Clinical trial results:
Open Label Phase II Evaluation of Pharmacokinetics, Efficacy, and Safety of Kedrion Human Plasma-derived Antihaemophilic Double Virus inactivated and Nanofiltered Factor IX Administered to Previously Treated Severe or Moderately Severe Hemophilia B Patients

Summary

EudraCT number	2005-006186-14
Trial protocol	IT
Global end of trial date	06 January 2016

Results information

Result version number	v1 (current)
This version publication date	20 April 2017
First version publication date	20 April 2017

Trial information

Trial identification

Sponsor protocol code	KB037

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Kedrion SpA
Sponsor organisation address	Località Ai Conti, Barga/Lucca, Italy, 55051
Public contact	Chiara Guarnieri/Roberta Macchia Kedrion SpA, Kedrion SpA, +39 0583767326, r.macchia@kedrion.com
Scientific contact	Chiara Guarnieri/Roberta Macchia Kedrion SpA, Kedrion SpA, +39 0583767320, c.guarnieri@kedrion.com

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	21 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 January 2016
Global end of trial reached?	Yes
Global end of trial date	06 January 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Pharmacokinetics (PK) evaluation in vivo incremental recovery; area under the curve (AUC);area under the moment curve (AUMC); plasma half-life (tœ),determination of the time necessary to reach the peak plasma concentration (Tmax),clearance (CL), mean permanence time (MRT),distribution volume at steady state (Vdss),peak plasma concentration (Cmax) Efficacy and Safety evaluation Efficacy: 1) Evaluation of the haemostatic efficacy of Kedrion human plasma-derived double virus inactivated and nanofiltered factor IX (henceforth: Investigational Medicinal Product- IMP) in the management of acute bleeding events. Safety: 1) Assessment of the risk of inhibitor (neutralizing anti factor IX antibodies) development in conjunction with infusion of the IMP throughout the study period 2) Assessment of thrombogenicity of the IMP 3) Assessment of the short and medium term safety of the IMP, when administered to severe/moderately severe Previously Treated Patients

Protection of trial subjects:

Subjects may withdraw their consent for participation in the study at any time without prejudice. Additionally, the Investigator may withdraw a subject if, in his/her clinical judgment, it is in the best interest of the subject or if the subject cannot comply with the protocol. Wherever possible, the tests and evaluations listed for the termination visit should be carried out. The sponsor should be notified of all study withdrawals within 24 hours.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 June 2010
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	Romania: 9
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Turkey: 1
Worldwide total number of subjects	16
EEA total number of subjects	15

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)	16
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	16
Number of subjects completed	16

Period 1

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

Arms

Arm title	single arm

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Nanofiltered Factor IX
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pharmacokinetic: 50 + 5 IU/Kg BW
Prophylactic regimen:
The frequency of FIX was twice/week. The IMP was administered iv at a maximum infusion rate of 10 ml/min. The dose administered was 30-40 IU/kg BW with the exact dose determined by the Investigator and rounded up to the nearest whole vial.
Once the prophylactic dose and regimen have been established, every effort had to be made to maintain that regimen throughout the study period. Changes in the dosing regimen might have been made at the Investigator’s discretion.
On-Demand regimen
In the event that the subject experienced a bleed that requires infusion of FIX, the subjects had to be treated exclusively with the IMP, administered iv at a maximum infusion rate of 10 mL/min. The dose and time intervals between doses used to treat the bleed will be at the discretion of the Investigator.
The required initial dosage may eventually be determined using the following formula:
BW (kg) x desired Factor IX increase% x 1.2

Number of subjects in period 1	single arm
Started	16
Completed	16

Baseline characteristics

Reporting groups

Reporting group title	overall trial (overall period)

Reporting group description: -

Reporting group values	overall trial (overall period)	Total	
Number of subjects	16	16	
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)	0	0	
Adolescents (12-17 years)	1	1	
Adults (18-64 years)	15	15	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	40.5		
full range (min-max)	17 to 69	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	16	16	

Subject analysis sets

Subject analysis set title	full population
Subject analysis set type	Full analysis

Subject analysis set description:

-All enrolled patients population: all enrolled subjects in the trial (16)
-Efficacy population: all enrolled subjects, who received at least one infusion of IMP, completing the planned minimum 6 months exposure days, plus additional 6 months or 50 exposure days (whichever comes first) (14)
-Per Protocol population: all Efficacy population subjects with no major protocol violations (14)
-PK population: all enrolled subjects who received at least one infusion of IMP and participated in the PK phase (two PK determinations, once at the study entry and the second one after 6 months) (14)
-Safety population: all enrolled subjects who received at least one infusion of IMP. An early termination does not result in the exclusion of patients from this population (16)

Reporting group values	full population		
Number of subjects	16		
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)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	1		
Adults (18-64 years)	15		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	40.5		
full range (min-max)	17 to 69		
Gender categorical			
Units: Subjects			
Female	0		
Male	16		

End points

End points reporting groups

Reporting group title	single arm
Reporting group description: -	
Subject analysis set title	full population
Subject analysis set type	Full analysis

Subject analysis set description:

-All enrolled patients population: all enrolled subjects in the trial (16)
-Efficacy population: all enrolled subjects, who received at least one infusion of IMP, completing the planned minimum 6 months exposure days, plus additional 6 months or 50 exposure days (whichever comes first) (14)
-Per Protocol population: all Efficacy population subjects with no major protocol violations (14)
-PK population: all enrolled subjects who received at least one infusion of IMP and participated in the PK phase (two PK determinations, once at the study entry and the second one after 6 months) (14)
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Primary: FIX concentration at 6 months (6 h post infusion)

End point title	FIX concentration at 6 months (6 h post infusion)[1]

End point description:

End point type	Primary

End point timeframe:

First PK at Time 0
Second PK after 6 months

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: Pharmacokinetic Analyses:
PK parameters were evaluated using a non-compartmental model.
Different types of paramenters were estimated: Slope, Rate constant, Elinination rate constant, α and β half life, Cmax, Tmax, AUC, AUMC and MRT, Vdss, Vd, Cl
Each parameter was summarized by mean and SD of the mean. The differences of means (baseline vs 6 months) will be evaluated using paired T test.
All PK concentrations were summarized by means of summary statistics for each timepoint

End point values	single arm			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: UI/dl				
arithmetic mean (standard deviation)	52.4 (± 15.28)			

Statistical analyses

No statistical analyses for this end point

Primary: Efficacy endpoint(mean of bleed/month)

End point title	Efficacy endpoint(mean of bleed/month)[2]

End point description:

End point type	Primary

End point timeframe:

mean number of new bleeds per month (both the total number and those secondary to trauma) during the all study period

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: Efficacy Analysis:
Efficacy data reported on the CRF and on the patient diary was combined and evaluated by analyzing:
- the number of new bleeds per month during the study, total or those secondary to trauma.
These parameters were summarized by means and 95% confidence interval of mean

End point values	single arm			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Number of bleed/Month				
median (full range (min-max))	0.1 (0 to 3.2)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: AEs were reported for all the study period	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1
Reporting groups	
Reporting group title	Safety population
Reporting group description: All patients who received at least 1 infusion with IMP	

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 16 (6.25%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Chest pain	Additional description: Chest wall pain		
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0.44 %

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 16 (37.50%)		
Investigations			
Alanine aminotransferase increased	Additional description: ALT increase		
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Vascular disorders			
Hypertension	Additional description: Arterial hypertension		
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		

Surgical and medical procedures			
dental operation	Additional description: Dental procedure		
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Nervous system disorders			
Headache	Additional description: Headache		
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Paresthesia	Additional description: Bilateral paresthesia left hand second third and fourth finger		
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
General disorders and administration site conditions			
asthenia	Additional description: Mild asthenia due to mild liver failure post surgery		
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Nausea	Additional description: Nausea		
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Teething	Additional description: Teeth pain		
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
erythema facial	Additional description: Facial and neck erythema		
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Muscle spasms	Additional description: Muscles cramps		
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Infections and infestations			
Upper respiratory tract infection	Additional description: Acute upper respiratory tract infection		
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		

Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 December 2009	Amendment 1 main changes: 1. Monitoring and Quality activities were outsourced to the CRO Sintesi Research S.r.l. 2. Number of patients updated from "not less than 20" to "at least 20" according to CPMP/BPWG/198/95 rev. 1 Guideline 3. Exclusion of adolescent patients from 12 to 18 years, and consequently deletion of the inclusion criteria "weight>35 Kg" 4. PK evaluations: wash-out period changed from "4-7 days" to "at least 4 (7 if possible)", according to the reference Guideline. 5. Safety: Inhibitors evaluations: IgE, IgG1, IgG2, IgG3 ed IgG4 dosage against FIX was added in case of patients who develop anaphylaxis and/or inhibitors according to CPMP/BPWG/198/95 rev. 1 "Note for Guidance on the Clinical Investigation of Human Plasma Derived Factor VIII and IX Products"
27 February 2012	Amendment 2 main changes: Only administrative changes

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
06 January 2016	Serious delays on the enrollment timelines in all the countries involved in the trial (Italy, Turkey and Romania), have had a negative impact on the IMP stocks dedicated to the study, and in some cases the IMP expired before its use. In order to guarantee the IMP delivery, the available IMP at that time was used to treat patients already enrolled, waiting for a new production of the product. After that the study was temporarily suspended waiting for the availability of new IMP. Unfortunately no new production of nanofiltered FIX was done and the final decision was to close definitely the study, with only 16 enrolled patients (Protocol required 20 patients)	-

Notes:

Limitations and caveats

None reported