Clinical trial results:
A Prospective Study to Evaluate the Effect of rFVIII-FS in Different Prophylactic Regimens on Bleeding Events Frequency and Development of Arthropathy in Previously Treated and Minimally Treated Hemophilia A Pediatric Population

Summary

EudraCT number	2014-005253-39
Trial protocol	Outside EU/EEA
Global end of trial date	28 September 2009

Results information

Result version number	v1
This version publication date	12 July 2016
First version publication date	20 June 2015

Trial information

Trial identification

Sponsor protocol code	BAY14-2222/12684

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00632814
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer HealthCare AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, D-51368, Leverkusen, Germany,
Public contact	Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.com
Scientific contact	Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.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	02 August 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 September 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate and compare the effect of 3 different prophylactic regimens (once per week, twice per week, and three times per week; dose escalation in case of insufficient bleeding protection) on frequency of joint bleeds in severe and moderate pediatric hemophilia A subjects.

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. Before entering the study, the informed consent form was read by and explained to all subjects and/or their legally authorized representatives. Participating subjects and/or their legally authorized representatives signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 June 2007
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	Russian Federation: 32
Worldwide total number of subjects	32
EEA total number of subjects	0

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)	3
Children (2-11 years)	27
Adolescents (12-17 years)	2

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

Subject disposition

Recruitment

Recruitment details:

The recruitment period took from first subject first visit 28 Jun 2007 to last subject first visit 26 Dec 2008. The study period took from first subject first visit 28 Jun 2007 to last subject last visit 28 Sep 2009. All 4 sites were medical clinics. Assignment to a group was based on subjects previous treatment schedule (non-randomized).

Pre-assignment

Screening details:

There was an indefinite time period between screening and baseline. Study treatment started at visit 2 (baseline).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw

Arm description:

rFVIII-FS (Octocog-alfa, antihemophilic factor [recombinant]) 70 international units per kilogram (IU/kg), dosing by injection once per week (qw) (weekly on Day 7 + 1 after previous injection) for 9 months. Dose escalation was permitted due to joint bleeding (escalation to 35 IU/kg twice a week [biw] or further escalation to 25 IU/kg three times a week [tiw]).

Arm type	Experimental
Investigational medicinal product name	Recombinant FVIII formulated with sucrose (rFVIII-FS)
Investigational medicinal product code	BAY14-2222
Other name	Octocog alfa, Kogenate® FS
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

rFVIII-FS (Octocog-alfa, antihemophilic factor [recombinant]) 70 IU/kg, dosing by injection qw (weekly on Day 7 + 1 after previous injection) for 9 months. Dose escalation was permitted due to joint bleeding (escalation to 35 IU/kg biw or further escalation to 25 IU/kg tiw).

Arm title	rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg)

Arm description:

rFVIII-FS (Octocog-alfa, antihemophilic factor [recombinant]) 70 IU/kg, dosing by injection biw (30 IU/kg [day 1] + 40 IU/kg [day 4]) for 9 months. Dose escalation was permitted due to joint bleeding (escalation to 25 IU/kg tiw).

Arm type	Experimental
Investigational medicinal product name	Recombinant FVIII formulated with sucrose (rFVIII-FS)
Investigational medicinal product code	BAY14-2222
Other name	Octocog alfa, Kogenate® FS
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

rFVIII-FS (Octocog-alfa, antihemophilic factor [recombinant]) 70 IU/kg, dosing by injection biw (30 IU/kg [day 1] + 40 IU/kg [day 4]) for 9 months. Dose escalation was permitted due to joint bleeding (escalation to 25 IU/kg tiw).

Arm title	rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg)

Arm description:

rFVIII-FS (Octocog-alfa, antihemophilic factor [recombinant]) 75 IU/kg, dosing by injection tiw (3 x 25 IU/kg [day 1, 3, 5]) for 9 months. No escalation opportunity for subjects in this group.

Arm type	Experimental
Investigational medicinal product name	Recombinant FVIII formulated with sucrose (rFVIII-FS)
Investigational medicinal product code	BAY14-2222
Other name	Octocog alfa, Kogenate® FS
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

rFVIII-FS (Octocog-alfa, antihemophilic factor [recombinant]) 75 IU/kg, dosing by injection tiw (3 x 25 IU/kg [day 1, 3, 5]) for 9 months. No escalation opportunity for subjects in this group.

Number of subjects in period 1	rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw	rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg)	rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg)
Started	11	13	8
Completed	11	13	8

Baseline characteristics

Reporting groups	
Reporting group title	rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw
Reporting group description:	
rFVIII-FS (Octocog-alfa, antihemophilic factor [recombinant]) 70 international units per kilogram (IU/kg), dosing by injection once per week (qw) (weekly on Day 7 + 1 after previous injection) for 9 months. Dose escalation was permitted due to joint bleeding (escalation to 35 IU/kg twice a week [biw] or further escalation to 25 IU/kg three times a week [tiw]).	
Reporting group title	rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg)
Reporting group description:	
rFVIII-FS (Octocog-alfa, antihemophilic factor [recombinant]) 70 IU/kg, dosing by injection biw (30 IU/kg [day 1] + 40 IU/kg [day 4]) for 9 months. Dose escalation was permitted due to joint bleeding (escalation to 25 IU/kg tiw).	
Reporting group title	rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg)
Reporting group description:	
rFVIII-FS (Octocog-alfa, antihemophilic factor [recombinant]) 75 IU/kg, dosing by injection tiw (3 x 25 IU/kg [day 1, 3, 5]) for 9 months. No escalation opportunity for subjects in this group.	

Reporting group values	rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw	rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg)	rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg)
Number of subjects	11	13	8
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	3.27	6.08	6
standard deviation	± 3.2	± 3.5	± 3.12
Gender Categorical Units: subjects			
Male	11	13	8
Ethnicity Units: Subjects			
Caucasian	11	13	7
Asian	0	0	1
Number of subjects on prophylaxis versus on-demand therapy prior to screening			
Number of subjects on prophylaxis versus on-demand therapy before screening			
Units: Subjects			
On demand	9	6	5
Prophylaxis	2	7	3
Number of subjects with different exposure days (ED) Units: Subjects			
0 ED	1	0	0
1 to <20 ED	0	0	0
20 to <100 ED	5	2	4
>=100 ED	5	11	4

Number of subjects with target joint present Units: Subjects			
Target joint present	4	7	7
Target joint absent	7	6	1
Number of subjects with bleeding rates in previous 6-9 Months Units: Subjects			
No bleedings	1	2	0
Any bleedings	10	11	8
Number of subjects with joint bleeding in previous 6-9 Months Units: Subjects			
Any joint bleeding	9	11	6
No joint bleeding	2	2	2
Body weight Units: kilograms			
arithmetic mean	17.48	24.39	25.45
standard deviation	± 10.43	± 11.35	± 9.87
Height Units: centimeters			
arithmetic mean	98.09	120.31	122
standard deviation	± 22.88	± 23.75	± 20.74
FVIII trough level at Baseline Units: percentage of FVIII activity			
arithmetic mean	1.43	1.62	0.78
standard deviation	± 0.7	± 1.79	± 0.24
Stockholm Joint Score			
The assessment of joint function using Stockholm Joint Score. The minimum value is 0 (the best condition), and the maximum value is 140 (the worst condition).			
Units: scores on a scale			
arithmetic mean	3.9	5.9	7.1
standard deviation	± 4.8	± 5.8	± 4.6

Reporting group values	Total		
Number of subjects	32		
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender Categorical Units: subjects			
Male	32		
Ethnicity Units: Subjects			
Caucasian	31		
Asian	1		
Number of subjects on prophylaxis versus on-demand therapy prior to			

screening			
Number of subjects on prophylaxis versus on-demand therapy before screening			
Units: Subjects			
On demand	20		
Prophylaxis	12		
Number of subjects with different exposure days (ED) Units: Subjects			
0 ED	1		
1 to <20 ED	0		
20 to <100 ED	11		
>=100 ED	20		
Number of subjects with target joint present Units: Subjects			
Target joint present	18		
Target joint absent	14		
Number of subjects with bleeding rates in previous 6-9 Months Units: Subjects			
No bleedings	3		
Any bleedings	29		
Number of subjects with joint bleeding in previous 6-9 Months Units: Subjects			
Any joint bleeding	26		
No joint bleeding	6		
Body weight Units: kilograms arithmetic mean standard deviation	--		
Height Units: centimeters arithmetic mean standard deviation	--		
FVIII trough level at Baseline Units: percentage of FVIII activity arithmetic mean standard deviation	--		
Stockholm Joint Score			
The assessment of joint function using Stockholm Joint Score. The minimum value is 0 (the best condition), and the maximum value is 140 (the worst condition).			
Units: scores on a scale arithmetic mean standard deviation	--		

End points

End points reporting groups

Reporting group title	rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw
Reporting group description:	
rFVIII-FS (Octocog-alfa, antihemophilic factor [recombinant]) 70 international units per kilogram (IU/kg), dosing by injection once per week (qw) (weekly on Day 7 + 1 after previous injection) for 9 months. Dose escalation was permitted due to joint bleeding (escalation to 35 IU/kg twice a week [biw] or further escalation to 25 IU/kg three times a week [tiw]).	
Reporting group title	rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg)
Reporting group description:	
rFVIII-FS (Octocog-alfa, antihemophilic factor [recombinant]) 70 IU/kg, dosing by injection biw (30 IU/kg [day 1] + 40 IU/kg [day 4]) for 9 months. Dose escalation was permitted due to joint bleeding (escalation to 25 IU/kg tiw).	
Reporting group title	rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg)
Reporting group description:	
rFVIII-FS (Octocog-alfa, antihemophilic factor [recombinant]) 75 IU/kg, dosing by injection tiw (3 x 25 IU/kg [day 1, 3, 5]) for 9 months. No escalation opportunity for subjects in this group.	

Primary: Percentage of Subjects With Less Than 2 Joint Bleeds During the 9-month Treatment Period

End point title	Percentage of Subjects With Less Than 2 Joint Bleeds During the 9-month Treatment Period[1]
End point description:	
End point type	Primary
End point timeframe:	
Up to 9 months	

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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw	rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg)	rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	13	8	
Units: Percentage of subjects				
number (not applicable)	72.7	84.6	75	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Bleeds per Subject During the 9-month Treatment Period

End point title	Number of Bleeds per Subject During the 9-month Treatment

	Period

End point description:

End point type	Secondary

End point timeframe:

Up to 9 months

End point values	rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw	rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg)	rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	13	8	
Units: bleeds per subject				
median (full range (min-max))				
All bleeds	3 (0 to 12)	2 (0 to 6)	1.5 (0 to 8)	
Joint bleeds	0 (0 to 2)	0 (0 to 3)	0 (0 to 8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Bleeding Events During the 9-month Treatment Period

End point title	Number of Subjects With Bleeding Events During the 9-month Treatment Period

End point description:

End point type	Secondary

End point timeframe:

Up to 9 months

End point values	rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw	rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg)	rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	13	8	
Units: subjects				
number (not applicable)				
no bleeds	3	4	4	
bleeds at all	8	9	4	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Joint Bleeds During the 9-month Treatment Period

End point title	Number of Subjects With Joint Bleeds During the 9-month Treatment Period

End point description:

End point type	Secondary

End point timeframe:

Up to 9 months

End point values	rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw	rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg)	rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	13	8	
Units: subjects				
number (not applicable)				
no bleeds	8	9	6	
bleeds at all	3	4	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects in Each Group at the End of the Study

End point title	Number of Subjects in Each Group at the End of the Study

End point description:

Subjects were allowed to switch treatment groups upon occurrence of joint bleed. Therefore, the number of subjects per group at the end of the study is different from the number of subjects per group at baseline.

End point type	Secondary

End point timeframe:

Up to 9 months

End point values	rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw	rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg)	rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	13	8	
Units: Subjects	8	14	10	

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Monthly rFVIII-FS Consumption

End point title	Actual Monthly rFVIII-FS Consumption

End point description:

End point type	Secondary

End point timeframe:

Up to 9 months

End point values	rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw	rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg)	rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	13	8	
Units: IU/kg				
arithmetic mean (standard deviation)	390.8 (± 106.9)	422.3 (± 138.2)	501.4 (± 241.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Stockholm Hemophilia Joint Score at 9 Months of Treatment

End point title	Change From Baseline in Stockholm Hemophilia Joint Score at 9 Months of Treatment

End point description:

The assessment of joint function using Stockholm Joint Score. The minimum value is 0 (the best condition), and the maximum value is 140 (the worst condition).

End point type	Secondary
End point timeframe: baseline and 9 months	

End point values	rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw	rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg)	rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	13	8	
Units: Scores on a scale				
arithmetic mean (standard deviation)	-1.4 (± 2.4)	-2 (± 4.5)	-1.8 (± 2.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Haemo-Quality of Life (QoL) Standardized Total Score at 9 Months of Treatment (Completed by Subjects in the Total Group)

End point title	Haemo-Quality of Life (QoL) Standardized Total Score at 9 Months of Treatment (Completed by Subjects in the Total Group)
End point description: QoL was measured by the Haemo-QoL standardized total Score, which ranged from 0 (the best condition) to 100 (the worst condition).	
End point type	Secondary
End point timeframe: 9 months	

End point values	rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw	rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg)	rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3[2]	10[3]	7[4]	
Units: Scores on a scale				
arithmetic mean (standard deviation)	30.28 (± 13.09)	39.07 (± 23.5)	30.27 (± 11.95)	

Notes:

[2] - Subjects who completed the questionnaire.

[3] - subjects who completed the questionnaire.

[4] - Subjects who completed the questionnaire.

Statistical analyses

No statistical analyses for this end point

Secondary: Haemo-Quality of Life (QoL) Standardized Total Score (Completed by Parents/Caregivers in the Total Group) at 9 Months of Treatment

End point title	Haemo-Quality of Life (QoL) Standardized Total Score (Completed by Parents/Caregivers in the Total Group) at 9 Months of Treatment

End point description:

QoL was measured by the Haemo-QoL standardized total Score, which ranged from 0 (the best condition) to 100 (the worst condition).

End point type	Secondary

End point timeframe:

9 months

End point values	rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw	rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg)	rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3[5]	10[6]	7[7]	
Units: Scores on a scale				
arithmetic mean (standard deviation)	29.13 (± 17.4)	28.43 (± 10.27)	31.38 (± 13.06)	

Notes:

[5] - Subjects who completed the questionnaire.

[6] - subjects who completed the questionnaire.

[7] - Subjects who completed the questionnaire.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the start of study drug administration until the end of study (9 months +/- 2 weeks)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw

Reporting group description:

rFVIII-FS (Octocog-alfa, antihemophilic factor [recombinant]) 70 IU/kg, dosing by injection once per week [qw] (weekly on Day 7 + 1 after previous injection) for 9 months. Dose escalation was permitted due to joint bleeding (escalation to 35 IU/kg twice a week or further escalation to 25 IU/kg three times a week).

Reporting group title	rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg)

Reporting group description:

rFVIII-FS (Octocog-alfa, antihemophilic factor [recombinant]) 70 IU/kg, dosing by injection twice per week [biw] (30 IU/kg [day 1] + 40 IU/kg [day 4]) for 9 months. Dose escalation was permitted due to joint bleeding (escalation to 25 IU/kg three times a week).

Reporting group title	rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg)

Reporting group description:

rFVIII-FS (Octocog-alfa, antihemophilic factor [recombinant]) 75 IU/kg, dosing by injection three times per week [tiw] (3 x 25 IU/kg [day 1, 3, 5]) for 9 months. No escalation opportunity for subjects in this group.

Serious adverse events	rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw	rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg)	rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 11 (9.09%)	2 / 13 (15.38%)	0 / 8 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Blood and lymphatic system disorders			
FACTOR VIII INHIBITION			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL PAIN			

subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
EAR INFECTION			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY TRACT INFECTION VIRAL			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw	rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg)	rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 11 (36.36%)	3 / 13 (23.08%)	3 / 8 (37.50%)
Injury, poisoning and procedural complications			
LOWER LIMB FRACTURE			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
IRON DEFICIENCY ANAEMIA			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
CHILLS			

subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
PYREXIA			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	4
Respiratory, thoracic and mediastinal disorders			
EPISTAXIS			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
LARYNGOSPASM			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
RESPIRATORY DISORDER			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
DERMATITIS ALLERGIC			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
ADENOIDITIS			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
RESPIRATORY TRACT INFECTION VIRAL			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
TONSILLITIS			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
TUBERCULOSIS			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
VARICELLA			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
YERSINIA INFECTION			

subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 13 (0.00%) 0	1 / 8 (12.50%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 December 2006	Modification of the study design from a single-center study into a multicenter study with 3 study centers. 1. The number of subjects to be enrolled was increased from 20 to 40. 2. The planned enrolment period was extended from 3 months to 8 months. 3. An additional vial size containing 1000 IU FVIII/milliliter was introduced. 4. It was specified that the sterile water for injection was provided in a prefilled syringe in the treatment kit.
22 September 2008	1. The number of study centers was increased from 3 to 6. 2. The number of subjects to be enrolled was reduced from 40 to 36 in order to balance the sizes of the 3 treatment groups (12 per treatment group).

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.

Protocol deviations were not excluded: For example, a previously untreated subject developed the transitory inhibitor; change to a higher group did not always occur according protocol; there was temporary lack of smaller vial sizes at the centers.

Notes: