Clinical trial results:
Randomized, controlled, parallel, prospective trial to evaluate the effect of secondary prophylaxis with rFVIII therapy in severe hemophilia A adult and/or adolescent subjects, as applicable, compared to that of episodic treatment (SPINART)

Summary

EudraCT number	2008-000985-21
Trial protocol	BG
Global end of trial date	22 November 2013

Results information

Result version number	v2 (current)
This version publication date	02 September 2016
First version publication date	03 May 2015
Version creation reason	• New data added to full data set • Correction of full data set Bayer sponsor contact information to be updated

Trial information

Trial identification

Sponsor protocol code	BAY14-2222/12800

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00623480
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.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	22 November 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of secondary prophylaxis on bleeding frequency (number of all bleeds per year) compared to on-demand (episodic) treatment.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Only after the subject voluntarily signed the informed consent form was he able to enter the study. In case of participation of adolescent subjects (12-17 years, in applicable countries), parents/legal representatives were informed first and upon their agreement, the information was presented to the subject. If the subject agreed, the formal consent was collected from parents/legal representatives and the subject.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 March 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 31
Country: Number of subjects enrolled	Romania: 14
Country: Number of subjects enrolled	United States: 54
Country: Number of subjects enrolled	Argentina: 7
Worldwide total number of subjects	106
EEA total number of subjects	45

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	3
Adults (18-64 years)	103
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted between 27 March 2008 (first subject first visit) and 22 November 2013 (last subject last visit) at 31 investigational centers in 4 countries.

Pre-assignment

Screening details:

Out of a total of 106 screened subjects and 84 subjects were randomized to either prophylaxis treatment with Kogenate formulated with sucrose (FS) or on-demand treatment with Kogenate FS using a 1:1 assignment ratio.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Recombinant Factor VIII Prophylaxis treatment

Arm description:

Subjects received 25 international units per kilogram (IU/kg) of Recombinant Factor VIII (Kogenate FS, BAY14-2222) intravenously (IV), 3 times per week. Dose escalation steps by 5 IU/kg (to 30 IU/kg or 35 IU/kg maximum) for subjects exhibiting a bleeding frequency of 12 bleeding episodes per year or greater.

Arm type	Experimental
Investigational medicinal product name	Recombinant Factor VIII
Investigational medicinal product code	BAY14-2222
Other name	Kogenate FS
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received 25 IU/kg of Recombinant Factor VIII (Kogenate FS, BAY14-2222) IV, 3 times per week. Dose escalation steps by 5 IU/kg (to 30 IU/kg or 35 IU/kg maximum) for subjects exhibiting a bleeding frequency of 12 bleeding episodes per year or greater.

Arm title	Recombinant Factor VIII On-demand Treatment

Arm description:

Subjects received Recombinant Factor VIII (Kogenate FS, BAY14-2222) IV for bleeds in accordance with package insert instructions and study physician recommendations.

Arm type	Experimental
Investigational medicinal product name	Recombinant Factor VIII
Investigational medicinal product code	BAY14-2222
Other name	Kogenate FS
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received Recombinant Factor VIII (Kogenate FS, BAY14-2222) IV for bleeds in accordance with package insert instructions and study physician recommendations.

Number of subjects in period 1[1]	Recombinant Factor VIII Prophylaxis treatment	Recombinant Factor VIII On-demand Treatment
Started	42	42
Completed	35	35
Not completed	7	7
Consent withdrawn by subject	2	4
Site closed by sponsor	-	1
Protocol violation	-	1
Non-compliant with study medication	4	-
Lost to follow-up	-	1
Lack of efficacy	1	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: All enrolled subjects were not treated with study drugs. As baseline included only treated subjects, the worldwide number enrolled in the trial differs with the number of subjects reported in the baseline period.

Baseline characteristics

Reporting groups	
Reporting group title	Recombinant Factor VIII Prophylaxis treatment
Reporting group description:	
Subjects received 25 international units per kilogram (IU/kg) of Recombinant Factor VIII (Kogenate FS, BAY14-2222) intravenously (IV), 3 times per week. Dose escalation steps by 5 IU/kg (to 30 IU/kg or 35 IU/kg maximum) for subjects exhibiting a bleeding frequency of 12 bleeding episodes per year or greater.	
Reporting group title	Recombinant Factor VIII On-demand Treatment
Reporting group description:	
Subjects received Recombinant Factor VIII (Kogenate FS, BAY14-2222) IV for bleeds in accordance with package insert instructions and study physician recommendations.	

Reporting group values	Recombinant Factor VIII Prophylaxis treatment	Recombinant Factor VIII On-demand Treatment	Total
Number of subjects	42	42	84
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	30.6	30.7	
standard deviation	± 8.8	± 9.7	-
Gender categorical			
Units: Subjects			
Male	42	42	84
Number of subjects with target joints			
A 'target joint' is a particular joint that has experienced repeated bleeds or at least four bleeds into one joint within a six month period.			
Units: Subjects			
Yes	28	31	59
No	14	11	25
Number of bleeds during last 6 months			
Units: Bleeds			
arithmetic mean	10	12.2	
standard deviation	± 4.4	± 5.1	-

End points

End points reporting groups

Reporting group title	Recombinant Factor VIII Prophylaxis treatment

Reporting group description:

Subjects received 25 international units per kilogram (IU/kg) of Recombinant Factor VIII (Kogenate FS, BAY14-2222) intravenously (IV), 3 times per week. Dose escalation steps by 5 IU/kg (to 30 IU/kg or 35 IU/kg maximum) for subjects exhibiting a bleeding frequency of 12 bleeding episodes per year or greater.

Reporting group title	Recombinant Factor VIII On-demand Treatment

Reporting group description:

Subjects received Recombinant Factor VIII (Kogenate FS, BAY14-2222) IV for bleeds in accordance with package insert instructions and study physician recommendations.

Primary: Bleeding Frequency (Number of Total Bleeds)

End point title	Bleeding Frequency (Number of Total Bleeds)

End point description:

End point type	Primary

End point timeframe:

After the last enrolled subject has been in the study for 1 year. At the cut-off, the median follow-up duration was 616 days (minimum was 111 days and maximum was 1109 days)

End point values	Recombinant Factor VIII Prophylaxis treatment	Recombinant Factor VIII On-demand Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[1]	42[2]		
Units: bleeds				
median (full range (min-max))	0 (0 to 57)	54.5 (0 to 149)		

Notes:

[1] - The intent-to-treat (ITT) population included all randomized subjects who received any study drug

[2] - The ITT population included all randomized subjects who received any study drug

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Recombinant Factor VIII On-demand Treatment v Recombinant Factor VIII Prophylaxis treatment
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Negative Binomial Regression Model
Parameter estimate	Ratio
Point estimate	14.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	8.1
upper limit	26.5

Notes:

[3] - Adjusted for time of follow-up.

Secondary: Change From Baseline to 3 Years in the MRI (Magnetic Resonance Imaging) Scale

End point title	Change From Baseline to 3 Years in the MRI (Magnetic Resonance Imaging) Scale

End point description:

The Extended MRI Scale total score had a range between 0 (normal unaffected joint) to 45 (maximal joint damage) points. It was composed of 2 domains, the soft tissue domain with a maximum of 9 points and the osteochondral domain with a maximum of 36 points. A single score for each subject was to be calculated from the sum of both domains and the average over all joints for the Extended MRI endpoint. Higher MRI score denotes greater joint structure damage thus a positive change from baseline means worsening.

End point type	Secondary

End point timeframe:

Baseline and 3 years

End point values	Recombinant Factor VIII Prophylaxis treatment	Recombinant Factor VIII On-demand Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[4]	38[5]		
Units: scores on a scale				
least squares mean (confidence interval 95%)	0.79 (0.27 to 1.32)	0.96 (0.34 to 1.58)		

Notes:

[4] - Full analysis set (FAS): all randomized subjects who had a baseline and/or post-baseline measurement

[5] - FAS: all randomized subjects who had a baseline and/or post-baseline measurement

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Recombinant Factor VIII Prophylaxis treatment v Recombinant Factor VIII On-demand Treatment
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6614 [6]
Method	cLDA model
Parameter estimate	Estimated difference
Point estimate	-0.17

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.92
upper limit	0.59

Notes:

[6] - Adjusted for presence/absence of target joint and prior 6 month bleeding frequency

Secondary: Change From Baseline to 3 Years in the Colorado Adult Joint Assessment Scale (CAJAS)

End point title	Change From Baseline to 3 Years in the Colorado Adult Joint Assessment Scale (CAJAS)

End point description:

The total joint score was derived for each of six joints: left and right sides for knees (score: 0-25), ankles (score: 0-25), and elbows (score: 0-21). Higher CAJAS score denotes greater joint structure damage thus a positive change from baseline means worsening. CAJAS total score is the sum of all 6 joints, ranging from 0 (best possible outcome) to 142 (worst possible outcome).

End point type	Secondary

End point timeframe:

Baseline and 3 years

End point values	Recombinant Factor VIII Prophylaxis treatment	Recombinant Factor VIII On-demand Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42[7]	42[8]		
Units: scores on a scale				
least squares mean (confidence interval 95%)	-0.31 (-0.79 to 0.18)	0.63 (0.08 to 1.18)		

Notes:

[7] - FAS: all randomized subjects who had a baseline and/or post-baseline measurement

[8] - FAS: all randomized subjects who had a baseline and/or post-baseline measurement

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Recombinant Factor VIII Prophylaxis treatment v Recombinant Factor VIII On-demand Treatment
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0072 [9]
Method	cLDA model
Parameter estimate	Estimated difference
Point estimate	-0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.61
upper limit	-0.26

Notes:

[9] - Adjusted for presence/absence of target joint and prior 6 month bleeding frequency.

Other pre-specified: Change From Baseline to 3 Years in the Physical Functioning Domain of the Haemo-Quality of Life (QoL)-A

End point title	Change From Baseline to 3 Years in the Physical Functioning Domain of the Haemo-Quality of Life (QoL)-A

End point description:

The Haemo-QoL-A total score as well as each of its domains have a range between 0 (worst QoL) and 100 (best QoL) points. Therefore, a higher Haemo-QoL-A score denotes greater QoL.

End point type	Other pre-specified

End point timeframe:

Baseline and 3 years

End point values	Recombinant Factor VIII Prophylaxis treatment	Recombinant Factor VIII On-demand Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41[10]	42[11]		
Units: scores on a scale				
least squares mean (confidence interval 95%)	7.86 (1.79 to 13.92)	-5.3 (-11.97 to 1.37)		

Notes:

[10] - FAS: all randomized subjects who had a baseline and/or post-baseline measurement

[11] - FAS: all randomized subjects who had a baseline and/or post-baseline measurement

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Recombinant Factor VIII Prophylaxis treatment v Recombinant Factor VIII On-demand Treatment
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
Method	cLDA model
Parameter estimate	Estimated difference
Point estimate	13.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.23
upper limit	21.08

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization until Month 37

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Recombinant Factor VIII Prophylaxis treatment

Reporting group description:

Subjects received 25 international units per kilogram (IU/kg) of Recombinant Factor VIII (Kogenate FS, BAY14-2222) intravenously (IV), 3 times per week. Dose escalation steps by 5 IU/kg (to 30 IU/kg or 35 IU/kg maximum) for subjects exhibiting a bleeding frequency of 12 bleeding episodes per year or greater.

Reporting group title	Recombinant Factor VIII On-demand Treatment

Reporting group description:

Subjects received Recombinant Factor VIII (Kogenate FS, BAY14-2222) IV for bleeds in accordance with package insert instructions and study physician recommendations.

Serious adverse events	Recombinant Factor VIII Prophylaxis treatment	Recombinant Factor VIII On-demand Treatment	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 42 (21.43%)	10 / 42 (23.81%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stab wound			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Tibia fracture			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Migraine			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Peritoneal haemorrhage			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haematoma			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth impacted			

subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Balanitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	0 / 42 (0.00%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint lock			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint contracture			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint range of motion decreased			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle haemorrhage			

subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	2 / 42 (4.76%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal cyst			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Recombinant Factor VIII Prophylaxis treatment	Recombinant Factor VIII On-demand Treatment	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 42 (30.95%)	27 / 42 (64.29%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 42 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 42 (4.76%)	7 / 42 (16.67%)	
occurrences (all)	2	12	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 42 (2.38%)	5 / 42 (11.90%)	
occurrences (all)	2	6	
Gastrointestinal disorders			
Dental caries			
subjects affected / exposed	0 / 42 (0.00%)	4 / 42 (9.52%)	
occurrences (all)	0	4	
Dyspepsia			
subjects affected / exposed	0 / 42 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	
Toothache			
subjects affected / exposed	3 / 42 (7.14%)	2 / 42 (4.76%)	
occurrences (all)	3	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 42 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 42 (11.90%)	5 / 42 (11.90%)	
occurrences (all)	7	5	
Back pain			
subjects affected / exposed	1 / 42 (2.38%)	4 / 42 (9.52%)	
occurrences (all)	1	5	

Myalgia			
subjects affected / exposed	3 / 42 (7.14%)	1 / 42 (2.38%)	
occurrences (all)	3	1	
Infections and infestations			
Influenza			
subjects affected / exposed	2 / 42 (4.76%)	7 / 42 (16.67%)	
occurrences (all)	2	7	
Nasopharyngitis			
subjects affected / exposed	2 / 42 (4.76%)	9 / 42 (21.43%)	
occurrences (all)	2	10	
Pharyngitis			
subjects affected / exposed	0 / 42 (0.00%)	4 / 42 (9.52%)	
occurrences (all)	0	5	
Upper respiratory tract infection			
subjects affected / exposed	2 / 42 (4.76%)	3 / 42 (7.14%)	
occurrences (all)	2	4	
Metabolism and nutrition disorders			
Vitamin D deficiency			
subjects affected / exposed	0 / 42 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 September 2008	Age listed on inclusion criteria changed from 25-50 to 20-50 years. Requirements for some study procedures were clarified, including joint assessment and timing of MRIs.
09 January 2009	Added countries and increased the number of investigational centers. Exclusion criteria for poor joint status was clarified. Data Monitoring Committee description was added.
05 November 2009	Allowed for changes in Inlcusion/Exclusion criteria: subjects were included who experienced more frequent bleeding events, more severe joint damage, as well as the existence of a single transient FVIII inhibitor more than 10 years prior to enrollment into the trial. Maximum limit of 12 subjects per site was removed. Elimination of the dose adjustment for subjects with a body mass index of greater than 30 in order to prevent suboptimal dosing resulting in a trough level that may fall below the target level of 1 percent for effective prophylaxis of spontaneous bleeding. Elimination of the requirement of a follow-up MRI for those subjects who discontinued the study prior to 18 months from the time of their enrollment.
22 November 2011	Changes in the primary and secondary objectives and inclusion and exclusion criteria. Requirement of recruitment limit per site was removed. Details of assessments were revised and endpoints were clarified. Elimination of the requirement of a follow-up MRI for those subjects who discontinued the study prior to 18 months from the time of their enrollment. Quality of life measurements were updated. Two new instruments for assessments of hypersensitivity and lack of drug effect were added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported