Clinical trial results:
An Open-Label, Single Dose Pharmacokinetic Study of Xyntha (Moroctocog Alfa [AF-CC], Recombinant Factor VIII) in Male Chinese Subjects with Hemophilia A

Summary

EudraCT number	2015-003685-88
Trial protocol	Outside EU/EEA
Global end of trial date	28 August 2015

Results information

Result version number	v2 (current)
This version publication date	18 August 2016
First version publication date	11 June 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	B1831082

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., +1 800-718-1021, ClinicalTrials.gov_Inquiries@Pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., +1 800-718-1021, 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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 August 2015
Global end of trial reached?	Yes
Global end of trial date	28 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to characterize single dose pharmacokinetic (PK) profile of Factor VIII (FVIII) activity after administration of Xyntha in male Chinese subjects with hemophilia A.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 July 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: 13
Worldwide total number of subjects	13
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)	3
Adolescents (12-17 years)	5
Adults (18-64 years)	5
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study enrolled Chinese male subjects who were age 6 years or older with severe hemophilia A (FVIII activity <1%) previously treated with >150 exposure days to any FVIII-containing product.

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 50 IU/kg

Arm description:

Subjects were administered a single dose of recombinant antihemophilic factor (Xyntha) at approximately 50 international units per kilogram (IU/kg) infused intravenously (IV) over 10 minutes (actual dose received ranged from 42.55 IU/kg to 60.00 IU/kg).

Arm type	Experimental
Investigational medicinal product name	moroctocog alfa, recombinant FVIII
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

single dose 50 IU/kg by IV infusion

Number of subjects in period 1	Xyntha 50 IU/kg
Started	13
Completed	13

Baseline characteristics

Reporting groups	
Reporting group title	Xyntha 50 IU/kg
Reporting group description:	
Subjects were administered a single dose of recombinant antihemophilic factor (Xyntha) at approximately 50 international units per kilogram (IU/kg) infused intravenously (IV) over 10 minutes (actual dose received ranged from 42.55 IU/kg to 60.00 IU/kg).	

Reporting group values	Xyntha 50 IU/kg	Total	
Number of subjects	13	13	
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)	3	3	
Adolescents (12-17 years)	5	5	
Adults (18-64 years)	5	5	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	24.4		
standard deviation	± 19.6	-	
Gender, Male/Female Units: participants			
Female	0	0	
Male	13	13	

End points

End points reporting groups

Reporting group title	Xyntha 50 IU/kg

Reporting group description:

Subjects were administered a single dose of recombinant antihemophilic factor (Xyntha) at approximately 50 international units per kilogram (IU/kg) infused intravenously (IV) over 10 minutes (actual dose received ranged from 42.55 IU/kg to 60.00 IU/kg).

Primary: Maximum Plasma FVIII Activity (Cmax)

End point title	Maximum Plasma FVIII Activity (Cmax)[1]

End point description:

The PK parameter analysis population is defined as all subjects enrolled and treated who have at least 1 of the PK parameters of primary interest reported.

End point type	Primary

End point timeframe:

Pre-dose and 0.25, 0.5, 1, 3, 6, 9, 24, 28, 32, 48, and 72 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: The study has no statistical analysis.

End point values	Xyntha 50 IU/kg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: IU/milliliter (mL)				
geometric mean (geometric coefficient of variation)	1.147 (± 44)			

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Plasma FVIII Activity-Time Profile from Time 0 to Time of the Last Quantifiable Concentration (AUClast)

End point title	Area Under the Plasma FVIII Activity-Time Profile from Time 0 to Time of the Last Quantifiable Concentration (AUClast)[2]

End point description:

The PK parameter analysis population is defined as all subjects enrolled and treated who have at least 1 of the PK parameters of primary interest reported.

End point type	Primary

End point timeframe:

Pre-dose and 0.25, 0.5, 1, 3, 6, 9, 24, 28, 32, 48, and 72 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: The study has no statistical analysis.

End point values	Xyntha 50 IU/kg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: IU*hour/mL				
geometric mean (geometric coefficient of variation)	14.49 (± 57)			

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Plasma FVIII Activity-Time Profile from Time 0 Extrapolated to Infinite Time (AUCinf)

End point title	Area Under the Plasma FVIII Activity-Time Profile from Time 0 Extrapolated to Infinite Time (AUCinf)[3]

End point description:

The PK parameter analysis population is defined as all subjects enrolled and treated who have at least 1 of the PK parameters of primary interest reported.

End point type	Primary

End point timeframe:

Pre-dose and 0.25, 0.5, 1, 3, 6, 9, 24, 28, 32, 48, and 72 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: The study has no statistical analysis.

End point values	Xyntha 50 IU/kg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: IU*hour/mL				
geometric mean (geometric coefficient of variation)	15.21 (± 58)			

Statistical analyses

No statistical analyses for this end point

Primary: Time to Reach Maximum Observed Plasma Concentration (Tmax)

End point title	Time to Reach Maximum Observed Plasma Concentration (Tmax)[4]

End point description:

The PK parameter analysis population is defined as all subjects enrolled and treated who have at least 1 of the PK parameters of primary interest reported.

End point type	Primary

End point timeframe:

Pre-dose and 0.25, 0.5, 1, 3, 6, 9, 24, 28, 32, 48, and 72 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: The study has no statistical analysis.

End point values	Xyntha 50 IU/kg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: hour				
median (full range (min-max))	0.5 (0.25 to 3)			

Statistical analyses

No statistical analyses for this end point

Primary: Clearance (CL)

End point title	Clearance (CL)[5]

End point description:

Drug clearance is a quantitative measure of the rate at which a drug substance is removed from the blood. The PK parameter analysis population is defined as all subjects enrolled and treated who have at least 1 of the PK parameters of primary interest reported.

End point type	Primary

End point timeframe:

Pre-dose and 0.25, 0.5, 1, 3, 6, 9, 24, 28, 32, 48, and 72 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: The study has no statistical analysis.

End point values	Xyntha 50 IU/kg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: mL/hour/kg				
geometric mean (geometric coefficient of variation)	3.295 (± 56)			

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)[6]

End point description:

Volume of distribution is the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired blood concentration of a drug. Vss is the volume of distribution at steady-state. The PK parameter analysis population is defined as all subjects enrolled and treated who have at least 1 of the PK parameters of primary interest reported.

End point type	Primary

End point timeframe:

Pre-dose and 0.25, 0.5, 1, 3, 6, 9, 24, 28, 32, 48, and 72 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: The study has no statistical analysis.

End point values	Xyntha 50 IU/kg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: mL/kg				
geometric mean (geometric coefficient of variation)	53.96 (± 29)			

Statistical analyses

No statistical analyses for this end point

Primary: Terminal Phase Rate Constant (Kel)

End point title	Terminal Phase Rate Constant (Kel)[7]

End point description:

Terminal phase rate constant is the absolute value of the slope of a linear regression during the terminal phase of the natural--logarithm transformed concentration--time profile. The PK parameter analysis population is defined as all subjects enrolled and treated who have at least 1 of the PK parameters of primary interest reported.

End point type	Primary

End point timeframe:

Pre-dose and 0.25, 0.5, 1, 3, 6, 9, 24, 28, 32, 48, and 72 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: The study has no statistical analysis.

End point values	Xyntha 50 IU/kg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: 1/hour				
geometric mean (geometric coefficient of variation)	0.06039 (± 39)			

Statistical analyses

No statistical analyses for this end point

Primary: Terminal Elimination Half-Life (t1/2)

End point title	Terminal Elimination Half-Life (t1/2)[8]

End point description:

Terminal half-life is the time measured for the plasma concentration to decrease by one half. The PK parameter analysis population is defined as all subjects enrolled and treated who have at least 1 of the PK parameters of primary interest reported.

End point type	Primary

End point timeframe:

Pre-dose and 0.25, 0.5, 1, 3, 6, 9, 24, 28, 32, 48, and 72 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: The study has no statistical analysis.

End point values	Xyntha 50 IU/kg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: hour				
arithmetic mean (standard deviation)	12.24 (± 4.4172)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Residence Time (MRT)

End point title	Mean Residence Time (MRT)[9]

End point description:

MRT = AUMCinf / AUCinf, where AUMCinf is the area under the first moment curve from zero time to infinity calculated as AUMCinf = AUMCt + ((t x Ct) / kel) + (Ct / kel^2). AUMCt is the area under the first moment curve from zero time to time t calculated using the trapezoidal method. The PK parameter analysis population is defined as all subjects enrolled and treated who have at least 1 of the PK parameters of primary interest reported.

End point type	Primary

End point timeframe:

Pre-dose and 0.25, 0.5, 1, 3, 6, 9, 24, 28, 32, 48, and 72 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: The study has no statistical analysis.

End point values	Xyntha 50 IU/kg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: hour				
geometric mean (geometric coefficient of variation)	16.37 (± 38)			

Statistical analyses

No statistical analyses for this end point

Primary: Incremental Recovery (INCREC)

End point title	Incremental Recovery (INCREC)[10]

End point description:

Incremental recovery is the increase in circulating FVIII activity for every IU of Xyntha administered per kilogram of body weight. The PK parameter analysis population is defined as all subjects enrolled and treated who have at least 1 of the PK parameters of primary interest reported.

End point type	Primary

End point timeframe:

Pre-dose and 0.25, 0.5, 1, 3, 6, 9, 24, 28, 32, 48, and 72 hours 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: The study has no statistical analysis.

End point values	Xyntha 50 IU/kg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: IU/deciliter (dL) per IU/kg				
geometric mean (geometric coefficient of variation)	2.284 (± 44)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects with Treatment-Emergent Adverse Events (AEs) or Serious Adverse Events (SAEs)

End point title	Number of Subjects with Treatment-Emergent Adverse Events (AEs) or Serious Adverse Events (SAEs)

End point description:

An AE was any untoward medical occurrence in a subject who received study drug. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent are events between first dose of study drug and up to 28 days after last dose that were absent before treatment or that worsened relative to pre-treatment state. AEs included both SAEs and non-SAEs. The safety analysis population included all subjects who received at least 1 dose of study drug.

End point type	Other pre-specified

End point timeframe:

Baseline up to Day 28

End point values	Xyntha 50 IU/kg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: subjects				
Number of Subjects with AEs	4			
Number of Subjects with SAEs	2			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects with Laboratory Abnormalities Meeting the Criteria for Potential Clinical Concern

End point title	Number of Subjects with Laboratory Abnormalities Meeting the Criteria for Potential Clinical Concern

End point description:

The following laboratory parameters were analyzed: hematology (hemoglobin, hematocrit, red blood cell count and morphology, platelet count, white blood cell count, total neutrophils, eosinophils, monocytes, basophils, lymphocytes); blood chemistry (blood urea nitrogen, creatinine, glucose, calcium, sodium, potassium, chloride, total bicarbonate, aspartate aminotransferase, alanine aminotransferase, total bilirubin, alkaline phosphatase, uric acid, albumin, and total protein); urinalysis (pH, glucose, protein, blood, ketones, nitrites, leukocyte esterase, urobilinogen, urine bilirubin, microscopy [if urine dipstick was positive for blood, protein, nitrites or leukocyte esterase]); others (urine drug screening, FVIII inhibitor assay, FVIII activity, prothrombin time [PT], activated partial thromboplastin time [APTT], anti-human immunodeficiency virus [HIV] 1, hepatitis C virus antibody [HCVAb], HAVAb, HBsAg, HBsAb, HBcAb). Only parameters which met abnormality criteria are reported.

End point type	Other pre-specified

End point timeframe:

Baseline up to Day 4

End point values	Xyntha 50 IU/kg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: subjects				
APTT >1.1X upper limit of normal (ULN)	13			
Potassium <0.9X lower limit of normal (LLN)	1			
Urine leukocyte esterase >=1	1			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects with Potentially Clinically Significant Vital Signs Findings

End point title	Number of Subjects with Potentially Clinically Significant Vital

	Signs Findings

End point description:

Vital signs assessment included pulse rate and blood pressure. Criteria for vital sign values meeting potential clinical concern included: supine pulse rate <50 beats per minute (bpm), >=30 bpm increase from baseline, or >25 bpm decrease from baseline; systolic blood pressure (SBP) <90 milliliters of mercury (mmHg), >=30 mmHg increase from baseline, or >=30 mmHg decrease from baseline; diastolic blood pressure (DBP) <50 mmHg, >=20 mmHg increase from baseline, or >=20 mmHg decrease from baseline. The safety analysis population included all subjects who received at least 1 dose of study drug.

End point type	Other pre-specified

End point timeframe:

Baseline up to Day 4

End point values	Xyntha 50 IU/kg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: subjects				
Supine SBP <90 mmHg	0			
Supine DBP <50 mmHg	0			
Supine Pulse Rate <50 bpm	0			
Supine SBP >=30 mmHg Increase from Baseline	0			
Supine DBP >=20 mmHg Increase from Baseline	0			
Supine Pulse Rate >=30 bpm Increase from Baseline	1			
Supine SBP >=30 mmHg Decrease from Baseline	0			
Supine DBP >=20 mmHg Decrease from Baseline	0			
Supine Pulse Rate >=25 bpm Decrease from Baseline	0			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects with Positive FVIII Inhibitor Activity at Day 4

End point title	Number of Subjects with Positive FVIII Inhibitor Activity at Day 4

End point description:

As with all FVIII products, subjects using Xyntha were monitored for the development of FVIII inhibitors. Values >= 0.6 Bethesda Unit (BU) per mL were considered positive results. The safety analysis population included all subjects who received at least 1 dose of study drug.

End point type	Other pre-specified

End point timeframe:

Day 4

End point values	Xyntha 50 IU/kg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: subjects	2			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Day 28

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, or 1 subject may have experienced both an AE and SAE during the study. All treated subjects were included in the analysis.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Xyntha 50 IU/kg

Reporting group description:

Subjects were administered a single dose of recombinant antihemophilic factor (Xyntha) at approximately 50 IU/kg infused IV over 10 minutes (actual dose received by subjects ranged from 42.55 IU/kg to 60.00 IU/kg).

Serious adverse events	Xyntha 50 IU/kg		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 13 (15.38%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Factor VIII inhibition			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Xyntha 50 IU/kg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 13 (15.38%)		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		

Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	 1 / 13 (7.69%) 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