Clinical trial results:
A diagnostic interventional, controlled, cross-sectional evaluation of joint status using MRI in subjects with severe hemophilia A treated with primary prophylaxis, secondary prophylaxis, or on-demand therapy

Summary

EudraCT number	2009-010147-14
Trial protocol	DE GB GR ES IT
Global end of trial date	31 December 2010

Results information

Result version number	v1 (current)
This version publication date	22 July 2016
First version publication date	22 July 2016

Trial information

Trial identification

Sponsor protocol code	BAY14-2222/12948

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00927667
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 April 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 December 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate bone and cartilage damage at different ages using magnetic resonance imaging (MRI) in four index joints of subjects with severe hemophilia A in relation to previous treatment schedule of primary or secondary prophylaxis with start at different ages, comparing to subjects who received only on-demand therapy.

Protection of trial subjects:

The conduct of this investigation met all local legal and regulatory requirements. The investigation was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization (ICH) guideline E6: Good Clinical Practice (GCP). Three different versions of informed consent forms (1 for test subjects, 1 for minors, and 1 for adults or legal representatives of minors) explaining the procedures of the investigation including the potential hazards were reviewed and approved by the IEC/IRB before their use. Before entering the investigation, the informed consent form was read by and explained to all subjects or their legally authorized representative. Each subject had ample opportunity to ask questions and was assured of the right to withdraw from the investigation at any time without any disadvantage and without having to provide a reason for this decision.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 June 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	Germany: 66
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Greece: 20
Country: Number of subjects enrolled	Italy: 22
Country: Number of subjects enrolled	Sweden: 10
Worldwide total number of subjects	129
EEA total number of subjects	129

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)	11
Adults (18-64 years)	118
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at fifteen study center in Germany, Greece, Italy, Spain, Sweden, United Kingdom, from 09 JUN 2009 (first subject first visit) to 31 DEC 2010 (last subject last visit).

Pre-assignment

Screening details:

In addition to 28 test subjects who underwent MRIs for the quality assessment of MRIs at each center, a total of 129 investigational subjects were recruited. All investigational subjects underwent the MRIs on 1 study Visit. 11 of all recruited subjects were excluded from the Per-protocol (PP) population due to major protocol deviation.

Period 1

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

Blinding implementation details:

Blinding was applicable to analysis of MRIs only. Central readers were blinded to bleeding and treatment history.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1

Arm description:

Subjects with a history of treatment using primary prophylaxis (starting before the age of 2 years and prior to the occurrence of a second joint bleed) and continuing for at least 10 years and presently on prophylaxis therapy without any therapy interruption or missing documentation for more than 12 consecutive months.

Arm type	Experimental
Investigational medicinal product name	Recombinant FVIII (rFVIII) or plasma-derived FVIII (pdFVIII) products
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Regular prophylaxis treatment for hemophilia. No interventional drug was administered in the study.

Arm title	Group 2

Arm description:

Subjects with a history of prophylactic treatment starting between the age of 2 to less than 6 years and after the occurrence of at least one joint bleed, continuing for at least 10 years and presently on prophylaxis therapy without any therapy interruption or missing documentation for more than 12 consecutive months.

Arm type	Experimental
Investigational medicinal product name	Recombinant FVIII (rFVIII) or plasma-derived FVIII (pdFVIII) products
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Regular prophylaxis treatment for hemophilia. No interventional drug was administered in the study.

Arm title	Group 3

Arm description:

Subjects with a history of prophylactic treatment starting between the age of 6 to less than 12 years and continuing for at least 10 years and presently on prophylaxis therapy without any therapy interruption or missing documentation for more than 12 consecutive months

Arm type	Experimental
Investigational medicinal product name	Recombinant FVIII (rFVIII) or plasma-derived FVIII (pdFVIII) products
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Regular prophylaxis treatment for hemophilia. No interventional drug was administered in the study.

Arm title	Group 4

Arm description:

Subjects with a history of prophylactic treatment starting between the age of 12 to 18 years and continuing for at least 10 years and presently on prophylaxis therapy without any therapy interruption or missing documentation for more than 12 consecutive months.

Arm type	Experimental
Investigational medicinal product name	Recombinant FVIII (rFVIII) or plasma-derived FVIII (pdFVIII) products
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Regular prophylaxis treatment for hemophilia. No interventional drug was administered in the study.

Arm title	Group 5

Arm description:

Subjects with a history of only on-demand treatment (ie, received never a regimen of regular prophylactic FVIII therapy lasting longer than 8 consecutive months) with more than 12 bleeds/year in the previous 5 years.

Arm type	Experimental
Investigational medicinal product name	Recombinant FVIII (rFVIII) or plasma-derived FVIII (pdFVIII) products
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Regular on-demand treatment for hemophilia. No interventional drug was administered in the study.

Number of subjects in period 1	Group 1	Group 2	Group 3
Started	27	24	27
Completed	27	24	27

Number of subjects in period 1	Group 4	Group 5

Started	23	28
Completed	23	28

Baseline characteristics

Reporting groups	
Reporting group title	Group 1
Reporting group description:	
Subjects with a history of treatment using primary prophylaxis (starting before the age of 2 years and prior to the occurrence of a second joint bleed) and continuing for at least 10 years and presently on prophylaxis therapy without any therapy interruption or missing documentation for more than 12 consecutive months.	
Reporting group title	Group 2
Reporting group description:	
Subjects with a history of prophylactic treatment starting between the age of 2 to less than 6 years and after the occurrence of at least one joint bleed, continuing for at least 10 years and presently on prophylaxis therapy without any therapy interruption or missing documentation for more than 12 consecutive months.	
Reporting group title	Group 3
Reporting group description:	
Subjects with a history of prophylactic treatment starting between the age of 6 to less than 12 years and continuing for at least 10 years and presently on prophylaxis therapy without any therapy interruption or missing documentation for more than 12 consecutive months	
Reporting group title	Group 4
Reporting group description:	
Subjects with a history of prophylactic treatment starting between the age of 12 to 18 years and continuing for at least 10 years and presently on prophylaxis therapy without any therapy interruption or missing documentation for more than 12 consecutive months.	
Reporting group title	Group 5
Reporting group description:	
Subjects with a history of only on-demand treatment (ie, received never a regimen of regular prophylactic FVIII therapy lasting longer than 8 consecutive months) with more than 12 bleeds/year in the previous 5 years.	

Reporting group values	Group 1	Group 2	Group 3
Number of subjects	27	24	27
Age categorical Units: Subjects			
12-16	4	4	0
17-21	8	8	12
22-26	10	6	12
27-35	5	6	3
Gender categorical Units: Subjects			
Female	0	0	0
Male	27	24	27

Reporting group values	Group 4	Group 5	Total
Number of subjects	23	28	129
Age categorical Units: Subjects			
12-16	0	0	8
17-21	0	3	31
22-26	8	11	47
27-35	15	14	43

Gender categorical Units: Subjects			
Female	0	0	0
Male	23	28	129

End points

End points reporting groups

Reporting group title	Group 1

Reporting group description:

Subjects with a history of treatment using primary prophylaxis (starting before the age of 2 years and prior to the occurrence of a second joint bleed) and continuing for at least 10 years and presently on prophylaxis therapy without any therapy interruption or missing documentation for more than 12 consecutive months.

Reporting group title	Group 2

Reporting group description:

Subjects with a history of prophylactic treatment starting between the age of 2 to less than 6 years and after the occurrence of at least one joint bleed, continuing for at least 10 years and presently on prophylaxis therapy without any therapy interruption or missing documentation for more than 12 consecutive months.

Reporting group title	Group 3

Reporting group description:

Subjects with a history of prophylactic treatment starting between the age of 6 to less than 12 years and continuing for at least 10 years and presently on prophylaxis therapy without any therapy interruption or missing documentation for more than 12 consecutive months

Reporting group title	Group 4

Reporting group description:

Subjects with a history of prophylactic treatment starting between the age of 12 to 18 years and continuing for at least 10 years and presently on prophylaxis therapy without any therapy interruption or missing documentation for more than 12 consecutive months.

Reporting group title	Group 5

Reporting group description:

Subjects with a history of only on-demand treatment (ie, received never a regimen of regular prophylactic FVIII therapy lasting longer than 8 consecutive months) with more than 12 bleeds/year in the previous 5 years.

Subject analysis set title	Secondary prophylaxis (Group 3 + Group 4)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

In the age group of subjects of 27-35 years, subjects on secondary prophylaxis started at an age between 6-18 years (= Group 3 + Group 4 combined; n=17)

Subject analysis set title	On-demand (Group 5)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

In the age group of subjects of 27-35 years, subjects treated on-demand (n=12).

Subject analysis set title	Per Protocol
Subject analysis set type	Per protocol

Subject analysis set description:

11 of the 129 recruited subjects had at least 1 major protocol deviation and were, therefore, excluded from the PP population, which the primary analysis was based on.

Primary: Maximum ankle MRI Score according to the Additive part of the Compatible MRI Scales

End point title	Maximum ankle MRI Score according to the Additive part of the Compatible MRI Scales[1]

End point description:

A MRI scoring scheme including a 10 step progressive scale and a 20 step additive scale with identical definitions of mutual steps is presented. The progressive (P) score equals the highest value reached with the progressive scale. The additive (A) score equals the sum of points accumulated with the additive scale. The maximum values are 10 and 20, respectively. Higher scores represent worse joint status.

End point type	Primary

End point timeframe:

At MRI visit

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 statistics was performed.

End point values	Secondary prophylaxis (Group 3 + Group 4)	On-demand (Group 5)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	12		
Units: Score				
median (full range (min-max))	16.5 (0 to 20)	18 (2 to 19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Compatible Additive MRI Score a for the maximally affected index joint

End point title	Compatible Additive MRI Score a for the maximally affected index joint

End point description:

4 index joints (2 ankles, 2 knees). '99999' indicates the results were not applicable because no subjects were enrolled in those age groups.

End point type	Secondary

End point timeframe:

At MRI visit

End point values	Group 1	Group 2	Group 3	Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25[2]	22[3]	27[4]	21[5]
Units: Score				
median (full range (min-max))				
12-16	0 (0 to 2)	1 (0 to 18)	99999 (99999 to 99999)	99999 (99999 to 99999)
17-21	0 (0 to 2)	2 (0 to 19)	14 (0 to 17)	99999 (99999 to 99999)
22-26	0 (0 to 9)	16 (0 to 19)	15.5 (0 to 20)	17 (7 to 19)
27-35	0 (0 to 2)	7 (0 to 19)	16 (15 to 16)	18.5 (0 to 20)

Notes:

[2] - PP population

[3] - PP population

[4] - PP population

[5] - PP population

End point values	Group 5			

Subject group type	Reporting group			
Number of subjects analysed	23[6]			
Units: Score				
median (full range (min-max))				
12-16	99999 (99999 to 99999)			
17-21	18 (18 to 18)			
22-26	18 (17 to 20)			
27-35	19 (2 to 20)			

Notes:

[6] - PP population

Statistical analyses

No statistical analyses for this end point

Secondary: Compatible Progressive MRI Score a for the maximally affected index joint

End point title	Compatible Progressive MRI Score a for the maximally affected index joint

End point description:

'99999' indicates the results were not applicable because no subjects were enrolled in those age groups.

End point type	Secondary

End point timeframe:

At MRI visit

End point values	Group 1	Group 2	Group 3	Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25[7]	22[8]	27[9]	21[10]
Units: Score				
median (full range (min-max))				
12-16	0.5 (0 to 4)	2.5 (1 to 10)	99999 (99999 to 99999)	99999 (99999 to 99999)
17-21	0 (0 to 5)	7 (1 to 10)	10 (1 to 10)	99999 (99999 to 99999)
22-26	1 (1 to 9)	10 (1 to 10)	10 (0 to 10)	10 (9 to 10)
27-35	1 (0 to 7)	5.5 (0 to 10)	10 (10 to 10)	10 (0 to 10)

Notes:

[7] - PP population

[8] - PP population

[9] - PP population

[10] - PP population

End point values	Group 5			
Subject group type	Reporting group			
Number of subjects analysed	23[11]			
Units: Score				
median (full range (min-max))				
12-16	99999 (99999 to 99999)			

17-21	10 (10 to 10)			
22-26	10 (10 to 10)			
27-35	10 (4 to 10)			

Notes:

[11] - PP population

Statistical analyses

No statistical analyses for this end point

Secondary: Basic MRI Score a for the maximally affected index joint

End point title	Basic MRI Score a for the maximally affected index joint

End point description:

'99999' indicates the results were not applicable because no subjects were enrolled in those age groups.

End point type	Secondary

End point timeframe:

At MRI visit

End point values	Group 1	Group 2	Group 3	Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25[12]	22[13]	27[14]	21[15]
Units: Score				
median (full range (min-max))				
12-16	0.5 (0 to 3)	2 (1 to 10)	99999 (99999 to 99999)	99999 (99999 to 99999)
17-21	0 (0 to 3)	2 (1 to 11)	7.5 (1 to 11)	99999 (99999 to 99999)
22-26	1 (1 to 8)	8 (1 to 12)	8.5 (0 to 13)	9 (7 to 12)
27-35	1 (0 to 1)	4 (0 to 12)	8 (7 to 9)	10.5 (0 to 15)

Notes:

[12] - PP population

[13] - PP population

[14] - PP population

[15] - PP population

End point values	Group 5			
Subject group type	Reporting group			
Number of subjects analysed	23[16]			
Units: Score				
median (full range (min-max))				
12-16	99999 (99999 to 99999)			
17-21	9 (9 to 9)			
22-26	12 (9 to 14)			
27-35	12.5 (2 to 17)			

Notes:

[16] - PP population

Statistical analyses

No statistical analyses for this end point

Secondary: Extended MRI Score a for the maximally affected index joint

End point title	Extended MRI Score a for the maximally affected index joint

End point description:

'99999' indicates the results were not applicable because no subjects were enrolled in those age groups.

End point type	Secondary

End point timeframe:

At MRI visit

End point values	Group 1	Group 2	Group 3	Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25[17]	22[18]	27[19]	21[20]
Units: Score				
median (full range (min-max))				
12-16	0.5 (0 to 3)	2 (1 to 27)	99999 (99999 to 99999)	99999 (99999 to 99999)
17-21	0 (0 to 3)	2 (1 to 26)	15.5 (1 to 28)	99999 (99999 to 99999)
22-26	1 (1 to 11)	16 (1 to 28)	19.5 (0 to 32)	25 (9 to 29)
27-35	1 (0 to 2)	9.5 (0 to 34)	21 (15 to 21)	27 (0 to 33)

Notes:

[17] - PP population

[18] - PP population

[19] - PP population

[20] - PP population

End point values	Group 5			
Subject group type	Reporting group			
Number of subjects analysed	23[21]			
Units: Score				
median (full range (min-max))				
12-16	99999 (99999 to 99999)			
17-21	25 (25 to 25)			
22-26	27.5 (19 to 37)			
27-35	34 (2 to 43)			

Notes:

[21] - PP population

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized number of joint bleeds in the previous 5 years - All joints

End point title	Annualized number of joint bleeds in the previous 5 years - All joints

End point description:

'99999' indicates the results were not applicable because no subjects were enrolled in those age groups.

End point type	Secondary

End point timeframe:

in previous 5 years

End point values	Group 1	Group 2	Group 3	Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25[22]	22[23]	27[24]	21[25]
Units: Number				
median (full range (min-max))				
12-16	0.3 (0 to 1.4)	4.1 (0.2 to 8.4)	99999 (99999 to 99999)	99999 (99999 to 99999)
17-21	0.1 (0 to 0.6)	0.6 (0 to 14.6)	0.6 (0 to 4)	99999 (99999 to 99999)
22-26	0.4 (0 to 1.4)	0.2 (0 to 0.4)	0.8 (0 to 7.8)	1 (0.2 to 4.6)
27-35	0.2 (0 to 0.4)	0.2 (0 to 4)	1.6 (0.4 to 2)	0.9 (0 to 9.2)

Notes:

[22] - PP population

[23] - PP population

[24] - PP population

[25] - PP population

End point values	Group 5			
Subject group type	Reporting group			
Number of subjects analysed	23[26]			
Units: Number				
median (full range (min-max))				
12-16	99999 (99999 to 99999)			
17-21	10.4 (10.4 to 10.4)			
22-26	14.3 (10.8 to 54.6)			
27-35	13.9 (5.2 to 37.8)			

Notes:

[26] - PP population

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized number of joint bleeds in the previous 5 years - Index joints

End point title	Annualized number of joint bleeds in the previous 5 years - Index joints

End point description:

'99999' indicates the results were not applicable because no subjects were enrolled in those age groups.

End point type	Secondary

End point timeframe:

in the previous 5 years

End point values	Group 1	Group 2	Group 3	Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25[27]	22[28]	27[29]	21[30]
Units: number				
median (full range (min-max))				
12-16	0.1 (0 to 1.2)	2.5 (0 to 4.6)	99999 (99999 to 99999)	99999 (99999 to 99999)
17-21	0 (0 to 0.6)	0.4 (0 to 10.6)	0.5 (0 to 3.6)	99999 (99999 to 99999)
22-26	0.2 (0 to 0.8)	0.2 (0 to 0.2)	0.5 (0 to 4)	0.8 (0.2 to 3.8)
27-35	0.1 (0 to 0.2)	1 (0 to 2)	1.2 (0.4 to 1.6)	0.5 (0 to 8.6)

Notes:

[27] - PP population

[28] - PP population

[29] - PP population

[30] - PP population

End point values	Group 5			
Subject group type	Reporting group			
Number of subjects analysed	23[31]			
Units: number				
median (full range (min-max))				
12-16	99999 (99999 to 99999)			
17-21	6.2 (6.2 to 6.2)			
22-26	10.7 (5.8 to 39.4)			
27-35	9.1 (5.2 to 28.4)			

Notes:

[31] - PP population

Statistical analyses

No statistical analyses for this end point

Secondary: Gilbert Score: Physical examination joint score for the mean of index joints

End point title	Gilbert Score: Physical examination joint score for the mean of index joints

End point description:

The orthopedic examination of the hemophilia subject included evaluation of hemorrhages, pain and joint function. Joint function was evaluated in absence of active bleeding episode by rating each joint (elbows, knees, and ankles) on an 18-point scale: 12 (8 points for elbows) points for physical examination, 3 points for pain and 3 points for bleeding. A joint score of zero (0) reflects a normal, unaffected joint. '99999' indicates the results were not applicable because no subjects were enrolled in those age groups.

End point type	Secondary

End point timeframe:

At Screening / Enrollment visit

End point values	Group 1	Group 2	Group 3	Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25[32]	22[33]	27[34]	21[35]
Units: Score				
median (full range (min-max))				
12-16	0.5 (0 to 6)	2.5 (0 to 5)	99999 (99999 to 99999)	99999 (99999 to 99999)
17-21	0 (0 to 0)	0 (0 to 5)	2 (0 to 11)	99999 (99999 to 99999)
22-26	0 (0 to 4)	0 (0 to 7)	3.5 (0 to 10)	4 (0 to 11)
27-35	0 (0 to 0)	1 (0 to 12)	7 (2 to 12)	5 (0 to 17)

Notes:

[32] - PP population

[33] - PP population

[34] - PP population

[35] - PP population

End point values	Group 5			
Subject group type	Reporting group			
Number of subjects analysed	23[36]			
Units: Score				
median (full range (min-max))				
12-16	99999 (99999 to 99999)			
17-21	0 (0 to 0)			
22-26	7 (2 to 26)			
27-35	6.5 (0 to 22)			

Notes:

[36] - PP population

Statistical analyses

No statistical analyses for this end point

Secondary: Gilbert Score: Physical examination joint score for the mean of six Joints

End point title	Gilbert Score: Physical examination joint score for the mean of six Joints

End point description:

'99999' indicates the results were not applicable because no subjects were enrolled in those age groups.

End point type	Secondary

End point timeframe:

At Screening / Enrollment visit

End point values	Group 1	Group 2	Group 3	Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25[37]	22[38]	27[39]	21[40]
Units: score				
median (full range (min-max))				
12-16	0.5 (0 to 7)	2.5 (0 to 5)	99999 (99999 to 99999)	99999 (99999 to 99999)
17-21	0 (0 to 0)	1 (0 to 6)	2 (0 to 14)	99999 (99999 to 99999)
22-26	0 (0 to 4)	0 (0 to 7)	6 (0 to 13)	4 (0 to 11)
27-35	0 (0 to 0)	3.5 (0 to 20)	9 (2 to 12)	6.5 (0 to 24)

Notes:

[37] - PP population

[38] - PP population

[39] - PP population

[40] - PP population

End point values	Group 5			
Subject group type	Reporting group			
Number of subjects analysed	23[41]			
Units: score				
median (full range (min-max))				
12-16	99999 (99999 to 99999)			
17-21	0 (0 to 0)			
22-26	12.5 (2 to 29)			
27-35	7.5 (0 to 23)			

Notes:

[41] - PP population

Statistical analyses

No statistical analyses for this end point

Secondary: Compatible Additive MRI Score a for the mean of all index joints

End point title	Compatible Additive MRI Score a for the mean of all index joints

End point description:

'99999' indicates the results were not applicable because no subjects were enrolled in those age groups.

End point type	Secondary

End point timeframe:

At MRI visit

End point values	Group 1	Group 2	Group 3	Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25[42]	22[43]	27[44]	21
Units: score				
median (full range (min-max))				
12-16	0 (0 to 0.5)	0.25 (0 to 8.5)	99999 (99999 to 99999)	99999 (99999 to 99999)
17-21	0 (0 to 0.8)	0.5 (0 to 9.3)	4 (0 to 9)	99999 (99999 to 99999)
22-26	0 (0 to 2.8)	4 (0 to 4.8)	5.13 (0 to 13)	8 (1.8 to 12)
27-35	0 (0 to 0.5)	3.5 (0 to 13.3)	4 (3.8 to 7.5)	8.13 (0 to 10.5)

Notes:

[42] - PP population

[43] - PP population

[44] - PP population

End point values	Group 5			
Subject group type	Reporting group			
Number of subjects analysed	23[45]			
Units: score				
median (full range (min-max))				
12-16	99999 (99999 to 99999)			
17-21	7.7 (7.7 to 7.7)			
22-26	11.63 (5.3 to 14.8)			
27-35	13.75 (0.5 to 19.5)			

Notes:

[45] - PP population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From obtaining informed consent until end of study

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13

Reporting groups

Reporting group title	Group 1

Reporting group description:

Subjects with a history of treatment using primary prophylaxis (starting before the age of 2 years and prior to the occurrence of a second joint bleed) and continuing for at least 10 years and presently on prophylaxis therapy without any therapy interruption or missing documentation for more than 12 consecutive months.

Reporting group title	Group 2

Reporting group description:

Subjects with a history of prophylactic treatment starting between the age of 2 to less than 6 years and after the occurrence of at least one joint bleed, continuing for at least 10 years and presently on prophylaxis therapy without any therapy interruption or missing documentation for more than 12 consecutive months.

Reporting group title	Group 3

Reporting group description:

Subjects with a history of prophylactic treatment starting between the age of 6 to less than 12 years and continuing for at least 10 years and presently on prophylaxis therapy without any therapy interruption or missing documentation for more than 12 consecutive months

Reporting group title	Group 4

Reporting group description:

Subjects with a history of prophylactic treatment starting between the age of 12 to 18 years and continuing for at least 10 years and presently on prophylaxis therapy without any therapy interruption or missing documentation for more than 12 consecutive months.

Reporting group title	Group 5

Reporting group description:

Subjects with a history of only on-demand treatment (ie, received never a regimen of regular prophylactic FVIII therapy lasting longer than 8 consecutive months) with more than 12 bleeds/year in the previous 5 years.

Serious adverse events	Group 1	Group 2	Group 3
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	0 / 24 (0.00%)	0 / 27 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	Group 4	Group 5	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 23 (0.00%)	0 / 28 (0.00%)	

number of deaths (all causes) number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Group 1	Group 2	Group 3
Total subjects affected by non-serious adverse events subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	0 / 27 (0.00%)
Infections and infestations Nasopharyngitis subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Group 4	Group 5	
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 23 (0.00%)	0 / 28 (0.00%)	
Infections and infestations Nasopharyngitis subjects affected / exposed	0 / 23 (0.00%)	0 / 28 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 May 2009	A. Coordinating radiologist's name and designation of function corrected B. Observations and measurements at screening and enrollment visit of the test subject completed C. MRI Scale: - two more MRI scales added - number of blinded readers changed from two to three - adjudication procedure in case of discrepancies changed - MRI Scale used for calculation of primary variable changed from Compatible - MRI Scales to Extended MRI scale

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.

Decimal places were automatically truncated if last decimal equals zero.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25470205