



Clinical trial results:

An Open-Label, Single-Arm, Post-Authorization Pragmatic Clinical Trial on the Safety and Efficacy of BeneFIX (Nonacog-Alfa, Recombinant Factor IX) in Subjects With Hemophilia B in Usual Care Settings in China Summary

EudraCT number	2016-000765-22
Trial protocol	Outside EU/EEA
Global end of trial date	22 August 2016

Results information

Result version number	v1 (current)
This version publication date	02 February 2017
First version publication date	02 February 2017

Trial information

Trial identification

Sponsor protocol code	B1821052
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

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., +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., +1 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	30 September 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 July 2016
Global end of trial reached?	Yes
Global end of trial date	22 August 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the occurrence and severity of product medically important events (Factor IX inhibitor development, allergic reactions, thrombotic events) of BeneFIX in subjects with hemophilia B in usual care settings in China.

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial subjects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 January 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	China: 70
Worldwide total number of subjects	70
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)	8
Children (2-11 years)	52
Adolescents (12-17 years)	4
Adults (18-64 years)	6
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study enrolled 70 subjects.

Pre-assignment

Screening details:

A total of 77 potential subjects were screened, 70 of them met the inclusion criteria and were enrolled into this 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	BeneFIX
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Arm description:

Subjects received treatment with BeneFIX according to usual care in China and in accord with the China BeneFIX Package Insert. The treatment duration was 6 months (± 7 days) or 50 Exposure Days (EDs) (± 5 EDs) whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	BeneFIX kit
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection in pre-filled syringe
Routes of administration	Intravenous use

Dosage and administration details:

Dosage was determined according to usual care in China and in accord with China BeneFIX Package Insert. BeneFIX was administered via intravenous injection.

Number of subjects in period 1	BeneFIX
Started	70
Completed	66
Not completed	4
Consent withdrawn by subject	1
Unspecified	1
Lost to follow-up	1
Protocol deviation	1

Baseline characteristics

Reporting groups

Reporting group title	BeneFIX
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Reporting group description:

Subjects received treatment with BeneFIX according to usual care in China and in accord with the China BeneFIX Package Insert. The treatment duration was 6 months (± 7 days) or 50 Exposure Days (EDs) (± 5 EDs) whichever occurred first.

Reporting group values	BeneFIX	Total	
Number of subjects	70	70	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	8	8	
Children (2-11 years)	52	52	
Adolescents (12-17 years)	4	4	
Adults (18-64 years)	6	6	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	7.8		
standard deviation	± 7.2	-	
Gender, Male/Female Units: Subjects			
MALE	70	70	
FEMALE	0	0	

End points

End points reporting groups

Reporting group title	BeneFIX
Reporting group description: Subjects received treatment with BeneFIX according to usual care in China and in accord with the China BeneFIX Package Insert. The treatment duration was 6 months (± 7 days) or 50 Exposure Days (EDs) (± 5 EDs) whichever occurred first.	

Primary: Proportion of subjects who developed Factor IX inhibitor

End point title	Proportion of subjects who developed Factor IX inhibitor ^[1]
End point description: Factor IX (FIX) inhibitor development was defined as Bethesda inhibitor titer ≥ 0.6 Bethesda Unit (BU)/mL. Proportion of subjects who developed FIX inhibitor during on-demand period and prophylaxis period is presented. All subjects who received at least 1 dose of BeneFIX during the study were included. Here, n refers to the total number of subjects in each category, and 24 subjects were included in both on-demand and prophylaxis category, therefore the total number was less than 37 + 57.	
End point type	Primary
End point timeframe: 7 months	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No statistical analyses were conducted.	

End point values	BeneFIX			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: percentage of subjects				
number (confidence interval 95%)				
On-demand period (n=37)	0 (0 to 9.5)			
Prophylaxis period (n=57)	1.8 (0 to 9.4)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with allergic reactions

End point title	Number of subjects with allergic reactions ^[2]
End point description: Number of subjects with allergic reactions is presented for on-demand and prophylaxis analysis set. All subjects who received at least 1 dose of BeneFIX during the study were included. Here, n refers to the total number of subjects in each category, and 24 subjects were included in both on-demand and prophylaxis category, therefore the total number was less than 37 + 57.	
End point type	Primary
End point timeframe: 7 months	

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: No statistical analyses were conducted.

End point values	BeneFIX			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: subjects				
On-demand period (n=37)	0			
Prophylaxis period (n=57)	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with thrombotic events

End point title	Number of subjects with thrombotic events ^[3]
End point description: Number of subjects with thrombotic events is presented for on-demand and prophylaxis analysis set. All subjects who received at least 1 dose of BeneFIX during the study were included. Here, n refers to the total number of subjects in each category, and 24 subjects were included in both on-demand and prophylaxis category, therefore the total number was less than 37 + 57.	
End point type	Primary
End point timeframe: 7 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: No statistical analyses were conducted.

End point values	BeneFIX			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: subjects				
On-demand period (n=37)	0			
Prophylaxis period (n=57)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)

End point title	Number of subjects with treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
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End point description:

An adverse event (AE) was any untoward medical occurrence in a clinical investigation subject,

regardless of the causality with study treatment. A serious adverse event (SAE) was any untoward occurrence that resulted in death; was life threatening (immediate risk of death); required inpatient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity; resulted in congenital anomaly/birth defect. AEs included both serious and non-serious AEs. Treatment-emergent AEs were those with initial onset or increasing in severity after the first dose of study drug. Number of subjects with treatment-emergent AEs and SAEs is presented for on-demand and prophylaxis analysis set. All subjects who received at least 1 dose of BeneFIX were included. Here, n refers to the total number of subjects in each category, and 24 subjects were included in both on-demand and prophylaxis category, therefore the total number was less than 37 + 57.

End point type	Secondary
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End point timeframe:

7 months

End point values	BeneFIX			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: subjects				
On-demand period (n=37): AEs	17			
Prophylaxis period (n=57): AEs	46			
On-demand period (n=37): SAEs	0			
Prophylaxis period (n=57): SAEs	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized bleeding rates (ABRs) in subjects receiving prophylaxis treatment with BeneFIX during their prophylaxis period

End point title	Annualized bleeding rates (ABRs) in subjects receiving prophylaxis treatment with BeneFIX during their prophylaxis period
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End point description:

For prophylaxis treatment period, annualized bleeding rate (ABR) was derived for each subject by the following formula: $ABR = \text{number of bleeds in prophylaxis period} / (\text{number of days in prophylaxis period} / 365.25)$. In this formula, number of days in prophylaxis period was the sum of time from all prophylaxis treatment periods for the subject. The number of bleeds for the ABR calculation included all bleeds during all the prophylaxis periods. Time on a single treatment period was defined as first day of the treatment period through the day before the start of the next treatment period. For a prophylaxis regimen to be qualified to have ABR calculated, the sum of its periods needs to be equal to or more than 14 days. All subjects who participated in at least one day of a prophylaxis period (ie, had at least one prophylaxis dose) were included.

End point type	Secondary
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End point timeframe:

Up to 6 months or 50 exposure days whichever occurred first

End point values	BeneFIX			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: episodes/year				
arithmetic mean (standard deviation)	6.5 ($\pm$ 9.06)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of spontaneous/non-traumatic breakthrough bleeds within 48 hours of a prophylaxis dose of BeneFIX

End point title	Number of spontaneous/non-traumatic breakthrough bleeds within 48 hours of a prophylaxis dose of BeneFIX
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End point description:

The number of spontaneous, non-traumatic breakthrough bleeds within 48 hours following a prophylaxis dose of BeneFIX was summarized. The prophylaxis infusion time, bleed start time and bleed type (etiology) were used to determine the number of spontaneous, non-traumatic breakthrough bleeds that occurred ≤ 48 hours after a prophylaxis infusion. If there was more than 1 bleed location (eg, ankle and joint) with identical bleed start date and time, it was treated as 1 bleed occurrence. All subjects who participated in at least one day of a prophylaxis period (ie, had at least one prophylaxis dose) were included. A total of 2032 prophylaxis infusions were administered during the study. In the prophylaxis analysis set, 23 breakthrough bleeds occurred in 11 subjects.

End point type	Secondary
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End point timeframe:

Up to 6 months or 50 exposure days whichever occurred first

End point values	BeneFIX			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: breakthrough bleeds				
arithmetic mean (standard deviation)	2.1 ($\pm$ 1.92)			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized bleeding rates (ABRs) in subjects receiving on-demand treatment with BeneFIX during their on-demand period

End point title	Annualized bleeding rates (ABRs) in subjects receiving on-demand treatment with BeneFIX during their on-demand period
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End point description:

For on-demand treatment period, the annualized bleeding rate (ABR) was derived for each subject by the following formula: $ABR = \text{number of bleeds in on-demand period} / (\text{number of days in on-demand period} / 365.25)$. In this formula, number of days in on-demand period was the sum of time from all on-demand treatment periods for the subject. The number of bleeds for the ABR calculation included all

bleeds during all the on-demand periods. Time on a single treatment period was defined as first day of the treatment period through the day before the start of the next treatment period. For an on-demand regimen to be qualified to have ABR calculated, the sum of its periods needs to be equal to or more than 14 days. All subjects who participated in at least one day of on-demand period were included in this analysis. Number of subjects analyzed represents the number of subjects who were evaluable for this endpoint.

End point type	Secondary
End point timeframe:	
Up to 6 months or 50 exposure days whichever occurred first	

End point values	BeneFIX			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: episodes/year				
arithmetic mean (standard deviation)	26.3 (± 23.08)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of infusions resulted in the following response to on-demand treatment of bleeds: excellent, good, moderate, no response

End point title	Number of infusions resulted in the following response to on-demand treatment of bleeds: excellent, good, moderate, no response
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End point description:

Response was assessed using 4-point On-Demand Hemostasis Efficacy Rating Scale, based on a) definite pain relief and b) improvement in signs of bleeding. Excellent: a) and/or b) within 8 hours after an infusion, with no additional infusion administered; good: a) and/or b) within 8 hours after an infusion, with at least 1 additional infusion administered for complete resolution of bleeding, or a) and/or b) after 8 hours following an infusion, with no additional infusion administered; moderate: probable or slight improvement after 8 hours following an infusion, with at least 1 additional infusion administered for complete resolution of bleeding; no response: no improvement between infusions or during the 24 hour interval following an infusion, or condition worsens. Number of subjects analyzed represents the number of subjects who received at least one on-demand infusion of BeneFIX during the study. A total of 520 on-demand infusions were given during the study.

End point type	Secondary
End point timeframe:	
Up to 6 months or 50 exposure days whichever occurred first	

End point values	BeneFIX			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: infusions				
Excellent	254			
Good	204			
Moderate	54			

No response	8			
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Statistical analyses

No statistical analyses for this end point

Secondary: Average infusion dose and total Factor IX consumption in prophylaxis, on-demand and recovery settings

End point title	Average infusion dose and total Factor IX consumption in prophylaxis, on-demand and recovery settings
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End point description:

The total amount (international units [IU]) infused for each BeneFIX infusion was summed to calculate the total factor IX consumption for each subject. The average infusion dose for each subject was calculated as his total factor IX consumption (in IU) divided by the number of infusions administered. All subjects who received at least one dose of BeneFIX were included in this analysis. Here, n refers to the total number of subjects who were evaluable for this endpoint in each category, and subjects in each category were not mutually exclusive.

End point type	Secondary
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End point timeframe:

Up to 6 months or 50 exposure days whichever occurred first

End point values	BeneFIX			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: IU				
arithmetic mean (standard deviation)				
Total FIX consumption: on-demand setting (n=46)	9826.1 (± 14816.3)			
Total FIX consumption: prophylaxis setting (n=57)	19224.1 (± 15424.7)			
Total FIX consumption: recovery setting (n=24)	1419.8 (± 1192.6)			
Average infusion dose: on-demand setting (n=46)	731.6 (± 498.6)			
Average infusion dose: prophylaxis setting (n=57)	540.1 (± 316.6)			
Average infusion dose: recovery setting (n=24)	929.1 (± 475.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of BeneFIX infusions to treat each new bleed

End point title	Number of BeneFIX infusions to treat each new bleed
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End point description:

The number of BeneFIX infusions administered to treat each new bleed was calculated by adding the on-demand initial treatment and any on-demand follow-up treatments for the same bleed. If there was more than one bleed location (eg, ankle and joint) with identical bleed start date and time, it was treated as one bleed occurrence. All subjects who received at least one on-demand infusion of BeneFIX to treat new bleed were included. A total of 353 new bleeds occurred during the study.

End point type	Secondary
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End point timeframe:

Up to 6 months or 50 exposure days whichever occurred first

End point values	BeneFIX			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: infusions				
arithmetic mean (standard deviation)	1.5 ($\pm$ 1.71)			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence rate of less than expected therapeutic effects (LETes) in on-demand, prophylaxis, and low recovery settings

End point title	Incidence rate of less than expected therapeutic effects (LETes) in on-demand, prophylaxis, and low recovery settings
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End point description:

Less than expected therapeutic effect (LETE) in the on-demand setting was defined as 2 successive "no response" ratings recorded after 2 successive BeneFIX drug infusions, respectively. LETe in the prophylaxis setting was defined as occurrence of any spontaneous bleed within 48 hours after a regularly scheduled prophylactic dose of BeneFIX (which was not used to treat a bleed). LETe could also be lower than expected recovery of FIX in the opinion of the investigator following infusion of BeneFIX, which didn't occur in this study. All subjects who received at least one dose of BeneFIX were included in this analysis. Here, n refers to the total number of infusions in each category.

End point type	Secondary
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End point timeframe:

Up to 6 months or 50 exposure days whichever occurred first

End point values	BeneFIX			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: percentage				
number (confidence interval 95%)				
On-demand setting (n=353)	0 (0 to 1)			
Prophylaxis setting (n=2032)	0.1 (0 to 0.4)			
Low recovery setting (n=0)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 28 calendar days after the last administration of the investigational product

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 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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	BeneFIX
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Reporting group description:

Subjects received treatment with BeneFIX according to usual care in China and in accord with the China BeneFIX Package Insert. The treatment duration was 6 months (± 7 days) or 50 Exposure Days (EDs) (± 5 EDs) whichever occurred first.

Serious adverse events	BeneFIX		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 70 (2.86%)		
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 / 70 (1.43%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Oral mucosa haematoma			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	BeneFIX		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 70 (78.57%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	5 / 70 (7.14%)		
occurrences (all)	7		
Fall			
subjects affected / exposed	8 / 70 (11.43%)		
occurrences (all)	10		
General disorders and administration site conditions			
Peripheral swelling			
subjects affected / exposed	6 / 70 (8.57%)		
occurrences (all)	9		
Pyrexia			
subjects affected / exposed	11 / 70 (15.71%)		
occurrences (all)	18		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 70 (7.14%)		
occurrences (all)	6		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 70 (17.14%)		
occurrences (all)	14		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	17 / 70 (24.29%)		
occurrences (all)	76		
Joint range of motion decreased			
subjects affected / exposed	6 / 70 (8.57%)		
occurrences (all)	20		
Joint swelling			
subjects affected / exposed	15 / 70 (21.43%)		
occurrences (all)	32		
Pain in extremity			

subjects affected / exposed occurrences (all)	7 / 70 (10.00%) 8		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	5 / 70 (7.14%)		
occurrences (all)	8		
Nasopharyngitis			
subjects affected / exposed	19 / 70 (27.14%)		
occurrences (all)	27		

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