 (0.00%)	1 / 31 (3.23%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RASH ERYTHEMATOUS			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (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
SKIN ULCER			
subjects affected / exposed	0 / 42 (0.00%)	1 / 31 (3.23%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URTICARIA			
subjects affected / exposed	2 / 42 (4.76%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
FANCONI SYNDROME ACQUIRED			
subjects affected / exposed	0 / 42 (0.00%)	1 / 31 (3.23%)	0 / 29 (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

NEPHROLITHIASIS			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
DELAYED PUBERTY			
subjects affected / exposed	0 / 42 (0.00%)	1 / 31 (3.23%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
BONE PAIN			
subjects affected / exposed	0 / 42 (0.00%)	1 / 31 (3.23%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BONE SWELLING			
subjects affected / exposed	0 / 42 (0.00%)	1 / 31 (3.23%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	0 / 42 (0.00%)	1 / 31 (3.23%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
BACTERIAL INFECTION			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHITIS			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHOPNEUMONIA			

subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	1 / 29 (3.45%)
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	0 / 42 (0.00%)	1 / 31 (3.23%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENTEROCOLITIS INFECTIOUS			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FUNGAEMIA			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FUNGAL OESOPHAGITIS			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTRITIS VIRAL			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROENTERITIS			
subjects affected / exposed	0 / 42 (0.00%)	1 / 31 (3.23%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HERPES ZOSTER			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFECTION			

subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFLUENZA			
subjects affected / exposed	0 / 42 (0.00%)	0 / 31 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MENINGITIS			
subjects affected / exposed	0 / 42 (0.00%)	0 / 31 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ORAL HERPES			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PARONYCHIA			
subjects affected / exposed	0 / 42 (0.00%)	0 / 31 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERTUSSIS			
subjects affected / exposed	0 / 42 (0.00%)	1 / 31 (3.23%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PHARYNGITIS			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	4 / 42 (9.52%)	0 / 31 (0.00%)	3 / 29 (10.34%)
occurrences causally related to treatment / all	1 / 6	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPSIS			

subjects affected / exposed	2 / 42 (4.76%)	0 / 31 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPTIC SHOCK			
subjects affected / exposed	2 / 42 (4.76%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			
subjects affected / exposed	3 / 42 (7.14%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIRAL INFECTION			
subjects affected / exposed	0 / 42 (0.00%)	1 / 31 (3.23%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ZYGOMYCOSIS			
subjects affected / exposed	0 / 42 (0.00%)	1 / 31 (3.23%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERCALCAEMIA			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERGLYCAEMIA			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOGLYCAEMIA			

subjects affected / exposed	2 / 42 (4.76%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPONATRAEMIA			
subjects affected / exposed	0 / 42 (0.00%)	1 / 31 (3.23%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
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	myelodysplastic syndrome	Other	aplastic anemia
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 42 (92.86%)	25 / 31 (80.65%)	25 / 29 (86.21%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
MYELODYSPLASTIC SYNDROME			
subjects affected / exposed	4 / 42 (9.52%)	0 / 31 (0.00%)	1 / 29 (3.45%)
occurrences (all)	4	0	1
Vascular disorders			
HYPOTENSION			
subjects affected / exposed	2 / 42 (4.76%)	0 / 31 (0.00%)	2 / 29 (6.90%)
occurrences (all)	3	0	3
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	2 / 42 (4.76%)	1 / 31 (3.23%)	2 / 29 (6.90%)
occurrences (all)	3	1	2
CHEST PAIN			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	3 / 29 (10.34%)
occurrences (all)	1	0	4
FACE OEDEMA			
subjects affected / exposed	2 / 42 (4.76%)	0 / 31 (0.00%)	2 / 29 (6.90%)
occurrences (all)	2	0	3
FATIGUE			
subjects affected / exposed	2 / 42 (4.76%)	3 / 31 (9.68%)	1 / 29 (3.45%)
occurrences (all)	3	3	1
MALAISE			

subjects affected / exposed	2 / 42 (4.76%)	2 / 31 (6.45%)	4 / 29 (13.79%)
occurrences (all)	2	2	6
OEDEMA PERIPHERAL			
subjects affected / exposed	14 / 42 (33.33%)	1 / 31 (3.23%)	7 / 29 (24.14%)
occurrences (all)	19	2	15
PYREXIA			
subjects affected / exposed	11 / 42 (26.19%)	6 / 31 (19.35%)	9 / 29 (31.03%)
occurrences (all)	22	11	16
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	2 / 42 (4.76%)	5 / 31 (16.13%)	2 / 29 (6.90%)
occurrences (all)	2	5	3
DYSPNOEA			
subjects affected / exposed	3 / 42 (7.14%)	1 / 31 (3.23%)	1 / 29 (3.45%)
occurrences (all)	3	2	1
EPISTAXIS			
subjects affected / exposed	1 / 42 (2.38%)	2 / 31 (6.45%)	2 / 29 (6.90%)
occurrences (all)	1	2	2
NASAL CONGESTION			
subjects affected / exposed	0 / 42 (0.00%)	2 / 31 (6.45%)	0 / 29 (0.00%)
occurrences (all)	0	3	0
OROPHARYNGEAL PAIN			
subjects affected / exposed	1 / 42 (2.38%)	1 / 31 (3.23%)	3 / 29 (10.34%)
occurrences (all)	1	1	3
PRODUCTIVE COUGH			
subjects affected / exposed	0 / 42 (0.00%)	0 / 31 (0.00%)	2 / 29 (6.90%)
occurrences (all)	0	0	2
RHINITIS ALLERGIC			
subjects affected / exposed	0 / 42 (0.00%)	2 / 31 (6.45%)	1 / 29 (3.45%)
occurrences (all)	0	3	1
Psychiatric disorders			
DELIRIUM			
subjects affected / exposed	3 / 42 (7.14%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences (all)	3	0	0
INSOMNIA			

subjects affected / exposed occurrences (all)	6 / 42 (14.29%) 8	1 / 31 (3.23%) 1	1 / 29 (3.45%) 1
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	3 / 42 (7.14%)	3 / 31 (9.68%)	1 / 29 (3.45%)
occurrences (all)	4	3	4
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 42 (2.38%)	1 / 31 (3.23%)	2 / 29 (6.90%)
occurrences (all)	2	1	3
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	1 / 42 (2.38%)	2 / 31 (6.45%)	3 / 29 (10.34%)
occurrences (all)	1	2	4
BLOOD CREATININE INCREASED			
subjects affected / exposed	16 / 42 (38.10%)	2 / 31 (6.45%)	8 / 29 (27.59%)
occurrences (all)	29	4	19
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed	4 / 42 (9.52%)	0 / 31 (0.00%)	5 / 29 (17.24%)
occurrences (all)	7	0	9
PROTEIN URINE PRESENT			
subjects affected / exposed	3 / 42 (7.14%)	5 / 31 (16.13%)	1 / 29 (3.45%)
occurrences (all)	3	10	1
WEIGHT DECREASED			
subjects affected / exposed	2 / 42 (4.76%)	2 / 31 (6.45%)	2 / 29 (6.90%)
occurrences (all)	2	2	2
Injury, poisoning and procedural complications			
ALLERGIC TRANSFUSION REACTION			
subjects affected / exposed	3 / 42 (7.14%)	1 / 31 (3.23%)	1 / 29 (3.45%)
occurrences (all)	4	1	1
CONTUSION			
subjects affected / exposed	6 / 42 (14.29%)	0 / 31 (0.00%)	3 / 29 (10.34%)
occurrences (all)	6	0	5
FALL			
subjects affected / exposed	2 / 42 (4.76%)	0 / 31 (0.00%)	3 / 29 (10.34%)
occurrences (all)	2	0	3

SPINAL COMPRESSION FRACTURE subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 2	0 / 31 (0.00%) 0	2 / 29 (6.90%) 2
TOOTH INJURY subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	0 / 31 (0.00%) 0	2 / 29 (6.90%) 2
TRANSFUSION REACTION subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 5	1 / 31 (3.23%) 1	2 / 29 (6.90%) 3
Cardiac disorders ATRIAL FIBRILLATION subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 4	0 / 31 (0.00%) 0	2 / 29 (6.90%) 2
CARDIAC FAILURE subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 4	1 / 31 (3.23%) 1	2 / 29 (6.90%) 2
TACHYCARDIA subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	1 / 31 (3.23%) 1	2 / 29 (6.90%) 3
Nervous system disorders DYSGEUSIA subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1	0 / 31 (0.00%) 0	2 / 29 (6.90%) 2
HEADACHE subjects affected / exposed occurrences (all)	8 / 42 (19.05%) 9	3 / 31 (9.68%) 5	4 / 29 (13.79%) 5
SOMNOLENCE subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1	1 / 31 (3.23%) 1	2 / 29 (6.90%) 2
Blood and lymphatic system disorders ANAEMIA subjects affected / exposed occurrences (all)	5 / 42 (11.90%) 5	1 / 31 (3.23%) 1	1 / 29 (3.45%) 1
APLASTIC ANAEMIA subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	0 / 31 (0.00%) 0	2 / 29 (6.90%) 2
FEBRILE NEUTROPENIA			

subjects affected / exposed	0 / 42 (0.00%)	1 / 31 (3.23%)	2 / 29 (6.90%)
occurrences (all)	0	1	2
THROMBOCYTOPENIA			
subjects affected / exposed	3 / 42 (7.14%)	0 / 31 (0.00%)	2 / 29 (6.90%)
occurrences (all)	4	0	2
Eye disorders			
CATARACT			
subjects affected / exposed	4 / 42 (9.52%)	0 / 31 (0.00%)	2 / 29 (6.90%)
occurrences (all)	4	0	2
CONJUNCTIVAL HAEMORRHAGE			
subjects affected / exposed	3 / 42 (7.14%)	0 / 31 (0.00%)	1 / 29 (3.45%)
occurrences (all)	4	0	1
EYE PAIN			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	2 / 29 (6.90%)
occurrences (all)	1	0	3
RETINAL HAEMORRHAGE			
subjects affected / exposed	2 / 42 (4.76%)	3 / 31 (9.68%)	3 / 29 (10.34%)
occurrences (all)	2	3	5
Gastrointestinal disorders			
ABDOMINAL DISCOMFORT			
subjects affected / exposed	0 / 42 (0.00%)	1 / 31 (3.23%)	3 / 29 (10.34%)
occurrences (all)	0	3	6
ABDOMINAL DISTENSION			
subjects affected / exposed	3 / 42 (7.14%)	0 / 31 (0.00%)	1 / 29 (3.45%)
occurrences (all)	3	0	1
ABDOMINAL PAIN			
subjects affected / exposed	7 / 42 (16.67%)	2 / 31 (6.45%)	4 / 29 (13.79%)
occurrences (all)	8	2	4
ABDOMINAL PAIN UPPER			
subjects affected / exposed	2 / 42 (4.76%)	1 / 31 (3.23%)	3 / 29 (10.34%)
occurrences (all)	4	1	3
APHTHOUS STOMATITIS			
subjects affected / exposed	1 / 42 (2.38%)	1 / 31 (3.23%)	2 / 29 (6.90%)
occurrences (all)	1	2	2
CONSTIPATION			

subjects affected / exposed	13 / 42 (30.95%)	3 / 31 (9.68%)	5 / 29 (17.24%)
occurrences (all)	15	3	6
DENTAL CARIES			
subjects affected / exposed	3 / 42 (7.14%)	0 / 31 (0.00%)	2 / 29 (6.90%)
occurrences (all)	3	0	2
DIARRHOEA			
subjects affected / exposed	10 / 42 (23.81%)	5 / 31 (16.13%)	7 / 29 (24.14%)
occurrences (all)	13	7	8
GASTRITIS			
subjects affected / exposed	1 / 42 (2.38%)	0 / 31 (0.00%)	2 / 29 (6.90%)
occurrences (all)	1	0	2
HAEMORRHOIDS			
subjects affected / exposed	3 / 42 (7.14%)	0 / 31 (0.00%)	3 / 29 (10.34%)
occurrences (all)	3	0	3
NAUSEA			
subjects affected / exposed	9 / 42 (21.43%)	2 / 31 (6.45%)	6 / 29 (20.69%)
occurrences (all)	10	2	7
STOMATITIS			
subjects affected / exposed	8 / 42 (19.05%)	0 / 31 (0.00%)	7 / 29 (24.14%)
occurrences (all)	8	0	10
VOMITING			
subjects affected / exposed	3 / 42 (7.14%)	0 / 31 (0.00%)	4 / 29 (13.79%)
occurrences (all)	5	0	4
Hepatobiliary disorders			
HEPATIC FUNCTION ABNORMAL			
subjects affected / exposed	2 / 42 (4.76%)	0 / 31 (0.00%)	2 / 29 (6.90%)
occurrences (all)	3	0	2
Skin and subcutaneous tissue disorders			
DERMATITIS ALLERGIC			
subjects affected / exposed	0 / 42 (0.00%)	2 / 31 (6.45%)	0 / 29 (0.00%)
occurrences (all)	0	3	0
DRY SKIN			
subjects affected / exposed	1 / 42 (2.38%)	4 / 31 (12.90%)	3 / 29 (10.34%)
occurrences (all)	1	4	3
MADAROSIS			

subjects affected / exposed	0 / 42 (0.00%)	2 / 31 (6.45%)	0 / 29 (0.00%)
occurrences (all)	0	3	0
PETECHIAE			
subjects affected / exposed	3 / 42 (7.14%)	1 / 31 (3.23%)	0 / 29 (0.00%)
occurrences (all)	4	1	0
PRURITUS			
subjects affected / exposed	2 / 42 (4.76%)	1 / 31 (3.23%)	4 / 29 (13.79%)
occurrences (all)	2	2	4
RASH			
subjects affected / exposed	11 / 42 (26.19%)	1 / 31 (3.23%)	3 / 29 (10.34%)
occurrences (all)	17	1	3
SKIN ULCER			
subjects affected / exposed	2 / 42 (4.76%)	2 / 31 (6.45%)	0 / 29 (0.00%)
occurrences (all)	2	3	0
Renal and urinary disorders			
PROTEINURIA			
subjects affected / exposed	4 / 42 (9.52%)	1 / 31 (3.23%)	1 / 29 (3.45%)
occurrences (all)	4	1	1
RENAL FAILURE			
subjects affected / exposed	4 / 42 (9.52%)	2 / 31 (6.45%)	3 / 29 (10.34%)
occurrences (all)	6	2	7
RENAL IMPAIRMENT			
subjects affected / exposed	4 / 42 (9.52%)	2 / 31 (6.45%)	6 / 29 (20.69%)
occurrences (all)	7	4	7
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	3 / 42 (7.14%)	0 / 31 (0.00%)	1 / 29 (3.45%)
occurrences (all)	3	0	1
BACK PAIN			
subjects affected / exposed	7 / 42 (16.67%)	1 / 31 (3.23%)	2 / 29 (6.90%)
occurrences (all)	7	1	3
MUSCLE SPASMS			
subjects affected / exposed	3 / 42 (7.14%)	1 / 31 (3.23%)	3 / 29 (10.34%)
occurrences (all)	3	1	3
MUSCULOSKELETAL PAIN			

subjects affected / exposed	3 / 42 (7.14%)	3 / 31 (9.68%)	1 / 29 (3.45%)
occurrences (all)	3	3	1
MYALGIA			
subjects affected / exposed	2 / 42 (4.76%)	2 / 31 (6.45%)	1 / 29 (3.45%)
occurrences (all)	4	2	1
PAIN IN EXTREMITY			
subjects affected / exposed	5 / 42 (11.90%)	3 / 31 (9.68%)	2 / 29 (6.90%)
occurrences (all)	5	4	2
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	2 / 42 (4.76%)	4 / 31 (12.90%)	0 / 29 (0.00%)
occurrences (all)	2	6	0
CYSTITIS			
subjects affected / exposed	5 / 42 (11.90%)	0 / 31 (0.00%)	3 / 29 (10.34%)
occurrences (all)	9	0	4
EAR INFECTION			
subjects affected / exposed	0 / 42 (0.00%)	2 / 31 (6.45%)	0 / 29 (0.00%)
occurrences (all)	0	2	0
FURUNCLE			
subjects affected / exposed	0 / 42 (0.00%)	0 / 31 (0.00%)	2 / 29 (6.90%)
occurrences (all)	0	0	3
HERPES SIMPLEX			
subjects affected / exposed	3 / 42 (7.14%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences (all)	3	0	0
HERPES ZOSTER			
subjects affected / exposed	4 / 42 (9.52%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences (all)	4	0	0
INFLUENZA			
subjects affected / exposed	1 / 42 (2.38%)	2 / 31 (6.45%)	3 / 29 (10.34%)
occurrences (all)	1	2	3
NASOPHARYNGITIS			
subjects affected / exposed	14 / 42 (33.33%)	6 / 31 (19.35%)	10 / 29 (34.48%)
occurrences (all)	36	18	21
ORAL CANDIDIASIS			
subjects affected / exposed	3 / 42 (7.14%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences (all)	3	0	0

OTITIS MEDIA			
subjects affected / exposed	0 / 42 (0.00%)	1 / 31 (3.23%)	2 / 29 (6.90%)
occurrences (all)	0	3	2
OTITIS MEDIA CHRONIC			
subjects affected / exposed	0 / 42 (0.00%)	0 / 31 (0.00%)	2 / 29 (6.90%)
occurrences (all)	0	0	2
PHARYNGITIS			
subjects affected / exposed	3 / 42 (7.14%)	2 / 31 (6.45%)	1 / 29 (3.45%)
occurrences (all)	3	5	1
TONSILLITIS			
subjects affected / exposed	2 / 42 (4.76%)	3 / 31 (9.68%)	0 / 29 (0.00%)
occurrences (all)	2	9	0
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 42 (2.38%)	9 / 31 (29.03%)	2 / 29 (6.90%)
occurrences (all)	3	29	3
URINARY TRACT INFECTION			
subjects affected / exposed	3 / 42 (7.14%)	3 / 31 (9.68%)	0 / 29 (0.00%)
occurrences (all)	6	5	0
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	7 / 42 (16.67%)	1 / 31 (3.23%)	4 / 29 (13.79%)
occurrences (all)	9	1	7
DEHYDRATION			
subjects affected / exposed	5 / 42 (11.90%)	0 / 31 (0.00%)	3 / 29 (10.34%)
occurrences (all)	6	0	4
DIABETES MELLITUS			
subjects affected / exposed	4 / 42 (9.52%)	1 / 31 (3.23%)	2 / 29 (6.90%)
occurrences (all)	4	1	2
HYPOGLYCAEMIA			
subjects affected / exposed	4 / 42 (9.52%)	1 / 31 (3.23%)	4 / 29 (13.79%)
occurrences (all)	6	1	5
HYPOKALAEMIA			
subjects affected / exposed	3 / 42 (7.14%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences (all)	4	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 October 2006	<ul style="list-style-type: none"> Added a recommendation to refer patients whose serum creatinine remained elevated despite dose reduction and interruption, and in whom there was also a persistent abnormality of another marker of renal function (e.g. proteinuria, Fanconi's syndrome), to a renal specialist for further specialized investigations Updated the language for a potential dose adjustment, which was updated as a standard for all Exjade clinical protocols Amended the exclusion criterion for patients with a baseline serum creatinine level that was above the ULN Removed the language regarding the availability of commercial Exjade that triggered a withdrawal of the patient from the study Changed the collection of data with an eCRF to collection on a paper CRF.
02 May 2007	<ul style="list-style-type: none"> Modified the study design and scope to investigate the safety and efficacy of deferasirox in patients with transfusion-dependent anemias other than β-thalassemia or sickle cell disease, especially in Japanese patients; this included the removal of the baseline LIC classification (i.e. < 7 mg Fe/g dw vs. ≥ 7 mg Fe/g dw) Revised the primary endpoint: absolute change in LIC from baseline to end of Year 1 Revised the endpoint, change in serum ferritin from baseline to end of study, to a secondary efficacy assessment Excluded patients with either β-thalassemia or sickle cell disease Increased the serum ferritin inclusion criterion to more than 1000 ng/mL Reduced the sample size estimate to 114 enrolled patients, which included 50 Japanese patients enrolled in Japan, using nQuery Advisor Version 5.0 Extended the ophthalmologic assessments for an additional year (i.e. Year 2) in at least 60 patients Updated the informed consent form
29 August 2007	<ul style="list-style-type: none"> Revised the protocol to include reference to the yearly audiometric tests: this was part of the revised informed consent form issued with Amendment 2 Modified the collection of ECG assessments at baseline only and can be repeated in the event of a cardiac adverse event Clarified the assessments for the routine urinalysis and microscopic analysis only in case of a positive dipstick
29 April 2008	<ul style="list-style-type: none"> Revised the protocol introduction to include new safety information on deferasirox that has emerged since the original protocol was issued Increased clarity on the definition of the Per-protocol population Modified the criteria for the analyses on serum ferritin changes during the study Introduced greater protocol adherence by avoidance of protocol deviations Updated the informed consent form
05 August 2008	<ul style="list-style-type: none"> Extended the duration of the study to include Year 2 to collect long-term data for safety and efficacy Continued assessments for hematology, biochemistry, and urinalysis on a monthly basis Repeated physical examination every 6 months Performed measurements of LIC, audiometry, and prothrombin time after one year of treatment again Assessed growth velocity and sexual development in pediatric patients Clarified when Year 2 started in relation to the end of Year 1 dosing Defined that baseline values during the core phase were used as a reference for a potential dose adjustment

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported