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 (± 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 (± 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 (>=) 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 (± 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. A n 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	1 / 25 (4.00%)		
occurrences (all)	2		
Laboratory test abnormal			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	2		
Bite			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	3		
Eye injury			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Face injury			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	4		
Head injury			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Injury			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	6		
Joint injury			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Laceration			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	5		
Ligament sprain			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	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 occurrences (all)	1 / 25 (4.00%) 1		
Diarrhoea subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 3		
Flatulence subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Gingival inflammation subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Lip oedema subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Oral mucosal eruption subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Stomatitis subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Teething subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Vomiting subjects affected / exposed occurrences (all)	9 / 25 (36.00%) 12		
Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 2		
Rash subjects affected / exposed occurrences (all)	4 / 25 (16.00%) 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