Clinical trial results:
A Phase 3, Multicenter, Open Label Study of Efficacy and Safety of PEGylated rFVIII (BAX 855) in Previously Treated Patients With Severe Hemophilia A Undergoing Surgical or Other Invasive Procedures

Summary

EudraCT number	2013-001359-11
Trial protocol	GB BE LT BG ES DE NL
Global end of trial date	23 September 2016

Results information

Result version number	v1 (current)
This version publication date	06 April 2017
First version publication date	06 April 2017

Trial information

Trial identification

Sponsor protocol code	261204

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01913405
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Baxalta Innovations GmbH
Sponsor organisation address	Industriestrasse 67, Vienna, Austria, 1221
Public contact	Clinical Trial Registries and Results Disclosure, Baxalta Innovations GmbH, ClinicalTrialsDisclosure@baxalta.com
Scientific contact	Clinical Trial Registries and Results Disclosure, Baxalta Innovations GmbH, ClinicalTrialsDisclosure@baxalta.com
Sponsor organisation name	Baxalta US Inc.
Sponsor organisation address	One Baxter Way, Westlake Village, United States, CA 91362
Public contact	Clinical Trial Registries and Results Disclosure, Baxalta US Inc., ClinicalTrialsDisclosure@baxalta.com
Scientific contact	Clinical Trial Registries and Results Disclosure, Baxalta US Inc., ClinicalTrialsDisclosure@baxalta.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001296-PIP01-12
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 September 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 September 2016
Global end of trial reached?	Yes
Global end of trial date	23 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the perioperative hemostatic efficacy of BAX 855 in male previously treated patients aged 2-75 years with severe hemophilia A (FVIII<1%) undergoing major or minor elective or minor emergency surgical, dental or other invasive procedures as determined by the Global Hemostatic Efficacy Assessment.

Protection of trial subjects:

The study was conducted in accordance with the study protocol, the International Conference on Harmonization Guideline for Good Clinical Practice E6 (ICH GCP April 1996), Title 21 of the US Code of Federal Regulations (US CFR), the European Clinical Trial Directive (2001/20/EC and 2005/28/EC), and applicable national and local regulatory requirements. The enrollment of subjects <12years of age was limited to subjects participating in the pediatric study 261202. In the Russian Federation, all subjects were required to be >18 years old at the time of enrollment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 December 2013
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	United States: 8
Country: Number of subjects enrolled	Russian Federation: 2
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Bulgaria: 6
Country: Number of subjects enrolled	Lithuania: 1
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Switzerland: 2
Worldwide total number of subjects	23
EEA total number of subjects	11

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)	1
Adults (18-64 years)	22
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Twelve study sites have enrolled subjects in seven countries (US, Russia, UK, Bulgaria, Lithuania, Spain, Switzerland). There were 30 surgical enrollments in a total of 23 unique subjects. Seven unique subjects enrolled more than once, of whom five received study product for more than one surgical procedure.

Pre-assignment

Screening details:

A total of 23 subjects provided informed consent and were screened for study participation. There were 3 screen failures, of which 2 participated and completed the study. 22 unique subjects (29 surgical enrollments) were exposed to study product. One subject discontinued prior to surgery and one subject discontinued after surgery.

Pre-assignment period milestones

Number of subjects started	23
Number of subjects completed	22

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screen failure: 1

Period 1

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

Arms

Arm title	Overall trial

Arm description:

Treatment with BAX855 for pre-surgical PK infusion, surgery and postoperative treatment.

Arm type	Experimental
Investigational medicinal product name	BAX 855
Investigational medicinal product code	
Other name	Adynovate, Adynovi
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects undergoing major surgery initially underwent a pharmacokinetic (PK) evaluation with BAX855 (60 +/-5 IU/kg), if PK parameters were not already available from a BAX855 parent study. For subjects undergoing minor surgery an individual IR was determined. Individual dosing based on the patients PK/IR parameters was outlined in the FVIII substitution plan. For the loading dose prior surgery the FVIII target levels were to be 80-100% of normal (major surgery) and 30-60% of normal (minor surgery). Subsequent infusions were preceeded by measurement of residual FVIII levels and the dose adjusted as needed. The following FVIII trough levels were to be targeted: Postoperative day 1-3: not below 80%, day 4-7: not below 50%, day 8 to discharge: not below 30%

Number of subjects in period 1[1]	Overall trial
Started	22
Completed	20
Not completed	2
Consent withdrawn by subject	1
Adverse event, non-fatal	1

Notes:

[1] - 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: A total of 23 subjects provided informed consent and were screened for study participation. One subject was a screen failure and did not enter the baseline period. Two other subjects were also screen failures but did enter the baseline period and were treated with study product.

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial
Reporting group description:	
Overall trial	

Reporting group values	Overall trial	Total	
Number of subjects	22	22	
Age categorical Units: Subjects			
2 to <18 years	1	1	
18 to 75 years	21	21	
Age continuous Units: years			
arithmetic mean	34.8		
standard deviation	± 13.47	-	
Gender categorical Units:			
Male	22	22	

Subject analysis sets	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS comprises all subjects with at least one available hemostatic assessment. N=26 surgical enrollments in 21 unique subjects.	
Subject analysis set title	Per-Protocol Analysis Set
Subject analysis set type	Per protocol
Subject analysis set description:	
The PPAS comprises all subjects with available intraoperative efficacy assessment performed by the surgeon within 60 minutes post-surgery, postoperative hemostatic control assessed by the operating surgeon postoperatively at 24 hours and perioperative hemostatic control assessed by the investigator during end of study visit. Only subjects who met all study entry criteria and who had no major protocol violation that impacted hemostatic efficacy assessment were included in the PPAS. N=12 surgical enrollments in 11 unique subjects.	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The SAS comprises all subjects who received at least one infusion of BAX855. N= 29 surgical enrollments in 22 unique subjects.	
Subject analysis set title	Pharmacokinetic Analysis Set
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The PKAS comprises only subjects who underwent a PK assessment. N=25 surgical enrollments in 20 unique subjects.	
Subject analysis set title	Major orthopedic surgery
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Comprises all subjects treated with BAX855 for major orthopedic surgery.	

N=14 surgical enrollments in 12 unique subjects.

Subject analysis set title	Major non-orthopedic surgery
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Comprises all subjects treated with BAX855 for major non-orthopedic surgery.
N=7 surgical enrollments in 6 unique subjects.

Subject analysis set title	Minor surgery
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Comprises all subjects treated with BAX855 for minor surgery.
N=5 surgical enrollments in 4 unique subjects.

Reporting group values	Full Analysis Set	Per-Protocol Analysis Set	Safety Analysis Set
Number of subjects	21	11	22
Age categorical Units: Subjects			
2 to <18 years	1	1	1
18 to 75 years	20	10	21
Age continuous Units: years			
arithmetic mean	34	30.2	34.8
standard deviation	± 13.3	± 10.15	± 13.47
Gender categorical Units:			
Male	21	11	22

Reporting group values	Pharmacokinetic Analysis Set	Major orthopedic surgery	Major non-orthopedic surgery
Number of subjects	20	12	6
Age categorical Units: Subjects			
2 to <18 years	1	1	0
18 to 75 years	19	11	6
Age continuous Units: years			
arithmetic mean	36.7		
standard deviation	± 13.48	±	±
Gender categorical Units:			
Male	20	12	6

Reporting group values	Minor surgery		
Number of subjects	4		
Age categorical Units: Subjects			
2 to <18 years	0		
18 to 75 years	4		
Age continuous Units: years			
arithmetic mean			
standard deviation	±		

Gender categorical Units:			
Male	4		

End points

End points reporting groups

Reporting group title	Overall trial

Reporting group description:

Treatment with BAX855 for pre-surgical PK infusion, surgery and postoperative treatment.

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS comprises all subjects with at least one available hemostatic assessment.
N=26 surgical enrollments in 21 unique subjects.

Subject analysis set title	Per-Protocol Analysis Set
Subject analysis set type	Per protocol

Subject analysis set description:

The PPAS comprises all subjects with available intraoperative efficacy assessment performed by the surgeon within 60 minutes post-surgery, postoperative hemostatic control assessed by the operating surgeon postoperatively at 24 hours and perioperative hemostatic control assessed by the investigator during end of study visit. Only subjects who met all study entry criteria and who had no major protocol violation that impacted hemostatic efficacy assessment were included in the PPAS.
N=12 surgical enrollments in 11 unique subjects.

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The SAS comprises all subjects who received at least one infusion of BAX855.
N= 29 surgical enrollments in 22 unique subjects.

Subject analysis set title	Pharmacokinetic Analysis Set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PKAS comprises only subjects who underwent a PK assessment.
N=25 surgical enrollments in 20 unique subjects.

Subject analysis set title	Major orthopedic surgery
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Comprises all subjects treated with BAX855 for major orthopedic surgery.
N=14 surgical enrollments in 12 unique subjects.

Subject analysis set title	Major non-orthopedic surgery
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Comprises all subjects treated with BAX855 for major non-orthopedic surgery.
N=7 surgical enrollments in 6 unique subjects.

Subject analysis set title	Minor surgery
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Comprises all subjects treated with BAX855 for minor surgery.
N=5 surgical enrollments in 4 unique subjects.

Primary: Global Hemostatic Efficacy Assessment score (GHEA)

End point title	Global Hemostatic Efficacy Assessment score (GHEA)[1]

End point description:

The GHEA is composed of three individual ratings:
a. Assessment of intraoperative hemostatic efficacy of BAX 855 performed by the operating surgeon;
b. Assessment of postoperative hemostatic efficacy of BAX 855 at postoperative Day 1 (approx. 24 hours post surgery) performed by the operating surgeon;
c. Assessment of perioperative hemostatic efficacy of BAX855 at Day 14 or discharge, whichever is first, performed by the investigator.

The scores of the individual ratings are added for the GHEA.
Treatment success is a GHEA score of excellent or good. Point estimates and corresponding two-sided exact (Clopper-Pearson) confidence intervals at 90% confidence level are calculated.
Number of subjects analysed is based on surgical enrollments and the same as number of surgeries.
Main analysis was done on the FAS with 24 surgeries with at least one available hemostatic assessment, supportive analysis was done on the PPAS with 12 surgeries with all hemostatic assessments available.

End point type	Primary

End point timeframe:

Hemostatic efficacy assessments were performed intraoperatively, postoperatively on day 1 (approximately 24 hours after surgery) and perioperatively at day 14 or discharge (whichever was first).

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: Per protocol, only descriptive statistics were collected for this endpoint.

End point values	Full Analysis Set	Per-Protocol Analysis Set	Major orthopedic surgery	Major non-orthopedic surgery
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	12	14	7
Units: Percentage of surgeries				
number (confidence interval 90%)				
Treatment Success (GHEA score excellent or good)	100 (88.3 to 100)	100 (77.9 to 100)	100 (80.7 to 100)	100 (65.2 to 100)
Excellent	100 (88.3 to 100)	100 (77.9 to 100)	100 (80.7 to 100)	100 (65.2 to 100)
Good	0 (0 to 11.7)	0 (0 to 22.1)	0 (0 to 19.3)	0 (0 to 34.8)

End point values	Minor surgery			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: Percentage of surgeries				
number (confidence interval 90%)				
Treatment Success (GHEA score excellent or good)	100 (36.8 to 100)			
Excellent	100 (36.8 to 100)			
Good	0 (0 to 63.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Intraoperative blood loss

End point title	Intraoperative blood loss

End point description:

Actual intraoperative blood loss was assessed at the end of surgery and was compared to the estimated volume of expected average and maximum blood loss in a hemostatically normal individual of the same sex, age and stature as the study subject. Expected intraoperative blood loss was predicted pre-operatively by the investigator/surgeon.
Number of subjects is counted based on surgical enrollment.

End point type	Secondary

End point timeframe:

From initiation of surgery until end of surgery.

End point values	Full Analysis Set	Major orthopedic surgery	Major non-orthopedic surgery	Minor surgery
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[2]	14	6[3]	5
Units: Milliliter				
median (inter-quartile range (Q1-Q3))				
Actual blood loss	10 (4 to 30)	10 (10 to 30)	4.5 (3 to 50)	5 (0 to 15)
Predicted average blood loss	20 (5 to 150)	150 (10 to 150)	10 (5 to 50)	5 (0 to 15)
Difference from predicted average blood loss	6 (0 to 135)	125 (0 to 140)	1.5 (0 to 6)	0 (0 to 0)
Predicted maximum blood loss	100 (7 to 300)	300 (100 to 300)	20 (5 to 150)	5 (0 to 30)
Difference from predicted maximum blood loss	100 (4 to 280)	275 (95 to 290)	25 (3 to 100)	0 (0 to 15)

Notes:

[2] - n=26 for predicted average and maximum blood loss

[3] - n=7 for predicted average and maximum blood loss

Statistical analyses

No statistical analyses for this end point

Secondary: Postoperative blood loss

End point title	Postoperative blood loss

End point description:

Actual post-operative blood loss assessed at postoperative day 1 was compared to the estimated volume of expected average and maximum blood loss in a hemostatically normal individual of the same sex, age and stature as the study subject. Expected postoperative blood loss was predicted pre-operatively by the investigator/surgeon.
Number of subjects is counted based on surgical enrollment.

End point type	Secondary

End point timeframe:

From completion of surgery until 24 hours after surgery.

End point values	Full Analysis Set	Major orthopedic surgery	Major non-orthopedic surgery	Minor surgery
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	16[4]	9[5]	4[6]	3[7]
Units: Milliliter				
median (inter-quartile range (Q1-Q3))				
Actual blood loss	10 (0 to 825)	750 (15 to 1100)	1 (0 to 33.5)	0 (0 to 4)

Predicted average blood loss	27.5 (0 to 300)	213.5 (30 to 700)	1 (0 to 25)	0 (0 to 0)
Difference from predicted average blood loss	-7.5 (-125 to 4)	-50 (-400 to -15)	4 (-7.5 to 16.5)	0 (0 to 196)
Predicted maximum blood loss	75 (0 to 600)	450 (100 to 1200)	2 (0 to 50)	0 (0 to 0)
Difference from predicted maximum blood loss	67.5 (0 to 148)	100 (0 to 300)	34 (9 to 67.5)	0 (0 to 196)

Notes:

[4] - n=26 for predicted average and maximum blood loss

[5] - n=14 for predicted average and maximum blood loss

[6] - n=7 for predicted average and maximum blood loss

[7] - n=5 for predicted average and maximum blood loss

Statistical analyses

No statistical analyses for this end point

Secondary: Overall perioperative blood loss

End point title	Overall perioperative blood loss

End point description:

Actual overall perioperative blood loss (assessed at the end of surgery, at postoperative day 1 and until discharge or day 14 - whichever is first) was compared to the estimated volume of expected average and maximum blood loss in a hemostatically normal individual of the same sex, age and stature as the study subject. Expected perioperative blood loss was predicted pre-operatively by the investigator/surgeon.
Number of subjects is counted based on surgical enrollment.

End point type	Secondary

End point timeframe:

From start of surgery until discharge or day 14, whichever occurred last.

End point values	Full Analysis Set	Major orthopedic surgery	Major non-orthopedic surgery	Minor surgery
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[8]	14	6[9]	5
Units: Milliliter				
median (inter-quartile range (Q1-Q3))				
Actual blood loss	50 (5 to 305)	246 (15 to 1210)	5.5 (3 to 50)	9 (0 to 15)
Predicted average blood loss	40 (5 to 800)	675 (30 to 1000)	20 (5 to 50)	0 (0 to 15)
Difference from predicted average blood loss	0 (-50 to 20)	-5 (-210 to 25)	2.5 (0 to 14)	0 (0 to 0)
Predicted maximum blood loss	125 (20 to 1500)	1500 (100 to 1500)	20 (6 to 150)	0 (0 to 30)
Difference from predicted maximum blood loss	64 (6 to 250)	122.5 (50 to 400)	5.5 (0 to 64)	0 (0 to 15)

Notes:

[8] - n=26 for predicted average and maximum blood loss

[9] - n=7 for predicted average and maximum blood loss

Statistical analyses

No statistical analyses for this end point

Secondary: Blood transfusion requirements

End point title	Blood transfusion requirements

End point description:

Volume of blood, red blood cells, platelets, and other blood products transfused. Only packed red blood cells were transfused in this study.
Subjects are counted based on surgical enrollment.
No blood transfusions were required for minor surgeries and no blood transfusion were required intraoperatively for major surgeries.

End point type	Secondary

End point timeframe:

From initiation of the surgery to 24 hours after completion of the surgery.

End point values	Full Analysis Set	Major orthopedic surgery	Major non-orthopedic surgery	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	4	3	1[10]	
Units: Milliliter				
arithmetic mean (standard deviation)				
Volume of all blood products - postoperative	438 (± 152.86)	384 (± 132.49)	600 (± 999.99)	

Notes:

[10] - Dispersion is not applicable as there is only 1 subject in the analysis set.

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of bleeding episodes and additional need for surgical intervention

End point title	Occurrence of bleeding episodes and additional need for surgical intervention

End point description:

Any clinically relevant bleeding episodes (as assessed by the investigator) and any need for additional surgical intervention were recorded. If the subject had not resumed his previous treatment after discharge, the occurrence and treatment of bleeding episodes were recorded in the subject's diary.
Only surgical enrollments that have encountered bleeding episodes are listed as subjects analysed.
The additional need for surgeries was assessed for all 26 surgical enrollments.

End point type	Secondary

End point timeframe:

From start of surgery until the last intensified treatment after hospital discharge (or until hospital discharge if there was no intensified treatment).

End point values	Full Analysis Set	Major orthopedic surgery	Major non-orthopedic surgery	Minor surgery
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	2	2	1
Units: Events				
Bleeding episodes site mucosal	2	0	1	1
Bleeding episodes site joint	1	1	0	0
Bleeding episodes site gastrointestinal	1	0	1	0
Bleeding episodes site muscle	1	1	0	0
Bleeding episodes cause spontaneous	0	0	0	0
Bleeding episodes cause injury	5	2	2	1
Bleeding episodes severity mild	3	1	1	1
Bleeding episodes severity moderate	1	0	1	0
Bleeding episodes severity severe	1	1	0	0
Additional need for surgery	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Daily and total weight-adjusted consumption of BAX855 per subject

End point title	Daily and total weight-adjusted consumption of BAX855 per subject

End point description:

Daily weight-adjusted BAX855 consumption is listed from preoperative loading dose until discharge.
Total weight-adjusted BAX855 consumption is calculated from first study infusion (PK/IR) until end of study. PK infusions from previous studies are not included.
Subjects are counted based on their surgical enrollment.
Number of subjects=surgeries (n) varies on each postoperative day as described in the categories for non-orthopedic major surgery (NOS), orthopedic major surgery (OS) and minor surgery (MS) and the full analysis set (FAS). 99.999 is listed if result is not available due to n=0 or standard deviation is not available due to n=1.

End point type	Secondary

End point timeframe:

From initial loading dose until discharge for daily weight-adjusted dose and from first infusion (PK/IR) until end of study for total weight-adjusted dose.

End point values	Full Analysis Set	Major orthopedic surgery	Major non-orthopedic surgery	Minor surgery
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	26	14	7	5
Units: IU/kg				
arithmetic mean (standard deviation)				
Total weight adjusted BAX855 consumption	562.076 (± 343.7305)	746.103 (± 320.4581)	507.881 (± 161.8075)	122.673 (± 20.0076)
Preoperative	62.492 (± 15.7678)	69.442 (± 14.4532)	56.852 (± 14.8899)	50.928 (± 12.27)

Postop day 0: n=18(FAS) n=11(OS) n=6(NOS) n=1(MS)	34.195 (± 13.6755)	37.082 (± 16.016)	31.141 (± 7.5641)	20.762 (± 99.999)
Postop day 1: n=24(FAS) n=14(OS) n=6(NOS) n=4(MS)	56.409 (± 24.8718)	62.005 (± 25.4147)	50.698 (± 29.2373)	45.388 (± 12.0692)
Postop day 2: n=19(FAS) n=13(OS) n=6(NOS) n=0(MS)	51.697 (± 27.7558)	52.445 (± 27.4771)	50.076 (± 30.9322)	99.999 (± 99.999)
Postop day 3: n=17(FAS) n=12(OS) n=5(NOS) n=0(MS)	45.023 (± 24.2793)	47.139 (± 27.1069)	39.943 (± 17.0764)	99.999 (± 99.999)
Postop day 4: n=16(FAS) n=12(OS) n=4(NOS) n=0(MS)	36.593 (± 12.2194)	38.009 (± 13.6782)	32.345 (± 5.3374)	99.999 (± 99.999)
Postop day 5: n=12(FAS) n=10(OS) n=2(NOS) n=0(MS)	32.24 (± 15.1497)	32.333 (± 15.1071)	31.775 (± 21.6822)	99.999 (± 99.999)
Postop day 6: n=9(FAS) n=7(OS) n=2(NOS) n=0(MS)	34.135 (± 13.3132)	35.198 (± 12.8578)	30.415 (± 19.7589)	99.999 (± 99.999)
Postop day 7: n=4(FAS) n=3(OS) n=1(NOS) n=0(MS)	22.955 (± 6.0531)	24.866 (± 5.7495)	17.223 (± 99.999)	99.999 (± 99.999)
Postop day 8+: n=2(FAS) n=2(OS) n=0(NOS) n=0(MS)	136.808 (± 139.3781)	136.808 (± 139.3781)	99.999 (± 99.999)	99.999 (± 99.999)

Statistical analyses

No statistical analyses for this end point

Secondary: Presurgical PK - Area under the plasma concentration/time curve

End point title	Presurgical PK - Area under the plasma concentration/time curve

End point description:

The area under the plasma concentration/time curve from time 0 to infinity (AUC 0-inf) and the area under the first movement curve from time 0 to infinity (AUMC 0-inf) was calculated as the sum of AUC and AUMC from time 0 to the time of the last quantifiable concentration plus a tail area correction calculated as Ct/λz and Ct/λz(t+1/λz), respectively, where Ct is the last quantifiable concentration, t is the time of last quantifiable concentration and λz is the terminal or disposition rate constant.
The area under the plasma concentration/time curve from time 0 to 96 hours postinfusion (AUC 0-96h) was computed using the linear trapezoidal rule. For the calculation of AUC 0-96h the levels at 96 hours were linearly interpolated/extrapolated from the 2 nearest sampling time points.
Number of subjects is counted based on surgical enrollment.
Main analysis was done on the one-stage clotting assay results, supportive analysis was done on the chromogenic assay results.

End point type	Secondary

End point timeframe:

PK measurements were done within 30 minutes pre-infusion, and post infusion at 15 (± 5) minutes, 3 hours (± 30 minutes), 9 hours (± 30 minutes), 32 (± 2) hours, 56 (± 4) hours and 96 (± 4) hours.

End point values	Pharmacokinetic Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	25			
Units: IU*h/dL				
arithmetic mean (standard deviation)				
AUC (0-96h) one-stage clotting	2701.3 (± 719.52)			
AUC (0-96h) chromogenic	3153.7 (± 980.27)			

AUC (0-inf) one-stage clotting AUC (0-inf) chromogenic	2743.3 (± 751.83) 3201.8 (± 1019.13)			

Statistical analyses

No statistical analyses for this end point

Secondary: Presurgical PK - Terminal Half-Life

End point title	Presurgical PK - Terminal Half-Life

End point description:

Terminal or disposition half-life (HL) was calculated as log e(2)/λz where the terminal or disposition rate constant (λz) was estimated as the slope of a log-linear least squares regression model.
Number of subjects is counted based on surgical enrollment.
Main analysis was done on the one-stage clotting assay results, supportive analysis was done on the chromogenic assay results.

End point type	Secondary

End point timeframe:

PK measurements were done within 30 minutes pre-infusion, and post infusion at 15 (± 5) minutes, 3 hours (± 30 minutes), 9 hours (± 30 minutes), 32 (± 2) hours, 56 (± 4) hours and 96 (± 4) hours.

End point values	Pharmacokinetic Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	25			
Units: hours				
arithmetic mean (standard deviation)				
One-stage clotting Chromogenic	14.63 (± 3.179) 14.53 (± 3.137)			

Statistical analyses

No statistical analyses for this end point

Secondary: Presurgical PK - Mean residence time (MRT)

End point title	Presurgical PK - Mean residence time (MRT)

End point description:

Mean residence time (MRT) was calculated as total area under the moment curve divided by the total area under the curve.
Number of subjects is counted based on surgical enrollment.
Main analysis was done on the one-stage clotting assay results, supportive analysis was done on the chromogenic assay results.

End point type	Secondary

End point timeframe:

PK measurements were done within 30 minutes pre-infusion, and post infusion at 15 (± 5) minutes, 3

hours (± 30 minutes), 9 hours (± 30 minutes), 32 (± 2) hours, 56 (± 4) hours and 96 (± 4) hours.

End point values	Pharmacokinetic Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	25			
Units: hours				
arithmetic mean (standard deviation)				
One-stage clotting	19.26 (± 4.901)			
Chromogenic	18.68 (± 4.16)			

Statistical analyses

No statistical analyses for this end point

Secondary: Presurgical PK - Clearance (CL)

End point title	Presurgical PK - Clearance (CL)

End point description:

Systemic clearance (CL) was calculated as the dose in IU/kg divided by the total AUC.
Number of subjects is counted based on surgical enrollment.
Main analysis was done on the one-stage clotting assay results, supportive analysis was done on the chromogenic assay results.

End point type	Secondary

End point timeframe:

PK measurements were done within 30 minutes pre-infusion, and post infusion at 15 (± 5) minutes, 3 hours (± 30 minutes), 9 hours (± 30 minutes), 32 (± 2) hours, 56 (± 4) hours and 96 (± 4) hours.

End point values	Pharmacokinetic Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	25			
Units: dL/(kg*h)				
arithmetic mean (standard deviation)				
One-stage clotting	0.02347 (± 0.006821)			
Chromogenic	0.02042 (± 0.006041)			

Statistical analyses

No statistical analyses for this end point

Secondary: Presurgical PK - Apparent volume of distribution at steady state (Vss)

End point title	Presurgical PK - Apparent volume of distribution at steady state (Vss)

End point description:

Apparent steady state volume of distribution (Vss) was calculated as dose multiplied with AUMC(0-inf) divided by AUC(0-inf) to square.
Number of subjects is counted based on surgical enrollment.
Main analysis was done on the one-stage clotting assay results, supportive analysis was done on the chromogenic assay results.

End point type	Secondary

End point timeframe:

PK measurements were done within 30 minutes pre-infusion, and post infusion at 15 (± 5) minutes, 3 hours (± 30 minutes), 9 hours (± 30 minutes), 32 (± 2) hours, 56 (± 4) hours and 96 (± 4) hours.

End point values	Pharmacokinetic Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	25			
Units: dL/kg				
arithmetic mean (standard deviation)				
One-stage clotting	0.4316 (± 0.09633)			
Chromogenic	0.3673 (± 0.09559)			

Statistical analyses

No statistical analyses for this end point

Secondary: Presurgical PK - Incremental recovery

End point title	Presurgical PK - Incremental recovery

End point description:

Incremental recovery (IR) was calculated as C post infusion minus C pre-infusion divided by the dose.
Number of subjects is counted based on surgical enrollment.
Main analysis was done on the one-stage clotting assay results, supportive analysis was done on the chromogenic assay results.

End point type	Secondary

End point timeframe:

PK measurements were done within 30 minutes pre-infusion, and post infusion at 15 (± 5) minutes, 3 hours (± 30 minutes), 9 hours (± 30 minutes), 32 (± 2) hours, 56 (± 4) hours and 96 (± 4) hours.

End point values	Pharmacokinetic Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	25			
Units: (IU/dL)/(IU/kg)				
arithmetic mean (standard deviation)				
IR at 15 min post infusion - one-stage clotting	2.106 (± 0.3823)			

IR at 15 min post infusion - chromogenic	2.721 (± 0.5981)			
IR at Cmax - one-stage clotting	2.123 (± 0.4041)			
IR at Cmax - chromogenic	2.677 (± 0.596)			

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of safety outcome measures (development of antibodies, thrombotic events, severe allergic reactions and other IP related AEs)

End point title	Summary of safety outcome measures (development of antibodies, thrombotic events, severe allergic reactions and other IP related AEs)

End point description:

Development of treatment emerging binding antibodies to FVIII IgG, FVIII IgM, BAX855 IgG, BAX855 IgM, PEG IgG, PEG IgM and CHO proteins was assessed as well as any thrombotic events and severe allergic reactions and any other Adverse Events related to the investigational product. Unique subjects with a safety outcome measure are counted.

End point type	Secondary

End point timeframe:

From screening visit to end of study visit.

End point values	Safety Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Subjects				
Inhibitory antibodies to FVIII	0			
Treatment emerging binding antibodies to FVIII IgG	0			
Treatment emerging binding antibodies to FVIII IgM	0			
Treatment emerging binding antibodies to BAX855IgG	0			
Treatment emergingbinding antibodies to BAX855IgM	0			
Treatment emerging binding antibodies to PEG IgG	0			
Treatment emerging binding antibodies to PEG IgM	0			
Treatment emerg.binding antibodies to CHO proteins	0			
Thrombotic events	0			
Severe allergic reactions	0			
Other IP related Adverse Events	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in vital signs - Pulse rate

End point title	Changes in vital signs - Pulse rate

End point description:

Changes in vital signs were assessed 15 minutes after the PK/IR infusion compared to the pre-infusion values.
Number of subjects is counted based on surgical enrollment. The 15 minutes post-infusion measurement includes 1 hour post infusion assessments for two subjects.

End point type	Secondary

End point timeframe:

Vital signs measurement prior to the PK/IR infusion and 15 minutes post-infusion.

End point values	Safety Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	23[11]			
Units: beats/minute				
median (inter-quartile range (Q1-Q3))				
Pre-infusion	70 (68 to 74)			
15 minutes post-infusion	70 (66 to 77)			
Change at 15 min post-infusion	-1 (-3 to 2)			

Notes:

[11] - n=25 for pre-infusion measurement

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in vital signs - Blood pressure

End point title	Changes in vital signs - Blood pressure

End point description:

Changes in vital signs were assessed 15 minutes after the PK/IR infusion compared to the pre-infusion values.
Number of subjects is counted based on surgical enrollment. The 15 minutes post-infusion measurement includes 1 hour post infusion assessments for two subjects.

End point type	Secondary

End point timeframe:

Vital signs measurement prior to the PK/IR infusion and 15 minutes post-infusion.

End point values	Safety Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	23[12]			
Units: mmHg				
median (inter-quartile range (Q1-Q3))				
Systolic BP - Pre-infusion	120 (115 to 125)			
Systolic BP - 15 minutes post-infusion	115 (110 to 125)			
Systolic BP - Change at 15 min post-infusion	-5 (-5 to 4)			
Diastolic BP - Pre-infusion	75 (69 to 80)			
Diastolic BP - 15 minutes post-infusion	75 (70 to 80)			
Diastolic BP - Change at 15 min post-infusion	0 (-5 to 1)			

Notes:

[12] - n=25 for pre-infusion measurement

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in vital signs - Respiratory rate

End point title	Changes in vital signs - Respiratory rate

End point description:

Changes in vital signs were assessed 15 minutes after the PK/IR infusion compared to the pre-infusion values.
Number of subjects is counted based on surgical enrollment. The 15 minutes post-infusion measurement includes 1 hour post infusion assessments for two subjects.

End point type	Secondary

End point timeframe:

Vital signs measurement prior to the PK/IR infusion and 15 minutes post-infusion.

End point values	Safety Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	23[13]			
Units: breaths/minute				
median (inter-quartile range (Q1-Q3))				
Pre-infusion	14 (12 to 16)			
15 minutes post-infusion	14 (12 to 16)			
Change at 15 min post-infusion	0 (0 to 0)			

Notes:

[13] - n=25 for pre-infusion measurement

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in vital signs - Temperature

End point title	Changes in vital signs - Temperature

End point description:

Changes in vital signs were assessed 15 minutes after the PK/IR infusion compared to the pre-infusion values.
Number of subjects is counted based on surgical enrollment. The 15 minutes post-infusion measurement includes 1 hour post infusion assessments for two subjects.

End point type	Secondary

End point timeframe:

Vital signs measurement prior to the PK/IR infusion and 15 minutes post-infusion.

End point values	Safety Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	23[14]			
Units: Celsius				
median (inter-quartile range (Q1-Q3))				
Pre-infusion	36.6 (36.3 to 36.7)			
15 minutes post-infusion	36.6 (36.2 to 36.7)			
Change at 15 min post-infusion	0 (-0.1 to 0.2)			

Notes:

[14] - n=25 for pre-infusion measurement

Statistical analyses

No statistical analyses for this end point

Secondary: Clinically significant changes in routine labor parameters (hematology and chemistry)

End point title	Clinically significant changes in routine labor parameters (hematology and chemistry)

End point description:

Changes in clinical chemistry and hematology parameters from a normal or abnormal not clinically significant (ncs) result at screening to an abnormal and clinically significant (cs) result at the end of study assessment (EOS) are listed. Changes did occur in the following laboratory parameters: Alanine Aminotransferase (ALT) (U/L), Hemoglobin (g/L), Hematocrit, Erythrocytes(TI/L), Eosinophils/Leucocytes. Number of subjects is counted based on surgical enrollment.

End point type	Secondary

End point timeframe:

Laboratory assessment were done throughout the study from screening to study completion/termination.

End point values	Safety Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	26[15]			
Units: Subjects				
ALT: normal at Screening-abnormal cs at EOS	1			

Hemoglobin: abnormal ncs Screening-abnormal cs EOS	1			
Hematocrit: abnormal ncs Screening-abnormal cs EOS	1			
Erythrocytes: normal Screening-abnormal cs EOS	1			
Eosinop/Leucocyt: normal Screening-abnormal cs EOS	1			

Notes:

[15] - ALT: n=27, Hematocrit: n=25

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout the entire study period (2 years and 9 months).
For each subject the duration of treatment and therefore for the entire study period depended on the nature of each subject's invasive procedure (ranged from 43 days to 162 days).

Adverse event reporting additional description:

Adverse Events (AEs) were recorded throughout the entire study period from screening to completion/termination. AEs that occurred during or after treatment are summarized here, AEs that occurred prior to study treatment were listed separately and are not included.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Safety Analysis Set

Reporting group description:

The Safety Analysis Set comprises all subjects who received at least one infusion of BAX855.

Serious adverse events	Safety Analysis Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 22 (9.09%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
Diabetic gastroparesis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Oesophageal ulcer			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety Analysis Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 22 (36.36%)		
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Tooth fracture			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Procedural hypotension			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Procedural pain			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Wound			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Hyperacusis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			

Dyspnoea subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1 1 / 22 (4.55%) 1		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Infections and infestations Peritonsillitis subjects affected / exposed occurrences (all) Rhinitis subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1 1 / 22 (4.55%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 July 2013	The overall study duration was extended from 24 to 41 months. The recruitment period was extended from 18 to 34 months. Pediatric PTPs transitioning from the pediatric study with BAX855 were excluded from participation in this study. Information was added to justify the inclusion of adolescents in this study with two ICH guidelines referenced. The level of detectable FVIII inhibitory antibodies which would exclude a subject from participation was changed from ≥ 0.6 BU using the Nijmegen modification of the Bethesda assay to ≥0.4 BU (due to validation of the central laboratory for this value). The wash-out period for the PK assessment was changed from 96 to 72 hours. Criteria were listed that would require a repetition of the PK assessment (e.g. bleeding episode prior to 72-hour timepoint, 2 or more PK blood sample results not evaluable). A requirement for a 72-hour wash-out period before the immunogenicity tests was added. The requirement that major surgery may only be started when the required target FVIII level (range 80-150%) has been attained was removed (as test results may not have been available within 60 minutes in most standard laboratories). In the assessment scales for ntraoperative and postoperative efficacy, the description of products for rescue therapy was deleted from the rating criterion 'none'. Viral serology tests (HBV, HCV, HIV) were added to the laboratory tests to be performed at the end-of-study/termination visit (in alignment with the pivotal study). A planned safety review was added which was to be performed upon completion of BAX855 pivotal study 261201 and was to include all major and minor surgeries performed until that time.
30 January 2014	Overall study duration decreased from 41 to 36 months.Recruitment period changed from 34 to 33 months.Targeted accrual changed to approx. 50 surgical/invasive procedures in approx. 40 subjects, to include at least 10 major procedures in at least 5 subjects. Age range changed from previously 12-65 years to 2-75 years. Enrollment of subjects < 12 years of age limited to subjects participating in the BAX855 pediatric study. For newly recruited subjects the age range 12-75 years applies. Inclusion crit. were split according to whether subjects were transitioning form another BAX 855 study or were newly recruited. Emergency procedures now allowed in this study, provided these were minor emergency surgeries. Only subjects transitioning from another BAX855 study were allowed to undergo minor emergency surgery, newly recruited subjects had to undergo major procedures. If IR<1.5 in the parent study or after screening, no participation in this study. FVIII activity analysis at the central lab to be performed by 1-stage clotting and chromogenic assay. PK not required for minor surgeries and major surgeries if done in previous study, IR sufficient for subsequent dosing. Rating from EOS done at day 14, wording of definitions changed slightly. Changes in virology status removed from sec.outcome measures and not assessed at EOS. Antibodies to murine IgG not assessed. Wash-out for immunogenicity was 72h (FVIII) and 96h (BAX855). Addition of single dose vials with nominal potency of 3000 IU rFVIII. Instructions for use of vials, potencies and lots given. Dosing schedule changed (instead of PK guided dosing target levels provided). Surgery to start after normalization of aPTT and dose adjustments based on FVIII activity. Short half life removed from criteria for withdrawal. Detailed info for thrombosis prophy and topical hemostatics. Subject diary added. ECG and thrombotic markers removed. Vital signs timepoints changed and removed at EOS. Blood pressure measured in supine position.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported