Clinical trial results:
An Evaluation of the Safety and Efficacy of On-Demand Treatment with Xyntha (B-Domain Deleted Recombinant Factor VIII, Albumin Free) in Chinese Subjects with Hemophilia A

Summary

EudraCT number	2014-004106-15
Trial protocol	Outside EU/EEA
Global end of trial date	04 December 2009

Results information

Result version number	v1 (current)
This version publication date	01 June 2016
First version publication date	09 July 2015

Trial information

Trial identification

Sponsor protocol code	3082B2-3316

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00868530
WHO universal trial number (UTN)	-
Other trial identifiers	Alias: B1831015

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	27 June 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 December 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 September 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	China: 53
Worldwide total number of subjects	53
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)	6
Adolescents (12-17 years)	11
Adults (18-64 years)	36
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited in China from September 2008 to December 2009.

Pre-assignment

Screening details:

Overall, 55 subjects were screened, out of which 53 subjects were enrolled in the study.

Period 1

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

Arms

Arm title	Xyntha

Arm description:

Subjects received on-demand treatments with Xyntha (which occurred each time a subject experienced bleeding episode during the active phase of the study) according to investigator's prescription over a 6-month (calendar day) period.

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

Dosage and administration details:

A single 50 International Unit (IU)/kg (+/-5 IU/kg) intravenous (IV) bolus infusion of Xyntha was given for recovery assessments.

Number of subjects in period 1	Xyntha
Started	53
Completed	49
Not completed	4
Adverse Event	3
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Xyntha
Reporting group description:	
Subjects received on-demand treatments with Xyntha (which occurred each time a subject experienced bleeding episode during the active phase of the study) according to investigator's prescription over a 6-month (calendar day) period.	

Reporting group values	Xyntha	Total	
Number of subjects	53	53	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 23.2 ± 10	 -	
Gender categorical Units: Subjects			
Female	0	0	
Male	53	53	

End points

End points reporting groups

Reporting group title	Xyntha

Reporting group description:

Subjects received on-demand treatments with Xyntha (which occurred each time a subject experienced bleeding episode during the active phase of the study) according to investigator's prescription over a 6-month (calendar day) period.

Primary: Investigator Hemostatic Efficacy Assessment 8 Hours Post Infusion

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

End point description:

The Investigator Hemostatic Efficacy Assessment was based on a 4-point rating scale (Excellent = 1: definite pain relief or improvement in signs of bleeding, with no additional infusion, Good = 2: definite pain relief or improvement in signs of bleeding, Moderate = 3: probable or slight improvement, No Response = 4: no improvement at all between infusions). The Full Analysis Set (FAS) consisted of all subjects who were treated and had at least 1 evaluable efficacy assessment after treatment.

End point type	Primary

End point timeframe:

8 hours post infusion

Notes:

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

End point values	Xyntha			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: Units on a scale				
arithmetic mean (standard deviation)	1.86 (± 0.65)			

Statistical analyses

No statistical analyses for this end point

Primary: Investigator Hemostatic Efficacy Assessment 24 Hours Post Infusion

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

End point description:

The Investigator Hemostatic Efficacy Assessment was based on a 4-point rating scale (Excellent = 1: definite pain relief or improvement in signs of bleeding, with no additional infusion, Good = 2: definite pain relief or improvement in signs of bleeding, Moderate = 3: probable or slight improvement, No Response = 4: no improvement at all between infusions). The FAS consisted of all subjects who were treated and had at least 1 evaluable efficacy assessment after treatment.

End point type	Primary

End point timeframe:

24 hours post infusion

Notes:

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

End point values	Xyntha			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: Units on a scale				
arithmetic mean (standard deviation)	1.74 (± 0.61)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Factor VIII (FVIII) Inhibitor Development

End point title	Number of Subjects With Factor VIII (FVIII) Inhibitor Development[3]

End point description:

Incidence of FVIII inhibitor was defined as any result determined as positive at local laboratory, and confirmed at central laboratory. Incidence was stratified by subject exposure history: Minimally Treated Patients (MTPs): those who had received at least 1 prior FVIII infusion, and less than or equal to (<=) 100 documented Exposure Days (EDs), while Previously Treated Patients (PTPs): those who had received greater than (>) 100 documented prior EDs. When number of prior EDs for an individual was not known to be at least 100, subjects were included in the MTP population. The FAS consisted of all subjects who were treated and had at least 1 evaluable efficacy assessment after treatment.

End point type	Primary

End point timeframe:

Day 1 and Month 6 or Early Termination Visit

Notes:

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

End point values	Xyntha			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: subjects				
MTP (n=34)	6			
PTP (n=17)	1			

Statistical analyses

No statistical analyses for this end point

Primary: FVIII Recovery : Change From Baseline in FVIII Concentration

End point title	FVIII Recovery : Change From Baseline in FVIII

End point description:

FVIII recovery was assessed by evaluating the change in FVIII concentration at 6 months compared to baseline. The FAS consisted of all subjects who were treated and had at least 1 evaluable efficacy assessment after treatment. Subjects with missing data were not included.

End point type	Primary

End point timeframe:

Day 1 and Month 6 or Early Termination Visit

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: Statistical analysis has been provided separately as an attachment.

End point values	Xyntha			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: IU/dL per IU/kg				
arithmetic mean (standard deviation)	-0.11 (± 0.45)			

Attachments (see zip file)	Statistical Analyses for FVIII Recovery/Statistical Analyses for

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

24 hours after each of 2 successive infusion, up to 6 months

End point values	Xyntha			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Thrombosis Allergic-Type Reactions

End point title	Number of Subjects With Thrombosis Allergic-Type Reactions

End point description:

The Safety Set (SS) consisted of all subjects who had taken at least 1 dose of investigational drug.

End point type	Secondary

End point timeframe:

Baseline up to 6 months

End point values	Xyntha			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: subjects	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Thrombosis

End point title	Number of Subjects With Thrombosis

End point description:

The SS consisted of all subjects who had taken at least 1 dose of investigational drug.

End point type	Secondary

End point timeframe:

Baseline up to 6 months

End point values	Xyntha			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Frequency of Xyntha Infusions Required Per Hemorrhage

End point title	Frequency of Xyntha Infusions Required Per Hemorrhage

End point description:

The mean frequency of Xyntha infusions per hemorrhage was calculated as total number of injections throughout the study divided by total number of hemorrhagic events. The FAS consisted of all subjects who were treated and had at least 1 evaluable efficacy assessment after treatment.

End point type	Other pre-specified

End point timeframe:

Day 1 to Month 6 or Early Termination Visit

End point values	Xyntha			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: Infusions				
arithmetic mean (standard deviation)	1.16 (± 0.72)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Average Dose of Xyntha Infusions Required Per Hemorrhage

End point title	Average Dose of Xyntha Infusions Required Per Hemorrhage

End point description:

The average dose of Xyntha per hemorrhagic event was calculated as total dose of Xyntha throughout the study (in IU) divided by total number of hemorrhage incidence. The FAS consisted of all subjects who were treated and had at least 1 evaluable efficacy assessment after treatment.

End point type	Other pre-specified

End point timeframe:

Day 1 to Month 6 or Early Termination Visit

End point values	Xyntha			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: Dose/Bleed (IU)				
arithmetic mean (standard deviation)	1226.28 (± 1208.49)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) and Serious AEs (SAEs) were collected from the signing of the informed consent form to approximately 30 days following the Month 6/Final/Early Termination visit

Adverse event reporting additional description:

Safety population: who received at least 1 dose of Xyntha. Same event may appear as AE, SAE. However,what is presented are distinct events. An event may be categorized as serious in 1 subject and nonserious in another,or 1 subject may experience both SAE, Non-SAE. EU BR AE tables generated separately as per EU format using latest coding dictionary.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Xyntha

Reporting group description:

Subjects received on-demand treatments with Xyntha (which occurred each time a subject experienced bleeding episode during the active phase of the study) according to investigator's prescription over a 6-month (calendar day) period. A single 50 International Unit (IU)/kg (+/-5 IU/kg) intravenous (IV) bolus infusion of Xyntha was given for recovery assessments.

Serious adverse events	Xyntha		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 53 (15.09%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Anti factor VIII antibody positive			
subjects affected / exposed	6 / 53 (11.32%)		
occurrences causally related to treatment / all	5 / 6		
deaths causally related to treatment / all	0 / 0		
Investigation			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Gingival bleeding			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Xyntha		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 53 (22.64%)		
Investigations			
Blood potassium decreased			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Injury			
subjects affected / exposed	4 / 53 (7.55%)		
occurrences (all)	4		
Joint dislocation			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Joint injury			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	3		
Ligament sprain			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	2		
Limb injury			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences (all)	1		
Vascular disorders			
Haemorrhage			

subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	 1 / 53 (1.89%) 1		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	 1 / 53 (1.89%) 1		
Skin and subcutaneous tissue disorders Dermatitis allergic subjects affected / exposed occurrences (all)	 1 / 53 (1.89%) 2		
Musculoskeletal and connective tissue disorders Arthritis subjects affected / exposed occurrences (all)	 1 / 53 (1.89%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported