Clinical trial results:
An open label study of the safety and efficacy of Refacto AF in previously untreated patients in usual care settings.

Summary

EudraCT number	2008-008436-93
Trial protocol	DE FR AT ES IT SE NL GR
Global end of trial date	24 November 2016

Results information

Result version number	v1 (current)
This version publication date	09 June 2017
First version publication date	09 June 2017

Trial information

Trial identification

Sponsor protocol code	B1831006

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 Est 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)	
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	24 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 November 2016
Global end of trial reached?	Yes
Global end of trial date	24 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety of ReFacto albumin free (AF) in previously untreated male participants less than 6 years of age.

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 participants.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 February 2010
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	France: 1
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Turkey: 9
Country: Number of subjects enrolled	Ukraine: 1
Worldwide total number of subjects	23
EEA total number of subjects	13

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	21

months)	
Children (2-11 years)	2
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:

A total of 23 participants were enrolled in this non-randomized open-label study. Participants received ReFacto AF at a dose & frequency prescribed by each participant's treating physician as per local standard of care & in accordance with summary of product characteristics (SmPC). Participants were expected to be in the study for about 26 months.

Pre-assignment

Screening details:

The study was conducted at 11 centers across various countries. All participants were male less than 6 years of age with severe hemophilia A (FVIII activity in plasma [FVIII:C]<1%) who had not received any prior factor products or blood products for their hemophilia A were enrolled in this study.

Period 1

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

Arms

Arm title	Overall participants

Arm description:

This group consisted of all participants enrolled in the study who had received at least one dose of ReFacto AF.

Arm type	Experimental
Investigational medicinal product name	Moroctocog alfa (AF CC)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Participants received ReFacto AF at a dose and frequency
prescribed by each participant's treating physician as per local standard of care and in accordance with the SmPC.

Number of subjects in period 1	Overall participants
Started	23
Completed	20
Not completed	3
Adverse event, non-fatal	2
Parent/Legal Guardian Request	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall participants
Reporting group description:	
This group consisted of all participants enrolled in the study who had received at least one dose of ReFacto AF.	

Reporting group values	Overall participants	Total	
Number of subjects	23	23	
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 < 1 year)	17	17	
Children (1 year to < 6 years)	6	6	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous Units: Years			
arithmetic mean	1		
standard deviation	± 1.09	-	
Gender, Male/Female Units: Subjects			
Female	0	0	
Male	23	23	

Subject analysis sets	
Subject analysis set title	Observed clinically significant inhibitor rate
Subject analysis set type	Full analysis
Subject analysis set description:	
Observed inhibitor recorded in participants. NOTE: Total number of participants with clinically significant FVIII inhibitor = 5.	
Subject analysis set title	Annualized bleed rate (ABR)
Subject analysis set type	Full analysis
Subject analysis set description:	
The ABR recorded in participants receiving treatment with ReFacto AF.	
Subject analysis set title	First intravenous (IV) infusion per bleed
Subject analysis set type	Full analysis
Subject analysis set description:	
First IV infusions of ReFacto AF received by the participants. NOTE: One participant who had an infusion with a response of 'Good' on 17 Apr 2012 was not included in the bleed count for this analysis, as the infusion reason was not recorded as 'on-demand' treatment.	

Subject analysis set title	Follow-up IV infusions
Subject analysis set type	Full analysis

Subject analysis set description:

Follow-up IV infusions of ReFacto AF received by the participants.

Subject analysis set title	All IV infusions
Subject analysis set type	Full analysis

Subject analysis set description:

A sum of all IV infusions of ReFacto AF received by the participants.

Subject analysis set title	One IV infusion
Subject analysis set type	Full analysis

Subject analysis set description:

Number of bleeds requiring 1 IV infusion to resolve

Subject analysis set title	Two IV infusions
Subject analysis set type	Full analysis

Subject analysis set description:

Number of bleeds requiring 2 IV infusions to resolve

Subject analysis set title	Three IV infusions
Subject analysis set type	Full analysis

Subject analysis set description:

Number of bleeds requiring 3 IV infusions to resolve

Subject analysis set title	Four IV infusions
Subject analysis set type	Full analysis

Subject analysis set description:

Number of bleeds requiring 4 IV infusions to resolve

Subject analysis set title	Greater than 4 IV infusions
Subject analysis set type	Full analysis

Subject analysis set description:

Number of bleeds requiring > 4 IV infusions to resolve

Subject analysis set title	Total number of bleeds
Subject analysis set type	Full analysis

Subject analysis set description:

Total number of bleeds reported in the study.

Subject analysis set title	Number of bleeds within 48 hours of a prophylaxis dose
Subject analysis set type	Full analysis

Subject analysis set description:

Total number of bleeds reported within 48 hours of a prophylaxis dose.

NOTE: A total of 22 participants who had received at least one prophylaxis dose were analyzed. Nine participants experienced a total of 12 bleeds.

Subject analysis set title	Reason for IV Infusion = On Demand
Subject analysis set type	Full analysis

Subject analysis set description:

The average IV infusion dose and total
factor consumption recorded in participants in on demand setting.

Subject analysis set title	Reason for IV infusion = Preventive
Subject analysis set type	Full analysis

Subject analysis set description:

The average IV infusion dose and total
factor consumption recorded in participants in on preventive setting

Subject analysis set title	Reason for IV infusion=Prophylaxis
Subject analysis set type	Full analysis

Subject analysis set description:

The average IV infusion dose and total

factor consumption recorded in participants in prophylaxis setting.

Subject analysis set title	Reason for IV infusion=Not Specified
Subject analysis set type	Full analysis

Subject analysis set description:

The average IV infusion dose and total factor consumption recorded in participants in unspecified setting.

Subject analysis set title	Total: All Reasons for IV infusion
Subject analysis set type	Full analysis

Subject analysis set description:

The average IV infusion dose and total factor consumption recorded for all participants in the study.

Subject analysis set title	Number of participants who required dose escalation
Subject analysis set type	Full analysis

Subject analysis set description:

Number of participants who require dose escalation of their prescribed prophylaxis regimen during their participation in this study.

Subject analysis set title	LETE in the Prophylaxis Setting
Subject analysis set type	Full analysis

Subject analysis set description:

Number of bleeds recorded in participants.

NOTE: This was prophylaxis Setting LETEs with no confounding factors

Subject analysis set title	Number of Potential LETEs in Low Recovery Setting
Subject analysis set type	Full analysis

Subject analysis set description:

Number of bleeds recorded in participants.

NOTE:
1) A potential LETE: Recovery lower-than-expected recovery of FVIII in the opinion of the investigator following infusion of ReFacto AF in the absence of confounding factors.

Subject analysis set title	LETE in the On-Demand Setting
Subject analysis set type	Full analysis

Subject analysis set description:

Number of bleeds recorded in participants.

NOTE: Based on the response to treatment of a bleeding episode.

Reporting group values	Observed clinically significant inhibitor rate	Annualized bleed rate (ABR)	First intravenous (IV) infusion per bleed
Number of subjects	23	23	23
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days < 1 year)			
Children (1 year to < 6 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			

Age Continuous			
Units: Years			
arithmetic mean	0	0	0
standard deviation	± 0	± 0	± 0
Gender, Male/Female			
Units: Subjects			
Female			
Male			

Reporting group values	Follow-up IV infusions	All IV infusions	One IV infusion
Number of subjects	23	23	23
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days < 1 year)			
Children (1 year to < 6 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age Continuous			
Units: Years			
arithmetic mean	0	0	0
standard deviation	± 0	± 0	± 0
Gender, Male/Female			
Units: Subjects			
Female			
Male			

Reporting group values	Two IV infusions	Three IV infusions	Four IV infusions
Number of subjects	23	23	23
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days < 1 year)			
Children (1 year to < 6 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age Continuous			
Units: Years			
arithmetic mean	0	0	0
standard deviation	± 0	± 0	± 0

Gender, Male/Female Units: Subjects			
Female Male			

Reporting group values	Greater than 4 IV infusions	Total number of bleeds	Number of bleeds within 48 hours of a prophylaxis dose
Number of subjects	23	23	22
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days < 1 year) Children (1 year to < 6 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: Years			
arithmetic mean	0	0	0
standard deviation	± 0	± 0	± 0
Gender, Male/Female Units: Subjects			
Female Male			

Reporting group values	Reason for IV Infusion = On Demand	Reason for IV infusion = Preventive	Reason for IV infusion=Prophylaxis
Number of subjects	21	7	22
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days < 1 year) Children (1 year to < 6 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: Years			
arithmetic mean	0	0	0
standard deviation	± 0	± 0	± 0

Gender, Male/Female Units: Subjects			
Female Male			

Reporting group values	Reason for IV infusion=Not Specified	Total: All Reasons for IV infusion	Number of participants who required dose escalation
Number of subjects	4	23	22
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days < 1 year) Children (1 year to < 6 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: Years			
arithmetic mean	0	0	0
standard deviation	± 0	± 0	± 0
Gender, Male/Female Units: Subjects			
Female Male			

Reporting group values	LETE in the Prophylaxis Setting	Number of Potential LETEs in Low Recovery Setting	LETE in the On-Demand Setting
Number of subjects	22	23	23
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days < 1 year) Children (1 year to < 6 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: Years			
arithmetic mean	0	0	0
standard deviation	± 0	± 0	± 0

Gender, Male/Female Units: Subjects			
Female Male			

End points

End points reporting groups

Reporting group title	Overall participants
Reporting group description:	
This group consisted of all participants enrolled in the study who had received at least one dose of ReFacto AF.	
Subject analysis set title	Observed clinically significant inhibitor rate
Subject analysis set type	Full analysis
Subject analysis set description:	
Observed inhibitor recorded in participants. NOTE: Total number of participants with clinically significant FVIII inhibitor = 5.	
Subject analysis set title	Annualized bleed rate (ABR)
Subject analysis set type	Full analysis
Subject analysis set description:	
The ABR recorded in participants receiving treatment with ReFacto AF.	
Subject analysis set title	First intravenous (IV) infusion per bleed
Subject analysis set type	Full analysis
Subject analysis set description:	
First IV infusions of ReFacto AF received by the participants. NOTE: One participant who had an infusion with a response of 'Good' on 17 Apr 2012 was not included in the bleed count for this analysis, as the infusion reason was not recorded as 'on-demand' treatment.	
Subject analysis set title	Follow-up IV infusions
Subject analysis set type	Full analysis
Subject analysis set description:	
Follow-up IV infusions of ReFacto AF received by the participants.	
Subject analysis set title	All IV infusions
Subject analysis set type	Full analysis
Subject analysis set description:	
A sum of all IV infusions of ReFacto AF received by the participants.	
Subject analysis set title	One IV infusion
Subject analysis set type	Full analysis
Subject analysis set description:	
Number of bleeds requiring 1 IV infusion to resolve	
Subject analysis set title	Two IV infusions
Subject analysis set type	Full analysis
Subject analysis set description:	
Number of bleeds requiring 2 IV infusions to resolve	
Subject analysis set title	Three IV infusions
Subject analysis set type	Full analysis
Subject analysis set description:	
Number of bleeds requiring 3 IV infusions to resolve	
Subject analysis set title	Four IV infusions
Subject analysis set type	Full analysis
Subject analysis set description:	
Number of bleeds requiring 4 IV infusions to resolve	
Subject analysis set title	Greater than 4 IV infusions
Subject analysis set type	Full analysis
Subject analysis set description:	
Number of bleeds requiring > 4 IV infusions to resolve	

Subject analysis set title	Total number of bleeds
Subject analysis set type	Full analysis

Subject analysis set description:

Total number of bleeds reported in the study.

Subject analysis set title	Number of bleeds within 48 hours of a prophylaxis dose
Subject analysis set type	Full analysis

Subject analysis set description:

Total number of bleeds reported within 48 hours of a prophylaxis dose.

NOTE: A total of 22 participants who had received at least one prophylaxis dose were analyzed. Nine participants experienced a total of 12 bleeds.

Subject analysis set title	Reason for IV Infusion = On Demand
Subject analysis set type	Full analysis

Subject analysis set description:

The average IV infusion dose and total
factor consumption recorded in participants in on demand setting.

Subject analysis set title	Reason for IV infusion = Preventive
Subject analysis set type	Full analysis

Subject analysis set description:

The average IV infusion dose and total
factor consumption recorded in participants in on preventive setting

Subject analysis set title	Reason for IV infusion=Prophylaxis
Subject analysis set type	Full analysis

Subject analysis set description:

The average IV infusion dose and total
factor consumption recorded in participants in prophylaxis setting.

Subject analysis set title	Reason for IV infusion=Not Specified
Subject analysis set type	Full analysis

Subject analysis set description:

The average IV infusion dose and total
factor consumption recorded in participants in unspecified setting.

Subject analysis set title	Total: All Reasons for IV infusion
Subject analysis set type	Full analysis

Subject analysis set description:

The average IV infusion dose and total
factor consumption recorded for all participants in the study.

Subject analysis set title	Number of participants who required dose escalation
Subject analysis set type	Full analysis

Subject analysis set description:

Number of participants who require dose escalation of their prescribed prophylaxis regimen during their participation in this study.

Subject analysis set title	LETE in the Prophylaxis Setting
Subject analysis set type	Full analysis

Subject analysis set description:

Number of bleeds recorded in participants.

NOTE: This was prophylaxis Setting LETEs with no confounding factors

Subject analysis set title	Number of Potential LETEs in Low Recovery Setting
Subject analysis set type	Full analysis

Subject analysis set description:

Number of bleeds recorded in participants.

NOTE:
1) A potential LETE: Recovery lower-than-expected recovery of FVIII in the opinion of the investigator following infusion of ReFacto AF in the absence of confounding factors.

Subject analysis set title	LETE in the On-Demand Setting

Subject analysis set type	Full analysis

Subject analysis set description:

Number of bleeds recorded in participants.

NOTE: Based on the response to treatment of a bleeding episode.

Primary: Proportion of participants who develop clinically significant FVIII inhibitors during the course of the study.

End point title	Proportion of participants who develop clinically significant FVIII inhibitors during the course of the study.[1]

End point description:

To evaluate the proportion of participants who developed clinically significant FVIII inhibitors (those persistent over a defined period with clinically impactful effects (ie breakthrough bleed, low recovery, etc)) during the course of the study.

End point type	Primary

End point timeframe:

At protocol defined time-points during approximately 2 years study period

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: No statistical analyses have been specified for this primary end point. No inferential statistical analysis was done.

End point values	Observed clinically significant inhibitor rate			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Percentage				
number (confidence interval 95%)	21.74 (7.46 to 43.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized bleeding rates (ABR).

End point title	Annualized bleeding rates (ABR).

End point description:

Annualized bleeding rate was calculated as the number of bleeds divided by the treatment interval duration (enrollment visit to final visit) and then multiplied by 365.25. If there was more than 1 bleed location (ie, ankle and joint) with identical bleed start date and time, it was treated as 1 bleed occurrence.
NOTE: The ABR listed is regardless of regimen (regimen was not collected).

End point type	Secondary

End point timeframe:

At protocol defined time-points during approximately 2 years study period

End point values	Annualized bleed rate (ABR)			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Number				
arithmetic mean (standard deviation)	5.88 (± 8.082)			

Statistical analyses

No statistical analyses for this end point

Secondary: Response to the first on-demand treatment with Refacto AF for all new bleeds.

End point title	Response to the first on-demand treatment with Refacto AF for all new bleeds.

End point description:

The 4-point response scale of assessment (excellent, good, moderate and no response) was completed each time a participant experienced a new bleed requiring an 'on-demand' infusion. All participant assessments were provided by the parent/legal representative or investigator.

End point type	Secondary

End point timeframe:

At protocol defined time-points during approximately 2 years study period

End point values	First intravenous (IV) infusion per bleed	Follow-up IV infusions	All IV infusions	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	23	23	23	
Units: Number				
Excellent	51	7	58	
Good	48	19	67	
Moderate	28	12	40	
No response	3	5	8	
Data Not Recorded	19	1	20	
Total	149	44	193	

Statistical analyses

No statistical analyses for this end point

Secondary: Response to First Infusion with ReFacto AF

End point title	Response to First Infusion with ReFacto AF

End point description:

To assess the response of each bleed to first 'on-demand' infusion and also to assess number of infusions required to treat each bleed ie.1, 2, 3, 4, or more than 4 infusions. Result: A total of 21

participants had 150 bleeding episodes. After the first infusion, the majority (132/150 [88.0%]) of bleeds resolved.

End point type	Secondary

End point timeframe:

At protocol defined time-points during approximately 2 years study period

End point values	One IV infusion	Two IV infusions	Three IV infusions	Four IV infusions
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	23	23	23
Units: Number				
Excellent (15 participants)	48	3	0	0
Good (14 participants)	43	5	0	0
Moderate (6 participants)	22	4	0	0
No response (2 participants)	2	0	0	0
Data Not Recorded (7 participants)	17	1	1	0
Total (Any) (21 participants)	132	13	1	0

End point values	Greater than 4 IV infusions	Total number of bleeds		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	23		
Units: Number				
Excellent (15 participants)	0	51		
Good (14 participants)	1	49		
Moderate (6 participants)	2	28		
No response (2 participants)	1	3		
Data Not Recorded (7 participants)	0	19		
Total (Any) (21 participants)	4	150		

Statistical analyses

No statistical analyses for this end point

Secondary: The number of bleeds within 48 hours of a prophylaxis dose of ReFacto AF.

End point title	The number of bleeds within 48 hours of a prophylaxis dose of ReFacto AF.

End point description:

To assess the number of bleeds within 48 hours of a prophylaxis infusion of ReFacto AF. Nine participants experienced a total of 12 bleeds.

End point type	Secondary

End point timeframe:

At protocol defined time-points during approximately 2 years study period

End point values	Number of bleeds within 48 hours of a prophylaxis dose			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Number				
arithmetic mean (standard deviation)	1.3 (± 1)			

Statistical analyses

No statistical analyses for this end point

Secondary: The average infusion dose and total factor consumption. Summary of Moroctocog ALFA (AF -CC) consumption.

End point title	The average infusion dose and total factor consumption. Summary of Moroctocog ALFA (AF -CC) consumption.

End point description:

The total factor consumption (by weight) for each participant was calculated by summing the total amount (IU) infused. The average infusion dose for each participant was calculated by dividing total factor consumption (in IU) by the number of infusions administered.

End point type	Secondary

End point timeframe:

At protocol defined time-points during approximately 2 years study period

End point values	Reason for IV Infusion = On Demand	Reason for IV infusion = Preventive	Reason for IV infusion=Prophylaxis	Reason for IV infusion=Not Specified
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	21	7	22	4
Units: Number				
arithmetic mean (standard deviation)				
Total Units (IU) per Participant TFC)	4186 (± 3038.4)	1857 (± 2357.5)	55543 (± 55535.5)	1634 (± 2523.8)
Dose (IU) per Infusion	552 (± 296.7)	544 (± 285.6)	628 (± 389.6)	481 (± 401.5)
Total Unit by Weight (IU/kg) per Participant	388 (± 297)	93 (± 56.8)	4766 (± 4933.5)	187 (± 256.5)
Total Unit (IU) per Participant Annualized TFC)	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
IU/kg per Participant (Annualized TFC by Weight)	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
Dose by Weight (IU/kg) per Infusion	49 (± 26.1)	42 (± 16.9)	55 (± 34.4)	50 (± 41)
Number of Infusions per Participant	9 (± 8)	5 (± 8.9)	80 (± 36.9)	2 (± 1.9)
Exposure Days per Participant	8 (± 6.3)	3 (± 3.7)	76 (± 31.3)	2 (± 1.9)

End point values	Total: All Reasons for IV infusion			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Number				
arithmetic mean (standard deviation)				
Total Units (IU) per Participant TFC)	57799 (± 55125.8)			
Dose (IU) per Infusion	619 (± 386.5)			
Total Unit by Weight (IU/kg) per Participant	4966 (± 4891.4)			
Total Unit (IU) per Participant Annualized TFC)	72336 (± 123407.9)			
IU/kg per Participant (Annualized TFC by Weight)	6398 (± 11102.8)			
Dose by Weight (IU/kg) per Infusion	53 (± 33.5)			
Number of Infusions per Participant	86 (± 37.5)			
Exposure Days per Participant	81 (± 32.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: The number of participants who require dose escalation of their prescribed prophylaxis regimen during their participation in this study.

End point title	The number of participants who require dose escalation of their prescribed prophylaxis regimen during their participation in this study.

End point description:

The number of participants who met the dose escalation criteria were prescribed a higher dose and/or were prescribed more frequent doses. When dose escalation was required, the specific dose and dosing schedule was at the investigator’s discretion.

End point type	Secondary

End point timeframe:

At protocol defined time-points during approximately 2 years study period

End point values	Number of participants who required dose escalation			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Number	15			

Statistical analyses

No statistical analyses for this end point

Secondary: The incidence of less-than-expected therapeutic effect (LETE) in the Prophylaxis Setting.

End point title	The incidence of less-than-expected therapeutic effect (LETE) in the Prophylaxis Setting.

End point description:

LETE on the prophylaxis setting occurred when there was a spontaneous bleed within 48 hours after a regularly scheduled prophylactic dose of ReFacto AF in the absence of confounding factors.

End point type	Secondary

End point timeframe:

At protocol defined time-points during approximately 2 years study period

End point values	LETE in the Prophylaxis Setting			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Percentage				
number (confidence interval 95%)	0.11 (0.01 to 0.41)			

Statistical analyses

No statistical analyses for this end point

Secondary: The incidence of less-than-expected therapeutic effect (LETE) in Low Recovery Setting.

End point title	The incidence of less-than-expected therapeutic effect (LETE) in Low Recovery Setting.

End point description:

To assess the occurrence of low recovery LETE in the absence of confounding factors. Investigators reported 10 instances of potential low recovery (LETE) in 6 participants, including one subject in whom there were 3 instances of potential LETE in the low recovery setting for which no confounders were reported.

End point type	Secondary

End point timeframe:

At protocol defined time-points during approximately 2 years study period

End point values	Number of Potential LETEs in Low Recovery Setting			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Number				
No. of participants: 1	1			
No. of participants: 1 with no confounders	3			
No. of participants: 2	2			
No. of participants: 3	4			
Total particpants	10			

Statistical analyses

No statistical analyses for this end point

Secondary: The incidence of less-than-expected therapeutic effect (LETE) in On-Demand Setting.

End point title	The incidence of less-than-expected therapeutic effect (LETE) in On-Demand Setting.

End point description:

LETE in the on-demand setting occurred when a participant recorded 2 successive "No Response" ratings after 2 successive ReFacto AF infusions for treatment of the same bleed in the absence of confounding factors.

End point type	Secondary

End point timeframe:

At protocol defined time-points during approximately 2 years study period

End point values	LETE in the On-Demand Setting			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Number				
number (confidence interval 95%)	0 (0 to 2.43)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were recorded from the time the participants provides informed consent, through completion of the final contact (Follow-up Phone Call). All serious AEs and all treatment emergent AEs with the threshold of more than 5% were reported.

Adverse event reporting additional description:

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Any AE that meets any of the seriousness criteria listed in the study protocol will be considered as an SAE.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Hemophilia related + Non-Hemophilia (All Causalities)

Reporting group description:

Overall number of participants in the study.

Serious adverse events	Hemophilia related + Non-Hemophilia (All Causalities)		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 23 (47.83%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Tongue injury			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Febrile convulsion			
subjects affected / exposed	1 / 23 (4.35%)		
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	8 / 23 (34.78%)		
occurrences causally related to treatment / all	8 / 8		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Milk allergy			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intussusception			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enterobacter sepsis			

subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Hemophilia related + Non-Hemophilia (All Causalities)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 23 (86.96%)		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	4 / 23 (17.39%)		
occurrences (all)	8		
Head injury			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	3		
Lip injury			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Procedural pain			

subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2		
Vascular disorders Haematoma subjects affected / exposed occurrences (all)	 4 / 23 (17.39%) 5		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	 10 / 23 (43.48%) 13		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 5 / 23 (21.74%) 5		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	 2 / 23 (8.70%) 2		
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	 2 / 23 (8.70%) 2		
Gastrointestinal disorders Mouth haemorrhage subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Teething subjects affected / exposed occurrences (all)	 4 / 23 (17.39%) 4 3 / 23 (13.04%) 3 3 / 23 (13.04%) 3 2 / 23 (8.70%) 3		
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	4 / 23 (17.39%) 7		
Skin and subcutaneous tissue disorders Eczema subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 2 / 23 (8.70%) 2 2 / 23 (8.70%) 2		
Musculoskeletal and connective tissue disorders Haemarthrosis subjects affected / exposed occurrences (all)	 3 / 23 (13.04%) 5		
Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Conjunctivitis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all)	 6 / 23 (26.09%) 7 6 / 23 (26.09%) 14 3 / 23 (13.04%) 5 3 / 23 (13.04%) 4 2 / 23 (8.70%) 2 2 / 23 (8.70%) 2 2 / 23 (8.70%) 3		

Rhinitis subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 May 2010	Amendment 2: Implemented the following changes • Minor clarifications to existing wording, administrative changes, and corrections of typographical errors. • Globally implemented changes outlined in Amendment 1, with the exception of exclusion criterion for body weight <5.4 kilograms.
22 March 2011	Amendment 4: Implemented the following changes: • Minor clarifications to existing wording, administrative changes, and corrections of typographical errors. • Globally implemented changes outlined in Amendment 3.
23 October 2012	Amendment 6: Implemented the following changes: • Minor clarifications to existing wording, administrative changes, and corrections of typographical errors. • Globally implemented changes outlined in Amendment 5.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported