Clinical trial results:
An Open-Label, Single Dose Pharmacokinetic Study of BeneFIX (Nonacog Alfa, Recombinant Factor IX) in Male Chinese Subjects With Hemophilia B

Summary

EudraCT number	2015-003027-61
Trial protocol	Outside EU/EEA
Global end of trial date	08 April 2015

Results information

Result version number	v1 (current)
This version publication date	29 June 2016
First version publication date	29 June 2016

Trial information

Trial identification

Sponsor protocol code	B1821048

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02213250
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc
Sponsor organisation address	235 E 42nd Street, New York, United States, 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	06 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 April 2015
Global end of trial reached?	Yes
Global end of trial date	08 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective was to characterize single dose pharmacokinetic profiles of BeneFIX (50 IU/kg) in male 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	02 March 2015
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: 12
Worldwide total number of subjects	12
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)	0
Adults (18-64 years)	8
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Twelve (12) subjects that were age 6 years or older (weight ≥20 kg) with moderate severe to severe hemophilia B (FIX activity ≤2%) were enrolled. Four (4) subjects were at the younger age range of ≥6 and <12 years; remaining subjects were 12 years or older.

Pre-assignment

Screening details:

Subjects did not receive an infusion of any FIX products for at least 4 days and were required to be in a non-bleeding state before the administration of BeneFIX on Day 1.

Pre-assignment period milestones

Number of subjects started	12
Number of subjects completed	12

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	BeneFIX 50 IU/kg; Age group: >=6 and <12 years

Arm description:

Subjects received a single dose of 50 IU/kg BeneFIX administered by IV infusion within 10 minutes at approximately 0800 hours (±2 hours) on Day 1.

Arm type	Experimental
Investigational medicinal product name	BeneFIX
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

a single of BeneFIX 50 IU/kg by intravenous infusion

Arm title	BeneFIX 50 IU/kg; Age group: >=12 years

Arm description:

Subejcts received a single dose of 50 IU/kg BeneFIX administered by IV infusion within 10 minutes at approximately 0800 hours (±2 hours) on Day 1.

Arm type	Experimental
Investigational medicinal product name	BeneFIX
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

a single dose of BeneFIX 50 IU/kg by intravenous infusion

Number of subjects in period 1	BeneFIX 50 IU/kg; Age group: >=6 and <12 years	BeneFIX 50 IU/kg; Age group: >=12 years
Started	4	8
Completed	4	8

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	12	12	
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)	0	0	
Children (2-11 years)	4	4	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	8	8	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	24.8		
standard deviation	± 15.4	-	
Gender Categorical Units: Subjects			
Male	12	12	
Female	0	0	

End points

End points reporting groups

Reporting group title	BeneFIX 50 IU/kg; Age group: >=6 and <12 years
Reporting group description:	
Subjects received a single dose of 50 IU/kg BeneFIX administered by IV infusion within 10 minutes at approximately 0800 hours (±2 hours) on Day 1.	
Reporting group title	BeneFIX 50 IU/kg; Age group: >=12 years
Reporting group description:	
Subejcts received a single dose of 50 IU/kg BeneFIX administered by IV infusion within 10 minutes at approximately 0800 hours (±2 hours) on Day 1.	

Primary: Maximum Observed Plasma Concentration (Cmax)

End point title	Maximum Observed Plasma Concentration (Cmax)[1]
End point description:	
The pharmacokinetics (PK) parameter analysis population was defined as all subjects enrolled and treated who had at least 1 of the PK parameters of primary interest. All subjects were included in the PK analysis population.	
End point type	Primary
End point timeframe:	
Pre-dose, 0.25, 0.5, 1, 3, 6, 9, 24, 50, 72 and 96 hours post-dose	

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 done for this end point.

End point values	BeneFIX 50 IU/kg; Age group: >=6 and <12 years	BeneFIX 50 IU/kg; Age group: >=12 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	8		
Units: IU/milliliter (IU/mL)				
geometric mean (geometric coefficient of variation)	0.388 (± 26)	0.4226 (± 16)		

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Concentration Time Curve From Time 0 to the Time of the Last Quantifiable Concentration (AUClast)

End point title	Area Under the Concentration Time Curve From Time 0 to the Time of the Last Quantifiable Concentration (AUClast)[2]
End point description:	
The pharmacokinetics (PK) parameter analysis population was defined as all subjects enrolled and treated who had at least 1 of the PK parameters of primary interest. All subjects were included in the PK analysis population.	
End point type	Primary

End point timeframe:

Pre-dose, 0.25, 0.5, 1, 3, 6, 9, 24, 50, 72 and 96 hours post-dose

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 done for this end point.

End point values	BeneFIX 50 IU/kg; Age group: >=6 and <12 years	BeneFIX 50 IU/kg; Age group: >=12 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	8		
Units: IU*hour/milliliter (IU*hr/mL)				
geometric mean (geometric coefficient of variation)	6.93 (± 18)	9.707 (± 15)		

Statistical analyses

No statistical analyses for this end point

Primary: Primary: Area Under the Concentration Time Curve From Time 0 to Infinity (AUCinf)

End point title	Primary: Area Under the Concentration Time Curve From Time 0 to Infinity (AUCinf)[3]

End point description:

The pharmacokinetics (PK) parameter analysis population was defined as all subjects enrolled and treated who had at least 1 of the PK parameters of primary interest. All subjects were included in the PK analysis population.

End point type	Primary

End point timeframe:

Pre-dose, 0.25, 0.5, 1, 3, 6, 9, 24, 50, 72 and 96 hours post-dose

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 done for this end point.

End point values	BeneFIX 50 IU/kg; Age group: >=6 and <12 years	BeneFIX 50 IU/kg; Age group: >=12 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	8		
Units: IU*hr/ml				
geometric mean (geometric coefficient of variation)	7.841 (± 16)	11.66 (± 15)		

Statistical analyses

No statistical analyses for this end point

Primary: Time to Reach Cmax (Tmax)

End point title	Time to Reach Cmax (Tmax)[4]

End point description:

The pharmacokinetics (PK) parameter analysis population was defined as all subjects enrolled and treated who had at least 1 of the PK parameters of primary interest. All subjects were included in the PK analysis population.

End point type	Primary

End point timeframe:

Pre-dose, 0.25, 0.5, 1, 3, 6, 9, 24, 50, 72 and 96 hours post-dose

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: No statistical analyses were done for this end point.

End point values	BeneFIX 50 IU/kg; Age group: >=6 and <12 years	BeneFIX 50 IU/kg; Age group: >=12 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	8		
Units: hours				
median (full range (min-max))	0.5 (0.25 to 3)	0.375 (0.25 to 3)		

Statistical analyses

No statistical analyses for this end point

Primary: Volume of Distribution at Steady State (Vss)

End point title	Volume of Distribution at Steady State (Vss)[5]

End point description:

The pharmacokinetics (PK) parameter analysis population was defined as all subjects enrolled and treated who had at least 1 of the PK parameters of primary interest. All subjects were included in the PK analysis population.

End point type	Primary

End point timeframe:

Pre-dose, 0.25, 0.5, 1, 3, 6, 9, 24, 50, 72 and 96 hours post-dose

Notes:

[5] - 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 done for this end point.

End point values	BeneFIX 50 IU/kg; Age group: >=6 and <12 years	BeneFIX 50 IU/kg; Age group: >=12 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	8		
Units: milliliter/kilogram (mL/kg)				
geometric mean (geometric coefficient of variation)	227.9 (± 20)	218.8 (± 19)		

Statistical analyses

No statistical analyses for this end point

Primary: Terminal Phase Rate Constant (Kel)

End point title	Terminal Phase Rate Constant (Kel)[6]

End point description:

The pharmacokinetics (PK) parameter analysis population was defined as all subjects enrolled and treated who had at least 1 of the PK parameters of primary interest. All subjects were included in the PK analysis population.

End point type	Primary

End point timeframe:

Pre-dose, 0.25, 0.5, 1, 3, 6, 9, 24, 50, 72 and 96 hours post-dose

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: No statistical analyses were done for this end point.

End point values	BeneFIX 50 IU/kg; Age group: >=6 and <12 years	BeneFIX 50 IU/kg; Age group: >=12 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	8		
Units: 1/hr				
geometric mean (geometric coefficient of variation)	0.02509 (± 16)	0.01781 (± 20)		

Statistical analyses

No statistical analyses for this end point

Primary: Mean Residence Time (MRT)

End point title	Mean Residence Time (MRT)[7]

End point description:

The pharmacokinetics (PK) parameter analysis population was defined as all subjects enrolled and treated who had at least 1 of the PK parameters of primary interest. All subjects were included in the PK analysis population.

End point type	Primary

End point timeframe:

Pre-dose, 0.25, 0.5, 1, 3, 6, 9, 24, 50, 72 and 96 hours post-dose

Notes:

[7] - 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 done for this end point.

End point values	BeneFIX 50 IU/kg; Age group: >=6 and <12 years	BeneFIX 50 IU/kg; Age group: >=12 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	8		
Units: hours				
geometric mean (geometric coefficient of variation)	35.78 (± 14)	51.01 (± 16)		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Decay Half-Life (t½)

End point title	Plasma Decay Half-Life (t½)[8]

End point description:

The pharmacokinetics (PK) parameter analysis population was defined as all subjects enrolled and treated who had at least 1 of the PK parameters of primary interest. All subjects were included in the PK analysis population.

End point type	Primary

End point timeframe:

Pre-dose, 0.25, 0.5, 1, 3, 6, 9, 24, 50, 72 and 96 hours post-dose

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: No statistical analyses were done for this end point.

End point values	BeneFIX 50 IU/kg; Age group: >=6 and <12 years	BeneFIX 50 IU/kg; Age group: >=12 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	8		
Units: hours				
arithmetic mean (standard deviation)	27.88 (± 4.4903)	39.56 (± 7.3832)		

Statistical analyses

No statistical analyses for this end point

Primary: Systemic Clearance (CL)

End point title	Systemic Clearance (CL)[9]

End point description:

The pharmacokinetics (PK) parameter analysis population was defined as all subjects enrolled and treated who had at least 1 of the PK parameters of primary interest. All subjects were included in the PK analysis population.

End point type	Primary

End point timeframe:

Pre-dose, 0.25, 0.5, 1, 3, 6, 9, 24, 50, 72 and 96 hours post-dose

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: No statistical analyses were done for this end point.

End point values	BeneFIX 50 IU/kg; Age group: >=6 and <12 years	BeneFIX 50 IU/kg; Age group: >=12 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	8		
Units: mL/hr/kg				
geometric mean (geometric coefficient of variation)	6.378 (± 16)	4.291 (± 15)		

Statistical analyses

No statistical analyses for this end point

Primary: Incremental Recovery

End point title	Incremental Recovery[10]

End point description:

The pharmacokinetics (PK) parameter analysis population was defined as all subjects enrolled and treated who had at least 1 of the PK parameters of primary interest. All subjects were included in the PK analysis population.

End point type	Primary

End point timeframe:

Pre-dose, 0.25, 0.5 and 1 hour post-dose

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: No statistical analyses were done for this end point.

End point values	BeneFIX 50 IU/kg; Age group: >=6 and <12 years	BeneFIX 50 IU/kg; Age group: >=12 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	8		
Units: (IU/dL)/(IU/Kg)				
geometric mean (geometric coefficient of variation)	0.7759 (± 26)	0.8199 (± 17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Abnormal Clinical Laboratory Measurements

(Without Regard to Baseline Abnormality)

End point title	Number of Subjects With Abnormal Clinical Laboratory Measurements (Without Regard to Baseline Abnormality)

End point description:

Clinical laboratory analysis tests included hematology, serium chemistry, prothrombin time and urianalysis. Numbers of subjects with laboratory test abnormalities without regard to baseline abnormality were reported.

End point type	Secondary

End point timeframe:

Screening, Day 0 and 96 hours post-dose (Day 5 or early termination)

End point values	BeneFIX 50 IU/kg; Age group: >=6 and <12 years	BeneFIX 50 IU/kg; Age group: >=12 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	8		
Units: subjects	4	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Vital Signs Post-Dose Data Met Criteria of Potential Clinical Concern (Without Regard to Baseline Abnormality)

End point title	Number of Subjects With Vital Signs Post-Dose Data Met Criteria of Potential Clinical Concern (Without Regard to Baseline Abnormality)

End point description:

The safety analysis population included All participants who received at least 1 dose of BeneFIX.

End point type	Secondary

End point timeframe:

Screening, pre-dose (baseline) and 96 hours post-dose (Day 5 or early termination)

End point values	BeneFIX 50 IU/kg; Age group: >=6 and <12 years	BeneFIX 50 IU/kg; Age group: >=12 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	8[11]		
Units: subjects	1	0		

Notes:

[11] - None of the vital signs values met the criteria for potential clinical concern.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with inhibitor development

End point title	Number of Subjects with inhibitor development

End point description:

The safety analysis population included All subjects who received at least 1 dose of BeneFIX.

End point type	Secondary

End point timeframe:

Screening, Day 0 and 96 hours post-dose (Day 5 or early termination)

End point values	BeneFIX 50 IU/kg; Age group: >=6 and <12 years	BeneFIX 50 IU/kg; Age group: >=12 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[12]	8[13]		
Units: subjects	0	0		

Notes:

[12] - There were no subjects with inhibitor development.

[13] - There were no subjects with inhibitor development.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with allergic reactions

End point title	Number of Subjects with allergic reactions

End point description:

The safety analysis population included all subjects who received at least 1 dose of BeneFIX.

End point type	Secondary

End point timeframe:

Baseline up to 28 calendar days post the last administration of study drug

End point values	BeneFIX 50 IU/kg; Age group: >=6 and <12 years	BeneFIX 50 IU/kg; Age group: >=12 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[14]	8[15]		
Units: subjects	0	0		

Notes:

[14] - There were no subjects with allergic reactions.

[15] - There were no subjects with allergic reactions.

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:

The safety analysis population included all subjects who received at least 1 dose of BeneFIX.

End point type	Secondary

End point timeframe:

Day 0 and 96 hours post-dose (Day 5 or early termination)

End point values	BeneFIX 50 IU/kg; Age group: >=6 and <12 years	BeneFIX 50 IU/kg; Age group: >=12 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[16]	8[17]		
Units: subjects	0	0		

Notes:

[16] - There were no subjects with thrombogenicity.

[17] - There were no subjects with thrombogenicity.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Baseline up to 28 calendar days post the last administration of study drug (BeneFIX).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	BeneFIX 50 IU/kg; Age group: >=12 years

Reporting group description:

Subejcts received a single dose of 50 IU/kg BeneFIX administered by IV infusion within 10 minutes at approximately 0800 hours (±2 hours) on Day 1.

Reporting group title	BeneFIX 50 IU/kg; Age group: >=6 and <12 years

Reporting group description:

Subjects received a single dose of 50 IU/kg BeneFIX administered by IV infusion within 10 minutes at approximately 0800 hours (±2 hours) on Day 1.

Serious adverse events	BeneFIX 50 IU/kg; Age group: >=12 years	BeneFIX 50 IU/kg; Age group: >=6 and <12 years	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	BeneFIX 50 IU/kg; Age group: >=12 years	BeneFIX 50 IU/kg; Age group: >=6 and <12 years	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: There were no adverse events reported in this study.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 August 2014	Schedule of activities, Section 3.1, Section 6.2.2 & 6.2.3, and Section 7.3.1: PK collection timpoints: 96 hours post dose is added for all subjects as it will provide additional information on the PK profile. 48 hour post dose is deleted for subjects who are 12 years old since the 48 hour and 50 hour are very close to each other and the concentrations observed in other trials at these two times are quite similar to each other. Section 6.2.2: The languages regarding the collection time of PK FIX activity samples relevant to infusion are revised from completion of the infusion to start of the infusion as the drug enters the blood at the start of the infusion, thus time 'zero' is the start of the infusion. Exclusion criterion #24, and Section 4.4.4: Contraception are deleted as there is no label restriction requiring contraception in males taking Benefix. Section 1.3.1: a statement regarding no contraception requirement on male subjects is added. Exclusion criteria 10, 11, 12 is combined as one criterion and standard language is added. Schedule of activities, Section 3.1 & Section 6.2.1: The requirement on stay in CRU is revised from completion of DAY4/early termination visit activities to completion of the 24 hours post dose PK sample collections, after that, it will be at investigator's discretion on whether the subjects should stay in CRU or not. The visits that follow hour 24 could be conducted outpatient at investigator's discretion. For Pediatric subjects, their parents/legal representatives will accompany them during the study if applicable. K–value is replaced by incremental recovery throughout the protocol as K–value is a past used term for incremental recovery and should not continue to be used. Updated Blood Volume table for subjects 6 <12 years old from 55.1 mL to 57.8 mL. Section 6.1.1: height is added to Demography. Section 7.3.3.: FIX inhibitor analysis is added. Pfizer protocol standard language update.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported