Clinical trial results:
Randomized, active-controlled, double-blind, parallel design study to evaluate the efficacy and safety of a once-a-week prophylaxis treatment with BAY79-4980 compared to three times-per-week prophylaxis with rFVIII-FS in previously treated patients with severe hemophilia A

Summary

EudraCT number	2007-003718-32
Trial protocol	DE FR NL DK ES BE AT GB IT NO
Global end of trial date	05 October 2010

Results information

Result version number	v1
This version publication date	12 July 2016
First version publication date	03 May 2015

Trial information

Trial identification

Sponsor protocol code	BAY79-4980/12781

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00623727
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer HealthCare AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, D-51368, 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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 October 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 October 2010
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the effect of a once-a-week prophylaxis regimen with BAY79-4980 on the protection from total bleeds compared to a three times-per-week prophylaxis regimen with recombinant factor VIII formulated with sucrose (rFVIII-FS).

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. An independent Data and Safety Monitoring Board (DSMB) supervised the subjects' safety and performed the pre-specified interim analyses according to the protocol. Before entering the study, the informed consent form was read by and explained to all subjects and/or their legally authorized representative. Participating subjects 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. A Data and Safety Monitoring Board supervised the safety of study subjects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 June 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Poland: 28
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Croatia: 3
Country: Number of subjects enrolled	Israel: 18
Country: Number of subjects enrolled	Germany: 8

Country: Number of subjects enrolled	United States: 36
Country: Number of subjects enrolled	Belgium: 2
Worldwide total number of subjects	143
EEA total number of subjects	86

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)	5
Adults (18-64 years)	138
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Previously treated subjects with severe hemophilia A [less than (<) 1 percent (%) Factor VIII (FVIII)], who were currently on on-demand or secondary prophylaxis treatment with any FVIII for greater than or equal to (>=)150 exposure days with documented bleeds/injections during the last 6 months prior to study entry could participate in the study.

Pre-assignment

Screening details:

Of 168 enrolled subjects, 25 failed screening.

Period 1

Period 1 title	Double blind (DB)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	rFVIII-FS/Pegylated Liposomes (BAY79-4980)

Arm description:

35 international units per kilogram (IU/kg) body weight of BAY79-4980 1x/week plus 2 dummy injections/week [dummy = rFVIII-FS excipient reconstituted in sterile water for injection (WFI)].

Arm type	Experimental
Investigational medicinal product name	rFVIII-FS/Pegylated Liposomes
Investigational medicinal product code	BAY79-4980
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

35 IU/kg body weight of BAY79-4980 1x/week.

Investigational medicinal product name	Placebo injection: placebo/WFI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Two placebo injections/week (dummy injections for blinding purposes) containing excipient of rFVIII-FS (packed with WFI solvent for reconstitution).

Arm title	rFVIII-FS/WFI (BAY14-2222)

Arm description:

25 IU/kg body weight of rFVIII-FS 3x/week [employing 1% POPC-alone liposome (rFVIII-FS-POPC) as blinding agent used for first weekly injection and rFVIII-FS in WFI for 2nd and 3rd injection].

Arm type	Active comparator
Investigational medicinal product name	rFVIII-FS/WFI
Investigational medicinal product code	BAY14-2222
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

25 IU/kg body weight of rFVIII-FS 3x/week [employing 1% POPC-alone liposome (rFVIII-FS-POPC) as blinding agent used for first weekly injection and rFVIII-FS in WFI for 2nd and 3rd injection].

Number of subjects in period 1	rFVIII-FS/Pegylated Liposomes (BAY79-4980)	rFVIII-FS/WFI (BAY14-2222)
Started	70	73
Participants received treatment	67	72
Completed	34	41
Not completed	36	32
Consent withdrawn by subject	8	2
Physician decision	-	1
Protocol violation	2	2
Termination of the double-blind period	22	21
Adverse event	1	3
Lost to follow-up	1	1
Lack of efficacy	2	2

Period 2

Period 2 title	Open label
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	rFVIII-FS/WFI (BAY14-2222): Follow up

Arm description:

Few subjects of each group after DB period terminated were entered in to the open label follow up period and received 25 IU/kg body weight of rFVIII-FS 3x/week [employing 1% POPC-alone liposome (rFVIII-FS-POPC) as blinding agent used for first weekly injection and rFVIII-FS in WFI for 2nd and 3rd injection] for a period of 6 months or until completion of 12 months trial participation.

Arm type	Active comparator
Investigational medicinal product name	rFVIII-FS/WFI
Investigational medicinal product code	BAY14-2222
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

25 IU/kg body weight of rFVIII-FS 3x/week [employing 1% POPC-alone liposome (rFVIII-FS-POPC) as blinding agent used for first weekly injection and rFVIII-FS in WFI for 2nd and 3rd injection].

Arm title	rFVIII-FS/Pegylated Liposomes (BAY79-4980): Extension period

Arm description:

Ten subjects of each group entered open-label extension period after completion of DB study and received 35 IU/kg body weight of BAY79-4980 1x/week.

Arm type	Experimental
Investigational medicinal product name	rFVIII-FS/Pegylated Liposomes
Investigational medicinal product code	BAY79-4980
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

35 IU/kg body weight of BAY79-4980 1x/week.

Number of subjects in period 2[1]	rFVIII-FS/WFI (BAY14-2222): Follow up	rFVIII-FS/Pegylated Liposomes (BAY79-4980): Extension period
Started	26	20
Completed	18	20
Not completed	8	0
Consent withdrawn by subject	1	-
Subject convenience	1	-
Study termination	6	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Subjects who completed double blind treatment, were offered continuation of open label treatment and due to the early termination of the double-blind study phase, subjects who had not completed double blind treatment were offered continuation in control arm (follow up phase). Hence, the number of subjects starting the period is not consistent with the number completing the preceding period.

Period 3

Period 3 title	Baseline period
Is this the baseline period?	Yes[2]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Carer, Assessor, Subject, Investigator

Arms

Are arms mutually exclusive?	No

Arm title	rFVIII-FS/Pegylated Liposomes (BAY79-4980)

Arm description:

35 IU/kg body weight of BAY79-4980 1x/week plus 2 dummy injections/week (dummy = rFVIII-FS excipient reconstituted in WFI). Subjects who received treatment were included in baseline period.

Arm type	Experimental
Investigational medicinal product name	rFVIII-FS/Pegylated Liposomes
Investigational medicinal product code	BAY79-4980
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

35 IU/kg body weight of BAY79-4980 1x/week plus 2 dummy injections/week (dummy = rFVIII-FS excipient reconstituted in WFI). Subjects who received treatment were included in baseline period.

Arm title	rFVIII-FS/WFI (BAY14-2222)

Arm description:

25 IU/kg body weight of rFVIII-FS 3x/week [employing 1% POPC-alone liposome (rFVIII-FS-POPC) as blinding agent used for first weekly injection and rFVIII-FS in WFI for 2nd and 3rd injection]. Subjects who received treatment were included in baseline period.

Arm type	Active comparator
Investigational medicinal product name	rFVIII-FS/WFI
Investigational medicinal product code	BAY14-2222
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

25 IU/kg body weight of rFVIII-FS 3x/week [employing 1% POPC-alone liposome (rFVIII-FS-POPC) as blinding agent used for first weekly injection and rFVIII-FS in WFI for 2nd and 3rd injection].

Notes:

[2] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: In overall trial, subjects who were randomized included and the baseline characteristics were provided for only subjects who were treated. Hence, the baseline period of treated subjects was created to publish the baseline characteristics data.

Number of subjects in period 3	rFVIII-FS/Pegylated Liposomes (BAY79-4980)	rFVIII-FS/WFI (BAY14-2222)
Started	67	72
Completed	67	72

Baseline characteristics

Reporting groups[1]	
Reporting group title	rFVIII-FS/Pegylated Liposomes (BAY79-4980)
Reporting group description:	
35 IU/kg body weight of BAY79-4980 1x/week plus 2 dummy injections/week (dummy = rFVIII-FS excipient reconstituted in WFI). Subjects who received treatment were included in baseline period.	
Reporting group title	rFVIII-FS/WFI (BAY14-2222)
Reporting group description:	
25 IU/kg body weight of rFVIII-FS 3x/week [employing 1% POPC-alone liposome (rFVIII-FS-POPC) as blinding agent used for first weekly injection and rFVIII-FS in WFI for 2nd and 3rd injection]. Subjects who received treatment were included in baseline period.	

Notes:

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

Reporting group values	rFVIII-FS/Pegylated Liposomes (BAY79-4980)	rFVIII-FS/WFI (BAY14-2222)	Total
Number of subjects	67	72	139
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	33	34.1	
standard deviation	± 11.3	± 13	-
Gender categorical Units: Subjects			
Male	67	72	139
Target joint			
The presence or absence of target joints (defined as joints with at least 3 bleeds into the same joint within 6 months) was evaluated.			
Units: Subjects			
Yes	54	56	110
No	13	16	29
Previous treatment			
Previous treatment was categorized as prophylaxis versus on demand.			
Units: Subjects			
On demand	35	44	79
Prophylaxis	32	28	60

End points

End points reporting groups

Reporting group title	rFVIII-FS/Pegylated Liposomes (BAY79-4980)

Reporting group description:

35 international units per kilogram (IU/kg) body weight of BAY79-4980 1x/week plus 2 dummy injections/week [dummy = rFVIII-FS excipient reconstituted in sterile water for injection (WFI)].

Reporting group title	rFVIII-FS/WFI (BAY14-2222)

Reporting group description:

25 IU/kg body weight of rFVIII-FS 3x/week [employing 1% POPC-alone liposome (rFVIII-FS-POPC) as blinding agent used for first weekly injection and rFVIII-FS in WFI for 2nd and 3rd injection].

Reporting group title	rFVIII-FS/WFI (BAY14-2222): Follow up

Reporting group description:

Few subjects of each group after DB period terminated were entered in to the open label follow up period and received 25 IU/kg body weight of rFVIII-FS 3x/week [employing 1% POPC-alone liposome (rFVIII-FS-POPC) as blinding agent used for first weekly injection and rFVIII-FS in WFI for 2nd and 3rd injection] for a period of 6 months or until completion of 12 months trial participation.

Reporting group title	rFVIII-FS/Pegylated Liposomes (BAY79-4980): Extension period

Reporting group description:

Ten subjects of each group entered open-label extension period after completion of DB study and received 35 IU/kg body weight of BAY79-4980 1x/week.

Reporting group title	rFVIII-FS/Pegylated Liposomes (BAY79-4980)

Reporting group description:

35 IU/kg body weight of BAY79-4980 1x/week plus 2 dummy injections/week (dummy = rFVIII-FS excipient reconstituted in WFI). Subjects who received treatment were included in baseline period.

Reporting group title	rFVIII-FS/WFI (BAY14-2222)

Reporting group description:

25 IU/kg body weight of rFVIII-FS 3x/week [employing 1% POPC-alone liposome (rFVIII-FS-POPC) as blinding agent used for first weekly injection and rFVIII-FS in WFI for 2nd and 3rd injection]. Subjects who received treatment were included in baseline period.

Subject analysis set title	Per protocol (PP) population
Subject analysis set type	Per protocol

Subject analysis set description:

PP population included those subjects of the ITT population in whom no major protocol violations were identified.

Subject analysis set title	Intent-to-treat (ITT) population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

ITT population included all subjects randomized into the study who received study drug.

Subject analysis set title	rFVIII-FS/pegylated liposomes (subgroup)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects who completed open label extension period.

Primary: Percentage of Subjects With Less Than 9 Total Bleeds per Year

End point title	Percentage of Subjects With Less Than 9 Total Bleeds per

End point description:

Bleeds occurring on the same day were counted as one bleeding event. Bleeds occurring within 72 hours into the same location were also counted as one bleeding event.

End point type	Primary

End point timeframe:

Up to one year

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: Statistical analysis was not performed since descriptive statistical analysis was only planned for this endpoint due to the premature termination of the study.

End point values	rFVIII-FS/Pegylated Liposomes (BAY79-4980)	rFVIII-FS/WFI (BAY14-2222)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63[2]	68[3]		
Units: percentage of subjects				
number (not applicable)	38.1	72.1		

Notes:

[2] - PP population

[3] - PP population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Less Than 5 Joint Bleeds per Year

End point title	Percentage of Subjects With Less Than 5 Joint Bleeds per Year

End point description:

Bleeds occurring on the same day were counted as one bleeding event. Bleeds occurring within 72 hours into the same location were also counted as one bleeding event.

End point type	Secondary

End point timeframe:

Up to one year

End point values	rFVIII-FS/Pegylated Liposomes (BAY79-4980)	rFVIII-FS/WFI (BAY14-2222)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63[4]	68[5]		
Units: percentage of subjects				
number (not applicable)	38.1	63.2		

Notes:

[4] - PP population

[5] - PP population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Joint Bleeds per Subject per Year in Responders

End point title	Number of Joint Bleeds per Subject per Year in Responders

End point description:

Bleeds occurring on the same day were counted as one bleeding event. Bleeds occurring within 72 hours into the same location were also counted as one bleeding event. Responders were the subjects with less than 9 total bleeds per year.

End point type	Secondary

End point timeframe:

Up to one year

End point values	rFVIII-FS/Pegylated Liposomes (BAY79-4980)	rFVIII-FS/WFI (BAY14-2222)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[6]	49[7]		
Units: joint bleeds per year				
median (full range (min-max))	2.341 (0 to 8.91)	0 (0 to 7.59)		

Notes:

[6] - PP population included subjects with less than 9 total bleeds per year.

[7] - PP population included subjects with less than 9 total bleeds per year.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Bleeds per Year

End point title	Number of Bleeds per Year

End point description:

Bleeds occurring on the same day were counted as one bleeding event. Bleeds occurring within 72 hours into the same location were also counted as one bleeding event. Number of bleeds 3 weeks after the first infusion per 12 months.

End point type	Other pre-specified

End point timeframe:

Up to one year

End point values	rFVIII-FS/Pegylated Liposomes (BAY79-4980)	rFVIII-FS/WFI (BAY14-2222)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63[8]	68[9]		
Units: bleeds per year				
median (full range (min-max))	9.96 (0 to 72.2)	2.2 (0 to 22.8)		

Notes:

[8] - PP population

[9] - PP population

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Bleeds Treated by Various Numbers of Injections

End point title	Percentage of Bleeds Treated by Various Numbers of Injections

End point description:

Bleeds occurring on the same day were counted as one bleeding event. Bleeds occurring within 72 hours into the same location were also counted as one bleeding event.

End point type	Other pre-specified

End point timeframe:

Up to one year

End point values	rFVIII-FS/Pegylated Liposomes (BAY79-4980)	rFVIII-FS/WFI (BAY14-2222)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63[10]	68[11]		
Units: percentage of bleeds				
number (not applicable)				
1-2 injections	88.5	93		
1 injection	73.2	81.7		
2 injections	15.3	11.3		
3 injections	6.5	2.3		
>3 injections	5	4.7		

Notes:

[10] - PP population

[11] - PP population

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Total rFVIII Consumption per Year

End point title	Total rFVIII Consumption per Year

End point description:

Total number of units per kg of study medication (rFVIII) administered to participant for one year. rFVIII is recombinant factor VIII, factor VIII is functional coagulation factor

End point type	Other pre-specified

End point timeframe:

Up to one year

End point values	rFVIII-FS/Pegylated Liposomes (BAY79-4980)	rFVIII-FS/WFI (BAY14-2222)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67[12]	72[13]		
Units: IU per kg				
median (full range (min-max))	2524 (1580 to	4378 (3701 to		

	11788)	12789)

Notes:

[12] - ITT population

[13] - ITT population

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects With Less Than 9 Total Bleeds per Year in the Open Label Extension Period

End point title	Percentage of Subjects With Less Than 9 Total Bleeds per Year in the Open Label Extension Period

End point description:

Bleeds occurring on the same day were counted as one bleeding event. Bleeds occurring within 72 hours into the same location were also counted as one bleeding event.

End point type	Other pre-specified

End point timeframe:

6 months after start of open label extension period

End point values	rFVIII-FS/pegylated liposomes (subgroup)			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: percentage of subjects				
number (not applicable)	55			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From randomization until end of study	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups	
Reporting group title	rFVIII-FS/pegylated liposomes (BAY79-4980) - Double Blind
Reporting group description:	
Reporting Group 1 (RG1): Double Blind Study, 35 IU/kg body weight of BAY79-4980 1x/week plus 2 dummy injections/week (dummy = rFVIII-FS excipient reconstituted in WFI).	
Reporting group title	rFVIII-FS/WFI (BAY14-2222) - Double Blind
Reporting group description:	
Reporting group 2 (RG2): Double Blind Study, 25 IU/kg body weight of rFVIII-FS 3x/week (employing 1 percent POPC-alone liposome (rFVIII-FS-POPC) as blinding agent used for first weekly injection and rFVIII-FS in WFI for 2nd and 3rd injection).	
Reporting group title	rFVIII-FS/WFI (BAY14-2222) - Follow-up
Reporting group description:	
Reporting group 3 (RG3): Open Label Follow-up, 25 IU/kg body weight of rFVIII-FS 3x/week (employing 1 percent POPC-alone liposome (rFVIII-FS-POPC) as blinding agent used for first weekly injection and rFVIII-FS in WFI for 2nd and 3rd injection).	
Reporting group title	rFVIII-FS/pegylated liposomes (BAY79-4980) - Extension
Reporting group description:	
Reporting group 4 (RG4): Open Label Extension, 35 IU/kg body weight of BAY79-4980 1x/week plus 2 dummy injections/week (dummy = rFVIII-FS excipient reconstituted in WFI).	

Serious adverse events	rFVIII-FS/pegylated liposomes (BAY79-4980) - Double Blind	rFVIII-FS/WFI (BAY14-2222) - Double Blind	rFVIII-FS/WFI (BAY14-2222) - Follow-up
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 67 (10.45%)	1 / 72 (1.39%)	0 / 26 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	1 / 67 (1.49%)	0 / 72 (0.00%)	0 / 26 (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
Immune system disorders			
Hypersensitivity			

subjects affected / exposed	1 / 67 (1.49%)	0 / 72 (0.00%)	0 / 26 (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
Eye disorders			
Glaucoma			
subjects affected / exposed	1 / 67 (1.49%)	0 / 72 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Melaena			
subjects affected / exposed	1 / 67 (1.49%)	0 / 72 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	1 / 67 (1.49%)	0 / 72 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 67 (1.49%)	0 / 72 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Compartment syndrome			
subjects affected / exposed	1 / 67 (1.49%)	0 / 72 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Device related infection			
subjects affected / exposed	0 / 67 (0.00%)	1 / 72 (1.39%)	0 / 26 (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
Tinea pedis			

subjects affected / exposed	1 / 67 (1.49%)	0 / 72 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella			
subjects affected / exposed	0 / 67 (0.00%)	0 / 72 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Abnormal weight gain			
subjects affected / exposed	1 / 67 (1.49%)	0 / 72 (0.00%)	0 / 26 (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

Serious adverse events	rFVIII-FS/pegylated liposomes (BAY79-4980) - Extension		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 20 (5.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Melaena			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Compartment syndrome			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Device related infection			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tinea pedis			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Varicella			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Abnormal weight gain			

subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	rFVIII-FS/pegylated liposomes (BAY79-4980) - Double Blind	rFVIII-FS/WFI (BAY14-2222) - Double Blind	rFVIII-FS/WFI (BAY14-2222) - Follow-up
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 67 (40.30%)	27 / 72 (37.50%)	2 / 26 (7.69%)
Investigations			
Blood amylase increased			
subjects affected / exposed	1 / 67 (1.49%)	1 / 72 (1.39%)	0 / 26 (0.00%)
occurrences (all)	1	4	0
Lipase increased			
subjects affected / exposed	1 / 67 (1.49%)	1 / 72 (1.39%)	0 / 26 (0.00%)
occurrences (all)	1	3	0
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	0 / 67 (0.00%)	0 / 72 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 67 (0.00%)	0 / 72 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 67 (8.96%)	8 / 72 (11.11%)	0 / 26 (0.00%)
occurrences (all)	8	11	0
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 67 (0.00%)	2 / 72 (2.78%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	3 / 67 (4.48%)	3 / 72 (4.17%)	1 / 26 (3.85%)
occurrences (all)	3	3	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	4 / 67 (5.97%)	2 / 72 (2.78%)	0 / 26 (0.00%)
occurrences (all)	5	3	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	4 / 67 (5.97%)	4 / 72 (5.56%)	0 / 26 (0.00%)
occurrences (all)	4	8	0
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	0 / 67 (0.00%)	0 / 72 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	3 / 67 (4.48%)	4 / 72 (5.56%)	0 / 26 (0.00%)
occurrences (all)	6	4	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 67 (0.00%)	0 / 72 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	0 / 67 (0.00%)	0 / 72 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 67 (5.97%)	2 / 72 (2.78%)	0 / 26 (0.00%)
occurrences (all)	4	2	0
Arthralgia			
subjects affected / exposed	7 / 67 (10.45%)	5 / 72 (6.94%)	1 / 26 (3.85%)
occurrences (all)	9	12	1
Neck pain			
subjects affected / exposed	0 / 67 (0.00%)	0 / 72 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Haemophilic arthropathy			

subjects affected / exposed	0 / 67 (0.00%)	0 / 72 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Influenza			
subjects affected / exposed	5 / 67 (7.46%)	2 / 72 (2.78%)	0 / 26 (0.00%)
occurrences (all)	6	2	0
Nasopharyngitis			
subjects affected / exposed	10 / 67 (14.93%)	12 / 72 (16.67%)	0 / 26 (0.00%)
occurrences (all)	15	18	0
Localised infection			
subjects affected / exposed	0 / 67 (0.00%)	0 / 72 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Varicella			
subjects affected / exposed	0 / 67 (0.00%)	0 / 72 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	rFVIII-FS/pegylated liposomes (BAY79-4980) - Extension		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 20 (50.00%)		
Investigations			
Blood amylase increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Lipase increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Nervous system disorders			

Headache subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Blood and lymphatic system disorders Lymphadenopathy subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Skin and subcutaneous tissue disorders Dermatitis contact subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1 0 / 20 (0.00%) 0		
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) Haematuria subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1 2 / 20 (10.00%) 2		
Musculoskeletal and connective tissue disorders Back pain			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Arthralgia			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Neck pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Haemophilic arthropathy			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	6 / 20 (30.00%)		
occurrences (all)	8		
Localised infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Varicella			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 February 2008	- The dosage for the treatment of bleeds and minor surgical interventions was limited to 1 single infusion with 35 IU/kg of BAY 79-4980 or rFVIII-POPC. The proposed treatment of bleeds and minor surgical interventions with extended dosages of BAY 79-4980 with up to 70 IU/kg/day was not accepted by a national authority. - The definition of a target joint was added. - The physical assessment of joints for the determination of the Gilbert Score was deleted at Month 6 and end of trial, as no change was expected during a 1-year observation period in subjects treated with prophylaxis. - The screening period was prolonged to from 1-3 weeks to 3-5 weeks due to logistical requirements. - Inhibitor development as reason for withdrawal was clarified. - The exclusion criterion regarding active hepatic disease was clarified.
21 July 2009	- The interim safety analysis on lipid kinetics was to be performed in a subset of 20 subjects and the interim efficacy analysis was to be performed after 100 subjects had completed 6 months of treatment. This change was due to the slow recruitment into the study. In addition, the study was extended to new countries where prophylaxis is not the treatment standard in adult hemophilia subjects. Inclusion criterion number 4 was adapted accordingly to increase the percentage of subjects on on-demand treatment. - The screening period was prolonged to 3-8 weeks due to logistic reasons. - The upper dose limit was set to 4500 IU/infusion corresponding to a body weight of 131 kg, because extreme overweight is not related to a proportional increase in distribution volume. - The endpoint related to change in joint status was deleted because no Gilbert score was determined at the end of the study. - Specification that fasting after infusion of study medication was no longer required for the lipid PK, because this has no impact on the first sample after 6 hour. Lipid values for inclusion into the lipid pharmacokinetics (PK) were defined based on American Heart Association's Adult Treatment Panel (AHA-ATP) III recommendations. - For the repeat FVIII PK at Week 26, specification that the study medication had to be administered with the same infusion rate as used during the first infusion (20-30 minutes). - The original protocol specified that the efficacy analyses would be performed on the ITT population. A modification was made to specify that the primary efficacy analysis would be performed on the PP population and the secondary analysis on the ITT population since this is a more conservative approach for non-inferiority trials.
15 January 2010	- Based on the DSMB's interim efficacy check of the data of 108 subjects with a treatment period of 6 months, this amendment specified that recruitment had been halted on 22 December 2009 and would not be re-started. The double-blind treatment period was prematurely terminated and study participants were offered a participation in an open treatment arm (follow-up period). All subjects were offered a treatment with the comparator drug (rFVIII-FS-POPC/rFVIII-FS-WFI) and/or open-label rFVIII-FS-WFI for 6 months or until completion of the 12-month total study duration. Participation was according to the subjects' preference. This applied also to subjects who had not yet started the treatment phase. Blinding was to be preserved until clean data base of the blinded study. - The DSMB concluded that the study would not be able to establish non-inferiority of BAY79-4980 compared to the control treatment with a non-inferiority margin of 15% and recommended to halt recruitment. The sponsor decided to discontinue the investigational treatment and to guarantee the treatment of subjects until study completion or at least 6 months in the comparator arm.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
22 December 2009	The recruitment and double-blind study phase were prematurely terminated after a scheduled interim analysis confirmed overt failure regarding the primary endpoint as judged by the independent DSMB.	-

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/20059562

http://www.ncbi.nlm.nih.gov/pubmed/23014711