



Clinical trial results:

An Open-Label, Single-Arm, Safety and Efficacy Study of Recombinant Human Factor IX (rFIX, BeneFIX) in Children Less Than 6 Years of Age With Severe Hemophilia B

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2014-004155-32 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 13 November 2007 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 13 April 2016 |
| First version publication date | 23 July 2015 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | 3090A1-301 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00037557 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Alias: B1821035 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Pfizer Inc. |
| Sponsor organisation address | 235 E 42nd Street, New York, United States, NY 10017 |
| Public contact | Pfizer Clinical Trials.gov Call Centre, Pfizer Inc, 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact | Pfizer Clinical Trials.gov Call Centre, Pfizer Inc, 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.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 | 06 June 2008 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|------------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 13 November 2007 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To characterize the safety and efficacy of recombinant factor IX (rFIX) in children less than 6 years of age with severe hemophilia B in the setting of acute bleeding episodes, prophylaxis, and/or surgery.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 14 October 2002 |
| 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 | Canada: 1 |
| Country: Number of subjects enrolled | Netherlands: 1 |
| Country: Number of subjects enrolled | Sweden: 2 |
| Country: Number of subjects enrolled | Spain: 2 |
| Country: Number of subjects enrolled | France: 1 |
| Country: Number of subjects enrolled | United States: 16 |
| Country: Number of subjects enrolled | United Kingdom: 2 |
| Worldwide total number of subjects | 25 |
| EEA total number of subjects | 8 |

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) | 7 |

| | |
|---------------------------|----|
| Children (2-11 years) | 18 |
| 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: -

Pre-assignment

Screening details:

Total 25 subjects were enrolled in 16 centres of 7 countries. Study started on 14 Oct 2002 and completed on 13 Nov 2007.

Period 1

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

Arms

| | |
|-----------|-----------------------|
| Arm title | Recombinant Factor IX |
|-----------|-----------------------|

Arm description:

Subjects received on-demand treatments with rFIX, prophylactic treatment or administered related to a surgical procedure according to investigator's discretion over a 12-month (calendar day) period.

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | rFIX |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

A single 75 International Unit (IU)/kg intravenous (IV) bolus infusion of rFIX was given for recovery assessments on Day 1 followed by rFIX bolus infusions or continuous infusion (CI). Subjects also received doses for treatment of bleeding episodes, prophylaxis and surgery. Doses were at the investigators' discretion.

| Number of subjects in period 1 | Recombinant Factor IX |
|--------------------------------|-----------------------|
| Started | 25 |
| Completed | 23 |
| Not completed | 2 |
| Consent withdrawn by subject | 1 |
| Protocol violation | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------------------|
| Reporting group title | Recombinant Factor IX |
|-----------------------|-----------------------|

Reporting group description:

Subjects received on-demand treatments with rFIX, prophylactic treatment or administered related to a surgical procedure according to investigator's discretion over a 12-month (calendar day) period.

| Reporting group values | Recombinant Factor IX | Total | |
|---|-----------------------|-------|--|
| Number of subjects | 25 | 25 | |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years arithmetic mean standard deviation | 2.4 ± 1.2 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 0 | 0 | |
| Male | 25 | 25 | |

End points

End points reporting groups

| | |
|--|-----------------------|
| Reporting group title | Recombinant Factor IX |
| Reporting group description: | |
| Subjects received on-demand treatments with rFIX, prophylactic treatment or administered related to a surgical procedure according to investigator's discretion over a 12-month (calendar day) period. | |

Primary: Number of Subjects With Laboratory Abnormalities

| | |
|---|---|
| End point title | Number of Subjects With Laboratory Abnormalities ^[1] |
| End point description: | |
| Laboratory tests included hematology (hematocrit, hemoglobin, red blood cell count, white blood cell count, platelet count) and chemistry (glucose, albumin, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, bicarbonate, total bilirubin, total protein, creatinine, sodium, potassium, chloride, lactate dehydrogenase). Assays were based on World Health Organization Recommendations for grading scale for AEs (grade 0 [none], grade 1 [mild AE: did not cause any significant problem]; grade 2 [moderate AE: caused problem that did not interfere significantly with usual activities or the clinical status]; grade 3 [severe AE: caused problem that interfered significantly with usual activities or the clinical status] and grade 4 [life threatening AE]). Intent-to-treat (ITT) population included all subjects who received at least 1 dose of study drug. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline up to Month 12 | |

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: Only descriptive data was planned to be reported for this end point.

| | | | | |
|-----------------------------|-----------------------|--|--|--|
| End point values | Recombinant Factor IX | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 25 | | | |
| Units: Subjects | | | | |
| number (not applicable) | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Dose Per Infusion Required for On-demand Therapy

| | |
|--|---|
| End point title | Dose Per Infusion Required for On-demand Therapy ^[2] |
| End point description: | |
| Mean dose per infusion in international unit(s)/kilogram (IU/kg) was the average dose for all infusions (including loading dose) needed to maintain bleeding episodes on demand. Efficacy analysis population included all subjects who receive at least one dose of on-demand study drug and accumulated at least 30 exposure days (EDs) to rFIX over a minimum of 6 months. Minimally treated patient (MTPs) and previously untreated patient (PUPs) were considered evaluable if they accumulated at least 10 EDs to rFIX and completed 12 months of study participation. | |
| End point type | Primary |

End point timeframe:

Day 1 up to Month 12

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: Only descriptive data was planned to be reported for this end point.

| End point values | Recombinant Factor IX | | | |
|--------------------------------------|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 16 ^[3] | | | |
| Units: IU/kg | | | | |
| arithmetic mean (standard deviation) | 75 (\pm 24.6) | | | |

Notes:

[3] - Subjects evaluable for this end point.

Statistical analyses

No statistical analyses for this end point

Primary: Number of Infusions Per Subject Required For On-demand Therapy

| | |
|-----------------|---|
| End point title | Number of Infusions Per Subject Required For On-demand Therapy ^[4] |
|-----------------|---|

End point description:

The number of rFIX infusions per subject required to treat bleeding episodes on demand, were analyzed. Efficacy analysis population included all subjects who receive at least one dose of on-demand study drug and accumulated at least 30 EDs to rFIX over a minimum of 6 months. MTPs and PUPs were considered evaluable if they accumulated at least 10 EDs to rFIX and completed 12 months of study participation.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 1 up to Month 12

Notes:

[4] - 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: Only descriptive data was planned to be reported for this end point.

| End point values | Recombinant Factor IX | | | |
|--------------------------------------|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 16 ^[5] | | | |
| Units: Infusions | | | | |
| arithmetic mean (standard deviation) | 5.9 (\pm 4.4) | | | |

Notes:

[5] - Subjects evaluable for this end point.

Statistical analyses

No statistical analyses for this end point

Primary: Response to On-Demand Treatment for All Bleeding Episodes

| | |
|-----------------|--|
| End point title | Response to On-Demand Treatment for All Bleeding Episodes ^[6] |
|-----------------|--|

End point description:

Response to the infusions of rFIX treatment was assessed using a 4-point scale. The 4-point scale was

used by the patient, caregiver or investigator to measure response to on-demand treatment of a bleed. This assessment was made approximately 24 hours after the infusion or before the next infusion for the same bleeding episode. Grading of the response rate was: Excellent (dramatic response with clear reduction in joint or bleed site's size), Good (required additional infusion for resolution), Moderate (requiring several additional infusions for resolution), and No Response (no improvement at all). Responses to number of observations were noted. Efficacy analysis population included all subjects who receive at least one dose of on-demand study drug and accumulated at least 30 EDs to rFIX over a minimum of 6 months. MTPs and PUPs were considered evaluable if they accumulated at least 10 EDs to rFIX and completed 10 EDs to rFIX and completed 12 months of study participation.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 1 up to Month 12

Notes:

[6] - 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: Only descriptive data was planned to be reported for this end point.

| End point values | Recombinant Factor IX | | | |
|-----------------------------|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 16 ^[7] | | | |
| Units: Infusions | | | | |
| number (not applicable) | | | | |
| Excellent | 41 | | | |
| Good | 42 | | | |
| Moderate | 8 | | | |
| No Response | 0 | | | |

Notes:

[7] - From 16 subjects receiving on demand therapy, 91 infusions were evaluable for this end point.

Statistical analyses

No statistical analyses for this end point

Primary: Dose Per Infusion Required For Prophylaxis Therapy

| | |
|-----------------|---|
| End point title | Dose Per Infusion Required For Prophylaxis Therapy ^[8] |
|-----------------|---|

End point description:

Mean dose per infusion was the average dose for all infusions (including loading dose) needed for prophylaxis therapy. Efficacy analysis population included all subjects who receive at least one dose of prophylaxis study drug and accumulated at least 30 EDs to rFIX over a minimum of 6 months. MTPs and PUPs were considered evaluable if they accumulated at least 10 EDs to rFIX and completed 10 EDs to rFIX and completed 12 months of study participation.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 1 up to Month 12

Notes:

[8] - 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: Only descriptive data was planned to be reported for this end point.

| | | | | |
|--------------------------------------|-----------------------|--|--|--|
| End point values | Recombinant Factor IX | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 22 | | | |
| Units: IU/kg | | | | |
| arithmetic mean (standard deviation) | 64.6 (± 21.3) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Infusions Per Subject Required for Prophylaxis Therapy

| | |
|-----------------|---|
| End point title | Number of Infusions Per Subject Required for Prophylaxis Therapy ^[9] |
|-----------------|---|

End point description:

The number of rFIX infusions required for prophylaxis therapy per subject were analyzed. Efficacy analysis population included all subjects who receive at least one dose of prophylaxis study drug and accumulated at least 30 EDs to rFIX over a minimum of 6 months. MTPs and PUPs were considered evaluable if they accumulated at least 10 EDs to rFIX and completed 10 EDs to rFIX and completed 12 months of study participation.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 1 up to Month 12

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: Only descriptive data was planned to be reported for this end point.

| | | | | |
|--------------------------------------|-----------------------|--|--|--|
| End point values | Recombinant Factor IX | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 22 | | | |
| Units: Infusions | | | | |
| arithmetic mean (standard deviation) | 36.5 (± 13.1) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Breakthrough (Spontaneous and Traumatic) Bleeds Within 48 Hours of a Prophylaxis Dose of Recombinant Factor IX

| | |
|-----------------|--|
| End point title | Number of Breakthrough (Spontaneous and Traumatic) Bleeds Within 48 Hours of a Prophylaxis Dose of Recombinant Factor IX ^[10] |
|-----------------|--|

End point description:

The number of spontaneous and traumatic breakthrough bleeds within 48 hours following a prophylaxis dose of rFIX were summarized. If there was more than one bleed location with identical bleed start date and time, it was treated as one bleed occurrence. Breakthrough bleeding episodes for subjects on prophylaxis was analyzed based on the day of the bleeding episode relative to the last infusion and whether the episodes were due to injury (traumatic) or occurred spontaneously. Efficacy analysis population included all subjects who receive at least one dose of prophylaxis study drug and

accumulated at least 30 EDs to rFIX over a minimum of 6 months. MTPs and PUPs were considered evaluable if they accumulated at least 10 EDs to rFIX and completed 10 EDs to rFIX and completed 12 months of study participation.

| | |
|----------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| Day 1 up to Month 12 | |

Notes:

[10] - 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: Only descriptive data was planned to be reported for this end point.

| | | | | |
|--|-----------------------|--|--|--|
| End point values | Recombinant Factor IX | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 22 | | | |
| Units: breakthrough bleeds within 48 hours | | | | |
| number (not applicable) | | | | |
| Spontaneous breakthrough bleeds | 1 | | | |
| Traumatic breakthrough bleeds | 16 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Dose Per Infusion Required For Surgical Prophylaxis

| | |
|-----------------|---|
| End point title | Dose Per Infusion Required For Surgical Prophylaxis ^[11] |
|-----------------|---|

End point description:

Mean dose per infusion was the average dose for all infusions (including loading dose) needed for surgical prophylaxis. Efficacy analysis population included all subjects who receive at least one dose of study drug for surgical purposes and accumulated at least 30 EDs to rFIX over a minimum of 6 months. MTPs and PUPs were considered evaluable if they accumulated at least 10 EDs to rFIX and completed 10 EDs to rFIX and completed 12 months of study participation.

| | |
|------------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| Month 1 up to Month 12 | |

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: Only descriptive data was planned to be reported for this end point.

| | | | | |
|--------------------------------------|-----------------------|--|--|--|
| End point values | Recombinant Factor IX | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2 ^[12] | | | |
| Units: IU/kg | | | | |
| arithmetic mean (standard deviation) | 91.7 (± 21.2) | | | |

Notes:

[12] - Subjects evaluable for this end point.

Statistical analyses

No statistical analyses for this end point

Primary: Number of Infusions Per Subject Required for Surgical Prophylaxis

| | |
|-----------------|---|
| End point title | Number of Infusions Per Subject Required for Surgical Prophylaxis ^[13] |
|-----------------|---|

End point description:

The number of rFIX infusions required for surgical prophylaxis per subject were analyzed. Efficacy analysis population included all subjects who receive at least one dose of study drug for surgical purposes and accumulated at least 30 EDs to rFIX over a minimum of 6 months. MTPs and PUPs were considered evaluable if they accumulated at least 10 EDs to rFIX and completed 10 EDs to rFIX and completed 12 months of study participation.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 1 up to Month 12

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: Only descriptive data was planned to be reported for this end point.

| | | | | |
|--------------------------------------|-----------------------|--|--|--|
| End point values | Recombinant Factor IX | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2 ^[14] | | | |
| Units: Infusions | | | | |
| arithmetic mean (standard deviation) | 12 (± 2.8) | | | |

Notes:

[14] - Subjects evaluable for this end point.

Statistical analyses

No statistical analyses for this end point

Primary: Physician's Global Assessment of Efficacy

| | |
|-----------------|---|
| End point title | Physician's Global Assessment of Efficacy ^[15] |
|-----------------|---|

End point description:

Physician used the 5-point scale to provide an overall assessment of the subjects treatment with study drug. The assessment was based on subjects diary records, adverse events (AEs), laboratory results and response to treatment. The parameters of the 5-point scale were Very Useful, Useful, Slightly Useful, Useless, and Unfavorable. Efficacy analysis population included all subjects who receive at least one dose of study drug and accumulated at least 30 EDs to rFIX over a minimum of 6 months. MTPs and PUPs were considered evaluable if they accumulated at least 10 EDs to rFIX and completed 10 EDs to rFIX and completed 12 months of study participation.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 1 up to Month 12

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: Only descriptive data was planned to be reported for this end point.

| End point values | Recombinant Factor IX | | | |
|-----------------------------|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 25 ^[16] | | | |
| Units: Assessments | | | | |
| number (not applicable) | | | | |
| Very Useful | 65 | | | |
| Useful | 11 | | | |
| Slightly Useful | 0 | | | |
| Useless | 0 | | | |
| Unfavorable | 0 | | | |

Notes:

[16] - From 25 subjects, 76 physician's assessments were evaluable for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Anti-FIX Inhibitor

| | |
|---|--|
| End point title | Number of Subjects With Anti-FIX Inhibitor |
| End point description: | |
| Presence of activity-neutralizing antibodies against FIX (FIX inhibitor) was detected using the Bethesda Inhibitor Assay (BIA). An inhibitor test result greater than or equal to (\geq) 0.6 Bethesda units per milliliter (BU/mL), identified and confirmed by re-testing of a second sample obtained within 2 to 4 weeks, was considered positive by the central laboratory. ITT population included all subjects who received at least 1 dose of study drug. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to Month 12 | |

| End point values | Recombinant Factor IX | | | |
|-----------------------------|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 25 | | | |
| Units: Subjects | | | | |
| number (not applicable) | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Anti-FIX Antibody

| | |
|--|---|
| End point title | Number of Subjects With Anti-FIX Antibody |
| End point description: | |
| Anti-FIX Enzyme-linked immunosorbent assay (ELISA) was used for monitoring clinically significant anti-FIX antibody. Anti-FIX ELISA was an assay that detects neutralizing and non-neutralizing antibodies to FIX. All assays were performed at a central laboratory. ITT population included all subjects who received at least 1 dose of study drug. | |

| | |
|-------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to Month 12 | |

| | | | | |
|-----------------------------|-----------------------|--|--|--|
| End point values | Recombinant Factor IX | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 25 | | | |
| Units: Subjects | | | | |
| number (not applicable) | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Thrombogenicity

| | |
|--|---|
| End point title | Number of Subjects With Thrombogenicity |
| End point description: | |
| Thrombogenicity was defined as any event associated with the formation of a blood clot, including catheter-associated thrombi and thrombotic complications in treated subjects. Markers of coagulation including thrombin/antithrombin III complex (TAT), D-Dimer and prothrombin fragment 1+2 were assessed. ITT population included all subjects who received at least 1 dose of study drug. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to Month 12 | |

| | | | | |
|-----------------------------|-----------------------|--|--|--|
| End point values | Recombinant Factor IX | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 25 | | | |
| Units: Subjects | | | | |
| number (not applicable) | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Allergic-Type Manifestations

| | |
|---|--|
| End point title | Number of Subjects With Allergic-Type Manifestations |
| End point description: | |
| Allergic-type manifestations included any physiologic response following administration of rFIX characterized by urticaria, pruritus, eczema, fever, wheezing and/or acute asthma exacerbation. Symptoms also included dyspnea, tearing, sneezing, violent cough, chest constriction, skin eruptions, | |

skin rash, pulse variations, cyanosis, convulsions or circulatory collapse. ITT population included all subjects who received at least 1 dose of study drug.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to Month 12

| End point values | Recombinant Factor IX | | | |
|-----------------------------|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 25 | | | |
| Units: Subjects | | | | |
| number (not applicable) | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Red Blood Cell (RBC) Agglutination

| | |
|-----------------|--|
| End point title | Number of Subjects With Red Blood Cell (RBC) Agglutination |
|-----------------|--|

End point description:

RBC Agglutination was the clumping of red blood cells in the presence of an antibody. The antibody or other molecule bonded multiple particles and joined them, creating a large complex. ITT population included all subjects who received at least 1 dose of study drug.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to Month 12

| End point values | Recombinant Factor IX | | | |
|-----------------------------|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 25 | | | |
| Units: Subjects | | | | |
| number (not applicable) | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Seroconversion

| | |
|-----------------|--|
| End point title | Number of Subjects With Seroconversion |
|-----------------|--|

End point description:

Subjects with antibody formation to hepatitis types (A, B, C) and human immunodeficiency virus (HIV)-1 and HIV-2 were analyzed. Any positive ELISA results for HIV were to be confirmed by Western Blot.

ITT population included all subjects who received at least 1 dose of study drug.

| | |
|--------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to 12 months | |

| | | | | |
|-----------------------------|-----------------------|--|--|--|
| End point values | Recombinant Factor IX | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 25 | | | |
| Units: Subjects | | | | |
| number (not applicable) | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Incremental Recovery of Recombinant Factor IX in Subjects Following a 75-IU/kg Bolus Infusion

| | |
|-----------------|---|
| End point title | Incremental Recovery of Recombinant Factor IX in Subjects Following a 75-IU/kg Bolus Infusion |
|-----------------|---|

End point description:

Incremental recovery (K) in subjects following a 75-IU/kg bolus infusion, defined as the international units per deciliter (IU/dL) rise in plasma per IU/kg of drug administered. ITT population included all subjects who received at least 1 dose of study drug, n=number of subjects evaluable for this measure at specified time points. Here "99999" in the standard deviation at Month 9 signifies not available (NA). Standard deviation was not estimable as only 1 subject was evaluable for this time point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Month 1, Month 3, Month 6, Month 9, Month 12

| | | | | |
|--------------------------------------|-----------------------|--|--|--|
| End point values | Recombinant Factor IX | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 25 | | | |
| Units: IU/dL per IU/kg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=23) | 0.57 (± 0.09) | | | |
| Month 1 (n=21) | 0.55 (± 0.11) | | | |
| Month 3 (n=20) | 0.58 (± 0.07) | | | |
| Month 6 (n=6) | 0.58 (± 0.18) | | | |
| Month 9 (n=1) | 0.75 (± 99999) | | | |
| Month 12 (n=20) | 0.61 (± 0.1) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Total Dose of Recombinant Factor IX Required Per Subject Throughout the Study

| | |
|--|---|
| End point title | Total Dose of Recombinant Factor IX Required Per Subject Throughout the Study |
| End point description: Total dose was the sum across all infusions (including loading dose) throughout the study. Efficacy analysis population included all subjects who receive at least one dose of study drug and accumulated at least 30 EDs to rFIX over a minimum of 6 months. MTPs and PUPs were considered evaluable if they accumulated at least 10 EDs to rFIX and completed 10 EDs to rFIX and completed 12 months of study participation. | |
| End point type | Secondary |
| End point timeframe: Day 1 up to Month 12 | |

| | | | | |
|--------------------------------------|--------------------------|--|--|--|
| End point values | Recombinant Factor IX | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 22 | | | |
| Units: IU | | | | |
| arithmetic mean (standard deviation) | 47968.3 (\pm 14927.9) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Lack of Effect: For On-demand Treatment

| | |
|--|---|
| End point title | Number of Subjects With Lack of Effect: For On-demand Treatment |
| End point description: Failure of rFIX Also known as "Lack of Effect." For on-demand treatment: a "No Response" rating after each of 2 successive infusions of rFIX administered within 24 hours of each other for the treatment of the same bleeding episode in the absence of confounding factors. ITT population included all subjects who received at least 1 dose of study drug to treat a bleeding episode. | |
| End point type | Secondary |
| End point timeframe: Baseline up to Month 12 | |

| End point values | Recombinant Factor IX | | | |
|-----------------------------|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 16 ^[17] | | | |
| Units: Subjects | | | | |
| number (not applicable) | 0 | | | |

Notes:

[17] - Subjects evaluable for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Lack of Effect: For Prophylaxis

| | |
|---|---|
| End point title | Number of Subjects With Lack of Effect: For Prophylaxis |
| End point description: | |
| Failure to prevent breakthrough bleeding episodes within 48 hours of a routine prophylaxis rFIX infusion in the absence of other confounding factors (eg, trauma, injury, incorrect dose). ITT population included all subjects who received at least 1 prophylaxis dose of study drug. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to Month 12 | |

| End point values | Recombinant Factor IX | | | |
|-----------------------------|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 22 ^[18] | | | |
| Units: Subjects | | | | |
| number (not applicable) | 0 | | | |

Notes:

[18] - Subjects evaluable for this end point.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 30 days after last dose of study drug administration

Adverse event reporting additional description:

The same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as nonserious in another subject, or one subject may have experienced both a serious and nonserious event during the study.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------------|
| Reporting group title | Recombinant Factor IX |
|-----------------------|-----------------------|

Reporting group description:

Subjects received on

-demand treatments with rFIX or prophylactic treatment or administered related to a surgical procedure according to investigator's prescription over a 12- month (calendar day) period.

| Serious adverse events | Recombinant Factor IX | | |
|---|-----------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Blood and lymphatic system disorders | | | |
| Factor IX inhibition | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Recombinant Factor IX | | |
|---|-----------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 23 / 25 (92.00%) | | |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 2 | | |

| | | | |
|--|------------------|--|--|
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Infusion site extravasation | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 2 | | |
| Mass | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 5 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Pain | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Pyrexia | | | |
| subjects affected / exposed | 14 / 25 (56.00%) | | |
| occurrences (all) | 29 | | |
| Vaccination site pain | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 3 | | |
| Reproductive system and breast disorders | | | |
| Genital erythema | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Penile oedema | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Penile pain | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |

| | | | |
|---|------------------|--|--|
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 4 | | |
| Catarrh | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 4 | | |
| Cough | | | |
| subjects affected / exposed | 10 / 25 (40.00%) | | |
| occurrences (all) | 21 | | |
| Nasal congestion | | | |
| subjects affected / exposed | 7 / 25 (28.00%) | | |
| occurrences (all) | 15 | | |
| Pulmonary congestion | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 5 | | |
| Sinus disorder | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 2 | | |
| Sneezing | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Psychiatric disorders | | | |
| Irritability | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 3 | | |
| Investigations | | | |
| Blood urea increased | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Cardiac murmur | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |

| | | | |
|--|----------------------|--|--|
| Fibrin D dimer increased subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 2 | | |
| Laboratory test abnormal subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 3 | | |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 2 | | |
| Bite subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 3 | | |
| Eye injury subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | | |
| Face injury subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 4 | | |
| Head injury subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | | |
| Injury subjects affected / exposed occurrences (all) | 4 / 25 (16.00%) 6 | | |
| Joint injury subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 2 | | |
| Laceration subjects affected / exposed occurrences (all) | 3 / 25 (12.00%) 5 | | |
| Ligament sprain subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | | |
| Limb injury | | | |

| | | | |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 2 | | |
| Lip injury | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Mouth injury | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Procedural pain | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Skin abrasion | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Skin injury | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Transfusion reaction | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 3 | | |
| Lethargy | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 2 | | |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Eye disorders | | | |
| Orbital oedema | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |

| | | | |
|--|-----------------|--|--|
| Abdominal discomfort | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 25 (12.00%) | | |
| occurrences (all) | 3 | | |
| Flatulence | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Gingival inflammation | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Lip oedema | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Oral mucosal eruption | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Teething | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Vomiting | | | |
| subjects affected / exposed | 9 / 25 (36.00%) | | |
| occurrences (all) | 12 | | |
| Skin and subcutaneous tissue disorders | | | |
| Erythema | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 2 | | |
| Rash | | | |
| subjects affected / exposed | 4 / 25 (16.00%) | | |
| occurrences (all) | 4 | | |
| Rash macular | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Urticaria | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 2 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 2 | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal disorder | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 2 | | |
| Catheter site infection | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 3 / 25 (12.00%) | | |
| occurrences (all) | 3 | | |
| Croup infectious | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 3 | | |
| Ear infection | | | |
| subjects affected / exposed | 3 / 25 (12.00%) | | |
| occurrences (all) | 4 | | |
| Gastroenteritis | | | |

| | | | |
|------------------------------------|------------------|--|--|
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 11 / 25 (44.00%) | | |
| occurrences (all) | 19 | | |
| Otitis externa | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 2 | | |
| Otitis media | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 2 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 3 | | |
| Rash pustular | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 3 / 25 (12.00%) | | |
| occurrences (all) | 4 | | |
| Viral infection | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | | |
| occurrences (all) | 1 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | | |
| occurrences (all) | 3 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|--|
| 10 May 2002 | One exclusion criteria was modified to permit the inclusion of patients that test positive to hepatitis but do not have fulminant disease. Chemistry and hematology testing were reduced to be measured at 2 time-points only, in order to reduce the volume of blood drawn in the study. The total volume of blood drawn for this study was decreased to 175 mL. Information to describe the dose estimation and preparation of rFIX in the event continuous infusion was added. Addition of the information that all BIA positive inhibitors were to be reported as SAE. |
| 26 August 2004 | Evaluable criteria for minimally treated patient (MTPs) and previously untreated patient (PUPs) were modified to 10 exposure days in 12 months. Clarification that the times for recovery blood collections was based on the completion of the infusion was added. Change SAE and event of interest (EOI) reporting timeframe from 24 hours to 1 business day. Explanation of nominal versus actual potency of the study drug was added. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported