Clinical trial results:
A Phase II/III, multicenter, partially randomized, open label trial investigating safety and efficacy of on-demand and prophylactic treatment with BAY94-9027 in Severe Hemophilia A

Summary

EudraCT number	2011-005210-11
Trial protocol	GB BE NL NO AT DE DK PL FR IT Outside EU/EEA
Global end of trial date	

Results information

Result version number	v1
This version publication date	15 April 2016
First version publication date	15 April 2016

Trial information

Trial identification

Sponsor protocol code	BAY94-9027/13024

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01580293
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)	Yes
EMA paediatric investigation plan number(s)	EMEA-001229-PIP01-11
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	Interim
Date of interim/final analysis	08 September 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 June 2014
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

1. Part A main study: To assess the efficacy of BAY94-9027 in prevention and treatment of bleeding at different infusion schedules 2. Part A Optional Extension: To assess the long term safety of BAY94-9027 over at least 100 accumulated exposure days (ED) (main study plus extension) 3. Part B main study and extension: To assess the safety and efficacy of BAY94-9027 in the prevention of bleeding during major surgical procedures

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 representative. Participating subjects and/or their legally authorized representative 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	23 April 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Colombia: 5
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Israel: 16
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Japan: 11
Country: Number of subjects enrolled	Korea, Republic of: 8
Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Norway: 3
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Singapore: 9

Country: Number of subjects enrolled	Turkey: 5
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	United States: 30
Country: Number of subjects enrolled	Romania: 2
Worldwide total number of subjects	145
EEA total number of subjects	55

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)	14
Adults (18-64 years)	131
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 2 parts: Part A (main study [36-week treatment period] and an optional extension [a minimum of 6 months and at least 100 total exposure days, or until marketing authorization of the drug]) and Part B (main study [up to 3 weeks] and extension [until the end of Part A extension]).

Pre-assignment

Screening details:

Of 149 subjects screened in Part A, 134 were treated and the reasons for non-inclusion of 15 patients were screen failure, consent withdrawal, and non-adherence to protocol visit windows. A total of 16 subjects (including 5 subjects from Part A) were enrolled and treated in Part B.

Period 1

Period 1 title	Part A
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	BAY94-9027 On-demand Treatment – Part A

Arm description:

On-demand treatment with BAY94-9027 as an intravenous (IV) infusion over a period of 1 to 15 minutes at a dose as indicated based upon location and severity of bleeds (maximum of 60 international units per kilogram [IU/kg]).

Arm type	Experimental
Investigational medicinal product name	Damoctocog alfa pegol
Investigational medicinal product code	BAY94-9027
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

On-demand treatment with BAY94-9027 as an IV infusion over a period of 1 to 15 minutes at a dose as indicated based upon location and severity of bleeds (maximum of 60 IU/kg).

Arm title	BAY94-9027 Prophylaxis Treatment – Part A

Arm description:

All subjects in the prophylaxis arms started BAY94-9027 IV infusion over a period of 1 to 15 minutes, with 2 times per week (2x/week) at a dose of 25-40 IU/kg for 10 weeks. Thereafter, only subjects with less than (<) 2 breakthrough (spontaneous, no identified trauma) joint and/or muscle bleeds qualified for random assignment to the less frequent dosing regimens. High bleeders continued 2x/week infusion. Subjects who qualified to be randomized, but enrolled after the every 5 day and every 7 day treatment arms were filled, remained on 2x/week treatment (2x/week 'forced' group).

Arm type	Experimental
Investigational medicinal product name	Damoctocog alfa pegol
Investigational medicinal product code	BAY94-9027
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

All subjects in the prophylaxis arms started with BAY94-9027 IV infusion over a period of 1 to 15 minutes, 2x/week at a dose of 25-40 IU/kg for 10 weeks. Thereafter, only subjects with <2 breakthrough (spontaneous, no identified trauma) joint and/or muscle bleeds qualified for random assignment to the less frequent dosing regimens. High bleeders continued 2x/week infusion. Subjects

who qualified to be randomized, but enrolled after the every 5 day and every 7 day treatment arms were filled, remained on 2x/week treatment (2x/week 'forced' group).

Number of subjects in period 1	BAY94-9027 On-demand Treatment – Part A	BAY94-9027 Prophylaxis Treatment – Part A
Started	20	114
Completed	18	108
Not completed	2	6
Consent withdrawn by subject	1	4
Adverse event, non-fatal	-	2
Unspecified	1	-

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

Arms

Arm title	BAY949027 Treatment in Major Surgery - Part B

Arm description:

This reporting group included subjects who were treated in Part A and continued treatment in Part B, and subjects who were treated in Part B only. Subjects who underwent major surgery received BAY94-9027 IV infusion over a period of 1 to 15 minutes, for pre-surgical pharmacokinetic (PK) sampling, for surgery, and for the post-surgical period up to the time of discharge for a period not exceeding 3 weeks. Subjects were treated according to the type of procedure, using doses expected to maintain therapeutic levels of human coagulation factor VIII (FVIII) activity based upon pre-surgical PK measurements. The recommended maximum dose was 60 IU/kg. All treatments were administered as needed, and the dose was tailored to a subject's individual response.

Arm type	Experimental
Investigational medicinal product name	Damoctocog alfa pegol
Investigational medicinal product code	BAY94-9027
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects who underwent major surgery received BAY94-9027 IV infusion over a period of 1 to 15 minutes, for pre-surgical PK sampling, for surgery, and for the post-surgical period up to the time of discharge for a period not exceeding 3 weeks. Subjects were treated according to the type of procedure, using doses expected to maintain therapeutic levels of FVIII activity based upon pre-surgical PK measurements. The recommended maximum dose was 60 IU/kg. All treatments were administered as needed, and the dose was tailored to a subject's individual response.

Number of subjects in period 2[1]	BAY949027 Treatment in Major Surgery - Part B
Started	16
Completed	14
Not completed	2
Dropped-out	2

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: Not all the enrolled subjects were treated with study drugs. As baseline only included treated subjects, the worldwide number enrolled in the trial differs with the number of subjects reported in the baseline period.

Period 3

Period 3 title	Baseline period
Is this the baseline period?	Yes[2]
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	BAY94-9027 Treatment - Part A

Arm description:

This reporting group included both on-demand and prophylaxis arms treated with BAY94-9027 as an IV infusion over a period of 1 to 15 minutes in Part A, and included who continued treatment in Part B. On-demand arm: On-demand treatment at a dose as indicated based upon location and severity of bleeds (maximum of 60 IU/kg). Prophylaxis arm: All subjects in the prophylaxis arms started with 2x/week at a dose of 25-40 IU/kg for 10 weeks. Thereafter, only subjects with <2 breakthrough (spontaneous, no identified trauma) joint and/or muscle bleeds qualified for random assignment to the less frequent dosing regimens. High bleeders continued 2x/week infusion. Subjects who qualified to be randomized, but enrolled after the every 5 day and every 7 day treatment arms were filled, remained on 2x/week treatment (2x/week 'forced' group).

Arm type	Experimental
Investigational medicinal product name	Damoctocog alfa pegol
Investigational medicinal product code	BAY94-9027
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

BAY94-9027 as an IV infusion over a period of 1 to 15 minutes, and the dosage schedule as follows: On-demand arm: On-demand treatment at a dose as indicated based upon location and severity of bleeds (maximum of 60 IU/kg). Prophylaxis arm: All subjects in the prophylaxis arms started with 2x/week at a dose of 25-40 IU/kg for 10 weeks. Thereafter, only subjects with <2 breakthrough (spontaneous, no identified trauma) joint and/or muscle bleeds qualified for random assignment to the less frequent dosing regimens. High bleeders continued 2x/week infusion. Subjects who qualified to be randomized, but enrolled after the every 5 day and every 7 day treatment arms were filled, remained on 2x/week treatment (2x/week 'forced' group).

Arm title	BAY94-9027 Treatment in Major surgery - Part B Only

Arm description:

This reporting group included subjects who were treated in Part B only, and excluded subjects who were treated in Part A and continued treatment in Part B. Subjects who underwent major surgery received BAY94-9027 IV infusion over a period of 1 to 15 minutes, for pre-surgical PK sampling, for surgery, and

for the post-surgical period up to the time of discharge for a period not exceeding 3 weeks. Subjects were treated according to the type of procedure, using doses expected to maintain therapeutic levels of FVIII activity based upon pre-surgical PK measurements. The recommended maximum dose was 60 IU/kg. All treatments were administered as needed, and the dose was tailored to a subject's individual response.

Arm type	Experimental
Investigational medicinal product name	Damoctocog alfa pegol
Investigational medicinal product code	BAY94-9027
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects who underwent major surgery received BAY94-9027 IV infusion over a period of 1 to 15 minutes, for pre-surgical PK sampling, for surgery, and for the post-surgical period up to the time of discharge for a period not exceeding 3 weeks. Subjects were treated according to the type of procedure, using doses expected to maintain therapeutic levels of FVIII activity based upon pre-surgical PK measurements. The recommended maximum dose was 60 IU/kg. All treatments were administered as needed, and the dose was tailored to a subject's individual response.

Notes:

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

Justification: This study was conducted in 2 parts, Part A and Part B. Hence, following periods (Parts A and B), a separate baseline period combining all the arms under Parts A and B, was created to report baseline characteristics.

Number of subjects in period 3	BAY94-9027 Treatment - Part A	BAY94-9027 Treatment in Major surgery - Part B Only
Started	134	11
Completed	126	10
Not completed	8	1
Consent withdrawn by subject	5	-
Adverse event, non-fatal	2	-
Unspecified	1	-
Dropped-out	-	1

Baseline characteristics

Reporting groups

Reporting group title	BAY94-9027 Treatment - Part A

Reporting group description:

This reporting group included both on-demand and prophylaxis arms treated with BAY94-9027 as an IV infusion over a period of 1 to 15 minutes in Part A, and included who continued treatment in Part B. On-demand arm: On-demand treatment at a dose as indicated based upon location and severity of bleeds (maximum of 60 IU/kg). Prophylaxis arm: All subjects in the prophylaxis arms started with 2x/week at a dose of 25-40 IU/kg for 10 weeks. Thereafter, only subjects with <2 breakthrough (spontaneous, no identified trauma) joint and/or muscle bleeds qualified for random assignment to the less frequent dosing regimens. High bleeders continued 2x/week infusion. Subjects who qualified to be randomized, but enrolled after the every 5 day and every 7 day treatment arms were filled, remained on 2x/week treatment (2x/week 'forced' group).

Reporting group title	BAY94-9027 Treatment in Major surgery - Part B Only

Reporting group description:

This reporting group included subjects who were treated in Part B only, and excluded subjects who were treated in Part A and continued treatment in Part B. Subjects who underwent major surgery received BAY94-9027 IV infusion over a period of 1 to 15 minutes, for pre-surgical PK sampling, for surgery, and for the post-surgical period up to the time of discharge for a period not exceeding 3 weeks. Subjects were treated according to the type of procedure, using doses expected to maintain therapeutic levels of FVIII activity based upon pre-surgical PK measurements. The recommended maximum dose was 60 IU/kg. All treatments were administered as needed, and the dose was tailored to a subject's individual response.

Reporting group values	BAY94-9027 Treatment - Part A	BAY94-9027 Treatment in Major surgery - Part B Only	Total
Number of subjects	134	11	145
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 35.9 ± 13.5	 37.9 ± 13.7	 -
Gender categorical Units: Subjects			
Male	134	11	145

End points

End points reporting groups

Reporting group title	BAY94-9027 On-demand Treatment – Part A

Reporting group description:

On-demand treatment with BAY94-9027 as an intravenous (IV) infusion over a period of 1 to 15 minutes at a dose as indicated based upon location and severity of bleeds (maximum of 60 international units per kilogram [IU/kg]).

Reporting group title	BAY94-9027 Prophylaxis Treatment – Part A

Reporting group description:

All subjects in the prophylaxis arms started BAY94-9027 IV infusion over a period of 1 to 15 minutes, with 2 times per week (2x/week) at a dose of 25-40 IU/kg for 10 weeks. Thereafter, only subjects with less than (<) 2 breakthrough (spontaneous, no identified trauma) joint and/or muscle bleeds qualified for random assignment to the less frequent dosing regimens. High bleeders continued 2x/week infusion. Subjects who qualified to be randomized, but enrolled after the every 5 day and every 7 day treatment arms were filled, remained on 2x/week treatment (2x/week 'forced' group).

Reporting group title	BAY949027 Treatment in Major Surgery - Part B

Reporting group description:

This reporting group included subjects who were treated in Part A and continued treatment in Part B, and subjects who were treated in Part B only. Subjects who underwent major surgery received BAY94-9027 IV infusion over a period of 1 to 15 minutes, for pre-surgical pharmacokinetic (PK) sampling, for surgery, and for the post-surgical period up to the time of discharge for a period not exceeding 3 weeks. Subjects were treated according to the type of procedure, using doses expected to maintain therapeutic levels of human coagulation factor VIII (FVIII) activity based upon pre-surgical PK measurements. The recommended maximum dose was 60 IU/kg. All treatments were administered as needed, and the dose was tailored to a subject's individual response.

Reporting group title	BAY94-9027 Treatment - Part A

Reporting group description:

This reporting group included both on-demand and prophylaxis arms treated with BAY94-9027 as an IV infusion over a period of 1 to 15 minutes in Part A, and included who continued treatment in Part B. On-demand arm: On-demand treatment at a dose as indicated based upon location and severity of bleeds (maximum of 60 IU/kg). Prophylaxis arm: All subjects in the prophylaxis arms started with 2x/week at a dose of 25-40 IU/kg for 10 weeks. Thereafter, only subjects with <2 breakthrough (spontaneous, no identified trauma) joint and/or muscle bleeds qualified for random assignment to the less frequent dosing regimens. High bleeders continued 2x/week infusion. Subjects who qualified to be randomized, but enrolled after the every 5 day and every 7 day treatment arms were filled, remained on 2x/week treatment (2x/week 'forced' group).

Reporting group title	BAY94-9027 Treatment in Major surgery - Part B Only

Reporting group description:

This reporting group included subjects who were treated in Part B only, and excluded subjects who were treated in Part A and continued treatment in Part B. Subjects who underwent major surgery received BAY94-9027 IV infusion over a period of 1 to 15 minutes, for pre-surgical PK sampling, for surgery, and for the post-surgical period up to the time of discharge for a period not exceeding 3 weeks. Subjects were treated according to the type of procedure, using doses expected to maintain therapeutic levels of FVIII activity based upon pre-surgical PK measurements. The recommended maximum dose was 60 IU/kg. All treatments were administered as needed, and the dose was tailored to a subject's individual response.

Subject analysis set title	Part A Intent-To-Treat (ITT) Population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Part A ITT population (N=132) included all the subjects who were enrolled into Part A of the study and received at least 1 dose of the study medication during Part A, and has subsequent infusion for either prophylaxis or bleed.

Subject analysis set title	Part B Intent-To-Treat (ITT) Population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Part B ITT population (N=14) included all the subjects who were enrolled into Part B of the study, received at least 1 dose of the study medication during Part B, and had undergone surgery.

Subject analysis set title	Part B Safety Population

Subject analysis set type	Safety analysis

Subject analysis set description:

Part B Safety population (N=16) included all subjects who received at least 1 dose of study drug during Part B of the study.

Subject analysis set title	Pharmacokinetic Analysis Set (PKS)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PKS (N=22) included all subjects with a valid profile of BAY94-9027 during Part A of the study.

Subject analysis set title	BAY94-9027 Treatment – Part A, Week 36
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This reporting group (N=15) included all PKS subjects treated with multiple doses (last dose paired) of BAY94-9027 as an IV infusion over 10 minutes at Week 36. Paired data were defined as the single dose data for the sub-set of subjects who also had multiple dose PK data.

Subject analysis set title	BAY94-9027 Treatment – Part A, Week 0
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This reporting group (N=22) included all PKS subjects treated with a single (first) dose of BAY94-9027 as an IV infusion over 10 minutes at Week 0.

Subject analysis set title	Part A Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

Part A Safety population (N=134) included all subjects who received at least 1 dose of study drug during Part A of the study.

Primary: Annualized Number of Total Bleeds in On-demand Treatment arm (Weeks 0 -36) and Prophylaxis arm (Weeks 10 - 36, excluding rescue bleeds) – Part A

End point title	Annualized Number of Total Bleeds in On-demand Treatment arm (Weeks 0 -36) and Prophylaxis arm (Weeks 10 - 36, excluding rescue bleeds) – Part A[1]

End point description:

Annualized number of total bleeds was defined as the annualized sum of spontaneous bleeds and trauma bleeds.

End point type	Primary

End point timeframe:

On-demand: Weeks 0 -36 and Prophylaxis: Weeks 10 - 36 during Part A

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	BAY94-9027 On-demand Treatment – Part A	BAY94-9027 Prophylaxis Treatment – Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[2]	110[3]		
Units: bleeds				
median (full range (min-max))	23.42 (7.3 to 83.2)	2.09 (0 to 53.1)		

Notes:

[2] - Part A ITT population

[3] - Part A ITT population with evaluable subjects for this arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Physician's Assessment of Adequacy of Hemostasis in Major Surgery – Part B

End point title	Physician's Assessment of Adequacy of Hemostasis in Major Surgery – Part B

End point description:

Major surgery was defined as any surgical or invasive procedure (elective or emergent) in which the overall bleeding risk was excessive, required a general anesthetic in an individual without a bleeding disorder, penetrated or exposed a major body cavity, resulted in substantial impairment of physical or physiological functions, or required special anatomic knowledge or manipulative skill. Adequacy of hemostasis was assessed as excellent, good, moderate or poor, by the Physician during Part B of the study. No subjects were assessed as moderate or poor.

End point type	Secondary

End point timeframe:

Baseline up to 6 weeks during Part B

End point values	BAY949027 Treatment in Major Surgery - Part B			
Subject group type	Reporting group			
Number of subjects analysed	14[4]			
Units: Number of surgeries				
Good	10			
Excellent	7			

Notes:

[4] - Part B ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Recombinant Human Factor VIII (rFVIII) Usage Expressed as Number of Infusions for Major Surgery – Part B

End point title	Recombinant Human Factor VIII (rFVIII) Usage Expressed as Number of Infusions for Major Surgery – Part B

End point description:

Major surgery was defined as any surgical or invasive procedure (elective or emergent) in which the overall bleeding risk was excessive, required a general anesthetic in an individual without a bleeding disorder, penetrated or exposed a major body cavity, resulted in substantial impairment of physical or physiological functions, or required special anatomic knowledge or manipulative skill.

End point type	Secondary

End point timeframe:

Baseline up to 6 weeks during Part B

End point values	BAY949027 Treatment in Major Surgery - Part B			
Subject group type	Reporting group			
Number of subjects analysed	14[5]			
Units: infusions				
median (full range (min-max))	8 (2 to 37)			

Notes:

[5] - Part B ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Recombinant Human Factor VIII (rFVIII) Usage Expressed as Total Dose per Kilogram per Infusion for Major Surgery – Part B

End point title	Recombinant Human Factor VIII (rFVIII) Usage Expressed as Total Dose per Kilogram per Infusion for Major Surgery – Part B

End point description:

Major surgery was defined as any surgical or invasive procedure (elective or emergent) in which the overall bleeding risk was excessive, required a general anesthetic in an individual without a bleeding disorder, penetrated or exposed a major body cavity, resulted in substantial impairment of physical or physiological functions, or required special anatomic knowledge or manipulative skill. Total dose per kilogram per Infusion was expressed in international units per kilogram per infusion (IU/kg/infusion).

End point type	Secondary

End point timeframe:

Baseline up to 6 weeks during Part B

End point values	BAY949027 Treatment in Major Surgery - Part B			
Subject group type	Reporting group			
Number of subjects analysed	14[6]			
Units: IU/kg/infusion				
median (full range (min-max))	34 (26 to 51)			

Notes:

[6] - Part B ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator’s Assessment of Response to Treatment - Part B

End point title	Investigator’s Assessment of Response to Treatment - Part B

End point description:

Subject's response to treatment was assessed by Investigator as excellent, good, moderate, poor or missing during Part B of the study. No subjects were assessed as poor.

End point type	Secondary

End point timeframe:

Baseline up to 6 weeks during Part B

End point values	BAY949027 Treatment in Major Surgery - Part B			
Subject group type	Reporting group			
Number of subjects analysed	14[7]			
Units: Number of surgeries				
Excellent	8			
Good	5			
Moderate	3			
Missing	1			

Notes:

[7] - Part B ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Subject's Assessment of Response to Treatment of a Bleed – Part A

End point title	Subject's Assessment of Response to Treatment of a Bleed – Part A

End point description:

Adequacy of hemostasis was assessed by subject as excellent, good, moderate, poor or missing during Part A of the study.

End point type	Secondary

End point timeframe:

Weeks 0 to 36 during Part A

End point values	BAY94-9027 On-demand Treatment – Part A	BAY94-9027 Prophylaxis Treatment – Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[8]	112[9]		
Units: bleeds				
Excellent or Good	252	256		
Missing	3	6		
Excellent	81	107		
Good	171	149		
Moderate	115	47		
Poor	16	7		

Notes:

[8] - Part A ITT population

[9] - Part A ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Developed Human Coagulation Factor VIII (FVIII) Inhibitor – Part A

End point title	Number of Subjects Developed Human Coagulation Factor VIII (FVIII) Inhibitor – Part A

End point description:

End point type	Secondary

End point timeframe:

Weeks 0 to 36 during Part A

End point values	BAY94-9027 On-demand Treatment – Part A	BAY94-9027 Prophylaxis Treatment – Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[10]	114[11]		
Units: Subjects	0	0		

Notes:

[10] - Part A Safety population

[11] - Part A Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Overall Pain Severity and Interference due to Pain at Week 36 – Part A

End point title	Change From Baseline in Overall Pain Severity and Interference due to Pain at Week 36 – Part A

End point description:

Brief Pain Inventor (BPI) – Short Form (BPI-SF) was a 15-item, self-administered, clinically valid, reliable and responsive measure developed to assess pain. BPI-SF was typically scored by averaging the pain severity score and overall pain interference score. Scores ranged from 0 to 10 and a higher score indicates a higher level of pain/interference. Mean change from baseline was reported in the below table. In the listed categories below, 'N' signifies the number of subjects evaluable for this outcome.

End point type	Secondary

End point timeframe:

Week 0 (baseline) and Week 36 during Part A

End point values	BAY94-9027 On-demand Treatment – Part A	BAY94-9027 Prophylaxis Treatment – Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[12]	112[13]		
Units: scores on a scale				

number (not applicable)				
Pain severity subscale (N= 15, 83)	-0.8	0.1		
Interference subscale (N=15, 85)	-0.99	-0.06		

Notes:

[12] - Part A ITT population

[13] - Part A ITT population with subjects evaluable for this outcome

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Work Productivity and Activity Impairment (WPAI) Questionnaire at Week 36 – Part A

End point title	Change From Baseline in Work Productivity and Activity Impairment (WPAI) Questionnaire at Week 36 – Part A

End point description:

The WPAI is a validated instrument to assess the effect of hemophilia on ability to work, attend classes, and perform regular daily activities in subjects aged 12 and above. The WPAI also contained classroom impairment questions (CIQ). The questionnaire was self-administered and comprised of nine questions that elicited information on work, classroom, and daily activity impairment during the previous seven days. WPAI outcomes that are overall work and activity impairment, transformed to impairment percentages (range from 0 to 100), with higher numbers indicating greater impairment and less productivity. In the listed categories below, 'N' signifies the number of subjects evaluable for this outcome.

End point type	Secondary

End point timeframe:

Week 0 (baseline) and Week 36 during Part A

End point values	BAY94-9027 On-demand Treatment – Part A	BAY94-9027 Prophylaxis Treatment – Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[14]	112[15]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Activity impairment (N= 19,108)	4.74 (± 24.12)	-7.13 (± 20)		
Overall work impairment (N= 12,62)	4.44 (± 21.94)	-1.22 (± 21.94)		

Notes:

[14] - Part A ITT population

[15] - Part A ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Quality of Life by Hemophilia Specific Quality of Life for Adults (Haemo-QoL-A) Overall Score at Week 36 – Part A

End point title	Change From Baseline in Quality of Life by Hemophilia Specific Quality of Life for Adults (Haemo-QoL-A) Overall Score at Week 36 – Part A

End point description:

Quality of life (QoL) was measured by the Haemo-QoL-A overall score, which ranged from 0 (the best

condition) to 100 (the worst condition).

End point type	Secondary

End point timeframe:

Week 0 (baseline) and Week 36 during Part A

End point values	BAY94-9027 On-demand Treatment – Part A	BAY94-9027 Prophylaxis Treatment – Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[16]	97[17]		
Units: scores on a scale				
arithmetic mean (standard deviation)	-0.14 (± 9.7)	2.59 (± 7.98)		

Notes:

[16] - Part A ITT population with subjects evaluable for this outcome

[17] - Part A ITT population with subjects evaluable for this outcome

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Drug Plasma Concentration (Cmax) Following Single and Multiple Doses of BAY94-9027 – Part A

End point title	Maximum Drug Plasma Concentration (Cmax) Following Single and Multiple Doses of BAY94-9027 – Part A

End point description:

Maximum observed drug concentration, directly taken from analytical data. Geometric mean and percentage geometric coefficient of variation (%CV) were reported. Cmax was expressed in international Units per deciliter (IU/dL).

End point type	Secondary

End point timeframe:

Weeks 0 and 36: pre-infusion (0 hours), post-infusion 15, 30 minutes, 1, 3, 6, 8, 24, 48, 72, 96 hours

End point values	BAY94-9027 Treatment – Part A, Week 36	BAY94-9027 Treatment – Part A, Week 0		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15[18]	22[19]		
Units: IU/dL				
geometric mean (geometric coefficient of variation)	177.1 (± 20.98)	162.8 (± 14.74)		

Notes:

[18] - PKS with subjects evaluable for this outcome

[19] - PKS with subjects evaluable for this outcome

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration Versus Time Curve From Zero to Infinity (AUC) Following Single and Multiple Doses of BAY94-9027 – Part A

End point title	Area Under the Plasma Concentration Versus Time Curve From Zero to Infinity (AUC) Following Single and Multiple Doses of BAY94-9027 – Part A

End point description:

AUC=AUC(0-tlast)+Clast,calc/lambdaZ. AUC(0-tlast) is defined as AUC from time 0 to the last data point >lower limit of quantitation (LLOQ), calculated up by linear trapezoidal rule, down by logarithmic trapezoidal rule. Clast is the last concentration value above LLOQ, directly taken from analytical data. lambdaZ is the apparent terminal rate constant, calculated from the slope of a log-linear regression of the unweighted data considering the last concentration time points >LLOQ (3 IU/dL). AUC expressed in hour*IU/dL. Geometric mean and percentage geometric coefficient of variation (%CV) were reported.

End point type	Secondary

End point timeframe:

Weeks 0 and 36: pre-infusion (0 hours), post-infusion 15, 30 minutes, 1, 3, 6, 8, 24, 48, 72, 96 hours

End point values	BAY94-9027 Treatment – Part A, Week 36	BAY94-9027 Treatment – Part A, Week 0		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15[20]	22[21]		
Units: h*IU/dL				
geometric mean (geometric coefficient of variation)	4131 (± 28.8)	3708 (± 33.77)		

Notes:

[20] - PKS with subjects evaluable for this outcome

[21] - PKS with subjects evaluable for this outcome

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Elimination Half Life (t1/2) Following Single and Multiple Doses of BAY94-9027 – Part A

End point title	Terminal Elimination Half Life (t1/2) Following Single and Multiple Doses of BAY94-9027 – Part A

End point description:

t1/2=ln2/ lambdaZ. lambdaZ is the apparent terminal rate constant, calculated from the slope of a log-linear regression of the unweighted data considering the last concentration time points >LLOQ (3 IU/dL). Geometric mean and percentage geometric coefficient of variation (%CV) were reported.

End point type	Secondary

End point timeframe:

Weeks 0 and 36: pre-infusion (0 hours), post-infusion 15, 30 minutes, 1, 3, 6, 8, 24, 48, 72, 96 hours

End point values	BAY94-9027 Treatment – Part A, Week 36	BAY94-9027 Treatment – Part A, Week 0		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15[22]	22[23]		
Units: Hours				
geometric mean (geometric coefficient of variation)	19.6 (± 38.48)	17.1 (± 27.05)		

Notes:

[22] - PKS with subjects evaluable for this outcome

[23] - PKS with subjects evaluable for this outcome

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Human Coagulation Factor VIII (FVIII) Recovery Value in Chromogenic Assay – Part A

End point title	Overall Human Coagulation Factor VIII (FVIII) Recovery Value in Chromogenic Assay – Part A

End point description:

Recovery was calculated by the following formula: Recovery = (post-infusion FVIII activity – pre-infusion FVIII activity) * weight / dose (in IU).

End point type	Secondary

End point timeframe:

Weeks 0 to 36 during Part A

End point values	BAY94-9027 On-demand Treatment – Part A	BAY94-9027 Prophylaxis Treatment – Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[24]	112[25]		
Units: Kilogram per deciliter				
arithmetic mean (full range (min-max))	2.671 (1.87 to 3.85)	2.675 (1.32 to 4.48)		

Notes:

[24] - Part A ITT population

[25] - Part A ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Bleed Location – Part A

End point title	Bleed Location – Part A

End point description:

Bleed locations were categorised as joint, muscle, skin/mucosa, internal, others and missing.

End point type	Secondary

End point timeframe:

Weeks 0 to 36 during Part A

End point values	BAY94-9027 On-demand Treatment – Part A	BAY94-9027 Prophylaxis Treatment – Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[26]	112[27]		
Units: bleeds				
Missing	0	0		
Joint	303	235		
Muscle	54	59		
Skin/Mucosa	12	12		
Internal	7	7		
Other	26	16		

Notes:

[26] - Part A ITT population

[27] - Part A ITT population with subjects evaluable for this outcome

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Number of Joint Bleeds, Trauma, Spontaneous Bleeds for Subjects in Prophylaxis arm- Part A

End point title	Annualized Number of Joint Bleeds, Trauma, Spontaneous Bleeds for Subjects in Prophylaxis arm- Part A

End point description:

End point type	Secondary

End point timeframe:

Weeks 10 to 36

End point values	BAY94-9027 Prophylaxis Treatment – Part A			
Subject group type	Reporting group			
Number of subjects analysed	110[28]			
Units: bleeds				
median (full range (min-max))				
Joint Bleeds	1.93 (0 to 53.1)			
Trauma Bleeds	0 (0 to 14.4)			
Spontaneous Bleeds	0 (0 to 53.1)			

Notes:

[28] - Part A ITT population with subjects evaluable for this outcome

Statistical analyses

No statistical analyses for this end point

Secondary: Recombinant Human Factor VIII (rFVIII) Usage Expressed as Number of Infusions– Part A

End point title	Recombinant Human Factor VIII (rFVIII) Usage Expressed as Number of Infusions– Part A

End point description:

End point type	Secondary

End point timeframe:

Weeks 0 to 36

End point values	BAY94-9027 On-demand Treatment – Part A	BAY94-9027 Prophylaxis Treatment – Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[29]	112[30]		
Units: infusions				
median (full range (min-max))	29 (9 to 76)	59 (4 to 101)		

Notes:

[29] - Part A ITT population

[30] - Part A ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Recombinant Human Factor VIII (rFVIII) Usage Expressed as Total Dose per Kilogram per Year – Part A

End point title	Recombinant Human Factor VIII (rFVIII) Usage Expressed as Total Dose per Kilogram per Year – Part A

End point description:

End point type	Secondary

End point timeframe:

Weeks 0 to 36

End point values	BAY94-9027 On-demand Treatment – Part A	BAY94-9027 Prophylaxis Treatment – Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[31]	112[32]		
Units: IU/kg/year				
median (full range (min-max))	1518.5 (390 to 3655)	3255.7 (893 to 5915)		

Notes:
[31] - Part A ITT population
[32] - Part A ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Recombinant Human Factor VIII (rFVIII) Usage Expressed as Total Dose per Kilogram per Infusion - Part A

End point title	Recombinant Human Factor VIII (rFVIII) Usage Expressed as Total Dose per Kilogram per Infusion - Part A

End point description:

End point type	Secondary

End point timeframe:
Weeks 0 to 36 during Part A

End point values	BAY94-9027 On-demand Treatment – Part A	BAY94-9027 Prophylaxis Treatment – Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[33]	112[34]		
Units: IU/kg/infusion				
median (full range (min-max))	32.8 (23 to 58)	38.7 (25 to 48)		

Notes:
[33] - Part A ITT population
[34] - Part A ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Recombinant Human Factor VIII(rFVIII) Usage Expressed as Total Dose per Kilogram In Subjects with Prophylaxis Treatment – Part A

End point title	Recombinant Human Factor VIII(rFVIII) Usage Expressed as Total Dose per Kilogram In Subjects with Prophylaxis Treatment – Part A

End point description:

End point type	Secondary

End point timeframe:
Weeks 0 to 36 during Part A

End point values	BAY94-9027 Prophylaxis Treatment – Part A			
Subject group type	Reporting group			
Number of subjects analysed	112[35]			
Units: IU/kg				
median (full range (min-max))	2203.1 (100 to 2819)			

Notes:

[35] - Part A ITT population treated for prophylaxis

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Infusions to Control the Bleed – Part A

End point title	Number of Infusions to Control the Bleed – Part A

End point description:

End point type	Secondary

End point timeframe:

Weeks 0 to 36

End point values	BAY94-9027 On-demand Treatment – Part A	BAY94-9027 Prophylaxis Treatment – Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[36]	112[37]		
Units: bleeds				
1 infusion	307	262		
2 infusions	45	22		
Greater than or equal to (>=) 3 infusions	34	32		

Notes:

[36] - Part A ITT population

[37] - Part A ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Bleeds Over Time Since Previous Prophylaxis Infusion - Part A

End point title	Number of Bleeds Over Time Since Previous Prophylaxis Infusion - Part A

End point description:

End point type	Secondary

End point timeframe:

Weeks 0 to 36

End point values	BAY94-9027 Prophylaxis Treatment – Part A			
Subject group type	Reporting group			
Number of subjects analysed	110[38]			
Units: bleeds				
<1 day	19			
>=1 to <2 days	27			
>=2 to <3 days	43			
>=3 to <4 days	42			
>=4 to <5 days	28			
>=5 to <6 days	33			
>=6 to <7 days	11			
>=7 days	3			

Notes:

[38] - Part A ITT population with subjects evaluable for this ourcome

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Requiring Dose Escalation or Dose Increase During Weeks 10 to 36 – Part A

End point title	Number of Subjects Requiring Dose Escalation or Dose Increase During Weeks 10 to 36 – Part A[39]

End point description:

End point type	Secondary

End point timeframe:

Weeks 10 to 36 during Part A

Notes:

[39] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analysed during Part A only and reported as planned.

End point values	BAY94-9027 Treatment - Part A			
Subject group type	Reporting group			
Number of subjects analysed	110[40]			
Units: Subjects				
Dose frequency increased	11			
Dose increased	9			

Notes:

[40] - Part A ITT population with subjects evaluable for this outcome

Statistical analyses

No statistical analyses for this end point

Secondary: Physician's Assessment of Adequacy of Hemostasis During Minor Surgery – Part A

End point title	Physician's Assessment of Adequacy of Hemostasis During Minor Surgery – Part A[41]

End point description:

Minor surgery was defined as any surgical procedure that did not meet the definition of major, and included simple dental extractions, incision and drainage of abscesses, or simple excisions. A total of 17 minor surgeries performed in 10 subjects were reported during Part A of the study. Adequacy of hemostasis was assessed as excellent or good by the Physician during Part A of the study. The maximum blood loss during surgery was 100 mL during the draining of an abscess. No subjects required blood transfusions.

End point type	Secondary

End point timeframe:

Weeks 0 to 36 during Part A

Notes:

[41] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analysed during Part A and Part B, however, Physician's Assessment of Adequacy of Hemostasis during Part B was reported as a separate endpoint.

End point values	BAY94-9027 Treatment - Part A			
Subject group type	Reporting group			
Number of subjects analysed	10[42]			
Units: Number of surgeries				
Excellent	9			
Good	6			
Missing	2			

Notes:

[42] - Part A ITT population

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Change/Drop in Hemoglobin/Hematocrit Laboratory Assessments – Part B

End point title	Number of Subjects With Change/Drop in Hemoglobin/Hematocrit Laboratory Assessments – Part B

End point description:

Hematocrit is defined as the volume percentage (%) of red blood cells in blood. In the listed categories below, 'N' signifies the number of subjects evaluable for this outcome.

End point type	Other pre-specified

End point timeframe:

Baseline up to 6 weeks during Part B

End point values	BAY949027 Treatment in Major Surgery - Part B			
Subject group type	Reporting group			
Number of subjects analysed	16[43]			
Units: Subjects				
Hematocrit (N=11)	3			
Hemoglobin (N=11)	2			

Notes:

[43] - Part B Safety population

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Maximum Blood Loss in Major Surgery – Part B

End point title	Maximum Blood Loss in Major Surgery – Part B

End point description:

Major surgery was defined as any surgical or invasive procedure (elective or emergent) in which the overall bleeding risk was excessive, required a general anesthetic in an individual without a bleeding disorder, penetrated or exposed a major body cavity, resulted in substantial impairment of physical or physiological functions, or required special anatomic knowledge or manipulative skill.

End point type	Other pre-specified

End point timeframe:

Baseline up to 6 weeks during Part B

End point values	BAY949027 Treatment in Major Surgery - Part B			
Subject group type	Reporting group			
Number of subjects analysed	14[44]			
Units: milliliter				
number (not applicable)				
During surgery	1000			

Notes:

[44] - Part B ITT population with subjects treated for major surgery

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects who Took Anti-fibrinolytic Medications During Major Surgery – Part B

End point title	Number of Subjects who Took Anti-fibrinolytic Medications During Major Surgery – Part B

End point description:

Major surgery was defined as any surgical or invasive procedure (elective or emergent) in which the overall bleeding risk was excessive, required a general anesthetic in an individual without a bleeding disorder, penetrated or exposed a major body cavity, resulted in substantial impairment of physical or physiological functions, or required special anatomic knowledge or manipulative skill.

End point type	Other pre-specified

End point timeframe:

Baseline up to 6 weeks during Part B

End point values	BAY949027 Treatment in Major Surgery - Part B			
Subject group type	Reporting group			
Number of subjects analysed	14[45]			
Units: Subjects	6			

Notes:

[45] - Part B ITT population with subjects treated for major surgery

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Units of Blood Transfused in Major Surgery – Part B

End point title	Units of Blood Transfused in Major Surgery – Part B

End point description:

Major surgery was defined as any surgical or invasive procedure (elective or emergent) in which the overall bleeding risk was excessive, required a general anesthetic in an individual without a bleeding disorder, penetrated or exposed a major body cavity, resulted in substantial impairment of physical or physiological functions, or required special anatomic knowledge or manipulative skill.

End point type	Other pre-specified

End point timeframe:

Baseline up to 6 weeks during Part B

End point values	BAY949027 Treatment in Major Surgery - Part B			
Subject group type	Reporting group			
Number of subjects analysed	4[46]			
Units: Milliliter				
median (full range (min-max))	865 (600 to 1381.2)			

Notes:

[46] - Part B ITT population who had blood transfusions during major surgery

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collected after the first dose of study drug andup to 7 days after the last dose over a period of approximately two years

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	BAY94-9027 on-demand treatment - Part A

Reporting group description:

Subjects in on-demand treatment received BAY94-9027 as an intravenous (IV) infusion over a period of 1 to 15 minutes at a dose as indicated based upon location and severity of bleeds (maximum of 60 IU/kg (international units per kilogram)).

Reporting group title	BAY94-9027 treatment in Major surgery - Part B

Reporting group description:

Subjects who underwent major surgery received BAY 94-9027 IV infusion over a period of 1 to 15 minutes, for pre-surgical pharmacokinetic (PK) sampling, for surgery, and for the post-surgical period up to the time of discharge for a period not exceeding 3 weeks. Subjects were treated according to the type of procedure, using doses expected to maintain therapeutic levels of human coagulation factor VIII (FVIII) activity based upon pre-surgical PK measurements. The recommended maximum dose was 60 IU/kg. All treatments were administered as needed, and the dose was tailored to a subject's individual response.

Reporting group title	BAY94-9027 prophylaxis treatment - Part A

Reporting group description:

Subjects in prophylaxis treatment started BAY94-9027 IV infusion over a period of 1 to 15 minutes, with 2 times per week (2x/week) at a dose of 25-40 IU/kg for 10 weeks. Thereafter, only subjects with less than 2 breakthrough (spontaneous, no identified trauma) joint and/or muscle bleeds qualified for random assignment to the less frequent dosing regimens. High bleeders continued 2x/week infusion. Subjects who qualified to be randomized, but enrolled after the every 5 day and every 7 day treatment arms were filled, remained on 2x/week treatment (2x/week forced group).

Serious adverse events	BAY94-9027 on-demand treatment - Part A	BAY94-9027 treatment in Major surgery - Part B	BAY94-9027 prophylaxis treatment - Part A
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 20 (20.00%)	2 / 16 (12.50%)	9 / 114 (7.89%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Anti factor VIII antibody positive			
subjects affected / exposed	0 / 20 (0.00%)	2 / 16 (12.50%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonoscopy			

subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 114 (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
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 114 (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
Injury			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 114 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Knee arthroplasty			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 114 (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
General disorders and administration site conditions			
Device malfunction			

subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 114 (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
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthropathy			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemarthrosis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemophilic arthropathy			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Device related infection			

subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 114 (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
Gastroenteritis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 114 (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

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

Non-serious adverse events	BAY94-9027 on-demand treatment - Part A	BAY94-9027 treatment in Major surgery - Part B	BAY94-9027 prophylaxis treatment - Part A
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 20 (70.00%)	12 / 16 (75.00%)	61 / 114 (53.51%)
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 20 (0.00%)	2 / 16 (12.50%)	1 / 114 (0.88%)
occurrences (all)	0	2	1
Hypertension			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 114 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	1 / 114 (0.88%)
occurrences (all)	1	0	1
Fatigue			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	2 / 114 (1.75%)
occurrences (all)	1	0	3
Hyperthermia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 114 (0.00%)
occurrences (all)	0	2	0

Injection site rash			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 114 (0.00%)
occurrences (all)	1	0	0
Local swelling			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 114 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	1 / 20 (5.00%)	2 / 16 (12.50%)	0 / 114 (0.00%)
occurrences (all)	1	2	0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 114 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 20 (10.00%)	0 / 16 (0.00%)	6 / 114 (5.26%)
occurrences (all)	3	0	8
Dyspnoea			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	1 / 114 (0.88%)
occurrences (all)	1	0	1
Epistaxis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	8 / 114 (7.02%)
occurrences (all)	0	0	10
Oropharyngeal pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 114 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	3 / 114 (2.63%)
occurrences (all)	0	1	3
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	1 / 114 (0.88%)
occurrences (all)	2	0	1
Blood magnesium decreased			

subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 114 (0.00%)
occurrences (all)	1	0	0
Haemoglobin decreased			
subjects affected / exposed	0 / 20 (0.00%)	3 / 16 (18.75%)	0 / 114 (0.00%)
occurrences (all)	0	3	0
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 114 (0.00%)
occurrences (all)	0	1	0
Arthropod bite			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	1 / 114 (0.88%)
occurrences (all)	1	0	1
Excoriation			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	1 / 114 (0.88%)
occurrences (all)	1	0	1
Fall			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 114 (0.00%)
occurrences (all)	1	0	0
Ligament sprain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	4 / 114 (3.51%)
occurrences (all)	1	0	6
Post procedural oedema			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 114 (0.00%)
occurrences (all)	0	2	0
Procedural haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	3 / 16 (18.75%)	0 / 114 (0.00%)
occurrences (all)	0	3	0
Procedural hypotension			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 114 (0.00%)
occurrences (all)	0	1	0
Procedural nausea			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 114 (0.00%)
occurrences (all)	0	1	0
Procedural pain			

subjects affected / exposed	0 / 20 (0.00%)	3 / 16 (18.75%)	2 / 114 (1.75%)
occurrences (all)	0	4	2
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 114 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	15 / 114 (13.16%)
occurrences (all)	1	0	27
Blood and lymphatic system disorders			
Splenomegaly			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 114 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Cataract			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 114 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 114 (0.00%)
occurrences (all)	0	1	0
Dental caries			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	2 / 114 (1.75%)
occurrences (all)	1	0	3
Diarrhoea			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	3 / 114 (2.63%)
occurrences (all)	1	0	4
Dry mouth			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 114 (0.00%)
occurrences (all)	1	0	0
Food poisoning			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	1 / 114 (0.88%)
occurrences (all)	1	0	1
Melaena			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 114 (0.00%)
occurrences (all)	0	1	0

Nausea			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	4 / 114 (3.51%)
occurrences (all)	1	0	5
Toothache			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	3 / 114 (2.63%)
occurrences (all)	1	0	3
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 114 (0.00%)
occurrences (all)	1	0	0
Hepatic steatosis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 114 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 114 (0.00%)
occurrences (all)	0	1	0
Dermatitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Dermatitis allergic			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 114 (0.00%)
occurrences (all)	1	0	0
Haemorrhage subcutaneous			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 114 (0.00%)
occurrences (all)	0	1	0
Ingrowing nail			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 114 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	1 / 114 (0.88%)
occurrences (all)	2	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	1 / 20 (5.00%)	1 / 16 (6.25%)	9 / 114 (7.89%)
occurrences (all)	1	1	11
Arthritis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 114 (0.00%)
occurrences (all)	0	1	0
Back pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 16 (0.00%)	8 / 114 (7.02%)
occurrences (all)	0	0	10
Extremity contracture			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 114 (0.00%)
occurrences (all)	1	0	0
Haemarthrosis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Musculoskeletal discomfort			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 114 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	3 / 114 (2.63%)
occurrences (all)	1	0	4
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 114 (0.00%)
occurrences (all)	1	0	0
Herpes zoster			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	1 / 114 (0.88%)
occurrences (all)	1	0	1
Lymphangitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 16 (6.25%)	0 / 114 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	2 / 20 (10.00%)	1 / 16 (6.25%)	22 / 114 (19.30%)
occurrences (all)	3	1	31
Otitis externa			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	1 / 114 (0.88%)
occurrences (all)	1	0	1

Otitis media			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	1 / 114 (0.88%)
occurrences (all)	1	0	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	2 / 114 (1.75%)
occurrences (all)	1	0	2
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	1 / 114 (0.88%)
occurrences (all)	2	0	1
Hypertriglyceridaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 114 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 16 (0.00%)	0 / 114 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 April 2012	Implemented changes and clarifications secondary to the recommendations of regulatory agencies and in response to specific questions and comments received from pediatric specialists and investigators. The primary revision was a prolongation of the total treatment period from 32 to 36 weeks allowing for a longer observation period after subjects in the prophylaxis treatment arm had been randomized to a less frequent infusion schedule. Stopping rules in the event of inhibitor development were defined and a scheduled data monitoring committee review of the efficacy and safety of BAY94-9027 in the prophylaxis arms was added to occur after approximately 20 subjects had completed 2 months of treatment following randomization. The objectives were modified to clarify that inhibitor development was a specific important safety outcome and an additional laboratory assessment was added to measure possible peak antibody response following the first dose of BAY94-9027. Minor changes included clarification of the time points for PK assessments, the duration of wash-outs required for specific observations, and definition of objective criteria to assess efficacy of surgical interventions. The efficacy variables for Part A were categorized to aid understanding of the outcomes being assessed.
13 December 2012	Added an optional extension to allow subjects to continue treatment with BAY94-9027 after completion of Part A of the main study. Text was added to more fully define for investigators the effects of the longer half-life of BAY94-9027 on the intervals required for repeat and follow-up infusions for the treatment of bleeds, and additional information for situations when local monitoring of FVIII may have been obtained, including clarification of the reagents that may have been used. Information regarding the available vial sizes, storage, and use of BAY94-9027 was updated.
25 March 2014	The purpose of the amendment was to add to the protocol an optional extension of Part B to allow subjects to continue to undergo major surgeries using BAY94-9027 during the Part A extension and after ten Part B subjects had completed major surgery.

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.

"±" in relation with geometric CV is auto-generated.Decimal places automatically truncated.Patient satisfaction & burden were not reported due to concerns regarding instrument development & validation, and translation error in 2 questionnaire items.

Notes: