Clinical trial results:
Multicentre, randomised, open label, non-inferiority active-controlled trial to evaluate the efficacy and safety of deferiprone compared to deferasirox in paediatric patients aged from 1 month to less than 18 years of age affected by transfusion-dependent haemoglobinopathies

Summary

EudraCT number	2012-000353-31
Trial protocol	IT GR Outside EU/EEA GB
Global end of trial date	21 September 2017

Results information

Result version number	v1 (current)
This version publication date	
First version publication date	

Trial information

Trial identification

Sponsor protocol code	DEEP-2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01825512
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Consorzio per Valutazioni Biologiche e Farmacologiche
Sponsor organisation address	Via Nicolò Putignani 178, Bari, Italy, 70122
Public contact	Donato Bonifazi, Consorzio per Valutazioni Biologiche e Farmacologiche Via Nicolò Putignani 178 70122 Bari-Italy, +39 0809751974, donatobonifazi@cvbf.net
Scientific contact	Mariagrazia Felisi, Consorzio per Valutazioni Biologiche e Farmacologiche Via Luigi Porta 14 27100 Pavia-Italy, +39 0382.25075, mariagraziafelisi@cvbf.net

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001126-PIP01-10
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 September 2017
Global end of trial reached?	Yes
Global end of trial date	21 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the non-inferiority of Deferiprone compared to Deferasirox in terms of changes in ferritin levels and cardiac iron concentration in paediatric patients affected by hereditary haemoglobinopaties requiring chronic transfusions and chelation.

Protection of trial subjects:

Study procedures were compliant with the Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data (Strasbourg, 28.I.1981).
All laboratory specimens, evaluation forms, reports, video recordings, and other records that leave the site have been identified only by the patient sequential number to maintain subject confidentiality.
During the trial, at each visit, all the assessments have been conducted with a constant attention to the minimisation of pain and distress to the patient.
The sponsor obtained favourable opinion/approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements prior to a site initiating the study in that country. Information Document was provided and written consent was obtained from the legal guardian for each subject before participation in the study. Children took part in the information process under the responsibility of parents and the investigator according to their age and maturity level.

Background therapy:

None

Evidence for comparator:

Deferasirox is the only oral chelator already on the market for the treatment of chronic iron overload in patients with beta-thalassemia aged 2 years and older.

Actual start date of recruitment	17 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 26
Country: Number of subjects enrolled	Italy: 62
Country: Number of subjects enrolled	Tunisia: 59
Country: Number of subjects enrolled	Egypt: 229
Country: Number of subjects enrolled	Albania: 40
Country: Number of subjects enrolled	Greece: 11

Country: Number of subjects enrolled	Cyprus: 8
Worldwide total number of subjects	435
EEA total number of subjects	107

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)	15
Children (2-11 years)	275
Adolescents (12-17 years)	145
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment is started on March 2014 and finished on July 2016.
23 clinical centres were involved in 7 EU and non-EU countries: Albania (2), Cyprus (1), Greece (1), Egypt (3), Italy (12), Tunisia (1), UK (3).

Pre-assignment

Screening details:

Screening period (day -28 to –7): Patients on their standard chelator schedule have been screened for eligibility
Washout period (day –6 to –1)

Pre-assignment period milestones

Number of subjects started	435
Number of subjects completed	390

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Any study drug dose assumed: 3
Reason: Number of subjects	Consent withdrawn by subject: 5
Reason: Number of subjects	Lost to Follow-up: 20
Reason: Number of subjects	Not meeting inclusion criteria: 17

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Deferiprone

Arm description:

Experimental arm in which patients are administered deferiprone 80 mg/mL oral solution

Arm type	Experimental
Investigational medicinal product name	Deferiprone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Patients administered DFP at 75-100 mg/kg/day for seven days per week. In patients aged less than 6 years the dose has been defined according to the results of the PK Study (Study DEEP-1, EudraCT n. 2012-000658-67). DFP daily dose did not exceed 100 mg/kg.
The investigational drug has been provided as 80 mg/mL oral solution packaged in 250 mL amber polyethylene terephthalate bottles with threaded neck. White polypropylene child-resistant caps with foam liners have been used as closures. Administration devices (CE marked) that facilitate accurate measurement of appropriate dose volumes were provided: graduated syringe (10 mL in steps of 0.2 mL) and agraduated measuring cup (30 mL in steps of 2.5 mL).

Arm title	Deferasirox

Arm description:

Control arm in which patients were administered deferasirox dispersible tablets

Arm type	Active comparator
Investigational medicinal product name	Deferasirox
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Orodispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Patients have been enrolled in the control arm at a DFX starting dose which depends on patient current therapy at screening.
For all naïve patients and patients on Deferiprone at screening the starting Deferasirox dose was 20 mg/kg body weight. If the patient's chelation therapy at screening was Deferoxamine, the starting dose of Deferasirox was numerically half that of the Deferoxamine dose (e.g. a patient receiving 40 mg/kg/day of Deferoxamine for 5 days per week (or equivalent) could be transferred to a starting dose of 20 mg/kg/day of Deferrasirox) but, in any case, to a starting dose not inferior to 20 mg/kg/day.
If the patient's chelation therapy at screening is Deferasirox, the patient starting dose of DFX was his/her current posology as long as this did not exceed 40 mg/kg.

Number of subjects in period 1[1]	Deferiprone	Deferasirox
Started	193	197
Completed	140	170
Not completed	53	27
Protocol deviation	2	3
Adverse event, non-fatal	26	8
Consent withdrawn by subject	12	7
missing data	2	1
Lost to follow-up	11	8

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects enrolled in the trial (N=435) differs from the number of subjects in the baseline period (N=390) because 45 enrolled subjects did not assume the study drugs

Baseline characteristics

Reporting groups	
Reporting group title	Deferiprone
Reporting group description:	
Experimental arm in which patients are administered deferiprone 80 mg/mL oral solution	
Reporting group title	Deferasirox
Reporting group description:	
Control arm in which patients were administered deferasirox dispersible tablets	

Reporting group values	Deferiprone	Deferasirox	Total
Number of subjects	193	197	390
Age categorical Units: Subjects			
<6	59	58	117
>=6 and < 10	47	47	94
>=10	87	92	179
Age continuous Units: months			
arithmetic mean	111.4	113.8	
standard deviation	± 55.17	± 57.24	-
Gender categorical Units: Subjects			
Female	80	93	173
Male	113	104	217
Disease Units: Subjects			
beta-Thalassemia major	175	177	352
Sickle Cell Syndrome	12	15	27
Thalassodrepanocytosis	3	2	5
Other Haemoglobinopathy	3	3	6

End points

End points reporting groups

Reporting group title	Deferiprone
Reporting group description:	
Experimental arm in which patients are administered deferiprone 80 mg/mL oral solution	
Reporting group title	Deferasirox
Reporting group description:	
Control arm in which patients were administered deferasirox dispersible tablets	

Primary: percentage of patients successfully chelated, as assessed by serum ferritin levels and cardiac MRI T2*

End point title	percentage of patients successfully chelated, as assessed by serum ferritin levels and cardiac MRI T2*
End point description:	
End point type	Primary
End point timeframe:	
Ferritin and MRI levels were measured at baseline (V3) and at V15 after 1 year of completed protocol.	

End point values	Deferiprone	Deferasirox		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	146		
Units: 271				
YES	69	80		
NO	56	66		

Statistical analyses

Statistical analysis title	Non-inferiority efficacy analysis
Comparison groups	Deferiprone v Deferasirox
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	CI
Parameter estimate	treatment success rate
Point estimate	-12.5
Confidence interval	
level	95 %
sides	1-sided
lower limit	-12.5

Secondary: Ferritin level	
End point title	Ferritin level
End point description:	
End point type	Secondary
End point timeframe: end of study - baseline	

End point values	Deferiprone	Deferasirox		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	166		
Units: ng/mL				
arithmetic mean (standard error)	-397.583 (± 121.794)	-398.184 (± 110.619)		

Statistical analyses

Statistical analysis title	GLM Analysis
Comparison groups	Deferiprone v Deferasirox
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.997
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.601
Confidence interval	
level	95 %
sides	2-sided
lower limit	-323.58
upper limit	324.781
Variability estimate	Standard error of the mean
Dispersion value	164.734

Secondary: Cardiac MRI T2*	
End point title	Cardiac MRI T2*
End point description:	
End point type	Secondary
End point timeframe: end of study - baseline	

End point values	Deferiprone	Deferasirox		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	59		
Units: ms				
arithmetic mean (standard error)	0.488 (± 1.284)	1.121 (± 1.169)		

Statistical analyses

Statistical analysis title	GLM Analysis
Comparison groups	Deferiprone v Deferasirox
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.717
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.633
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.085
upper limit	2.819
Variability estimate	Standard error of the mean
Dispersion value	1.741

Secondary: Liver MRI

End point title	Liver MRI
End point description:	
End point type	Secondary
End point timeframe: end of study - baseline	

End point values	Deferiprone	Deferasirox		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	60		
Units: mg/g				
arithmetic mean (standard error)	-0.848 (± 0.887)	-2.975 (± 0.776)		

Statistical analyses

Statistical analysis title	GLM model
Comparison groups	Deferiprone v Deferasirox
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.074
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.128
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.213
upper limit	4.468
Variability estimate	Standard error of the mean
Dispersion value	1.18

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From Baseline (V3) to the end of treatment (V15)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	Safety population
Reporting group description: -	
Reporting group title	Deferiprone
Reporting group description: -	
Reporting group title	Deferasirox
Reporting group description: -	

Serious adverse events	Safety population	Deferiprone	Deferasirox
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 390 (6.92%)	13 / 193 (6.74%)	14 / 197 (7.11%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events		0	0
Injury, poisoning and procedural complications			
Testicular injury			
subjects affected / exposed	1 / 390 (0.26%)	1 / 193 (0.52%)	0 / 197 (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
Surgical and medical procedures			
Splenectomy			
subjects affected / exposed	1 / 390 (0.26%)	1 / 193 (0.52%)	0 / 197 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	3 / 390 (0.77%)	3 / 193 (1.55%)	0 / 197 (0.00%)
occurrences causally related to treatment / all	3 / 3	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			

subjects affected / exposed	2 / 390 (0.51%)	2 / 193 (1.04%)	0 / 197 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sickle cell anaemia with crisis			
subjects affected / exposed	2 / 390 (0.51%)	0 / 193 (0.00%)	2 / 197 (1.02%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 390 (0.26%)	1 / 193 (0.52%)	0 / 197 (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
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 390 (0.51%)	1 / 193 (0.52%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	2 / 390 (0.51%)	0 / 193 (0.00%)	2 / 197 (1.02%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	1 / 390 (0.26%)	0 / 193 (0.00%)	1 / 197 (0.51%)
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			
Diarrhoea			
subjects affected / exposed	1 / 390 (0.26%)	0 / 193 (0.00%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	3 / 390 (0.77%)	2 / 193 (1.04%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	3 / 3	2 / 2	1 / 1

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 390 (0.51%)	0 / 193 (0.00%)	2 / 197 (1.02%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 390 (0.26%)	0 / 193 (0.00%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 390 (0.26%)	0 / 193 (0.00%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis meningococcal			
subjects affected / exposed	1 / 390 (0.26%)	0 / 193 (0.00%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpangina			
subjects affected / exposed	1 / 390 (0.26%)	0 / 193 (0.00%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 390 (0.77%)	2 / 193 (1.04%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	1 / 3	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	1 / 390 (0.26%)	0 / 193 (0.00%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 390 (0.51%)	1 / 193 (0.52%)	1 / 197 (0.51%)

occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes virus infection			
subjects affected / exposed	1 / 390 (0.26%)	0 / 193 (0.00%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impetigo			
subjects affected / exposed	1 / 390 (0.26%)	0 / 193 (0.00%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 390 (0.26%)	0 / 193 (0.00%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	Safety population	Deferiprone	Deferasirox
Total subjects affected by non-serious adverse events			
subjects affected / exposed	241 / 390 (61.79%)	152 / 193 (78.76%)	89 / 197 (45.18%)
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	31 / 390 (7.95%)	15 / 193 (7.77%)	16 / 197 (8.12%)
occurrences (all)	46	21	25
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	29 / 390 (7.44%)	18 / 193 (9.33%)	11 / 197 (5.58%)
occurrences (all)	41	26	15
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	60 / 390 (15.38%)	28 / 193 (14.51%)	32 / 197 (16.24%)
occurrences (all)	96	40	56
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	28 / 390 (7.18%)	20 / 193 (10.36%)	8 / 197 (4.06%)
occurrences (all)	33	24	9
Vomiting			
subjects affected / exposed	41 / 390 (10.51%)	33 / 193 (17.10%)	8 / 197 (4.06%)
occurrences (all)	52	42	10
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	28 / 390 (7.18%)	23 / 193 (11.92%)	5 / 197 (2.54%)
occurrences (all)	33	28	5
Infections and infestations			
Pharyngitis			
subjects affected / exposed	24 / 390 (6.15%)	15 / 193 (7.77%)	9 / 197 (4.57%)
occurrences (all)	29	18	11

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 February 2014	- It has been included as follows: serum creatinine must be assessed in duplicate (for the assessment of inclusion/exclusion criteria only) - It has been included as follows: serum transamninases, biliribin and alkaline phosphatase will be checked before the initiation of treatrment, every 2 weeks during the first month and monthly thereafter
10 February 2015	1. "Pharmacokinetics" have been modified to limit the number of patients involved in this assessment. 2."Exclusion criteria": The exclusion of female lactating patients has been added to avoid risk to breast-feeding infant. 3. "Dose Adjustments" allows the increase of IMPs in situations of stable ferritin levels (> 1500). 4. "Scale down adjustment for DFP and DFX (safety reasons)" has been revised. 5. "Visit schedule and evaluations" has been revised to include ferritin, haematology/biochemistry and CHQ questionnaire assessments also in case of patient withdrawal. 6."Pregnancy test" has been revised with the inclusion of the procedures allowed for contraception. 7. "Urinalysis" has been revised specifying the frequency of the assessment during the first month after initiation or modification of therapy. 8."Neutrophil count and Neutropenia management" has been integrated giving precise information with different degree of severity: Neutropenia/Agranulocytosis. 9."Concomitant medications" has been revised including the list of drug commonly associated with neutropenia. 10. "INTERRUPTION OF TREATMENT" has been revised to include worsening of cardiac MRI T2* values and prolonged IMP suspension (> 4 weeks) as additional criteria leading to premature withdrawal of the patient. 11. "Sample size and power on cardiac MRI T2*": the number of patients according to the different proposed scenarios (DFX/DFP success, non inferiority margin, power) has been re-calculated and the correct numbers are reported. 12. "Sample size and power on cardiac MRI T2* (percentage of successfully chelated patients)": the number of patients according to the different proposed scenarios (DFX/DFP success, non inferiority margin, power) has been re-calculated and the correct numbers are reported. 13."Instructions for rapid notification of Neutropenia" has been added to detail the procedure for the notification.
10 December 2015	1. "Inclusion Criteria": as new PK/dosing data of deferiprone in this age group (Study DEEP-1, EudraCT n. 2012-000658-67) are available, the inclusion criterion "for patients aged from 1 month to less than 6 years: known intolerance or contraindication to DFO" has been modified in order to allow children aged from 1 month to less than 6 years without known intolerance or contraindication to deferoxamine to be included in this study. 2. The dropout rate has been increased from 10% to 20% according to a reliable evaluation of the percentage of patients able to complete the study. 3. "Serum Creatinine" and "Urinalysis": the frequency of the assessment [weekly (± 7 days) during the first month after initiation or modification of therapy] has been revised.

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.

None reported

Notes: