Clinical trial results:
A multicenter, randomized, open-label phase II trial evaluating deferasirox compared with deferoxamine in patients with cardiac iron overload due to chronic blood transfusions (CORDELIA)

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Summary

EudraCT number	2007-000766-20
Trial protocol	GB IT
Global end of trial date	05 March 2013

Results information

Result version number	v1 (current)
This version publication date	15 August 2018
First version publication date	15 August 2018

Trial information

Trial identification

Sponsor protocol code	CICL670A2206

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00600938
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	05 March 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 March 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate the efficacy of deferasirox, compared to deferoxamine in subjects with cardiac iron overload due to chronic blood transfusions by using T2-star (T2*) technique for measurement of iron in tissue after a treatment period of 12 months (core study) and to collect additional data on efficacy of deferasirox and deferoxamine when treated for more than 12 months (extension study).

Protection of trial subjects:

No rescue medication was allowed in the study.

Background therapy:

Regular medications required to treat concomitant medical conditions were allowed during the study. Subjects also continued blood transfusions according to the regimen that they had been receiving prior to enrollment to maintain a haemoglobin level of 9 gram/decilitre (g/dL).

Evidence for comparator:

Deferoxamine mesylate (DFO), is standard of care for treating transfusional myocardial iron overload, including severe cardiac iron overload. Hence, DFO was selected as the active comparator and administered via subcutaneous (s.c.) infusion over 8 to 10 hours, at least 5 days per week.

Actual start date of recruitment	26 November 2007
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	China: 26
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Cyprus: 6
Country: Number of subjects enrolled	United Arab Emirates: 20
Country: Number of subjects enrolled	Egypt: 44
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Lebanon: 5
Country: Number of subjects enrolled	Taiwan: 9
Country: Number of subjects enrolled	Thailand: 19
Country: Number of subjects enrolled	Turkey: 60
Country: Number of subjects enrolled	United Kingdom: 5

Worldwide total number of subjects	197
EEA total number of subjects	12

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)	12
Adolescents (12-17 years)	69
Adults (18-64 years)	116
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 22 centres in 11 countries.

Pre-assignment

Screening details:

A total of 925 subjects were screened, 728 were screen failures and remaining 197 subjects were randomized into the core study. Of the 160 subjects who completed the core study, 146 subjects were enrolled to extension study.

Period 1

Period 1 title	Core Study
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Investigators and subjects were not blinded but in order to minimize the potential impact of treatment, Central reader, Independent reader, Adjudicator, Central Imaging Contract Research Organization Technical and Medical Quality Readers and Novartis clinical team were blinded to the treatment allocation until database lock for the primary analysis.

Arms

Are arms mutually exclusive?	Yes
Arm title	Deferasirox (ICL)

Arm description:

Subjects received deferasirox as 20 milligram (mg)/kilogram (kg)/day once daily (od) for 2 weeks, followed by 30 mg/kg/day od for 1 week and a subsequent continuation of 40 mg/kg/day od as target dose. Deferasirox was administered every morning 30 minutes before breakfast. In subjects with gastro-intestinal symptoms required twice daily (bid) administration, the first half of the daily dose was provided in morning and remaining half was provided in the evening.

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 tablets were orally administered as 20 mg/kg/day for 2 weeks, followed by 30 mg/kg/day for 1 week and a subsequent continuation of 40 mg/kg/day as a target dose.

Arm title	Deferoxamine (DFO)

Arm description:

Deferoxamine mesylate was infused via s.c. route as target dose of 50 mg/kg/day to 60 mg/kg/day in 8 to 12 hour intervals administered 5 to 7 days/week.

Arm type	Active comparator
Investigational medicinal product name	Deferoxamine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Deferoxamine was infused via s.c. route as target dose of 50 mg/kg/day to 60 mg/kg/day in 8 to 12 hour intervals administered 5 to 7 days/week.

Number of subjects in period 1	Deferasirox (ICL)	Deferoxamine (DFO)
Started	98	99
Completed	82	78
Not completed	16	21
Adverse event, serious fatal	1	1
Consent withdrawn by subject	7	12
Unsatisfactory therapeutic effect	1	2
Lost to follow-up	3	2
Abnormal test procedure result	3	2
Protocol deviation	1	2

Period 2

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

Blinding implementation details:

Investigators and subjects were not blinded but in order to minimize the potential impact of treatment, Central reader, Independent reader and Adjudicator were blinded to the treatment allocation during the extension phase.

Arms

Are arms mutually exclusive?	Yes
Arm title	Deferasirox (ICL to ICL)

Arm description:

Subjects who received deferasirox in both core and extension study.

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 tablets were orally administered as 20 mg/kg/day for 2 weeks, followed by 30 mg/kg/day for 1 week and a subsequent continuation of 40 mg/kg/day as a target dose.

Arm title	Deferoxamine (DFO to DFO)

Arm description:

Subjects who received deferoxamine in both core and extension study.

Arm type	Active comparator

Investigational medicinal product name	Deferoxamine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Deferoxamine was infused via s.c. route as target dose of 50 mg/kg/day to 60 mg/kg/day in 8 to 12 hour intervals administered 5 to 7 days/week.

Arm title	Deferoxamine to Deferasirox (DFO to ICL)

Arm description:

Subjects who received deferoxamine in core study, but received deferasirox in extension study.

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 tablets were orally administered as 20 mg/kg/day for 2 weeks, followed by 30 mg/kg/day for 1 week and a subsequent continuation of 40 mg/kg/day as a target dose.

Arm title	Deferasirox to Deferoxamine (ICL to DFO)

Arm description:

Subjects who received deferasirox in core study but received deferoxamine in extension study.

Arm type	Active comparator
Investigational medicinal product name	Deferoxamine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Deferoxamine was infused via s.c. route as target dose of 50 mg/kg/day to 60 mg/kg/day in 8 to 12 hour intervals administered 5 to 7 days/week.

Number of subjects in period 2[1]	Deferasirox (ICL to ICL)	Deferoxamine (DFO to DFO)	Deferoxamine to Deferasirox (DFO to ICL)
Started	74	29	42
Completed	65	24	33
Not completed	9	5	9
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	2	2	3
Adverse event, non-fatal	1	-	2
Unsatisfactory therapeutic effect	4	1	1
Lost to follow-up	1	1	2
Abnormal test procedure result(s)	-	1	1

Number of subjects in period 2	Deferasirox to Deferoxamine (ICL

[1]	to DFO)
Started	1
Completed	0
Not completed	1
Adverse event, serious fatal	-
Consent withdrawn by subject	-
Adverse event, non-fatal	-
Unsatisfactory therapeutic effect	-
Lost to follow-up	-
Abnormal test procedure result(s)	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 160 subjects who completed the preceding period, only 146 subjects opted to enroll in extension stud y.

Baseline characteristics

Reporting groups	
Reporting group title	Deferasirox (ICL)

Reporting group description:

Subjects received deferasirox as 20 milligram (mg)/kilogram (kg)/day once daily (od) for 2 weeks, followed by 30 mg/kg/day od for 1 week and a subsequent continuation of 40 mg/kg/day od as target dose. Deferasirox was administered every morning 30 minutes before breakfast. In subjects with gastro-intestinal symptoms required twice daily (bid) administration, the first half of the daily dose was provided in morning and remaining half was provided in the evening.

Reporting group title	Deferoxamine (DFO)

Reporting group description:

Deferoxamine mesylate was infused via s.c. route as target dose of 50 mg/kg/day to 60 mg/kg/day in 8 to 12 hour intervals administered 5 to 7 days/week.

Reporting group values	Deferasirox (ICL)	Deferoxamine (DFO)	Total
Number of subjects	98	99	197
Age categorical Units: Subjects			
Children and Adolescents (10-<18)	40	41	81
Adults (18-<50)	58	58	116
Age continuous Units: years			
arithmetic mean	19.9	19.7	
standard deviation	± 6.53	± 6.32	-
Gender categorical Units: Subjects			
Female	58	57	115
Male	40	42	82

End points

End points reporting groups

Reporting group title	Deferasirox (ICL)
Reporting group description:	
Subjects received deferasirox as 20 milligram (mg)/kilogram (kg)/day once daily (od) for 2 weeks, followed by 30 mg/kg/day od for 1 week and a subsequent continuation of 40 mg/kg/day od as target dose. Deferasirox was administered every morning 30 minutes before breakfast. In subjects with gastro-intestinal symptoms required twice daily (bid) administration, the first half of the daily dose was provided in morning and remaining half was provided in the evening.	
Reporting group title	Deferoxamine (DFO)
Reporting group description:	
Deferoxamine mesylate was infused via s.c. route as target dose of 50 mg/kg/day to 60 mg/kg/day in 8 to 12 hour intervals administered 5 to 7 days/week.	
Reporting group title	Deferasirox (ICL to ICL)
Reporting group description:	
Subjects who received deferasirox in both core and extension study.	
Reporting group title	Deferoxamine (DFO to DFO)
Reporting group description:	
Subjects who received deferoxamine in both core and extension study.	
Reporting group title	Deferoxamine to Deferasirox (DFO to ICL)
Reporting group description:	
Subjects who received deferoxamine in core study, but received deferasirox in extension study.	
Reporting group title	Deferasirox to Deferoxamine (ICL to DFO)
Reporting group description:	
Subjects who received deferasirox in core study but received deferoxamine in extension study.	

Primary: Core Study: Change from baseline in cardiac iron content as measured by Myocardial T2* at Month 12

End point title	Core Study: Change from baseline in cardiac iron content as measured by Myocardial T2* at Month 12
End point description:	
Magnetic resonance (MR) T2-star (T2*) technique was used to measure tissue iron in cardiac iron overload condition. The ratio of cardiac iron concentration was measured as T2* after 12 months of study treatment divided by the T2* value at baseline. A T2* 10-20 milliseconds (ms) indicates mild/moderate cardiac iron overload, and a T2* less than (<) 10 ms indicates severe cardiac iron overload. Cardiovascular Magnetic Resonance (CMR) was utilized to evaluate the effects of chelation therapy with ICL or DFO on cardiac iron concentration. The primary analysis was performed in Per-Protocol Set (PPS), defined as all randomized subjects who received study treatment for at least 6 months and had no major protocol violations.	
End point type	Primary
End point timeframe:	
Baseline to Month 12	

End point values	Deferasirox (ICL)	Deferoxamine (DFO)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	81		
Units: Ratio				
geometric mean (confidence interval 95%)	1.12 (1.07 to 1.18)	1.07 (1.02 to 1.11)		

Statistical analyses

Statistical analysis title	Change in myocardial T2* from baseline at Month 12

Statistical analysis description:

The analysis was performed to show non-inferiority in efficacy of ICL compared to DFO in treating cardiac iron overload measured by T2*. According to null hypothesis, pre-specified non-inferiority margin of 0.9, was applied to the geometric mean ratio.

Comparison groups	Deferasirox (ICL) v Deferoxamine (DFO)
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.0567 [2]
Method	Stagewise ordering method
Parameter estimate	Geometric mean ratio
Point estimate	1.0557
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9981
upper limit	1.1331

Notes:

[1] - As non-inferiority of deferasirox was established, a superiority test was performed by comparing the lower limit of the repeated confidence interval (CI) to 0 which corresponds to a ratio of 100%.
[2] - P-value was based on the Tsiatis, Rosner and Mehta stagewise ordering testing.

Secondary: Core Study: Absolute change from baseline in Left Ventricular Ejection Fraction (LVEF) at Month 12

End point title	Core Study: Absolute change from baseline in Left Ventricular Ejection Fraction (LVEF) at Month 12

End point description:

Left Ventricular Ejection Fraction (LVEF) was defined as the fraction of blood pumped out of the heart's left ventricular chamber with each heartbeat, and was a measure of cardiac output for the heart. LVEF assessment was based on CMR echocardiography. The normal fraction of ejection was more than (>)55%. The analysis was performed in PPS population.

End point type	Secondary

End point timeframe:

Baseline to Month 12

End point values	Deferasirox (ICL)	Deferoxamine (DFO)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	81		
Units: Percentage of LVEF				
least squares mean (standard error)	-0.5 (± 0.47)	0 (± 0.49)		

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study: Change from baseline in Left Ventricular Ejection Fraction (LVEF) at Month 6

End point title	Core Study: Change from baseline in Left Ventricular Ejection Fraction (LVEF) at Month 6

End point description:

LVEF was defined as the fraction of blood pumped out of the heart's left ventricular chamber with each heartbeat, and was a measure of cardiac output for the heart. LVEF assessment was based on CMR echocardiography. The normal fraction of ejection was >55%. The analysis was performed in PPS population.

End point type	Secondary

End point timeframe:

Baseline to Month 6

End point values	Deferasirox (ICL)	Deferoxamine (DFO)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	73		
Units: Percentage of LVEF				
arithmetic mean (standard deviation)	-0.95 (± 4.485)	-0.37 (± 4.389)		

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study: Change from baseline in cardiac iron content as measured by Myocardial T2* at Month 6

End point title	Core Study: Change from baseline in cardiac iron content as measured by Myocardial T2* at Month 6

End point description:

Myocardial T2* technique was used to measure tissue iron in cardiac iron overload condition. The ratio of cardiac iron concentration was measured as T2* after 12 months of study treatment divided by the T2* value at baseline. A T2* 10-20 ms indicates mild/moderate cardiac iron overload, and a T2* <10 ms indicates severe cardiac iron overload. CMR was utilized to evaluate the effects of chelation therapy with
ICL or DFO on cardiac iron concentration. The analysis was performed in the PPS population.

End point type	Secondary

End point timeframe:

Baseline to Month 6

End point values	Deferasirox (ICL)	Deferoxamine (DFO)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	73		
Units: Ratio				
geometric mean (confidence interval 95%)	1.04 (1 to 1.08)	1.04 (1 to 1.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study: Change from baseline in Left Ventricular End Systolic Volume Index (LVESVI) at Month 6 and Month 12

End point title	Core Study: Change from baseline in Left Ventricular End Systolic Volume Index (LVESVI) at Month 6 and Month 12

End point description:

Left Ventricular End Systolic Volume Index (LVESVI) was defined as the volume of blood in the heart's left ventricular chamber at the end of the heart's contraction indexed to body surface area . LVESV assessment was based on CMR echocardiography. The analysis was performed in the PPS population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline, Month 6, Month 12

End point values	Deferasirox (ICL)	Deferoxamine (DFO)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	81		
Units: millilitre(s)/square meter				
arithmetic mean (standard deviation)				
Change from baseline at 6 Month (n= 85, 73)	1.8 (± 8.021)	0.88 (± 8.919)		
Change from baseline at 12 Month(n= 70, 67)	1.8 (± 8.342)	-0.01 (± 10.463)		

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study: Change from baseline in Left Ventricular End Diastolic Volume Index (LVEDVI) at Month 6 and Month 12

End point title	Core Study: Change from baseline in Left Ventricular End Diastolic Volume Index (LVEDVI) at Month 6 and Month 12

End point description:

Left Ventricular End Diastolic Volume Index (LVEDVI) was defined as the volume of blood in the heart's left ventricular chamber at the beginning of filling with blood indexed to body surface area. LVEDV assessment was based on CMR echocardiography. The analysis was performed in the PPS population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline, Month 6, Month 12

End point values	Deferasirox (ICL)	Deferoxamine (DFO)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	81		
Units: millilitre(s)/square meter				
arithmetic mean (standard deviation)				
Change from Baseline at 6 Month (n= 85, 73)	1.81 (± 14.515)	1.48 (± 19.188)		
Change from Baseline at 12 Month (n= 70, 67)	2.27 (± 12.787)	0.76 (± 20.166)		

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study: Change in Left Ventricular Mass Index (LVMI) at Month 6 and Month 12

End point title	Core Study: Change in Left Ventricular Mass Index (LVMI) at Month 6 and Month 12

End point description:

Left ventricular mass index (LVMI) was defined as left ventricular mass indexed by the body surface area. The LVM was calculated as left ventricular muscle volume multiplied by myocardial density. LVMI assessment was based on CMR echocardiography. The analysis was performed in the PPS population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline, Month 6, Month 12

End point values	Deferasirox (ICL)	Deferoxamine (DFO)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	81		
Units: gram(s)/square meter				
arithmetic mean (standard deviation)				
Change from Baseline at 6 Month (n= 85, 73)	1.01 (± 13.102)	3.32 (± 13.585)		
Change from Baseline at 12 Month (n= 70, 67)	4.36 (± 13.18)	5.51 (± 15.434)		

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study: Percentage of subjects who discontinued due to cardiac dysfunction at Month 12

End point title	Core Study: Percentage of subjects who discontinued due to cardiac dysfunction at Month 12

End point description:

Cardiac dysfunction was defined as clinical symptoms of shortness of breath at rest or exertion, orthopnea, exercise intolerance, lower extremity edema, arrythmias. Subjects who withdrew from the study due to following cardiac parameters: LVEF <50%, T2* <6 ms or significant decreases in T2* ≥33% from baseline. The analysis was performed in the FAS population defined as all subjects who received at least one dose of study treatment and had at least one post -baseline assessment for primary efficacy..

End point type	Secondary

End point timeframe:

12 Month

End point values	Deferasirox (ICL)	Deferoxamine (DFO)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	99		
Units: Percentage of subjects				
number (not applicable)	3.1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study: Number of subjects with adverse events, serious adverse events and death

End point title	Core Study: Number of subjects with adverse events, serious adverse events and death

End point description:

An adverse event for the purposes of this protocol is the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) occurring after signing the informed

consent even if the event is not considered to be related to the study drug(s). Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant or require therapy. Serious adverse events (SAEs) were defined as any untoward medical occurrences that result in death, are life threatening, require (or prolong) hospitalization, cause persistent or significant disability/incapacity, result in congenital anomalies or birth defects, or are other conditions which in judgment of investigators represent significant hazards. Death was defined as a fatal event leading to permanent cessation of all vital functions of the body.

End point type	Secondary

End point timeframe:

From start of study treatment to Month 12

End point values	Deferasirox (ICL)	Deferoxamine (DFO)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	91		
Units: Number of subjects				
AEs	65	69		
SAEs	10	10		
Death	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study: Area under the plasma concentration-time curve (AUCtau) of deferasirox

End point title	Core Study: Area under the plasma concentration-time curve (AUCtau) of deferasirox[3]

End point description:

The AUCtau was defined as area under the plasma concentration-time curve from time zero to dosing interval, calculated by a trapezoidal method. The analysis was performed in the Pharmacokinetics Analysis Set (PAS) defined as subjects who received the same dose of deferasirox for at least four consecutive days prior to PK sample collection and completed PK sample collection.

End point type	Secondary

End point timeframe:

Pre-dose, 1 hour, 2 hour and 4 hour post-dose

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The pharmacokinetic evaluation was planned for study drug only.

End point values	Deferasirox (ICL)			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: hours*nanograms/milliliters				
arithmetic mean (standard deviation)	2129.7 (± 930.202)			

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study: Maximum Plasma Concentration (Cmax) of deferasirox

End point title	Core Study: Maximum Plasma Concentration (Cmax) of deferasirox[4]

End point description:

Maximum plasma concentration (Cmax) was defined as the peak plasma level of deferasirox, derived from plasma concentration-time data of deferasirox. The analysis was performed in the PAS population.

End point type	Secondary

End point timeframe:

Pre-dose, 1 hour, 2 hour and 4 hour post-dose

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The pharmacokinetic evaluation was planned for study drug only.

End point values	Deferasirox (ICL)			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: micromole(s)/litre				
arithmetic mean (standard deviation)	150.09 (± 59.143)			

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study: Plasma concentration of deferasirox

End point title	Core Study: Plasma concentration of deferasirox[5]

End point description:

Amount of deferasirox present in plasma was determined. The analysis was performed in the PAS population. The'n' signifies those subjects evaluable for this measure at the specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Pre-dose, 1 hour, 2 hour and 4 hour post-dose

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The pharmacokinetic evaluation was planned for study drug only.

End point values	Deferasirox (ICL)			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: micromole(s)/litre				
arithmetic mean (standard deviation)				
1 hour (n= 15)	96.32 (± 35.799)			
2 hour (n= 15)	136.47 (± 51.831)			
4 hour (n= 13)	133.33 (± 62.815)			

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study: Time to Maximum Plasma Concentration (Tmax) of deferasirox

End point title	Core Study: Time to Maximum Plasma Concentration (Tmax) of deferasirox[6]

End point description:

Tmax was defined as the time taken to reach the maximum plasma concentration. The analysis was performed on the PAS population.

End point type	Secondary

End point timeframe:

Pre-dose, 1 hour, 2 hour and 4 hour post-dose

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The pharmacokinetic evaluation was planned for study drug only.

End point values	Deferasirox (ICL)			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: hour				
median (full range (min-max))	4 (1 to 4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Study: Change from baseline in cardiac iron content as measured by Myocardial T2* at Month 24

End point title	Extension Study: Change from baseline in cardiac iron content as measured by Myocardial T2* at Month 24

End point description:

Myocardial T2* technique was used to measure tissue iron in cardiac iron overload condition. The ratio of cardiac iron concentration was measured as T2* after 12 months of study treatment divided by the T2* value at baseline. A T2* 10-20 ms indicates mild/moderate cardiac iron overload, and a T2* <10

ms indicates severe cardiac iron overload. CMR was utilized to evaluate the effects of chelation therapy with ICL or DFO on cardiac iron concentration. The analysis was performed in the FAS population defined as all subjects who received at least one dose of study treatment and had at least one post-baseline assessment for primary efficacy. Here, "Number of subjects analysed" signifies those subjects who were evaluable for this outcome measure. The value -99999.9 and 99999.9 in the data field represents not available data because EudraCT system is not allowing user to enter "NA" or leave the measure dispersion data field blank where only one patient was analyzed.

End point type	Secondary

End point timeframe:

Baseline (Core study), Months 24 (Core + Extension study)

End point values	Deferasirox (ICL to ICL)	Deferoxamine (DFO to DFO)	Deferoxamine to Deferasirox (DFO to ICL)	Deferasirox to Deferoxamine (ICL to DFO)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	63	25	33	1[7]
Units: Ratio				
geometric mean (confidence interval 95%)	1.38 (1.28 to 1.49)	1.33 (1.13 to 1.55)	1.21 (1.09 to 1.34)	1.11 (-99999.9 to 99999.9)

Notes:

[7] - Only 1 patient, hence no dispersion data. System does not allow to put NA or to leave it blank.

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Study: Absolute change from baseline in Left Ventricular Ejection Fraction (LVEF) at Month 24

End point title	Extension Study: Absolute change from baseline in Left Ventricular Ejection Fraction (LVEF) at Month 24

End point description:

LVEF was defined as the fraction of blood pumped out of the heart’s left ventricular chamber with each heartbeat, and was a measure of cardiac output for the heart. LVEF assessment was based on CMR echocardiography. The normal fraction of ejection was >55%. The analysis was performed in the FAS population. Here, "Number of subjects analysed" signifies those
subjects who were evaluable for this outcome measure. The value '0' in the standard deviation data field represents not available data because EudraCT system is not allowing user to enter "NA" or leave the measure dispersion data field blank where only one patient was analyzed.

End point type	Secondary

End point timeframe:

Baseline (Core study), Months 24 (Core + Extension study)

End point values	Deferasirox (ICL to ICL)	Deferoxamine (DFO to DFO)	Deferoxamine to Deferasirox (DFO to ICL)	Deferasirox to Deferoxamine (ICL to DFO)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	63	25	33	1[8]
Units: Percentage of LVEF				
arithmetic mean (standard deviation)	0.6 (± 4.72)	-0.6 (± 5.02)	0.2 (± 4.82)	-18 (± 0)

Notes:

[8] - Standard deviation value (0) denotes not applicable, as only one subject was analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Study: Change from baseline in Left Ventricular End Systolic Volume Indices (LVESVI) at Month 24

End point title	Extension Study: Change from baseline in Left Ventricular End Systolic Volume Indices (LVESVI) at Month 24

End point description:

LVESVI was defined as the volume of blood in the heart's left ventricular chamber at the end of the heart's contraction indexed to body surface area. LVESV assessment was based on CMR echocardiography. The analysis was performed in the FAS population. Here, "Number of subjects analysed" signifies those subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline (Core study), Months 24 (Core + Extension study)

End point values	Deferasirox (ICL to ICL)	Deferoxamine (DFO to DFO)	Deferoxamine to Deferasirox (DFO to ICL)	Deferasirox to Deferoxamine (ICL to DFO)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	60	23	33	0[9]
Units: millilitre(s)/square meter				
arithmetic mean (standard deviation)	1.6 (± 10.21)	4.3 (± 8.66)	1.7 (± 8.56)	()

Notes:

[9] - No subject was evaluable at this time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Study: Change from baseline in Left Ventricular End Diastolic Volume Indices (LVEDVI) at Month 24

End point title	Extension Study: Change from baseline in Left Ventricular End Diastolic Volume Indices (LVEDVI) at Month 24

End point description:

LVEDVI was defined as the volume of blood in the heart's left ventricular chamber at the beginning of the chamber's filling with blood indexed to body surface area. LVEDV assessment was based on CMR echocardiography. The analysis was performed in the FAS population. Here, "Number of subjects analysed" signifies those subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline (Core study), Months 24 (Core + Extension study)

End point values	Deferasirox (ICL to ICL)	Deferoxamine (DFO to DFO)	Deferoxamine to Deferasirox (DFO to ICL)	Deferasirox to Deferoxamine (ICL to DFO)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	60	23	33	0[10]
Units: millilitre(s)/square meter				
arithmetic mean (standard deviation)	3.4 (± 21.15)	9.5 (± 14.6)	5.4 (± 13.97)	()

Notes:

[10] - No subject was evaluable at this time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Study: Change from baseline in Left Ventricular Mass Index (LVMI) at Month 24

End point title	Extension Study: Change from baseline in Left Ventricular Mass Index (LVMI) at Month 24

End point description:

Left ventricular mass index (LVMI) was defined as left ventricular mass indexed by the body surface area. The LVM was calculated as left ventricular muscle volume multiplied by myocardial density. LVMI assessment was based on CMR echocardiography. The analysis was performed in the FAS population. Here, "Number of subjects analysed" signifies those subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline (Core study), Months 24 (Core + Extension study)

End point values	Deferasirox (ICL to ICL)	Deferoxamine (DFO to DFO)	Deferoxamine to Deferasirox (DFO to ICL)	Deferasirox to Deferoxamine (ICL to DFO)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	60	23	33	0[11]
Units: gram(s)/square meter				
arithmetic mean (standard deviation)	5.6 (± 13)	6.7 (± 14.96)	10.3 (± 13.32)	()

Notes:

[11] - No subject was evaluable at this time point.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Timeframe for AE	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups	
Reporting group title	Core ICL670
Reporting group description:	
Core ICL670	
Reporting group title	Core DFO
Reporting group description:	
Core DFO	
Reporting group title	Extension ICL to ICL
Reporting group description:	
Extension ICL to ICL	
Reporting group title	Extension DFO to DFO
Reporting group description:	
Extension DFO to DFO	
Reporting group title	Extension DFO to ICL
Reporting group description:	
Extension DFO to ICL	
Reporting group title	Extension ICL to DFO
Reporting group description:	
Extension ICL to DFO	

Serious adverse events	Core ICL670	Core DFO	Extension ICL to ICL
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 96 (10.42%)	10 / 91 (10.99%)	14 / 73 (19.18%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events	0	1	0
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	0 / 96 (0.00%)	0 / 91 (0.00%)	1 / 73 (1.37%)
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			

Arrhythmia			
subjects affected / exposed	1 / 96 (1.04%)	0 / 91 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nervous system disorders			
Grand mal convulsion			
subjects affected / exposed	0 / 96 (0.00%)	1 / 91 (1.10%)	0 / 73 (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
Blood and lymphatic system disorders			
Hypersplenism			
subjects affected / exposed	0 / 96 (0.00%)	0 / 91 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 96 (0.00%)	0 / 91 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Face oedema			
subjects affected / exposed	0 / 96 (0.00%)	1 / 91 (1.10%)	0 / 73 (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
Local swelling			
subjects affected / exposed	0 / 96 (0.00%)	1 / 91 (1.10%)	0 / 73 (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
Pyrexia			
subjects affected / exposed	1 / 96 (1.04%)	0 / 91 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			

subjects affected / exposed	1 / 96 (1.04%)	1 / 91 (1.10%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 96 (1.04%)	0 / 91 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 96 (0.00%)	1 / 91 (1.10%)	0 / 73 (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
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 96 (0.00%)	0 / 91 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	0 / 96 (0.00%)	0 / 91 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	1 / 96 (1.04%)	0 / 91 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 96 (0.00%)	0 / 91 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 96 (0.00%)	1 / 91 (1.10%)	0 / 73 (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
Oesophageal rupture			

subjects affected / exposed	1 / 96 (1.04%)	0 / 91 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 96 (1.04%)	0 / 91 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 96 (0.00%)	0 / 91 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 96 (1.04%)	1 / 91 (1.10%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 96 (0.00%)	0 / 91 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wheezing			
subjects affected / exposed	0 / 96 (0.00%)	0 / 91 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypogonadism			
subjects affected / exposed	0 / 96 (0.00%)	1 / 91 (1.10%)	0 / 73 (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			
Back pain			

subjects affected / exposed	1 / 96 (1.04%)	0 / 91 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in jaw			
subjects affected / exposed	0 / 96 (0.00%)	1 / 91 (1.10%)	0 / 73 (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			
Abdominal abscess			
subjects affected / exposed	0 / 96 (0.00%)	1 / 91 (1.10%)	0 / 73 (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
Acute tonsillitis			
subjects affected / exposed	1 / 96 (1.04%)	1 / 91 (1.10%)	0 / 73 (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
Amoebiasis			
subjects affected / exposed	1 / 96 (1.04%)	0 / 91 (0.00%)	0 / 73 (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
Anal abscess			
subjects affected / exposed	0 / 96 (0.00%)	0 / 91 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 96 (0.00%)	1 / 91 (1.10%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 96 (0.00%)	0 / 91 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			

subjects affected / exposed	0 / 96 (0.00%)	0 / 91 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 96 (1.04%)	0 / 91 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	0 / 96 (0.00%)	1 / 91 (1.10%)	0 / 73 (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
Herpes zoster			
subjects affected / exposed	1 / 96 (1.04%)	0 / 91 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 96 (0.00%)	0 / 91 (0.00%)	1 / 73 (1.37%)
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	1 / 96 (1.04%)	0 / 91 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			
subjects affected / exposed	0 / 96 (0.00%)	1 / 91 (1.10%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Pneumonia			
subjects affected / exposed	0 / 96 (0.00%)	0 / 91 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth infection			

subjects affected / exposed	0 / 96 (0.00%)	1 / 91 (1.10%)	0 / 73 (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
Urinary tract infection			
subjects affected / exposed	1 / 96 (1.04%)	0 / 91 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 96 (0.00%)	0 / 91 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Yersinia infection			
subjects affected / exposed	0 / 96 (0.00%)	0 / 91 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Calcium deficiency			
subjects affected / exposed	0 / 96 (0.00%)	0 / 91 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemosiderosis			
subjects affected / exposed	0 / 96 (0.00%)	1 / 91 (1.10%)	2 / 73 (2.74%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 96 (1.04%)	1 / 91 (1.10%)	0 / 73 (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
Hypocalcaemia			
subjects affected / exposed	0 / 96 (0.00%)	0 / 91 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron overload			

subjects affected / exposed	0 / 96 (0.00%)	2 / 91 (2.20%)	2 / 73 (2.74%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Extension DFO to DFO	Extension DFO to ICL	Extension ICL to DFO
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 29 (13.79%)	9 / 42 (21.43%)	0 / 1 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	0 / 29 (0.00%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Grand mal convulsion			
subjects affected / exposed	0 / 29 (0.00%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Hypersplenism			
subjects affected / exposed	0 / 29 (0.00%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 42 (2.38%)	0 / 1 (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
General disorders and administration site conditions			

Face oedema			
subjects affected / exposed	0 / 29 (0.00%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Local swelling			
subjects affected / exposed	0 / 29 (0.00%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 29 (0.00%)	1 / 42 (2.38%)	0 / 1 (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
Colitis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 29 (0.00%)	1 / 42 (2.38%)	0 / 1 (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
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 29 (0.00%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			

subjects affected / exposed	0 / 29 (0.00%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 29 (0.00%)	1 / 42 (2.38%)	0 / 1 (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
Oesophageal rupture			
subjects affected / exposed	0 / 29 (0.00%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 29 (0.00%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 42 (0.00%)	0 / 1 (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
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 29 (3.45%)	0 / 42 (0.00%)	0 / 1 (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

Wheezing			
subjects affected / exposed	1 / 29 (3.45%)	0 / 42 (0.00%)	0 / 1 (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			
Hypogonadism			
subjects affected / exposed	0 / 29 (0.00%)	1 / 42 (2.38%)	0 / 1 (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			
Back pain			
subjects affected / exposed	0 / 29 (0.00%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in jaw			
subjects affected / exposed	0 / 29 (0.00%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 29 (0.00%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute tonsillitis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 42 (2.38%)	0 / 1 (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
Amoebiasis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			

subjects affected / exposed	1 / 29 (3.45%)	0 / 42 (0.00%)	0 / 1 (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
Appendicitis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 42 (2.38%)	0 / 1 (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
Bronchitis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 42 (0.00%)	0 / 1 (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 / 29 (0.00%)	1 / 42 (2.38%)	0 / 1 (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 infection			
subjects affected / exposed	0 / 29 (0.00%)	1 / 42 (2.38%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 29 (0.00%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 29 (0.00%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver abscess			

subjects affected / exposed	0 / 29 (0.00%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth infection			
subjects affected / exposed	0 / 29 (0.00%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 29 (0.00%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 29 (0.00%)	1 / 42 (2.38%)	0 / 1 (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
Yersinia infection			
subjects affected / exposed	0 / 29 (0.00%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Calcium deficiency			
subjects affected / exposed	0 / 29 (0.00%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemosiderosis			

subjects affected / exposed	0 / 29 (0.00%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 42 (2.38%)	0 / 1 (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
Hypocalcaemia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 42 (2.38%)	0 / 1 (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
Iron overload			
subjects affected / exposed	0 / 29 (0.00%)	1 / 42 (2.38%)	0 / 1 (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	Core ICL670	Core DFO	Extension ICL to ICL
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 96 (62.50%)	58 / 91 (63.74%)	56 / 73 (76.71%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 96 (1.04%)	2 / 91 (2.20%)	0 / 73 (0.00%)
occurrences (all)	1	2	0
Injection site reaction			
subjects affected / exposed	0 / 96 (0.00%)	3 / 91 (3.30%)	0 / 73 (0.00%)
occurrences (all)	0	5	0
Pyrexia			
subjects affected / exposed	5 / 96 (5.21%)	5 / 91 (5.49%)	6 / 73 (8.22%)
occurrences (all)	6	5	11
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	4 / 96 (4.17%)	2 / 91 (2.20%)	5 / 73 (6.85%)
occurrences (all)	4	2	5
Dyspnoea			
subjects affected / exposed	4 / 96 (4.17%)	3 / 91 (3.30%)	1 / 73 (1.37%)
occurrences (all)	5	5	1
Nasal congestion			
subjects affected / exposed	1 / 96 (1.04%)	1 / 91 (1.10%)	1 / 73 (1.37%)
occurrences (all)	1	1	1
Oropharyngeal pain			
subjects affected / exposed	6 / 96 (6.25%)	2 / 91 (2.20%)	6 / 73 (8.22%)
occurrences (all)	6	2	6
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 96 (2.08%)	1 / 91 (1.10%)	4 / 73 (5.48%)
occurrences (all)	2	1	6
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	9 / 96 (9.38%)	5 / 91 (5.49%)	9 / 73 (12.33%)
occurrences (all)	12	5	15
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 96 (7.29%)	3 / 91 (3.30%)	8 / 73 (10.96%)
occurrences (all)	11	3	15
Blood creatinine increased			
subjects affected / exposed	8 / 96 (8.33%)	2 / 91 (2.20%)	9 / 73 (12.33%)
occurrences (all)	8	3	12
Ejection fraction decreased			
subjects affected / exposed	0 / 96 (0.00%)	0 / 91 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 96 (0.00%)	1 / 91 (1.10%)	1 / 73 (1.37%)
occurrences (all)	0	1	1
Platelet count increased			
subjects affected / exposed	2 / 96 (2.08%)	5 / 91 (5.49%)	3 / 73 (4.11%)
occurrences (all)	2	6	6
Protein urine present			

subjects affected / exposed	11 / 96 (11.46%)	8 / 91 (8.79%)	6 / 73 (8.22%)
occurrences (all)	22	11	14
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	0 / 96 (0.00%)	3 / 91 (3.30%)	0 / 73 (0.00%)
occurrences (all)	0	3	0
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 96 (5.21%)	5 / 91 (5.49%)	7 / 73 (9.59%)
occurrences (all)	7	10	11
Blood and lymphatic system disorders			
Thrombocytosis			
subjects affected / exposed	0 / 96 (0.00%)	4 / 91 (4.40%)	1 / 73 (1.37%)
occurrences (all)	0	4	1
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 96 (1.04%)	2 / 91 (2.20%)	4 / 73 (5.48%)
occurrences (all)	1	2	4
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 96 (7.29%)	2 / 91 (2.20%)	7 / 73 (9.59%)
occurrences (all)	11	2	11
Abdominal pain upper			
subjects affected / exposed	5 / 96 (5.21%)	5 / 91 (5.49%)	6 / 73 (8.22%)
occurrences (all)	10	7	11
Diarrhoea			
subjects affected / exposed	12 / 96 (12.50%)	4 / 91 (4.40%)	10 / 73 (13.70%)
occurrences (all)	16	4	20
Nausea			
subjects affected / exposed	6 / 96 (6.25%)	2 / 91 (2.20%)	4 / 73 (5.48%)
occurrences (all)	6	2	4
Vomiting			
subjects affected / exposed	6 / 96 (6.25%)	1 / 91 (1.10%)	6 / 73 (8.22%)
occurrences (all)	7	1	7
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	4 / 96 (4.17%)	0 / 91 (0.00%)	4 / 73 (5.48%)
occurrences (all)	5	0	5
Urticaria			
subjects affected / exposed	3 / 96 (3.13%)	3 / 91 (3.30%)	4 / 73 (5.48%)
occurrences (all)	3	3	4
Endocrine disorders			
Hypogonadism			
subjects affected / exposed	2 / 96 (2.08%)	2 / 91 (2.20%)	0 / 73 (0.00%)
occurrences (all)	2	3	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 96 (7.29%)	4 / 91 (4.40%)	5 / 73 (6.85%)
occurrences (all)	12	5	14
Back pain			
subjects affected / exposed	7 / 96 (7.29%)	4 / 91 (4.40%)	7 / 73 (9.59%)
occurrences (all)	7	4	10
Osteoporosis			
subjects affected / exposed	5 / 96 (5.21%)	2 / 91 (2.20%)	3 / 73 (4.11%)
occurrences (all)	5	2	6
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	1 / 96 (1.04%)	3 / 91 (3.30%)	1 / 73 (1.37%)
occurrences (all)	1	3	1
Bronchitis			
subjects affected / exposed	1 / 96 (1.04%)	3 / 91 (3.30%)	1 / 73 (1.37%)
occurrences (all)	2	4	2
Influenza			
subjects affected / exposed	10 / 96 (10.42%)	6 / 91 (6.59%)	11 / 73 (15.07%)
occurrences (all)	10	8	17
Nasopharyngitis			
subjects affected / exposed	8 / 96 (8.33%)	4 / 91 (4.40%)	12 / 73 (16.44%)
occurrences (all)	10	5	18
Otitis media			
subjects affected / exposed	1 / 96 (1.04%)	0 / 91 (0.00%)	1 / 73 (1.37%)
occurrences (all)	1	0	1

Pharyngitis			
subjects affected / exposed	3 / 96 (3.13%)	2 / 91 (2.20%)	4 / 73 (5.48%)
occurrences (all)	4	2	5
Tonsillitis			
subjects affected / exposed	1 / 96 (1.04%)	2 / 91 (2.20%)	4 / 73 (5.48%)
occurrences (all)	1	2	4
Upper respiratory tract infection			
subjects affected / exposed	8 / 96 (8.33%)	8 / 91 (8.79%)	13 / 73 (17.81%)
occurrences (all)	9	9	24
Urinary tract infection			
subjects affected / exposed	0 / 96 (0.00%)	4 / 91 (4.40%)	1 / 73 (1.37%)
occurrences (all)	0	4	1
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	3 / 96 (3.13%)	1 / 91 (1.10%)	5 / 73 (6.85%)
occurrences (all)	3	1	8

Non-serious adverse events	Extension DFO to DFO	Extension DFO to ICL	Extension ICL to DFO
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 29 (65.52%)	36 / 42 (85.71%)	1 / 1 (100.00%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 29 (0.00%)	3 / 42 (7.14%)	0 / 1 (0.00%)
occurrences (all)	0	5	0
Injection site reaction			
subjects affected / exposed	0 / 29 (0.00%)	3 / 42 (7.14%)	0 / 1 (0.00%)
occurrences (all)	0	5	0
Pyrexia			
subjects affected / exposed	3 / 29 (10.34%)	5 / 42 (11.90%)	1 / 1 (100.00%)
occurrences (all)	3	8	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 29 (0.00%)	2 / 42 (4.76%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
Dyspnoea			

subjects affected / exposed	0 / 29 (0.00%)	3 / 42 (7.14%)	0 / 1 (0.00%)
occurrences (all)	0	8	0
Nasal congestion			
subjects affected / exposed	0 / 29 (0.00%)	3 / 42 (7.14%)	0 / 1 (0.00%)
occurrences (all)	0	3	0
Oropharyngeal pain			
subjects affected / exposed	0 / 29 (0.00%)	5 / 42 (11.90%)	1 / 1 (100.00%)
occurrences (all)	0	7	1
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 29 (0.00%)	1 / 42 (2.38%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 29 (6.90%)	4 / 42 (9.52%)	1 / 1 (100.00%)
occurrences (all)	2	7	3
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 29 (3.45%)	2 / 42 (4.76%)	1 / 1 (100.00%)
occurrences (all)	1	3	3
Blood creatinine increased			
subjects affected / exposed	1 / 29 (3.45%)	3 / 42 (7.14%)	0 / 1 (0.00%)
occurrences (all)	2	6	0
Ejection fraction decreased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 42 (2.38%)	1 / 1 (100.00%)
occurrences (all)	0	1	1
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 29 (3.45%)	3 / 42 (7.14%)	0 / 1 (0.00%)
occurrences (all)	1	3	0
Platelet count increased			
subjects affected / exposed	6 / 29 (20.69%)	0 / 42 (0.00%)	0 / 1 (0.00%)
occurrences (all)	14	0	0
Protein urine present			
subjects affected / exposed	1 / 29 (3.45%)	7 / 42 (16.67%)	0 / 1 (0.00%)
occurrences (all)	1	10	0
Injury, poisoning and procedural complications			

Ligament sprain			
subjects affected / exposed	0 / 29 (0.00%)	3 / 42 (7.14%)	0 / 1 (0.00%)
occurrences (all)	0	4	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 29 (6.90%)	4 / 42 (9.52%)	0 / 1 (0.00%)
occurrences (all)	3	9	0
Blood and lymphatic system disorders			
Thrombocytosis			
subjects affected / exposed	2 / 29 (6.90%)	2 / 42 (4.76%)	0 / 1 (0.00%)
occurrences (all)	2	3	0
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 29 (0.00%)	3 / 42 (7.14%)	0 / 1 (0.00%)
occurrences (all)	0	3	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 29 (3.45%)	3 / 42 (7.14%)	0 / 1 (0.00%)
occurrences (all)	1	6	0
Abdominal pain upper			
subjects affected / exposed	3 / 29 (10.34%)	5 / 42 (11.90%)	0 / 1 (0.00%)
occurrences (all)	3	7	0
Diarrhoea			
subjects affected / exposed	0 / 29 (0.00%)	9 / 42 (21.43%)	1 / 1 (100.00%)
occurrences (all)	0	13	1
Nausea			
subjects affected / exposed	1 / 29 (3.45%)	4 / 42 (9.52%)	0 / 1 (0.00%)
occurrences (all)	1	5	0
Vomiting			
subjects affected / exposed	0 / 29 (0.00%)	4 / 42 (9.52%)	0 / 1 (0.00%)
occurrences (all)	0	4	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 29 (0.00%)	1 / 42 (2.38%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Urticaria			

subjects affected / exposed	3 / 29 (10.34%)	2 / 42 (4.76%)	0 / 1 (0.00%)
occurrences (all)	3	3	0
Endocrine disorders			
Hypogonadism			
subjects affected / exposed	0 / 29 (0.00%)	2 / 42 (4.76%)	1 / 1 (100.00%)
occurrences (all)	0	5	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 29 (6.90%)	2 / 42 (4.76%)	1 / 1 (100.00%)
occurrences (all)	2	4	2
Back pain			
subjects affected / exposed	1 / 29 (3.45%)	2 / 42 (4.76%)	0 / 1 (0.00%)
occurrences (all)	1	2	0
Osteoporosis			
subjects affected / exposed	1 / 29 (3.45%)	2 / 42 (4.76%)	1 / 1 (100.00%)
occurrences (all)	2	3	2
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	1 / 29 (3.45%)	3 / 42 (7.14%)	0 / 1 (0.00%)
occurrences (all)	1	3	0
Bronchitis			
subjects affected / exposed	0 / 29 (0.00%)	3 / 42 (7.14%)	0 / 1 (0.00%)
occurrences (all)	0	4	0
Influenza			
subjects affected / exposed	1 / 29 (3.45%)	7 / 42 (16.67%)	0 / 1 (0.00%)
occurrences (all)	1	11	0
Nasopharyngitis			
subjects affected / exposed	1 / 29 (3.45%)	6 / 42 (14.29%)	0 / 1 (0.00%)
occurrences (all)	2	6	0
Otitis media			
subjects affected / exposed	0 / 29 (0.00%)	1 / 42 (2.38%)	1 / 1 (100.00%)
occurrences (all)	0	1	1
Pharyngitis			
subjects affected / exposed	0 / 29 (0.00%)	3 / 42 (7.14%)	0 / 1 (0.00%)
occurrences (all)	0	3	0
Tonsillitis			

subjects affected / exposed	1 / 29 (3.45%)	3 / 42 (7.14%)	0 / 1 (0.00%)
occurrences (all)	1	3	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 29 (3.45%)	9 / 42 (21.43%)	0 / 1 (0.00%)
occurrences (all)	1	17	0
Urinary tract infection			
subjects affected / exposed	1 / 29 (3.45%)	4 / 42 (9.52%)	0 / 1 (0.00%)
occurrences (all)	1	5	0
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 29 (0.00%)	1 / 42 (2.38%)	0 / 1 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 April 2008	• Inclusion of subjects with myelodysplastic syndromes (MDS) (low and intermediate-1-Risk (INT-1) risk as per International Prognostic Scoring System (IPSS) for MDS) with myocardial iron • Patient-reported outcomes/quality of life (QoL) assessments were removed • Safety monitoring of ocular and audiometry tests was clarified • Protocol deviations were no longer permissible • Introduction of deferasirox PK profile assessments • Extension of the screening period to 23 days and the washout period to 5 days • Clarification on the statistical analysis sections and analysis and reporting of CMR images • Safety section was updated with newly available information on deferasirox
29 October 2008	• Inclusion of subjects with severe myocardial siderosis (MRI T2* <10 ms) with additional CMR assessments. A T2* of 6 ms was specified as the lower cut-off; therefore, the trial was open to subjects with a myocardial T2* ≥ 6 to 20 ms • Clarification of the DFO dosing and regimen in order to ensure adequate dosing was in line with current guidelines for subjects with myocardial siderosis • Added that subjects will have an option to switch treatment to either deferasirox or DFO in the extension phase, if judged to be of therapeutic benefit by the investigator • Update of safety monitoring sections
15 May 2009	• Amendment of the exclusion criteria and concomitant medication sections in order to ensure consistency with the Exjade and Desferal labels. • Frequency of audiometry and height assessments increased • Pumps equivalent to "Microject Crono" allowed for use in the study • Dose administration section was revised due to findings of increased deferasirox concentrations in serum when taken with food • Increased urine protein from the notable laboratory abnormalities was replaced by increased urine protein/creatinine ratio • Dose modifications in case of low serum ferritin values were applied to both treatment groups to avoid any bias between these groups
17 March 2010	• Update of safety profile and monitoring sections • Inclusion/exclusion criteria modification in order to include more subjects with iron overload requiring chelation therapy in the study • Relaxing of re-screening criteria that allows subjects to be re-screened after 3 months when T2* values are above or below eligibility criteria or LVEF is below eligibility and after 1 month when alanine aminotransferase, serum creatinine, or urine protein/urine creatinine ratio is above the eligibility criterion • The screening period was extended to 35 days due to the inability of some subjects to complete the screening assessment period • New specification stating that visits were to be scheduled as closely as possible to the original planned date and that the planned date should always relate to the baseline • Addition of confirmatory assessment after 1 month in case LVEF falls below 50% or myocardial T2* decreases by ≥ 33% (withdrawal criteria) • MRI, ocular and audiometry assessments scheduled not later than within 30 days after the relevant visit date • Clarified and aligned with ICH-E9 guidelines the definition in the analysis section of the core protocol and added definitions on analysis sets and analysis to be conducted in the extension phase • To adapt the dosing scheme in for patients whose weight was greater than 70 kg • Additional ocular assessments in the extension phase at month 18 were added

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Notes: