



Clinical trial results:

A phase II/III, randomized, cross-over, open-label trial to demonstrate superiority of prophylaxis over on-demand therapy in previously treated subjects with severe hemophilia A treated with plasma protein-free recombinant FVIII formulated with sucrose (BAY 81-8973)

Summary

EudraCT number	2009-012150-20
Trial protocol	CZ
Global end of trial date	05 December 2012

Results information

Result version number	v1
This version publication date	12 July 2016
First version publication date	28 June 2015

Trial information

Trial identification

Sponsor protocol code	BAY81-8973/14319
-----------------------	------------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01233258
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer HealthCare AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368
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	06 May 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	05 December 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that 2-3 times per week prophylaxis therapy with BAY81-8973 is superior to on-demand therapy with BAY81-8973 in subjects with severe Hemophilia A. The hypothesis was that prophylaxis will result in fewer bleeds than on-demand treatment.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects and/or their legally authorized representatives. Participating subjects and/or their legally authorized representatives signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 January 2011
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	Japan: 9
Country: Number of subjects enrolled	Mexico: 9
Country: Number of subjects enrolled	Romania: 18
Country: Number of subjects enrolled	China: 31
Country: Number of subjects enrolled	Serbia: 5
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	Turkey: 5
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	United States: 2
Country: Number of subjects enrolled	South Africa: 6
Country: Number of subjects enrolled	Czech Republic: 2
Worldwide total number of subjects	97
EEA total number of subjects	20

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	11
Adults (18-64 years)	86
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from specialized hemophilia treatment centers.

Pre-assignment

Screening details:

A total of 83 subjects were randomized, but 3 of these terminated the study before their first injection of study drug.

Period 1

Period 1 title	First Intervention (6 Months)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	On Demand, BAY81-8973 Potency First EP Then ADJ

Arm description:

Subjects received on-demand treatment with recombinant factor VIII (rFVIII, BAY81-8973) assayed by Chromogenic Substrate Assay per European Pharmacopoeia (CS/EP) for 6 months, followed by crossover to study drug assayed by Chromogenic Substrate Assay/label adjusted to one-stage assay (CS/ADJ) for 6 months.

Arm type	Experimental
Investigational medicinal product name	Recombinant factor VIII
Investigational medicinal product code	BAY81-8973
Other name	rFVIII
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received BAY81-8973 as an intravenous (IV) injection manually over 1 to 15 minutes. The dosage was adjusted to bleeding location and severity and to current standard of care.

Arm title	On Demand, BAY81-8973 Potency First ADJ Then EP
------------------	---

Arm description:

Subjects received on-demand treatment with rFVIII (BAY81-8973) assayed by CS/ADJ for 6 months, followed by cross-over to study drug assayed by CS/EP for 6 months.

Arm type	Experimental
Investigational medicinal product name	Recombinant factor VIII
Investigational medicinal product code	BAY81-8973
Other name	rFVIII
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received BAY81-8973 as an IV injection manually over 1 to 15 minutes. The dosage was adjusted to bleeding location and severity and to current standard of care.

Arm title	Low Dose Prophylaxis, BAY81-8973 Potency First EP Then ADJ
------------------	--

Arm description:

Subjects received low dose prophylaxis treatment at 20, 25 or 30 international units per kilogram (IU/kg) twice per week with rFVIII (BAY81-8973) assayed by CS/EP for 6 months then crossed over to study drug assayed by CS/ADJ for 6 months.

Arm type	Experimental
----------	--------------

Investigational medicinal product name	Recombinant factor VIII
Investigational medicinal product code	BAY81-8973
Other name	rFVIII
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received low dose prophylaxis treatment at 20, 25 or 30 IU/kg twice per week with rFVIII (BAY81-8973) as an IV injection manually over 1 to 15 minutes, assayed by CS/EP for 6 months then crossed over to study drug assayed by CS/ADJ for 6 months.

Arm title	Low Dose Prophylaxis, BAY81-8973 Potency First ADJ Then EP
------------------	--

Arm description:

Subjects received low dose prophylaxis treatment at 20, 25 or 30 IU/kg twice per week with rFVIII (BAY81-8973) assayed by CS/ADJ for 6 months then crossed over to study drug assayed by CS/EP for 6 months.

Arm type	Experimental
Investigational medicinal product name	Recombinant factor VIII
Investigational medicinal product code	BAY81-8973
Other name	rFVIII
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received low dose prophylaxis treatment at 20, 25 or 30 IU/kg twice per week with rFVIII (BAY81-8973) as an IV injection manually over 1 to 15 minutes, assayed by CS/ADJ for 6 months then crossed over to study drug assayed by CS/EP for 6 months.

Arm title	High Dose Prophylaxis, BAY81-8973 Potency First EP Then ADJ
------------------	---

Arm description:

Subjects received high dose prophylaxis treatment at 30, 35 or 40 IU/kg 3 times per week with rFVIII (BAY81-8973) assayed by CS/EP for 6 months then crossed over to study drug assayed by CS/ADJ for 6 months.

Arm type	Experimental
Investigational medicinal product name	Recombinant factor VIII
Investigational medicinal product code	BAY81-8973
Other name	rFVIII
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received high dose prophylaxis treatment at 30, 35 or 40 IU/kg 3 times per week with rFVIII (BAY81-8973) as an IV injection manually over 1 to 15 minutes, assayed by CS/EP for 6 months then crossed over to study drug assayed by CS/ADJ for 6 months.

Arm title	High Dose Prophylaxis, BAY81-8973 Potency First ADJ Then EP
------------------	---

Arm description:

Subjects received high dose prophylaxis treatment at 30, 35 or 40 IU/kg 3 times per week with rFVIII (BAY81-8973) assayed by CS/ADJ for 6 months then crossed over to study drug assayed by CS/ EP for 6 months.

Arm type	Experimental
Investigational medicinal product name	Recombinant factor VIII
Investigational medicinal product code	BAY81-8973
Other name	rFVIII
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received high dose prophylaxis treatment at 30, 35 or 40 IU/kg 3 times per week with rFVIII (BAY81-8973) as an IV injection manually over 1 to 15 minutes, assayed by CS/ADJ for 6 months then crossed over to study drug assayed by CS/EP for 6 months.

Number of subjects in period 1	On Demand, BAY81-8973 Potency First EP Then ADJ	On Demand, BAY81-8973 Potency First ADJ Then EP	Low Dose Prophylaxis, BAY81-8973 Potency First EP Then ADJ
Started	11	10	14
Treated	11	10	13
Completed	10	10	13
Not completed	1	0	1
Consent withdrawn by subject	-	-	-
Non-compliance with study medication	1	-	-
Protocol deviation	-	-	1

Number of subjects in period 1	Low Dose Prophylaxis, BAY81-8973 Potency First ADJ Then EP	High Dose Prophylaxis, BAY81-8973 Potency First EP Then ADJ	High Dose Prophylaxis, BAY81-8973 Potency First ADJ Then EP
Started	16	16	16
Treated	15	16	15
Completed	15	16	15
Not completed	1	0	1
Consent withdrawn by subject	1	-	1
Non-compliance with study medication	-	-	-
Protocol deviation	-	-	-

Period 2

Period 2 title	Second Intervention (6 months)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	On Demand, BAY81-8973 Potency First EP Then ADJ

Arm description:

Subjects received on-demand treatment with recombinant factor VIII (rFVIII, BAY81-8973) assayed by CS/EP for 6 months, followed by cross-over to study drug assayed by CS/ADJ for 6 months.

Arm type	Experimental
Investigational medicinal product name	Recombinant factor VIII
Investigational medicinal product code	BAY81-8973
Other name	rFVIII
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received BAY81-8973 as an intravenous (IV) injection manually over 1 to 15 minutes. The dosage was adjusted to bleeding location and severity and to current standard of care.

Arm title	On Demand, BAY81-8973 Potency First ADJ Then EP
------------------	---

Arm description:

Subjects received on-demand treatment with rFVIII (BAY81-8973) assayed by CS/ADJ for 6 months, followed by cross-over to study drug assayed by CS/EP for 6 months.

Arm type	Experimental
Investigational medicinal product name	Recombinant factor VIII
Investigational medicinal product code	BAY81-8973
Other name	rFVIII
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received BAY81-8973 as an IV injection manually over 1 to 15 minutes. The dosage was adjusted to bleeding location and severity and to current standard of care.

Arm title	Low Dose Prophylaxis, BAY81-8973 Potency First EP Then ADJ
------------------	--

Arm description:

Subjects received low dose prophylaxis treatment at 20, 25 or 30 IU/kg twice per week with rFVIII (BAY81-8973) assayed by CS/ EP for 6 months then crossed over to study drug assayed by CS/ADJ for 6 months.

Arm type	Experimental
Investigational medicinal product name	Recombinant factor VIII
Investigational medicinal product code	BAY81-8973
Other name	rFVIII
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received low dose prophylaxis treatment at 20, 25 or 30 IU/kg twice per week with rFVIII (BAY81-8973) as an IV injection manually over 1 to 15 minutes, assayed by CS/EP for 6 months then crossed over to study drug assayed by CS/ADJ for 6 months.

Arm title	Low Dose Prophylaxis, BAY81-8973 Potency First ADJ Then EP
------------------	--

Arm description:

Subjects received low dose prophylaxis treatment at 20, 25 or 30 IU/kg twice per week with rFVIII (BAY81-8973) assayed by CS/ADJ for 6 months then crossed over to study drug assayed by CS/EP for 6 months.

Arm type	Experimental
Investigational medicinal product name	Recombinant factor VIII
Investigational medicinal product code	BAY81-8973
Other name	rFVIII
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received low dose prophylaxis treatment at 20, 25 or 30 IU/kg twice per week with rFVIII (BAY81-8973) as an IV injection manually over 1 to 15 minutes, assayed by CS/ADJ for 6 months then crossed over to study drug assayed by CS/EP for 6 months.

Arm title	High Dose Prophylaxis, BAY81-8973 Potency First EP Then ADJ
------------------	---

Arm description:

Subjects received high dose prophylaxis treatment at 30, 35 or 40 IU/kg 3 times per week with rFVIII (BAY81-8973) assayed by CS/EP for 6 months then crossed over to study drug assayed by CS/ADJ for 6 months.

Arm type	Experimental
----------	--------------

Investigational medicinal product name	Recombinant factor VIII
Investigational medicinal product code	BAY81-8973
Other name	rFVIII
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received high dose prophylaxis treatment at 30, 35 or 40 IU/kg 3 times per week with rFVIII (BAY81-8973) as an IV injection manually over 1 to 15 minutes, assayed by CS/EP for 6 months then crossed over to study drug assayed by CS/ADJ for 6 months.

Arm title	High Dose Prophylaxis, BAY81-8973 Potency First ADJ Then EP
------------------	---

Arm description:

Subjects received high dose prophylaxis treatment at 30, 35 or 40 IU/kg 3 times per week with rFVIII (BAY81-8973) assayed by CS/ADJ for 6 months then crossed over to study drug assayed by CS/ EP for 6 months.

Arm type	Experimental
Investigational medicinal product name	Recombinant factor VIII
Investigational medicinal product code	BAY81-8973
Other name	rFVIII
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received high dose prophylaxis treatment at 30, 35 or 40 IU/kg 3 times per week with rFVIII (BAY81-8973) as an IV injection manually over 1 to 15 minutes, assayed by CS/ADJ for 6 months then crossed over to study drug assayed by CS/EP for 6 months.

Number of subjects in period 2	On Demand, BAY81-8973 Potency First EP Then ADJ	On Demand, BAY81-8973 Potency First ADJ Then EP	Low Dose Prophylaxis, BAY81-8973 Potency First EP Then ADJ
Started	10	10	13
Completed	10	10	13

Number of subjects in period 2	Low Dose Prophylaxis, BAY81-8973 Potency First ADJ Then EP	High Dose Prophylaxis, BAY81-8973 Potency First EP Then ADJ	High Dose Prophylaxis, BAY81-8973 Potency First ADJ Then EP
Started	15	16	15
Completed	15	16	15

Period 3

Period 3 title	Baseline period
Is this the baseline period?	Yes ^[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
------------------------------	-----

Arm title	rFVIII (BAY81-8973) on Demand
------------------	-------------------------------

Arm description:

Subjects received on-demand treatment with rFVIII (BAY81-8973) assayed by CS/EP for 6 months and by CS/ADJ for 6 months, sequence according to randomization. Subjects who received treatment were included in baseline period.

Arm type	Experimental
Investigational medicinal product name	Recombinant factor VIII
Investigational medicinal product code	BAY81-8973
Other name	rFVIII
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received BAY81-8973 as an IV injection manually over 1 to 15 minutes. The dosage was adjusted to bleeding location and severity and to current standard of care.

Arm title	rFVIII (BAY81-8973) Prophylaxis Low-dose
------------------	--

Arm description:

Subjects received low dose prophylaxis treatment at 20, 25 or 30 IU/kg twice per week with rFVIII (BAY81-8973) assayed by CS/EP for 6 months and by CS/ADJ for 6 months, sequence according to randomization. Subjects who received treatment were included in baseline period.

Arm type	Experimental
Investigational medicinal product name	Recombinant factor VIII
Investigational medicinal product code	BAY81-8973
Other name	rFVIII
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received low dose prophylaxis treatment at 20, 25 or 30 IU/kg twice per week with rFVIII (BAY81-8973) as an IV injection manually over 1 to 15 minutes, assayed by CS/EP for 6 months then crossed over to study drug assayed by CS/ADJ for 6 months.

Arm title	rFVIII (BAY81-8973) Prophylaxis High-dose
------------------	---

Arm description:

Subjects received high dose prophylaxis treatment at 30, 35 or 40 IU/kg 3 times per week with rFVIII (BAY81-8973) assayed by CS/EP for 6 months and by CS/ADJ for 6 months, sequence according to randomization. Subjects who received treatment were included in baseline period.

Arm type	Experimental
Investigational medicinal product name	Recombinant factor VIII
Investigational medicinal product code	BAY81-8973
Other name	rFVIII
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received high dose prophylaxis treatment at 30, 35 or 40 IU/kg 3 times per week with rFVIII (BAY81-8973) assayed by CS/EP for 6 months and by CS/ADJ for 6 months, sequence according to randomization.

Notes:

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

Justification: All randomized subjects were included in the intervention periods but the baseline characteristics were recorded only for treated subjects as planned. Hence, a baseline period consisting of only treated subjects was created after the intervention periods.

Number of subjects in period 3 ^[2]	rFVIII (BAY81-8973) on Demand	rFVIII (BAY81-8973) Prophylaxis Low- dose	rFVIII (BAY81-8973) Prophylaxis High- dose
Started	21	28	31
Completed	21	28	31

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

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

Baseline characteristics

Reporting groups

Reporting group title	rFVIII (BAY81-8973) on Demand
Reporting group description:	
Subjects received on-demand treatment with rFVIII (BAY81-8973) assayed by CS/EP for 6 months and by CS/ADJ for 6 months, sequence according to randomization. Subjects who received treatment were included in baseline period.	
Reporting group title	rFVIII (BAY81-8973) Prophylaxis Low-dose
Reporting group description:	
Subjects received low dose prophylaxis treatment at 20, 25 or 30 IU/kg twice per week with rFVIII (BAY81-8973) assayed by CS/EP for 6 months and by CS/ADJ for 6 months, sequence according to randomization. Subjects who received treatment were included in baseline period.	
Reporting group title	rFVIII (BAY81-8973) Prophylaxis High-dose
Reporting group description:	
Subjects received high dose prophylaxis treatment at 30, 35 or 40 IU/kg 3 times per week with rFVIII (BAY81-8973) assayed by CS/EP for 6 months and by CS/ADJ for 6 months, sequence according to randomization. Subjects who received treatment were included in baseline period.	

Reporting group values	rFVIII (BAY81-8973) on Demand	rFVIII (BAY81-8973) Prophylaxis Low- dose	rFVIII (BAY81-8973) Prophylaxis High- dose
Number of subjects	21	28	31
Age categorical			
Units: Subjects			
Adolescents (12-17 years)	2	4	4
Adults (18-64 years)	19	24	27
Total			
Age continuous			
Units: years			
arithmetic mean	31.4	28.8	29.1
standard deviation	± 10.9	± 10.9	± 11.5
Total			
Gender categorical			
Units: participants			
Male	21	28	31

Reporting group values	Total		
Number of subjects	80		
Age categorical			
Units: Subjects			
Adolescents (12-17 years)	10		
Adults (18-64 years)	70		
Total			
Age continuous			
Units: years			
arithmetic mean	-		
standard deviation			
Total			
Gender categorical			
Units: participants			

Male	80		
------	----	--	--

End points

End points reporting groups

Reporting group title	On Demand, BAY81-8973 Potency First EP Then ADJ
Reporting group description: Subjects received on-demand treatment with recombinant factor VIII (rFVIII, BAY81-8973) assayed by Chromogenic Substrate Assay per European Pharmacopoeia (CS/EP) for 6 months, followed by crossover to study drug assayed by Chromogenic Substrate Assay/label adjusted to one-stage assay (CS/ADJ) for 6 months.	
Reporting group title	On Demand, BAY81-8973 Potency First ADJ Then EP
Reporting group description: Subjects received on-demand treatment with rFVIII (BAY81-8973) assayed by CS/ADJ for 6 months, followed by cross-over to study drug assayed by CS/EP for 6 months.	
Reporting group title	Low Dose Prophylaxis, BAY81-8973 Potency First EP Then ADJ
Reporting group description: Subjects received low dose prophylaxis treatment at 20, 25 or 30 international units per kilogram (IU/kg) twice per week with rFVIII (BAY81-8973) assayed by CS/EP for 6 months then crossed over to study drug assayed by CS/ADJ for 6 months.	
Reporting group title	Low Dose Prophylaxis, BAY81-8973 Potency First ADJ Then EP
Reporting group description: Subjects received low dose prophylaxis treatment at 20, 25 or 30 IU/kg twice per week with rFVIII (BAY81-8973) assayed by CS/ADJ for 6 months then crossed over to study drug assayed by CS/EP for 6 months.	
Reporting group title	High Dose Prophylaxis, BAY81-8973 Potency First EP Then ADJ
Reporting group description: Subjects received high dose prophylaxis treatment at 30, 35 or 40 IU/kg 3 times per week with rFVIII (BAY81-8973) assayed by CS/EP for 6 months then crossed over to study drug assayed by CS/ADJ for 6 months.	
Reporting group title	High Dose Prophylaxis, BAY81-8973 Potency First ADJ Then EP
Reporting group description: Subjects received high dose prophylaxis treatment at 30, 35 or 40 IU/kg 3 times per week with rFVIII (BAY81-8973) assayed by CS/ADJ for 6 months then crossed over to study drug assayed by CS/ EP for 6 months.	
Reporting group title	On Demand, BAY81-8973 Potency First EP Then ADJ
Reporting group description: Subjects received on-demand treatment with recombinant factor VIII (rFVIII, BAY81-8973) assayed by CS/EP for 6 months, followed by cross-over to study drug assayed by CS/ADJ for 6 months.	
Reporting group title	On Demand, BAY81-8973 Potency First ADJ Then EP
Reporting group description: Subjects received on-demand treatment with rFVIII (BAY81-8973) assayed by CS/ADJ for 6 months, followed by cross-over to study drug assayed by CS/EP for 6 months.	
Reporting group title	Low Dose Prophylaxis, BAY81-8973 Potency First EP Then ADJ
Reporting group description: Subjects received low dose prophylaxis treatment at 20, 25 or 30 IU/kg twice per week with rFVIII (BAY81-8973) assayed by CS/ EP for 6 months then crossed over to study drug assayed by CS/ADJ for 6 months.	
Reporting group title	Low Dose Prophylaxis, BAY81-8973 Potency First ADJ Then EP
Reporting group description: Subjects received low dose prophylaxis treatment at 20, 25 or 30 IU/kg twice per week with rFVIII (BAY81-8973) assayed by CS/ADJ for 6 months then crossed over to study drug assayed by CS/EP for 6 months.	
Reporting group title	High Dose Prophylaxis, BAY81-8973 Potency First EP Then ADJ
Reporting group description: Subjects received high dose prophylaxis treatment at 30, 35 or 40 IU/kg 3 times per week with rFVIII (BAY81-8973) assayed by CS/EP for 6 months then crossed over to study drug assayed by CS/ADJ for 6 months.	

Reporting group title	High Dose Prophylaxis, BAY81-8973 Potency First ADJ Then EP
Reporting group description:	
Subjects received high dose prophylaxis treatment at 30, 35 or 40 IU/kg 3 times per week with rFVIII (BAY81-8973) assayed by CS/ADJ for 6 months then crossed over to study drug assayed by CS/ EP for 6 months.	
Reporting group title	rFVIII (BAY81-8973) on Demand
Reporting group description:	
Subjects received on-demand treatment with rFVIII (BAY81-8973) assayed by CS/EP for 6 months and by CS/ADJ for 6 months, sequence according to randomization. Subjects who received treatment were included in baseline period.	
Reporting group title	rFVIII (BAY81-8973) Prophylaxis Low-dose
Reporting group description:	
Subjects received low dose prophylaxis treatment at 20, 25 or 30 IU/kg twice per week with rFVIII (BAY81-8973) assayed by CS/EP for 6 months and by CS/ADJ for 6 months, sequence according to randomization. Subjects who received treatment were included in baseline period.	
Reporting group title	rFVIII (BAY81-8973) Prophylaxis High-dose
Reporting group description:	
Subjects received high dose prophylaxis treatment at 30, 35 or 40 IU/kg 3 times per week with rFVIII (BAY81-8973) assayed by CS/EP for 6 months and by CS/ADJ for 6 months, sequence according to randomization. Subjects who received treatment were included in baseline period.	
Subject analysis set title	rFVIII (BAY81-8973) Prophylaxis Treatment
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received prophylaxis treatment with rFVIII (BAY81-8973) at low-dose (20, 25 or 30 IU/kg twice per week) and high-dose (30, 35 or 40 IU/kg 3 times per week) assayed by CS/EP for 6 months and by CS/ADJ for 6 months, sequence according to randomization.	
Subject analysis set title	rFVIII (BAY81-8973) on Demand Assayed by CS/EP
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received on-demand treatment with rFVIII (BAY81-8973) assayed by CS/EP for 6 months.	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects randomized into the study who received at least 1 injection of study medication.	
Subject analysis set title	rFVIII (BAY81-8973) Prophylaxis Treatment Assayed by CS/EP
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received prophylaxis treatment with rFVIII (BAY81-8973) at low-dose (20, 25 or 30 IU/kg twice per week) and high-dose (30, 35 or 40 IU/kg 3 times per week) assayed by CS/EP for 6 months.	
Subject analysis set title	rFVIII (BAY81-8973) Prophylaxis Treatment Assayed by CS/ADJ
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received prophylaxis treatment with rFVIII (BAY81-8973) at low-dose (20, 25 or 30 IU/kg twice per week) and high-dose (30, 35 or 40 IU/kg 3 times per week) assayed by CS/ADJ for 6 months.	
Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects in the safety population who have injection / bleeding data from the electronic patient diary (EPD) and/or case report form (CRF).	
Subject analysis set title	rFVIII (BAY81-8973) on Demand Assayed by CS/ADJ
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received on-demand treatment with rFVIII (BAY81-8973) assayed by CS/ADJ for 6 months.	

Primary: Annualized Number of All Bleeds

End point title	Annualized Number of All Bleeds ^[1]
-----------------	--

End point description:

The annualized number of bleeds experienced by subjects.

End point type	Primary
----------------	---------

End point timeframe:

Up to 12 months (6 months per mode of potency assignment according to the randomized cross-over design)

Notes:

[1] - 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: Low and high dose prophylaxis arms of the baseline period and both potencies combined as planned for the statistical analysis to achieve intended sample size. Hence, the end point is reporting statistics for a combined arm (created as a subject analysis set) instead of the individual arms in the baseline period.

End point values	rFVIII (BAY81-8973) on Demand	rFVIII (BAY81-8973) Prophylaxis Treatment		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	21 ^[2]	59 ^[3]		
Units: Bleeds per year per subject				
arithmetic mean (standard deviation)	57.7 (± 24.6)	4.9 (± 6.8)		

Notes:

[2] - ITT population

[3] - ITT population

Statistical analyses

Statistical analysis title	On Demand versus Prophylaxis Treatment
----------------------------	--

Statistical analysis description:

Null hypothesis: bleeding rates are equal, alternative hypothesis rates are unequal. Power calculation: Assumption 5 bleeds per year on prophylactic treatment, 15 on on-demand treatment; combined standard deviation of 11; 3:1 randomization; 2-sided alpha 5% and 90% power.

Comparison groups	rFVIII (BAY81-8973) on Demand v rFVIII (BAY81-8973) Prophylaxis Treatment
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	ANOVA

Secondary: Annualized Number of All Bleeds During CS/EP Period

End point title	Annualized Number of All Bleeds During CS/EP Period
-----------------	---

End point description:

The annualized number of bleeds experienced by subjects while they were taking rFVIII (BAY81-8973) assayed by CS/EP

End point type	Secondary
----------------	-----------

End point timeframe:

Up to 6 months (6 months on CS/EP potency assignment)

End point values	rFVIII (BAY81-8973) on Demand Assayed by CS/EP	rFVIII (BAY81-8973) Prophylaxis Treatment Assayed by CS/EP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21 ^[4]	59 ^[5]		
Units: Bleeds per year per subject				
arithmetic mean (standard deviation)	57.6 (± 24.3)	5.1 (± 8)		

Notes:

[4] - ITT population

[5] - ITT population

Statistical analyses

Statistical analysis title	On Demand versus Prophylaxis Treatment
Statistical analysis description:	
Null hypothesis: bleeding rates are equal, alternative hypothesis rates are unequal. Power calculation not done for this comparison as not primary comparison.	
Comparison groups	rFVIII (BAY81-8973) Prophylaxis Treatment Assayed by CS/EP v rFVIII (BAY81-8973) on Demand Assayed by CS/EP
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	ANOVA

Secondary: Annualized Number of All Bleeds During CS/ADJ Period

End point title	Annualized Number of All Bleeds During CS/ADJ Period
End point description:	
The annualized number of bleeds experienced by subjects while they were taking rFVIII (BAY81-8973) assayed by CS/ADJ.	
End point type	Secondary
End point timeframe:	
Up to 6 months (6 months on CS/ADJ potency assignment)	

End point values	rFVIII (BAY81-8973) on Demand Assayed by CS/ADJ	rFVIII (BAY81-8973) Prophylaxis Treatment Assayed by CS/ADJ		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20 ^[6]	59 ^[7]		
Units: Bleeds per year per subject				
arithmetic mean (standard deviation)	59.7 (± 25.1)	4.8 (± 6.8)		

Notes:

[6] - ITT population

[7] - ITT population

Statistical analyses

Statistical analysis title	On Demand versus Prophylaxis Treatment
Statistical analysis description: Null hypothesis: bleeding rates are equal, alternative hypothesis rates are unequal. Power calculation not done for this comparison as not primary comparison.	
Comparison groups	rFVIII (BAY81-8973) Prophylaxis Treatment Assayed by CS/ADJ v rFVIII (BAY81-8973) on Demand Assayed by CS/ADJ
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority ^[8]
P-value	= 0.0001
Method	ANOVA

Notes:

[8] - comment

Secondary: Percentage of Bleeds Per Subject Controlled With ≤ 2 Injections in Subjects Treated on Demand With rFVIII (BAY81-8973)

End point title	Percentage of Bleeds Per Subject Controlled With ≤ 2 Injections in Subjects Treated on Demand With rFVIII (BAY81-8973)
End point description: The percentage of bleeds per subject on on-demand treatment that stopped after two or fewer injections	
End point type	Secondary
End point timeframe: Up to 12 months (6 months per mode of potency assignment according to the randomized cross-over design)	

End point values	rFVIII (BAY81-8973) on Demand Assayed by CS/EP	rFVIII (BAY81-8973) on Demand Assayed by CS/ADJ		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21 ^[9]	20 ^[10]		
Units: Percentage of bleeds				
median (full range (min-max))	96.8 (77.8 to 100)	100 (65.7 to 100)		

Notes:

[9] - ITT population

[10] - ITT population

Statistical analyses

Statistical analysis title	CS/EP versus CS/ADJ
Statistical analysis description: Null hypothesis: the proportion of bleeds controlled by no more than 2 infusions in the CS/EP group +10% is less than the proportion of bleeds controlled by no more than 2 infusions in the CS/ADJ group. Alternative hypothesis: the proportion of bleeds controlled by no more than 2 infusions in the CS/EP group + 10% is greater than or equal to the proportion of bleeds controlled by no more than 2 infusions in the CS/ADJ group. Confidence interval calculated with exact Hodges-Lehmann estimates.	
Comparison groups	rFVIII (BAY81-8973) on Demand Assayed by CS/ADJ v rFVIII (BAY81-8973) on Demand Assayed by CS/EP
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[11]
P-value	= 0.0001 ^[12]
Method	Exact Permutation Test for paired sample
Parameter estimate	Median difference (net)
Point estimate	0
Confidence interval	
level	95 %
sides	1-sided
lower limit	-0.049

Notes:

[11] - Non-inferiority margin 10%

[12] - No multiplicity adjustment as this was not primary endpoint

Other pre-specified: Number of Bleeds During Treatment

End point title	Number of Bleeds During Treatment
End point description: The number of bleeds experienced by each subject	
End point type	Other pre-specified
End point timeframe: 12 months	

End point values	rFVIII (BAY81-8973) on Demand	rFVIII (BAY81-8973) Prophylaxis Low-dose	rFVIII (BAY81-8973) Prophylaxis High-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21 ^[13]	28 ^[14]	31 ^[15]	
Units: Bleeds				
median (inter-quartile range (Q1-Q3))	60 (42 to 77)	4 (0 to 8)	2 (0 to 5)	

Notes:

[13] - ITT population

[14] - ITT population

[15] - ITT population

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Inhibitory Antibody Formation

End point title	Number of Subjects With Inhibitory Antibody Formation
-----------------	---

End point description:

A test to ensure that subjects have not developed antibodies that will interfere with the action of rFVIII (BAY81-8973)

End point type	Other pre-specified
----------------	---------------------

End point timeframe:

3, 6, 9 and 12 months after baseline

End point values	rFVIII (BAY81-8973) on Demand	rFVIII (BAY81-8973) Prophylaxis Low-dose	rFVIII (BAY81-8973) Prophylaxis High-dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21 ^[16]	28 ^[17]	31 ^[18]	
Units: subjects				
number (not applicable)				
3 months after baseline	0	0	0	
6 months after baseline	0	0	0	
9 months after baseline	0	0	0	
12 months after baseline	0	0	0	

Notes:

[16] - Safety population.

[17] - Safety population.

[18] - Safety population.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse event data reported here were collected from start of first treatment up to 12.5 months (end of observation period) but no later than 3 days after last study medication intake

Assessment type	Non-systematic
-----------------	----------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	15.1
--------------------	------

Reporting groups

Reporting group title	rFVIII (BAY81-8973) treatment
-----------------------	-------------------------------

Reporting group description:

Subjects received on-demand or prophylaxis treatment with recombinant factor VIII(rFVIII, BAY81-8973) assayed by CS/EP for 6 months and by CS/ADJ for 6 months, sequence according to Randomization.

Serious adverse events	rFVIII (BAY81-8973) treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 80 (2.50%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	rFVIII (BAY81-8973) treatment		
Total subjects affected by non-serious adverse events subjects affected / exposed	23 / 80 (28.75%)		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	5 / 80 (6.25%) 18		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	4 / 80 (5.00%) 7		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	13 / 80 (16.25%) 23 4 / 80 (5.00%) 4 6 / 80 (7.50%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 March 2010	<ol style="list-style-type: none">1. Clarifications regarding the surgery indication, such as definitions of the surgery types, safety data required prior to surgery, and evaluation times of the surgery outcome data during the study, were given as requested by the regulatory agencies2. The regulatory agencies recommended studying two different dosing regimens to arrive at the optimal dose of BAY81-8973. Consistent with this recommendation, the study design was revised from prophylaxis (20-40 IU/kg BAY81-8973 administered 2-3 times/week) versus on-demand treatment to prophylaxis using 2 different dosing regimens (BAY81-8973 high-dose [30-40 IU 3 times/week] or low-dose [20-30 IU 2 times/week]) versus on-demand treatment3. Addition of a secondary objective of demonstration of non-inferiority of BAY81-8973 dose determined by CS/EP versus BAY81-8973 dose determined by CS/ADJ as measured by the proportion of bleeds controlled by 1 or 2 infusions (among all bleeds) in subjects treated on-demand
10 June 2010	<ol style="list-style-type: none">1. The definition of severe hemophilia A in the inclusion criteria was clarified and expanded to allow subjects with previous medical history documentation of < 1% FVIII:C, determined by one-stage clotting assay, included in the trial without further testing/confirmation of severe hemophilia A, if the screening result turned out to be equal to or higher than 1%. The rationale for the change was to allow subjects with previously documented severe hemophilia A enrolled into the trial without the delay of having another one-stage clotting assay performed, since severity is not known to change during the course of the disease. The documented historical evidence of severe hemophilia A could be either from a previous Bayer hemophilia clinical trial, or from a previously performed one-stage clotting assay from a certified laboratory2. The number of surgeries was increased from ≥ 10 to ≥ 15, and the classification of surgery types was clarified to enable a more thorough evaluation of the safety and efficacy of BAY 81-8973 in the surgical setting. The amendment further specified that ≥ 8 surgeries were major surgical procedures3. To further ensure subject safety, the requirement was added that BAY 81-8973 was not to be supplied for use in the surgical setting until its hemostatic activity had been assessed in at least 20 bleeding events4. To be consistent with the sister protocol (Study 12954; EudraCT Number: 2009-012149-43), the following exclusion criterion was added: "Any subject who cannot forego at least 3 days without receiving FVIII for washout purposes."5. The dosage range for prophylaxis treatment was clarified as occurring in 5 IU/kg increments over the range of 20-40 IU/kg 2-3 times per week (ie, low dose: 20, 25, or 30 IU/kg, administered 2 times per week; high dose 30, 35, or 40 IU/kg administered 3 times per week)
15 March 2011	<ol style="list-style-type: none">1. For safety reasons, subjects with known hypersensitivity to mouse protein were excluded from participation in the study2. Primary and secondary study objectives were revised and rearranged to include objectives for results of this study alone, and addendum objectives were added for the pooled results of this study and Study 12954

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported