Clinical trial results:
Open-label multi-center study of Exjade (deferasirox) for treatment of transfusional iron overload in MDS, thalassemia and other anemia patients.

Summary

EudraCT number	2015-003531-35
Trial protocol	Outside EU/EEA
Global end of trial date	18 May 2011

Results information

Result version number	v1 (current)
This version publication date	11 February 2017
First version publication date	11 February 2017

Trial information

Trial identification

Sponsor protocol code	CICL670ARU01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01250951
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	18 May 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 May 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective was to assess the degree of reduction of the ferritin level during Exjade therapy in the patients with transfusion iron overload.

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	18 May 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	Russian Federation: 108
Worldwide total number of subjects	108
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)	28
Adolescents (12-17 years)	15
Adults (18-64 years)	61
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Data about 3 subjects was not included in the statistical data management as it was decided by the Sponsoring Company (when these subjects were being included in the protocol) some regulations were violated. 111 subjects were enrolled but only 108 were analyzed.

Pre-assignment

Screening details:

A patient was given the study drug for the first time only when the results of the whole screening examination were obtained as well as the assessment of his correspondence to the inclusion/exclusion criteria was carried out.

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	Exjade

Arm description:

The patients were prescribed the drug in the initial dosage depending on the extent of iron overload and transfusion therapy.
-The initial dosage is 30 mg/kg/ day provided that the ferritin level >2500 µg/l and more than 4 transfusions of a donor erythrocytes is received per month
-The initial dosage is 10 mg/kg/day provided that the ferritin level <1500 µg/l and less than 2 transfusions of a donor erythrocytes is received per month;
-The initial dosage is 20 mg/kg/day in other cases.

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:

Each dosage of the drug was prepared when the dispersant tablets were dissolved in a glass of water or juice (100-200ml) until a homogeneous suspension occurred. The dosage was calculated in accordance with a patient's weight and was rounded upward to a full tablet. The drug was taken daily, 1 time a day, on an empty stomach, 30 minutes prior to a meal.

Number of subjects in period 1	Exjade
Started	108
Completed	63
Not completed	45
Adverse event, serious fatal	10
Non-medical reasons	1
Protocol violation	2
Adverse event, non-fatal	2

Drug side effect	1
Refusal to continue	17
Patient loss out of observation	9
Bone-marrow transplantation	3

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	108	108	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	28	28	
Adolescents (12-17 years)	15	15	
Adults (18-64 years)	61	61	
From 65-84 years	4	4	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	38.4		
standard deviation	± 26.37	-	
Gender categorical Units: Subjects			
Female	64	64	
Male	44	44	
Not recorded	0	0	

Subject analysis sets

Subject analysis set title	Adult group
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Adult group consisted of 65 patients the average age in this group is 59 years old.

Subject analysis set title	Children - 2-12 years old
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The mean age was 6.9 years old.

Subject analysis set title	Children - 13-17 years old
Subject analysis set type	Sub-group analysis

Subject analysis set description:

In the teenage group the average age was 15 years old.

Reporting group values	Adult group	Children - 2-12 years old	Children - 13-17 years old
Number of subjects	65	30	13
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	28	0
Adolescents (12-17 years)	0	2	13
Adults (18-64 years)	61	0	0
From 65-84 years	4	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	58	6.9	15.1
standard deviation	± 15.6	± 3.4	± 1.7
Gender categorical Units: Subjects			
Female	38	17	9
Male	27	13	4
Not recorded	0	0	0

End points

End points reporting groups

Reporting group title	Exjade

Reporting group description:

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Primary: To assess the degree of reduction of the ferritin level during Exjade therapy in the patients with transfusion iron overload.

End point title	To assess the degree of reduction of the ferritin level during Exjade therapy in the patients with transfusion iron overload.[1]

End point description:

Exjade efficacy was assessed by the degree of reduction of the ferritin serum level and by the evident manifestations of hemosiderosis of parenchymatous organs. For this reason the iron content in liver tissue and in cardiac muscle was conducted by means of magnetic resonance therapy once a month.

End point type	Primary

End point timeframe:

From Baseline for monthly assessments for up to 1 year

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: Analysis is not performed between 2 groups as this is a single arm study and combined output of all randomized patients that were analyzed.

End point values	Exjade			
Subject group type	Reporting group			
Number of subjects analysed	108[2]			
Units: mkg/l				
arithmetic mean (standard deviation)				
Baseline	3837.2 (± 3737.7)			
Month 1	3445.3 (± 3194.4)			
Month 2	3140.9 (± 2687.3)			

Month 3	2928.5 (± 2449.2)			
Month 4	2749 (± 2429.2)			
Month 5	2648.7 (± 2270)			
Month 6	2812.8 (± 2173)			
Month 7	2555.5 (± 2292.5)			
Month 8	2756.9 (± 2083.2)			
Month 9	1899.7 (± 1202.7)			
Month 10	3050.3 (± 5489.3)			
Month 11	2150.9 (± 1891.4)			
Month 12	2269.2 (± 2021.7)			

Notes:

[2] - 3 patients were not included in the statistical data management

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.

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	Unspecified
Dictionary version	0

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 108 (21.30%)		
number of deaths (all causes)	10		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute leukemia			
subjects affected / exposed	2 / 108 (1.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Cancer without primary neoplasm, bone metastasis			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Myelodysplastic Syndrome			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Vascular disorders			

Thromboembolia				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Vasovagal syncope				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombophlebitis, soft tissue infection				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorder, hypotension				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute coronary syndrome				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Aortic valve disorder				
subjects affected / exposed	2 / 108 (1.85%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac decompensation				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary edema				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			

Nervous system disorders			
Cerebrum neoplasm benign			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Flu-like semiotics			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oxymortia			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
DIC syndrome			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Thrombocytopenia			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Ear and labyrinth disorders			
Ear infection			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Toxic hepatitis			
subjects affected / exposed	2 / 108 (1.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			

subjects affected / exposed	2 / 108 (1.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 108 (51.85%)		
Investigations			
Transaminase level increase			
subjects affected / exposed	17 / 108 (15.74%)		
occurrences (all)	219		
Bilirubin level increase			
subjects affected / exposed	17 / 108 (15.74%)		
occurrences (all)	219		
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	11 / 108 (10.19%)		
occurrences (all)	219		
Infections and infestations			
Flu-like symptoms			
subjects affected / exposed	11 / 108 (10.19%)		
occurrences (all)	219		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 April 2009	It introduced the following changes: • Increasing the number of patients from 60 to 150; • Increasing the number of research centers from 7 to 20; • Increasing the patient observation duration from 4 to 4-6 months; • Lack of necessity to conduct all the completion procedures with the patients who have recalled their informed consent or refused to continue their participation in the trial; • New conditions for providing the study drug to the patients in terms of providing the centers with the drug at the expense of Novartis Pharma Company during the first 6 months of the therapy. Later if a medical institution isn't able to provide the drug, the patients continue to be observed within the protocol; • Lowering the cases of returning of the unused drug and giving the next portion of the study drug to the patients once every 3 months instead of once a month; • Optional mode of Visits 7-11 to the patients who have stopped taking the drug after 6 months of the trial; • Control MRI only to the patients who have been taking the drug during the whole period of the investigation; • Optional mode of clinical and biochemical blood and urine analyses and ferrum metabolism variables on Visits 7-11 with the patients who stopped taking the drug after 6 months of the trial; • Optional mode of USC, ECG, EchoCG, an oculist and an otolaryngologist consultations, audiographics on the Final Visit to the patients who stopped taking the drug after 6 months of the trial.
06 July 2009	The amendment introduced the following changes: • Change in the expected duration of the observation of the patients from 6 to 4 months after the last center was initiated. The whole period of patients selection was 8 months (from the time when the first center was initiated); • Addition to the inclusion criteria №2 the possibility to include patients with other rare forms of aplastic and hemolytic anemias after the Sponsor's preliminary approval; • Specification to the inclusion criteria №9 concerning the date when the pregnancy test should be done. Before the amendment fertile women must have done the test 7 days prior to the inclusion in the trial. After the amendment they should do the test 48 hours prior to the inclusion in the trial. Postmenopausal women must have their last menstruation not later than a year ago. • Allowance to conduct EchoCG, X-ray examination of the thoracic cage organs, MRI, audiogram from 2 weeks during the screening examination to 6 months prior to the inclusion in the trial; • Specification to dates when the interim Visits must be conducted (1 month ± 7 days from the date of inclusion in the protocol); • Prolonging the final Visit to 2 weeks; • Lack of necessity to conduct the glucose-resistance test to the patients who suffer from verified diabetes; • Allowance to use the standard methods of the particular institution to calculate the creatinine clearance; • In order to get the accurate results of the pregnancy tests some specification was done concerning the age categories of women patients (teenagers aged ≥ 10 y.o. with fixed menstrual cycle) and the number of negative results (there must be at least 2 negative results).

17 November 2009	The amendment introduced the following changes: • In accordance with the Sponsor’s decision the target number of patients must be decreased from 150 to 120; • Shortening of the expected duration of the patients selection from 4 to 2 months after the last center was initiated in order to make it 12 months total; • The patients should stay in the investigation and the Visits should continue even in case of the study drug has stopped being taken. Upon that the reasons for the participation completion weren’t alternated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported