



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 B171023_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: <ul style="list-style-type: none"> • 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 \geq 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