Clinical trial results:
A Non-randomized, Open-label Study To Evaluate The Pharmacokinetics, Safety And Efficacy Of Refacto Af In Previously Treated Pediatric Subjects Less Than Twelve Years Of Age With Severe Hemophilia A (Fviii:c <1%)

Summary

EudraCT number	2008-008435-29
Trial protocol	FR ES IT GR CZ SE DK FI BG
Global end of trial date	05 April 2016

Results information

Result version number	v1 (current)
This version publication date	02 September 2016
First version publication date	02 September 2016

Trial information

Trial identification

Sponsor protocol code	3082B2-4433

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00914459
WHO universal trial number (UTN)	-
Other trial identifiers	Alias: B1831005

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 800--718--1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 800--718--1021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 July 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the PK and incremental recovery of ReFacto AF in pediatric subjects less than 12 years of age after a single exposure to ReFacto AF. The secondary objectives of this study are to evaluate the efficacy of ReFacto AF in pediatric subjects less than 12 years of age, including the frequency of less-than-expected therapeutic effect (LETE) and to evaluate the safety of ReFacto AF in these subjects.

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 Council for Harmonisation (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	11 December 2009
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	Finland: 1
Country: Number of subjects enrolled	Georgia: 1
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Romania: 9
Country: Number of subjects enrolled	Serbia: 9
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	Turkey: 5
Country: Number of subjects enrolled	Ukraine: 5
Worldwide total number of subjects	37
EEA total number of subjects	17

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)	1
Children (2-11 years)	36
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study was started in 11 Dec 2009 and completed on 05 Apr 2016.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	ReFacto AF: Less Than 6 Years

Arm description:

Subjects below 6 years of age were treated with IV injections of ReFacto AF at a dose and frequency prescribed by the investigator (minimum dose of 17 international units per kilogram [IU/kg] up to maximum dose of 51 IU/kg) as per local standard of care in accordance with the Summary of Product Characteristics (SmPC).

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

Dosage and administration details:

Subjects received Refacto AF IV infusion as a single dose (minimum dose of 17 IU/kg up to maximum dose of 51 IU/kg) and frequency prescribed by the investigator as per local standard of care in accordance with the Summary of Product Characteristics (SmPC). A single 50 IU/kg dose was administered for assessment of PK parameters, including recovery.

Arm title	ReFacto AF: 6 to Less Than 12 Years

Arm description:

Subjects of 6 to 12 years of age were treated with IV injections of ReFacto AF at a dose and frequency prescribed by the investigator (minimum dose of 17 IU/kg up to maximum dose of 51 IU/kg) as per local standard of care in accordance with the SmPC.

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

Dosage and administration details:

Subjects received Refacto AF IV infusion as a single dose (minimum dose of 17 IU/kg up to maximum dose of 51 IU/kg) and frequency prescribed by the investigator as per local standard of care in accordance with the Summary of Product Characteristics (SmPC). A single 50 IU/kg dose was administered for assessment of PK parameters, including recovery.

Number of subjects in period 1	ReFacto AF: Less Than 6 Years	ReFacto AF: 6 to Less Than 12 Years
Started	18	19
Completed	17	18
Not completed	1	1
Parent/Legal guardian request	1	-
Protocol deviation	-	1

Baseline characteristics

Reporting groups

Reporting group title	ReFacto AF: Less Than 6 Years

Reporting group description:

Subjects below 6 years of age were treated with IV injections of ReFacto AF at a dose and frequency prescribed by the investigator (minimum dose of 17 international units per kilogram [IU/kg] up to maximum dose of 51 IU/kg) as per local standard of care in accordance with the Summary of Product Characteristics (SmPC).

Reporting group title	ReFacto AF: 6 to Less Than 12 Years

Reporting group description:

Subjects of 6 to 12 years of age were treated with IV injections of ReFacto AF at a dose and frequency prescribed by the investigator (minimum dose of 17 IU/kg up to maximum dose of 51 IU/kg) as per local standard of care in accordance with the SmPC.

Reporting group values	ReFacto AF: Less Than 6 Years	ReFacto AF: 6 to Less Than 12 Years	Total
Number of subjects	18	19	37
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	1	0	1
Children (2-11 years)	17	19	36
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	3.6	9.2	
standard deviation	± 1.42	± 1.47	-
Gender, Male/Female Units: participants			
Female	0	0	0
Male	18	19	37

Subject analysis sets

Subject analysis set title	ReFacto AF: All Subjects
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All subjects (aged less than or equal to [<=] 12 years of age) were treated with IV injections of ReFacto AF at a dose and frequency prescribed by the investigator (minimum dose of 17 IU/kg up to maximum dose of 51 IU/kg) as per local standard of care in accordance with the SmPC.

Reporting group values	ReFacto AF: All Subjects		
Number of subjects	37		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	1		
Children (2-11 years)	36		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean	6.5		
standard deviation	± 3.2		
Gender, Male/Female Units: participants			
Female	0		
Male	37		

End points

End points reporting groups

Reporting group title	ReFacto AF: Less Than 6 Years

Reporting group description:

Subjects below 6 years of age were treated with IV injections of ReFacto AF at a dose and frequency prescribed by the investigator (minimum dose of 17 international units per kilogram [IU/kg] up to maximum dose of 51 IU/kg) as per local standard of care in accordance with the Summary of Product Characteristics (SmPC).

Reporting group title	ReFacto AF: 6 to Less Than 12 Years

Reporting group description:

Subjects of 6 to 12 years of age were treated with IV injections of ReFacto AF at a dose and frequency prescribed by the investigator (minimum dose of 17 IU/kg up to maximum dose of 51 IU/kg) as per local standard of care in accordance with the SmPC.

Subject analysis set title	ReFacto AF: All Subjects
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All subjects (aged less than or equal to [<=] 12 years of age) were treated with IV injections of ReFacto AF at a dose and frequency prescribed by the investigator (minimum dose of 17 IU/kg up to maximum dose of 51 IU/kg) as per local standard of care in accordance with the SmPC.

Primary: Percentage of Subjects With Clinically Significant Factor VIII Inhibitor Development

End point title	Percentage of Subjects With Clinically Significant Factor VIII Inhibitor Development[1]

End point description:

Clinically significant factor VIII (FVIII) inhibitors were defined as a central laboratory confirmed positive inhibitor of greater than or equal to (>=) 0.6 Bethesda units (BU) using the Nijmegen modification of the Bethesda assay present at 2 consecutive blood draws within a 6-week interval and one of the following within 4 weeks before the initial or within 4 weeks following the second positive FVIII inhibitor sample collection: the need for the subject to administer alternative hemostatic products in order to achieve sufficient efficacy, or >=2 events indicating a decrease in the efficacy of the study treatment. Percentage of subjects who developed clinically significant Factor VIII inhibitor after study drug administration were reported. Safety analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF.

End point type	Primary

End point timeframe:

Baseline up to Month 24

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 endpoint.

End point values	ReFacto AF: Less Than 6 Years	ReFacto AF: 6 to Less Than 12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	19		
Units: percentage of subjects				
number (confidence interval 95%)	0 (0 to 18.53)	0 (0 to 17.65)		

Statistical analyses

No statistical analyses for this end point

Primary: Incremental Recovery

End point title	Incremental Recovery[2]

End point description:

Incremental recovery was the increase in circulating FVIII activity for every international unit (IU) of ReFacto AF administered per kilogram of body weight. It was measured in international units per deciliter (IU/dL) per international units per kilogram (IU/kg). The pharmacokinetic (PK) parameter analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF. Here, "n" signifies subjects who were evaluable at the specified time point for each reporting group respectively.

End point type	Primary

End point timeframe:

Days 1, 15, 50, Months 6, 18 and Final visit (up to Month 24)

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 endpoint.

End point values	ReFacto AF: Less Than 6 Years	ReFacto AF: 6 to Less Than 12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	19		
Units: (IU/dL)/(IU/kg)				
arithmetic mean (standard deviation)				
Day 1 (n= 17, 18)	1.67 (± 0.361)	1.97 (± 0.437)		
Day 15 (n= 18, 17)	1.23 (± 0.65)	1.91 (± 0.423)		
Day 50 (n= 17, 18)	1.66 (± 0.626)	1.96 (± 0.586)		
Month 6 (n= 2, 5)	1.69 (± 0.21)	2.17 (± 0.379)		
Month 18 (n= 4, 5)	1.81 (± 0.405)	1.8 (± 0.493)		
Final Visit (n= 17, 17)	1.98 (± 1.454)	1.89 (± 0.503)		

Statistical analyses

No statistical analyses for this end point

Primary: Terminal Elimination Half Life of ReFacto AF (t1/2)

End point title	Terminal Elimination Half Life of ReFacto AF (t1/2)[3][4]

End point description:

T1/2 was the time for the plasma concentration of drug to decrease by one-half of its original concentration. PK parameter analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint. Data was not planned to be collected and analysed for reporting arm “ReFacto AF: Less Than 6 Years”, as pre-specified in protocol.

End point type	Primary

End point timeframe:

Pre-dose, 0.5, 1, 3, 6, 9, 24, 28, 32, 48 hours post-dose on Day 1

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 endpoint.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be assessed for "ReFacto AF: 6 to Less Than 12 Years" reporting group only.

End point values	ReFacto AF: 6 to Less Than 12 Years			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: hours				
arithmetic mean (standard deviation)	9.12 (± 1.9429)			

Statistical analyses

No statistical analyses for this end point

Primary: Clearance (CL)

End point title	Clearance (CL)[5][6]

End point description:

Drug clearance is a quantitative measure of the rate at which a drug substance is removed from the blood. PK parameter analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint. Data was not planned to be collected and analysed for reporting arm “ReFacto AF: Less Than 6 Years”, as pre-specified in protocol.

End point type	Primary

End point timeframe:

Pre-dose, 0.5, 1, 3, 6, 9, 24, 28, 32, 48 hours post-dose on Day 1

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: Only descriptive data was planned to be reported for this endpoint.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be assessed for "ReFacto AF: 6 to Less Than 12 Years" reporting group only.

End point values	ReFacto AF: 6 to Less Than 12 Years			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: milliliter per hour per kilogram				
geometric mean (geometric coefficient of variation)	4.406 (± 30)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Annualized Bleeding Rates (ABRs): All Subjects

End point title	Mean Annualized Bleeding Rates (ABRs): All Subjects

End point description:

ABR for each subject was calculated as the number of bleeds requiring administration of FVIII replacement product (taken from the Infusion Log Diary case report form), divided by the total therapy duration (in days), then multiplied by 365.25. ABR for the participants who reported following a primary or secondary prophylaxis, on-demand regimen or preventive regimen at baseline were reported. Efficacy analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint and "n" signifies subjects who were evaluable at the specified time points. Here "99999" for mean and "+/-99999" for standard deviation signifies "not available" as the data was not calculated and reported because none of the subjects were reported at baseline as following a preventive regimen.

End point type	Secondary

End point timeframe:

Baseline up to Month 24

End point values	ReFacto AF: All Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	36			
Units: bleeds per year				
arithmetic mean (standard deviation)				
On-demand regimen (n=14)	27.51 (± 20.387)			
Preventive regimen (n=0)	99999 (± 99999)			
Primary or secondary prophylaxis regimen (n=22)	4.18 (± 3.849)			

Statistical analyses

No statistical analyses for this end point

Secondary: Response to the First On-Demand Treatment for all New Bleeds: All Subjects

End point title	Response to the First On-Demand Treatment for all New Bleeds: All Subjects

End point description:

Scale for assessment of ‘on-demand’ treatment is defined as: 1.Excellent:Definite pain relief and/or improvement (improve.)in signs of bleeding starting within 8 hours after an infusion (inf.),with no additional inf. Administered (adm.). 2.Good: Definite pain relief and/or improve. in signs of bleeding starting within 8 hours after an inf.,with at least 1 additional inf. adm. for complete resolution of bleeding episode;or,Definite pain relief and/or improve. in signs of bleeding starting after 8 hours following inf.,with no additional inf. adm. 3.Moderate:Probable or slight improve. starting after 8 hours following inf.,with at least 1 additional inf. adm. for complete resolution of bleeding episode. 4.No Response:No improve. at all between inf. or during 24-hour interval following inf.,or condition worsens.Efficacy population.Number of subjects analysed signifies subjects who were evaluable for this endpoint and received at least 1 dose of ReFacto AF for at least 1 bleeding episode.

End point type	Secondary

End point timeframe:

Baseline up to Month 24

End point values	ReFacto AF: All Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	30			
Units: responses				
Excellent	713			
Good	73			
Moderate	16			
Data Not Recorded	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of On-Demand ReFacto AF Infusions to Treat a New Bleed: All Subjects

End point title	Number of On-Demand ReFacto AF Infusions to Treat a New Bleed: All Subjects

End point description:

The infusion log diary case report form (CRF) was used to determine the number of on-demand (administration of an unscheduled bolus infusion of Refacto-AF to stop bleeding) ReFacto AF infusions administered to treat a new bleed. This was calculated by adding the initial for a new bleed (on-demand) infusion to any subsequent (on-demand) infusions for the same "previously treated bleed" (same bleed with same start date/time). Efficacy analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to Month 24

End point values	ReFacto AF: All Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	30			
Units: infusions				
arithmetic mean (standard deviation)	1.1 (± 0.55)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Breakthrough Bleeds Within 48 Hours of a Prophylaxis Dose of ReFacto AF: All Subjects

End point title	Number of Breakthrough Bleeds Within 48 Hours of a Prophylaxis Dose of ReFacto AF: All Subjects

End point description:

The number of breakthrough bleeds within 48 hours following a prophylaxis dose of ReFacto AF was summarized. The infusion log diary CRF was used to determine the number of infusions administered to treat a new bleed counting only those infusions which were administered less than or equal to (<=) 48 hours after an infusion marked as "prophylaxis" (which had no associated bleed). Efficacy analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF.

End point type	Secondary

End point timeframe:

Baseline up to Month 24

End point values	ReFacto AF: All Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: breakthrough bleeds				
arithmetic mean (standard deviation)	2 (± 1.15)			

Statistical analyses

No statistical analyses for this end point

Secondary: Average Infusion Dose of ReFacto AF: All Subjects

End point title	Average Infusion Dose of ReFacto AF: All Subjects

End point description:

The average infusion dose (by weight) for each subject was calculated as his total factor FVIII consumption (in IU) divided by weight (in kg) divided by the number of infusions administered in total study duration. Data was reported separately for subjects classified at baseline as following non-prophylaxis regimen (for example: on-demand regimen, preventive, or not specified), and subjects classified at baseline following a primary or secondary prophylaxis regimen. Efficacy analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF. Here, "n" signifies subjects who were evaluable for each specified baseline category.

End point type	Secondary

End point timeframe:

Baseline up to Month 24

End point values	ReFacto AF: All Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: IU/kg				
arithmetic mean (standard deviation)				
With prophylaxis regimen at baseline (n= 22)	37 (± 8.7)			
With non-prophylaxis regimen at baseline (n= 15)	29.5 (± 7.61)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Factor VIII Consumption: All Subjects

End point title	Total Factor VIII Consumption: All Subjects

End point description:

Total factor VIII consumption for each subject was calculated by sum of the total amount of ReFacto AF (in IU) infused for each ReFacto AF infusion (recorded in the infusion log diary CRF) divided by the weight (kg) recorded at the previous visit for each subject. Data was reported separately for subjects classified at baseline as following non-prophylaxis regimen (for example: on-demand regimen, preventive, or not specified), and subjects classified at baseline following a primary or secondary prophylaxis regimen. Efficacy analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF. Here, "n" signifies subjects who were evaluable for each specified baseline category.

End point type	Secondary

End point timeframe:

Baseline up to Month 24

End point values	ReFacto AF: All Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: IU				
arithmetic mean (standard deviation)				
With Prophylaxis regimen at baseline (n= 22)	97959.4 (± 48474.09)			
With non-prophylaxis regimen at baseline (n= 15)	84051.7 (± 47362.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Less-Than-Expected-Therapeutic Effect (LETE) Bleeds in the On-Demand Setting: All Subjects

End point title	Number of Less-Than-Expected-Therapeutic Effect (LETE) Bleeds in the On-Demand Setting: All Subjects

End point description:

LETE was based on response to treatment of bleeding episode and occurred if subject recorded 2 successive"no response"ratings after 2 ReFacto AF infusions(inf.)which were administered(admin.)at interval of 24 hours for treatment of same bleeding event in absence of confounding factor which included: known presence or identification of a FVIII inhibitor,known inadequate dose for type and/or severity of bleed in opinion of investigator,delay of greater than(>)4 hours between onset of bleed to inf.,delay of >24 hours before admin. of a follow-up inf.,known compromised ReFacto AF,faulty admin.

of ReFacto AF,subject had underlying, predisposing condition responsible for bleed in opinion of investigator(kidney stones or medications which impair platelet function like aspirin or NSAIDs),or ongoing trauma responsible for continued bleeding.Efficacy analysis population."Number of subjects analysed" are subjects who were evaluable for this endpoint and received treatment for at least 1 bleed.

End point type	Secondary

End point timeframe:

Baseline up to Month 24

End point values	ReFacto AF: All Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	30			
Units: LETE bleeds				
LETE bleeds	0			
Bleeding episodes	804			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Less-Than-Expected-Therapeutic Effect (LETE) Bleeds in the Prophylaxis Setting: All Subjects

End point title	Number of Less-Than-Expected-Therapeutic Effect (LETE) Bleeds in the Prophylaxis Setting: All Subjects

End point description:

LETE in the prophylaxis setting occurred if there was a spontaneous bleed within 48 hours(<=48 hours) after a regularly scheduled prophylactic dose of ReFacto AF(which was not used to treat a bleed) in the absence of confounding factors. Therefore, LETE in the prophylaxis setting is the occurrence of a bleed. Confounding factors include:Known presence or subsequent identification of a FVIII inhibitor, known inadequate prophylactic dose, known lack of adherence to the prescribed prophylaxis regimen, bleed occurs in a target joint identified at the start of the study, known compromised ReFacto AF, faulty administration of ReFacto AF, an underlying, predisposing condition responsible for the bleed in the opinion of the investigator (e.g., kidney stones or use of medications known to impair platelet function, such as aspirin or NSAIDs) or traumatic injury responsible for bleeding. Efficacy analysis population. Subjects who received at least 1 prophylaxis dose of ReFacto AF were reported.

End point type	Secondary

End point timeframe:

Baseline up to Month 24

End point values	ReFacto AF: All Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: LETE bleeds				
LETE bleeds	2			
Prophylaxis infusions	2457			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Occurrences of Less-Than-Expected-Therapeutic Effect (LETE) in the Low Recovery Setting: All Subjects

End point title	Number of Occurrences of Less-Than-Expected-Therapeutic Effect (LETE) in the Low Recovery Setting: All Subjects

End point description:

LETE in the low recovery setting was defined as lower than expected recovery of FVIII (in the opinion of investigator), following the infusion of ReFacto AF in the absence of confounding factors for the low recovery. The only confounding factors for low recovery are as follows: known presence or subsequent identification of a FVIII inhibitor, known compromised ReFacto AF, faulty administration of ReFacto AF, including inadequate dosing. Efficacy analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF.

End point type	Secondary

End point timeframe:

Baseline up to Month 24

End point values	ReFacto AF: All Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: LETE bleeds	9			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Requiring Escalated Dose of Prescribed Regimen During the Treatment Period: All Subjects

End point title	Number of Subjects Requiring Escalated Dose of Prescribed Regimen During the Treatment Period: All Subjects

End point description:

Subjects who met the dose escalation criteria were prescribed a higher dose and/or more frequent doses as per the investigator’s discretion. Efficacy analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF. Subjects who used a prophylaxis regimen were analysed for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to Month 24

End point values	ReFacto AF: All Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: subjects	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Factor VIII at 0.5 Hour Post-dose (C0.5)

End point title	Plasma Concentration of Factor VIII at 0.5 Hour Post-dose (C0.5)

End point description:

PK parameter analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF.

End point type	Secondary

End point timeframe:

0.5 hour post-dose on Day 1

End point values	ReFacto AF: Less Than 6 Years	ReFacto AF: 6 to Less Than 12 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	19		
Units: IU/mL				
geometric mean (geometric coefficient of variation)	0.752 (± 18)	0.903 (± 45)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Time Curve From Time 0 Extrapolated to Infinite Time (AUCinf)

End point title	Area Under the Plasma Time Curve From Time 0 Extrapolated to Infinite Time (AUCinf)[7]

End point description:

AUCinf is the area under the plasma concentration-time profile from time 0 extrapolated to infinite time. It was calculated as International units*hour per milliliter (IU*hr/mL). PK parameter analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint. Data was not planned to be collected and analysed for reporting group “ReFacto AF: Less Than 6 Years”, as pre-specified in protocol.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 1, 3, 6, 9, 24, 28, 32, 48 hours post-dose on Day 1

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be assessed for "ReFacto AF: 6 to Less Than 12 Years" reporting group only.

End point values	ReFacto AF: 6 to Less Than 12 Years			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: IU*hr/mL				
geometric mean (geometric coefficient of variation)	9.89 (± 41)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Time Curve From Time Zero to Time of Last Measurable Concentration (AUClast)

End point title	Area Under the Plasma Time Curve From Time Zero to Time of Last Measurable Concentration (AUClast)[8]

End point description:

AUClast is the area under the plasma versus time curve from time zero to time of last measurable concentration (AUClast). PK parameter analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint. Data was not planned to be collected and analysed for reporting group “ReFacto AF: Less Than 6 Years”, as pre-specified in protocol.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 1, 3, 6, 9, 24, 28, 32, 48 hours post-dose on Day 1

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be assessed for "ReFacto AF: 6 to Less Than 12 Years" reporting group only.

End point values	ReFacto AF: 6 to Less Than 12 Years			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: IU*hr/mL				
geometric mean (geometric coefficient of variation)	9.49 (± 41)			

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution at Steady State (Vss)

End point title	Volume of Distribution at Steady State (Vss)[9]

End point description:

Volume of distribution was defined as the theoretical volume in which the total amount of drug was uniformly distributed to produce the desired blood concentration of a drug. Steady state volume of distribution (Vss) was the apparent volume of distribution at steady-state. PK parameter analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint. Data was not planned to be collected and analysed for reporting group "ReFacto AF: Less Than 6 Years", as pre-specified in protocol.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 1, 3, 6, 9, 24, 28, 32, 48 hours post-dose on Day 1

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be assessed for "ReFacto AF: 6 to Less Than 12 Years" reporting group only.

End point values	ReFacto AF: 6 to Less Than 12 Years			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: mL/kg				
geometric mean (geometric coefficient of variation)	56.42 (± 15)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Residence Time (MRT) of ReFacto AF

End point title	Mean Residence Time (MRT) of ReFacto AF[10]

End point description:

MRT was calculated as AUMCinf / AUCinf-TI/2, where AUMCinf is the area under the first moment curve from time zero to infinity and TI was the duration of infusion. PK parameter analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint. Data was not planned to be collected and analysed for reporting group "ReFacto AF: Less Than 6 Years", as pre-specified in protocol.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 1, 3, 6, 9, 24, 28, 32, 48 hours post-dose on Day 1

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be assessed for "ReFacto AF: 6 to Less Than 12 Years" reporting group only.

End point values	ReFacto AF: 6 to Less Than 12 Years			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: hour				
median (full range (min-max))	13.91 (8.51 to 18.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs): All Subjects

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs): All Subjects

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject who received study treatment without regard to possibility of causal relationship. 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 or incapacity, congenital anomaly. Treatment-emergent are events between first dose of study drug and up to 30 days after last dose that were absent before treatment or that worsened relative to pretreatment state. AEs included both serious and non-serious adverse events.

End point type	Secondary

End point timeframe:

Baseline up to 30 days after last study visit (Month 25)

End point values	ReFacto AF: All Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: subjects				
AEs	28			
SAEs	6			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 30 days after last study visit (Month 25)

Adverse event reporting additional description:

Same event may appear both as an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as nonserious in another subject, or one subject may have experienced both serious and nonserious event during the study. Adverse events data was planned to be reported for the overall population.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	ReFacto AF: All Subjects

Reporting group description:

All subjects (aged less than or equal to [<=] 12 years of age) were treated with IV injections of ReFacto AF at a dose and frequency prescribed by the investigator (minimum dose of 17 IU/kg up to maximum dose of 51 IU/kg) as per local standard of care in accordance with the SmPC.

Serious adverse events	ReFacto AF: All Subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 37 (16.22%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Factor VIII inhibition			
subjects affected / exposed	4 / 37 (10.81%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Scrotal disorder			

subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Laryngitis			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rhinitis			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	ReFacto AF: All Subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 37 (75.68%)		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	4 / 37 (10.81%)		
occurrences (all)	6		
Head injury			
subjects affected / exposed	4 / 37 (10.81%)		
occurrences (all)	5		

Joint injury subjects affected / exposed occurrences (all)	3 / 37 (8.11%) 3		
Limb injury subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 6		
Tooth fracture subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2		
Arthropod sting subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1		
Contusion subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 3		
Craniocerebral injury subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1		
Laceration subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1		
Lip injury subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1		
Mouth injury subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1		
Vascular disorders Hypotension subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2		
Haematoma subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1		
Surgical and medical procedures			

Tooth extraction subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 10		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	3 / 37 (8.11%) 6		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 2		
Vomiting subjects affected / exposed occurrences (all)	3 / 37 (8.11%) 3		
Dental caries subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 2		
Dyspepsia subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1		
Lip haemorrhage subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1		
Mouth haemorrhage subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1		
Oral cavity fistula subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1		
Tooth pulp haemorrhage subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1		

Toothache			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 37 (8.11%)		
occurrences (all)	3		
Epistaxis			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Obstructive airways disorder			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Skin mass			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Solar urticaria			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 37 (18.92%)		
occurrences (all)	19		
Pain in extremity			
subjects affected / exposed	4 / 37 (10.81%)		
occurrences (all)	7		
Haemarthrosis			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Joint swelling			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		

Groin pain			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Joint range of motion decreased			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	2		
Muscle haemorrhage			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	12 / 37 (32.43%)		
occurrences (all)	16		
Influenza			
subjects affected / exposed	3 / 37 (8.11%)		
occurrences (all)	4		
Adenoiditis			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	6		
Bronchitis			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	4		
Otitis media acute			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Respiratory tract infection viral			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Rhinitis			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	6		
Cestode infection			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Gastroenteritis			

subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Infectious mononucleosis			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Laryngitis			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Otitis media			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Pyoderma streptococcal			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Tonsillitis			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Varicella			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Underweight			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 May 2009	The purpose of this amendment was to update safety section to provide further details of the primary and secondary safety outcome measures.
27 May 2009	The purpose of this amendment was to modify the definition of "clinically significant FVIII inhibitor" to remove any association of this definition with LETEs
24 March 2011	The purpose of this amendment was to clarify the the timing of the follow-up call and the SAE reporting time lines

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported