Clinical trial results:
A 12-week, Multicenter, Pharmacokinetic and Safety Study of Human Plasma-Derived Factor XIII Concentrate in Subjects with Congential Factor XIII Deficiency

Estudio de 12 semanas, multicéntrico, de farmacocinética y seguridad del concentrado de factor XIII derivado del plasma humano en sujetos con deficiencia congénita de factor XIII

Summary

EudraCT number	2009-010387-41
Trial protocol	ES
Global end of trial date	24 February 2010

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	BI71023_2002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00883090
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CSL Behring LLC
Sponsor organisation address	1020 First Avenue, King of Prussia, United States, 19406-0901
Public contact	Clinical Trial Disclosure Manager, CSL Behring, clinicaltrials@cslbehring.com
Scientific contact	Clinical Trial Disclosure Manager, CSL Behring, clinicaltrials@cslbehring.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 May 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 February 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to generate steady-state PK Factor XIII data in subjects with congential Factor XIII deficiency.

Protection of trial subjects:

This study was carried out in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice guidelines and standard operating procedures for clinical research and development at CSL Behring (CSLB).
The study protocol and all amendments were approved by the Independent Ethics Committee(s) (IECs) / Institutional Review Board(s) (IRBs) of the participating centers.
Before undergoing screening procedures for possible enrollment into the study, subjects were informed, in an understandable form, about the nature, scope, and possible consequences of the study. The investigator was responsible for obtaining a subject's written informed consent to participate in the study.

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	Spain: 5
Country: Number of subjects enrolled	United States: 10
Worldwide total number of subjects	15
EEA total number of subjects	5

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)	3

Adolescents (12-17 years)	2
Adults (18-64 years)	10
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eligible subjects had documented congenital FXIII deficiency requiring prophylactic treatment with a FXIII containing product. Males and females of any age with congenital FXIII deficiency could participate in the study.

Pre-assignment

Screening details:

At the Screening Visit, blood for determination of viral markers, serum aspartate transaminase (AST) and alanine transaminase (ALT) levels, and, if female of childbearing potential, pregnancy testing was obtained.

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	Factor XIII

Arm description:

Subjects received 40 U/kg of Factor XIII per administration every 28 days for 3 doses administered as a bolus IV injection.

Arm type	Experimental
Investigational medicinal product name	Factor XIII Concentrate (Human)
Investigational medicinal product code	B17023
Other name	Fibrogammin® P, Cluvot®
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received 40 U/kg of Factor XIII Concentrate (Human) per administration every 28 days for 3 doses administered as a bolus intravenous (IV) injection at 250 U/minute (when reconstituted 250 U/minute equals 4mL/minute).

Number of subjects in period 1	Factor XIII
Started	15
Treated	14
Completed	13
Not completed	2
Consent withdrawn by subject	1
Sponsor's administrative decision	1

Baseline characteristics

Reporting groups	
Reporting group title	Factor XIII
Reporting group description:	
Subjects received 40 U/kg of Factor XIII per administration every 28 days for 3 doses administered as a bolus IV injection.	

Reporting group values	Factor XIII	Total	
Number of subjects	15	15	
Age categorical Units: Subjects			
Age continuous			
Based on the safety population of 14 treated subjects			
Units: years			
arithmetic mean	24		
standard deviation	± 12.55	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	8	8	

End points

End points reporting groups

Reporting group title	Factor XIII

Reporting group description:

Subjects received 40 U/kg of Factor XIII per administration every 28 days for 3 doses administered as a bolus IV injection.

Primary: Peak FXIII Concentration at Steady State

End point title	Peak FXIII Concentration at Steady State[1]

End point description:

End point type	Primary

End point timeframe:

12 weeks

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 formal testing of hypotheses was performed.

End point values	Factor XIII			
Subject group type	Reporting group			
Number of subjects analysed	13[2]			
Units: IU/mL				
arithmetic mean (standard deviation)	0.9 (± 0.2)			

Notes:

[2] - The PK population comprised all subjects in the safety population who completed the study.

Statistical analyses

No statistical analyses for this end point

Primary: Trough FXIII Concentration at Steady State

End point title	Trough FXIII Concentration at Steady State[3]

End point description:

End point type	Primary

End point timeframe:

12 weeks

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: No formal testing of hypotheses was performed.

End point values	Factor XIII			
Subject group type	Reporting group			
Number of subjects analysed	13[4]			
Units: IU/mL				
arithmetic mean (standard deviation)	0.05 (± 0.05)			

Notes:

[4] - PK population

Statistical analyses

No statistical analyses for this end point

Primary: Time to Peak Concentration

End point title	Time to Peak Concentration[5]

End point description:

End point type	Primary

End point timeframe:

12 weeks

Notes:

[5] - 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 formal testing of hypotheses was performed.

End point values	Factor XIII			
Subject group type	Reporting group			
Number of subjects analysed	13[6]			
Units: hours				
arithmetic mean (standard deviation)	1.7 (± 1.44)			

Notes:

[6] - PK population

Statistical analyses

No statistical analyses for this end point

Primary: Incremental Recovery

End point title	Incremental Recovery[7]

End point description:

Incremental recovery is defined as the maximum (peak) FXIII activity (IU/mL) obtained after infusion, per dose of FXIII (IU/kg) administered.

End point type	Primary

End point timeframe:

12 weeks

Notes:

[7] - 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 formal testing of hypotheses was performed.

End point values	Factor XIII			
Subject group type	Reporting group			
Number of subjects analysed	13[8]			
Units: IU/mL/IU/kg				
arithmetic mean (standard deviation)	0.02 (± 0.01)			

Notes:

[8] - PK population

Statistical analyses

No statistical analyses for this end point

Primary: Terminal Half-life

End point title	Terminal Half-life[9]

End point description:

End point type	Primary

End point timeframe:

12 weeks

Notes:

[9] - 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 formal testing of hypotheses was performed.

End point values	Factor XIII			
Subject group type	Reporting group			
Number of subjects analysed	13[10]			
Units: days				
arithmetic mean (standard deviation)	6.6 (± 2.29)			

Notes:

[10] - PK population

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Curve at Steady State

End point title	Area Under the Curve at Steady State[11]

End point description:

End point type	Primary

End point timeframe:

12 weeks

Notes:

[11] - 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 formal testing of hypotheses was performed.

End point values	Factor XIII			
Subject group type	Reporting group			
Number of subjects analysed	13[12]			
Units: IU*hr/mL				
arithmetic mean (standard deviation)	184 (± 65.78)			

Notes:

[12] - PK Population

Statistical analyses

No statistical analyses for this end point

Primary: Clearance

End point title	Clearance[13]

End point description:

End point type	Primary

End point timeframe:

12 weeks

Notes:

[13] - 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 formal testing of hypotheses was performed.

End point values	Factor XIII			
Subject group type	Reporting group			
Number of subjects analysed	13[14]			
Units: mL/hr/kg				
arithmetic mean (standard deviation)	0.25 (± 0.09)			

Notes:

[14] - PK population

Statistical analyses

No statistical analyses for this end point

Primary: Volume of Distribution at Steady State

End point title	Volume of Distribution at Steady State[15]

End point description:

End point type	Primary

End point timeframe:

12 weeks

Notes:

[15] - 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 formal testing of hypotheses was performed.

End point values	Factor XIII			
Subject group type	Reporting group			
Number of subjects analysed	13[16]			
Units: mL/kg				
arithmetic mean (standard deviation)	51.1 (± 12.61)			

Notes:

[16] - PK population

Statistical analyses

No statistical analyses for this end point

Primary: Mean Residence Time

End point title	Mean Residence Time[17]

End point description:

End point type	Primary

End point timeframe:

12 weeks

Notes:

[17] - 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 formal testing of hypotheses was performed.

End point values	Factor XIII			
Subject group type	Reporting group			
Number of subjects analysed	13[18]			
Units: days				
arithmetic mean (standard deviation)	10 (± 3.45)			

Notes:

[18] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events

End point title	Number of Participants with Adverse Events

End point description:

End point type	Secondary

End point timeframe:

16 weeks

End point values	Factor XIII			
Subject group type	Reporting group			
Number of subjects analysed	14[19]			
Units: participants	8			

Notes:

[19] - The safety population comprised all subjects who received a dose of Factor XIII.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Clinically Significant Laboratory Safety Parameter Values

End point title	Number of Participants with Clinically Significant Laboratory Safety Parameter Values

End point description:

Number of participants with clinically significant laboratory safety parameter values. The laboratory safety parameters measured included serum chemistries, hematology and urinalysis.

End point type	Secondary

End point timeframe:

16 weeks

End point values	Factor XIII			
Subject group type	Reporting group			
Number of subjects analysed	14[20]			
Units: participants	0			

Notes:

[20] - Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Clinically Significant Vital Signs

End point title	Number of Participants with Clinically Significant Vital Signs

End point description:

Number of participants with clinically significant vital signs. The vital signs measured included blood pressure, pulse rate and temperature. Clinically significant changes in vital signs were to be reported as adverse events.

End point type	Secondary

End point timeframe:

16 weeks

End point values	Factor XIII			
Subject group type	Reporting group			
Number of subjects analysed	14[21]			
Units: participants	0			

Notes:

[21] - safety population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The time frame for adverse event (AE) reporting was up to 16 weeks and comprised the time from giving written informed consent (during screening) to 28 days after the last administration of study treatment.

Adverse event reporting additional description:

Reporting group is comprised of all subjects treated with Factor FXIII Concentrate (Human) (FXIII).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups

Reporting group title	Factor XIII

Reporting group description:

Subjects received 40 U/kg of Factor XIII per administration every 28 days for 3 doses administered as a bolus IV injection.

Serious adverse events	Factor XIII		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (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	Factor XIII		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 14 (57.14%)		
Investigations			
Fibrin D dimer increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Prothrombin increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Thrombin-antithrombin III complex increased			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Ankle injury			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Bruising of arm			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Contusion of knee			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Contusion of toe			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Penile adhesion			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Infections and infestations			
Acute bronchitis			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Flu			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Infected sebaceous cyst			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		

Tinea corporis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 1 1 / 14 (7.14%) 1		
Metabolism and nutrition disorders Borderline diabetes subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 February 2009	The dose for all 3 treatments was calculated based on screening weight rather than baseline weight Updated the inclusion criteria to include males and females of any age with congenital Factor XIII deficiency The AE reporting requirement was changed from 30 days to 28 days Removed the requirement to collect further information if any AEs were experienced after discontinuing participation in the study
09 July 2009	The number of subjects planned for enrollment was updated to "approximately" 15 An inclusion criterion was changed from "Eligible subjects will have been diagnosed with severe congenital Factor XIII deficiency (<10 U/dL at diagnosis)" to "Eligible subjects will have documented congenital Factor XIII deficiency that requires prophylactic treatment with a Factor XIII containing product" Updated the inclusion criteria to include receipt of full hepatitis B vaccination and/or was hepatitis B surface antibody positive Excluded subjects with known or suspected to have antibodies towards Factor XIII Removed the following exclusion criterion: "Negative serology for hepatitis B and has not received a full hepatitis B vaccination" Updated the PK statistical analysis to include calculation with and without adjustment for any unknown remaining endogenous Factor XIII levels Added guidance for subjects who experienced a bleeding event requiring additional dosing with a Factor XIII-containing product Added guidance for subjects who were actively bleeding at the time of Dose 3 (main PK visit)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported