Clinical trial results:
A Prospective, Multicenter, Open-label, Phase 3b Study of Human Plasma-Derived Factor XIII Concentrate in Subjects with Congenital Factor XIII Deficiency

Estudio prospectivo, multicéntrico, con etiqueta abierta, en fase 3b, del concentrado de factor XIII derivado del plasma humano en sujetos con deficiencia congénita de factor XIII

Summary

EudraCT number	2009-010722-19
Trial protocol	ES
Global end of trial date	27 April 2011

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_3001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00885742
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	22 August 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 April 2011
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 collect and evaluate observational long term efficacy data of Factor XIII Concentrate (Human) with regard to the frequency and severity of bleeding episodes in subjects with congenital 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	04 August 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: 3
Country: Number of subjects enrolled	United States: 38
Worldwide total number of subjects	41
EEA total number of subjects	3

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)	8

Adolescents (12-17 years)	8
Adults (18-64 years)	23
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects who completed the PK dosing study (Study BI71023_2002) were offered participation in this study. Participation was also offered to subjects not enrolled in the PK dosing study or who were enrolled in a clinical study being conducted under a separate investigator initiated Investigational new drug (IND) application (BB-IND 5986).

Pre-assignment

Screening details:

A 4-week screening period preceded the 12-month treatment phase. Forty one subjects were enrolled and received at least 1 dose of Factor XIII (FXIII) Concentrate (Human).

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:

Initially, subjects received Factor XIII Concentrate (Human) at a dose of 40 U/kg by intravenous (IV) infusion. Subsequent doses were guided by the individual subject's Factor XIII activity levels, with the objective of dosing every 28 days (4 weeks) to maintain a Factor XIII activity trough level of approximately 5 to 20%. Subjects remained in the study for up to approximately 1 year.

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:

Initially, subjects who were not enrolled in the PK study received Factor XIII Concentrate (Human) at a dose of 40 U/kg by IV infusion. Subsequent doses were guided by the individual subject's Factor XIII activity levels, with the objective of dosing every 28 days (4 weeks) to maintain a Factor XIII activity trough level of approximately 5 to 20%.
Subjects were administered the dose of Factor XIII Concentrate (Human) as a bolus IV injection at a rate of approximately 250 U/minute.

Number of subjects in period 1	Factor XIII
Started	41
Completed	41

Baseline characteristics

Reporting groups	
Reporting group title	Factor XIII

Reporting group description:

Initially, subjects received Factor XIII Concentrate (Human) at a dose of 40 U/kg by intravenous (IV) infusion. Subsequent doses were guided by the individual subject's Factor XIII activity levels, with the objective of dosing every 28 days (4 weeks) to maintain a Factor XIII activity trough level of approximately 5 to 20%. Subjects remained in the study for up to approximately 1 year.

Reporting group values	Factor XIII	Total	
Number of subjects	41	41	
Age categorical Units: Subjects			
< 16 years	18	18	
16 to < 65 years	23	23	
≥ 65 years	0	0	
Age continuous Units: years			
arithmetic mean	20.1		
standard deviation	± 11.2	-	
Gender categorical Units: Subjects			
Female	16	16	
Male	25	25	

End points

End points reporting groups

Reporting group title	Factor XIII

Reporting group description:

Initially, subjects received Factor XIII Concentrate (Human) at a dose of 40 U/kg by intravenous (IV) infusion. Subsequent doses were guided by the individual subject's Factor XIII activity levels, with the objective of dosing every 28 days (4 weeks) to maintain a Factor XIII activity trough level of approximately 5 to 20%. Subjects remained in the study for up to approximately 1 year.

Primary: Incidence of Spontaneous Bleeding Events Requiring Treatment

End point title	Incidence of Spontaneous Bleeding Events Requiring

End point description:

The number of subjects requiring treatment with a Factor XIII-containing product to treat a spontaneous bleeding event. Treatment is defined as administration of a Factor XIII-containing product to treat the bleeding event (e.g. FXIII concentrate, plasma or cryoprecipitate).

End point type	Primary

End point timeframe:

Up to 52 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 participants with a spontaneous bleeding episode required treatment with a FXIII-containing product, hence analysis of incidence could not be performed.

End point values	Factor XIII			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with spontaneous or traumatic bleeding episodes requiring treatment

End point title	Number of Participants with spontaneous or traumatic bleeding episodes requiring treatment

End point description:

The number of participants with spontaneous or traumatic bleeding episodes (including exercise-induced bleeding episodes) requiring treatment. Treatment is defined as administration of a Factor XIII-containing product to treat the bleeding event (e.g. FXIII concentrate, plasma or cryoprecipitate).

End point type	Secondary

End point timeframe:

Up to 52 weeks

End point values	Factor XIII			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: participants	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with spontaneous or traumatic bleeding episodes

End point title	Number of participants with spontaneous or traumatic bleeding episodes

End point description:

Number of participants with spontaneous or traumatic bleeding episodes without regard to treatment

End point type	Secondary

End point timeframe:

Up to 52 weeks

End point values	Factor XIII			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: participants	9			

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of bleeding episodes

End point title	Severity of bleeding episodes

End point description:

Each bleeding episode was rated by the investigator to indicate the primary location of the bleed, with a rating of minor, moderate, or severe, as follows:
• Minor: uncomplicated hemarthroses; superficial muscular or soft tissue hemorrhage,
• Moderate: intramuscular or soft tissue hemorrhage with dissection; hemorrhage in mucous membranes, gross hematuria, dental work, or
• Severe: hemorrhage in the pharynx, retropharynx, retroperitoneum, or central nervous system (CNS).

End point type	Secondary

End point timeframe:

Up to 52 weeks

End point values	Factor XIII			
Subject group type	Reporting group			
Number of subjects analysed	9[2]			
Units: participants				
Minor	7			
Moderate	2			
Severe	0			

Notes:

[2] - Participants with a bleeding episode (spontaneous, traumatic, and/or surgical)

Statistical analyses

No statistical analyses for this end point

Secondary: Bleeding episodes by CTCAE grade

End point title	Bleeding episodes by CTCAE grade

End point description:

Bleeding episode severity was categorized from Grade 1 to 5 by the investigator using the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (Version 3.0) (CTCAE) according to the following:
• Grade 1, Mild: Symptoms are easily tolerated and there is no interference with daily activities.
• Grade 2, Moderate: Discomfort enough to cause some interference with daily activities.
• Grade 3, Severe: Incapacitating with inability to work or do usual activity.
• Grade 4, Life-Threatening: Results in a threat to life or in an incapacitating disability.
• Grade 5, Death.

End point type	Secondary

End point timeframe:

Up to 52 weeks

End point values	Factor XIII			
Subject group type	Reporting group			
Number of subjects analysed	9[3]			
Units: participants				
Grade 1 - Mild	6			
Grade 2 - Moderate	3			
Grade 3 - Severe	0			
Grade 4 - Life-threatening	0			
Grade 5 - Fatal	0			

Notes:

[3] - Participants with a bleeding episode (spontaneous, traumatic and/or surgical)

Statistical analyses

No statistical analyses for this end point

Secondary: Etiology of bleeding episodes

End point title	Etiology of bleeding episodes

End point description:

The primary etiology of the bleeding episode was rated as spontaneous, traumatic (including exercise-induced bleeding), associated with surgery, or "other". Participants may have been counted in more than 1 etiology category due to experiencing more than one bleeding episode.

End point type	Secondary

End point timeframe:

Up to 52 weeks

End point values	Factor XIII			
Subject group type	Reporting group			
Number of subjects analysed	9[4]			
Units: participants				
Spontaneous	3			
Traumatic	8			
Associated with Surgery	1			
Other	0			

Notes:

[4] - Participants with a bleeding episode (spontaneous, traumatic and/or surgical)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with a primary hemostatic efficacy rating of successful after FXIII treatment of an acute bleeding episode or for prophylaxis before scheduled surgery

End point title	Number of participants with a primary hemostatic efficacy rating of successful after FXIII treatment of an acute bleeding episode or for prophylaxis before scheduled surgery

End point description:

Hemostatic efficacy following Factor XIII Concentrate (Human) treatment of spontaneous, traumatic, or acute bleeding episodes, and during scheduled surgery where an additional dose of Factor XIII Concentrate (Human) was given pre-surgery was assessed clinically by the investigator or treating physician.
Successful hemostatic efficacy following Factor XIII Concentrate (Human) treatment of an acute bleeding episode was defined as complete or incomplete restoration of hemostasis in the absence of other IV hemostatic intervention (e.g., cryo, plasma, Factor XIII).
Successful hemostatic efficacy during surgery (following Factor XIII Concentrate [Human] administration pre-surgery) was assessed as normal or mildly abnormal hemostasis in terms of quantity and/or quality (e.g., slight oozing, prolonged time to hemostasis with somewhat increased bleeding compared to a non-factor deficient subject) in the absence of other IV hemostatic intervention (e.g., cryo, plasma, Factor XIII).

End point type	Secondary

End point timeframe:

Up to 52 weeks

End point values	Factor XIII			
Subject group type	Reporting group			
Number of subjects analysed	3[5]			
Units: participants				
Acute bleeding episode (N=1)	1			
Prophylaxis before surgery (N=2)	2			

Notes:

[5] - Participants treated with FXIII for acute bleeding (1) or prophylaxis before surgery (2)

Statistical analyses

No statistical analyses for this end point

Secondary: Association of the Incidence of Spontaneous Bleeding Events Requiring Treatment and FXIII Activity Trough Levels

End point title	Association of the Incidence of Spontaneous Bleeding Events Requiring Treatment and FXIII Activity Trough Levels

End point description:

P-value determined from Generalized Estimating Equation (GEE) model parameter estimates with bleeding as the response variable and FXIII activity trough level as the explanatory variable. Note: no subjects had spontaneous bleeding events requiring treatment with a FXIII-containing product, so no subjects were analyzed.

End point type	Secondary

End point timeframe:

Up to 52 weeks

End point values	Factor XIII			
Subject group type	Reporting group			
Number of subjects analysed	0[6]			
Units: p-value				
number (not applicable)				

Notes:

[6] - Participants with spontaneous bleeding events requiring treatment with a FXIII-containing product.

Statistical analyses

No statistical analyses for this end point

Secondary: Peak FXIII Concentration at Steady State

End point title	Peak FXIII Concentration at Steady State

End point description:

End point type	Secondary

End point timeframe:

At 12, 24, 36 and 48 weeks: at 30 and 60 minutes after the end of the infusion.

End point values	Factor XIII			
Subject group type	Reporting group			
Number of subjects analysed	41[7]			
Units: IU/mL				
arithmetic mean (standard deviation)				
Week 12 (n = 40)	0.968 (± 0.2292)			
Week 24 (n = 40)	1.045 (± 0.3825)			
Week 36 (n = 41)	0.962 (± 0.2306)			
Week 48 (n = 40)	0.983 (± 0.2633)			

Notes:

[7] - Subjects who received a dose of FXIII Concentrate (human) for whom valid PK parameters were obtained

Statistical analyses

No statistical analyses for this end point

Secondary: Trough FXIII Concentration at Steady State

End point title	Trough FXIII Concentration at Steady State

End point description:

End point type	Secondary

End point timeframe:

At 12, 24, 36 and 48 weeks: immediately before infusion.

End point values	Factor XIII			
Subject group type	Reporting group			
Number of subjects analysed	41[8]			
Units: IU/mL				
arithmetic mean (standard deviation)				
Week 12 (n = 40)	0.132 (± 0.0305)			
Week 24 (n = 41)	0.136 (± 0.0362)			
Week 36 (n = 41)	0.13 (± 0.0254)			
Week 48 (n = 41)	0.15 (± 0.1138)			

Notes:

[8] - Subjects who received a dose of FXIII Concentrate (human) for whom valid PK parameters were obtained

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Peak Concentration

End point title	Time to Peak Concentration

End point description:

End point type	Secondary

End point timeframe:

At 12, 24, 36 and 48 weeks: immediately before infusion, then at 30 and 60 minutes after the end of the infusion

End point values	Factor XIII			
Subject group type	Reporting group			
Number of subjects analysed	41[9]			
Units: hours				
arithmetic mean (standard deviation)				
Week 12 (n = 40)	0.632 (± 0.2296)			
Week 24 (n = 40)	0.615 (± 0.1978)			
Week 36 (n = 39)	0.623 (± 0.235)			
Week 48 (n = 40)	0.636 (± 0.2328)			

Notes:

[9] - Subjects who received a dose of FXIII Concentrate (human) for whom valid PK parameters were obtained

Statistical analyses

No statistical analyses for this end point

Secondary: Incremental Recovery

End point title	Incremental Recovery

End point description:

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

End point type	Secondary

End point timeframe:

At 12, 24, 36 and 48 weeks: immediately before infusion, then at 30 and 60 minutes after the end of the infusion.

End point values	Factor XIII			
Subject group type	Reporting group			
Number of subjects analysed	41[10]			
Units: IU/mL/IU/kg				
arithmetic mean (standard deviation)				
Week 12 (n = 39)	0.021 (± 0.0059)			
Week 24 (n = 38)	0.023 (± 0.0104)			
Week 36 (n = 39)	0.021 (± 0.0056)			

Week 48 (n = 38)	0.02 (± 0.0056)			

Notes:

[10] - Subjects who received a dose of FXIII Concentrate (human) for whom valid PK parameters were obtained

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants Achieving Trough Factor XIII Levels of 5% or Higher

End point title	Number of participants Achieving Trough Factor XIII Levels of 5% or Higher

End point description:

The number of participants with Factor XIII level ≥ 5% before infusion at Week 12, Week 24, Week 36 and Week 48.

End point type	Secondary

End point timeframe:

At 12, 24, 36 and 48 weeks: immediately before infusion.

End point values	Factor XIII			
Subject group type	Reporting group			
Number of subjects analysed	41[11]			
Units: participants				
Week 12 (n = 40)	40			
Week 24 (n = 41)	41			
Week 36 (n = 41)	41			
Week 48 (n = 41)	40			

Notes:

[11] - Participants with data at each visit/time point.

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:

Number of subjects with any treatment-emergent adverse event (AE), treatment-related AE or serious AE (SAE). Treatment related AEs are defined as AEs whose relationship to study treatment is related, or possibly related, and AEs with missing relationship.

End point type	Secondary

End point timeframe:

Up to 52 weeks

End point values	Factor XIII			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: participants				
Any treatment-emergent AEs	33			
Any treatment-emergent and treatment-related AE	3			
Any treatment-emergent SAE	4			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

12 months

Adverse event reporting additional description:

The Safety Population comprised all subjects who received a dose of FXIII Concentrate (Human) during the study. Data presented for other, non-serious AEs are for treatment-emergent AEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups

Reporting group title	Factor XIII

Reporting group description:

Initially, subjects received Factor XIII Concentrate (Human) at a dose of 40 U/kg by intravenous (IV) infusion. Subsequent doses were guided by the individual subject's Factor XIII activity levels, with the objective of dosing every 28 days (4 weeks) to maintain a Factor XIII activity trough level of approximately 5 to 20%. Subjects remained in the study for up to approximately 1 year.

Serious adverse events	Factor XIII		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 41 (9.76%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Hip injury			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Traumatic chest injury NOS			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain with radiation to left arm			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Factor XIII		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 41 (65.85%)		
Investigations			
Thrombin-antithrombin III complex increased			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	5		
Injury, poisoning and procedural complications			
Abrasions			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	5		
Fall			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	4		
Bruising of thigh			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	10		
General disorders and administration site conditions			

Fever subjects affected / exposed occurrences (all)	5 / 41 (12.20%) 5		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 6		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Rhinorrhea subjects affected / exposed occurrences (all) Sore throat subjects affected / exposed occurrences (all)	 5 / 41 (12.20%) 6 4 / 41 (9.76%) 4 3 / 41 (7.32%) 4 3 / 41 (7.32%) 3		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	 3 / 41 (7.32%) 3		
Musculoskeletal and connective tissue disorders Wrist pain subjects affected / exposed occurrences (all)	 3 / 41 (7.32%) 3		
Infections and infestations Upper respiratory infection subjects affected / exposed occurrences (all)	 10 / 41 (24.39%) 11		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported