



Clinical trial results:

BAX 326 (recombinant factor IX): A Phase 3 Prospective, Multicenter Study Evaluating Efficacy and Safety in Previously Treated Patients With Severe (FIX level < 1%) or Moderately Severe (FIX level 1-2%) Hemophilia B Undergoing Surgical or Other Invasive Procedures

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2011-000413-39
Trial protocol	GB CZ SE BG PL
Global end of trial date	15 May 2014

Results information

Result version number	v1 (current)
This version publication date	27 February 2016
First version publication date	27 February 2016

Trial information

Trial identification

Sponsor protocol code	251002
-----------------------	--------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01507896
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)	EMA-001139-PIP01-11

Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 May 2014
Global end of trial reached?	Yes
Global end of trial date	15 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the haemostatic efficacy and safety of BAX326 in the peri- and postoperative setting in subjects with severe (FIX level < 1%) or moderately severe (FIX level 1-2%) haemophilia B undergoing major or minor elective or emergency surgical, dental or other invasive procedures.

Protection of trial subjects:

This study was conducted in accordance with the clinical protocol, the International Conference on Harmonisation 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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 December 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 6
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Russian Federation: 17
Country: Number of subjects enrolled	Ukraine: 3
Country: Number of subjects enrolled	Chile: 4
Country: Number of subjects enrolled	Colombia: 1
Worldwide total number of subjects	41
EEA total number of subjects	16

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)	40
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Enrollment was conducted at 10 clinical sites in 8 countries (Bulgaria, Czech Republic, Poland, Romania, Russia, Ukraine, Chile, Colombia). A total of 30 subjects were enrolled in the study; 38 surgical procedures were performed with BAX326.

Pre-assignment

Screening details:

Of 30 subjects enrolled, one discontinued prior to receiving BAX326; however, this subject was re-enrolled later and received treatment with BAX326. 28 subjects underwent 38 surgical procedures (7 subjects had at least 2 surgeries and were re-enrolled for each new surgical procedure); another 2 subjects discontinued after PK assessment with BAX326.

Pre-assignment period milestones

Number of subjects started	41
Number of subjects completed	40

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 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 BAX326 (38 subjects underwent surgery, another 2 subjects only had a pharmacokinetic evaluation)

Arm type	Experimental
Investigational medicinal product name	BAX326 (recombinant factor IX)
Investigational medicinal product code	
Other name	Rixubis
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects undergoing major surgery initially underwent a pharmacokinetic (PK) evaluation with BAX326, if PK parameters were not already available from the predecessor pivotal study (1 infusion). Following the loading dose(s) with BAX326 prior to surgery, subjects received BAX326 as a bolus infusion. The regimen was to be determined by the intensity and duration of the haemostatic challenge. The dose was to be tailored to raise FIX concentration to 80%-100% of normal for major surgeries and to 30%-60% of normal for minor surgeries to ensure that the recommended pre-infusion FIX activity levels were maintained in the perioperative period.

Number of subjects in period 1^[1]	Overall trial
Started	40
Underwent surgery	38
Underwent PK assessment	12 ^[2]
Completed	38
Not completed	2
Consent withdrawn by subject	1
Surgery denied by sponsor	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: Total of enrolled subjects (including re-enrolled subjects) = 41. One subject discontinued before treatment; two subjects discontinued after treatment.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Subjects undergoing major surgery initially underwent a pharmacokinetic (PK) evaluation with BAX326, if PK parameters were not already available from the predecessor pivotal study (1 infusion).

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description:	
Overall trial	

Reporting group values	Overall trial	Total	
Number of subjects	40	40	
Age categorical			
Units: Subjects			
85 years and over	0	0	
From 65-84 years	0	0	
Adults (18-64 years)	39	39	
Adolescents (12-17 years)	1	1	
Children (2-11 years)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Newborns (0-27 days)	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
In utero	0	0	
Age continuous			
Units: years			
arithmetic mean	39.7		
standard deviation	± 11.2	-	
Gender categorical			
Units:			
Female	0	0	
Male	40	40	

Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
Comprises all subjects (incl. re-enrolled subjects) who were exposed to investigational product (IP) during the study who provide data suitable for the hemostatic efficacy analysis	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Comprises all subjects (incl. re-enrolled subjects) exposed to IP during the study	
Subject analysis set title	Per-Protocol Analysis Set
Subject analysis set type	Per protocol
Subject analysis set description:	
Comprises subjects in the Full Analysis Set who do not have major protocol deviations that are associated with efficacy endpoints or serious breaches of protocol; there was 1 major protocol deviation among the 21 subjects who underwent major surgery, which brings the number of subjects undergoing major surgery in the per-protocol analysis set to 20.	
Subject analysis set title	PK Analysis Set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Comprises subjects in the Full Analysis Set who had a presurgical PK assessment

Subject analysis set title	Subjects undergoing major surgery
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The 21 major surgeries in the Full Analysis Set comprised 14 major, orthopedic surgeries (eg, joint replacement) and 7 non-orthopedic surgeries (3 abdominal, 3 dental, 1 excision of tumor from soft tissue).

Subject analysis set title	Subjects undergoing minor surgery
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The 17 minor surgeries in the Full/Per-Protocol Analysis Set comprised 5 orthopedic surgeries (4 intraarticular infiltration, 1 synoviorthesis) and 12 non-orthopedic surgeries (11 dental, 1 intra-articular injection).

Reporting group values	Full Analysis Set	Safety Analysis Set	Per-Protocol Analysis Set
Number of subjects	40	40	39
Age categorical Units: Subjects			
85 years and over	0	0	0
From 65-84 years	0	0	0
Adults (18-64 years)	39	39	38
Adolescents (12-17 years)	1	1	1
Children (2-11 years)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Newborns (0-27 days)	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
In utero	0	0	0
Age continuous Units: years			
arithmetic mean	39.7	39.7	39.8
standard deviation	± 11.2	± 11.2	± 11.3
Gender categorical Units:			
Female	0	0	0
Male	40	40	39

Reporting group values	PK Analysis Set	Subjects undergoing major surgery	Subjects undergoing minor surgery
Number of subjects	12	21	17
Age categorical Units: Subjects			
85 years and over	0	0	0
From 65-84 years	0	0	0
Adults (18-64 years)	12	21	16
Adolescents (12-17 years)	0	0	1
Children (2-11 years)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Newborns (0-27 days)	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0

In utero	0	0	0
----------	---	---	---

Age continuous			
Units: years			
arithmetic mean			
standard deviation	±	±	±
Gender categorical			
Units:			
Female	0	0	0
Male	12	21	17

End points

End points reporting groups

Reporting group title	Overall trial
Reporting group description: Treatment with BAX326 (38 subjects underwent surgery, another 2 subjects only had a pharmacokinetic evaluation)	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: Comprises all subjects (incl. re-enrolled subjects) who were exposed to investigational product (IP) during the study who provide data suitable for the hemostatic efficacy analysis	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description: Comprises all subjects (incl. re-enrolled subjects) exposed to IP during the study	
Subject analysis set title	Per-Protocol Analysis Set
Subject analysis set type	Per protocol
Subject analysis set description: Comprises subjects in the Full Analysis Set who do not have major protocol deviations that are associated with efficacy endpoints or serious breaches of protocol; there was 1 major protocol deviation among the 21 subjects who underwent major surgery, which brings the number of subjects undergoing major surgery in the per-protocol analysis set to 20.	
Subject analysis set title	PK Analysis Set
Subject analysis set type	Sub-group analysis
Subject analysis set description: Comprises subjects in the Full Analysis Set who had a presurgical PK assessment	
Subject analysis set title	Subjects undergoing major surgery
Subject analysis set type	Sub-group analysis
Subject analysis set description: The 21 major surgeries in the Full Analysis Set comprised 14 major, orthopedic surgeries (eg, joint replacement) and 7 non-orthopedic surgeries (3 abdominal, 3 dental, 1 excision of tumor from soft tissue).	
Subject analysis set title	Subjects undergoing minor surgery
Subject analysis set type	Sub-group analysis
Subject analysis set description: The 17 minor surgeries in the Full/Per-Protocol Analysis Set comprised 5 orthopedic surgeries (4 intraarticular infiltration, 1 synoviorthesis) and 12 non-orthopedic surgeries (11 dental, 1 intra-articular injection).	

Primary: Intraoperative hemostatic efficacy

End point title	Intraoperative hemostatic efficacy ^[1]
End point description: The intraoperative hemostatic efficacy was to be assessed by the operating surgeon according to the following criteria (4-point ordinal scale): <ul style="list-style-type: none">- Excellent: Intraoperative blood loss was less than or equal to that expected for the type of procedure performed in a hemostatically normal subject ($\leq 100\%$)- Good: Intraoperative blood loss was up to 50% more than expected for the type of procedure performed in a hemostatically normal subject (101 – 150%)- Fair: Intraoperative blood loss was more than 50% of that expected for the type of procedure performed in a hemostatically normal subject ($> 150\%$)- None: Uncontrolled hemorrhage that was the result of inadequate therapeutic response despite proper dosing, necessitating a change of FIX concentrate Descriptive statistics: The intraoperative (at the end of surgery) hemostatic efficacy assessments were summarized by percentage of subjects in each efficacy categories ("excellent", "good", "fair" and "none").	

End point type	Primary
End point timeframe:	
At completion of surgery	
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, descriptive statistics were collected for this endpoint.	

End point values	Full Analysis Set	Per-Protocol Analysis Set	Subjects undergoing major surgery	Subjects undergoing minor surgery
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	37	21	17
Units: subjects				
Excellent	37	36	20	17
Good	1	1	1	0
Fair	0	0	0	0
None	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Actual intraoperative blood loss

End point title	Actual intraoperative blood loss ^[2]
End point description:	
Actual intraoperative blood loss was summarized using descriptive statistics including median and range.	
End point type	Primary
End point timeframe:	
At completion of surgery	
Notes:	
[2] - 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, descriptive statistics were collected for this endpoint.	

End point values	Full Analysis Set	Per-Protocol Analysis Set	Subjects undergoing major surgery	Subjects undergoing minor surgery
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	37	21	17
Units: mL				
arithmetic mean (standard deviation)	191.1 (± 354.1)	177.4 (± 348.5)	344.9 (± 420.1)	1.2 (± 1.1)

Statistical analyses

No statistical analyses for this end point

Primary: Actual intraoperative blood loss compared to average and maximum blood

loss predicted preoperatively by the operating surgeon

End point title	Actual intraoperative blood loss compared to average and maximum blood loss predicted preoperatively by the operating surgeon ^[3]
-----------------	--

End point description:

Predicted average/maximum blood loss minus actual blood loss. The differences from the expected average and maximum blood loss was summarized using descriptive statistics including median and range.

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

End point timeframe:

At completion of surgery

Notes:

[3] - 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, descriptive statistics were collected for this endpoint.

End point values	Full Analysis Set	Per-Protocol Analysis Set	Subjects undergoing major surgery	Subjects undergoing minor surgery
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	37	21	17
Units: mL				
arithmetic mean (standard deviation)				
Difference from predicted average blood loss	-27 (± 158.9)	-22.4 (± 158.4)	-50.9 (± 213)	2.4 (± 4.9)
Difference from predicted maximum blood loss	128.3 (± 260.8)	123.7 (± 262.8)	222 (± 323.7)	12.5 (± 24.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Postoperative hemostatic efficacy at drain removal

End point title	Postoperative hemostatic efficacy at drain removal
-----------------	--

End point description:

Only 14 subjects who underwent major surgery had a drain placed. The postoperative hemostatic efficacy was to be assessed by the operating surgeon according to the following criteria (4-point ordinal scale):

- Excellent: Volume in drain was less than or equal than that expected for the type of procedure performed in a hemostatically normal subject ($\leq 100\%$)
- Good: Volume in drain was up to 50% more than expected for the type of procedure performed in a hemostatically normal subject (101% - 150%)
- Fair: Volume in drain was more than 50% of that expected for the type of procedure performed in a hemostatically normal subject ($> 150\%$)
- None: Uncontrolled bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating a change of FIX concentrate

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

End point timeframe:

At drain removal (if a drain was placed)

End point values	Full Analysis Set	Per-Protocol Analysis Set	Subjects undergoing major surgery	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	14	13	14	
Units: subjects				
Excellent	10	10	10	
Good	4	3	4	
Fair	0	0	0	
None	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Postoperative hemostatic efficacy at postoperative day 3

End point title	Postoperative hemostatic efficacy at postoperative day 3
End point description:	
<p>If no drain was placed, the postoperative hemostatic efficacy was to be assessed for major surgeries by the operating surgeon on postoperative day 3 according to the following criteria (4-point ordinal scale):</p> <ul style="list-style-type: none"> - Excellent: Postoperative hemostasis achieved with BAX 326 was as good or better than that expected for the type of surgical procedure performed in a hemostatically normal subject - Good: Postoperative hemostasis achieved with BAX 326 was probably as good as that expected for the type of surgical procedure performed in a hemostatically normal subject - Fair: Postoperative hemostasis with BAX 326 was clearly less than optimal for the type of procedure performed but was maintained without the need to change the FIX concentrate - None: Subject experienced uncontrolled bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating a change of FIX concentrate 	
End point type	Secondary
End point timeframe:	
At postoperative day 3 (approximately 72 hours postoperatively)	

End point values	Full Analysis Set	Per-Protocol Analysis Set	Subjects undergoing major surgery	Subjects undergoing minor surgery
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	8	7	1
Units: subjects				
Excellent	7	7	6	1
Good	1	1	1	0
Fair	0	0	0	0
None	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Postoperative hemostatic efficacy on day of discharge

End point title	Postoperative hemostatic efficacy on day of discharge
-----------------	---

End point description:

On the day of discharge from hospital, the hemostatic efficacy was to be assessed by the investigator, ie, hemophilia physician. The rating criteria for "excellent", "good", "fair" and "none" were the same as for postoperative day 3.

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

End point timeframe:

At discharge from hospital

End point values	Full Analysis Set	Per-Protocol Analysis Set	Subjects undergoing major surgery	Subjects undergoing minor surgery
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	37	21	17
Units: subjects				
Excellent	29	29	12	17
Good	7	6	7	0
Fair	2	2	2	0
None	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Actual postoperative blood loss

End point title	Actual postoperative blood loss
-----------------	---------------------------------

End point description:

Postoperative blood loss was based on the drainage fluid and was only assessed for subjects who had a drain placed (n=14).

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

End point timeframe:

At drain removal

End point values	Full Analysis Set	Per-Protocol Analysis Set	Subjects undergoing major surgery	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	14	13	14	
Units: mL				
arithmetic mean (standard deviation)	603.6 (± 388.7)	552.4 (± 351.9)	603.6 (± 388.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Actual postoperative blood loss compared to average and maximum blood loss predicted preoperatively by the operating surgeon

End point title	Actual postoperative blood loss compared to average and maximum blood loss predicted preoperatively by the operating surgeon
-----------------	--

End point description:

Predicted average/maximum blood loss minus actual blood loss; was only assessed for subjects with major surgery who had a drain placed (n=14).

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

End point timeframe:

At drain removal

End point values	Full Analysis Set	Per-Protocol Analysis Set	Subjects undergoing major surgery	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	14	13	14	
Units: mL				
arithmetic mean (standard deviation)				
Difference from predicted average blood loss	-221.4 (± 331.7)	-171.5 (± 285.4)	-221.4 (± 331.7)	
Difference from predicted maximum blood loss	147.1 (± 330.1)	179.2 (± 320)	147.1 (± 330.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Daily weight-adjusted dose of BAX326 per subject

End point title	Daily weight-adjusted dose of BAX326 per subject
-----------------	--

End point description:

Daily weight-adjusted doses of BAX326 per subject were recorded from the day of surgery until postoperative day 11+. The number of subjects in the FAS and the reporting groups who were exposed to daily doses of BAX326 after surgery decreases towards day 11.

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

End point timeframe:

From initiation of surgery until the time of discharge (minor surgery: 1-3 days, major surgery: approximately 2 weeks)

End point values	Full Analysis Set	Per-Protocol Analysis Set	Subjects undergoing major surgery	Subjects undergoing minor surgery
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38 ^[4]	37 ^[5]	21 ^[6]	17 ^[7]
Units: IU/kg				
arithmetic mean (standard deviation)				
Day of surgery	144.8 (± 70.3)	142.6 (± 69.9)	191.5 (± 50.6)	87.2 (± 42.9)
Postoperative Day 1	103.9 (± 44.6)	102.7 (± 44.5)	136.7 (± 30.1)	63.5 (± 18)
Postoperative Day 2	115 (± 40.2)	113.7 (± 40.3)	134.2 (± 27.6)	64.6 (± 16.2)
Postoperative Day 3	111.6 (± 43.9)	110 (± 44.1)	123.5 (± 39.4)	61.6 (± 20.8)
Postoperative Day 4	115.2 (± 63)	113.6 (± 64)	123.5 (± 62.4)	56.9 (± 29.3)
Postoperative Day 5	104.4 (± 47.4)	102.3 (± 47.4)	108.6 (± 46.6)	60.4 (± 41.9)
Postoperative Day 6	105.6 (± 44)	103.3 (± 43.9)	106.6 (± 44.9)	86 (± 0)
Postoperative Day 7	94.6 (± 46.7)	91.8 (± 46.1)	96.1 (± 47.4)	65.5 (± 0)
Postoperative Day 8	93 (± 45.8)	94 (± 46.9)	93 (± 45.8)	0 (± 0)
Postoperative Day 9	93 (± 46.9)	94 (± 48.1)	93 (± 46.9)	0 (± 0)
Postoperative Day 10	89.9 (± 49.7)	90.8 (± 51.1)	89.9 (± 49.7)	0 (± 0)
Postoperative Day 11+	75.3 (± 44.8)	75.3 (± 44.8)	75.3 (± 44.8)	0 (± 0)

Notes:

[4] - Day2:n=29,Day3:n=26,Day4:n=24,Day5:n=23,Day6:n=21,Day7:n=21,Day8:n=19,Day9:n=19, D10:n=18,D11+:n=15

[5] - Day2:n=28,Day3:n=25,Day4:n=23,Day5:n=22,Day6:n=20,Day7:n=20,Day8:n=18,Day9:n=18, D10:n=17,D11+:n=15

[6] - Day 6: n=20, Day 7: n=20, Day 8: n=19, Day 9: n=19, Day 10: n=18, Day 11+: n=15

[7] - Day 2: n=8, Day 3: n=5, Day 4: n=3, Day 5: n=2, Day 6: n=1, Day 7: n=1, Days 8-11: n=0

Statistical analyses

No statistical analyses for this end point

Secondary: Total weight-adjusted dose of BAX326 per subject

End point title	Total weight-adjusted dose of BAX326 per subject
End point description:	
Assessed for the intra- and postoperative periods	
End point type	Secondary
End point timeframe:	
From initiation of surgery until the time of discharge (minor surgery: 1-3 days, major surgery: approximately 2 weeks)	

End point values	Full Analysis Set	Per-Protocol Analysis Set	Subjects undergoing major surgery	Subjects undergoing minor surgery
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	37	21	17
Units: IU/kg				
arithmetic mean (standard deviation)				
Intraoperative period	145 (± 70)	143 (± 70)	191 (± 51)	87 (± 43)
Postoperative period	808 (± 766)	795 (± 773)	1350 (± 617)	138 (± 136)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of units of blood product transfused

End point title	Number of units of blood product transfused
End point description: Blood product transfusions consisted of packed red blood cells (PRBC) or fresh frozen plasma (FFP) or both. Six subjects who underwent major orthopedic surgery received blood product transfusions in the intraoperative period; 2 of these subjects also received blood product infusions in the postoperative period.	
End point type	Secondary
End point timeframe: From initiation of surgery until the time of discharge (minor surgery: 1-3 days, major surgery: approximately 2 weeks)	

End point values	Full Analysis Set	Per-Protocol Analysis Set	Subjects undergoing major surgery	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	6 ^[8]	5 ^[9]	6 ^[10]	
Units: units				
arithmetic mean (standard deviation)				
Intraoperative period	2.8 (± 1.2)	2.8 (± 1.3)	2.8 (± 1.2)	
Postoperative period	1.5 (± 0.7)	1 (± 0)	1.5 (± 0.7)	

Notes:

[8] - Only 2 subjects received blood product transfusions in the postoperative period.

[9] - Only 1 subject received blood product transfusions in the postoperative period.

[10] - Only 2 subjects received blood product transfusions in the postoperative period.

Statistical analyses

No statistical analyses for this end point

Secondary: Amount of blood product transfused (in mL)

End point title	Amount of blood product transfused (in mL)
End point description: Blood product transfusions consisted of packed red blood cells (PRBC) or fresh frozen plasma (FFP) or both. Six subjects who underwent major orthopedic surgery received blood product transfusions in the intraoperative period; 2 of these subjects also received blood product infusions in the postoperative period.	
End point type	Secondary
End point timeframe: From initiation of surgery until the time of discharge (minor surgery: 1-3 days, major surgery: approximately 2 weeks)	

End point values	Full Analysis Set	Per-Protocol Analysis Set	Subjects undergoing major surgery	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	6 ^[11]	5 ^[12]	6 ^[13]	
Units: mL				
arithmetic mean (standard deviation)				
Intraoperative period	834.3 (± 358.7)	756.2 (± 339.1)	834.3 (± 358.7)	
Postoperative period	414 (± 227.7)	253 (± 0)	414 (± 227.7)	

Notes:

[11] - Only 2 subjects received blood product transfusions in the postoperative period.

[12] - Only 1 subject received blood product transfusions in the postoperative period.

[13] - Only 2 subjects received blood product transfusions in the postoperative period.

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Development of inhibitory antibodies to FIX

End point title	Safety: Development of inhibitory antibodies to FIX
-----------------	---

End point description:

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

End point timeframe:

Entire study duration: approx. 2.5 years; study participation per subject: mean of 43.3 days (standard deviation: 30.1 days (range: 4-110 days))

End point values	Safety Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	40			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Development of total binding antibodies to FIX

End point title	Safety: Development of total binding antibodies to FIX
-----------------	--

End point description:

If more than 2-dilution increase as compared to pre-study level at screening

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

End point timeframe:

Entire study duration: approx. 2.5 years; study participation per subject: mean of 43.3 days (standard deviation: 30.1 days (range: 4-110 days))

End point values	Safety Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	40			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Adverse events (AEs) related to BAX326

End point title	Safety: Adverse events (AEs) related to BAX326
-----------------	--

End point description:

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

End point timeframe:

Entire study duration: approx. 2.5 years; study participation per subject: mean of 43.3 days (standard deviation: 30.1 days (range: 4-110 days))

End point values	Safety Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	40			
Units: Related AEs	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Occurrence of thrombotic events

End point title	Safety: Occurrence of thrombotic events
-----------------	---

End point description:

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

End point timeframe:

Entire study duration: approx. 2.5 years; study participation per subject: mean of 43.3 days (standard deviation: 30.1 days (range: 4-110 days))

End point values	Safety Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	40			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Presurgical Pharmacokinetics (PK): Area under the plasma concentration versus time curve from 0 to 72 hours post-infusion per dose (AUC 0-72h/dose)

End point title	Presurgical Pharmacokinetics (PK): Area under the plasma concentration versus time curve from 0 to 72 hours post-infusion per dose (AUC 0-72h/dose)
-----------------	---

End point description:

AUC0-72h [IU·hr/dL] (area under the plasma concentration/time curve from time 0 to 72 hours) was computed using the linear trapezoidal method. The concentration at 72 hours was interpolated from the two nearest sampling time points or extrapolated using the last quantifiable concentration and the terminal rate constant λ_z . λ_z was estimated from the slope of natural log-linear fitting to latter quantifiable concentrations, with largest adjusted R².

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

End point timeframe:

0.5 hour (h) before start of PK infusion to 72±2 h after the infusion

End point values	PK Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: [IU·hour (hr)/dL] : IU/kg				
arithmetic mean (standard deviation)	18.48 (± 6.43)			

Statistical analyses

No statistical analyses for this end point

Secondary: Presurgical PK: Total area under the plasma concentration versus time curve per dose (total AUC/dose)

End point title	Presurgical PK: Total area under the plasma concentration versus time curve per dose (total AUC/dose)
-----------------	---

End point description:

AUC0-inf [IU·hr/dL] (area under the plasma concentration/time curve from time 0 to infinity) was

defined as $AUC_{0-t} + C_t / \lambda_z$, where t is the time of last quantifiable concentration, and C_t is the last quantifiable concentration.

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

End point timeframe:

0.5 hour (h) before start of PK infusion to 72 ± 2 h after the infusion

End point values	PK Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: [IU•hour (hr)/dL] : IU/kg				
arithmetic mean (standard deviation)	20.6 (\pm 7.32)			

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:

MRT [hr] was computed as $AUMC_{0-inf} / AUC_{0-\infty}$, where $AUMC_{0-inf}$ was determined in a similar manner as AUC_{0-inf} .

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

End point timeframe:

0.5 hour (h) before start of PK infusion to 72 ± 2 h after the infusion

End point values	PK Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: hours (hr)				
arithmetic mean (standard deviation)	27.17 (\pm 4.03)			

Statistical analyses

No statistical analyses for this end point

Secondary: Presurgical PK: Factor IX clearance (CL)

End point title	Presurgical PK: Factor IX clearance (CL)
-----------------	--

End point description:

CL [dL/(kg•hr)] (clearance) was computed as Dose / AUC_{0-inf} .

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

End point timeframe:

0.5 hour (h) before start of PK infusion to 72±2 h after the infusion

End point values	PK Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: dL/(kg•hr)				
arithmetic mean (standard deviation)	0.0523 (± 0.0126)			

Statistical analyses

No statistical analyses for this end point

Secondary: Presurgical PK: Incremental recovery (IR) at 30 min

End point title Presurgical PK: Incremental recovery (IR) at 30 min

End point description:

IR [IU/dL:IU/kg] was defined as (C post-infusion - C pre-infusion) / Dose, where C post-infusion is the measured concentration achieved at 30±5 minutes for pre-surgical PK and at 15±5 minutes for loading dose.

End point type Secondary

End point timeframe:

0.5 hour (h) before start of PK infusion and at 0.5 h ± 5 min after the infusion

End point values	PK Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: IU/dL : IU/kg				
arithmetic mean (standard deviation)	1 (± 0.29)			

Statistical analyses

No statistical analyses for this end point

Secondary: Presurgical PK: Elimination phase half-life (T_{1/2})

End point title Presurgical PK: Elimination phase half-life (T_{1/2})

End point description:

T_{1/2} [hr] (elimination phase half-life) was determined as $\ln 2 / \lambda_z$.

End point type Secondary

End point timeframe:

0.5 hour (h) before start of PK infusion to 72±2 h after the infusion

End point values	PK Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: hr				
arithmetic mean (standard deviation)	23.6 (± 3.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Presurgical PK: Volume of distribution at steady state (Vss)

End point title	Presurgical PK: Volume of distribution at steady state (Vss)
End point description:	
Vss [dL/kg] (volume of distribution at steady state) was computed as CL·MRT.	
End point type	Secondary
End point timeframe:	
0.5 hour (h) before start of PK infusion to 72±2 h after the infusion	

End point values	PK Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: dL/kg				
arithmetic mean (standard deviation)	1.41 (± 0.38)			

Statistical analyses

No statistical analyses for this end point

Secondary: Presurgical PK: Incremental recovery (IR) at 15±5 minutes following loading dose prior to surgery

End point title	Presurgical PK: Incremental recovery (IR) at 15±5 minutes following loading dose prior to surgery
End point description:	
End point type	Secondary
End point timeframe:	
Within 60 minutes prior to surgery and 15±5 minutes after loading dose/rebolus, if applicable	

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	36			
Units: [IU/dL] : [IU/kg]				
arithmetic mean (standard deviation)	0.91 (\pm 0.1787)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Entire study duration: approx. 2.5 years; study participation per subject: mean of 43.3 days (standard deviation: 30.1 days (range: 4-110 days))

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

Dictionary used

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

Dictionary version	N/A
--------------------	-----

Reporting groups

Reporting group title	Safety Analysis Set
-----------------------	---------------------

Reporting group description:

Comprises all subjects exposed to investigational product during the study (n=40)

Serious adverse events	Safety Analysis Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 40 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Safety Analysis Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 40 (37.50%)		
Injury, poisoning and procedural complications			
Post procedural haematoma			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Post procedural swelling			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		
Procedural pain			
subjects affected / exposed	9 / 40 (22.50%)		
occurrences (all)	15		
Blood and lymphatic system disorders			

Haemorrhagic anaemia subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3		
Thrombocytosis subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 4		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 October 2011	<ul style="list-style-type: none">- Design was modified so that subjects taking part in the BAX326 pediatric study (251101) could also be recruited into the surgery study.- Occurrence of thrombotic events was added as a safety endpoint. A daily clinical evaluation of thrombosis following surgery was added to the schedule of study procedures and assessments.- Subjects could undergo 2 parallel surgeries, such as bilateral knee replacement, but prior approval had to be obtained from the sponsor.
26 February 2013	<ul style="list-style-type: none">- Tailoring of dose was specified 'to raise FIX concentration to at least 80%-100% of normal for major surgeries and to at least 30%-60% of normal for minor surgeries to ensure that the recommended pre-infusion FIX levels are maintained in the perioperative period'.- To ensure that subjects were hemostatically sufficiently covered on the day of surgery, the results of the pre-infusion FIX activity had to be available within 4 hours of infusion of BAX 326, and a second FIX activity level had to be determined within 12 hours of surgery, preferably within 6-8 h.- In case of major surgery, the subject's individual PK parameters, in particular IR and half-life, determined as part of the PK assessment, had to be available prior to the start of surgery, to determine the adequate dose and dose frequency.- The formula for calculating the required units was revised as follows due to a revised IR based on the PK data of the BAX326 pivotal study (from 0.8 to 0.9) in subjects ≥ 12 years of age: 'body weight (kg) x desired FIX rise (% or IU/dL) x 1.1 IU/kg' (previously 1.3 IU/kg).- Dosing adjustments based on aPTT values were no longer allowed. The following text was added: 'ALL subsequent infusions of BAX 326 must be preceded by measurement of residual FIX levels and the dose adjusted as needed – dosing adjustments based on aPTT values are not allowed'. Postoperative aPTT assessments were removed from the protocol.- In the event that high doses of BAX326 were required, it was recommended that these should be administered in 1-3 infusions over 24 hours, most commonly in 2 infusions, to avoid supraphysiological peaks.- For subjects transitioning to the surgery study from the BAX326 pivotal, continuation, or pediatric study, the transition stages from one study to another were clarified.- In the event that at least 3 pediatric subjects <12 years of age had been enrolled, a separate analysis of the pediatric cohort would have had to be performed.
12 April 2013	<ul style="list-style-type: none">- The previous number of approximately 30 elective or emergency surgical, dental or other invasive procedures in approximately 30 subjects was increased to 40 procedures/subjects.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/24697870>