Clinical trial results:
A Multicenter, Open-Label Study to Compare On-Demand Treatment With 2 Prophylaxis Regimens of Recombinant Coagulation Factor IX (BeneFIX) Reformulated Drug Product (rFIX-R) in Subjects With Severe Hemophilia B

Summary

EudraCT number	2005-005246-40
Trial protocol	HU BE IT DE Outside EU/EEA
Global end of trial date	12 October 2010

Results information

Result version number	v1 (current)
This version publication date	23 May 2016
First version publication date	29 July 2015

Trial information

Trial identification

Sponsor protocol code	3090A1-400

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00364182
WHO universal trial number (UTN)	-
Other trial identifiers	alias: B1821002

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	29 March 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 October 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of BeneFIX infused as prophylaxis regimens, compared with BeneFIX administered in an on-demand regimen only.

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	07 May 2007
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	Hungary: 3
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Croatia: 3
Country: Number of subjects enrolled	Romania: 7
Country: Number of subjects enrolled	Russian Federation: 13
Country: Number of subjects enrolled	Serbia: 5
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United States: 11
Worldwide total number of subjects	50
EEA total number of subjects	19

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)	6
Adolescents (12-17 years)	4
Adults (18-64 years)	40
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

3 subjects who enrolled in the study were not randomized to either prophylaxis treatment regimen, but participated in the study during the first on demand treatment period.

Period 1

Period 1 title	First Intervention
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Pre-Randomization

Arm description:

Subjects were enrolled and received BeneFIX (recombinant coagulation factor IX) as intravenous (IV) bolus infusion in the first on-demand (OD1) period but were never randomized.

Arm type	Experimental
Investigational medicinal product name	BeneFIX
Investigational medicinal product code	
Other name	recombinant coagulation factor IX (rFIX), nonacog alfa
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

Subjects were enrolled and received BeneFIX (recombinant coagulation factor IX) as IV bolus infusion in the first on-demand (OD1) period but were never randomized.

Arm title	BeneFIX OD1, 100 IU/kg, OD2, 50 IU/kg: First Intervention

Arm description:

BeneFIX (recombinant coagulation factor IX) on-demand for 16 weeks (OD1), followed by 100 international units per kilogram (IU/kg) once per week (QW) for 16 weeks prophylactically, followed by 8 weeks BeneFIX on-demand (OD2), followed by 50 IU/kg twice weekly (BW) for 16 weeks prophylactically. Subjects received BeneFIX OD1 during the first intervention period.

Arm type	Experimental
Investigational medicinal product name	BeneFIX
Investigational medicinal product code	
Other name	recombinant coagulation factor IX (rFIX), nonacog alfa
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

BeneFIX on-demand for 16 weeks (OD1) during the first intervention period.

Arm title	BeneFIX OD1, 50 IU/kg, OD2, 100 IU/kg; First Intervention

Arm description:

BeneFIX (recombinant coagulation factor IX) on-demand for 16 weeks (OD1), followed by 50 IU/kg BW for 16 weeks prophylactically, followed by 8 weeks BeneFIX on-demand (OD2), followed by 100 IU/kg QW for 16 weeks prophylactically. Subjects received BeneFIX OD1 during the first intervention period.

Arm type	Experimental

Investigational medicinal product name	BeneFIX
Investigational medicinal product code	
Other name	recombinant coagulation factor IX (rFIX), nonacog alfa
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

BeneFIX on-demand for 16 weeks (OD1) during the first intervention period.

Number of subjects in period 1	Pre-Randomization	BeneFIX OD1, 100 IU/kg, OD2, 50 IU/kg: First Intervention	BeneFIX OD1, 50 IU/kg, OD2, 100 IU/kg; First Intervention
Started	3	22	25
Completed	0	22	25
Not completed	3	0	0
Consent withdrawn by subject	2	-	-
Secondary prophylaxis	1	-	-

Period 2

Period 2 title	Second Intervention
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	BeneFIX OD1, 100 IU/kg, OD2, 50 IU/kg: Second Intervention

Arm description:

BeneFIX (recombinant coagulation factor IX) on-demand for 16 weeks (OD1), followed by 100 IU/kg QW for 16 weeks prophylactically, followed by 8 weeks BeneFIX on-demand (OD2), followed by 50 IU/kg BW for 16 weeks prophylactically. Subjects received BeneFIX (100 IU/kg) during the second intervention period.

Arm type	Experimental
Investigational medicinal product name	BeneFIX
Investigational medicinal product code	
Other name	recombinant coagulation factor IX (rFIX), nonacog alfa
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

BeneFIX 100 IU/kg QW for 16 weeks prophylactically during the second intervention period.

Arm title	BeneFIX OD1, 50 IU/kg, OD2, 100 IU/kg: Second Intervention

Arm description:

BeneFIX (recombinant coagulation factor IX) on-demand for 16 weeks (OD1), followed by 50 IU/kg BW for 16 weeks prophylactically, followed by 8 weeks BeneFIX on-demand (OD2), followed by 100 IU/kg QW for 16 weeks prophylactically. Subjects received BeneFIX (50 IU/kg) during the second intervention period.

Arm type	Experimental
Investigational medicinal product name	BeneFIX
Investigational medicinal product code	
Other name	recombinant coagulation factor IX (rFIX), nonacog alfa
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

BeneFIX 50 IU/kg BW for 16 weeks prophylactically during the second intervention period.

Number of subjects in period 2	BeneFIX OD1, 100 IU/kg, OD2, 50 IU/kg: Second Intervention	BeneFIX OD1, 50 IU/kg, OD2, 100 IU/kg: Second Intervention
Started	22	25
Randomized	22	25
Completed	20	23
Not completed	2	2
Adverse Event	-	1
Non-compliance	1	1
Protocol Violation	1	-

Period 3

Period 3 title	Third Intervention
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	BeneFIX OD1, 100 IU/kg, OD2, 50 IU/kg: Third Intervention

Arm description:

BeneFIX (recombinant coagulation factor IX) on-demand for 16 weeks (OD1), followed by 100 IU/kg QW for 16 weeks prophylactically, followed by 8 weeks BeneFIX on-demand (OD2), followed by 50 IU/kg BW for 16 weeks prophylactically. Subjects received BeneFIX OD2 during the third intervention period.

Arm type	Experimental
Investigational medicinal product name	BeneFIX
Investigational medicinal product code	
Other name	recombinant coagulation factor IX (rFIX), nonacog alfa
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

BeneFIX on-demand for 8 weeks (OD2) during the third intervention period.

Arm title	BeneFIX OD1, 50 IU/kg, OD2, 100 IU/kg: Third Intervention

Arm description:

BeneFIX (recombinant coagulation factor IX) on-demand for 16 weeks (OD1), followed by 50 IU/kg BW for 16 weeks prophylactically, followed by 8 weeks BeneFIX on-demand (OD2), followed by 100 IU/kg QW for 16 weeks prophylactically. Subjects received BeneFIX OD2 during the third intervention period.

Arm type	Experimental
Investigational medicinal product name	BeneFIX
Investigational medicinal product code	
Other name	recombinant coagulation factor IX (rFIX), nonacog alfa
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

BeneFIX on-demand for 8 weeks (OD2) during the third intervention period.

Number of subjects in period 3	BeneFIX OD1, 100 IU/kg, OD2, 50 IU/kg: Third Intervention	BeneFIX OD1, 50 IU/kg, OD2, 100 IU/kg: Third Intervention
Started	20	23
Completed	19	22
Not completed	1	1
Non-compliance	1	-
Lost to follow-up	-	1

Period 4

Period 4 title	Fourth Intervention
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	BeneFIX OD1, 100 IU/kg, OD2, 50 IU/kg: Fourth Intervention

Arm description:

BeneFIX (recombinant coagulation factor IX) on-demand for 16 weeks (OD1), followed by 100 IU/kg QW for 16 weeks prophylactically, followed by 8 weeks BeneFIX on-demand (OD2), followed by 50 IU/kg BW for 16 weeks prophylactically. Subjects received BeneFIX (50 IU/kg) during the fourth intervention period.

Arm type	Experimental
Investigational medicinal product name	BeneFIX
Investigational medicinal product code	
Other name	recombinant coagulation factor IX (rFIX), nonacog alfa
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

BeneFIX 50 IU/kg BW for 16 weeks prophylactically during the fourth intervention period.

Arm title	BeneFIX OD1, 50 IU/kg, OD2, 100 IU/kg: Fourth intervention

Arm description:

BeneFIX (recombinant coagulation factor IX) on-demand for 16 weeks (OD1), followed by 50 IU/kg BW for 16 weeks prophylactically, followed by 8 weeks BeneFIX on-demand (OD2), followed by 100 IU/kg QW for 16 weeks prophylactically. Subjects received BeneFIX (100 IU/kg) during the fourth intervention period.

Arm type	Experimental
Investigational medicinal product name	BeneFIX
Investigational medicinal product code	
Other name	recombinant coagulation factor IX (rFIX), nonacog alfa
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

BeneFIX 100 IU/kg QW for 16 weeks prophylactically during the fourth intervention period.

Number of subjects in period 4	BeneFIX OD1, 100 IU/kg, OD2, 50 IU/kg: Fourth Intervention	BeneFIX OD1, 50 IU/kg, OD2, 100 IU/kg: Fourth intervention
Started	19	22
Completed	19	22

Baseline characteristics

Reporting groups	
Reporting group title	Pre-Randomization
Reporting group description:	
Subjects were enrolled and received BeneFIX (recombinant coagulation factor IX) as intravenous (IV) bolus infusion in the first on-demand (OD1) period but were never randomized.	
Reporting group title	BeneFIX OD1, 100 IU/kg, OD2, 50 IU/kg: First Intervention
Reporting group description:	
BeneFIX (recombinant coagulation factor IX) on-demand for 16 weeks (OD1), followed by 100 international units per kilogram (IU/kg) once per week (QW) for 16 weeks prophylactically, followed by 8 weeks BeneFIX on-demand (OD2), followed by 50 IU/kg twice weekly (BW) for 16 weeks prophylactically. Subjects received BeneFIX OD1 during the first intervention period.	
Reporting group title	BeneFIX OD1, 50 IU/kg, OD2, 100 IU/kg; First Intervention
Reporting group description:	
BeneFIX (recombinant coagulation factor IX) on-demand for 16 weeks (OD1), followed by 50 IU/kg BW for 16 weeks prophylactically, followed by 8 weeks BeneFIX on-demand (OD2), followed by 100 IU/kg QW for 16 weeks prophylactically. Subjects received BeneFIX OD1 during the first intervention period.	

Reporting group values	Pre-Randomization	BeneFIX OD1, 100 IU/kg, OD2, 50 IU/kg: First Intervention	BeneFIX OD1, 50 IU/kg, OD2, 100 IU/kg; First Intervention
Number of subjects	3	22	25
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	19.3	31.7	25.1
standard deviation	± 4.5	± 13.4	± 14.4
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	3	22	25

Reporting group values	Total		
Number of subjects	50		
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	0		
Male	50		

End points

End points reporting groups

Reporting group title	Pre-Randomization
Reporting group description:	
Subjects were enrolled and received BeneFIX (recombinant coagulation factor IX) as intravenous (IV) bolus infusion in the first on-demand (OD1) period but were never randomized.	
Reporting group title	BeneFIX OD1, 100 IU/kg, OD2, 50 IU/kg: First Intervention
Reporting group description:	
BeneFIX (recombinant coagulation factor IX) on-demand for 16 weeks (OD1), followed by 100 international units per kilogram (IU/kg) once per week (QW) for 16 weeks prophylactically, followed by 8 weeks BeneFIX on-demand (OD2), followed by 50 IU/kg twice weekly (BW) for 16 weeks prophylactically. Subjects received BeneFIX OD1 during the first intervention period.	
Reporting group title	BeneFIX OD1, 50 IU/kg, OD2, 100 IU/kg; First Intervention
Reporting group description:	
BeneFIX (recombinant coagulation factor IX) on-demand for 16 weeks (OD1), followed by 50 IU/kg BW for 16 weeks prophylactically, followed by 8 weeks BeneFIX on-demand (OD2), followed by 100 IU/kg QW for 16 weeks prophylactically. Subjects received BeneFIX OD1 during the first intervention period.	
Reporting group title	BeneFIX OD1, 100 IU/kg, OD2, 50 IU/kg: Second Intervention
Reporting group description:	
BeneFIX (recombinant coagulation factor IX) on-demand for 16 weeks (OD1), followed by 100 IU/kg QW for 16 weeks prophylactically, followed by 8 weeks BeneFIX on-demand (OD2), followed by 50 IU/kg BW for 16 weeks prophylactically. Subjects received BeneFIX (100 IU/kg) during the second intervention period.	
Reporting group title	BeneFIX OD1, 50 IU/kg, OD2, 100 IU/kg: Second Intervention
Reporting group description:	
BeneFIX (recombinant coagulation factor IX) on-demand for 16 weeks (OD1), followed by 50 IU/kg BW for 16 weeks prophylactically, followed by 8 weeks BeneFIX on-demand (OD2), followed by 100 IU/kg QW for 16 weeks prophylactically. Subjects received BeneFIX (50 IU/kg) during the second intervention period.	
Reporting group title	BeneFIX OD1, 100 IU/kg, OD2, 50 IU/kg: Third Intervention
Reporting group description:	
BeneFIX (recombinant coagulation factor IX) on-demand for 16 weeks (OD1), followed by 100 IU/kg QW for 16 weeks prophylactically, followed by 8 weeks BeneFIX on-demand (OD2), followed by 50 IU/kg BW for 16 weeks prophylactically. Subjects received BeneFIX OD2 during the third intervention period.	
Reporting group title	BeneFIX OD1, 50 IU/kg, OD2, 100 IU/kg: Third Intervention
Reporting group description:	
BeneFIX (recombinant coagulation factor IX) on-demand for 16 weeks (OD1), followed by 50 IU/kg BW for 16 weeks prophylactically, followed by 8 weeks BeneFIX on-demand (OD2), followed by 100 IU/kg QW for 16 weeks prophylactically. Subjects received BeneFIX OD2 during the third intervention period.	
Reporting group title	BeneFIX OD1, 100 IU/kg, OD2, 50 IU/kg: Fourth Intervention
Reporting group description:	
BeneFIX (recombinant coagulation factor IX) on-demand for 16 weeks (OD1), followed by 100 IU/kg QW for 16 weeks prophylactically, followed by 8 weeks BeneFIX on-demand (OD2), followed by 50 IU/kg BW for 16 weeks prophylactically. Subjects received BeneFIX (50 IU/kg) during the fourth intervention period.	
Reporting group title	BeneFIX OD1, 50 IU/kg, OD2, 100 IU/kg: Fourth intervention
Reporting group description:	
BeneFIX (recombinant coagulation factor IX) on-demand for 16 weeks (OD1), followed by 50 IU/kg BW for 16 weeks prophylactically, followed by 8 weeks BeneFIX on-demand (OD2), followed by 100 IU/kg QW for 16 weeks prophylactically. Subjects received BeneFIX (100 IU/kg) during the fourth intervention period.	
Subject analysis set title	BeneFIX OD1
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
BeneFIX on-demand IV bolus infusion for 16 weeks (first intervention).	
Subject analysis set title	BeneFIX 100 IU/kg

Subject analysis set type	Intention-to-treat
Subject analysis set description:	
BeneFIX 100 IU/kg IV bolus infusion QW for 16 weeks.	
Subject analysis set title	BeneFIX 50 IU/kg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
BeneFIX 50 IU/kg IV bolus infusion BW for 16 weeks.	
Subject analysis set title	BeneFIX OD2
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
BeneFIX on-demand IV bolus infusion for 8 weeks (third intervention).	

Primary: Annualized Number of Bleeding Episodes

End point title	Annualized Number of Bleeding Episodes
End point description:	
Annualized bleed rate (ABR) or number of bleeds per year derived for each subject for each treatment regimen by using the following formula: ABR = number of bleeds / (days on treatment regimen / 365.25). Intention-to-treat (ITT) population: all enrolled subjects.	
End point type	Primary
End point timeframe:	
Baseline up to Week 56.	

End point values	BeneFIX OD1	BeneFIX 100 IU/kg	BeneFIX 50 IU/kg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	50	44	44	
Units: episodes				
least squares mean (confidence interval 95%)	35.1 (28.8 to 41.4)	4.6 (2.1 to 7.2)	2.6 (-0.1 to 5.3)	

Statistical analyses

Statistical analysis title	ABR: BeneFIX OD1 vs. BeneFIX 100 IU/kg
Statistical analysis description:	
As this was a cross over study, same subjects were to receive all the formulations. Total number of subjects in the analysis were 44. Point estimate was calculated by subtracting BeneFIX OD1 from BeneFIX 100 IU/kg. For 95 percent (%) CI, upper limit value was subtracted from lower limit value.	
Comparison groups	BeneFIX OD1 v BeneFIX 100 IU/kg
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-30.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.5
upper limit	-24.5

Notes:

[1] - P-values based on a model including terms for treatment regimen, treatment sequence, and the interaction of these terms with repeated measures on subjects.

Statistical analysis title	ABR: BeneFIX OD1 vs. BeneFIX 50 IU/kg

Statistical analysis description:

As this was a cross over study, same subjects were to receive all the formulations. Total number of subjects in the analysis were 43. Point estimate was calculated by subtracting BeneFIX OD1 from BeneFIX 50 IU/kg. For 95 percent (%) CI, upper limit value was subtracted from lower limit value.

Comparison groups	BeneFIX OD1 v BeneFIX 50 IU/kg
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-32.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.5
upper limit	-26.6

Notes:

[2] - P-values based on a model including terms for treatment regimen, treatment sequence, and the interaction of these terms with repeated measures on subjects.

Statistical analysis title	ABR: BeneFIX 100 IU/kg vs. BeneFIX 50 IU/kg

Statistical analysis description:

As this was a cross over study, same subjects were to receive all the formulations. Total number of subjects in the analysis were 41. Point estimate was calculated by subtracting BeneFIX 50 IU/kg from BeneFIX 100 IU/kg. For 95 % CI, upper limit value was subtracted from lower limit value.

Comparison groups	BeneFIX 100 IU/kg v BeneFIX 50 IU/kg
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2167 [3]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	5.2

Notes:

[3] - P-values based on a model including terms for treatment regimen, treatment sequence, and the interaction of these terms with repeated measures on subjects.

Secondary: Amount of Sleep Measured by Sleep Diary After Hemarthrosis

End point title	Amount of Sleep Measured by Sleep Diary After Hemarthrosis

End point description:

For each bleeding event, a diary was filled out that night and the subsequent night. Questions included: How long do you think you slept last night? Reported as average duration of sleep during study. ITT population.

End point type	Secondary

End point timeframe:

24 and 48 hours post-bleed

End point values	BeneFIX OD1	BeneFIX 100 IU/kg	BeneFIX 50 IU/kg	BeneFIX OD2
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	50	44	44	43
Units: hours				
arithmetic mean (standard deviation)				
24 hours post-bleed	7.5 (± 2)	7.3 (± 1.8)	7.1 (± 1.6)	7.4 (± 1.9)
48 hours post-bleed	7.9 (± 1.7)	7.8 (± 1.6)	7.5 (± 1.4)	8 (± 1.7)

Attachments (see zip file)	Statistical Analysis for Amount of Sleep/20150702_3090A1-

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Sleep Measured by Sleep Diary After Hemarthrosis

End point title	Quality of Sleep Measured by Sleep Diary After Hemarthrosis

End point description:

For each bleeding event, a diary was filled out that night and the subsequent night. Questions included: How would you describe the quality of your sleep last night? 1=Very Good, 2=Good, 3=Fair, 4=Poor, 5=Very Poor. Reported as quality of sleep during study.

End point type	Secondary

End point timeframe:

24 and 48 hours post-bleed

End point values	BeneFIX OD1	BeneFIX 100 IU/kg	BeneFIX 50 IU/kg	BeneFIX OD2
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	50	44	44	43
Units: Units on a scale				
arithmetic mean (standard deviation)				
24 hours post-bleed	2.4 (± 0.9)	2.5 (± 0.9)	2.3 (± 0.9)	2.4 (± 0.9)
48 hours post-bleed	2.1 (± 0.7)	2.1 (± 0.8)	2.1 (± 0.7)	2.1 (± 0.9)

Attachments (see zip file)	Statistical Analysis for Quality of Sleep/20150702_3090A1-400

Statistical analyses

No statistical analyses for this end point

Secondary: Acute Pain After Hemarthrosis

End point title	Acute Pain After Hemarthrosis

End point description:

For each bleeding event, a diary was filled out that night and the subsequent night and included a Brief Pain Inventory (BPI): self-reported scale that measured severity of pain experienced over the past 24 hours. Questions included How much pain right now? 0 (no pain) to 10 (pain as severe as you can imagine). ITT population.

End point type	Secondary

End point timeframe:

24 and 48 hours post-bleed

End point values	BeneFIX OD1	BeneFIX 100 IU/kg	BeneFIX 50 IU/kg	BeneFIX OD2
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	50	44	44	43
Units: units on a scale				
arithmetic mean (standard deviation)				
24 hours post-bleed	2.8 (± 2.1)	2.8 (± 2)	3.1 (± 2.2)	3 (± 2.1)
48 hours post-bleed	2.3 (± 1.6)	1.8 (± 1.2)	2.7 (± 1.5)	4.1 (± 2.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Health-Related Productivity Questionnaire (HRPQ) Score: Hours Lost From Work or School at 24 Hours Post-bleed

End point title	Health-Related Productivity Questionnaire (HRPQ) Score: Hours Lost From Work or School at 24 Hours Post-bleed

End point description:

HRPQ: self-reported scale that measured for each bleed event, hours lost from work, school and housework because of hemophilia and its treatments. Mean and standard deviations calculated from measured values. ITT population.

End point type	Secondary

End point timeframe:

24 hours post-bleed

End point values	BeneFIX OD1	BeneFIX 100 IU/kg	BeneFIX 50 IU/kg	BeneFIX OD2
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	50	44	44	43
Units: hours				
arithmetic mean (standard deviation)				
Work missed	0.4 (± 1.6)	1.2 (± 2.6)	0.6 (± 1.9)	0.6 (± 1.3)
Housework couldn't do	0.7 (± 2.4)	0.3 (± 0.8)	0.4 (± 0.7)	0.2 (± 0.5)
Classwork couldn't do	0.8 (± 1.7)	0.7 (± 2.2)	0.4 (± 1.1)	0 (± 0)

Statistical analyses

No statistical analyses for this end point

Secondary: HRPQ Score: Hours Lost From Work or School at 48 Hours Post-bleed

End point title	HRPQ Score: Hours Lost From Work or School at 48 Hours Post-bleed

End point description:

HRPQ: self-reported scale that measured for each bleed event, hours lost from work, school and housework because of hemophilia and its treatments. Mean and standard deviations calculated from measured values. ITT Population.

End point type	Secondary

End point timeframe:

48 hours post-bleed.

End point values	BeneFIX OD1	BeneFIX 100 IU/kg	BeneFIX 50 IU/kg	BeneFIX OD2
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	50	44	44	43
Units: hours				
arithmetic mean (standard deviation)				
Work missed	0.2 (± 1)	0.7 (± 2.1)	0.1 (± 0.4)	0.2 (± 0.5)
Housework couldn't do	0.5 (± 1.4)	0.3 (± 0.7)	0 (± 0.2)	0 (± 0)
Classwork couldn't do	0.4 (± 1.2)	0.7 (± 2.4)	0 (± 0)	1.7 (± 2.6)

Statistical analyses

No statistical analyses for this end point

Secondary: 36-Item Short-Form Health Survey (SF-36): Physical Functioning Domain

End point title	36-Item Short-Form Health Survey (SF-36): Physical

	Functioning Domain

End point description:

SF-36: standardized survey evaluating 8 aspects of functional health and well being: physical and social functioning, physical and emotional role limitations, bodily pain, general health, vitality, and mental health. The physical functioning domain score was an average of the individual physical functioning question scores across all time points, which was scaled 0-100 (100=highest level of functioning). ITT; N=number of subjects with evaluable data.

End point type	Secondary

End point timeframe:

Weeks 16, 32, and 56

End point values	BeneFIX OD1	BeneFIX 100 IU/kg	BeneFIX 50 IU/kg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	40[4]	35[5]	34[6]	
Units: units on a scale				
arithmetic mean (standard deviation)	64 (± 26)	66 (± 25)	63 (± 28)	

Notes:

[4] - Number of subjects with evaluable data.

[5] - Number of subjects with evaluable data.

[6] - Number of subjects with evaluable data.

Statistical analyses

Statistical analysis title	SF-36: BeneFIX OD1 vs. BeneFIX 100 IU/kg

Statistical analysis description:

As this was a cross over study, same subjects were to receive all the formulations. Total number of subjects in the analysis were 50.

Comparison groups	BeneFIX OD1 v BeneFIX 100 IU/kg
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.544
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.2
upper limit	4.9

Statistical analysis title	SF-36: BeneFIX OD1 vs. BeneFIX 50 IU/kg

Statistical analysis description:

As this was a cross over study, same subjects were to receive all the formulations. Total number of subjects in the analysis were 50.

Comparison groups	BeneFIX OD1 v BeneFIX 50 IU/kg

Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.592
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.5
upper limit	4.3

Statistical analysis title	SF-36: BeneFIX 100 IU/kg vs. BeneFIX 50 IU/kg

Statistical analysis description:

As this was a cross over study, same subjects were to receive all the formulations. Total number of subjects in the analysis were 50.

Comparison groups	BeneFIX 100 IU/kg v BeneFIX 50 IU/kg
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.131
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	8.4

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 15 days after last administration dose of BeneFIX

Adverse event reporting additional description:

The same event may appear as both an AE and an SAE. However, what is presented are distinct events. An event may be categorized as serious in 1 subject and as nonserious in another subject, or 1 subject may have experienced both a serious and nonserious event during the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	BeneFIX OD1

Reporting group description:

BeneFIX in an on-demand IV bolus infusion for 16 weeks (first intervention).

Reporting group title	BeneFIX 100 IU/kg

Reporting group description:

BeneFIX 100 IU/kg IV bolus infusion QW for 16 weeks.

Reporting group title	BeneFIX 50 IU/kg

Reporting group description:

BeneFIX 50 IU/kg IV bolus infusion BW for 16 weeks.

Reporting group title	BeneFIX OD2

Reporting group description:

BeneFIX on-demand IV bolus infusion for 8 weeks (third intervention).

Serious adverse events	BeneFIX OD1	BeneFIX 100 IU/kg	BeneFIX 50 IU/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 50 (2.00%)	2 / 44 (4.55%)	2 / 44 (4.55%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Ulna fracture			
subjects affected / exposed	1 / 50 (2.00%)	0 / 44 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Testicular pain			

subjects affected / exposed	0 / 50 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 50 (0.00%)	1 / 44 (2.27%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 50 (0.00%)	1 / 44 (2.27%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	0 / 50 (0.00%)	1 / 44 (2.27%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthropathy			
subjects affected / exposed	0 / 50 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 50 (0.00%)	0 / 44 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	BeneFIX OD2		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 43 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Ulna fracture			

subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Testicular pain			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal colic			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthropathy			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	BeneFIX OD1	BeneFIX 100 IU/kg	BeneFIX 50 IU/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 50 (16.00%)	8 / 44 (18.18%)	4 / 44 (9.09%)
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 50 (6.00%)	6 / 44 (13.64%)	2 / 44 (4.55%)
occurrences (all)	3	7	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 50 (10.00%)	4 / 44 (9.09%)	2 / 44 (4.55%)
occurrences (all)	13	21	2

Non-serious adverse events	BeneFIX OD2		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 43 (9.30%)		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	6		

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Although the protocol-defined endpoint was days lost from work or school after hemarthrosis, data was collected and reported in hours.

Notes: