



Clinical trial results:

A Phase 3b Continuation study of the Safety and Efficacy of PEGylated Recombinant Factor VIII (PEG-rFVIII; BAX 855) in Prophylaxis of Bleeding in Previously Treated Patients with Severe Hemophilia A Summary

EudraCT number	2013-002236-24
Trial protocol	BE LT BG SE GB CZ AT NL DE ES PL
Global end of trial date	02 March 2018

Results information

Result version number	v1 (current)
This version publication date	16 September 2018
First version publication date	16 September 2018

Trial information

Trial identification

Sponsor protocol code	261302
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01945593
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire
Sponsor organisation address	300 Shire Way, Lexington, United States, MA 02421
Public contact	Study Director, Shire, ClinicalTransparency@shire.com
Scientific contact	Study Director, Shire, ClinicalTransparency@shire.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 March 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	02 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The co-primary objectives of the study were to determine the safety of BAX 855 based on the incidence of FVIII inhibitory antibody development and to determine the efficacy of BAX 855 based on annualized bleed rate (ABR) as determined by the development of spontaneous bleeds (bleeds not associated with trauma).

Protection of trial subjects:

This study was conducted in accordance with 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	15 October 2013
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: 4
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Bulgaria: 12
Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	Czech Republic: 6
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	Hong Kong: 2
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Japan: 9
Country: Number of subjects enrolled	Korea, Republic of: 14
Country: Number of subjects enrolled	Lithuania: 6
Country: Number of subjects enrolled	Malaysia: 24
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Romania: 2
Country: Number of subjects enrolled	Russian Federation: 2

Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Turkey: 5
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	Ukraine: 19
Country: Number of subjects enrolled	United States: 53
Worldwide total number of subjects	216
EEA total number of subjects	75

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)	3
Children (2-11 years)	62
Adolescents (12-17 years)	30
Adults (18-64 years)	121
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 86 centers in 23 countries between 15 October 2013 (first subject first visit) and 02 March 2018 (last subject last visit).

Pre-assignment

Screening details:

A total of 218 subjects were enrolled, of them 216 subjects received treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	BAX 855: Age < 6 Years

Arm description:

Subjects of age < 6 years received an infusion of 50 +/- 10 International Units/kilogram (IU/kg) of BAX 855 twice weekly; may be increased to 80 IU/kg or a pharmacokinetically tailored (PK-tailored) prophylactic dose (should not exceed 80 IU/kg and the FVIII peak levels were not to exceed 200%) twice weekly based on the subject's individual PK to maintain Factor VIII (FVIII) trough levels of greater than or equal to ($\geq$) 3% until reached at least 100 exposure days (EDs).

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

Dosage and administration details:

Subjects received age-dependent intravenous infusion of BAX855 twice weekly until at least 100 EDs.

Arm title	BAX 855: Age $\geq$ 6 to <12 Years
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Arm description:

Subjects of age $\geq$ 6 to <12 years received an infusion of 50 +/- 10 IU/kg of BAX 855 twice weekly; may be increased to 80 IU/kg or a PK-tailored prophylactic dose (should not exceed 80 IU/kg and the FVIII peak levels were not to exceed 200%) twice weekly based on the subject's individual PK to maintain FVIII trough levels of $\geq$ 3% until reached at least 100 EDs.

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

Dosage and administration details:

Subjects received age-dependent intravenous infusion of BAX855 twice weekly until at least 100 EDs.

Arm title	BAX 855: Age $\geq$ 12 to <18 Years
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Arm description:

Subjects of age $\geq$ 12 to <18 years received an infusion of 45 +/- 5 IU/kg of BAX 855 twice weekly; may be increased to 80 IU/kg or a PK-tailored prophylactic dose (should not exceed 80 IU/kg and the FVIII peak levels were not to exceed 200%) twice weekly based on the subject's individual PK to maintain FVIII trough levels of $\geq$ 3% until reached at least 100 EDs.

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

Dosage and administration details:

Subjects received age-dependent intravenous infusion of BAX855 twice weekly until at least 100 EDs.

Arm title	BAX 855: Age $\geq$ 18 Years
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Arm description:

Subjects of age $\geq$ 18 years received an infusion of 45 +/- 5 IU/kg of BAX 855 twice weekly; may be increased to 80 IU/kg or a PK-tailored prophylactic dose (should not exceed 80 IU/kg and the FVIII peak levels were not to exceed 200%) twice weekly based on the subject's individual PK to maintain FVIII trough levels of $\geq$ 3% until reached at least 100 EDs.

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

Dosage and administration details:

Subjects received age-dependent intravenous infusion of BAX855 twice weekly until at least 100 EDs.

Number of subjects in period 1	BAX 855: Age < 6 Years	BAX 855: Age $\geq$ 6 to <12 Years	BAX 855: Age $\geq$ 12 to <18 Years
Started	32	33	30
Completed	31	28	27
Not completed	1	5	3
Adverse event, serious fatal	-	-	1
Consent withdrawn by subject	-	2	-
Physician decision	-	-	1
Adverse event, non-fatal	-	-	-
Other	-	2	-
Protocol deviation	1	1	1

Number of subjects in period 1	BAX 855: Age $\geq$ 18 Years
Started	121
Completed	101
Not completed	20
Adverse event, serious fatal	-
Consent withdrawn by subject	4
Physician decision	1
Adverse event, non-fatal	5
Other	7
Protocol deviation	3

Baseline characteristics

Reporting groups

Reporting group title	BAX 855: Age < 6 Years
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Reporting group description:

Subjects of age < 6 years received an infusion of 50 +/- 10 International Units/kilogram (IU/kg) of BAX 855 twice weekly; may be increased to 80 IU/kg or a pharmacokinetically tailored (PK-tailored) prophylactic dose (should not exceed 80 IU/kg and the FVIII peak levels were not to exceed 200%) twice weekly based on the subject's individual PK to maintain Factor VIII (FVIII) trough levels of greater than or equal to ($\geq$) 3% until reached at least 100 exposure days (EDs).

Reporting group title	BAX 855: Age $\geq$ 6 to <12 Years
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Reporting group description:

Subjects of age $\geq$ 6 to <12 years received an infusion of 50 +/- 10 IU/kg of BAX 855 twice weekly; may be increased to 80 IU/kg or a PK-tailored prophylactic dose (should not exceed 80 IU/kg and the FVIII peak levels were not to exceed 200%) twice weekly based on the subject's individual PK to maintain FVIII trough levels of $\geq$ 3% until reached at least 100 EDs.

Reporting group title	BAX 855: Age $\geq$ 12 to <18 Years
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Reporting group description:

Subjects of age $\geq$ 12 to <18 years received an infusion of 45 +/- 5 IU/kg of BAX 855 twice weekly; may be increased to 80 IU/kg or a PK-tailored prophylactic dose (should not exceed 80 IU/kg and the FVIII peak levels were not to exceed 200%) twice weekly based on the subject's individual PK to maintain FVIII trough levels of $\geq$ 3% until reached at least 100 EDs.

Reporting group title	BAX 855: Age $\geq$ 18 Years
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Reporting group description:

Subjects of age $\geq$ 18 years received an infusion of 45 +/- 5 IU/kg of BAX 855 twice weekly; may be increased to 80 IU/kg or a PK-tailored prophylactic dose (should not exceed 80 IU/kg and the FVIII peak levels were not to exceed 200%) twice weekly based on the subject's individual PK to maintain FVIII trough levels of $\geq$ 3% until reached at least 100 EDs.

Reporting group values	BAX 855: Age < 6 Years	BAX 855: Age $\geq$ 6 to <12 Years	BAX 855: Age $\geq$ 12 to <18 Years
Number of subjects	32	33	30
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	3.6	7.8	14.2
standard deviation	± 1.29	± 1.70	± 1.63
Gender categorical Units:			
Male	32	32	30
Female	0	1	0

Reporting group values	BAX 855: Age $\geq$ 18 Years	Total	
Number of subjects	121	216	
Age categorical Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	34.1		
standard deviation	± 11.47	-	
Gender categorical			
Units:			
Male	121	215	
Female	0	1	

End points

End points reporting groups

Reporting group title	BAX 855: Age < 6 Years
Reporting group description: Subjects of age < 6 years received an infusion of 50 +/- 10 International Units/kilogram (IU/kg) of BAX 855 twice weekly; may be increased to 80 IU/kg or a pharmacokinetically tailored (PK-tailored) prophylactic dose (should not exceed 80 IU/kg and the FVIII peak levels were not to exceed 200%) twice weekly based on the subject's individual PK to maintain Factor VIII (FVIII) trough levels of greater than or equal to ($\geq$) 3% until reached at least 100 exposure days (EDs).	
Reporting group title	BAX 855: Age $\geq$ 6 to <12 Years
Reporting group description: Subjects of age $\geq$ 6 to <12 years received an infusion of 50 +/- 10 IU/kg of BAX 855 twice weekly; may be increased to 80 IU/kg or a PK-tailored prophylactic dose (should not exceed 80 IU/kg and the FVIII peak levels were not to exceed 200%) twice weekly based on the subject's individual PK to maintain FVIII trough levels of $\geq$ 3% until reached at least 100 EDs.	
Reporting group title	BAX 855: Age $\geq$ 12 to <18 Years
Reporting group description: Subjects of age $\geq$ 12 to <18 years received an infusion of 45 +/- 5 IU/kg of BAX 855 twice weekly; may be increased to 80 IU/kg or a PK-tailored prophylactic dose (should not exceed 80 IU/kg and the FVIII peak levels were not to exceed 200%) twice weekly based on the subject's individual PK to maintain FVIII trough levels of $\geq$ 3% until reached at least 100 EDs.	
Reporting group title	BAX 855: Age $\geq$ 18 Years
Reporting group description: Subjects of age $\geq$ 18 years received an infusion of 45 +/- 5 IU/kg of BAX 855 twice weekly; may be increased to 80 IU/kg or a PK-tailored prophylactic dose (should not exceed 80 IU/kg and the FVIII peak levels were not to exceed 200%) twice weekly based on the subject's individual PK to maintain FVIII trough levels of $\geq$ 3% until reached at least 100 EDs.	
Subject analysis set title	BAX 855: Overall
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects received an infusion of 30-80 +/- 5 IU/kg of BAX 855 twice weekly; may be increased to 80 IU/kg or a PKtailored prophylactic dose (should not exceed 80 IU/kg and the FVIII peak levels were not to exceed 200%) twice weekly based on the subject's individual PK to maintain FVIII trough levels of $\geq$ 3% until reached at least 100 EDs.	

Primary: Number of Subjects With Inhibitory Antibodies to Factor VIII (FVIII)

End point title	Number of Subjects With Inhibitory Antibodies to Factor VIII (FVIII) ^[1]
End point description: Inhibitory antibodies to Factor VIII was measured by the Nijmegen modification of the Bethesda assay. Inhibitors must be confirmed by 2 separate assessments within a 2 to 4 week period from the central laboratory. Safety analysis set (SAS) included all subjects with at least 1 BAX 855 infusion. The analysis included subjects that developed inhibitory antibodies to FVIII and subjects that did not develop inhibitory antibodies to FVIII and had 100 or more EDs to BAX 855 across all studies and a FVIII inhibitory test result after the 100th exposure day.	
End point type	Primary
End point timeframe: Baseline through end of study assessed every 3 months (53 months)	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Descriptive statistics were done, no inferential statistical analyses were performed.	

End point values	BAX 855: Age < 6 Years	BAX 855: Age >= 6 to <12 Years	BAX 855: Age >= 12 to <18 Years	BAX 855: Age >= 18 Years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29	31	30	114
Units: Subjects	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Annualized Bleed Rate (ABR) - Spontaneous Bleeds

End point title	Annualized Bleed Rate (ABR) - Spontaneous Bleeds ^[2]
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End point description:

The ABR was assessed based upon each individual bleeding episode. A bleeding episode was defined as subjective (pain consistent with a joint bleed) or objective evidence of bleeding which may or may not require treatment with FVIII. Bleeding episodes occurring at the same anatomical location with the same etiology within 24 hours (+/- 2 hours) of onset of the first episode, bleeding occurring at multiple locations related to the same injury was counted as a single bleeding episode. The ABR of spontaneous bleeds was reported separately for twice weekly, PK-t R, each of the every 5 days and every 7 days treatment regimens at the time of bleed. Here, FDR refers to fixed-dose regimen, PK-t R to PK-tailored regimen and "n" indicates the number of subjects evaluable for this endpoint. Full analysis set (FAS) included all subjects with at least 1 BAX 855 infusion. 99999 indicates the data was not calculated due to less number of subjects.

End point type	Primary
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End point timeframe:

Baseline through end of study assessed every 3 months (53 months)

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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	BAX 855: Age < 6 Years	BAX 855: Age >= 6 to <12 Years	BAX 855: Age >= 12 to <18 Years	BAX 855: Age >= 18 Years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	33	30	121
Units: Annualized bleed rate				
number (confidence interval 95%)				
FDR: Every 5 Days (n=0,0,8,48)	99999 (99999 to 99999)	99999 (99999 to 99999)	1.034 (0.498 to 2.147)	1.184 (0.741 to 1.894)
FDR: Every 7 Days (n=0,0,2,13)	99999 (99999 to 99999)	99999 (99999 to 99999)	0.000 (0.000 to 0.000)	2.215 (0.914 to 5.368)
FDR: Twice Weekly (n=31,31,23,101)	0.656 (0.394 to 1.094)	0.762 (0.438 to 1.325)	1.768 (1.093 to 2.859)	1.259 (0.876 to 1.812)
PK-t R (n=4,6,6,9)	0.915 (0.221 to 3.792)	0.874 (0.407 to 1.875)	0.842 (0.122 to 5.821)	1.006 (0.449 to 2.252)

Statistical analyses

No statistical analyses for this end point

Secondary: Total Annualized Bleed Rate (ABR)

End point title	Total Annualized Bleed Rate (ABR)
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End point description:

The ABR was assessed based upon each individual bleeding episode. A bleeding episode was defined as subjective (pain consistent with a joint bleed) or objective evidence of bleeding which may or may not require treatment with FVIII. Bleeding episodes occurring at the same anatomical location with the same etiology within 24 hours (+/- 2 hours) of onset of the first episode, bleeding occurring at multiple locations related to the same injury was counted as a single bleeding episode. Bleeding occurring at multiple locations related to the same injury (e.g., knee and ankle bleed following a fall) was counted as a single bleeding episode. Total annualized bleed rate (spontaneous and traumatic bleeding episodes) was reported. FAS included all subjects with at least 1 BAX 855 infusion.

End point type	Secondary
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End point timeframe:

Baseline through end of study assessed every 3 months (53 months)

End point values	BAX 855: Age < 6 Years	BAX 855: Age >= 6 to <12 Years	BAX 855: Age >= 12 to <18 Years	BAX 855: Age >= 18 Years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	33	30	121
Units: Annualized bleed rate				
arithmetic mean (standard deviation)	2.311 (± 3.510)	2.380 (± 2.371)	3.163 (± 2.673)	2.404 (± 3.295)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Hemostatic Efficacy Rating of BAX 855 for Treatment of Breakthrough Bleeding Episodes

End point title	Overall Hemostatic Efficacy Rating of BAX 855 for Treatment of Breakthrough Bleeding Episodes
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End point description:

The subject or caregiver rated the severity (minor, moderate, or major) of the bleeding episode and rated the overall treatment response at 24 (+/- 2) hours after the initiation of treatment 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: 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 with at least 1 BAX 855 infusion.

End point type	Secondary
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End point timeframe:

Baseline through end of study assessed every 3 months (53 months)

End point values	BAX 855: Age < 6 Years	BAX 855: Age >= 6 to <12 Years	BAX 855: Age >= 12 to <18 Years	BAX 855: Age >= 18 Years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	22	28	91
Units: Treated bleeds				
Excellent	37	74	104	223
Good	26	43	76	223
Fair	3	2	8	35
None	0	0	1	3
Not Reported	6	7	13	26

Statistical analyses

No statistical analyses for this end point

Secondary: BAX 855 Infusions Needed to Treat Bleeding Episodes

End point title	BAX 855 Infusions Needed to Treat Bleeding Episodes
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End point description:

The BAX 855 infusions to treat each bleeding episode was determined by the subject, the subject's caregiver, and/or investigator, and was based upon the subject's response to treatment. A bleeding episode was defined as subjective (pain consistent with a joint bleed) or objective evidence of bleeding which may or may not require treatment with FVIII. Bleeding episodes occurring at the same anatomical location with the same etiology within 24 hours (+/- 2 hours) of onset of the first episode, bleeding occurring at multiple locations related to the same injury was counted as a single bleeding episode. FAS included all subjects with at least 1 BAX 855 infusion.

End point type	Secondary
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End point timeframe:

Baseline through end of study assessed every 3 months (53 months)

End point values	BAX 855: Age < 6 Years	BAX 855: Age >= 6 to <12 Years	BAX 855: Age >= 12 to <18 Years	BAX 855: Age >= 18 Years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	33	30	121
Units: Infusions				
arithmetic mean (standard deviation)	1.4 (± 1.46)	1.4 (± 0.88)	1.4 (± 1.68)	1.4 (± 1.12)

Statistical analyses

No statistical analyses for this end point

Secondary: Total Time Intervals Between Bleeding Episodes

End point title	Total Time Intervals Between Bleeding Episodes
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End point description:

The time interval between bleeding episodes was calculated based upon the date and time reported for each bleeding episode. A bleeding episode was defined as subjective (pain consistent with a joint bleed)

or objective evidence of bleeding which may or may not require treatment with FVIII. Bleeding episodes occurring at the same anatomical location with the same etiology within 24 hours (+/- 2 hours) of onset of the first episode, bleeding occurring at multiple locations related to the same injury was counted as a single bleeding episode. FAS with evaluable subjects for this endpoint were analyzed.

End point type	Secondary
End point timeframe:	
Baseline through end of study assessed every 3 months (53 months)	

End point values	BAX 855: Age < 6 Years	BAX 855: Age >= 6 to <12 Years	BAX 855: Age >= 12 to <18 Years	BAX 855: Age >= 18 Years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	21	25	80
Units: Months				
median (full range (min-max))	5.460 (0.756 to 14.867)	4.158 (1.405 to 10.760)	5.232 (1.228 to 14.571)	5.818 (0.617 to 22.686)

Statistical analyses

No statistical analyses for this end point

Secondary: Average Dose of BAX 855 per Prophylactic Infusion

End point title	Average Dose of BAX 855 per Prophylactic Infusion
End point description:	
The average dose of BAX 855 per prophylactic infusion was reported. SAS included all subjects with at least 1 BAX 855 infusion.	
End point type	Secondary
End point timeframe:	
Baseline through end of study assessed every 3 months (53 months)	

End point values	BAX 855: Age < 6 Years	BAX 855: Age >= 6 to <12 Years	BAX 855: Age >= 12 to <18 Years	BAX 855: Age >= 18 Years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	33	30	121
Units: International units per kilogram (IU/kg)				
arithmetic mean (standard deviation)	53.303 ($\pm$ 7.569)	54.109 ($\pm$ 8.224)	53.940 ($\pm$ 10.588)	49.462 ($\pm$ 8.447)

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)
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End point description:

An AE was any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever, dizziness, etc.), disease (eg, 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 serious adverse event (SAE) was defined as an untoward medical occurrence that at any dose met one or more of the following criteria: outcome was fatal/resulted in death; was life-threatening; required inpatient 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. SAS included all subjects with at least 1 BAX 855 infusion.

End point type	Secondary
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End point timeframe:

Baseline through end of study assessed every 3 months (53 months)

End point values	BAX 855: Age < 6 Years	BAX 855: Age >= 6 to <12 Years	BAX 855: Age >= 12 to <18 Years	BAX 855: Age >= 18 Years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	33	30	121
Units: Subjects				
AE	26	29	21	98
SAE	5	2	4	22

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Body Temperature

End point title	Change From Baseline in Body Temperature
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End point description:

Change in body temperature at pre-infusion and post-infusion was reported. In the below table, FDR refers to fixed dose regimen, PK-tR refers to PK tailored regimen at the time of sampling and "n" indicates the number of subjects evaluable for this endpoint. SAS included all subjects with at least 1 BAX 855 infusion.

End point type	Secondary
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End point timeframe:

Baseline, end of study (53 months)

End point values	BAX 855: Overall			
Subject group type	Subject analysis set			
Number of subjects analysed	216			
Units: Degree celsius				
arithmetic mean (standard deviation)				
FDR: Pre-Infusion (n=186)	-0.03 (± 0.380)			
FDR: Post-Infusion (n=148)	-0.01 (± 0.388)			
PK-tR: Pre-Infusion (n=23)	0.03 (± 0.468)			
PK-tR: Post-Infusion (n=21)	0.06 (± 0.447)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pulse Rate

End point title	Change From Baseline in Pulse Rate
End point description:	
Change in pulse rate at pre-infusion and post-infusion was reported. In the below table, FDR refers to fixed dose regimen, PK-tR refers to PK tailored regimen at the time of sampling and "n" indicates the number of subjects evaluable for this endpoint. SAS included all subjects with at least 1 BAX 855 infusion.	
End point type	Secondary
End point timeframe:	
Baseline, end of study (53 months)	

End point values	BAX 855: Overall			
Subject group type	Subject analysis set			
Number of subjects analysed	214			
Units: Beats per minute (beats/min)				
arithmetic mean (standard deviation)				
FDR: Pre-Infusion (n=186)	-1.5 (± 12.69)			
FDR: Post-Infusion (n=149)	-1.0 (± 12.59)			
PK-tR: Pre-Infusion (n=23)	1.7 (± 9.83)			
PK-tR: Post-Infusion (n=21)	-4.0 (± 11.66)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Respiratory Rate

End point title	Change From Baseline in Respiratory Rate
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End point description:

Change in respiratory rate at pre-infusion and post-infusion was reported. In the below table, FDR refers to fixed dose regimen, PK-tR refers to PK tailored regimen at the time of sampling and "n" indicates the number of subjects evaluable for this endpoint. SAS included all subjects with at least 1 BAX 855 infusion.

End point type	Secondary
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End point timeframe:

Baseline, end of study (53 months)

End point values	BAX 855: Overall			
Subject group type	Subject analysis set			
Number of subjects analysed	214			
Units: Breaths per minute (breaths/min)				
arithmetic mean (standard deviation)				
FDR: Pre-Infusion (n=185)	-0.2 (± 3.26)			
FDR: Post-Infusion (n=149)	-0.6 (± 3.18)			
PK-tR: Pre-Infusion (n=23)	0.0 (± 5.17)			
PK-tR: Post-Infusion (n=21)	-0.3 (± 4.62)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Blood Pressure

End point title	Change From Baseline in Blood Pressure
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End point description:

Change in systolic and diastolic blood pressure at pre-infusion and post-infusion were reported. In the below table, FDR refers to fixed dose regimen, PK-tR refers to PK tailored regimen at the time of sampling, SBP refers to systolic blood pressure, DBP refers to diastolic blood pressure and "n" indicates the number of subjects evaluable for this endpoint. SAS with evaluable subjects for this endpoint were analyzed.

End point type	Secondary
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End point timeframe:

Baseline, end of study (53 months)

End point values	BAX 855: Overall			
Subject group type	Subject analysis set			
Number of subjects analysed	214			
Units: Millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)				
FDR: SBP: Pre-Infusion (n=186)	2.7 (± 12.13)			
FDR: SBP: Post-Infusion (n=146)	0.2 (± 11.64)			
PK-tR: SBP: Pre-Infusion (n=23)	1.4 (± 11.36)			
PK-tR: SBP: Post-Infusion (n=21)	2.1 (± 11.57)			

FDR: DBP: Pre-Infusion (n=186)	1.7 (± 9.00)			
FDR: DBP: Post-Infusion (n=146)	1.2 (± 9.05)			
PK-tR: DBP: Pre-Infusion (n=23)	1.6 (± 8.53)			
PK-tR: DBP: Post-Infusion (n=21)	-1.7 (± 7.08)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Shifts in Clinical Chemistry Laboratory Assessments

End point title	Number of Subjects with Shifts in Clinical Chemistry Laboratory Assessments
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End point description:

The number of subjects with clinically significant shifts from "normal" and "abnormal not clinically significant (abnormal NCS)" at baseline to "abnormal clinically significant (CS)" at completion were reported. In the below table, FDR refers to fixed dose regimen at the time of sampling, AIA refers to alanine aminotransferase, AP refers to alkaline phosphatase, AsA refers to aspartate aminotransferase and "n" indicates the number of subjects evaluable for this endpoint. SAS included all subjects with at least 1 BAX 855 infusion.

End point type	Secondary
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End point timeframe:

Baseline through end of study assessed every 3 months (53 months)

End point values	BAX 855: Overall			
Subject group type	Subject analysis set			
Number of subjects analysed	216			
Units: Subjects				
FDR: AIA- Normal to CS (n=214)	2			
FDR: AIA- Abnormal NCS to CS (n=214)	1			
FDR: AP- Normal to CS (n=214)	3			
FDR: AP- Abnormal NCS to CS (n=214)	0			
FDR: AsA- Normal to CS (n=214)	1			
FDR: AsA- Abnormal NCS to CS (n=214)	1			
FDR: Bilirubin- Normal to CS (n=214)	0			
FDR: Bilirubin- Abnormal NCS to CS (n=214)	1			
FDR: Glucose- Normal to CS (n=214)	1			
FDR: Glucose- Abnormal NCS to CS (n=214)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Shifts in Hematology Laboratory Assessments

End point title	Number of Subjects with Shifts in Hematology Laboratory Assessments
End point description: The number of subjects with clinically significant shifts from "normal" and "abnormal not clinically significant (abnormal NCS)" at baseline to "abnormal clinically significant (CS)" at completion were reported. In the below table, FDR refers to fixed dose regimen, PK-tR refers to PK tailored regimen at the time of sampling, Leu refers to leukocytes, MCV refers to mean corpuscular volume, Lym/Leu refers to lymphocytes/leukocytes and "n" indicates the number of subjects evaluable for this endpoint. SAS included all subjects with at least 1 BAX 855 infusion.	
End point type	Secondary
End point timeframe: Baseline through end of study assessed every 3 months (53 months)	

End point values	BAX 855: Overall			
Subject group type	Subject analysis set			
Number of subjects analysed	216			
Units: Subjects				
FDR: Eosinophils/Leu- Normal to CS (n=214)	1			
FDR:Eosinophils/Leu- Abnormal NCS to CS (n=214)	0			
FDR: Erythrocytes MCV- Normal to CS (n=214)	1			
FDR: Erythrocytes MCV- Abnormal NCS to CS (n=214)	1			
FDR: Erythrocytes- Normal to CS (n=214)	0			
FDR: Erythrocytes- Abnormal NCS to CS (n=214)	1			
FDR: Hematocrit- Normal to CS (n=214)	1			
FDR: Hematocrit- Abnormal NCS to CS (n=214)	2			
FDR: Hemoglobin- Normal to CS (n=214)	1			
FDR: Hemoglobin- Abnormal NCS to CS (n=214)	1			
FDR: Leukocytes- Normal to CS (n=214)	1			
FDR: Leukocytes- Abnormal NCS to CS (n=214)	0			
FDR: Lym/Leu- Normal to CS (n=214)	1			
FDR: Lym/Leu- Abnormal NCS to CS (n=214)	0			
FDR: Platelets- Normal to CS (n=214)	1			
FDR: Platelets- Abnormal NCS to CS (n=214)	0			
PK-t R: Hematocrit- Normal to CS (n=25)	1			
PK-t R: Hematocrit- Abnormal NCS to CS (n=25)	0			
PK-t R: Hemoglobin- Normal to CS (n=25)	1			
PK-t R: Hemoglobin- Abnormal NCS to CS (n=25)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Shifts in Lipid Panel Assessments

End point title	Number of Subjects with Shifts in Lipid Panel Assessments
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End point description:

The number of subjects with clinically significant shifts from "normal" and "abnormal not clinically significant (abnormal NCS)" at baseline to "abnormal clinically significant (CS)" at completion were reported. In the below table, HDL refers to high density lipoprotein, LDL refers to low density lipoprotein, VLDL refers to very low density lipoprotein and "n" indicates the number of subjects evaluable for this endpoint. SAS included all subjects with at least 1 BAX 855 infusion.

End point type	Secondary
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End point timeframe:

Baseline through end of study assessed every 3 months (53 months)

End point values	BAX 855: Overall			
Subject group type	Subject analysis set			
Number of subjects analysed	216			
Units: Subjects				
FDR: Cholesterol- Normal to CS (n=214)	2			
FDR: Cholesterol- Abnormal NCS to CS (n=214)	0			
FDR: HDL Cholesterol- Normal to CS (n=214)	1			
FDR: HDL Cholesterol- Abnormal NCS to CS (n=214)	0			
FDR: LDL Cholesterol- Normal to CS (n=214)	2			
FDR: LDL Cholesterol- Abnormal NCS to CS (n=214)	0			
FDR: Triglycerides- Normal to CS (n=214)	2			
FDR: Triglycerides- Abnormal NCS to CS (n=214)	1			
FDR: VLDL Cholesterol- Normal to CS (n=214)	2			
FDR: VLDL Cholesterol- Abnormal NCS to CS (n=214)	0			
PK-tR: VLDL Cholesterol- Normal to CS (n=25)	2			
PK-tR: VLDL Cholesterol- Abnormal NCS to CS (n=25)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Binding antibodies

End point title	Number of Subjects With Binding antibodies
End point description: Binding antibodies (IgG and IgM) against FVIII, polyethylene glycol (PEG) and PEGylated FVIII (PEG-FVIII) were analyzed using enzyme-linked immunosorbent assay (ELISA). SAS included all subjects with at least 1 BAX 855 infusion.	
End point type	Secondary
End point timeframe: Baseline through end of study assessed every 3 months (53 months)	

End point values	BAX 855: Age < 6 Years	BAX 855: Age ≥ 6 to <12 Years	BAX 855: Age ≥ 12 to <18 Years	BAX 855: Age ≥ 18 Years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	33	30	121
Units: Subjects				
IgG to FVIII	0	2	1	2
IgM to FVIII	0	0	0	0
IgG to PEG-FVIII	2	2	0	4
IgM to PEG-FVIII	0	0	0	0
IgG to PEG	0	0	0	0
IgM to PEG	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Anti-Chinese Hamster Ovary (CHO) Antibodies

End point title	Number of Subjects With Anti-Chinese Hamster Ovary (CHO) Antibodies
End point description: Testing for binding of anti-CHO protein antibodies was performed on citrate-anti-coagulated plasma using an ELISA employing polyclonal antihuman IgG antibodies. SAS included all subjects with at least 1 BAX 855 infusion.	
End point type	Secondary
End point timeframe: Baseline through end of study assessed every 3 months (53 months)	

End point values	BAX 855: Age < 6 Years	BAX 855: Age >= 6 to <12 Years	BAX 855: Age >= 12 to <18 Years	BAX 855: Age >= 18 Years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	33	30	121
Units: Subjects	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Bleed Severity

End point title	Change From Baseline in Bleed Severity ^[3]
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End point description:

Hemophilia symptom (haemo-SYM) questionnaire has two subscales: pain and bleed. It was used to assess the bleed severity for subjects >=18 years of age as: severity of spontaneous bleeding in my joints (unrelated to injury or activity), spontaneous bleeding in my muscles (unrelated to injury or activity), prolonged bleeding after injury in spite of treatment, intense pain because of bleeding event, joint pain due to active bleed and bleeding during personal hygiene routine, blood in my urine, nose bleeds and assigned a score of 0=Absent, 1=very mild, 2=mild, 3=moderate, 4=severe and 5=very severe. The score was determined as (mean score/5)*100 where mean score is the mean of the available results in the particular subscale. Higher scores on the Haemo-SYM indicate more severe symptoms. Therefore, negative change scores indicate that symptoms have improved. Here, "n" indicates the number of subjects evaluable for this endpoint. FAS included all subjects with at least 1 BAX 855 infusion.

End point type	Secondary
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End point timeframe:

Baseline, end of study (53 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: Haemo-SYM questionnaire was used to measure bleed severity in subjects >=18 years of age.

End point values	BAX 855: Age >= 18 Years			
Subject group type	Reporting group			
Number of subjects analysed	108			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Fixed dose regimen (n=72)	-7.824 (± 18.514)			
PK-tailored regimen (n=9)	-16.667 (± 14.337)			

Statistical analyses

Secondary: Change From Baseline in Pain Severity

End point title	Change From Baseline in Pain Severity ^[4]
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End point description:

Hemophilia symptom (haemo-SYM) questionnaire has two subscales: pain and bleed. It was used to assess the pain severity for subjects ≥ 18 years of age as: pain because of swelling in my joints, climbing stairs, upon waking in the morning, active arthritis; constant pain, in my muscles, that needs medication; joint sensitivity to weather conditions; reduced range of joint movement, joint deformity, sleep disturbance because of pain or bleeds, blood in my urine, nose bleeds and assigned a score of 0=Absent, 1=very mild, 2=mild, 3=moderate, 4=severe and 5=very severe. The score was determined as $(\text{mean score}/5)*100$ where mean score is the mean of the available results in the particular subscale. Higher scores on the Haemo-SYM indicate more severe symptoms. Therefore, negative change scores indicate that symptoms have improved. Here, "n" indicates the number of subjects evaluable for this endpoint. FAS included all subjects with at least 1 BAX 855 infusion.

End point type	Secondary
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End point timeframe:

Baseline, end of study (53 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: Haemo-SYM questionnaire was used to measure pain severity in subjects ≥ 18 years of age.

End point values	BAX 855: Age ≥ 18 Years			
Subject group type	Reporting group			
Number of subjects analysed	108			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Fixed dose regimen (n=72)	-1.341 ($\pm$ 11.531)			
PK-tailored regimen (n=9)	-8.889 ($\pm$ 20.659)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patient Reported Outcomes: Health-related Quality of Life (HRQoL): Short Form-36 (SF-36)

End point title	Change From Baseline in Patient Reported Outcomes: Health-related Quality of Life (HRQoL): Short Form-36 (SF-36) ^[5]
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End point description:

HRQoL in subjects aged ≥ 14 years was measured using the SF-36 questionnaire. The questionnaire was divided into 8 domains and scored as: physical functioning (1=yes, limited a lot to 3=no, not limited at all), role-physical (1=all of the time to 5=none of the time), bodily pain (1=very severe to 6=none), general health (1=poor to 5=excellent), vitality (1=none of the time to 5=all of the time), social functioning (1=all of the time to 5=none of the time), role emotional (1=all of the time to 5=none of the time) and mental health (1=all of the time to 5=none of the time). The score for each domain is then to be transformed to a 0-100 range as $[(\text{actual raw score} - \text{lowest possible raw score}) / \text{possible raw score range}] * 100$. Positive change scores indicate improved HRQoL. Here "n" indicates the number of subjects evaluable for this endpoint. FAS included all subjects with at least 1 BAX 855 infusion.

End point type	Secondary
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End point timeframe:

Baseline, end of study (53 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: SF-36 questionnaire was used to measure HRQoL in subjects aged ≥ 14 years.

End point values	BAX 855: Age ≥ 12 to <18 Years	BAX 855: Age ≥ 18 Years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	108		
Units: Score on a scale				
arithmetic mean (standard deviation)				
FDR: Physical functioning (n=9,74)	3.778 ($\pm$ 4.604)	-0.150 ($\pm$ 3.019)		
PK-t R: Physical functioning (n=4,9)	1.250 ($\pm$ 1.500)	-0.778 ($\pm$ 4.816)		
FDR: Role-physical (n=9,74)	1.4 ($\pm$ 4.39)	0.3 ($\pm$ 3.85)		
PK-t R: Role-physical (n=4,9)	1.8 ($\pm$ 2.63)	1.0 ($\pm$ 3.00)		
FDR: Bodily pain (n=9,74)	1.69 ($\pm$ 2.639)	0.76 ($\pm$ 2.011)		
PK-t R: Bodily pain (n=4,9)	0.95 ($\pm$ 2.119)	-0.01 ($\pm$ 3.493)		
FDR: General health (n=9,73)	2.80 ($\pm$ 3.599)	0.39 ($\pm$ 3.795)		
PK-t R: General health (n=4,9)	3.15 ($\pm$ 3.419)	1.02 ($\pm$ 4.196)		
FDR: Vitality (n=9,73)	0.3 ($\pm$ 3.46)	-0.01 ($\pm$ 2.34)		
PK-t R: Vitality (n=4,9)	1.0 ($\pm$ 4.55)	1.0 ($\pm$ 3.54)		
FDR: Social functioning (n=9,74)	0.6 ($\pm$ 1.67)	-0.03 ($\pm$ 1.37)		
PK-t R: Social functioning (n=4,9)	1.0 ($\pm$ 1.15)	-1.7 ($\pm$ 2.06)		
FDR: Role emotional (n=9,74)	-0.6 ($\pm$ 2.13)	-0.4 ($\pm$ 2.46)		
PK-t R: Role emotional (n=4,9)	0.3 ($\pm$ 0.50)	-1.3 ($\pm$ 2.69)		
FDR: Mental health (n=9,73)	-0.7 ($\pm$ 2.06)	-0.4 ($\pm$ 3.18)		
PK-t R: Mental health (n=4,9)	0.0 ($\pm$ 1.41)	-0.6 ($\pm$ 2.92)		
FDR: Physical component score (n=9,73)	9.381 ($\pm$ 12.588)	1.764 ($\pm$ 6.843)		
PK-t R: Physical component score (n=4,9)	5.631 ($\pm$ 6.997)	2.258 ($\pm$ 9.817)		
FDR: Mental component score (n=9,73)	-3.854 ($\pm$ 6.839)	-1.570 ($\pm$ 9.102)		
PK-t R: Mental component score (n=4,9)	0.980 ($\pm$ 7.125)	-4.677 ($\pm$ 9.195)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patient Reported Outcomes: Health-related Quality of Life (HRQoL): Pediatrics Quality of Life (PedsQL) Questionnaire

End point title	Change From Baseline in Patient Reported Outcomes: Health-related Quality of Life (HRQoL): Pediatrics Quality of Life (PedsQL) Questionnaire ^[6]
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End point description:

HRQoL in subjects aged <14 years was measured using the PedsQL. It capture data for the following domains: physical functioning, emotional functioning, social functioning, school functioning, psychosocial

functioning, physical health and a total score. Each question of the PedsQL was scored as Never: 100, almost never: 75, sometimes: 50, often: 25, almost always: 0. The mean of the individual question scores was calculated. Lower scores on the PedsQL indicating worse HRQoL. Here, FDR refers to fixed dose regimen, PK-t R refers to PK-tailored regimen and "n" indicates the number of subjects evaluable for this endpoint. FAS included all subjects with at least 1 BAX 855 infusion.

End point type	Secondary
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End point timeframe:

Baseline, end of study (53 months)

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: PedsQL questionnaire was used to measure HRQoL in subjects aged <14 years.

End point values	BAX 855: Age < 6 Years	BAX 855: Age >= 6 to <12 Years	BAX 855: Age >= 12 to <18 Years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	33	8	
Units: Score on a scale				
arithmetic mean (standard deviation)				
FDR: Physical functioning (n=21,20,3)	-1.190 (± 18.181)	2.344 (± 17.876)	3.125 (± 15.625)	
PK-t R: Physical functioning (n=3,4,2)	-7.292 (± 15.415)	4.688 (± 8.268)	7.813 (± 6.629)	
FDR: Emotional functioning (n=21,20,3)	-1.0 (± 17.00)	-1.0 (± 17.29)	8.3 (± 20.21)	
PK-t R: Emotional functioning (n=3,4,2)	-11.7 (± 10.41)	5.0 (± 7.07)	10.0 (± 14.14)	
FDR: Social functioning (n=21,20,3)	-0.2 (± 14.70)	-0.5 (± 18.06)	8.3 (± 15.28)	
PK-t R: Social functioning (n=3,4,2)	-18.3 (± 23.63)	2.5 (± 12.58)	5.0 (± 7.07)	
FDR: School functioning (n=16,20,3)	5.625 (± 20.966)	1.750 (± 26.768)	15.000 (± 13.229)	
PK-t R: School functioning (n=2,4,2)	-12.500 (± 29.463)	-7.500 (± 12.583)	-12.500 (± 17.678)	
FDR: Psychosocial functioning (n=21,20,3)	0.568 (± 14.728)	0.083 (± 16.226)	10.556 (± 15.486)	
PK-t R: Psychosocial functioning (n=3,4,2)	-14.231 (± 14.881)	0.000 (± 8.714)	0.833 (± 3.536)	
FDR: Total score (n=21,20,3)	-0.113 (± 14.629)	0.870 (± 15.362)	7.971 (± 15.230)	
PK-t R: Total score (n=3,4,2)	-11.310 (± 15.023)	1.630 (± 7.183)	3.261 (± 0.000)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study drug administration up to 36 months

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	BAX 855: Age < 6 Years
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Reporting group description:

Subjects of age less than 6 years received an infusion of 50 +/- 10 International Units (IU)/ kilogram (kg) of BAX 855 or a pharmacokinetically tailored (PK-tailored) prophylactic dose based on the participant's individual PK to maintain FVIII trough levels of greater than or equal to 3% twice weekly until they had reached at least 100 exposure days (EDs).

Reporting group title	BAX 855: Age >= 6 to <12 Years
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Reporting group description:

Subjects of age greater than or equal to 6 to less than 12 years received an infusion of 50 +/- 10 IU/ kg of BAX 855 or a PK-tailored prophylactic dose based on the participant's individual PK to maintain FVIII trough levels of greater than or equal to 3% twice weekly until they had reached at least 100 exposure days (EDs).

Reporting group title	BAX 855: Age >= 12 to <18 Years
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Reporting group description:

Subjects of age greater than or equal to 12 to less than 18 years received an infusion of 45 +/- 5 IU/ kg of BAX 855 or a PK-tailored prophylactic dose based on the participant's individual PK to maintain FVIII trough levels of greater than or equal to 3% twice weekly until they had reached at least 100 exposure days (EDs).

Reporting group title	BAX 855: Age >= 18 Years
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Reporting group description:

Subjects of age greater than or equal to 18 years received an infusion of 45 +/- 5 IU/ kg of BAX 855 or a PK-tailored prophylactic dose based on the participant's individual PK to maintain FVIII trough levels of greater than or equal to 3% twice weekly until they had reached at least 100 exposure days (EDs).

Serious adverse events	BAX 855: Age < 6 Years	BAX 855: Age >= 6 to <12 Years	BAX 855: Age >= 12 to <18 Years
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 32 (15.63%)	2 / 33 (6.06%)	4 / 30 (13.33%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to lung			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cancer metastatic			

subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 32 (3.13%)	1 / 33 (3.03%)	0 / 30 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 33 (3.03%)	0 / 30 (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
Pleural effusion			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Transaminases increased			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Facial bones fracture			

subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 32 (0.00%)	1 / 33 (3.03%)	0 / 30 (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
Femoral neck fracture			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	0 / 30 (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
Nasal injury			
subjects affected / exposed	0 / 32 (0.00%)	1 / 33 (3.03%)	0 / 30 (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
Scapula fracture			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic rupture			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic fracture			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound haemorrhage			

subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic haematoma			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 32 (0.00%)	1 / 33 (3.03%)	0 / 30 (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
Renal and urinary disorders			
Ureterolithiasis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	2 / 32 (6.25%)	0 / 33 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle haemorrhage			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess oral			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			

subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 33 (3.03%)	0 / 30 (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
Device related infection			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related sepsis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incision site abscess			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	0 / 30 (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
Plasmodium falciparum infection			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			

subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal bacteraemia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 33 (3.03%)	0 / 30 (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
Upper respiratory tract infection			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	0 / 30 (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
Urinary tract infection			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	BAX 855: Age >= 18 Years		
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 121 (18.18%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to lung			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal cancer metastatic			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Vascular disorders			
Haematoma			
subjects affected / exposed	2 / 121 (1.65%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	0 / 121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Transaminases increased			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			

subjects affected / exposed	0 / 121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Femoral neck fracture			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Head injury			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nasal injury			
subjects affected / exposed	0 / 121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Scapula fracture			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Splenic rupture			
subjects affected / exposed	0 / 121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Traumatic fracture			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound haemorrhage			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wrist fracture			

subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Splenic haematoma			
subjects affected / exposed	0 / 121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	2 / 121 (1.65%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			

subjects affected / exposed	0 / 121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Ureterolithiasis			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	0 / 121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Muscle haemorrhage			
subjects affected / exposed	0 / 121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess oral			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bacteraemia			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	0 / 121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Device related infection				
subjects affected / exposed	1 / 121 (0.83%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Device related sepsis				
subjects affected / exposed	1 / 121 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Incision site abscess				
subjects affected / exposed	1 / 121 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Laryngitis				
subjects affected / exposed	0 / 121 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Plasmodium falciparum infection				
subjects affected / exposed	1 / 121 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 121 (1.65%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Skin infection				
subjects affected / exposed	1 / 121 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Streptococcal bacteraemia				
subjects affected / exposed	1 / 121 (0.83%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tonsillitis				

subjects affected / exposed	0 / 121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	0 / 121 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	2 / 121 (1.65%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	BAX 855: Age < 6 Years	BAX 855: Age >= 6 to <12 Years	BAX 855: Age >= 12 to <18 Years
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 32 (62.50%)	26 / 33 (78.79%)	16 / 30 (53.33%)
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	2 / 32 (6.25%)	1 / 33 (3.03%)	0 / 30 (0.00%)
occurrences (all)	2	1	0
Joint injury			
subjects affected / exposed	0 / 32 (0.00%)	2 / 33 (6.06%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Laceration			
subjects affected / exposed	1 / 32 (3.13%)	1 / 33 (3.03%)	2 / 30 (6.67%)
occurrences (all)	2	1	2
Ligament sprain			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	3 / 30 (10.00%)
occurrences (all)	1	0	3
Limb injury			
subjects affected / exposed	0 / 32 (0.00%)	2 / 33 (6.06%)	3 / 30 (10.00%)
occurrences (all)	0	2	3
Skin abrasion			

subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 2	2 / 33 (6.06%) 2	0 / 30 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	5 / 33 (15.15%) 5	1 / 30 (3.33%) 1
Blood and lymphatic system disorders Iron deficiency anaemia subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	0 / 33 (0.00%) 0	0 / 30 (0.00%) 0
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	8 / 32 (25.00%) 12	3 / 33 (9.09%) 3	0 / 30 (0.00%) 0
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Loose tooth subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2 4 / 32 (12.50%) 6 0 / 32 (0.00%) 0 4 / 32 (12.50%) 4	1 / 33 (3.03%) 1 2 / 33 (6.06%) 2 2 / 33 (6.06%) 2 2 / 33 (6.06%) 4	0 / 30 (0.00%) 0 1 / 30 (3.33%) 1 0 / 30 (0.00%) 0 1 / 30 (3.33%) 2
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Oropharyngeal pain	10 / 32 (31.25%) 13 1 / 32 (3.13%) 1	3 / 33 (9.09%) 4 2 / 33 (6.06%) 2	0 / 30 (0.00%) 0 1 / 30 (3.33%) 1

subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	2 / 33 (6.06%) 2	1 / 30 (3.33%) 1
Rhinorrhoea subjects affected / exposed occurrences (all)	4 / 32 (12.50%) 5	2 / 33 (6.06%) 2	0 / 30 (0.00%) 0
Skin and subcutaneous tissue disorders			
Rash subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 3	1 / 33 (3.03%) 1	1 / 30 (3.33%) 1
Urticaria subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	0 / 33 (0.00%) 0	0 / 30 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 2	2 / 33 (6.06%) 2	2 / 30 (6.67%) 2
Back pain subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	0 / 33 (0.00%) 0	1 / 30 (3.33%) 1
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 3	1 / 33 (3.03%) 1	0 / 30 (0.00%) 0
Ear infection subjects affected / exposed occurrences (all)	5 / 32 (15.63%) 10	0 / 33 (0.00%) 0	1 / 30 (3.33%) 2
Gastroenteritis subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	0 / 33 (0.00%) 0	0 / 30 (0.00%) 0
Gastroenteritis viral subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	0 / 33 (0.00%) 0	0 / 30 (0.00%) 0
Influenza subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	3 / 33 (9.09%) 3	0 / 30 (0.00%) 0
Nasopharyngitis			

subjects affected / exposed	6 / 32 (18.75%)	7 / 33 (21.21%)	3 / 30 (10.00%)
occurrences (all)	12	12	6
Pharyngitis			
subjects affected / exposed	2 / 32 (6.25%)	2 / 33 (6.06%)	0 / 30 (0.00%)
occurrences (all)	2	2	0
Pharyngitis streptococcal			
subjects affected / exposed	1 / 32 (3.13%)	3 / 33 (9.09%)	1 / 30 (3.33%)
occurrences (all)	1	4	1
Rhinitis			
subjects affected / exposed	2 / 32 (6.25%)	2 / 33 (6.06%)	3 / 30 (10.00%)
occurrences (all)	2	2	5
Sinusitis			
subjects affected / exposed	2 / 32 (6.25%)	0 / 33 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Skin infection			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
Upper respiratory tract infection			
subjects affected / exposed	6 / 32 (18.75%)	5 / 33 (15.15%)	1 / 30 (3.33%)
occurrences (all)	12	10	1
Viral infection			
subjects affected / exposed	2 / 32 (6.25%)	1 / 33 (3.03%)	1 / 30 (3.33%)
occurrences (all)	5	1	1

Non-serious adverse events	BAX 855: Age >= 18 Years		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 121 (54.55%)		
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	0 / 121 (0.00%)		
occurrences (all)	0		
Joint injury			
subjects affected / exposed	3 / 121 (2.48%)		
occurrences (all)	3		
Laceration			

subjects affected / exposed	2 / 121 (1.65%)		
occurrences (all)	2		
Ligament sprain			
subjects affected / exposed	3 / 121 (2.48%)		
occurrences (all)	5		
Limb injury			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Skin abrasion			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 121 (9.92%)		
occurrences (all)	23		
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 121 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 121 (4.13%)		
occurrences (all)	5		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	3 / 121 (2.48%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	7 / 121 (5.79%)		
occurrences (all)	8		
Loose tooth			
subjects affected / exposed	0 / 121 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	2		

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 121 (5.79%)		
occurrences (all)	8		
Nasal congestion			
subjects affected / exposed	4 / 121 (3.31%)		
occurrences (all)	6		
Oropharyngeal pain			
subjects affected / exposed	4 / 121 (3.31%)		
occurrences (all)	7		
Rhinorrhoea			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	2 / 121 (1.65%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	14 / 121 (11.57%)		
occurrences (all)	20		
Back pain			
subjects affected / exposed	7 / 121 (5.79%)		
occurrences (all)	7		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Ear infection			
subjects affected / exposed	0 / 121 (0.00%)		
occurrences (all)	0		
Gastroenteritis			

subjects affected / exposed	2 / 121 (1.65%)		
occurrences (all)	2		
Gastroenteritis viral			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	3 / 121 (2.48%)		
occurrences (all)	3		
Nasopharyngitis			
subjects affected / exposed	24 / 121 (19.83%)		
occurrences (all)	38		
Pharyngitis			
subjects affected / exposed	5 / 121 (4.13%)		
occurrences (all)	9		
Pharyngitis streptococcal			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences (all)	2		
Sinusitis			
subjects affected / exposed	4 / 121 (3.31%)		
occurrences (all)	4		
Skin infection			
subjects affected / exposed	0 / 121 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	12 / 121 (9.92%)		
occurrences (all)	13		
Viral infection			
subjects affected / exposed	0 / 121 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 October 2013	- The timing of the first Follow-up visit changed from 1 month (+/- 2 weeks) to 6 weeks (- 1 or + 2 weeks). - Additional information was added to the description of the IP to more completely describe the BAX 855 molecule, the purpose of the study, how the data with BAX 855 be assessed in this study and the dosing rationale in this study. - The minimal duration of the washout period was changed to 72 hours to align with the pivotal study (Study 2012-003599-38) and to avoid additional risk of bleeding episodes. - A section on Treatment for Surgery or Dental Procedures was added to provide clarity on how subjects would be transferred to and from the surgery study (Study NCT01913405), what factor would be used, what and where the clinical data would be recorded. - A requirement for a 72-hour washout period before immunogenicity tests was added to implement the laboratory requirements and to avoid false results. - The level of detectable FVIII inhibitory antibodies determined by the central laboratory was changed to 0.4 Bethesda Units (BU) because the central laboratory was validated for this value. - To ensure safety and to be able to provide safety review data upon completion of the pivotal study, a safety review was added as planned interim analyses.
23 May 2014	- Primary study completion date and duration of subject participation to reach 100 EDs were adapted. - Instead of the rate of success of BAX 855 in the treatment of breakthrough bleeding episodes, an overall hemostatic efficacy rating was used. - Additional guidance was provided on the treatment of bleeding episodes and maintenance of hemostasis. - It was clarified that only BAX 855 would be used for the control of bleeding episodes. - The more general term PROs was introduced instead of HRQoL. - PROs were to be assessed every 6 months during the study, in addition to baseline and end of study visits. - The dose and dosage frequency of BAX 855 were revised. - The reference to male previously treated patients (PTPs) was removed (i.e., females could now be included). - The age limit was changed to ≤ 75 years at screening of the previous BAX 855 study for transitioning subjects. - BAX 855 naive subjects < 6 years old needed to have ≥ 50 documented EDs to plasma-derived FVIII. - The cut-off for detectable FVIII inhibitory antibodies was increased to ≥ 0.6 BU from ≥ 0.4 BU in alignment with other BAX 855 studies and to avoid the risk of false positive results at this low level given the assay variability. - BAX 855-naive subjects < 12 years of age were not to be enrolled until enrollment in the BAX 855 pediatric PTP study in children aged < 12 years (Study 2014-000742-30) had been completed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported