Clinical trial results:
An Evaluation of the Safety and Efficacy of On-Demand Treatment with BeneFIX (Nonacog Alfa, Recombinant Factor IX) in Chinese Subjects with Hemophilia B

Summary

EudraCT number	2014-004156-65
Trial protocol	Outside EU/EEA
Global end of trial date	24 December 2009
Results information	
Result version number	v1 (current)
This version publication date	16 May 2016
First version publication date	01 August 2015

Trial information

Trial identification	
Sponsor protocol code	3090A1-3305
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00866606
WHO universal trial number (UTN)	-
Other trial identifiers	alias: B1821004

Notes:

Sponsors	
Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 800-718-1021, 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	19 September 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 December 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To describe the safety and clinical efficacy of BeneFIX in previously treated Chinese subjects with hemophilia B.

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 pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 September 2008
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	China: 35
Worldwide total number of subjects	35
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	4
Adolescents (12-17 years)	6
Adults (18-64 years)	25
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled in six centers in China.

Pre-assignment

Screening details:

Study was initiated on 18 September 2008 and completed on 24 December 2009. A total of 35 subjects were enrolled in the study.

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	BeneFactor IX (BeneFIX)

Arm description:

Subjects received on-demand treatments with BeneFIX according to investigator's prescription over a 6-month (calendar day) period. All BeneFIX administrations occurred in the clinic (hospital).

Arm type	Experimental
Investigational medicinal product name	BeneFIX
Investigational medicinal product code	
Other name	Nonacog Alfa, Recombinant Factor IX
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

A single 75 International Unit (IU)/kilogram (kg) (±5 IU/kg) intravenous (IV) bolus infusion of BeneFIX was given for recovery assessments.

Number of subjects in period 1	BeneFactor IX (BeneFIX)
Started	35
Completed	31
Not completed	4
Adverse Event	1
Lost to follow-up	3

Baseline characteristics

Reporting groups	
Reporting group title	BeneFactor IX (BeneFIX)

Reporting group description:

Subjects received on-demand treatments with BeneFIX according to investigator's prescription over a 6-month (calendar day) period. All BeneFIX administrations occurred in the clinic (hospital).

Reporting group values	BeneFactor IX (BeneFIX)	Total	
Number of subjects	35	35	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 25.7 ± 13.6	 -	
Gender categorical Units: Subjects			
Female	0	0	
Male	35	35	

End points

End points reporting groups

Reporting group title	BeneFactor IX (BeneFIX)

Reporting group description:

Subjects received on-demand treatments with BeneFIX according to investigator's prescription over a 6-month (calendar day) period. All BeneFIX administrations occurred in the clinic (hospital).

Primary: Investigator Hemostatic Efficacy Assessment of Subjects After 8 Hours Post Infusion

End point title	Investigator Hemostatic Efficacy Assessment of Subjects After 8 Hours Post Infusion[1]

End point description:

Investigator Hemostatic Efficacy Assessment was based on response of bleeding episodes to BeneFIX treatment on 4-point rating scale: Excellent(1): definite pain relief or improvement in signs of bleeding starting within 8 hours after infusion, with no additional infusion; Good(2): definite pain relief or improvement in signs of bleeding starting within 8 hrs or following infusion; Moderate(3): probable or slight improvement starting after 8 hours following infusion; No Response(4): no improvement at all between infusions or during 24 hour interval following an infusion, or condition worsens. Full Analysis set (FAS) population included all subjects who were treated and had at least 1 evaluable efficacy assessment after treatment.

End point type	Primary

End point timeframe:

8 hours post infusion.

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 analysis was planned to be reported for this end point.

End point values	BeneFactor IX (BeneFIX)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Units on a scale				
arithmetic mean (standard deviation)	1.7 (± 0.72)			

Statistical analyses

No statistical analyses for this end point

Primary: Investigator Hemostatic Efficacy Assessment of Subjects After 24 Hours Post Infusion

End point title	Investigator Hemostatic Efficacy Assessment of Subjects After 24 Hours Post Infusion[2]

End point description:

Investigator Hemostatic Efficacy Assessment was based on response of bleeding episodes to BeneFIX treatment on 4-point rating scale: Excellent(1): definite pain relief or improvement in signs of bleeding starting within 8 hours after infusion, with no additional infusion; Good(2): definite pain relief or improvement in signs of bleeding starting within 8 hrs or following infusion; Moderate(3): probable or slight improvement starting after 8 hours following infusion; No Response(4): no improvement at all

between infusions or during 24 hour interval following an infusion, or condition worsens. FAS population included all subjects who were treated and had at least 1 evaluable efficacy assessment after treatment.

End point type	Primary

End point timeframe:

24 hours post infusion

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 analysis was planned to be reported for this end point.

End point values	BeneFactor IX (BeneFIX)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Units on a scale				
arithmetic mean (standard deviation)	1.58 (± 0.71)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With FIX Inhibitor Development

End point title	Percentage of Subjects With FIX Inhibitor Development[3]

End point description:

Incidence of FIX inhibitor was defined as any result determined as positive at local laboratory, and confirmed at central laboratory with Nijmegen assay result greater than or equal to (>=)0.6 Bethesda Unit (BU). Incidence was stratified by subject exposure history - Minimally Treated Patients (MTPs): those who had received at least one prior FIX infusion, and less than or equal to (<=) 100 documented Exposure Days (EDs); while Previously Treated Patients (PTPs): those who had received >100 documented prior EDs. When number of prior EDs for an individual was not known to be at least 100, subjects were included in the MTP population. Safety Set (SS) population included all enrolled subjects who had taken at least 1 dose of drug. The 'n' is signifying those subjects who received study drug and were evaluated for this measure at the timepoint for each visit respectively.

End point type	Primary

End point timeframe:

Baseline up to 6 months

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned to be reported for this end point.

End point values	BeneFactor IX (BeneFIX)			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Percentage of Subjects				
number (not applicable)				
Total (n=35) MTP (n=24) PTP (n=11)	2.86 4.17 0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Infusions Required to Treat Each Bleed

End point title	Number of Infusions Required to Treat Each Bleed

End point description:

The number of BeneFIX infusions required to treat each bleeding episode were analyzed. The average frequency of BeneFIX infusions per hemorrhage incidence to treat every hemorrhage was equal to the total number of injections throughout the study divided by total number of hemorrhagic events. FAS population included all subjects who were treated and had at least 1 evaluable efficacy assessment after treatment.

End point type	Secondary

End point timeframe:

Baseline up to 6 months

End point values	BeneFactor IX (BeneFIX)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Infusions				
arithmetic mean (standard deviation)	1.2 (± 0.86)			

Statistical analyses

No statistical analyses for this end point

Secondary: FIX Incremental Recovery

End point title	FIX Incremental Recovery

End point description:

FIX recovery was assessed by evaluating FIX:C after initial exposure and following 6 months of repeated exposures to BeneFIX. A modified FIX recovery study was performed at Day 1 (Visit 2) and Month 6/Final/Early Termination visits (Visit 4) and when clinically indicated at the applicable on-demand visits. Blood samples for determination of FIX:C were collected immediately before BeneFIX infusion and at 30 minutes (±5 minutes) after the start of infusion. Post-infusion blood samples were collected via venipuncture in arm contralateral to arm used for infusion. FAS population included all subjects who were treated and had at least 1 evaluable efficacy assessment after treatment. The 'n' is signifying those subjects who received study drug and were evaluated for this measure at the timepoint for each visit respectively.

End point type	Secondary

End point timeframe:

Baseline (Visit 2) up to 6 months (Visit 4)

End point values	BeneFactor IX (BeneFIX)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: IU/deciliter (dL) per IU/kg				
arithmetic mean (standard deviation)				
Visit 2 (n=30) Visit 4 (n=31)	0.76 (± 0.222) 0.727 (± 0.275)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Less Than Expected Therapeutic Effect (LETE)

End point title	Percentage of Subjects With Less Than Expected Therapeutic Effect (LETE)

End point description:

The incidence of LETE for on-demand treatment was defined as no response after each of 2 successive infusions within 24 hours for the same bleeding event in the absence of confounding factors. FAS population included all subjects who were treated and had at least 1 evaluable efficacy assessment after treatment.

End point type	Secondary

End point timeframe:

Baseline up to 6 months

End point values	BeneFactor IX (BeneFIX)			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Percentage of Subjects				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Allergic-Type Allergic Reactions

End point title	Percentage of Subjects With Allergic-Type Allergic Reactions

End point description:

Hypersensitivity to undesirable (damaging, discomfort-producing and sometimes fatal) reactions produced by the normal immune system. Hypersensitivity reactions require a pre-sensitized (immune)

state of the host. SS population included all enrolled subjects who had taken at least 1 dose of drug.

End point type	Secondary

End point timeframe:

Baseline up to 6 months

End point values	BeneFactor IX (BeneFIX)			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Percentage of Subjects				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Thrombosis

End point title	Percentage of Subjects With Thrombosis

End point description:

Thrombosis is the formation of a blood clot (thrombus) inside a blood vessel, obstructing the flow of blood through the circulatory system. When a blood vessel is injured, the body uses platelets and fibrin to form a blood clot to prevent blood loss. SS population included all enrolled subjects who had taken at least 1 dose of drug.

End point type	Secondary

End point timeframe:

Baseline up to 6 months

End point values	BeneFactor IX (BeneFIX)			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Percentage of Subjects				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Subjects With Red Blood Cell (RBC) Agglutination

End point description:

RBC Agglutination is 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. SS population

included all enrolled subjects who had taken at least 1 dose of drug.

End point type	Secondary

End point timeframe:

Baseline up to 6 months

End point values	BeneFactor IX (BeneFIX)			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Percentage of Subjects				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From screening until 30 days after the last visit (Month 6/Final/Early Termination visit)

Adverse event reporting additional description:

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

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	BeneFactor IX (BeneFIX)

Reporting group description:

Subjects received on-demand treatments with BeneFIX according to investigator's prescription over a 6-month (calendar day) period. A single 75 IU/kg (±5 IU/kg) IV bolus infusion of BeneFIX was given for recovery assessments. All BeneFIX administrations occurred in the clinic (hospital).

Serious adverse events	BeneFactor IX (BeneFIX)		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 35 (5.71%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Surgical and medical procedures			
Synovectomy			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	BeneFactor IX (BeneFIX)		
Total subjects affected by non-serious adverse events subjects affected / exposed	10 / 35 (28.57%)		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1		
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) Ligament sprain subjects affected / exposed occurrences (all) Limb injury subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1 2 / 35 (5.71%) 2 2 / 35 (5.71%) 2		
Vascular disorders Haemorrhage subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1 1 / 35 (2.86%) 1		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1		
Gastrointestinal disorders			

Abdominal pain subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1		
Musculoskeletal and connective tissue disorders Arthritis subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1		
Infections and infestations Infection subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1		

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