Clinical trial results:
A Two-Part, Randomized, Cross-Over, Open-Label Trial to Evaluate the Pharmacokinetics, Efficacy, and Safety Profile of Plasma Protein-Free Recombinant FVIII Formulated With Sucrose (BAY81-8973) in Previously Treated Subjects With Severe Hemophilia A Under Prophylaxis Therapy

Summary

EudraCT number	2009-012149-43
Trial protocol	ES SE GB NO DE IT AT DK
Global end of trial date	14 March 2013

Results information

Result version number	v3 (current)
This version publication date	03 September 2016
First version publication date	09 July 2015
Version creation reason	• New data added to full data set • Correction of full data set Bayer sponsor contact information to be updated

Trial information

Trial identification

Sponsor protocol code	BAY81-8973/12954

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01029340
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 March 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 March 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part A:
To demonstrate the pharmacokinetic (PK) non-inferiority of BAY81-8973 as compared to sucrose formulated successor Kogenate (Kogenate FS) using bioequivalence criteria following single dose administration.
Part B:
To demonstrate the efficacy and safety of BAY81-8973 for the treatment of bleeds and prophylaxis.
Part C:
To demonstrate efficacy for hemostasis during major surgery.

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. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 December 2009
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	Hong Kong: 6
Country: Number of subjects enrolled	Israel: 19
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	South Africa: 7
Country: Number of subjects enrolled	Turkey: 3
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	74
EEA total number of subjects	32

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)	15
Adults (18-64 years)	59
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:

Fourteen subjects were enrolled in each of Arms 1 and 2 in Part A. Of these, 11 subjects continued into each of Arms 3 and 4 in Part B. Arm 3 enrolled 20 and Arm 4 enrolled 21 additional subjects who had not participated in Part A. Arm 5 enrolled 5 subjects specifically for surgery in Part C who had not participated in Parts A or B.

Period 1

Period 1 title	Part A Treatment Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm 1: Recombinant Factor VIII (BAY81-8973) Then Kogenate FS

Arm description:

Part A - Arm 1: Subjects first received one single IV injection of BAY81-8973, 50 international unit per kilogram (IU/kg), then 1 single IV injection of Kogenate FS (BAY14-2222) 50 IU/kg with a wash-out period of at least 2-3 days in between.

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

Dosage and administration details:

Exactly 50 IU/kg (without rounding to full vials), single injection (potency determined by Chromogenic substrate assay per European Pharmacopoeia [CS/EP]), manual IV injection over a 10-minute period.

Investigational medicinal product name	Kogenate FS
Investigational medicinal product code	BAY14-2222
Other name	Kogenate Bayer
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Exactly 50 IU/kg (without rounding to full vials), single injection (potency determined by CS/EP), manual IV injection over a 10-minute period.

Arm title	Arm 2: Kogenate FS Then Recombinant Factor VIII (BAY81-8973)

Arm description:

Part A - Arm 2: Subjects first received one single IV injection of Kogenate FS (BAY14-2222) 50 IU/kg, then 1 single IV injection of BAY81-8973, 50 IU/kg with a wash-out period of at least 2-3 days in between.

Arm type	Experimental

Investigational medicinal product name	Kogenate FS
Investigational medicinal product code	BAY14-2222
Other name	Kogenate Bayer
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Exactly 50 IU/kg (without rounding to full vials), single injection (potency determined by CS/EP), manual IV injection over a 10-minute period.

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

Dosage and administration details:

Exactly 50 IU/kg (without rounding to full vials), single injection (potency determined by CS/EP), manual IV injection over a 10-minute period.

Number of subjects in period 1	Arm 1: Recombinant Factor VIII (BAY81-8973) Then Kogenate FS	Arm 2: Kogenate FS Then Recombinant Factor VIII (BAY81-8973)
Started	14	14
Subjects Received Treatment	14	14
Completed	14	14

Period 2

Period 2 title	Part A Follow up Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Arm 1: Recombinant Factor VIII (BAY81-8973) Then Kogenate FS

Arm description:

Part A - Arm 1: Subjects first received one single IV injection of BAY81-8973, 50 IU/kg, then 1 single IV injection of Kogenate FS (BAY14-2222) 50 IU/kg with a wash-out period of at least 2-3 days in between.

Arm type	Experimental
Investigational medicinal product name	Kogenate FS
Investigational medicinal product code	BAY14-2222
Other name	Kogenate Bayer
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Exactly 50 IU/kg (without rounding to full vials), single injection (potency determined by CS/EP),

manual IV injection over a 10-minute period.

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

Dosage and administration details:

Exactly 50 IU/kg (without rounding to full vials), single injection (potency determined by CS/EP), manual IV injection over a 10-minute period.

Arm title	Arm 2: Kogenate FS Then Recombinant Factor VIII (BAY81-8973)

Arm description:

Part A - Arm 2: Subjects first received one single IV injection of Kogenate FS (BAY14-2222) 50 IU/kg, then 1 single IV injection of BAY81-8973, 50 IU/kg with a wash-out period of at least 2-3 days in between.

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

Dosage and administration details:

Exactly 50 IU/kg (without rounding to full vials), single injection (potency determined by CS/EP), manual IV injection over a 10-minute period.

Investigational medicinal product name	Kogenate FS
Investigational medicinal product code	BAY14-2222
Other name	Kogenate Bayer
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Exactly 50 IU/kg (without rounding to full vials), single injection (potency determined by CS/EP), manual IV injection over a 10-minute period.

Number of subjects in period 2	Arm 1: Recombinant Factor VIII (BAY81-8973) Then Kogenate FS	Arm 2: Kogenate FS Then Recombinant Factor VIII (BAY81-8973)
Started	14	14
Completed	14	14

Period 3

Period 3 title	Part B Treatment Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm 3: Recombinant Factor VIII by CS/EP Then by CS/ADJ

Arm description:

Part B - Arm 3: Subjects received IV injection of BAY81-8973 at 20-50 IU/kg 2-3 times per week with BAY81-8973 potency measured by CS/EP for 6 months and then crossed over to study drug measured by Chromogenic substrate assay/adjusted to one-stage assay (CS/ADJ) to Label Potency for 6 months.

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

Dosage and administration details:

20-50 IU/kg (20, 25, 30, 35, 40, or 50 IU/kg) rounded to full vials, 2-3 times per week (treatment potency assignments determined by CS/EP and CS/ADJ), manual IV injection over 1 to 15 minutes.

Arm title	Arm 4: Recombinant Factor VIII by CS/ADJ Then by CS/EP

Arm description:

Part B - Arm 4:. Subjects received IV injection of BAY81-8973 at 20-50 IU/kg 2-3 times per week with BAY81-8973 measured by CS/ADJ to Label Potency for 6 months and then crossed over to study drug measured by CS/EP for 6 months.

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

Dosage and administration details:

Dosage: 20-50 IU/kg (20, 25, 30, 35, 40, or 50 IU/kg) rounded to full vials, 2-3 times per week (treatment potency assignments determined by CS/EP and CS/ADJ), manual IV injection over 1 to 15 minutes.

Number of subjects in period 3	Arm 3: Recombinant Factor VIII by CS/EP Then by CS/ADJ	Arm 4: Recombinant Factor VIII by CS/ADJ Then by CS/EP
Started	31	32
Subjects Received Treatment	30	32
Completed	29	32
Not completed	2	0
Consent withdrawn by subject	1	-
Protocol violation	1	-

Period 4

Period 4 title	Part B Follow up Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Arm 3: Recombinant Factor VIII by CS/EP Then by CS/ADJ

Arm description:

Part B - Arm 3: Subjects received IV injection of BAY81-8973 at 20-50 IU/kg 2-3 times per week with BAY81-8973 measured by CS/EP for 6 months and then crossed over to study drug measured by CS/ADJ to Label Potency for 6 months. Subjects were followed by a phone call 1-2 weeks after the end of part B treatment period.

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

Dosage and administration details:

20-50 IU/kg (20, 25, 30, 35, 40, or 50 IU/kg) rounded to full vials, 2-3 times per week (treatment potency assignments determined by CS/EP and CS/ADJ), manual IV injection over 1 to 15 minutes.

Arm title	Arm 4: Recombinant Factor VIII by CS/ADJ Then by CS/EP

Arm description:

Part B - Arm 4:. Subjects received IV injection of BAY81-8973 at 20-50 IU/kg 2-3 times per week with BAY81-8973 measured by CS/ADJ to Label Potency for 6 months and then crossed over to study drug measured by CS/EP for 6 months. Subjects were followed by a phone call 1-2 weeks after the end of part B treatment period.

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

Dosage and administration details:

Dosage: 20-50 IU/kg (20, 25, 30, 35, 40, or 50 IU/kg) rounded to full vials, 2-3 times per week (treatment potency assignments determined by CS/EP and CS/ADJ), manual IV injection over 1 to 15 minutes.

Number of subjects in period 4	Arm 3: Recombinant Factor VIII by CS/EP Then by CS/ADJ	Arm 4: Recombinant Factor VIII by CS/ADJ Then by CS/EP
Started	29	32
Completed	29	32

Period 5

Period 5 title	Extension period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Arm 6: Recombinant Factor VIII (BAY81-8973) Part B + extension

Arm description:

Subjects received IV injections of BAY81-8973 at 20-50 IU/kg 2-3 times per week with BAY81-8973 potency measured by CS/EP for 6 months and CS/ADJ for 6 months sequence according to randomization and up to 12 months (CS/EP) during extension.

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

Dosage and administration details:

Subjects received IV injections of BAY81-8973 at 20-50 IU/kg 2-3 times per week with BAY81-8973 potency measured by Chromogenic Substrate Assay Per European Pharmacopeia (CS/EP) for 6 months and CS/ADJ for 6 months sequence according to randomization and up to 12 months (CS/EP) during extension.

Number of subjects in period 5	Arm 6: Recombinant Factor VIII (BAY81-8973) Part B + extension
Started	55
Completed	43
Not completed	12
Consent withdrawn by subject	1
Physician decision	1
Adverse event	1
Non-compliance	1
Starting another study	8

Period 6

Period 6 title	Part C Treatment Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Arm 5: Recombinant Factor VIII by CS/EP

Arm description:

Part C - Arm 5: Subjects received a loading dose of approximately 50 IU/kg of BAY81-8973 before the first surgical incision followed by further treatment with BAY81-8973 according to surgical requirements for up to 3 weeks.

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

Dosage and administration details:

All subjects were to receive a pre-op dose of BAY81-8973 at 50 IU/kg for in vivo recovery assessment.

Number of subjects in period 6	Arm 5: Recombinant Factor VIII by CS/EP
Started	5
Subjects Received Treatment	5
Completed	5

Period 7

Period 7 title	Part C Follow up Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Arm 5: Recombinant Factor VIII by CS/EP

Arm description:

Part C - Arm 5: Subjects received a loading dose of approximately 50 IU/kg of BAY81-8973 before the first surgical incision followed by further treatment with BAY81-8973 according to surgical requirements and for up to 3 weeks. Subjects were followed up by telephone after 1 week.

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

Dosage and administration details:

All subjects were to receive a pre-op dose of BAY81-8973 at 50 IU/kg for in vivo recovery assessment.

Number of subjects in period 7	Arm 5: Recombinant Factor VIII by CS/EP
Started	5
Completed	5

Period 8

Period 8 title	Baseline period
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Arm 1: Recombinant Factor VIII (BAY81-8973) Then Kogenate FS

Arm description:

Part A - Arm 1: Subjects first received one single IV injection of BAY81-8973, 50 IU/kg, then 1 single IV injection of Kogenate FS (BAY14-2222) 50 IU/kg with a wash-out period of at least 2-3 days in between.

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

Dosage and administration details:

Exactly 50 IU/kg (without rounding to full vials), single injection (potency determined by CS/EP), manual IV injection over a 10-minute period.

Investigational medicinal product name	Kogenate FS
Investigational medicinal product code	BAY14-2222
Other name	Kogenate Bayer
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Exactly 50 IU/kg (without rounding to full vials), single injection (potency determined by CS/EP), manual IV injection over a 10-minute period.

Arm title	Arm 2: Kogenate FS Then Recombinant Factor VIII (BAY81-8973)

Arm description:

Part A - Arm 2: Subjects first received one single IV injection of Kogenate FS (BAY14-2222) 50 IU/kg, then 1 single IV injection of BAY81-8973, 50 IU/kg with a wash-out period of at least 2-3 days in between.

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

Dosage and administration details:

Exactly 50 IU/kg (without rounding to full vials), single injection (potency determined by CS/EP), manual IV injection over a 10-minute period.

Investigational medicinal product name	Kogenate FS
Investigational medicinal product code	BAY14-2222
Other name	Kogenate Bayer
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Exactly 50 IU/kg (without rounding to full vials), single injection (potency determined by CS/EP), manual IV injection over a 10-minute period.

Arm title	Arm 3: Recombinant Factor VIII by CS/EP Then by CS/ADJ

Arm description:

Part B - Arm 3: Subjects received IV injection of BAY81-8973 at 20-50 IU/kg 2-3 times per week with BAY81-8973 potency measured by CS/EP for 6 months and then crossed over to study drug measured by CS/ADJ to Label Potency for 6 months.

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

Dosage and administration details:

20-50 IU/kg (20, 25, 30, 35, 40, or 50 IU/kg) rounded to full vials, 2-3 times per week (treatment potency assignments determined by CS/EP and CS/ADJ), manual IV injection over 1 to 15 minutes.

Arm title	Arm 4: Recombinant Factor VIII by CS/ADJ Then by CS/EP

Arm description:

Part B - Arm 4:. Subjects received IV injection of BAY81-8973 at 20-50 IU/kg 2-3 times per week with BAY81-8973 measured by CS/ADJ to Label Potency for 6 months and then crossed over to study drug measured by CS/EP for 6 months.

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

Dosage and administration details:

Dosage: 20-50 IU/kg (20, 25, 30, 35, 40, or 50 IU/kg) rounded to full vials, 2-3 times per week (treatment potency assignments determined by CS/EP and CS/ADJ), manual IV injection over 1 to 15 minutes.

Arm title	Arm 5: Recombinant Factor VIII by CS/EP

Arm description:

Part C - Arm 5: Subjects received a loading dose of approximately 50 IU/kg of BAY81-8973 before the first surgical incision followed by further treatment with BAY81-8973 according to surgical requirements and for up to 3 weeks.

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

Dosage and administration details:

All subjects were to receive a pre-op dose of BAY81-8973 at 50 IU/kg for in vivo recovery assessment.

Notes:

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

Justification: The study was conducted in three different parts, as Part A, Part B and Part C. Hence, the baseline period of all enrolled subjects in a study was created to publish the baseline characteristics data.

Number of subjects in period 8	Arm 1: Recombinant Factor VIII (BAY81-8973) Then Kogenate FS	Arm 2: Kogenate FS Then Recombinant Factor VIII (BAY81-8973)	Arm 3: Recombinant Factor VIII by CS/EP Then by CS/ADJ
Started	14	14	30
Completed	14	14	30

Number of subjects in period 8	Arm 4: Recombinant Factor VIII by CS/ADJ Then by CS/EP	Arm 5: Recombinant Factor VIII by CS/EP
Started	32	5
Completed	32	5

Baseline characteristics

Reporting groups	
Reporting group title	Arm 1: Recombinant Factor VIII (BAY81-8973) Then Kogenate FS
Reporting group description:	
Part A - Arm 1: Subjects first received one single IV injection of BAY81-8973, 50 IU/kg, then 1 single IV injection of Kogenate FS (BAY14-2222) 50 IU/kg with a wash-out period of at least 2-3 days in between.	
Reporting group title	Arm 2: Kogenate FS Then Recombinant Factor VIII (BAY81-8973)
Reporting group description:	
Part A - Arm 2: Subjects first received one single IV injection of Kogenate FS (BAY14-2222) 50 IU/kg, then 1 single IV injection of BAY81-8973, 50 IU/kg with a wash-out period of at least 2-3 days in between.	
Reporting group title	Arm 3: Recombinant Factor VIII by CS/EP Then by CS/ADJ
Reporting group description:	
Part B - Arm 3: Subjects received IV injection of BAY81-8973 at 20-50 IU/kg 2-3 times per week with BAY81-8973 potency measured by CS/EP for 6 months and then crossed over to study drug measured by CS/ADJ to Label Potency for 6 months.	
Reporting group title	Arm 4: Recombinant Factor VIII by CS/ADJ Then by CS/EP
Reporting group description:	
Part B - Arm 4:. Subjects received IV injection of BAY81-8973 at 20-50 IU/kg 2-3 times per week with BAY81-8973 measured by CS/ADJ to Label Potency for 6 months and then crossed over to study drug measured by CS/EP for 6 months.	
Reporting group title	Arm 5: Recombinant Factor VIII by CS/EP
Reporting group description:	
Part C - Arm 5: Subjects received a loading dose of approximately 50 IU/kg of BAY81-8973 before the first surgical incision followed by further treatment with BAY81-8973 according to surgical requirements and for up to 3 weeks.	

Reporting group values	Arm 1: Recombinant Factor VIII (BAY81-8973) Then Kogenate FS	Arm 2: Kogenate FS Then Recombinant Factor VIII (BAY81-8973)	Arm 3: Recombinant Factor VIII by CS/EP Then by CS/ADJ
Number of subjects	14	14	30
Age categorical			
Part A based on pharmacokinetic (PK) analysis set; Parts B and C based on safety analysis set. Two subjects in Part A were excluded, as they were not valid for PK analysis set. The data was not available for one subject who was excluded since receiving Kogenate FS twice.			
Units: subjects			
< 18 years	1	4	5
=/> 18 years	13	10	25
Gender categorical			
Part A based on PK analysis set; Parts B and C based on safety analysis set.			
Units: subjects			
Male	14	14	30

Reporting group values	Arm 4: Recombinant Factor VIII by CS/ADJ Then by CS/EP	Arm 5: Recombinant Factor VIII by CS/EP	Total
Number of subjects	32	5	95

Age categorical			
Part A based on pharmacokinetic (PK) analysis set; Parts B and C based on safety analysis set. Two subjects in Part A were excluded, as they were not valid for PK analysis set. The data was not available for one subject who was excluded since receiving Kogenate FS twice.			
Units: subjects			
< 18 years	5	0	15
=/> 18 years	27	5	80
Gender categorical			
Part A based on PK analysis set; Parts B and C based on safety analysis set.			
Units: subjects			
Male	32	5	95

End points

End points reporting groups

Reporting group title	Arm 1: Recombinant Factor VIII (BAY81-8973) Then Kogenate FS

Reporting group description:

Part A - Arm 1: Subjects first received one single IV injection of BAY81-8973, 50 international unit per kilogram (IU/kg), then 1 single IV injection of Kogenate FS (BAY14-2222) 50 IU/kg with a wash-out period of at least 2-3 days in between.

Reporting group title	Arm 2: Kogenate FS Then Recombinant Factor VIII (BAY81-8973)

Reporting group description:

Part A - Arm 2: Subjects first received one single IV injection of Kogenate FS (BAY14-2222) 50 IU/kg, then 1 single IV injection of BAY81-8973, 50 IU/kg with a wash-out period of at least 2-3 days in between.

Reporting group title	Arm 1: Recombinant Factor VIII (BAY81-8973) Then Kogenate FS

Reporting group description:

Part A - Arm 1: Subjects first received one single IV injection of BAY81-8973, 50 IU/kg, then 1 single IV injection of Kogenate FS (BAY14-2222) 50 IU/kg with a wash-out period of at least 2-3 days in between.

Reporting group title	Arm 2: Kogenate FS Then Recombinant Factor VIII (BAY81-8973)

Reporting group description:

Part A - Arm 2: Subjects first received one single IV injection of Kogenate FS (BAY14-2222) 50 IU/kg, then 1 single IV injection of BAY81-8973, 50 IU/kg with a wash-out period of at least 2-3 days in between.

Reporting group title	Arm 3: Recombinant Factor VIII by CS/EP Then by CS/ADJ

Reporting group description:

Part B - Arm 3: Subjects received IV injection of BAY81-8973 at 20-50 IU/kg 2-3 times per week with BAY81-8973 potency measured by CS/EP for 6 months and then crossed over to study drug measured by Chromogenic substrate assay/adjusted to one-stage assay (CS/ADJ) to Label Potency for 6 months.

Reporting group title	Arm 4: Recombinant Factor VIII by CS/ADJ Then by CS/EP

Reporting group description:

Part B - Arm 4:. Subjects received IV injection of BAY81-8973 at 20-50 IU/kg 2-3 times per week with BAY81-8973 measured by CS/ADJ to Label Potency for 6 months and then crossed over to study drug measured by CS/EP for 6 months.

Reporting group title	Arm 3: Recombinant Factor VIII by CS/EP Then by CS/ADJ

Reporting group description:

Part B - Arm 3: Subjects received IV injection of BAY81-8973 at 20-50 IU/kg 2-3 times per week with BAY81-8973 measured by CS/EP for 6 months and then crossed over to study drug measured by CS/ADJ to Label Potency for 6 months. Subjects were followed by a phone call 1-2 weeks after the end of part B treatment period.

Reporting group title	Arm 4: Recombinant Factor VIII by CS/ADJ Then by CS/EP

Reporting group description:

Part B - Arm 4:. Subjects received IV injection of BAY81-8973 at 20-50 IU/kg 2-3 times per week with BAY81-8973 measured by CS/ADJ to Label Potency for 6 months and then crossed over to study drug measured by CS/EP for 6 months. Subjects were followed by a phone call 1-2 weeks after the end of part B treatment period.

Reporting group title	Arm 6: Recombinant Factor VIII (BAY81-8973) Part B + extension

Reporting group description:

Subjects received IV injections of BAY81-8973 at 20-50 IU/kg 2-3 times per week with BAY81-8973 potency measured by CS/EP for 6 months and CS/ADJ for 6 months sequence according to randomization and up to 12 months (CS/EP) during extension.

Reporting group title	Arm 5: Recombinant Factor VIII by CS/EP

Reporting group description:

Part C - Arm 5: Subjects received a loading dose of approximately 50 IU/kg of BAY81-8973 before the first surgical incision followed by further treatment with BAY81-8973 according to surgical requirements

for up to 3 weeks.

Reporting group title	Arm 5: Recombinant Factor VIII by CS/EP

Reporting group description:

Part C - Arm 5: Subjects received a loading dose of approximately 50 IU/kg of BAY81-8973 before the first surgical incision followed by further treatment with BAY81-8973 according to surgical requirements and for up to 3 weeks. Subjects were followed up by telephone after 1 week.

Reporting group title	Arm 1: Recombinant Factor VIII (BAY81-8973) Then Kogenate FS

Reporting group description:

Part A - Arm 1: Subjects first received one single IV injection of BAY81-8973, 50 IU/kg, then 1 single IV injection of Kogenate FS (BAY14-2222) 50 IU/kg with a wash-out period of at least 2-3 days in between.

Reporting group title	Arm 2: Kogenate FS Then Recombinant Factor VIII (BAY81-8973)

Reporting group description:

Part A - Arm 2: Subjects first received one single IV injection of Kogenate FS (BAY14-2222) 50 IU/kg, then 1 single IV injection of BAY81-8973, 50 IU/kg with a wash-out period of at least 2-3 days in between.

Reporting group title	Arm 3: Recombinant Factor VIII by CS/EP Then by CS/ADJ

Reporting group description:

Part B - Arm 3: Subjects received IV injection of BAY81-8973 at 20-50 IU/kg 2-3 times per week with BAY81-8973 potency measured by CS/EP for 6 months and then crossed over to study drug measured by CS/ADJ to Label Potency for 6 months.

Reporting group title	Arm 4: Recombinant Factor VIII by CS/ADJ Then by CS/EP

Reporting group description:

Part B - Arm 4:. Subjects received IV injection of BAY81-8973 at 20-50 IU/kg 2-3 times per week with BAY81-8973 measured by CS/ADJ to Label Potency for 6 months and then crossed over to study drug measured by CS/EP for 6 months.

Reporting group title	Arm 5: Recombinant Factor VIII by CS/EP

Reporting group description:

Part C - Arm 5: Subjects received a loading dose of approximately 50 IU/kg of BAY81-8973 before the first surgical incision followed by further treatment with BAY81-8973 according to surgical requirements and for up to 3 weeks.

Subject analysis set title	ITT population: Recombinant Factor VIII (BAY81-8973) - Part B
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects received IV injections of BAY81-8973 at 20-50 IU/kg 2-3 times per week with BAY81-8973 measured by CS/EP for 6 months and by CS/ADJ for 6 months, sequence according to randomization. All subjects in the safety population who have injection / bleeding data from the EPD and/or CRF were included in the ITT population in Part B.

Subject analysis set title	PK population: Part A-Recombinant Factor VIII (BAY81-8973)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All subjects who received one single IV injection of recombinant factor VIII (BAY81-8973) 50 IU/kg and with a valid PK profile in part A were included in PK population.

Subject analysis set title	PK population: Part A-Kogenate-FS (BAY14-2222)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received one single IV injection of Kogenate FS (BAY14-2222) 50 IU/kg and with a valid PK profile in part A were included in the PK population.

Subject analysis set title	Recombinant Factor VIII (BAY81-8973) and Kogenate FS - Part A
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received one single IV injection of BAY81-8973 50 IU/kg and one single IV injection of Kogenate FS (BAY14-2222) 50 IU/kg were included in the safety population in Part A.

Subject analysis set title	Safety population: Recombinant Factor VIII (BAY81-8973)-Part B
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received IV injections of BAY81-8973 at 20-50 IU/kg 2-3 times per week with BAY81-8973 measured by CS/EP for 6 months and by CS/ADJ for 6 months, sequence according to randomization. All subjects randomized into the study who received study drug or who were surgery-only subjects were included in safety population in Part B.

Subject analysis set title	Recombinant Factor VIII (BAY81-8973) by CS/EP - Part B
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects received IV injections of recombinant factor VIII (BAY81-8973) at 20-50 IU/kg 2-3 times per week with BAY81-8973 measured by CS/EP for 6 months and have injection / bleeding data from the electronic patient diary (EPD) and/or case report form (CRF) were included in the intent-to-treat (ITT) population in Part B.

Subject analysis set title	Recombinant Factor VIII (BAY81-8973) by CS/ADJ - Part B
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects received IV injection of BAY81-8973 at 20-50 IU/kg 2-3 times per week with BAY81-8973 measured by CS/ADJ to Label Potency for 6 months and have injection / bleeding data from the EPD and/or CRF were included in the ITT population in Part B.
One subject in Part B did not receive any Recombinant Factor VIII measured by the CS/ADJ method, leading to 61 subjects (not 62) in that group.

Subject analysis set title	Recombinant Factor VIII (BAY81-8973) by CS/EP - Part C
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects received a loading dose of approximately 50 IU/kg of BAY81-8973 before the first surgical incision, followed by further treatment with BAY81-8973 according to surgical requirements for upto 3 weeks. All subjects in the safety population who have injection / bleeding data from the EPD and/or CRF were included in ITT population in Part C.

Primary: Part A - Area Under the Drug Concentration-time Curve (AUC)

End point title	Part A - Area Under the Drug Concentration-time Curve

End point description:

To examine the Pharmacokinetic (PK) characteristics of BAY 81-8973 and ensure that the new drug was similar to Kogenate FS. All results were based on the chromogenic assay and expressed in international units*hours/deciliter (IU*h/dL). Geometric mean and percentage geometric coefficient of variation (%CV) were reported.

End point type	Primary

End point timeframe:

Samples taken at pre-injection, and at 0.25, 0.5, 1, 3, 6, 8, 24, 30 and 48 hours post injection. AUC calculated from time of injection to infinity.

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	PK population: Part A-Recombinant Factor VIII (BAY81-8973)	PK population: Part A-Kogenate-FS (BAY14-2222)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[2]	26[3]		
Units: IU*h/dL				
geometric mean (geometric coefficient of variation)	1889.23 (± 36.11)	1583.91 (± 39.89)		

Notes:

[2] - PK Analysis Population

[3] - PK Analysis Population

Statistical analyses

No statistical analyses for this end point

Primary: Part A - Half-life (t 1/2)

End point title	Part A - Half-life (t 1/2)[4]

End point description:

To examine the PK characteristics of BAY81-8973 and ensure that the new drug is similar to Kogenate FS. All results are based on the chromogenic assay. Geometric mean and percentage geometric coefficient of variation (%CV) were reported.

End point type	Primary

End point timeframe:

Samples taken at pre-injection, and at 0.25, 0.5, 1, 3, 6, 8, 24, 30 and 48 hours post injection.

Notes:

[4] - 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	PK population: Part A-Recombinant Factor VIII (BAY81-8973)	PK population: Part A-Kogenate-FS (BAY14-2222)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[5]	26[6]		
Units: Hours				
geometric mean (geometric coefficient of variation)	13.77 (± 28)	12 (± 28.2)		

Notes:

[5] - PK Analysis Population

[6] - PK Analysis Population

Statistical analyses

No statistical analyses for this end point

Primary: Part B - Annualized Number of Total Bleeds

End point title	Part B - Annualized Number of Total Bleeds[7]

End point description:

The annualized number of bleeds experienced by subjects.

End point type	Primary

End point timeframe:

12 months after randomization

Notes:

[7] - 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	ITT population: Recombinant Factor VIII (BAY81-8973) - Part B			
Subject group type	Subject analysis set			
Number of subjects analysed	62[8]			
Units: bleeds				

median (inter-quartile range (Q1-Q3))	1.03 (0 to 5.09)			

Notes:

[8] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Part B - The in Vivo Recovery Values of Human Factor VIII (FVIII)

End point title	Part B - The in Vivo Recovery Values of Human Factor VIII (FVIII)

End point description:

The amount of Factor VIII found in blood samples taken after the injection of the study drug at the beginning of the CS/EP treatment period.
One measurement was taken in all subjects at the start of the CS/EP labelled treatment period (CS/ADJ labelled treatment was experimental and will not be used for the future commercial drug, measurements were taken but are artificial because of the adjusted label).

End point type	Secondary

End point timeframe:

15-30 minutes after the injection

End point values	ITT population: Recombinant Factor VIII (BAY81-8973) - Part B			
Subject group type	Subject analysis set			
Number of subjects analysed	59[9]			
Units: kilogram per deciliter (kg/dL)				
median (inter-quartile range (Q1-Q3))	2.5 (2.09 to 2.77)			

Notes:

[9] - ITT population, only 59 of the 62 subjects had valid recovery data.

Statistical analyses

No statistical analyses for this end point

Secondary: Part B - Annualized Number of Bleeds in Each 6-month Potency Assignment Period

End point title	Part B - Annualized Number of Bleeds in Each 6-month Potency Assignment Period

End point description:

The annualized number of bleeds experienced by subjects in each of the two treatment periods.
Note: One subject in Part B did not receive any Recombinant Factor VIII measured by the CS/ADJ method, leading to 61 subjects (not 62) in that group.

End point type	Secondary

End point timeframe:

6 months on each potency

End point values	Recombinant Factor VIII (BAY81-8973) by CS/EP - Part B	Recombinant Factor VIII (BAY81-8973) by CS/ADJ - Part B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62[10]	61[11]		
Units: bleeds				
median (inter-quartile range (Q1-Q3))				
all subjects	1.9 (0 to 4.4)	1.9 (0 to 7.3)		

Notes:

[10] - ITT.

[11] - ITT.

Statistical analyses

No statistical analyses for this end point

Secondary: Part B - Control of Bleeding as Measured by the Number of Injections Required to Treat a Bleed

End point title	Part B - Control of Bleeding as Measured by the Number of Injections Required to Treat a Bleed

End point description:

The number of injections needed by subject to stop a bleed.
Note: One subject in Part B did not receive any Recombinant Factor VIII measured by the CS/ADJ method, leading to 61 subjects (not 62) in that group.

End point type	Secondary

End point timeframe:

6 months on each potency

End point values	Recombinant Factor VIII (BAY81-8973) by CS/EP - Part B	Recombinant Factor VIII (BAY81-8973) by CS/ADJ - Part B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62[12]	61[13]		
Units: injections				
median (full range (min-max))				
Number of Bleeds Analyzed (N = 108, 128)	1 (0 to 11)	1 (1 to 48)		

Notes:

[12] - ITT.

[13] - ITT.

Statistical analyses

No statistical analyses for this end point

Secondary: Part B - Changes From Baseline at 12 Months in Quality of Life (QoL) as Measured by Transformed Total Score of Haemo-QoL Questionnaire

End point title	Part B - Changes From Baseline at 12 Months in Quality of Life (QoL) as Measured by Transformed Total Score of Haemo-QoL Questionnaire

End point description:

A measure of how treatment with BAY81-8973 affected the daily life of subjects. the scoring system has 100 points. 0 is the worst possible score. 100 is the best possible score. Positive changes from baseline indicate an improvement in quality of life and negative changes indicate a deterioration.

End point type	Secondary

End point timeframe:

Baseline and 12 months

End point values	ITT population: Recombinant Factor VIII (BAY81-8973) - Part B			
Subject group type	Subject analysis set			
Number of subjects analysed	51[14]			
Units: scores on a scale				
median (full range (min-max))	2.02 (-22.9 to 26.5)			

Notes:

[14] - ITT population, only 51 of the 62 subjects had data available for the 12-month QoL analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Part B - Changes From Baseline at 12 Months in Utility Index as Measured by EQ–5D Questionaire

End point title	Part B - Changes From Baseline at 12 Months in Utility Index as Measured by EQ–5D Questionaire

End point description:

A measure of how treatment with BAY81-8973 affected the daily life of subjects. 1.0 = Best possible score, -0.594 = Worst possible score. Positive changes from baseline indicate an improvement and negative changes indicate a deterioration. Only 61 of the 62 subjects had data available for the Utility Index of the EQ-5D questionnaire at Month 12.

End point type	Secondary

End point timeframe:

Baseline and 12 months

End point values	ITT population: Recombinant Factor VIII (BAY81-8973) - Part B			
Subject group type	Subject analysis set			
Number of subjects analysed	61[15]			

Units: Scores on a scale				
median (full range (min-max))	0 (-0.6 to 0.5)			

Notes:

[15] - ITT population.

Statistical analyses

No statistical analyses for this end point

Secondary: Part A - Number of Subjects With Inhibitory Antibody Formation

End point title	Part A - 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 BAY81-8973.

End point type	Secondary

End point timeframe:

Up to 6 weeks after drug administration

End point values	Recombinant Factor VIII (BAY81-8973) and Kogenate FS - Part A			
Subject group type	Subject analysis set			
Number of subjects analysed	28[16]			
Units: subjects	0			

Notes:

[16] - Safety population.

Statistical analyses

No statistical analyses for this end point

Secondary: Part A - Number of Subjects With Incidence of Antibody Formation to Heat-shock Protein (HSP-70)

End point title	Part A - Number of Subjects With Incidence of Antibody Formation to Heat-shock Protein (HSP-70)

End point description:

A test to analyze the formation of antibodies to HSP-70.

End point type	Secondary

End point timeframe:

Up to 6 weeks after drug administration

End point values	Recombinant Factor VIII (BAY81-8973) and Kogenate FS - Part A			
Subject group type	Subject analysis set			
Number of subjects analysed	28[17]			
Units: subjects	0			

Notes:

[17] - Safety population.

Statistical analyses

No statistical analyses for this end point

Secondary: Part C - Number of Subjects With Incidence of Inhibitory Antibody Formation

End point title	Part C - Number of Subjects With Incidence of Inhibitory Antibody Formation

End point description:

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

End point type	Secondary

End point timeframe:

before and 3 weeks after surgery

End point values	Recombinant Factor VIII (BAY81-8973) by CS/EP - Part C			
Subject group type	Subject analysis set			
Number of subjects analysed	5[18]			
Units: subjects	0			

Notes:

[18] - ITT.

Statistical analyses

No statistical analyses for this end point

Secondary: Part B - Number of Subjects With Incidence of Inhibitory Antibody Formation

End point title	Part B - Number of Subjects With Incidence of Inhibitory Antibody Formation

End point description:

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

End point type	Secondary

End point timeframe:

Up to 12 months after drug administration

End point values	Safety population: Recombinant Factor VIII (BAY81-8973)-Part B			
Subject group type	Subject analysis set			
Number of subjects analysed	62[19]			
Units: subjects	0			

Notes:

[19] - Safety population.

Statistical analyses

No statistical analyses for this end point

Secondary: Part B - Number of Subjects With Incidence of Antibody Formation to Heat-shock Protein (HSP-70)

End point title	Part B - Number of Subjects With Incidence of Antibody Formation to Heat-shock Protein (HSP-70)

End point description:

A test to analyze the formation of antibodies to HSP-70.

End point type	Secondary

End point timeframe:

Up to 12 months after drug administration

End point values	ITT population: Recombinant Factor VIII (BAY81-8973) - Part B			
Subject group type	Subject analysis set			
Number of subjects analysed	62[20]			
Units: subjects	1			

Notes:

[20] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Part C - Number of Subjects With Incidence of Antibody Formation to Heat-shock Protein (HSP-70)

End point title	Part C - Number of Subjects With Incidence of Antibody Formation to Heat-shock Protein (HSP-70)

End point description:

A test to analyze the formation of antibodies to HSP-70.

End point type	Secondary

End point timeframe:

before and 3 weeks after surgery

End point values	Recombinant Factor VIII (BAY81-8973) by CS/ADJ - Part B			
Subject group type	Subject analysis set			
Number of subjects analysed	5[21]			
Units: subjects	0			

Notes:

[21] - ITT.

Statistical analyses

No statistical analyses for this end point

Secondary: Part A - Number of Subjects With Incidence of Antibody Formation to Host Cell Proteins (HCP)

End point title	Part A - Number of Subjects With Incidence of Antibody Formation to Host Cell Proteins (HCP)

End point description:

A test to ensure that subjects have not developed antibodies to HCP during the study.

End point type	Secondary

End point timeframe:

Up to 4 weeks after drug administration

End point values	Recombinant Factor VIII (BAY81-8973) and Kogenate FS - Part A			
Subject group type	Subject analysis set			
Number of subjects analysed	26[22]			
Units: subjects	0			

Notes:

[22] - ITT.

Statistical analyses

No statistical analyses for this end point

Secondary: Part B - Number of Subjects With Incidence of Antibody Formation to Host Cell Proteins (HCP)

End point title	Part B - Number of Subjects With Incidence of Antibody Formation to Host Cell Proteins (HCP)

End point description:

A test to ensure that subjects have not developed antibodies to HCP during the study.

End point type	Secondary

End point timeframe:

Up to 12 months after drug administration

End point values	ITT population: Recombinant Factor VIII (BAY81-8973) - Part B			
Subject group type	Subject analysis set			
Number of subjects analysed	62[23]			
Units: subjects	0			

Notes:

[23] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Part B - Number of Subjects With Assessment of the Hemostasis During Major Surgery

End point title	Part B - Number of Subjects With Assessment of the Hemostasis During Major Surgery

End point description:

An assessment made by surgeons of how effective BAY81-8973 was in stopping bleeding during major operations.

End point type	Secondary

End point timeframe:

An average of 1 month after start of treatment

End point values	ITT population: Recombinant Factor VIII (BAY81-8973) - Part B			
Subject group type	Subject analysis set			
Number of subjects analysed	5[24]			
Units: subjects				
Excellent	1			
Good	4			
Moderate	0			
Poor	0			

Notes:

[24] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Part C - Number of Subjects With Incidence of Antibody Formation to Host Cell Proteins (HCP)

End point title	Part C - Number of Subjects With Incidence of Antibody Formation to Host Cell Proteins (HCP)

End point description:

A test to ensure that subjects have not developed antibodies to HCP during the study.

End point type	Secondary

End point timeframe:

before and 3 weeks after surgery

End point values	Recombinant Factor VIII (BAY81-8973) by CS/EP - Part C			
Subject group type	Subject analysis set			
Number of subjects analysed	5[25]			
Units: subjects	0			

Notes:

[25] - ITT.

Statistical analyses

No statistical analyses for this end point

Secondary: Part C - Number of Subjects With Assessment of the Hemostasis During Major Surgery

End point title	Part C - Number of Subjects With Assessment of the Hemostasis During Major Surgery

End point description:

An assessment made by surgeons of how effective BAY81-8973 was in stopping bleeding during major operations.

End point type	Secondary

End point timeframe:

at the time of surgery

End point values	Recombinant Factor VIII (BAY81-8973) by CS/EP - Part C			
Subject group type	Subject analysis set			
Number of subjects analysed	5[26]			
Units: subjects				
Excellent	1			

Good	4			
Moderate	0			
Poor	0			

Notes:
[26] - ITT.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of signing informed consent through study completion ie 21 Dec 2009 to 14 Mar 2013

Adverse event reporting additional description:

The objective of Part C was efficacy assessment of surgery hemostasis, not safety assessment. It was allowed to include the same subject for several surgeries and for each surgery the subject was assigned a new subject number. Due to this approach, one subject with 3 surgeries was analyzed as 3 different subjects, therefore the number at risk is 7.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Recombinant Factor VIII (BAY81-8973) - Part A

Reporting group description:

Participants received one single intravenous (IV) injection of BAY81-8973 50 IU/kg

Reporting group title	Recombinant Factor VIII (BAY81-8973) Part B and extension

Reporting group description:

Participants received IV injections of BAY81-8973 at 20-50 IU/kg 2-3 times per week with BAY81-8973 measured by Chromogenic Substrate Assay Potency Per European Pharmacopeia (CS/EP) for 6 months and CS/ADJ for 6 mon seq according to random

Reporting group title	Recombinant Factor VIII (BAY81-8973) by CS/EP - Part C

Reporting group description:

Partic received a loading dose of approx 50 IU/kg of BAY81-8973 (nearest whole vial amount) for less than 15min before the first surgical incision Then they will rec further treatment with BAY81-8973 accord to surgical requir for up to 3 weeks

Reporting group title	Kogenate FS (BAY14-2222) - Part A

Reporting group description:

Participants received one single intravenous (IV) injection of Kogenate FS (BAY14-2222) 50 IU/kg

Serious adverse events	Recombinant Factor VIII (BAY81-8973) - Part A	Recombinant Factor VIII (BAY81-8973) Part B and extension	Recombinant Factor VIII (BAY81-8973) by CS/EP - Part C
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	12 / 62 (19.35%)	1 / 7 (14.29%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Injury			
subjects affected / exposed	0 / 27 (0.00%)	1 / 62 (1.61%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Acute myocardial infarction			
subjects affected / exposed	0 / 27 (0.00%)	1 / 62 (1.61%)	0 / 7 (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
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 27 (0.00%)	1 / 62 (1.61%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 27 (0.00%)	1 / 62 (1.61%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 27 (0.00%)	1 / 62 (1.61%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Cephalhaematoma			
subjects affected / exposed	0 / 27 (0.00%)	1 / 62 (1.61%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 27 (0.00%)	2 / 62 (3.23%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	0 / 27 (0.00%)	1 / 62 (1.61%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			
Miscarriage of partner			

subjects affected / exposed	0 / 27 (0.00%)	1 / 62 (1.61%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	0 / 27 (0.00%)	0 / 62 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 27 (0.00%)	1 / 62 (1.61%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somatoform disorder			
subjects affected / exposed	0 / 27 (0.00%)	1 / 62 (1.61%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 62 (1.61%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Compartment syndrome			
subjects affected / exposed	0 / 27 (0.00%)	1 / 62 (1.61%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint range of motion decreased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 62 (1.61%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Erysipelas			

subjects affected / exposed	0 / 27 (0.00%)	1 / 62 (1.61%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Kogenate FS (BAY14-2222) - Part A		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 28 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Injury			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Loss of consciousness			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Cephalhaematoma			

subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal pain			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Social circumstances			
Miscarriage of partner			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Somatoform disorder			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Compartment syndrome			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Joint range of motion decreased			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Erysipelas			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Recombinant Factor VIII (BAY81-8973) - Part A	Recombinant Factor VIII (BAY81-8973) Part B and extension	Recombinant Factor VIII (BAY81-8973) by CS/EP - Part C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	43 / 62 (69.35%)	5 / 7 (71.43%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 27 (0.00%)	5 / 62 (8.06%)	0 / 7 (0.00%)
occurrences (all)	0	5	0
Blood and lymphatic system disorders			
Thymus disorder			
subjects affected / exposed	0 / 27 (0.00%)	0 / 62 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Anaemia			
subjects affected / exposed	0 / 27 (0.00%)	0 / 62 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
General disorders and administration site conditions			

Chest pain			
subjects affected / exposed	0 / 27 (0.00%)	4 / 62 (6.45%)	0 / 7 (0.00%)
occurrences (all)	0	4	0
Pyrexia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 62 (1.61%)	2 / 7 (28.57%)
occurrences (all)	0	1	2
Gastrointestinal disorders			
Dental caries			
subjects affected / exposed	0 / 27 (0.00%)	4 / 62 (6.45%)	0 / 7 (0.00%)
occurrences (all)	0	4	0
Diarrhoea			
subjects affected / exposed	0 / 27 (0.00%)	4 / 62 (6.45%)	2 / 7 (28.57%)
occurrences (all)	0	7	2
Dyspepsia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 62 (1.61%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Nausea			
subjects affected / exposed	0 / 27 (0.00%)	4 / 62 (6.45%)	1 / 7 (14.29%)
occurrences (all)	0	4	2
Vomiting			
subjects affected / exposed	0 / 27 (0.00%)	4 / 62 (6.45%)	0 / 7 (0.00%)
occurrences (all)	0	4	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 27 (0.00%)	5 / 62 (8.06%)	0 / 7 (0.00%)
occurrences (all)	0	5	0
Pleural effusion			
subjects affected / exposed	0 / 27 (0.00%)	0 / 62 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Pulmonary artery dilatation			
subjects affected / exposed	0 / 27 (0.00%)	0 / 62 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	0 / 27 (0.00%)	0 / 62 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1

Renal and urinary disorders			
Anuria			
subjects affected / exposed	0 / 27 (0.00%)	0 / 62 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 27 (0.00%)	6 / 62 (9.68%)	0 / 7 (0.00%)
occurrences (all)	0	10	0
Back pain			
subjects affected / exposed	0 / 27 (0.00%)	4 / 62 (6.45%)	0 / 7 (0.00%)
occurrences (all)	0	4	0
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 27 (0.00%)	6 / 62 (9.68%)	0 / 7 (0.00%)
occurrences (all)	0	6	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 27 (0.00%)	8 / 62 (12.90%)	0 / 7 (0.00%)
occurrences (all)	0	14	0
Nasopharyngitis			
subjects affected / exposed	0 / 27 (0.00%)	14 / 62 (22.58%)	0 / 7 (0.00%)
occurrences (all)	0	22	0
Pharyngitis			
subjects affected / exposed	0 / 27 (0.00%)	5 / 62 (8.06%)	0 / 7 (0.00%)
occurrences (all)	0	7	0
Device related infection			
subjects affected / exposed	0 / 27 (0.00%)	0 / 62 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1

Non-serious adverse events	Kogenate FS (BAY14-2222) - Part A		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 28 (3.57%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			

Thymus disorder subjects affected / exposed occurrences (all) Anaemia subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0 0 / 28 (0.00%) 0		
General disorders and administration site conditions Chest pain subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	 0 / 28 (0.00%) 0 0 / 28 (0.00%) 0		
Gastrointestinal disorders Dental caries subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 0 / 28 (0.00%) 0 0 / 28 (0.00%) 0 0 / 28 (0.00%) 0 0 / 28 (0.00%) 0 0 / 28 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all)	 0 / 28 (0.00%) 0 0 / 28 (0.00%) 0		

Pulmonary artery dilatation subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0		
Skin and subcutaneous tissue disorders Dermatitis contact subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0		
Renal and urinary disorders Anuria subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0 0 / 28 (0.00%) 0		
Infections and infestations Influenza subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all) Device related infection subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0 1 / 28 (3.57%) 2 0 / 28 (0.00%) 0 0 / 28 (0.00%) 0 0 / 28 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 November 2009	Amendment 1, specified the following modifications: 1. The regulatory agencies requested clarification regarding the surgery indication, such as a definition of the surgery types, safety data required prior to surgery, and evaluation times of the surgery outcome data during the study. 2. The study criteria were clarified as >= 10 surgeries in >= 10 subjects. 3. The PK blood sampling scheme was revised to include an additional timepoint, 30 h post-injection, to comply with the regulatory agencies' request for additional timepoints. 4. Amendment 1 specified that following randomization, subjects were to be supplied with and were to use only antihemophilic factor (recombinant), Kogenate FS where there was a need for FVIII treatment, and the investigational product, BAY81-8973, was not provided. 5.The one-time titration and change in dose per injection was removed, thus, a fixed, consistent dose was to be administered for each injection. 6. The injection time for PK (Part A) and for in vivo recovery (Part A and Part B) was changed to 10 min instead of 5-10 min. Treatment interruption of prophylaxis treatment was revised as not permitted. The dosage range for prophylaxis treatment was clarified as occurring in 5 IU/kg increments over the range of 20-40 IU/kg (ie, 20, 25, 30, 35, or 40 IU/kg), administered 2-3 times per week, at the investigator's discretion. 7. Editorial changes in primary objective and changes in most efficacy objectives to reflect that efficacy data will be combined with Protocol 2009-012150-20 (14319) for statistical analysis. Change in secondary objective of the study from "demonstrate the non-inferiority of BAY 81-8973 based on potency determinations (CS/EP vs CS/ADJ)" to "compare BAY 81-8973 based on potency determinations (CS/EP vs CS/ADJ) as measured by in vivo recovery".
08 April 2010	Amendment 5, specified the following modifications: - The inclusion criterion for current inhibitor antibody was clarified and the washout time was revised to be consistent with a washout period of 3 days specified throughout the protocol. In addition, the inhibitor history inclusion criterion was corrected from >1.0 to 1 BU. In the original protocol, the inhibitor inclusion criterion was 1 Bethesda unit (BU). It was changed in error to >1 BU in Amendment 1. In Amendment 5 it was corrected back to 1 BU. - The exclusion criterion for CD4 lymphocyte cell count (< 400 cells/microliter) was revised to be consistent with previous studies (< 250 cells/microliter). In addition, the exclusion criterion of portal vein hypertension was clarified as "significant portal vein hypertension in the judgement of the investigator". - The number of subjects to be enrolled into Part A of the protocol was revised from 16 to up to 30. - Since it was not required that Kogenate was to be administered within 15 minutes (min) of surgery, this condition was deleted. Also, since a urine dipstick test was not performed (only urinalysis), the dipstick test was deleted. - The treatment administration time was changed from 5 – 10 min to 1 – 15 min. This change was made to be consistent with the product labeling for Kogenate FS. - Concomitant therapy was revised to allow subjects with arthritis to receive treatment with NSAIDS.

11 May 2010	Amendment 6, specified the following modifications: - The definition for 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 the one-stage clotting assay, to be included in the trial without further testing/confirmation of severe hemophilia A if the screening result turned out to be >=1%. - The number of surgeries (across both studies 12954 and 14319) was increased from ">=10 surgeries in >= 10 subjects" to " >=15 surgeries in >=15 subjects", and the classification of surgery types was clarified ("at least 8 must be classified as major surgical procedures") to enable a more thorough evaluation of the safety and efficacy of BAY 81-8973 in the surgical setting. - To further ensure subject safety, the requirement was added that BAY81-8973 should not be supplied for use in the surgical setting until at least 20 bleeding events (across both studies) had been assessed to ensure the hemostatic activity of BAY81-8973. It was further specified that all sites were to be informed by the Sponsor when surgical treatment using BAY81-8973 was allowed to commence. - Editorial revision of the change regarding dipstick urine test. - Since the 3-day washout of FVIII applied to both Part A and B and not just Part A, the appropriate exclusion criterion was revised. "Any subject in Part A who cannot forego at least 3 days without receiving FVIII before the PK sessions for washout purposes." was changed to "Any subject who cannot forego at least 3 days without receiving FVIII for washout purposes.
21 September 2010	Amendment 7, became effective after 28 subjects had started treatment. It specified the following modification: Addition of "known hypersensitivity against mouse protein" as an exclusion criterion.
13 January 2011	Amendment 8, specified the following modifications: - The study objectives of Part B of the study were reorganized to ensure that the primary and secondary study objectives included objectives for results of this study alone, and a separate category, "addendum objectives", was added to include objectives for the pooled results of this study and Study 2009-012150-20 (14319). Importantly, no Part B objectives were deleted or significantly revised. - The highest dosage was increased from 40 IU/kg to 50 IU/kg in Part B of the study, in order to account for standard of care of some centers who use this dose as a standard prophylaxis dosing. - A pharmacogenetic sample for FVIII genetic analysis was added which allows the genetic analysis of FVIII polymorphism in different ethnic groups participating in this trial. - If another product had to be used during the study to control the bleed (according to the local standard of care), the product was no longer required to be a marketed recombinant FVIII product, and could be another marketed FVIII product as not all participating sites were using recombinant products as standard of care. - Visit 4 and Visit 5 were combined into one visit, Visit 4/5, because 2 visits within 3 days were thought to be very difficult to arrange for young subjects who are in an active life, and could be a barrier for recruitment. The recovery required at Visit 4, the end of the first period, was changed to Visit 3.
01 April 2011	Amendment 9, specified the following modifications: - Additions to study objectives ("additional objectives"), description of Part C ("Major Surgery Arm"), inclusion criteria, and other protocol sections to account for major surgeries. - Introduction of the extension period (treatment beyond the 1-year treatment period for 1 further year) and a detailed description of this in the appropriate protocol sections.

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.

The study specific characteristics 'Most recent treatment before enrolment in the study' could not be reported due to database constrains. Occurrence of "±” in relation with geometric CV(%) is auto-generated and cannot be deleted.

Notes: