Clinical trial results:
Phase 3, prospective, randomized, multi-center clinical study comparing the safety and efficacy of BAX 855 following PK-guided prophylaxis targeting two different FVIII trough levels in subjects with severe hemophilia A

Summary

EudraCT number	2014-005477-37
Trial protocol	GB DE AT SE CZ ES HU BG PL IT
Global end of trial date	05 August 2018

Results information

Result version number	v2 (current)
This version publication date	13 November 2019
First version publication date	20 February 2019
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	261303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02585960
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Baxalta Innovations GmbH (now part of Shire)
Sponsor organisation address	Industriestrasse 67, Vienna, Austria, A-1221
Public contact	Study Director, Baxalta Innovations GmbH (now part of Shire), ClinicalTransparency@shire.com
Scientific contact	Study Director, Baxalta Innovations GmbH (now part of Shire), ClinicalTransparency@shire.com
Sponsor organisation name	Baxalta US Inc. (now part of Shire)
Sponsor organisation address	300 Shire Way, Lexington, United States, MA 02421
Public contact	Study Director, Baxalta US Inc. (now part of Shire), ClinicalTransparency@shire.com
Scientific contact	Study Director, Baxalta US Inc. (now part of Shire), ClinicalTransparency@shire.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	Yes

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 August 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 August 2018
Global end of trial reached?	Yes
Global end of trial date	05 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to compare 2 prophylactic dosing regimens of BAX 855 targeting 2 different FVIII trough levels, by comparing the proportions of subjects achieving a total annualized bleeding rate (ABR) of 0 in the second 6-month study period.

Protection of trial subjects:

This study was conducted in accordance with the standards of Good Clinical Practice (GCP) in effect at the time of the study. All records have been attached per GCP requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 November 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Bulgaria: 5
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Hong Kong: 5
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Malaysia: 16
Country: Number of subjects enrolled	Poland: 16
Country: Number of subjects enrolled	Singapore: 7
Country: Number of subjects enrolled	Turkey: 8
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	Ukraine: 15

Country: Number of subjects enrolled	United States: 8
Worldwide total number of subjects	121
EEA total number of subjects	55

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	17
Adults (18-64 years)	104
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 62 study centers in 19 countries between 23 November 2015 (first subject first visit) and 05 August 2018 (last subject last visit).

Pre-assignment

Screening details:

A total of 135 subjects were enrolled in the study. Of them, 14 subjects were dropped out and did not receive any treatment 121 subjects underwent initial pharmacokinetic (PK) assessment with a single administration of BAX 855 and based on their individual PK values, 115 subjects were randomized to any one of the prophylactic regimens.

Period 1

Period 1 title	Pharmacokinetic (PK) Assessment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	BAX 855-Low Level

Arm description:

Subjects with severe hemophilia A received a single BAX 855 dose of 60 +/- 5 international units per kilogram (IU/kg) intravenous (IV) infusion (PK assessment) followed by a PK-guided dose of BAX 855 twice weekly (Alternating 3 and 4-day infusion intervals or an infusion every 3.5 days), targeting factor VIII (FVIII) trough levels of 1-3%. Depending on subject's individual PK, more frequent dosing was considered if single doses of greater than (>) 80 IU/kg were required or regular FVIII peak levels of 200% were reached.

Arm type	Experimental
Investigational medicinal product name	BAX 855
Investigational medicinal product code	
Other name	Pegylated rFVIII
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received IV infusion of BAX 855.

Arm title	BAX 855-High Level

Arm description:

Subjects with severe hemophilia A received a single BAX 855 dose of 60 +/- 5 IU/kg IV infusion (PK assessment) followed by a PK-guided dose of BAX 855 every other day, targeting FVIII trough levels of 8-12%. Depending on subject's individual PK, a different dosing interval was considered to prevent regular high FVIII peak levels.

Arm type	Experimental
Investigational medicinal product name	BAX 855
Investigational medicinal product code	
Other name	Pegylated rFVIII
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received IV infusion of BAX 855.

Arm title	BAX 855-Non-randomized

Arm description:

Subjects with severe hemophilia A received a single BAX 855 dose of 60 +/- 5 IU/kg IV infusion (PK

assessment) and were not randomized to any treatments.

Arm type	Experimental
Investigational medicinal product name	BAX 855
Investigational medicinal product code	
Other name	Pegylated rFVIII
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received IV infusion of BAX 855.

Number of subjects in period 1	BAX 855-Low Level	BAX 855-High Level	BAX 855-Non-randomized
Started	57	58	6
Completed	52	48	0
Not completed	5	10	6
Consent withdrawn by subject	1	2	5
Physician decision	-	1	-
Non-compliance to study procedures	-	2	-
Screen Failure	-	-	1
Unspecified	4	4	-
Withdrawn by sponsor	-	1	-

Period 2

Period 2 title	Prophylactic Treatment Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	BAX 855-Low Level

Arm description:

Subjects with severe hemophilia A received a single BAX 855 dose of 60 +/- 5 international units per kilogram (IU/kg) intravenous (IV) infusion (PK assessment) followed by a PK-guided dose of BAX 855 twice weekly (Alternating 3 and 4-day infusion intervals or an infusion every 3.5 days), targeting factor VIII (FVIII) trough levels of 1-3%. Depending on subject's individual PK, more frequent dosing was considered if single doses of greater than (>) 80 IU/kg were required or regular FVIII peak levels of 200% were reached.

Arm type	Experimental
Investigational medicinal product name	BAX 855
Investigational medicinal product code	
Other name	Pegylated rFVIII
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received IV infusion of BAX 855.

Arm title	BAX 855-High Level

Arm description:

Subjects with severe hemophilia A received a single BAX 855 dose of 60 +/- 5 IU/kg IV infusion (PK assessment) followed by a PK-guided dose of BAX 855 every other day, targeting FVIII trough levels of 8-12%. Depending on subject's individual PK, a different dosing interval was considered to prevent regular high FVIII peak levels.

Arm type	Experimental
Investigational medicinal product name	BAX 855
Investigational medicinal product code	
Other name	Pegylated rFVIII
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received IV infusion of BAX 855.

Number of subjects in period 2	BAX 855-Low Level	BAX 855-High Level
Started	52	48
Completed	52	43
Not completed	0	5
Subject less than 75% exposed to BAX 855	-	1
Protocol deviation	-	4

Baseline characteristics

Reporting groups	
Reporting group title	BAX 855-Low Level
Reporting group description:	
Subjects with severe hemophilia A received a single BAX 855 dose of 60 +/- 5 international units per kilogram (IU/kg) intravenous (IV) infusion (PK assessment) followed by a PK-guided dose of BAX 855 twice weekly (Alternating 3 and 4-day infusion intervals or an infusion every 3.5 days), targeting factor VIII (FVIII) trough levels of 1-3%. Depending on subject's individual PK, more frequent dosing was considered if single doses of greater than (>) 80 IU/kg were required or regular FVIII peak levels of 200% were reached.	
Reporting group title	BAX 855-High Level
Reporting group description:	
Subjects with severe hemophilia A received a single BAX 855 dose of 60 +/- 5 IU/kg IV infusion (PK assessment) followed by a PK-guided dose of BAX 855 every other day, targeting FVIII trough levels of 8-12%. Depending on subject's individual PK, a different dosing interval was considered to prevent regular high FVIII peak levels.	
Reporting group title	BAX 855-Non-randomized
Reporting group description:	
Subjects with severe hemophilia A received a single BAX 855 dose of 60 +/- 5 IU/kg IV infusion (PK assessment) and were not randomized to any treatments.	

Reporting group values	BAX 855-Low Level	BAX 855-High Level	BAX 855-Non-randomized
Number of subjects	57	58	6
Age categorical Units: Subjects			
Age continuous			
Age at the time of informed consent was reported.			
Units: years			
arithmetic mean	31.1	31.2	25.8
standard deviation	± 13.76	± 12.22	± 10.03
Gender categorical Units: Subjects			
Female	0	0	0
Male	57	58	6
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	5	2
Not Hispanic or Latino	53	53	4
Unknown or Not Reported	2	0	0
Race/Ethnicity, Customized Units: Subjects			
Asian	14	18	2
White	40	36	4
Native Latin American	1	1	0
Mestizo	0	1	0
Other	2	2	0

Reporting group values	Total		

Number of subjects	121		
Age categorical Units: Subjects			

Age continuous			
Age at the time of informed consent was reported.			
Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	0		
Male	121		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	9		
Not Hispanic or Latino	110		
Unknown or Not Reported	2		
Race/Ethnicity, Customized Units: Subjects			
Asian	34		
White	80		
Native Latin American	2		
Mestizo	1		
Other	4		

End points

End points reporting groups

Reporting group title	BAX 855-Low Level

Reporting group description:

Subjects with severe hemophilia A received a single BAX 855 dose of 60 +/- 5 international units per kilogram (IU/kg) intravenous (IV) infusion (PK assessment) followed by a PK-guided dose of BAX 855 twice weekly (Alternating 3 and 4-day infusion intervals or an infusion every 3.5 days), targeting factor VIII (FVIII) trough levels of 1-3%. Depending on subject’s individual PK, more frequent dosing was considered if single doses of greater than (>) 80 IU/kg were required or regular FVIII peak levels of 200% were reached.

Reporting group title	BAX 855-High Level

Reporting group description:

Subjects with severe hemophilia A received a single BAX 855 dose of 60 +/- 5 IU/kg IV infusion (PK assessment) followed by a PK-guided dose of BAX 855 every other day, targeting FVIII trough levels of 8-12%. Depending on subject’s individual PK, a different dosing interval was considered to prevent regular high FVIII peak levels.

Reporting group title	BAX 855-Non-randomized

Reporting group description:

Subjects with severe hemophilia A received a single BAX 855 dose of 60 +/- 5 IU/kg IV infusion (PK assessment) and were not randomized to any treatments.

Reporting group title	BAX 855-Low Level

Reporting group description:

Subjects with severe hemophilia A received a single BAX 855 dose of 60 +/- 5 international units per kilogram (IU/kg) intravenous (IV) infusion (PK assessment) followed by a PK-guided dose of BAX 855 twice weekly (Alternating 3 and 4-day infusion intervals or an infusion every 3.5 days), targeting factor VIII (FVIII) trough levels of 1-3%. Depending on subject's individual PK, more frequent dosing was considered if single doses of greater than (>) 80 IU/kg were required or regular FVIII peak levels of 200% were reached.

Reporting group title	BAX 855-High Level

Reporting group description:

Subjects with severe hemophilia A received a single BAX 855 dose of 60 +/- 5 IU/kg IV infusion (PK assessment) followed by a PK-guided dose of BAX 855 every other day, targeting FVIII trough levels of 8-12%. Depending on subject's individual PK, a different dosing interval was considered to prevent regular high FVIII peak levels.

Primary: Proportion of Subjects with a Total Annualized Bleeding Rate (ABR) of Zero for Second Six Months

End point title	Proportion of Subjects with a Total Annualized Bleeding Rate (ABR) of Zero for Second Six Months[1]

End point description:

Annualized bleeding rate was determined by dividing the number of bleeds by observation period in years. Full analysis set (FAS) included all subjects who were randomized to one of the two prophylactic arms and treated prophylactically for any period of time.

End point type	Primary

End point timeframe:

Day 183 to Day 364 (6 months)

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was related to subjects randomized to prophylactic treatment, hence not reporting statistics for all the arms in the baseline period

End point values	BAX 855-Low Level	BAX 855-High Level		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	58		
Units: Percentage of subjects				
number (not applicable)				
Percentage of subjects	42.1	62.1		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The proportion of subjects with an ABR of 0 during the second 6-month period on BAX 855 prophylaxis, was compared between the 2 prophylaxis arms using a chi-square test with continuity correction at a 2-sided 5% level of significance.

Comparison groups	BAX 855-High Level v BAX 855-Low Level
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0545
Method	Chi-squared
Parameter estimate	Gaussian Statistic estimate
Point estimate	1.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.038
upper limit	3.958

Secondary: Total Annualized Bleeding Rate for Second Six Months

End point title	Total Annualized Bleeding Rate for Second Six Months[2]

End point description:

Annualized bleeding rate was determined by dividing the number of bleeds by observation period in years. FAS included all subjects who were randomized to one of the two prophylactic arms and treated prophylactically for any period of time. Here "Number of subjects analyzed" refer to number of subjects evaluable for this outcome at specified time point.

End point type	Secondary

End point timeframe:

Day 183 to Day 364 (6 months)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was related to subjects randomized to prophylactic treatment, hence not reporting statistics for all the arms in the baseline period

End point values	BAX 855-Low Level	BAX 855-High Level		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	53		
Units: Bleeds per year				
arithmetic mean (standard deviation)				
Bleeds per year	3.603 (± 7.512)	1.649 (± 3.433)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Spontaneous Bleeding Rate for Second Six Months

End point title	Annualized Spontaneous Bleeding Rate for Second Six

End point description:

Annualized spontaneous bleeding rate was determined by dividing the number of spontaneous bleeds by observation period in years. A bleed was defined as spontaneous if it was not related to injury/trauma. FAS included all subjects who were randomized to one of the two prophylactic arms and treated prophylactically for any period of time. Here "Number of subjects analyzed" refer to number of subjects evaluable for this outcome at specified time point.

End point type	Secondary

End point timeframe:

Day 183 to Day 364 (6 months)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was related to subjects randomized to prophylactic treatment, hence not reporting statistics for all the arms in the baseline period

End point values	BAX 855-Low Level	BAX 855-High Level		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	53		
Units: Bleeds per year				
arithmetic mean (standard deviation)				
Bleeds per year	2.489 (± 6.554)	0.737 (± 1.738)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Traumatic Bleeding Rate for Second Six Months

End point title	Annualized Traumatic Bleeding Rate for Second Six Months[4]

End point description:

Annualized traumatic bleeding rate was determined by dividing the number of traumatic bleeds by observation period in years. A bleed was defined as traumatic if it was related to injury/trauma. FAS included all subjects who were randomized to one of the two prophylactic arms and treated prophylactically for any period of time. Here "Number of subjects analyzed" refer to number of subjects

evaluable for this outcome at specified time point.

End point type	Secondary

End point timeframe:

Day 183 to Day 364 (6 months)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was related to subjects randomized to prophylactic treatment, hence not reporting statistics for all the arms in the baseline period

End point values	BAX 855-Low Level	BAX 855-High Level		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	53		
Units: Bleeds per year				
arithmetic mean (standard deviation)				
Bleeds per year	1.114 (± 2.037)	0.912 (± 2.647)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Joint Bleeding Rate (AJBR) for Second Six Months

End point title	Annualized Joint Bleeding Rate (AJBR) for Second Six Months[5]

End point description:

Annualized joint bleeding rate was determined by dividing the number of joint bleeds by observation period in years. An acute joint bleed include some or all of the following: ‘aura’, pain, swelling, warmth of the skin over the joint, decreased range of motion and difficulty in using the limb compared with baseline or loss of function. FAS included all subjects who were randomized to one of the two prophylactic arms and treated prophylactically for any period of time. Here "Number of subjects analyzed" refer to number of subjects evaluable for this outcome at specified time point.

End point type	Secondary

End point timeframe:

Day 183 to Day 364 (6 months)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was related to subjects randomized to prophylactic treatment, hence not reporting statistics for all the arms in the baseline period

End point values	BAX 855-Low Level	BAX 855-High Level		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	53		
Units: Bleeds per year				
arithmetic mean (standard deviation)				
Bleeds per year	2.617 (± 7.361)	1.079 (± 2.553)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Weight-adjusted Consumption of BAX 855

End point title	Total Weight-adjusted Consumption of BAX 855[6]

End point description:

Total weight-adjusted consumption of BAX 855 was reported. FAS included all subjects who were randomized to one of the two prophylactic arms and treated prophylactically for any period of time.

End point type	Secondary

End point timeframe:

From start of study treatment up to 12 months (completion or termination)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was related to subjects randomized to prophylactic treatment, hence not reporting statistics for all the arms in the baseline period

End point values	BAX 855-Low Level	BAX 855-High Level		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	58		
Units: International units per kilogram (IU/kg)				
arithmetic mean (standard deviation)				
International units per kilogram (IU/kg)	3984.593 (± 1678.461)	7030.714 (± 3208.049)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Bleeding Episodes: Overall Hemostatic Efficacy Rating by Number of Infusions

End point title	Number of Bleeding Episodes: Overall Hemostatic Efficacy Rating by Number of Infusions[7]

End point description:

The subject or caregiver rated overall treatment response using a 4-point efficacy rating scale as Excellent: Full relief of pain and cessation of objective signs of bleeding after a single infusion and no additional infusion is required for the control of bleeding; Good: Definite pain relief and/or improvement in signs of bleeding after a single infusion and possibly requires more than 1 infusion for complete resolution; Fair: Probable and/or slight relief of pain and slight improvement in signs of bleeding after a single infusion and required more than 1 infusion for complete resolution and None: No improvement or condition worsens. FAS included all subjects who were randomized to one of the two prophylactic arms and treated prophylactically for any period of time. Here "Number of subjects analyzed" refer to number of subjects evaluable for this outcome at specified time point and "n" refer to total number of bleeds in infusion category with available hemostatic efficacy rating.

End point type	Secondary

End point timeframe:

8 +/- 1 hours after study drug administration

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was related to subjects randomized to prophylactic treatment, hence not reporting statistics for all the arms in the baseline period

End point values	BAX 855-Low Level	BAX 855-High Level		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	19		
Units: Bleeds				
Excellent:Bleeds treated with 1 infusion (n=58,33)	19	17		
Excellent:Bleeds treated with 2 infusions (n=27,7)	3	1		
Excellent:Bleeds treated with 3 infusions (n=9,3)	0	1		
Excellent: Bleeds treated with>=4 infusions(n=3,3)	0	0		
Good:Bleeds treated with 1 infusion (n=58,33)	36	16		
Good:Bleeds treated with 2 infusions (n=27,7)	16	6		
Good:Bleeds treated with 3 infusions (n=9,3)	5	1		
Good:leeds treated with >= 4 infusion (n=3,3)	2	2		
Fair:Bleeds treated with 1 infusion (n=58,33)	2	0		
Fair:Bleeds treated with 2 infusions (n=27,7)	7	0		
Fair:Bleeds treated with 3 infusions (n=9,3)	4	0		
Fair:Bleeds treated with >= 4 infusions (n=3,3)	1	0		
None:Bleeds treated with 1 infusion (n=58,33)	1	0		
None:Bleeds treated with 2 infusions (n=27,7)	1	0		
None:Bleeds treated with 3 infusions (n=9,3)	0	1		
None:Bleeds treated with >= 4 infusions (n=3,3)	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Bleeding Episodes: Overall Hemostatic Efficacy Rating at Bleed Resolution

End point title	Number of Bleeding Episodes: Overall Hemostatic Efficacy Rating at Bleed Resolution

End point description:

The subject or caregiver rated the treatment response using a 4-point efficacy rating scale as Excellent: Full relief of pain and cessation of objective signs of bleeding after a single infusion and no additional infusion is required for the control of bleeding; Good: Definite pain relief and/or improvement in signs of bleeding after a single infusion and possibly requires more than 1 infusion for complete resolution; Fair: Probable and/or slight relief of pain and slight improvement in signs of bleeding after a single infusion and required more than 1 infusion for complete resolution and None: No improvement or condition worsens. FAS included all subjects who were randomized to one of the two prophylactic arms and treated prophylactically for any period of time. Here "Number of subjects analyzed" refer to number of subjects evaluable for this outcome at specified time point and "n" refer to total number of bleeds in infusion category with available hemostatic efficacy rating.

End point type	Secondary

End point timeframe:

From start of study treatment up to bleed resolution (up to 12 months)

End point values	BAX 855-Low Level	BAX 855-High Level		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	26		
Units: Bleeds				
Excellent:Bleeds treated with 1 infusion(n=100,58)	50	34		
Excellent:Bleeds treated with 2 infusions(n=29,10)	4	2		
Good:Bleeds treated with 1 infusion(n=100,58)	47	24		
Good:Bleeds treated with 2 infusions(n=29,10)	19	7		
Good:Bleeds treated with 3 infusions (n=13,4)	6	3		
Good:Bleeds treated with >= 4 infusions (n=6,6)	3	6		
Fair:Bleeds treated with 1 infusion(n=100,58)	3	0		
Fair:Bleeds treated with 2 infusions(n=29,10)	5	1		
Fair:Bleeds treated with 3 infusions (n=13,4)	7	0		
Fair:Bleeds treated with >= 4 infusions (n=6,6)	3	0		
None:Bleeds treated with 2 infusions(n=29,10)	1	0		
None:Bleeds treated with 3 infusions (n=13,4)	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment of Bleeding Episodes: Number of BAX 855 Infusions per Bleeding Episode Required Until Bleed Resolution

End point title	Treatment of Bleeding Episodes: Number of BAX 855 Infusions per Bleeding Episode Required Until Bleed Resolution[8]

End point description:

Infusions of BAX 855 that were required until bleed resolution were reported. FAS included all subjects who were randomized to one of the two prophylactic arms and treated prophylactically for any period of time. Here "Number of subjects analyzed" refer to number of subjects evaluable for this outcome at specified time point.

End point type	Secondary

End point timeframe:

From start of study treatment up to 12 months (completion or termination)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was related to subjects randomized to prophylactic treatment, hence not reporting statistics for all the arms in the baseline period

End point values	BAX 855-Low Level	BAX 855-High Level		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	26		
Units: Infusions				
arithmetic mean (standard deviation)				
Infusions	1.6 (± 1.19)	1.6 (± 1.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Hemophilia Joint Health Score (HJHS)- Total Score

End point title	Change From Baseline in Hemophilia Joint Health Score (HJHS)- Total Score[9]

End point description:

HJHS was assessed based on the following components of the elbow, knee, and ankle joints: swelling, duration of swelling, muscle atrophy, crepitus on motion, flexion loss, extension loss, joint pain, and strength, together with an assessment of the global gait. The HJHS is a validated 11-item scoring tool based on radiologic and clinical evaluation, sensitive to detect early signs and minor changes. HJHS ranges from 0 to 124. Higher values in the HJHS represent worse situation for the subject. FAS included all subjects who were randomized to one of the two prophylactic arms and treated prophylactically for any period of time. Here "Number of subjects analyzed" refer to number of subjects evaluable for this outcome at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was related to subjects randomized to prophylactic treatment, hence not reporting statistics for all the arms in the baseline period

End point values	BAX 855-Low Level	BAX 855-High Level		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	54		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Score on a scale	-1.9 (± 5.25)	-1.1 (± 7.77)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Hemostatic Efficacy Ratings for BAX 855 Treatment of Operative Bleeds

End point title	Number of Subjects With Hemostatic Efficacy Ratings for BAX 855 Treatment of Operative Bleeds[10]

End point description:

The operating surgeon rated hemostatic efficacy compared to that expected for the type of procedure performed using a 4-point efficacy rating scale as Excellent: blood loss was less than or equal to that expected (<=100%); Good: blood loss was up to 50% more than expected (101-150%); Fair: blood loss was more than 50% of that expected (>150%) and None: Uncontrolled hemorrhage/ Significant postoperative bleeding/ Significant perioperative bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating rescue therapy. Hemostatic efficacy was evaluated intra-operatively (from start to end of the procedure), post-operatively (from the end of procedure up to 24 h post procedure), and perioperatively (from the start of procedure to subject discharge from hospital or 14 days after completion of procedure; whichever was first). FAS with evaluable subjects were analyzed.

End point type	Secondary

End point timeframe:

Day 0 through discharge or 14 days post-surgery

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was related to subjects randomized to prophylactic treatment, hence not reporting statistics for all the arms in the baseline period

End point values	BAX 855-Low Level	BAX 855-High Level		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: Subjects				
Excellent: Intra-operative	1	3		
Excellent: Post-operative	3	4		
Excellent: Peri-operative	2	4		
Good: Intra-operative	0	0		
Good: Post-operative	0	0		
Good: Peri-operative	0	0		
Fair: Intra-operative	0	1		
Fair: Post-operative	0	0		
Fair: Peri-operative	0	0		
None: Intra-operative	0	0		
None: Post-operative	0	0		
None: Peri-operative	0	0		
Unknown: Intra-operative	2	0		
Unknown: Post-operative	0	0		
Unknown: Peri-operative	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Blood Loss per Subject in Case of Surgery

End point title	Blood Loss per Subject in Case of Surgery[11]

End point description:

Intraoperative blood loss was measured by determining volume of blood and fluid removal through

suction into collection container and estimated blood loss into swabs and towels during procedure, per anesthesiologist's record. Postoperatively, blood loss was determined by drainage volume collected (via vacuum or gravity drain). In cases where no drain was present, blood loss was determined by surgeon's clinical judgment, as applicable or entered as "not available". Blood loss was evaluated intra-operatively (from start to end of the procedure), post-operatively (from the end of procedure up to 24 h post procedure), and perioperatively (from the start of procedure to subject discharge or 14 days after completion of procedure; whichever was first). Surgery analysis set included all subjects in FAS who underwent some form of surgery during the study participation. Blood loss per subject was reported. "99999" indicates data was not calculated.

End point type	Secondary

End point timeframe:

Day 0 through discharge or 14 days post-surgery

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was related to subjects randomized to prophylactic treatment, hence not reporting statistics for all the arms in the baseline period

End point values	BAX 855-Low Level	BAX 855-High Level		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: Milliliters (mL)				
arithmetic mean (standard deviation)				
Intra-operative: Observed (n=3,4)	4.400 (± 4.017)	72.000 (± 160.741)		
Intra-operative: Predicted Average (n=3,4)	10.600 (± 9.227)	65.833 (± 139.290)		
Intra-operative: Predicted Maximum (n=3,4)	20.800 (± 18.089)	128.333 (± 231.790)		
Post-operative: Observed (n=0,1)	99999 (± 99999)	820.000 (± 99999)		
Post-operative: Predicted Average (n=3,4)	10.000 (± 9.129)	145.000 (± 320.967)		
Post-operative: Predicted Maximum (n=3,4)	20.200 (± 17.987)	230.000 (± 475.563)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE was any unfavorable and unintended sign, symptom (rash, pain, discomfort, fever, dizziness, etc.), disease (peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an investigational product (IP), whether or not considered causally related to the IP. A SAE was defined as an untoward medical occurrence that at any dose met one or more of the following criteria: outcome was fatal/results in death, life-threatening, required in-patient hospitalization or resulted in prolongation of an existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, was a medically important event that was not immediately life-threatening or resulted in death or required hospitalization but jeopardize the subject or required medical or surgical intervention to prevent any of the above outcomes. Safety analysis set (SAS) included all subjects enrolled who had at least one BAX 855 infusion.

End point type	Secondary

End point timeframe:

From start of study treatment up to 12 months (completion or termination)

End point values	BAX 855-Low Level	BAX 855-High Level	BAX 855-Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	58	6	
Units: Subjects				
Number of Subjects with SAE	5	5	0	
Number of Subjects with AE	35	38	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Changes in Vital Signs Reported as Treatment Related Adverse Events

End point title	Number of Subjects With Clinically Significant Changes in Vital Signs Reported as Treatment Related Adverse Events

End point description:

Vital signs included systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature. SAS included all subjects enrolled who had at least one BAX 855 infusion.

End point type	Secondary

End point timeframe:

From start of study treatment up to 12 months (completion or termination)

End point values	BAX 855-Low Level	BAX 855-High Level	BAX 855-Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	58	6	
Units: Subjects				
Subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Changes in Clinical Laboratory Parameters Reported as Treatment Related Adverse Events

End point title	Number of Subjects With Clinically Significant Changes in Clinical Laboratory Parameters Reported as Treatment Related Adverse Events

End point description:

Clinical laboratory assessments included clinical chemistry, hematology, lipid panel, genetics, T-cell, B-cell and NK cell (TBNK) and viral serology. SAS included all subjects enrolled who had at least one BAX 855 infusion.

End point type	Secondary

End point timeframe:

From start of study treatment up to 12 months (completion or termination)

End point values	BAX 855-Low Level	BAX 855-High Level	BAX 855-Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	58	6	
Units: Subjects				
Subjects	2	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Positive Inhibitory Antibodies and Binding Antibodies to Factor VIII (FVIII), BAX 855, Polyethylene Glycol (PEG), and Chinese Hamster Ovary (CHO) Protein were reported here.

End point title	Number of Subjects With Positive Inhibitory Antibodies and Binding Antibodies to Factor VIII (FVIII), BAX 855, Polyethylene Glycol (PEG), and Chinese Hamster Ovary (CHO) Protein were reported here.[12]

End point description:

Positive Inhibitory Antibodies and Binding Antibodies to Factor VIII (FVIII), BAX 855, Polyethylene Glycol (PEG), and Chinese Hamster Ovary (CHO) Protein were reported.

End point type	Secondary

End point timeframe:

From start of study treatment up to 12 months (completion or termination)

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was related to subjects randomized to prophylactic treatment, hence not reporting statistics for all the arms in the baseline period

End point values	BAX 855-Low Level	BAX 855-High Level		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	58		
Units: Subjects				
Binding IgG antibodies to FVIII	0	3		
Binding IgM antibodies to FVIII	0	0		
Binding IgG antibodies to PEG-FVIII	2	7		
Binding IgM antibodies to PEG-FVIII	0	1		
Binding IgG antibodies to PEG	0	0		
Binding IgM antibodies to PEG	1	3		

Binding Ig antibodies to CHO	0	0		
Inhibitory antibodies to FVIII	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Physical Component Scores (PCS) of the Short Form-36 (SF-36) Health Survey

End point title	Change from Baseline in Physical Component Scores (PCS) of the Short Form-36 (SF-36) Health Survey[13]

End point description:

Short Form (36) Health Survey (SF-36) is a 36-item validated, generic health related quality of life (HR QoL) instrument. PCS is a summary scale of the dimensions physical functioning, role physical, bodily pain, and general health. The component score is normalized to a standard population. Scores range from 0 to 100 with higher scores representing better health. There is no total overall score; scoring is done for both sub-scores and summary scores. FAS included all subjects who were randomized to one of the two prophylactic arms and treated prophylactically for any period of time. Here "Number of subjects analyzed" refer to number of subjects evaluable for this outcome at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Month 12 (completion or termination)

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was related to subjects randomized to prophylactic treatment, hence not reporting statistics for all the arms in the baseline period

End point values	BAX 855-Low Level	BAX 855-High Level		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	48		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Score on a scale	3.551 (± 8.351)	2.846 (± 8.658)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration of BAX 855 From Zero to Infinity (AUC0-inf)

End point title	Area Under the Plasma Concentration of BAX 855 From Zero to Infinity (AUC0-inf)

End point description:

Area under the plasma concentration versus time curve from time 0 to infinity of BAX 855 was reported. Pharmacokinetic analysis set (PKAS) included all subjects in the SAS that had at least one quantifiable post-dose FVIII activity level without major protocol deviations or events with potential to affect the PK analysis. Here "Number of subjects analyzed" refer to number of subjects evaluable for this outcome at

specified time points.

End point type	Secondary

End point timeframe:

Pre-infusion, 15 - 30 minutes, 3, 8, 24, 48, 72 and 96 hours post-infusion

End point values	BAX 855-Low Level	BAX 855-High Level	BAX 855-Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54	57	5	
Units: International units*hour per deciliter				
arithmetic mean (standard deviation)				
International units*hour per deciliter	2673 (± 877.3)	2659 (± 1041)	2214 (± 355.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Incremental Recovery (IR) at Maximum Plasma Concentration (Cmax) of BAX 855

End point title	Incremental Recovery (IR) at Maximum Plasma Concentration (Cmax) of BAX 855

End point description:

IR at Cmax of BAX 855 was reported. PKAS included all subjects in the SAS that had at least one quantifiable post-dose FVIII activity level without major protocol deviations or events with potential to affect the PK analysis.

End point type	Secondary

End point timeframe:

Pre-infusion, 15 - 30 minutes, 3, 8, 24, 48, 72 and 96 hours post-infusion

End point values	BAX 855-Low Level	BAX 855-High Level	BAX 855-Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	58	5	
Units: (IU/dL) / (IU/kg)				
arithmetic mean (standard deviation)				
(IU/dL) / (IU/kg)	2.227 (± 0.5201)	2.231 (± 0.5451)	2.478 (± 0.2016)	

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Half-life (T1/2) of BAX 855

End point title	Plasma Half-life (T1/2) of BAX 855

End point description:

T1/2 of BAX 855 in plasma was reported. PKAS included all subjects in the SAS that had at least one quantifiable post-dose FVIII activity level without major protocol deviations or events with potential to affect the PK analysis.

End point type	Secondary

End point timeframe:

Pre-infusion, 15 - 30 minutes, 3, 8, 24, 48, 72 and 96 hours post-infusion

End point values	BAX 855-Low Level	BAX 855-High Level	BAX 855-Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	58	5	
Units: hour (h)				
median (full range (min-max))				
hour (h)	15.28 (8.77 to 31.9)	14.66 (6.78 to 35.8)	10.97 (8.67 to 12.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Residence Time (MRT) of BAX 855

End point title	Mean Residence Time (MRT) of BAX 855

End point description:

MRT of BAX 855 was reported. PKAS included all subjects in the SAS that had at least one quantifiable post-dose FVIII activity level without major protocol deviations or events with potential to affect the PK analysis.

End point type	Secondary

End point timeframe:

Pre-infusion, 15 - 30 minutes, 3, 8, 24, 48, 72 and 96 hours post-infusion

End point values	BAX 855-Low Level	BAX 855-High Level	BAX 855-Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	58	5	
Units: hour (h)				
median (full range (min-max))				
hour (h)	22.77 (12.6 to 41.7)	21.50 (10.1 to 52.5)	16.18 (12.6 to 18.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) of BAX 855

End point title	Maximum Plasma Concentration (Cmax) of BAX 855

End point description:

Cmax of BAX 855 was reported. PKAS included all subjects in the SAS that had at least one quantifiable post-dose FVIII activity level without major protocol deviations or events with potential to affect the PK analysis. Here "Number of subjects analyzed" refer to number of subjects evaluable for this outcome at specified time points.

End point type	Secondary

End point timeframe:

Pre-infusion, 15 - 30 minutes, 3, 8, 24, 48, 72 and 96 hours post-infusion

End point values	BAX 855-Low Level	BAX 855-High Level	BAX 855-Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54	57	5	
Units: International units per deciliter(IU/dL)				
arithmetic mean (standard deviation)				
International units per deciliter(IU/dL)	132.54 (± 31.83)	135.65 (± 33.10)	149.18 (± 12.86)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Concentration of BAX 855 in Plasma (Tmax)

End point title	Time to Maximum Concentration of BAX 855 in Plasma (Tmax)

End point description:

Tmax of BAX 855 was reported. PKAS included all subjects in the SAS that had at least one quantifiable post-dose FVIII activity level without major protocol deviations or events with potential to affect the PK analysis.

End point type	Secondary

End point timeframe:

Pre-infusion, 15 - 30 minutes, 3, 8, 24, 48, 72 and 96 hours post-infusion

End point values	BAX 855-Low Level	BAX 855-High Level	BAX 855-Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	58	5	
Units: hour (h)				
median (full range (min-max))				
hour (h)	0.467 (0.30 to 3.08)	0.475 (0.25 to 3.25)	0.417 (0.38 to 0.53)	

Statistical analyses

No statistical analyses for this end point

Secondary: Total Body Clearance (CL) of BAX 855

End point title	Total Body Clearance (CL) of BAX 855

End point description:

Total body clearance of BAX 855 from blood by the kidney was reported. PKAS included all subjects in the SAS that had at least one quantifiable post-dose FVIII activity level without major protocol deviations or events with potential to affect the PK analysis.

End point type	Secondary

End point timeframe:

Pre-infusion, 15 - 30 minutes, 3, 8, 24, 48, 72 and 96 hours post-infusion

End point values	BAX 855-Low Level	BAX 855-High Level	BAX 855-Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	58	5	
Units: Deciliters per kilogram * hour (dL/kg*h)				
arithmetic mean (standard deviation)				
Deciliters per kilogram * hour (dL/kg*h)	0.02477 (± 0.009580)	0.02624 (± 0.009333)	0.02774 (± 0.004385)	

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution at steady state (Vss)

End point title	Volume of Distribution at steady state (Vss)

End point description:

Volume of distribution was defined as the theoretical volume in which the total amount of drug was uniformly distributed to produce the desired blood concentration of a drug. Vss is the apparent volume of distribution at steadystate. PKAS included all subjects in the SAS that had at least one quantifiable post-dose FVIII activity level without major protocol deviations or events with potential to affect the PK analysis.

End point type	Secondary

End point timeframe:

Pre-infusion, 15 - 30 minutes, 3, 8, 24, 48, 72 and 96 hours post-infusion

End point values	BAX 855-Low Level	BAX 855-High Level	BAX 855-Non-randomized	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	58	5	
Units: Deciliters per kilogram (dL/kg)				
arithmetic mean (standard deviation)				
Deciliters per kilogram (dL/kg)	0.5147 (± 0.1209)	0.5158 (± 0.1062)	149.18 (± 12.86)	

Statistical analyses

No statistical analyses for this end point

Secondary: Incremental recovery (IR) Over Time

End point title	Incremental recovery (IR) Over Time[14]

End point description:

Incremental recovery was calculated by BAX 855 increment (IU/dL) / BAX 855 dose (IU/kg). PKAS included all subjects in the SAS that had at least one quantifiable post-dose FVIII activity level without major protocol deviations or events with potential to affect the PK analysis. Here "n" refer to number of subjects evaluable for this outcome at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Month 3, 6, 7.5, 9, 10.5, 12 (Completion or termination)

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was related to subjects randomized to prophylactic treatment, hence not reporting statistics for all the arms in the baseline period

End point values	BAX 855-Low Level	BAX 855-High Level		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	58		
Units: IU/dL per IU/kg				
arithmetic mean (standard deviation)				
Baseline (n=53,54)	2.68 (± 0.513)	2.70 (± 0.450)		
Month 3 (n=56,54)	2.68 (± 0.515)	2.66 (± 0.459)		
Month 6 (n=51,49)	2.62 (± 0.585)	2.76 (± 0.552)		
Month 7.5 (n=13,11)	2.53 (± 0.360)	2.71 (± 0.545)		
Month 9 (n=55,52)	2.65 (± 0.511)	2.68 (± 0.545)		
Month 10.5 (n=12,5)	2.61 (± 0.467)	2.58 (± 0.584)		
Completion/ Termination (n=56,53)	2.71 (± 0.553)	2.73 (± 0.689)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of study treatment up to 12 months (completion or termination)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	BAX 855-Low Level
Reporting group description:	
Subjects with severe hemophilia A received a single BAX 855 dose of 60 +/- 5 IU/kg IV infusion (PK assessment) followed by a PK-guided dose of BAX 855 twice weekly (Alternating 3 and 4-day infusion intervals or an infusion every 3.5 days), FVIII trough levels of 1-3%. Depending on subject's individual PK, more frequent dosing was considered if single doses of > 80 IU/kg were required or regular FVIII peak levels of 200% were reached.	
Reporting group title	BAX 855-High Level
Reporting group description:	
Subjects with severe hemophilia A received a single BAX 855 dose of 60 +/- 5 IU/kg IV infusion (PK assessment) followed by a PK-guided dose of BAX 855 every other day, targeting FVIII trough levels of 8-12%. Depending on subject's individual PK, a different dosing interval was considered to prevent regular high FVIII peak levels.	
Reporting group title	BAX 855-Non-randomized
Reporting group description:	
Subjects with severe hemophilia A received a single BAX 855 dose of 60 +/- 5 IU/kg IV infusion (PK assessment) and were not randomized to any treatments.	

Serious adverse events	BAX 855-Low Level	BAX 855-High Level	BAX 855-Non-randomized
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 57 (8.77%)	5 / 58 (8.62%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	0 / 57 (0.00%)	1 / 58 (1.72%)	0 / 6 (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
Head injury			
subjects affected / exposed	1 / 57 (1.75%)	1 / 58 (1.72%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			

subjects affected / exposed	0 / 57 (0.00%)	1 / 58 (1.72%)	0 / 6 (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
Multiple injuries			
subjects affected / exposed	0 / 57 (0.00%)	1 / 58 (1.72%)	0 / 6 (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
Radius fracture			
subjects affected / exposed	1 / 57 (1.75%)	0 / 58 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebellar haematoma			
subjects affected / exposed	0 / 57 (0.00%)	1 / 58 (1.72%)	0 / 6 (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
Blood and lymphatic system disorders			
Factor VIII inhibition			
subjects affected / exposed	0 / 57 (0.00%)	1 / 58 (1.72%)	0 / 6 (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
Musculoskeletal and connective tissue disorders			
Synovitis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 58 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 57 (1.75%)	0 / 58 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			

subjects affected / exposed	1 / 57 (1.75%)	0 / 58 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 58 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	BAX 855-Low Level	BAX 855-High Level	BAX 855-Non-randomized
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 57 (43.86%)	25 / 58 (43.10%)	0 / 6 (0.00%)
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 57 (8.77%)	6 / 58 (10.34%)	0 / 6 (0.00%)
occurrences (all)	7	7	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 57 (3.51%)	3 / 58 (5.17%)	0 / 6 (0.00%)
occurrences (all)	2	3	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 57 (5.26%)	2 / 58 (3.45%)	0 / 6 (0.00%)
occurrences (all)	3	2	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 57 (10.53%)	5 / 58 (8.62%)	0 / 6 (0.00%)
occurrences (all)	7	5	0
Back pain			
subjects affected / exposed	1 / 57 (1.75%)	3 / 58 (5.17%)	0 / 6 (0.00%)
occurrences (all)	2	3	0
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed	6 / 57 (10.53%)	5 / 58 (8.62%)	0 / 6 (0.00%)
occurrences (all)	8	6	0
Rhinitis			
subjects affected / exposed	3 / 57 (5.26%)	3 / 58 (5.17%)	0 / 6 (0.00%)
occurrences (all)	3	3	0
Sinusitis			
subjects affected / exposed	3 / 57 (5.26%)	0 / 58 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Upper respiratory tract infection			
subjects affected / exposed	6 / 57 (10.53%)	12 / 58 (20.69%)	0 / 6 (0.00%)
occurrences (all)	11	16	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 May 2015	1) The Chi-squared test with continuity correction is used which results in a lower but acceptable power of 80%. 2) The blood sampling time points for PK study were modified as follows: Postinfusion at 15-30 minutes and at 3, 8, 24, 48, 72 and 96 hours.
03 September 2015	1) The term for the primary outcome measure was changed from "total ABR" to "Presence or absence of any bleedings in the second 6- month study period". 2) SF-36 Physical activity level was replaced by SF-36 Health Survey. 3) HrQoL including SF-36, EQ-5D, Haemo-SYM and healthcare resource utilization was added to pharmacoeconomic outcomes. 4) The time point for the initial hemostatic efficacy rating for treatment of bleeding episodes was changed from 24±2 hours to 8+/-1 hours. 5) It was made clear that the second 6-month study period will consist of at least 26 weeks following the 6 month-study visit scheduled at 26 (+/-1) weeks and that the subject will have received his PK-tailored dosing regimen for at least 52 weeks.
18 October 2016	1) The washout periods have been revised to be consistent with the infusion interval according to the treatment regimen provided to the subject. 2) The dose to determine IR has been revised. Instead of a set dose of 60 +/- 5 IU, the PK-guided prophylactic dose of BAX 855 will be used. 3) Description of EQ-5D questionnaire amended to reflect 3 levels for each of the 5 measured dimensions.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported