Clinical trial results:
Multicenter, open label, prospective study to evaluate the efficacy and safety of deferasirox 30 mg/kg/day for 52 weeks, in transfusion-dependent beta-thalassemic patients with cardiac MRI T2* <20 msec

Summary

EudraCT number	2008-003230-22
Trial protocol	IT
Global end of trial date	05 May 2011

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	05 August 2015

Trial information

Trial identification

Sponsor protocol code	CICL670AIT07

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00879242
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 May 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 May 2011
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate the efficacy of deferasirox, administered daily at the dose of 30 mg/kg for 52 weeks, on iron overload and cardiac function in transfusion-dependent beta-thalassemic subjects with cardiac magnetic resonance imaging (MRI) T2* to be greater than (>) 5 milliseconds (msec) and less than (<) 20 msec.

The study was terminated when 20 subjects (less than required sample size i.e. 50) were included due to slow study recruitment rate as well as the concomitant availability of cardiac MRI T2* data in large cohorts of subjects treated with deferasirox.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 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	Italy: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	20
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was planned to be conducted at 4 centres in Italy. However, subjects were enrolled only at 2 centres.

Pre-assignment

Screening details:

A total of 20 subjects were enrolled into the study.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

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

Arms

Arm title	Deferasirox

Arm description:

Subjects received body-weight stratified dose of deferasirox 30 miligrams/kilograms (mg/kg) once daily for 52 weeks.

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

Dosage and administration details:

Deferasirox 30 mg/kg/day was administered for 52 weeks.

Number of subjects in period 1	Deferasirox
Started	20
Completed	14
Not completed	6
Consent withdrawn by subject	2
Adverse event, non-fatal	1
Protocol deviation	2
Lack of efficacy	1

Baseline characteristics

Reporting groups	
Reporting group title	Deferasirox
Reporting group description:	
Subjects received body-weight stratified dose of deferasirox 30 miligrams/kilograms (mg/kg) once daily for 52 weeks.	

Reporting group values	Deferasirox	Total	
Number of subjects	20	20	
Age categorical Units: Subjects			
Adults (20-37 years)	20	20	
Age continuous Units: years			
arithmetic mean	30.6		
standard deviation	± 4.9	-	
Gender categorical Units: Subjects			
Female	11	11	
Male	9	9	

End points

End points reporting groups

Reporting group title	Deferasirox

Reporting group description:

Subjects received body-weight stratified dose of deferasirox 30 miligrams/kilograms (mg/kg) once daily for 52 weeks.

Primary: Change from baseline in cardiac iron content as measured by Myocardial T2* technique at Week 52

End point title	Change from baseline in cardiac iron content as measured by Myocardial T2* technique at Week 52[1]

End point description:

Magnetic resonance Imaging (MRI) T2* technique was used to measure tissue iron in cardiac iron overload condition. A T2* 10--20 milliseconds (msec) indicated mild/moderate cardiac iron overload, and a T2* less than (<) 10 msec indicated severe cardiac iron overload. An unsatisfactory response was considered to be a monthly T2* improvement lower than 3% versus baseline. The analysis was performed in per-protocol (PP) population, defined as all enrolled subjects who received at least 1 dose of study drug, had no major protocol violations and completed the treatment study phase or withdrew from the study due to: a decrease of equal to or more than 1.2 msec in T2* versus baseline or a significant reduction in left ventricular ejection fraction (LVEF) according to clinical judgement, despite the deferasirox dose increase up to 40 mg/kg/day.

End point type	Primary

End point timeframe:

Baseline (screening), Week 52

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: No analysis provided for terminated study.

End point values	Deferasirox			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: milliseconds (msec)				
arithmetic mean (standard deviation)	()			

Notes:

[2] - Study was terminated, the required sample size for analysis was not met.

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	11.1

Reporting groups	
Reporting group title	Deferasirox 30 mg/kg/day
Reporting group description:	
Deferasirox 30 mg/kg/day	

Serious adverse events	Deferasirox 30 mg/kg/day		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 20 (10.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic neoplasm			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic steatosis			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 20 (5.00%)		
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	Deferasirox 30 mg/kg/day		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 20 (95.00%)		
Vascular disorders			
Hyperaemia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 20 (30.00%)		
occurrences (all)	8		
Chest pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Gait disturbance			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Influenza like illness			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Malaise			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	5		
Reproductive system and breast disorders			
Genital pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	6 / 20 (30.00%)		
occurrences (all)	9		
Rhinorrhoea			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Throat irritation			
subjects affected / exposed	6 / 20 (30.00%)		
occurrences (all)	10		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Blood creatinine increased			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Injury, poisoning and procedural			

complications			
Transfusion reaction			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Wound secretion			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Atrial tachycardia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Bradycardia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Palpitations			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	10 / 20 (50.00%)		
occurrences (all)	17		
Paraesthesia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		

Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Vestibular neuronitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Foreign body sensation in eyes			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Photophobia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	6		
Abdominal pain upper			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	7		
Colitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	5		
Flatulence			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Gastritis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Toothache			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Dermal cyst			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Eczema			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Pityriasis rosea			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	6		
Skin lesion			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Renal colic			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Back pain			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	6		
Bone pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Flank pain			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Pain in extremity			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Infections and infestations			
Cystitis			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Ear infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Influenza			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	5		
Oral herpes			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	4		
Rhinitis			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 October 2008	• Updating the safety assessment according to latest European Union label of deferasirox regarding liver safety and symptoms of gastrointestinal ulceration and hemorrhage • Updating exclusion criteria to comply with recommendations for liver safety. Treatment has been initiated only in patients with baseline liver transaminase levels up to 5 times the upper limit of the normal range. • Information about concomitant use of other medicinal products was updated according to latest SmPC as well. • Furthermore, the statistical methods and data analysis section was modified as it was specified how changes in growth velocity parameters had to be analyzed and reported.
18 November 2010	The anticipating closure of subject enrollment was reduced to 20, prior reaching the target sample size of 50 subjects.

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.

The study was terminated when 20 subjects were included due to slow study recruitment rate as well as the concomitant availability of cardiac MRI T2* data in large cohorts of subjects treated with deferasirox.

Notes: