Clinical trial results:
An Open Label Trial Evaluating Cardiac T2* in Beta-thalassemia Patients on Deferasirox (ICL670) Treatment for 18 Months

Summary

EudraCT number	2015-003532-12
Trial protocol	Outside EU/EEA
Global end of trial date	04 November 2009

Results information

Result version number	v1 (current)
This version publication date	05 October 2016
First version publication date	05 October 2016

Trial information

Trial identification

Sponsor protocol code	CICL670AUS04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00447694
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 November 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 November 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate changes in cardiac iron as measured by MRI T2* from baseline to 25, 49, and 77 weeks of study in β-thalassemia patients with evidence of cardiac iron overload and normal cardiac function.

Protection of trial subjects:

Although not specified in the study protocol, use of rescue medication was recorded on the Concomitant medications/Significant non-drug therapies CRF after the start of study drug. Ongoing patient safety evaluations recommended in the Exjade package insert to be completed as standard of care and data will be recorded in patient' medical charts.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 February 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 28
Worldwide total number of subjects	28
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	2
Adolescents (12-17 years)	3
Adults (18-64 years)	23
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Thirty patients with abnormal T2*, but normal cardiac function were to be enrolled into this open-label, single-arm pilot trial. The screening period was to last up to 4 weeks. Patients were to be screened for eligibility to determine if they met all inclusion/exclusion criteria.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Deferasirox

Arm description:

Deferasirox was taken orally daily, 30 minutes before breakfast, at the same time every morning if possible.

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

Dosage and administration details:

Deferasirox tablets were dropped into water, orange juice, or apple juice and stirred until completely dispersed. For doses less than 1 g, tablets were dissolved in at least 100 mL (3.5 ounces) of liquid; for doses of 1 to 3 g, tablets were dissolved in at least 200 mL (7 ounces). After tablets were fully disintegrated, the liquid was promptly consumed. The starting dose chosen for all patients in this study was 30mg/kg/day. Patients who were currently on > 30 mg/kg/day of deferasirox could have continued on their pre-existing dose at study entry.

Number of subjects in period 1	Deferasirox
Started	28
Completed	22
Not completed	6
Abnormal laboratory value(s)	1
Consent withdrawn by subject	2
Adverse event, non-fatal	2
Abnormal test procedure result(s)	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	28	28	
Age categorical Units: Subjects			
Children (2-11 years)	2	2	
Adolescents (12-17 years)	3	3	
Adults (18-64 years)	23	23	
Age continuous Units: years			
arithmetic mean	22.6		
standard deviation	± 8.67	-	
Gender categorical Units: Subjects			
Female	20	20	
Male	8	8	

End points

End points reporting groups

Reporting group title	Deferasirox
Reporting group description: Deferasirox was taken orally daily, 30 minutes before breakfast, at the same time every morning if possible.	
Subject analysis set title	Intent-to-treat population (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Consisted of all patients registered on the study, whether or not they received treatment .	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description: Consisted of all patients who received at least one dose of study drug.	
Subject analysis set title	Completer population (CP)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Consisted of those patients who have a Week 77 MRI .	

Primary: MRI T2* and absolute change from baseline in MRI T2* during study

End point title	MRI T2* and absolute change from baseline in MRI T2* during study[1]
End point description: Cardiac T2* was measured in the short axis plane at the widest point of a 4-chamber localizer using custom breath-hold R2* gradient echo sequences modeled after techniques used by Anderson et al (2001) and Westwood et al (2003).	
End point type	Primary
End point timeframe: Baseline to 25, 49, 77, and 101 weeks of study	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analyses have not been specified for this primary end point. Study represents data in one arm only.

End point values	Completer population (CP)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: msec				
arithmetic mean (standard deviation)				
Baseline	9.92 (± 3.922)			
Week 25 (n= 21, 21, 21)	11.73 (± 6.091)			
Week 25 (n= 21, 21, 21) Change from Baseline	1.77 (± 3.203)			
Week 49	11.93 (± 6.489)			
Week 49 Change from Baseline	2.01 (± 3.792)			
Week 77	12.1 (± 6.461)			
Week 77 Change from Baseline	2.18 (± 3.927)			
Week 101 (n = 10, 10, 10)	11.3 (± 3.808)			

Week 101 (n = 10, 10, 10) Change from Baseline	3.31 (± 2.84)			

Statistical analyses

No statistical analyses for this end point

Secondary: Liver iron concentration (LIC) using MRI R2 methodology and change from baseline in LIC during study

End point title	Liver iron concentration (LIC) using MRI R2 methodology and change from baseline in LIC during study

End point description:

End point type	Secondary

End point timeframe:

Baseline to 25, 49, 77, and 101 weeks of study

End point values	Completer population (CP)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: mg Fe/g dw liver				
arithmetic mean (standard deviation)				
Baseline	19.85 (± 3.309)			
Week 25 (n= 21, 21, 21)	17.23 (± 15.393)			
Week 25 (n= 21, 21, 21) Change from Baseline	-2.89 (± 4.169)			
Week 49	17 (± 17.548)			
Week 49 Change from Baseline	-2.85 (± 4.883)			
Week 77	16.62 (± 20.114)			
Week 77 Change from Baseline	-3.23 (± 7.708)			
Week 101 (n = 10, 10, 10)	13.91 (± 19.44)			
Week 101 (n = 10, 10, 10) Change from Baseline	-6.42 (± 4.715)			

Statistical analyses

No statistical analyses for this end point

Secondary: Left Ventricular Ejection Fraction (LVEF) and change from baseline in

left ventricular ejection fraction during study

End point title	Left Ventricular Ejection Fraction (LVEF) and change from baseline in left ventricular ejection fraction during study

End point description:

End point type	Secondary

End point timeframe:

Baseline to 25, 49, 77, and 101 weeks of study

End point values	Completer population (CP)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: percent				
arithmetic mean (standard deviation)				
Baseline	64.01 (± 6.751)			
Week 25 (n = 21 21 21)	62.17 (± 6.352)			
Week 25 (n=21,21,21) Absolute change from baseline	-1.84 (± 7.306)			
Week 49 (n= 22,21,21)	61.61 (± 13.726)			
Week 49 (n=22,21,21)Absolute change from baseline	-2.68 (± 14.546)			
Week 77 (n= 22,21,21)	63.84 (± 6.112)			
Week 77 (n=22,21,21) Absolute change from baseline	0.11 (± 7.299)			
Week 101 (n=10,10,10)	67.1 (± 3.643)			
Week 101 (n=10,10,10)Absolute change from baseline	3.56 (± 3.983)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum ferritin and change from baseline in serum ferritin during study

End point title	Serum ferritin and change from baseline in serum ferritin during study

End point description:

End point type	Secondary

End point timeframe:

Baseline to 25, 49, 77, and 101 weeks of study

End point values	Completer population (CP)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: µg/L				
arithmetic mean (standard deviation)				
Baseline	4343.75 (± 3486.525)			
Week 25	4280.77 (± 5261.563)			
Week 25 Absolute change from baseline	-62.98 (± 2294.635)			
Week 49 (n= 21,21,21)	3759.29 (± 3966.107)			
Week 49 (n= 21,21,21)Absolute change from baseline	-593.36 (± 1534.04)			
Week 77 (n= 21,21,21)	3179.81 (± 3439.357)			
Week 77 (n= 21,21,21)Absolute change from baseline	-882.74 (± 1368.202)			
Week 101 (n = 10,10,10)	3339.4 (± 4320.809)			
Week 101(n =10,10,10)Absolute change from baseline	-425.05 (± 2245.139)			

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 Last Patient Last Visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups

Reporting group title	All patients

Reporting group description:

All patients

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 27 (29.63%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypoperfusion			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Shock			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Multi-organ failure			

subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	5 / 27 (18.52%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pharyngolaryngeal pain				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Mental status changes				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychotic disorder				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood phosphorus decreased				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Blood creatinine increased				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ejection fraction decreased				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urine analysis abnormal				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Splenic rupture				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fibula fracture				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Congenital, familial and genetic disorders				
Fanconi syndrome				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Arrhythmia				

subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tachycardia				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Unresponsive to stimuli				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Depressed level of consciousness				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Thrombocytopenia				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Disseminated intravascular coagulation				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal compartment syndrome				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Abdominal pain				
subjects affected / exposed	4 / 27 (14.81%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal oedema				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	3 / 27 (11.11%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatic failure				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic steatosis				

subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatitis			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Polyuria			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Aspergillosis			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis viral			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Bacterial infection				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes simplex				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection fungal				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Acidosis				
subjects affected / exposed	1 / 27 (3.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acidosis hyperchloraemic				

subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Anorexia			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 27 (100.00%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	4		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	4		
Urine output decreased			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Electrocardiogram ST-T change			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		

Blood creatinine increased subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Injury, poisoning and procedural complications Excoriation subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 3		
Vascular disorders Hypotension subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all) Left ventricular hypertrophy subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2 2 / 27 (7.41%) 2		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all)	9 / 27 (33.33%) 9 5 / 27 (18.52%) 5		
General disorders and administration site conditions Chest discomfort subjects affected / exposed occurrences (all) Chills subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Pyrexia	3 / 27 (11.11%) 3 2 / 27 (7.41%) 2 9 / 27 (33.33%) 10		

subjects affected / exposed	10 / 27 (37.04%)		
occurrences (all)	17		
Pain			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Abdominal pain			
subjects affected / exposed	7 / 27 (25.93%)		
occurrences (all)	7		
Vomiting			
subjects affected / exposed	6 / 27 (22.22%)		
occurrences (all)	8		
Nausea			
subjects affected / exposed	16 / 27 (59.26%)		
occurrences (all)	22		
Diarrhoea			
subjects affected / exposed	12 / 27 (44.44%)		
occurrences (all)	13		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 27 (37.04%)		
occurrences (all)	15		
Nasal congestion			
subjects affected / exposed	4 / 27 (14.81%)		
occurrences (all)	6		
Pharyngolaryngeal pain			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	7		
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Rash			

subjects affected / exposed	7 / 27 (25.93%)		
occurrences (all)	8		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 27 (22.22%)		
occurrences (all)	8		
Myalgia			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Pain in extremity			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Infections and infestations			
Sinusitis			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Nasopharyngitis			
subjects affected / exposed	11 / 27 (40.74%)		
occurrences (all)	20		
Vulvovaginal mycotic infection			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	4 / 27 (14.81%)		
occurrences (all)	5		
Metabolism and nutrition disorders			
Carnitine deficiency			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Vitamin B complex deficiency			

subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Hyperglycaemia			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Vitamin D deficiency			
subjects affected / exposed	5 / 27 (18.52%)		
occurrences (all)	5		
Zinc deficiency			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 November 2005	•visit schedule and frequency of laboratory assessments (reduced and/or simplified schedules) • laboratory assessments (changed frequency of iron metabolism assessments and addition of NTBI) • imaging assessments (omitted reproducibility of MRI T2* as a main study objective) • clarification of process (qualified study discontinuation secondary to decreases in MRI Ejection Fraction; reporting of SAEs) • dose escalation algorithm (allowed escalation to 40 mg/kg/day of study drug)
03 May 2006	• exclusion criteria (addition of AST > 250 U/L) • potential dose adjustments and discontinuations (simplified the algorithm) • dosing table (new table added for the 35 and 40 mg/kg/day doses) • appendix 2 (included the MRI details from all study sites) • appendix 3 (clarified methodology for sample collection and handling)
15 May 2007	• study extension (included a six month extension for eligible patients) • safety assessments/package insert updates (added safety assessments per the recommendation of the revised Exjade® package insert) • initial dose level (patients being treated at > 30 mg/kg/day prior to screening may have entered the trial at their pre-existing dose) • use of SQUID analysis for LIC determination • dose interruption and adjustment (changes made to simplify the algorithms)
09 October 2007	• SIR analysis (omitted from the study) • extension phase (changed T2* and LIC eligibility criteria; allowed local MRI results for meeting inclusion requirements)
10 September 2008	• extension phase (allowed patients to enter even if their additional 6 months extended beyond the completion of the core study)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported