Clinical trial results:
A Postauthorization Safety Surveillance Study of Patients Switching to ReFacto AF From ReFacto or Other Factor VIII Products in Usual Care Settings

Summary

EudraCT number	2008-007997-39
Trial protocol	DE BE ES SE AT FI DK FR IT PT NL GB CZ GR HU
Global end of trial date	28 March 2013

Results information

Result version number	v1 (current)
This version publication date	30 May 2016
First version publication date	30 July 2015

Trial information

Trial identification

Sponsor protocol code	3082B2-4432-WW

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00884390
WHO universal trial number (UTN)	-
Other trial identifiers	Alias: B1831004

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 August 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 March 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the safety of ReFacto AF. The secondary objective was to evaluate the efficacy of ReFacto AF.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 May 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	Romania: 10
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Spain: 62
Country: Number of subjects enrolled	Sweden: 10
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	Finland: 8
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Germany: 35
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Hungary: 20
Country: Number of subjects enrolled	Italy: 11
Worldwide total number of subjects	208
EEA total number of subjects	208

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)	0
Adolescents (12-17 years)	42
Adults (18-64 years)	166
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Two hundred and eight (208) subjects were enrolled into the study (146 subjects into the ReFacto Switch group [Cohort 1: subjects who switched from ReFacto to ReFacto Albumin Free [AF]] and 62 subjects into the Other Switch group [Cohort 2: subjects who switched from other Factor VIII (FVIII) products other than ReFacto to ReFacto AF]).

Pre-assignment

Screening details:

Study started on 07 May 2009 and ended on 28 March 2013. Overall, 208 subjects were enrolled into the study across 14 countries.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	ReFacto Switch

Arm description:

Subjects who switched from ReFacto to ReFacto AF.

Arm type	Experimental
Investigational medicinal product name	ReFacto AF
Investigational medicinal product code	PF-05208756
Other name	Moroctocog alfa (Albumin Free Cell Culture[AF-CC])
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects who switched from ReFacto to ReFacto AF.

Arm title	Other Switch

Arm description:

Subjects who switched from other FVIII products other than ReFacto to ReFacto AF.

Arm type	Experimental
Investigational medicinal product name	ReFacto AF
Investigational medicinal product code	PF-05208756
Other name	Moroctocog alfa (AF-CC)
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects who switched from other FVIII products other than ReFacto to ReFacto AF.

Number of subjects in period 1	ReFacto Switch	Other Switch
Started	146	62
Completed	123	54
Not completed	23	8
Consent withdrawn by subject	4	1
Physician decision	2	1
Adverse Event	-	1
Not Specified	11	1
Discontinuation of Study by Sponsor	2	2
Protocol Violation	4	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	ReFacto Switch
Reporting group description:	
Subjects who switched from ReFacto to ReFacto AF.	
Reporting group title	Other Switch
Reporting group description:	
Subjects who switched from other FVIII products other than ReFacto to ReFacto AF.	

Reporting group values	ReFacto Switch	Other Switch	Total
Number of subjects	146	62	208
Age categorical Units: Subjects			
12-17 years	33	9	42
18-65 years	113	53	166
Gender categorical Units: Subjects			
Female	0	0	0
Male	146	62	208

End points

End points reporting groups

Reporting group title	ReFacto Switch
Reporting group description:	
Subjects who switched from ReFacto to ReFacto AF.	
Reporting group title	Other Switch
Reporting group description:	
Subjects who switched from other FVIII products other than ReFacto to ReFacto AF.	
Subject analysis set title	Annualized Bleed Rate
Subject analysis set type	Safety analysis
Subject analysis set description:	
Annualized Bleed Rate (ABR) by regimen at baseline is summarized for all subjects for on-demand regimen, preventive regimen and prophylaxis regimen, respectively.	
Subject analysis set title	First Infusion Per Bleed
Subject analysis set type	Safety analysis
Subject analysis set description:	
Includes the first infusion for an associated bleeding episode.	
Subject analysis set title	All Subjects With Bleeds
Subject analysis set type	Safety analysis
Subject analysis set description:	
Includes any infusion with an associated bleeding episode, regardless of the reason for treatment indicated on the case report form.	
Subject analysis set title	Subjects Who Received at Least One Prophylactic Infusion
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects who had at least one prophylaxis dose, and at least one bleed.	
Subject analysis set title	All Subjects
Subject analysis set type	Safety analysis
Subject analysis set description:	
All enrolled subjects following a prophylaxis regimen at baseline.	
Subject analysis set title	Subjects Following a Non-prophylaxis Regimen at Baseline
Subject analysis set type	Safety analysis
Subject analysis set description:	
All enrolled subjects following an on-demand or preventive regimen at baseline.	
Subject analysis set title	Subjects Following a Prophylaxis Regimen at Baseline
Subject analysis set type	Safety analysis
Subject analysis set description:	
All enrolled subjects following a prophylaxis regimen at baseline.	
Subject analysis set title	All Subjects With at Least One Bleed
Subject analysis set type	Safety analysis
Subject analysis set description:	
All enrolled subjects with at least one bleed.	
Subject analysis set title	All Subjects With at Least One Prophylaxis Infusion
Subject analysis set type	Safety analysis
Subject analysis set description:	
All enrolled subjects with at least one prophylaxis infusion.	

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

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

End point description:

Number of subjects with clinically significant FVIII inhibitor development after switching from ReFacto to moroctocog alfa (AF-CC). Clinically significant inhibitors are defined as a central laboratory confirmed positive inhibitor (greater than or equal to [≥] 0.6 Bethesda unit [BU] using the Nijmegen modification of the Bethesda assay present at 2 consecutive blood draws within a 6-week interval) and within 28 days before the initial or within 28 days following the second positive FVIII inhibitor sample collection one of the following: the need for the subject to administer alternative hemostatic products in order to achieve sufficient efficacy, or ≥2 adverse event reports of decreased drug effect (or other adverse event indicating a decrease in the efficacy of the test article). All enrolled subjects who took at least 1 dose of ReFacto AF study drug were included in the safety and efficacy analyses.

End point type	Primary

End point timeframe:

100 exposure days to study medication (approximately 2 years)

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 Switch	Other Switch		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	146	62		
Units: Number of subjects				
number (confidence interval 95%)	0 (0 to 2.49)	0 (0 to 5.78)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Bleeding Rates (ABRs)

End point title	Annualized Bleeding Rates (ABRs)

End point description:

An ABR for each subject will be calculated as the number of bleeds requiring administration of FVIII replacement product (taken from the Infusion Log Diary case report form), divided by his total therapy duration (in days), then multiplied by 365.25. All enrolled subjects who took at least 1 dose of ReFacto AF study drug were included in the safety and efficacy analyses.

End point type	Secondary

End point timeframe:

100 exposure days to study medication (approximately 2 years)

End point values	Annualized Bleed Rate			
Subject group type	Subject analysis set			
Number of subjects analysed	208			
Units: number of bleeds				
arithmetic mean (standard deviation)				

On-demand regimen (N=52)	28.35 (± 18.781)			
Preventive regimen (N=2)	1.08 (± 1.528)			
Primary or secondary prophylaxis regimen (N=154)	8.43 (± 17.362)			

Statistical analyses

No statistical analyses for this end point

Secondary: Response Assessment of First On-demand Treatment of New Bleeds

End point title	Response Assessment of First On-demand Treatment of New Bleeds

End point description:

A 4-point scale of assessment of 'on-demand' treatment is defined as:Excellent: Definite pain relief and/or improvement in signs of bleeding starting within 8 hours after an infusion, with no additional infusion administered.Good: Definite pain relief and/or improvement in signs of bleeding starting within 8 hours after an infusion, with at least one additional infusion administered for complete resolution of the bleeding episode; or, Definite pain relief and/or improvement in signs of bleeding starting after 8 hours following the infusion, with no additional infusion administered.Moderate: Probable or slight improvement starting after 8 hours following the infusion, with at least one additional infusion administered for complete resolution of the bleeding episode.No Response: No improvement at all between infusions or during the 24-hour interval following an infusion, or condition worsens. All enrolled subjects who took at least 1 dose of ReFacto AF study drug.

End point type	Secondary

End point timeframe:

100 exposure days to study medication (approximately 2 years)

End point values	First Infusion Per Bleed			
Subject group type	Subject analysis set			
Number of subjects analysed	156			
Units: number of observations				
Excellent	1650			
Good	1031			
Moderate	191			
No response	26			
Data not recorded	343			
Total	3241			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of ReFacto AF Infusions to Treat Each New Bleed

End point title	Number of ReFacto AF Infusions to Treat Each New Bleed

End point description:

The Infusion Log Diary case report form (CRF) was used to determine the number of test article infusions administered to treat a bleed. This was calculated by adding the initial (on-demand) infusion to any subsequent (on-demand) infusions for the same bleed (same bleed start date/time). The mean of infusions to produce an excellent, good, moderate and no response was reported. All enrolled subjects who took at least 1 dose of ReFacto AF study drug were included in the safety and efficacy analyses.

End point type	Secondary

End point timeframe:

100 exposure days to study medication (approximately 2 years)

End point values	All Subjects With Bleeds			
Subject group type	Subject analysis set			
Number of subjects analysed	156			
Units: number of infusions				
arithmetic mean (standard deviation)				
Excellent	1.1 (± 0.66)			
Good	1.4 (± 1.45)			
Moderate	2 (± 1.63)			
No response	2.5 (± 2.6)			
Data not recorded	1.3 (± 1.55)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Bleeding Episodes Occurring Less Than Equal To (≤) 48 Hours After a Prophylaxis Infusion

End point title	Number of Bleeding Episodes Occurring Less Than Equal To (≤) 48 Hours After a Prophylaxis Infusion

End point description:

First, the bleed start time from the Infusion Log Diary CRF was used to determine the number of breakthrough bleeds that occurred ≤48 hours after an infusion marked as "Prophylaxis" (which had no associated bleed). If there was more than 1 bleed location (i.e. ankle and joint) with identical bleed start date and time, it was treated as 1 bleed occurrence. If a response was given, or if a bleed time was given, but "On Demand" was not listed as "treatment type", it was still counted as an on-demand bleed for analyses/summaries. Bleeding episodes were not categorized as spontaneous (atraumatic) or traumatic. All enrolled subjects who took at least 1 dose of ReFacto AF study drug were included in the safety and efficacy analyses.

End point type	Secondary

End point timeframe:

100 exposure days to study medication (approximately 2 years)

End point values	Subjects Who Received at Least One Prophylactic Infusion			
Subject group type	Subject analysis set			
Number of subjects analysed	108			
Units: bleeds	96			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Breakthrough Bleeds

End point title	Number of Subjects With Breakthrough Bleeds

End point description:

The number of subjects with any breakthrough bleed were reported. All enrolled Subjects who took at least 1 dose of ReFacto AF study drug were included in the safety and efficacy analyses.

End point type	Secondary

End point timeframe:

100 exposure days to study medication (approximately 2 years)

End point values	Subjects Who Received at Least One Prophylactic Infusion			
Subject group type	Subject analysis set			
Number of subjects analysed	108			
Units: subjects	33			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Factor Consumption (TFC) Following a Non-prophylaxis Regimen at Baseline for All Subjects

End point title	Total Factor Consumption (TFC) Following a Non-prophylaxis Regimen at Baseline for All Subjects

End point description:

The total amount (in International Units [IU]) infused for each test article infusion recorded in the Infusion Log Diary CRF was summed to calculate the TFC for each subject. All enrolled subjects who took at least 1 dose of ReFacto AF study drug were included in the safety and efficacy analyses.

End point type	Secondary

End point timeframe:

100 exposure days to study medication (approximately 2 years)

End point values	All Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	54			
Units: IU				
arithmetic mean (standard deviation)				
On demand (n=50)	115451.5 (± 67186.92)			
Preventive (n=43)	35156.8 (± 40690.91)			
Prophylaxis (n=19)	73001.9 (± 66969.64)			
Not specified (n=54)	39268.3 (± 65013.77)			
Total (n=54)	199848.9 (± 79308.82)			

Statistical analyses

No statistical analyses for this end point

Secondary: TFC Following a Prophylaxis Regimen at Baseline for All Subjects

End point title	TFC Following a Prophylaxis Regimen at Baseline for All Subjects

End point description:

The total amount (in IU) infused for each test article infusion recorded in the Infusion Log Diary CRF was summed to calculate the TFC for each subject. All enrolled subjects who took at least 1 dose of ReFacto AF study drug were included in the safety and efficacy analyses.

End point type	Secondary

End point timeframe:

100 exposure days to study medication (approximately 2 years)

End point values	Subjects Following a Prophylaxis Regimen at Baseline			
Subject group type	Subject analysis set			
Number of subjects analysed	154			
Units: IU				
arithmetic mean (standard deviation)				
On demand (n=98)	26063.4 (± 32876.96)			
Preventive (n=65)	22498.8 (± 29987.52)			
Prophylaxis (n=143)	165124.6 (± 88373.55)			

Not specified (n=154)	43812.8 (± 67588.23)			
Total (n=154)	223224.8 (± 86493.58)			

Statistical analyses

No statistical analyses for this end point

Secondary: Average Infusion Dose

End point title	Average Infusion Dose

End point description:

The average infusion dose for each subject was calculated as his total factor consumption (in IU) divided by the number of infusions administered. Summary statistics were reported for both of these variables separately for those subjects classified at baseline as following an on-demand regimen, and for those on a primary or secondary prophylaxis regimen. All enrolled subjects who took at least 1 dose of ReFacto AF study drug were included in the safety and efficacy analyses.

End point type	Secondary

End point timeframe:

100 exposure days to study medication (approximately 2 years)

End point values	Subjects Following a Non-prophylaxis Regimen at Baseline	Subjects Following a Prophylaxis Regimen at Baseline		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	54	154		
Units: IU				
arithmetic mean (standard deviation)	2326.8 (± 691.31)	2290.3 (± 701.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Less-Than-Expected-Therapeutic Effect (LETE) in the On-demand Setting

End point title	Incidence of Less-Than-Expected-Therapeutic Effect (LETE) in the On-demand Setting

End point description:

The calculation of incidence of on-demand LETE used the number of bleeds identified as, or with a result of, LETE as the numerator (from the On Demand LETE CRF), and the denominator was the number of bleeding episodes treated in an on-demand setting. This denominator could include new bleeding episodes in prophylaxis subjects breakthrough bleeds), and if subsequent on-demand doses for such a bleed met the on-demand LETE criteria, then an on-demand LETE was reported. All enrolled subjects who took at least 1 dose of ReFacto AF study drug were included in the safety and efficacy analyses.

End point type	Secondary

End point timeframe:

100 exposure days to study medication (approximately 2 years)

End point values	All Subjects With at Least One Bleed			
Subject group type	Subject analysis set			
Number of subjects analysed	208			
Units: percentage of bleeds LETE				
number (confidence interval 95%)	0.06 (0.01 to 0.22)			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Less-than-expected-therapeutic Effect (LETE) in the Prophylaxis Setting

End point title	Incidence of Less-than-expected-therapeutic Effect (LETE) in the Prophylaxis Setting

End point description:

The calculation of incidence of prophylaxis LETE used the number of bleeds identified as, or with a result of, LETE as the numerator (from the Prophylactic LETE CRF), and the denominator was the number of routine prophylaxis infusions. Each infusion was classified in the infusion log ("Prophylaxis/ On Demand/ Preventive"), and subjects were instructed to select "On Demand" if the infusion was to treat a bleed, even if the subject typically followed a prophylaxis regimen. Only the infusions classified as "Prophylaxis" were counted in this denominator.

End point type	Secondary

End point timeframe:

100 exposure days to study medication (approximately 2 years)

End point values	All Subjects With at Least One Prophylaxis Infusion			
Subject group type	Subject analysis set			
Number of subjects analysed	208			
Units: percentage of bleeding episodes				
number (confidence interval 95%)	0.19 (0.12 to 0.28)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Duration of participation in study (Baseline up to 28 days after last dose of investigational product)

Adverse event reporting additional description:

The same event may appear as both 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 a serious and nonserious event during the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	All Subjects

Reporting group description:

The primary safety analysis was performed on all subjects who received at least 1 dose of ReFacto AF.

Serious adverse events	All Subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 208 (9.62%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Anti factor VIII antibody positive			
subjects affected / exposed	1 / 208 (0.48%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	1 / 208 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tooth fracture			
subjects affected / exposed	1 / 208 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			

Hypertension			
subjects affected / exposed	1 / 208 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 208 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 208 (0.48%)		
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	5 / 208 (2.40%)		
occurrences causally related to treatment / all	4 / 5		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 208 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 208 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Photophobia			
subjects affected / exposed	1 / 208 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Visual impairment			

subjects affected / exposed	1 / 208 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Acute abdomen			
subjects affected / exposed	1 / 208 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspepsia			
subjects affected / exposed	1 / 208 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematemesis			
subjects affected / exposed	1 / 208 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal haematoma			
subjects affected / exposed	1 / 208 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	1 / 208 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mallory-Weiss syndrome			
subjects affected / exposed	1 / 208 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 208 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Oropharyngeal pain			
subjects affected / exposed	1 / 208 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	1 / 208 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Muscle haemorrhage			
subjects affected / exposed	1 / 208 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal stiffness			
subjects affected / exposed	1 / 208 (0.48%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 208 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	1 / 208 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural infection			
subjects affected / exposed	1 / 208 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic arthritis streptococcal			

subjects affected / exposed	1 / 208 (0.48%)		
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	All Subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	90 / 208 (43.27%)		
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	15 / 208 (7.21%)		
occurrences (all)	25		
Nervous system disorders			
Headache			
subjects affected / exposed	21 / 208 (10.10%)		
occurrences (all)	47		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	26 / 208 (12.50%)		
occurrences (all)	69		
Haemarthrosis			
subjects affected / exposed	24 / 208 (11.54%)		
occurrences (all)	86		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	32 / 208 (15.38%)		
occurrences (all)	44		
Influenza			
subjects affected / exposed	13 / 208 (6.25%)		
occurrences (all)	18		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 May 2009	1) Modification of definition of "clinically significant FVIII inhibitor" to remove any association of this definition with LETEs. 2) Deleted definition of "lack of effect" to disassociate this term with "LETE", so as to allow sites to report lack of effect as an AE. This was independent of occurrences of LETE. 3) Added an exclusion that subjects who have had previous exposure to ReFacto AF were not permitted to participate in this study.
30 August 2010	1) Modified the time specified for the interim analysis. Previously, it was "An interim analysis will be conducted when approximately 50% of the subjects have achieved 50 EDs" and now it is "An interim analysis will be conducted before 2 years of enrollment, when data is available for 50% of the subjects who have achieved 50 EDs".
24 March 2011	1) The efficacy endpoint, number of spontaneous/breakthrough bleeds within 48 hours of a preventive or prophylaxis dose of ReFacto AF, ABR was modified to indicate that all bleeds reported within 48 hours of a prophylaxis dose would be included.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated early by agreement with the EMA (European Medicines Agency) before full recruitment was attained, but this is not considered to affect the overall results and the ability of the study to address its objectives.

Notes: