



Clinical trial results:

A randomized, double-blind, placebo-controlled, phase II study to evaluate efficacy and safety of deferasirox in nontransfusion-dependent thalassemia patients with iron overload (THALASSA)

A one-year open-label extension to a randomized, double-blind, placebo-controlled, phase II study to evaluate efficacy and safety of deferasirox in non-transfusion-dependent thalassemia patients with iron overload (THALASSA)

Summary

EudraCT number	2007-007000-15
Trial protocol	GB IT GR
Global end of trial date	13 June 2012

Results information

Result version number	v1 (current)
This version publication date	29 July 2016
First version publication date	29 July 2016

Trial information

Trial identification

Sponsor protocol code	CICL670A2209/E1
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00873041
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)	Yes
EMA paediatric investigation plan number(s)	EMA-001103-PIP01-10
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	13 June 2012
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	13 June 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of two regimens of deferasirox administration (starting doses of 5 and 10 mg/kg/day) in patients with NTDT based on change in LIC from baseline after one year of treatment compared to placebo-treated patients and A one-year open-label extension to a randomized, double-blind, placebo-controlled, phase II study to evaluate efficacy and safety of deferasirox in non-transfusion-dependent thalassemia patients with iron overload (THALASSA)

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	24 November 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 4
Country: Number of subjects enrolled	Turkey: 16
Country: Number of subjects enrolled	Malaysia: 10
Country: Number of subjects enrolled	Thailand: 55
Country: Number of subjects enrolled	Lebanon: 29
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Greece: 12
Country: Number of subjects enrolled	Italy: 31
Worldwide total number of subjects	166
EEA total number of subjects	51

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)	4
Adolescents (12-17 years)	17
Adults (18-64 years)	144
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 24 centres in 9 countries.

Pre-assignment

Screening details:

A total of 166 subjects were randomized and treated in the core period. Out of the 148 subjects who completed the core study, 133 subjects were enrolled to extension period.

Period 1

Period 1 title	Core period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Assessor

Blinding implementation details:

Randomization data were kept strictly confidential and the identity of treatments were concealed by the use of identical study drugs. Unblinding was allowed from randomization to database lock, except in case of subject emergencies and at the conclusion of the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Deferasirox 5 mg/kg/day (Core)

Arm description:

Subjects were administered with deferasirox at a starting dose of 5 mg/kg daily through oral route based on daily iron removal. The dose was up-titrated to 10 mg/kg if LIC assessment indicated insufficient iron chelation (LIC > 7 mg Fe/g dw and LIC reduction < 15% compared to baseline) at Week 24.

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

Dosage and administration details:

Deferasirox 5 mg/kg daily was administered orally as starting dose.

Arm title	Deferasirox 10 mg/kg/day (Core)
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Arm description:

Subjects were administered with deferasirox at a starting dose of 10 mg/kg daily through oral route based on daily iron removal. The dose was up-titrated to 20 mg/kg if LIC assessment indicated insufficient iron chelation (LIC > 7 mg Fe/g dw and LIC reduction < 15% compared to baseline) at Week 24.

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

Dosage and administration details:

Deferasirox 10 mg/kg daily was administered orally as starting dose.

Arm title	Placebo (Core)
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Arm description:

Placebo matched to deferasirox was administered in subjects daily through oral route.

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

Dosage and administration details:

Placebo matched to deferasirox was daily administered in subjects orally.

Number of subjects in period 1	Deferasirox 5 mg/kg/day (Core)	Deferasirox 10 mg/kg/day (Core)	Placebo (Core)
Started	55	55	56
Completed	48	49	51
Not completed	7	6	5
Consent withdrawn by subject	1	2	2
Adverse event, non-fatal	2	3	1
Abnormal laboratory value	-	-	1
Lost to follow-up	3	1	-
Protocol deviation	1	-	1

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Deferasirox any dose (Extension)

Arm description:

Subjects were administered with deferasirox at a starting dose of 5 mg/kg and 10 mg/kg daily through oral route based on daily iron removal. The dose was up-titrated to 10 mg/kg and 20 mg/kg if LIC assessment indicated insufficient iron chelation (LIC > 7 mg Fe/g dw and LIC reduction < 15% compared to baseline) at Week 24.

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

Dosage and administration details:

Deferasirox 5 mg/kg and 10 mg/kg daily was administered orally as starting dose. The dose was up-titrated to 10 mg/kg and 20 mg/kg if LIC assessment indicated insufficient iron chelation (LIC > 7 mg

Fe/g dw and LIC reduction < 15% compared to baseline) at Week 24.

Arm title	Placebo/Deferasirox any dose (Extension)
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Arm description:

Open label deferasirox was administered in subjects daily through oral route of patients formerly on placebo

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

Dosage and administration details:

Deferasirox 5 mg/kg daily was administered orally as starting dose.

Number of subjects in period 2^[1]	Deferasirox any dose (Extension)	Placebo/Deferasirox any dose (Extension)
Started	85	48
Completed	84	46
Not completed	1	2
Adverse event, non-fatal	1	1
Administrative reasons	-	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: The number of subjects reported in the baseline period are different from the worldwide number enrolled in the trial, as of 148 subjects who completed the preceding period, only 133 subjects opted to enroll in extension study.

Baseline characteristics

Reporting groups

Reporting group title	Deferasirox 5 mg/kg/day (Core)
Reporting group description:	
Subjects were administered with deferasirox at a starting dose of 5 mg/kg daily through oral route based on daily iron removal. The dose was up-titrated to 10 mg/kg if LIC assessment indicated insufficient iron chelation (LIC > 7 mg Fe/g dw and LIC reduction < 15% compared to baseline) at Week 24.	
Reporting group title	Deferasirox 10 mg/kg/day (Core)
Reporting group description:	
Subjects were administered with deferasirox at a starting dose of 10 mg/kg daily through oral route based on daily iron removal. The dose was up-titrated to 20 mg/kg if LIC assessment indicated insufficient iron chelation (LIC > 7 mg Fe/g dw and LIC reduction < 15% compared to baseline) at Week 24.	
Reporting group title	Placebo (Core)
Reporting group description:	
Placebo matched to deferasirox was administered in subjects daily through oral route.	

Reporting group values	Deferasirox 5 mg/kg/day (Core)	Deferasirox 10 mg/kg/day (Core)	Placebo (Core)
Number of subjects	55	55	56
Age categorical Units: Subjects			
2 years to < 18 years	6	7	8
18 years to <50 years	44	45	42
50 years to <65 years	5	2	6
>=65 years	0	1	0
Age continuous Units: years			
arithmetic mean	33.1	31.7	31.4
standard deviation	± 12.3	± 11.68	± 12.23
Gender categorical Units: Subjects			
Female	26	26	25
Male	29	29	31

Reporting group values	Total		
Number of subjects	166		
Age categorical Units: Subjects			
2 years to < 18 years	21		
18 years to <50 years	131		
50 years to <65 years	13		
>=65 years	1		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		

Gender categorical			
Units: Subjects			
Female	77		
Male	89		

End points

End points reporting groups

Reporting group title	Deferasirox 5 mg/kg/day (Core)
Reporting group description: Subjects were administered with deferasirox at a starting dose of 5 mg/kg daily through oral route based on daily iron removal. The dose was up-titrated to 10 mg/kg if LIC assessment indicated insufficient iron chelation (LIC > 7 mg Fe/g dw and LIC reduction < 15% compared to baseline) at Week 24.	
Reporting group title	Deferasirox 10 mg/kg/day (Core)
Reporting group description: Subjects were administered with deferasirox at a starting dose of 10 mg/kg daily through oral route based on daily iron removal. The dose was up-titrated to 20 mg/kg if LIC assessment indicated insufficient iron chelation (LIC > 7 mg Fe/g dw and LIC reduction < 15% compared to baseline) at Week 24.	
Reporting group title	Placebo (Core)
Reporting group description: Placebo matched to deferasirox was administered in subjects daily through oral route.	
Reporting group title	Deferasirox any dose (Extension)
Reporting group description: Subjects were administered with deferasirox at a starting dose of 5 mg/kg and 10 mg/kg daily through oral route based on daily iron removal. The dose was up-titrated to 10 mg/kg and 20 mg/kg if LIC assessment indicated insufficient iron chelation (LIC > 7 mg Fe/g dw and LIC reduction < 15% compared to baseline) at Week 24.	
Reporting group title	Placebo/Deferasirox any dose (Extension)
Reporting group description: Open label deferasirox was administered in subjects daily through oral route of patients formerly on placebo	
Subject analysis set title	All randomized subjects (Core study)
Subject analysis set type	Full analysis
Subject analysis set description: Subjects were administered with deferasirox at a starting dose of 5 mg/kg, 10 mg/kg and matching placebo daily through oral route based on daily iron removal. The dose was up-titrated to 10 mg/kg and 20 mg/kg if LIC assessment indicated insufficient iron chelation (LIC > 7 mg Fe/g dw and LIC reduction < 15% compared to baseline) at Week 24.	
Subject analysis set title	All deferasirox treated subjects (Extension study)
Subject analysis set type	Full analysis
Subject analysis set description: Subjects were administered with deferasirox at a starting dose of 5 mg/kg and 10 mg/kg daily through oral route based on daily iron removal. The dose was up-titrated to 10 mg/kg and 20 mg/kg if LIC assessment indicated insufficient iron chelation (LIC > 7 mg Fe/g dw and LIC reduction < 15% compared to baseline) at Week 24.	
Subject analysis set title	All randomized subjects (Extension study)
Subject analysis set type	Full analysis
Subject analysis set description: Subjects were administered with deferasirox at a starting dose of 5 mg/kg, 10 mg/kg and matching placebo daily through oral route based on daily iron removal. The dose was up-titrated to 10 mg/kg and 20 mg/kg if LIC assessment indicated insufficient iron chelation (LIC > 7 mg Fe/g dw and LIC reduction < 15% compared to baseline) at Week 24.	
Subject analysis set title	All placebo treated subjects (Extension study)
Subject analysis set type	Full analysis
Subject analysis set description: Subjects were administered with deferasirox matching placebo daily through oral route.	

Primary: Change in Liver Iron Concentration (LIC) from baseline to week 52

End point title	Change in Liver Iron Concentration (LIC) from baseline to week 52
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End point description:

Liver iron concentration (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 < 5 , $5-7$, ≥ 7 to < 15 , and ≥ 15 milligram of iron/tissue dry weight (mgFe/g dw). A negative change from baseline favoured study treatment in reducing LIC. The analysis was performed in the Full Analysis Set (FAS) population, defined as all randomized subjects. The last available post-baseline LIC was carried forward if no LIC value was available at Week 52. Here, "Number of subjects analysed" signifies the subjects assessed for LIC during the core period for each arm, respectively. Only subjects with both baseline and at least one post baseline value were included for the analysis.

End point type	Primary
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End point timeframe:

Baseline to Week 52 (Month 12: End of core study period)

End point values	Deferasirox 5 mg/kg/day (Core)	Deferasirox 10 mg/kg/day (Core)	Placebo (Core)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51	54	54	
Units: mg Fe/g dw				
least squares mean (standard error)	-1.95 (\pm 0.5)	-3.8 (\pm 0.484)	0.38 (\pm 0.486)	

Statistical analyses

Statistical analysis title	Change in LIC deferiasirox 5 mg/kg v/s 10 mg/kg
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Statistical analysis description:

Estimates were obtained from an Analysis of Covariance (ANCOVA) model for change in LIC with treatment as factor and baseline LIC as covariate. Two-sided p-value testing the hypothesis that the change in LIC is identical in the two deferiasirox groups.

Comparison groups	Deferasirox 10 mg/kg/day (Core) v Deferasirox 5 mg/kg/day (Core)
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.009
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	-1.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.22
upper limit	-0.48
Variability estimate	Standard error of the mean
Dispersion value	0.695

Statistical analysis title	Difference of deferasirox 5 mg/kg v/s Placebo
Comparison groups	Deferasirox 5 mg/kg/day (Core) v Placebo (Core)
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	-2.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.89
upper limit	-0.76
Variability estimate	Standard error of the mean
Dispersion value	0.7

Statistical analysis title	Difference of deferasirox 10 mg/kg v/s Placebo
Comparison groups	Placebo (Core) v Deferasirox 10 mg/kg/day (Core)
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	-4.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.71
upper limit	-2.64
Variability estimate	Standard error of the mean
Dispersion value	0.687

Primary: LIC responses by the end of the extension phase

End point title	LIC responses by the end of the extension phase ^[1]
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 < 5, 5-7, ≥ 7 to < 15, and ≥ 15 mg Fe/g dw. The subjects with LIC < 5 mg Fe/g dw change from baseline to end of the extension period were reported. Subjects with post-baseline LIC satisfying criteria were considered as responder. The analysis was performed in the FAS population.
End point type	Primary

End point timeframe:

Baseline (Core study) to End of Extension study (24 months)

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 descriptive summary statistics was planned for this outcome measure.

End point values	All placebo treated subjects (Extension study)	All deferasirox treated subjects (Extension study)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	110		
Units: Percentage of subjects				
number (confidence interval 95%)	37.5 (26 to 56)	39.1 (30.5 to 48.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Liver Iron Concentration (LIC) from baseline to Week 24

End point title	Change in Liver Iron Concentration (LIC) from baseline to Week 24
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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 of subjects was categorized as < 5 , $5-7$, ≥ 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 the FAS population. Here, "Number of subjects analysed" signifies the subjects assessed for LIC during the core and extension period for each arm, respectively. The last available post-baseline LIC was carried forward if no LIC value was available at Week 24 and Month 24 for core and extension period, respectively.

End point type	Secondary
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End point timeframe:

Baseline (Core study), Week 24 (Core study)

End point values	Deferasirox 5 mg/kg/day (Core)	Deferasirox 10 mg/kg/day (Core)	Placebo (Core)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	49	48	51	
Units: mg Fe/g dw				
least squares mean (standard error)	-0.87 (\pm 0.448)	-0.9 (\pm 0.45)	-0.24 (\pm 0.439)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in serum ferritin from baseline to second and fourth quarter

End point title	Change in serum ferritin from baseline to second and fourth quarter
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End point description:

Change from baseline: second and fourth quarter average serum ferritin - baseline average serum ferritin. Serum ferritin changes were defined as the difference between post-baseline average - baseline average and ratio of post-baseline average/baseline average. Serum ferritin < 100 microgram (mcg)/mL was considered notable. Second quarter average serum ferritin was defined as the average of all serum ferritin values obtained within days 106 to 195. Fourth quarter average serum ferritin was defined as the average of all serum ferritin values obtained within days 286 to end of study. Negative change from baseline indicates reduced iron burden. The analysis was performed in the FAS population. The last available average of serum ferritin per quarter was carried forward if no serum ferritin was available during the fourth quarter. Here, "Number of subjects analysed" signifies the subjects assessed for serum ferritin during the core period for each arm, respectively.

End point type	Secondary
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End point timeframe:

Baseline, (Day 106 to Day 195), (Day 286 up to End of study [Day 365])

End point values	Deferasirox 5 mg/kg/day (Core)	Deferasirox 10 mg/kg/day (Core)	Placebo (Core)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52	54	56	
Units: Microgram/litre				
arithmetic mean (standard deviation)				
Second quarter (n= 52, 54, 56)	8.2 (± 244.443)	-17.75 (± 368.812)	106.45 (± 330.217)	
Fourth quarter (n= 51, 50, 53)	-130.47 (± 260.555)	-249.16 (± 389.356)	128.63 (± 249.689)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Liver Iron Concentration (LIC) from baseline to Week 24 and to Week 52 in subjects with escalated dose after Week 24

End point title	Change in Liver Iron Concentration (LIC) from baseline to Week 24 and to Week 52 in subjects with escalated dose after Week 24
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End point description:

LIC, a predictor of iron burden, was measured using R2-MRI technique. Relaxation rate was determined as $R2 = 1/T2$. Dose of deferasirox was doubled if at Week 24 LIC assessment indicated insufficient iron chelation (LIC >7 mg Fe/g dw and LIC reduction <15% compared to baseline). A negative change from baseline favoured study treatment in reducing LIC. The analysis was performed in the FAS population. Here, "Number of subjects analysed" signifies the subjects with dose increases after week 24, with both baseline and at least one post-baseline value. The last available post-baseline LIC was carried forward if no LIC value was available at Week 24 and Week 52.

End point type	Secondary
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End point timeframe:

Baseline, Week 24, Week 52

End point values	Deferasirox 5 mg/kg/day (Core)	Deferasirox 10 mg/kg/day (Core)	Placebo (Core)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	25	30	
Units: mg Fe/g dw				
arithmetic mean (standard deviation)				
Change from baseline at Week 24 (n=26,24,30)	0.56 (± 2.992)	0.69 (± 3.131)	0.94 (± 2.693)	
Change from baseline at Week 52 (n=26,25,30)	-1.82 (± 3.101)	-4.02 (± 4.849)	0.62 (± 4.128)	

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation between Serum Ferritin and LIC (Liver Iron Concentration)

End point title	Correlation between Serum Ferritin and LIC (Liver Iron Concentration)
End point description:	
The correlation between absolute change in serum ferritin and absolute change in LIC was determined using a scatter plot with a regression line for serum ferritin versus LIC from baseline at Week 52. A value of 1.0 indicates a perfect correlation. The analysis was performed in the FAS population of core study. Subjects with LIC and serum ferritin values at the specified time points were included in analysis	
End point type	Secondary
End point timeframe:	
Baseline (Core study), Week 52 (End of core study), Month 24 (End of extension study)	

End point values	All randomized subjects (Core study)	All randomized subjects (Extension study)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	165	129		
Units: Correlation coefficient				
number (not applicable)	0.639	0.735		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in haemoglobin absolute levels from baseline to Week 52 and Month 24

End point title	Change in haemoglobin absolute levels from baseline to Week 52 and Month 24
End point description: Absolute change from baseline was defined as weekly average – baseline average of haemoglobin absolute levels. A negative change from baseline indicated improvement. The analysis was performed in the FAS population of core study. Here, "Number of subjects analysed" signifies the subjects with values both at baseline and at Week 52 for each arm, respectively.	
End point type	Secondary
End point timeframe: Baseline (Core study), Week 52 (End of core study), Month 24 (End of extension study)	

End point values	Deferasirox 5 mg/kg/day (Core)	Deferasirox 10 mg/kg/day (Core)	Placebo (Core)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	55 ^[2]	55 ^[3]	56 ^[4]	
Units: Gram/litre				
arithmetic mean (standard deviation)				
12 months	-1.8 (± 5.5)	-0.6 (± 6.1)	-3 (± 7.7)	
24 months	-3.9 (± 5.55)	-1.2 (± 6.41)	-3.1 (± 9.48)	

Notes:

[2] - month 12 n=45

month 24 = 31

[3] - month 12 n=47

month 24 n=28

[4] - month 12 n=45

month 24 n=29

Statistical analyses

No statistical analyses for this end point

Secondary: Change in transferrin saturation levels from baseline to Week 52 and Month 24

End point title	Change in transferrin saturation levels from baseline to Week 52 and Month 24
End point description: Absolute change from baseline was defined as weekly average – baseline average for transferrin saturation levels. A negative change from baseline indicated improvement. The analysis was performed in the FAS population of core study. Here, "Number of subjects analysed" signifies the subjects with values both at baseline and at Week 52 and month 24 for each arm, respectively.	
End point type	Secondary
End point timeframe: Baseline (Core study), Week 52 (End of core study), Month 24 (End of extension study)	

End point values	Deferasirox 5 mg/kg/day (Core)	Deferasirox 10 mg/kg/day (Core)	Placebo (Core)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	55 ^[5]	55 ^[6]	56 ^[7]	
Units: Percent saturation				
arithmetic mean (standard deviation)				
month 12	-3.76 (± 11.762)	-3.13 (± 20.973)	2.42 (± 9.031)	
month 24	-7.93 (± 22.037)	-2.26 (± 26.394)	1.35 (± 13.013)	

Notes:

[5] - month12 n=38

month 24 n=32

[6] - month12 n=31

month 24 n=34

[7] - month12 n=36

month 24 n=33

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in liver iron concentration (LIC) in placebo treated subjects from baseline to Week 52

End point title	Absolute change in liver iron concentration (LIC) in placebo treated subjects from baseline to Week 52
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End point description:

Change in LIC was measured using relaxation R2-MRI technique at Week 24, Week 52 and last available LIC after stopping the treatment. The change in liver iron concentration for placebo treated subjects was used to assess the iron accumulation rate in pooled placebo subjects. The analysis was performed in the FAS population. The last available post-baseline LIC was carried forward if no LIC value was available at Week 52. Here, "Number of subjects analysed" signifies the subjects assessed for LIC during the core period for each arm, respectively.

End point type	Secondary
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End point timeframe:

Baseline to Week 52

End point values	All randomized subjects (Core study)			
Subject group type	Subject analysis set			
Number of subjects analysed	54			
Units: mg Fe/g dw				
arithmetic mean (standard deviation)	0.26 (± 3.501)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in serum ferritin from baseline to eighth quarter

End point title	Absolute change in serum ferritin from baseline to eighth
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End point description:

Change from baseline: second and fourth quarter average serum ferritin - baseline average serum ferritin. Serum ferritin changes were defined as the difference between post-baseline eighth quarterly average - baseline average and ratio of post-baseline average/baseline average. Serum ferritin < 100 mcg/mL was considered notable. A negative change from baseline indicated improvement. The analysis was performed in the FAS population of extension study. Subjects with both baseline and at least one post baseline value were included for this analysis. Here, "Number of subjects analysed" signifies the subjects assessed for serum ferritin during the extension period for each arm, respectively.

End point type	Secondary
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End point timeframe:

Baseline (Core study), Eighth Quarter (last 3 months of extension study)
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End point values	Deferasirox any dose (Extension)	Placebo/Deferasirox any dose (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	46		
Units: Milligram(s)/litre				
arithmetic mean (standard deviation)	-565.9 (± 504.25)	-504.3 (± 770.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in LIC for subjects who stopped deferasirox treatment

End point title	Absolute change in LIC for subjects who stopped deferasirox treatment
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End point description:

Iron accumulation rate was evaluated for change in LIC from therapy stop for 6 month and for last available LIC measurement. The absolute change in LIC for subjects who stopped treatment was used to assess the iron accumulation rate. The analysis was performed in the SAF population of extension study. Here, "Number of subjects analysed" signifies the subjects assessed for LIC during the extension period for each arm, respectively.

End point type	Secondary
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End point timeframe:

Baseline (Core study), Month 12 (End of core study), Month 24 (End of extension study)
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End point values	All deferasirox treated subjects (Extension study)			
Subject group type	Subject analysis set			
Number of subjects analysed	24 ^[8]			
Units: mg Fe/g dw				
arithmetic mean (standard deviation)	0.73 (± 0.621)			

Notes:

[8] - subjects who stopped deferasirox treatment

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Liver Iron Concentration (LIC) from baseline Month 24

End point title	Change in Liver Iron Concentration (LIC) from baseline Month 24
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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 of subjects was categorized as < 5 , $5-7$, ≥ 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 the FAS population. Here, "Number of subjects analysed" signifies the subjects assessed for LIC during the core and extension period for each arm, respectively. The last available post-baseline LIC was carried forward if no LIC value was available at Week 24 and Month 24 for core and extension period, respectively.

End point type	Secondary
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End point timeframe:

baseline and month 24

End point values	Deferasirox any dose (Extension)	Placebo/Deferasirox any dose (Extension)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	46		
Units: mg Fe/g dw				
arithmetic mean (standard deviation)	-7.1 (\pm 5.3)	-6.7 (\pm 6.67)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until LPLV.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.0
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Reporting groups

Reporting group title	Deferasirox 5 mg/kg/day
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Reporting group description:

Subjects were administered with deferasirox at a starting dose of 5 mg/kg daily through oral route based on daily iron removal. The dose was up-titrated to 10 mg/kg if LIC assessment indicated insufficient iron chelation (LIC > 7 mg Fe/g dw and LIC reduction < 15% compared to baseline).

Reporting group title	Placebo/Deferasirox any dose
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Reporting group description:

Deferasirox/Placebo matched to deferasirox was administered in subjects daily through oral route.

Reporting group title	Deferasirox 10 mg/kg/day
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Reporting group description:

Subjects were administered with deferasirox at a starting dose of 10 mg/kg daily through oral route based on daily iron removal. The dose was up-titrated to 20 mg/kg if LIC assessment indicated insufficient iron chelation (LIC > 7 mg Fe/g dw and LIC reduction < 15% compared to baseline).

Serious adverse events	Deferasirox 5 mg/kg/day	Placebo/Deferasirox any dose	Deferasirox 10 mg/kg/day
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 55 (20.00%)	16 / 56 (28.57%)	12 / 55 (21.82%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 55 (1.82%)	1 / 56 (1.79%)	3 / 55 (5.45%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian cyst ruptured			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	0 / 55 (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			

C-reactive protein			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	0 / 55 (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
Weight decreased			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	0 / 55 (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
Injury, poisoning and procedural complications			
Ligament rupture			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	0 / 55 (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
Lower limb fracture			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	0 / 55 (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
Meniscus lesion			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	0 / 55 (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
Pelvic fracture			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	0 / 55 (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
Road traffic accident			
subjects affected / exposed	0 / 55 (0.00%)	0 / 56 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	0 / 55 (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

Upper limb fracture			
subjects affected / exposed	0 / 55 (0.00%)	0 / 56 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	0 / 55 (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 disorders			
Arrhythmia			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	0 / 55 (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
Atrial fibrillation			
subjects affected / exposed	0 / 55 (0.00%)	0 / 56 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Optic neuritis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	0 / 55 (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
Syncope			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	0 / 55 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 55 (1.82%)	3 / 56 (5.36%)	2 / 55 (3.64%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolysis			

subjects affected / exposed	0 / 55 (0.00%)	0 / 56 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	0 / 55 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal tenderness			
subjects affected / exposed	0 / 55 (0.00%)	0 / 56 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	0 / 55 (0.00%)	0 / 56 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Food poisoning			
subjects affected / exposed	0 / 55 (0.00%)	0 / 56 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 56 (0.00%)	2 / 55 (3.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 55 (0.00%)	0 / 56 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Cholangitis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	0 / 55 (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
Cholecystitis acute			
subjects affected / exposed	0 / 55 (0.00%)	0 / 56 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis chronic			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	0 / 55 (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
Cholelithiasis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	0 / 55 (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
Hepatotoxicity			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	0 / 55 (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
Portal vein thrombosis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	0 / 55 (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
Skin and subcutaneous tissue disorders			

Pruritus			
subjects affected / exposed	0 / 55 (0.00%)	0 / 56 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 55 (0.00%)	0 / 56 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Babesiosis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	0 / 55 (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
Cellulitis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dengue fever			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	0 / 55 (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
Gastroenteritis			
subjects affected / exposed	3 / 55 (5.45%)	2 / 56 (3.57%)	4 / 55 (7.27%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Helicobacter gastritis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 56 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 55 (0.00%)	0 / 56 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver abscess			

subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	0 / 55 (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
Osteomyelitis			
subjects affected / exposed	0 / 55 (0.00%)	0 / 56 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 55 (0.00%)	2 / 56 (3.57%)	0 / 55 (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
Respiratory tract infection			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	0 / 55 (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
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 55 (0.00%)	1 / 56 (1.79%)	0 / 55 (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	0 / 55 (0.00%)	1 / 56 (1.79%)	0 / 55 (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	Deferasirox 5 mg/kg/day	Placebo/Deferasirox any dose	Deferasirox 10 mg/kg/day
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 55 (67.27%)	48 / 56 (85.71%)	45 / 55 (81.82%)
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 55 (1.82%)	2 / 56 (3.57%)	3 / 55 (5.45%)
occurrences (all)	1	2	6

Heart rate increased subjects affected / exposed occurrences (all)	0 / 55 (0.00%) 0	3 / 56 (5.36%) 5	0 / 55 (0.00%) 0
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	4 / 55 (7.27%) 4	1 / 56 (1.79%) 2	0 / 55 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 10	12 / 56 (21.43%) 21	11 / 55 (20.00%) 33
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	6 / 55 (10.91%) 7	3 / 56 (5.36%) 3	4 / 55 (7.27%) 6
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	2 / 55 (3.64%) 2	3 / 56 (5.36%) 6	1 / 55 (1.82%) 1
Fatigue subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 4	6 / 56 (10.71%) 8	7 / 55 (12.73%) 8
Oedema peripheral subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1	4 / 56 (7.14%) 6	1 / 55 (1.82%) 1
Pain subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 3	1 / 56 (1.79%) 2	0 / 55 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	10 / 55 (18.18%) 11	15 / 56 (26.79%) 22	5 / 55 (9.09%) 5
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 3	1 / 56 (1.79%) 1	1 / 55 (1.82%) 1
Gastrointestinal disorders			

Abdominal pain subjects affected / exposed occurrences (all)	4 / 55 (7.27%) 5	9 / 56 (16.07%) 13	4 / 55 (7.27%) 4
Abdominal pain upper subjects affected / exposed occurrences (all)	4 / 55 (7.27%) 6	7 / 56 (12.50%) 7	9 / 55 (16.36%) 10
Constipation subjects affected / exposed occurrences (all)	0 / 55 (0.00%) 0	3 / 56 (5.36%) 3	0 / 55 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	8 / 55 (14.55%) 11	12 / 56 (21.43%) 17	7 / 55 (12.73%) 23
Dyspepsia subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 2	2 / 56 (3.57%) 2	3 / 55 (5.45%) 4
Food poisoning subjects affected / exposed occurrences (all)	0 / 55 (0.00%) 0	4 / 56 (7.14%) 5	3 / 55 (5.45%) 3
Gastritis subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 3	2 / 56 (3.57%) 2	1 / 55 (1.82%) 1
Nausea subjects affected / exposed occurrences (all)	5 / 55 (9.09%) 7	12 / 56 (21.43%) 13	9 / 55 (16.36%) 13
Tooth disorder subjects affected / exposed occurrences (all)	0 / 55 (0.00%) 0	3 / 56 (5.36%) 3	0 / 55 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	4 / 55 (7.27%) 5	8 / 56 (14.29%) 8	3 / 55 (5.45%) 3
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 3	8 / 56 (14.29%) 9	4 / 55 (7.27%) 4
Dyspnoea			

subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1	3 / 56 (5.36%) 3	1 / 55 (1.82%) 1
Epistaxis subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 3	0 / 56 (0.00%) 0	1 / 55 (1.82%) 1
Oropharyngeal pain subjects affected / exposed occurrences (all)	4 / 55 (7.27%) 6	3 / 56 (5.36%) 3	7 / 55 (12.73%) 7
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 5	5 / 56 (8.93%) 5	6 / 55 (10.91%) 6
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1	4 / 56 (7.14%) 5	3 / 55 (5.45%) 3
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 3	5 / 56 (8.93%) 6	2 / 55 (3.64%) 2
Back pain subjects affected / exposed occurrences (all)	2 / 55 (3.64%) 2	6 / 56 (10.71%) 7	1 / 55 (1.82%) 1
Flank pain subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1	3 / 56 (5.36%) 5	0 / 55 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	2 / 55 (3.64%) 3	3 / 56 (5.36%) 3	2 / 55 (3.64%) 2
Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 3	4 / 56 (7.14%) 5	5 / 55 (9.09%) 5
Gastroenteritis viral subjects affected / exposed occurrences (all)	0 / 55 (0.00%) 0	2 / 56 (3.57%) 2	3 / 55 (5.45%) 3

Influenza			
subjects affected / exposed	4 / 55 (7.27%)	5 / 56 (8.93%)	6 / 55 (10.91%)
occurrences (all)	8	5	8
Nasopharyngitis			
subjects affected / exposed	6 / 55 (10.91%)	6 / 56 (10.71%)	5 / 55 (9.09%)
occurrences (all)	14	9	6
Pharyngitis			
subjects affected / exposed	6 / 55 (10.91%)	2 / 56 (3.57%)	2 / 55 (3.64%)
occurrences (all)	11	2	3
Rhinitis			
subjects affected / exposed	2 / 55 (3.64%)	3 / 56 (5.36%)	5 / 55 (9.09%)
occurrences (all)	3	4	5
Tonsillitis			
subjects affected / exposed	5 / 55 (9.09%)	5 / 56 (8.93%)	3 / 55 (5.45%)
occurrences (all)	7	10	3
Upper respiratory tract infection			
subjects affected / exposed	9 / 55 (16.36%)	14 / 56 (25.00%)	14 / 55 (25.45%)
occurrences (all)	12	27	28
Viral infection			
subjects affected / exposed	2 / 55 (3.64%)	4 / 56 (7.14%)	0 / 55 (0.00%)
occurrences (all)	2	5	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 55 (5.45%)	3 / 56 (5.36%)	1 / 55 (1.82%)
occurrences (all)	4	3	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 June 2009	The purpose of this local amendment was to be in accordance with Greek National Ethical Committee which approved the clinical study protocol "under the condition that persons participating in the study are non-transfusion-dependent and over 18 years old". Therefore the population criteria and the first inclusion criteria were modified to only allow inclusion of patients over 18 years old. Moreover, the collection of an additional blood sample for UGT1A1 genotyping was defined in original protocol part 7.6.6 was not performed in Greek patients. Finally, according to Greek Law, the modalities of the contracted convention insurance for the cover of responsibility of Researcher and Sponsor were to be reported in the protocol, section 11 "Administrative procedures", provided in Appendix 16.1.1.
14 August 2009	<p>The purpose of this amendment was to:</p> <ul style="list-style-type: none">• Allow dose adjustment after 6 months to study the impact of a dose increase in patients who may have required higher doses of deferasirox to reduce a high iron burden or to compensate for a high rate of gastrointestinal iron intake based on the following criterion :<ul style="list-style-type: none">• Patients with a LIC >7 mg Fe/g dw after 6 months of treatment and with a LIC reduction by less than 15% compared to baseline had their treatment dose doubled• Patients with a LIC >7 mg Fe/g dw after 6 months of treatment and with a LIC reduction by 15% or more compared to baseline kept the same dose of treatment• Patients with a LIC equal to or lower than 7 mg stayed on the same dose• The wording of the primary objective was changed to reflect the amended treatment regimens• A description of a supportive analysis was added to the primary objective• Other objectives were replaced with secondary objectives• Exclusion criteria were added, deleted or modified:<ul style="list-style-type: none">• to allow patients with a known lifetime history of transfusion in excess of 20 PRBC• to exclude patients for whom phlebotomy can be indicated• to exclude patients with ALT > 5 ULN (previously ALT > 3 ULN)• to exclude patients with urine protein/urine creatinine ratio > 1.0 mg/mg (previously urine protein/urine creatinine ratio > 0.5 mg/mg)• to exclude patients who received chelation within 1 month (previously 6 months)• to exclude patients with a history of drug or alcohol abuse within 12 months prior to enrollment• To modify the upper limit of liver enzymes (from 3xULN to 5xULN) in the "definition of notable ranges for laboratory tests"• LIC in the treatment stopping rule has been changed from <2 mg Fe /g dw to <3 mg Fe/g dw• To add an algorithm to manage gastrointestinal disturbances due to the investigational treatment• To update the protocol provided in Appendix 16.1.1. ("Other concomitant medications") to be consistent Exjade® label

14 August 2009	<p>CONTINUED:</p> <p>To update the informed consent form to reflect the changes of the amendment and to add the following : (1) a new heading "Contacts" as the last section after "Pregnancy" (2) a paragraph on emergency testing in instances of occupational blood exposure in the section "Risks and inconveniences" as follow-up action to an audit by the Food and Drug Administration</p> <ul style="list-style-type: none"> • To update the visit schedule assessment as follows: • To delete " Hematology/blood chemistry/iron metabolism" at Visit 3 • To check "Relevant medical history/current medical condition" also at screening visit 2 • To ensure that a pregnancy test is performed on all women with childbearing potential within 48 hours before first drug administration. If serum pregnancy test was done more than 48 hours before visit 3, an additional urinary pregnancy test was to be performed at Visit 3 • Weekly serum creatinine assessments were added to the patients who receive dose escalation at 6 months • To allow patient to be re-screened after 3 months when LIC and/or serum ferritin were below eligibility criteria, when ALT was above the eligibility criterion, or when urine protein/urine creatinine ratio was above the eligibility criterion. • To make it known that any patients participating in clinical study ICL670A2209 would be offered to continue in an open-label study extension. • To add the brand name THALASSA to the title of the study following the Novartis branding initiative.
13 October 2009	The purpose of this amendment was to include a one-year extension study to study CICAL670A2209.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported