Clinical trial results:
A MULTICENTER, OPEN LABEL STUDY TO COMPARE ON DEMAND TREATMENT TO A PROPHYLAXIS REGIMEN OF NONACOG ALFA (BENEFIX) IN SUBJECTS WITH MODERATELY SEVERE TO SEVERE HEMOPHILIA B (FIX:C 2%)

Summary

EudraCT number	2011-000520-15
Trial protocol	PL BG GR Outside EU/EEA
Global end of trial date	23 April 2014

Results information

Result version number	v1 (current)
This version publication date	11 May 2016
First version publication date	08 July 2015

Trial information

Trial identification

Sponsor protocol code	B1821010

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01335061
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd St,, New York,, United States,
Public contact	Clinical Trials.gov Call Center, Pfizer Inc., 011 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Clinical Trials.gov Call Center, Pfizer Inc., 011 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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 April 2014
Global end of trial reached?	Yes
Global end of trial date	23 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to demonstrate that a prophylaxis regimen of BeneFIX reduces the ABR compared to on-demand treatment in subjects with moderately-severe to severe hemophilia B.
The secondary objective is to describe the safety and efficacy of BeneFIX when administered for prophylaxis at a dose of 100 IU/kg once weekly.

Protection of trial subjects:

The External Data Monitoring Committee met approximately every 6 months to review safety data. Per the DMC charter, safety data included line listings and summaries of all AEs, SAEs, discontinuations, demographic and other baseline characteristics, treatment information, and medically important events. Efficacy data could be reviewed if necessary for an accurate risk-benefit assessment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 September 2011
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	Poland: 4
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Croatia: 3
Country: Number of subjects enrolled	Korea, Republic of: 3
Country: Number of subjects enrolled	Malaysia: 4
Country: Number of subjects enrolled	Singapore: 2
Country: Number of subjects enrolled	Turkey: 5
Country: Number of subjects enrolled	Mexico: 2
Worldwide total number of subjects	25
EEA total number of subjects	8

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	5
Adults (18-64 years)	20
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participation included 25 enrolled participants from 15 study centers and 9 countries.

Pre-assignment

Screening details:

The duration of participation was approximately 86 weeks, consisting of a Screening period (1 day to 4 weeks), Period 1 (on-demand treatment for 26 weeks), Period 2 (prophylaxis therapy for 52 weeks), and a follow-up safety period (4 weeks).

Period 1

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

Arms

Arm title	All participants

Arm description:

Data for all the participants were analyzed.

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

Dosage and administration details:

The first treatment period was 6 months (26 weeks) of on-demand treatment when BeneFIX was to be administered by participants according to the locally approved BeneFIX label or the BeneFIX Core Data Sheet to treat bleeding events at the discretion of the study physician. The participant began the second treatment period when the BeneFIX prophylaxis regimen of approximately 100 IU/kg was used once weekly for 12 months (52 weeks).

Number of subjects in period 1	All participants
Started	25
Completed	25

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	25	25	
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)	0	0	
Adolescents (12-17 years)	5	5	
Adults (18-64 years)	20	20	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	31.3		
standard deviation	± 12.6	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	25	25	

End points

End points reporting groups

Reporting group title	All participants
Reporting group description: Data for all the participants were analyzed.	
Subject analysis set title	On-Demand Therapy
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants were treated for the bleeding events at the discretion of the study physician according to BeneFIX label.	
Subject analysis set title	Prophylaxis therapy
Subject analysis set type	Sub-group analysis
Subject analysis set description: The prophylaxis regimen of approximately 100 IU/kg once weekly was initiated at Visit 4.	
Subject analysis set title	On-Demand therapy-First infusion
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants were treated for the bleeding events at the discretion of the study physician according to BeneFIX label.	
Subject analysis set title	On-Demand therapy-Follow-up infusions
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants were treated for the bleeding events at the discretion of the study physician according to BeneFIX label.	

Primary: Annualized number of bleeding episodes

End point title	Annualized number of bleeding episodes
End point description: The annualized bleed rate (ABR) or the annualized number of bleeding episodes per year, will be derived for each participant for each treatment period by using the following formula: ABR = number of bleeds / (Days on treatment period / 365.25) The number of bleeds for the ABR calculation includes all bleeds requiring treatment with factor IX product during the time on treatment. The efficacy analysis set (EAS) was used for the primary efficacy analyses with respect to ABR.	
End point type	Primary
End point timeframe: 2 years	

End point values	On-Demand Therapy	Prophylaxis therapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	25		
Units: Number of bleeds per year				
arithmetic mean (standard deviation)	32.9 (± 17.4)	3.6 (± 4.6)		

Statistical analyses

Statistical analysis title	Annualized number of bleeding episodes

Statistical analysis description:

This analysis compares within-subject difference in ABRs between 2 treatment periods (crossover design): On-Demand and Prophylaxis therapy. Both the groups (On-Demand and prophylaxis therapy) are not mutually exclusive, overall 25 participants data were analysed.

Comparison groups	On-Demand Therapy v Prophylaxis therapy
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Paired t-test

Secondary: Response to On-Demand Treatment for all Bleeding Episodes

End point title	Response to On-Demand Treatment for all Bleeding Episodes

End point description:

Assessment scores on a 4-point Response Scale for an on-demand bleeding episode, as assessed by participant/caregiver or investigator/qualified staff. The 4-point scale assessments are Excellent, Good, Moderate or No response. Responses to number of observations were noted. The safety analysis set (SAS) was used. The SAS was any participant who received at least one dose of BeneFIX, including the dose given during the enrollment visit (Visit 2) for the factor IX (FIX) recovery study. 507 bleeds were analysed in the On-Demand therapy-First infusion group and 152 bleeds were analysed in the On-Demand therapy-Follow-up infusion group.

End point type	Secondary

End point timeframe:

2 years

End point values	On-Demand therapy-First infusion	On-Demand therapy-Follow-up infusions		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	18[1]		
Units: Number of observations with response				
number (not applicable)				
Excellent	271	39		
Good	177	80		
Moderate	55	33		
No response	3	0		
Data not recorded	1	0		

Notes:

[1] - Follow-up infusion was only required for 18 participants.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Nonacog Alfa, Recombinant Factor IX (BeneFIX) Infusions Used to Treat Each Bleeding Episode

End point title	Number of Nonacog Alfa, Recombinant Factor IX (BeneFIX) Infusions Used to Treat Each Bleeding Episode

End point description:

The number of study drug infusions administered to treat a bleed will be calculated by adding the initial (on-demand) infusion to any subsequent (on-demand) infusions for the same bleed (same bleed start date/time). The number of infusions needed to treat a bleed will be classified into the following categories: 1, 2, 3, 4 and >4 infusions. If there were more than one bleed location (e.g., ankle and joint) with identical bleed start date and time, it was treated as one bleed occurrence. The SAS was any participant who received at least one dose of BeneFIX, including the dose given during the enrollment visit (Visit 2) for the factor IX (FIX) recovery study. 507 bleeds were analysed.

End point type	Secondary

End point timeframe:

2 years

End point values	All participants			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Number of bleeds requiring infusion				
number (not applicable)				
Number of Infusion: 1	416			
Number of Infusions: 2	69			
Number of Infusions: 3	9			
Number of Infusions: 4	3			
Number of Infusions: >4	10			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Breakthrough (Spontaneous/Non-Traumatic) Bleeds within 48 Hours of a Prophylaxis Dose of BeneFIX.

End point title	Number of Breakthrough (Spontaneous/Non-Traumatic) Bleeds within 48 Hours of a Prophylaxis Dose of BeneFIX.

End point description:

The number of spontaneous, non-traumatic breakthrough bleeds within 48 hours following a prophylaxis dose of BeneFIX were summarized. 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. The SAS was any participant who received at least one dose of BeneFIX, including the dose given during the enrollment visit (Visit 2) for the factor IX (FIX) recovery study. Three participants experienced 1 spontaneous bleeding episode each within 48 hours of a previous prophylaxis infusion.

End point type	Secondary

End point timeframe:

2 years

End point values	All participants			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Number of breakthrough bleeds				
arithmetic mean (standard deviation)	1 (± 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Average Infusion Dose.

End point title	Average Infusion Dose.

End point description:

The mean dose by per infusion by weight (IU/kg) was reported for both prophylaxis and on demand infusions. The SAS was any participant who received at least one dose of BeneFIX, including the dose given during the enrollment visit (Visit 2) for the factor IX (FIX) recovery study.

End point type	Secondary

End point timeframe:

2 years

End point values	On-Demand Therapy	Prophylaxis therapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	25		
Units: IU/Kg				
arithmetic mean (standard deviation)	52 (± 16)	99 (± 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Factor Consumption.

End point title	Total Factor Consumption.

End point description:

The total amount (IU) infused for each infusion recorded were summed to calculate the total factor consumption for each participant. For each infusion, IU/kg was calculated, using the most recently recorded weight measurement and the total factor consumption, divided by number of infusions, and was summarized similarly to average infusion dose (IU). Annualized TFC by weight was reported. Annualized TFC by weight = (Total IU/kg / treatment interval duration)*365.25. The SAS was any participant who received at least one dose of BeneFIX, including the dose given during the enrollment visit (Visit 2) for the factor IX (FIX) recovery study.

End point type	Secondary

End point timeframe:

2 years

End point values	On-Demand Therapy	Prophylaxis therapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	25		
Units: IU/Kg				
arithmetic mean (standard deviation)	707 (± 519)	4985 (± 233)		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Less than Expected Therapeutic Effect (LETE)

End point title	Incidence of Less than Expected Therapeutic Effect (LETE)

End point description:

The following criteria are the definitions for LETE in this study: 1. LETE in the On-Demand Setting: LETE occurs in the on-demand setting if 2 successive "No Response" ratings are recorded after 2 successive BeneFIX drug infusions in the absence of confounding factors. 2. LETE in the Prophylaxis Setting: LETE occurs in the prophylaxis setting if there is a spontaneous bleed within 48 hours (≤ 48 hours) after a regularly scheduled prophylactic dose of BeneFIX in the absence of confounding factors. 3. LETE (Low Recovery): LETE can also be lower than expected recovery of FIX in the opinion of the investigator following infusion of BeneFIX in the absence of confounding factors. Each reported occurrence of low recovery LETE was listed. The SAS was any participant who received at least one dose of BeneFIX, including the dose given during the enrollment visit (Visit 2) for the factor IX (FIX) recovery study.

End point type	Secondary

End point timeframe:

2 years

End point values	All participants			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Percentage of occurence				
number (not applicable)				
LETE in On-Demand setting	0			
LETE in prophylaxis setting	0			
LETE (Low recovery)	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Until follow-up 82 weeks +/- 4 days.

Adverse event reporting additional description:

Five participants experienced six SAEs since one participant experienced the same event twice (nephrolithiasis).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	On-Demand Therapy

Reporting group description:

Participants were treated for the bleeding events at the discretion of the study physician according to BeneFIX label.

Reporting group title	Prophylaxis therapy

Reporting group description:

The prophylaxis regimen of approximately 100IU/kg once weekly was initiated at Visit 4.

Serious adverse events	On-Demand Therapy	Prophylaxis therapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 25 (4.00%)	4 / 25 (16.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood pressure decreased			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pain			

subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Varicella			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	On-Demand Therapy	Prophylaxis therapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 25 (64.00%)	20 / 25 (80.00%)	
Injury, poisoning and procedural complications			
Inappropriate schedule of drug administration			
subjects affected / exposed	0 / 25 (0.00%)	6 / 25 (24.00%)	
occurrences (all)	0	17	
Drug dose omission			
subjects affected / exposed	0 / 25 (0.00%)	4 / 25 (16.00%)	
occurrences (all)	0	6	
Medication error			
subjects affected / exposed	0 / 25 (0.00%)	3 / 25 (12.00%)	
occurrences (all)	0	4	
Underdose			
subjects affected / exposed	0 / 25 (0.00%)	3 / 25 (12.00%)	
occurrences (all)	0	3	
Wrong dose administered			

subjects affected / exposed	0 / 25 (0.00%)	3 / 25 (12.00%)	
occurrences (all)	0	3	
Head injury			
subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 25 (32.00%)	4 / 25 (16.00%)	
occurrences (all)	20	33	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 25 (16.00%)	4 / 25 (16.00%)	
occurrences (all)	8	7	
Local swelling			
subjects affected / exposed	1 / 25 (4.00%)	3 / 25 (12.00%)	
occurrences (all)	1	4	
Gastrointestinal disorders			
Toothache			
subjects affected / exposed	3 / 25 (12.00%)	5 / 25 (20.00%)	
occurrences (all)	4	9	
Gastritis			
subjects affected / exposed	1 / 25 (4.00%)	2 / 25 (8.00%)	
occurrences (all)	1	2	
Abdominal pain upper			
subjects affected / exposed	1 / 25 (4.00%)	2 / 25 (8.00%)	
occurrences (all)	2	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 25 (20.00%)	5 / 25 (20.00%)	
occurrences (all)	13	13	
Joint swelling			

subjects affected / exposed	3 / 25 (12.00%)	2 / 25 (8.00%)	
occurrences (all)	4	3	
Back pain			
subjects affected / exposed	1 / 25 (4.00%)	3 / 25 (12.00%)	
occurrences (all)	2	16	
Neck pain			
subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	3	
Pain in extremity			
subjects affected / exposed	2 / 25 (8.00%)	1 / 25 (4.00%)	
occurrences (all)	4	1	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	4 / 25 (16.00%)	5 / 25 (20.00%)	
occurrences (all)	6	8	
Pharyngitis			
subjects affected / exposed	2 / 25 (8.00%)	3 / 25 (12.00%)	
occurrences (all)	2	3	
Nasopharyngitis			
subjects affected / exposed	3 / 25 (12.00%)	1 / 25 (4.00%)	
occurrences (all)	6	3	
Influenza			
subjects affected / exposed	2 / 25 (8.00%)	1 / 25 (4.00%)	
occurrences (all)	3	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 September 2011	Amendment 1 was due to addition of study procedures, as requested by the Food and Drug Administration (FDA) and changes to statistical methods section of protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported