Clinical trial results:
Multi-centre, oral single dose experimental and modelling study to evaluate the pharmacokinetics of deferiprone in patients aged from 1 month to less than 6 years of age affected by transfusion-dependent haemoglobinopathies

Summary

EudraCT number	2012-000658-67
Trial protocol	IT Outside EU/EEA
Global end of trial date	10 December 2013

Results information

Result version number	v1 (current)
This version publication date	23 March 2016
First version publication date	23 March 2016
Summary attachment (see zip file)	DEEP-1 Clinical Study Synopsis v1.8 25MAY15 (DEEP-1 Clinical Study Synopsis v1.8 25MAY15.pdf)

Trial information

Trial identification

Sponsor protocol code	DEEP-1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01740713
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Consorzio per Valutazioni Biologiche e Farmacologiche
Sponsor organisation address	via Luigi Porta, 14, Pavia, Italy, 27100
Public contact	Clinical Research Unit, Consorzio per Valutazioni Biologiche e Farmacologiche , 0039 0382 25075, mariagraziafelisi@cvbf.net
Scientific contact	Clinical Research Unit, Consorzio per Valutazioni Biologiche e Farmacologiche , 0039 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 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 February 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 December 2013
Global end of trial reached?	Yes
Global end of trial date	10 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the pharmacokinetics of deferiprone in paediatric patients aged from 1 month to less than 6 years

Protection of trial subjects:

The study was conducted in accordance with all applicable regulatory requirements: the European Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data, and the Convention of Human Rights and Biomedicine and its Additional Protocol on Biomedical Research (2005) and in accordance with "good clinical practice" (GCP), all applicable subject privacy requirements, and, the guiding principles of the 2008 Declaration of Helsinki. 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: -

Evidence for comparator: -

Actual start date of recruitment	31 January 2013
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: 21
Worldwide total number of subjects	21
EEA total number of subjects	21

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)	2

Children (2-11 years)	19
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment lasted from January 2013 to November 2013.

Pre-assignment

Screening details:

A total of 23 children affected by transfusion-dependent haemoglobinopathies were enrolled in this study. Of these 23 children, 2 were screening failures and 3 early terminations.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

This is a single blind PK study, i.e. both the site investigator and internal per sonnel at the University of Leiden are not blinded with regard to the administered dose level. Patients were randomised to 3 dose-levels:
Dose level 1: 25 mg/kg/day, equivalent to AUC values | 20-50 mg/L • h
Dose level 2: 50 mg/kg/day, equivalent to AUC values | 50.1-125 mg/L • h
Dose level 3: 100 mg/kg/day, equivalent to AUC values >125 mg/L • h

Arms

Are arms mutually exclusive?	Yes
Arm title	Dose level 1

Arm description:

25 mg/Kg/day

Arm type	Dose level
Investigational medicinal product name	deferiprone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Syrup
Routes of administration	Oral use

Dosage and administration details:

25 mg/Kg/day

Arm title	Dose level 2

Arm description:

50mg/Kg/day

Arm type	Dose level
Investigational medicinal product name	deferiprone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Syrup
Routes of administration	Oral use

Dosage and administration details:

50mg/Kg/day

Arm title	Dose level 3

Arm description:

100 mg/Kg/day

Arm type	Dose level
Investigational medicinal product name	deferiprone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Syrup
Routes of administration	Oral use

Dosage and administration details:

100 mg/Kg/die

Number of subjects in period 1	Dose level 1	Dose level 2	Dose level 3
Started	6	8	7
Completed	6	6	6
Not completed	0	2	1
Adverse event, non-fatal	-	2	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	21	21	
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)	2	2	
Children (2-11 years)	19	19	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	11	11	
Male	10	10	

Subject analysis sets

Subject analysis set title	PK population
Subject analysis set type	Full analysis

Subject analysis set description:

Data from 18 evaluable children (9 males and 9 females) were used for the pharmacokinetic analysis. Patients were randomised to 3 dose levels (8.3, 16.7 and 33.3 mg/kg) with 6 patients assigned to each group. 16 patients were diagnosed with β-thalassaemia major and 2 with thalassodrepanocytosis.

Reporting group values	PK population		
Number of subjects	18		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	2		
Children (2-11 years)	16		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		

Gender categorical Units: Subjects			
Female	9		
Male	9		

End points

End points reporting groups

Reporting group title	Dose level 1
Reporting group description: 25 mg/Kg/day	
Reporting group title	Dose level 2
Reporting group description: 50mg/Kg/day	
Reporting group title	Dose level 3
Reporting group description: 100 mg/Kg/day	
Subject analysis set title	PK population
Subject analysis set type	Full analysis

Subject analysis set description:

Data from 18 evaluable children (9 males and 9 females) were used for the pharmacokinetic analysis. Patients were randomised to 3 dose levels (8.3, 16.7 and 33.3 mg/kg) with 6 patients assigned to each group. 16 patients were diagnosed with β-thalassaemia major and 2 with thalassodrepanocytosis.

Primary: CL/F

End point title	CL/F[1]

End point description:

End point type	Primary

End point timeframe:

Blood samples, for quantification of DFP in plasma, were collected at the pre-defined sampling times.

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: THis is a modelling study. Concentrations was analysed with Nonlinear mixed effects modelling in NONMEM, version 7.2.0

End point values	PK population			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: litre/h				
number (not applicable)	8.3			

Statistical analyses

No statistical analyses for this end point

Primary: V/F

End point title	V/F[2]

End point description:

End point type	Primary

End point timeframe:

Blood samples, for quantification of DFP in plasma, were collected at the pre-defined sampling times.

Notes:

[2] - 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: This is a modelling study. Concentrations was analysed with Nonlinear mixed effects modelling in NONMEM, version 7.2.0

End point values	PK population			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: litre(s)				
number (not applicable)	18.7			

Statistical analyses

No statistical analyses for this end point

Primary: Ka

End point title	Ka[3]

End point description:

End point type	Primary

End point timeframe:

Blood samples, for quantification of DFP in plasma, were collected at the pre-defined sampling times.

Notes:

[3] - 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: This is a modelling study. Concentrations was analysed with Nonlinear mixed effects modelling in NONMEM, version 7.2.0

End point values	PK population			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: h*-1				
number (not applicable)	9.13			

Statistical analyses

No statistical analyses for this end point

Secondary: AUC_0-8

End point title	AUC_0-8

End point description:

End point type	Secondary

End point timeframe:

Blood samples, for quantification of DFP in plasma, were collected at the pre-defined sampling times.

End point values	Dose level 1	Dose level 2	Dose level 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: micromole(s)/litre*hour				
median (inter-quartile range (Q1-Q3))	116.7 (90.6 to 129)	210 (173.1 to 266.6)	428.8 (291.4 to 547.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax

End point title	Cmax

End point description:

End point type	Secondary

End point timeframe:

Blood samples, for quantification of DFP in plasma, were collected at the pre-defined sampling times.

End point values	Dose level 1	Dose level 2	Dose level 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: micromole(s)/litre				
median (inter-quartile range (Q1-Q3))	61.7 (45.1 to 80.7)	119.8 (106 to 154)	229.5 (179.7 to 278.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax

End point title	Tmax

End point description:

End point type	Secondary

End point timeframe:

Blood samples, for quantification of DFP in plasma, were collected at the pre-defiend sampling times.

End point values	Dose level 1	Dose level 2	Dose level 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: hour				
median (inter-quartile range (Q1-Q3))	0.33 (0.19 to 0.92)	0.33 (0.21 to 0.63)	0.37 (0.27 to 0.42)	

Statistical analyses

No statistical analyses for this end point

Secondary: Css

End point title	Css

End point description:

End point type	Secondary

End point timeframe:

Blood samples, for quantification of DFP in plasma, were collected at the pre-defiend sampling times.

End point values	Dose level 1	Dose level 2	Dose level 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: micromole(s)/litre				
median (inter-quartile range (Q1-Q3))	2.1 (1.6 to 2.3)	3.7 (3.1 to 4.9)	7.7 (5.1 to 10)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cmin

End point title	Cmin

End point description:

End point type	Secondary

End point timeframe:

Blood samples, for quantification of DFP in plasma, were collected at the pre-defiend sampling times.

End point values	Dose level 1	Dose level 2	Dose level 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: micromole(s)/litre				
median (inter-quartile range (Q1-Q3))	1.5 (0.92 to 2.6)	1.9 (0.79 to 5.5)	6.8 (3.1 to 13.9)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All the medical occurrences that started after the administration of the drug under investigation have been recorded as AEs till the follow-up visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Safety population

Reporting group description: -

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 21 (14.29%)		
Pregnancy, puerperium and perinatal conditions			
Infantile spitting up			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 September 2012	A substantial amendment (Amendment 1) for the notification of the change of sponsor's responsibility from Universiteit Leiden to Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) was approved on 26/09/2012.
29 October 2013	A last amendment (Amendment 2) was notified and accepted on 29/10/2013 to include an additional clinical site (Clinica Pediatrica Università – ASL 1, D.H: per Talassemia, Sassari, Italy).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported